Guidance for Investigators
Investigational New Drug (IND) and New Drug Application (NDA)
Process Overview

July 2015

Funding Source: This guidance document was prepared for the Clinical Trials Development Resource for Hematologic Disorders (U24) initiative supported by National Heart, Lung and Blood Institute grant U24-HL114577.

Available at: https://accthd.rti.org/

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1. DEFINITIONS

The following is a list of definitions for terms used in, and for the purposes of, this guidance document:

- **FDA**: The Food and Drug Administration for which all drug exemption approvals must be obtained.

- **CDER**: The Center for Drug Evaluation and Research, a division of the Food and Drug Administration responsible for the oversight of drug development and approval for marketing and sales in the United States.

- **Applicant**: Any person or company who submits an application, amendment, or supplement to the FDA or owns an approved application for a drug or an antibiotic drug.

- **New Drug Application (NDA)**: Terminology used when referencing the submission of a package of information to the Food and Drug Administration in support of a new drug's approval.

- **Institution**: A person, other than an individual, who engages in the conduct of research on subjects or in the delivery of medical services to individuals as a primary activity or as an adjunct to providing residential or custodial care to humans.

- **DMF**: Drug Master File is a submission to the FDA that may be used to provide information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.

- **Investigational new drug (IND)**: a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes.

- **Code of Federal Regulations (CFR)**: An annual codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the Federal Government. The CFR is divided into 50 titles representing broad areas subject to Federal regulation. The purpose of the CFR is to present the official and complete text of agency regulations in one organized publication and to provide a comprehensive and convenient reference for all those who may need to know the text of general and permanent Federal regulations.

- **Good Clinical Practice (GCP)**: The standards for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials or studies.

- **Good Manufacturing Practice (GMP)**: The regulations and manufacturing standards that are frequently referred to as the Quality Systems Regulations. These regulations describe the methods used in the design, development, manufacturing, packing, and storage, as well as facilities and controls for, all finished drug products intended for human use.
▪ **Good Laboratory Practice (GLP):** The regulations for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing of among other things, drugs for human use. These regulations ensure the quality and integrity of safety data and describe the requirements for personnel, facilities, equipment, test and control articles, protocols, records, and reports.

▪ **Guidance/Guidelines:** FDA issued documents that provide procedures or standards to assist in the clarification of existing minimal regulatory requirements and/or the expectations and/or industry standards acceptable to FDA. These are not legal requirements and are not binding on FDA or the regulated industry unless they are promulgated through regulations. However, failure to adhere to these expectations should be documented with justification and FDA’s concurrence.

▪ **Investigator:** Person who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team. The Investigator must meet requirements set forth by the Food and Drug Administration (FDA) or other regulatory bodies. The qualifications must be outlined in a current resume and readily available for auditors.

▪ **Institutional review board (IRB):** Any board, committee, or other group formally designated by an institution to review biomedical research involving subjects and established, operated, and functioning in conformance with 21 CFR Part 56.

▪ **Monitor:** An individual designated by a sponsor or contract research organization to oversee the progress of an investigation.

▪ **Sponsor:** A person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual.

▪ **Specification:** The quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of the drug substances, drug products, intermediates, raw materials, reagents, components, in process materials, container closure systems, and other materials used in the production of a drug or drug product.

▪ **Drug Product:** A finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

▪ **Drug Substance:** An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use in the synthesis of such ingredient.

▪ **Biologic License Application (BLA):** Therapeutic biologics application is the mechanism to request permission from the Food and Drug Administration to introduce, or deliver for introduction, a biologic product into interstate commerce. This process applies to any therapeutic drug with a biologics component.
2. INTRODUCTION

The process for approving new drugs in the United States is one of the most documented and well known processes in the Food and Drug Administration's Center for Drug Evaluation and Research (CDER). Although complex and sometimes confusing, the steps to drug approval are consistent from one form to another with minor exceptions. That having been said, it is important for the investigator to know the method in which one gets to the approval can vary greatly depending on a variety of factors such as, the formulation of the drug, delivery method, raw materials, and supporting evidence for use.

This guidance document provides an overview of the information regarding the design, development, and regulatory US Food and Drug Administration approval of new drugs and/or studies involving the use of investigational new drugs. It is designed to provide the investigator with a general understanding of the role and responsibility as a Sponsor and/or investigator, where to find direction and regulatory requirements, and how to complete the IND exemption or NDA submission process.

3. TYPES OF APPLICATIONS

There are five main types of applications involving the various aspects of drug approval and/or use for clinical studies. Each process is designed to address a specific aspect of the development and release of a new drug through FDA approval. All of these processes are documented in the current Federal laws and outlined in numerous guidance documents.

3.1 The Investigational New Drug (IND) application process is used in two categories, commercial and research or non-commercial experimental drug use. Both categories are used to obtain permission for a pharmaceutical manufacturing company to ship an experimental drug across state lines to clinical investigators, before a marketing application for the drug has been approved. The IND application is reviewed by FDA officials to determine if research subjects receiving the drugs will be subjected to unreasonable risk. If the FDA clears the IND, the drug is ready to be entered into a Phase I Clinical Trial.

Within the IND process there exist three types of applications; the Investigator IND (submitted when a physician is initiating and conducting an investigation and under whose immediate direction the investigational drug is administered or dispensed), the Emergency Use IND (authorizing the use of an experimental drug in an emergency situation for which there is not time for an IND submission), and the Treatment IND (for experimental drugs showing promise in clinical testing for serious or immediately life threatening conditions while clinical work is conducted and the FDA review takes place).

3.2 A New Drug Application (NDA) is presented to the FDA for approval to market and sale a new drug when the sponsor has enough evidence to support the drug’s safety and effectiveness. Evidential Data must be provided through specific technical viewpoints that include pharmacology, medical biopharmaceutics, and statistical significance to support conclusions. The documentation required for submission in the NDA process is designed to give the entire history of the drug and must include, among other things, results of the animal testing, what happened during clinical testing in humans, how the drug behaves in the body, and how it is manufactured, processed, and packaged.
3.3 An **Abbreviated New Drug Application (ANDA)** is used for the submission of a generic drug application. The focus of these applications is to establish bio-equivalency to an already marketed and approved drug. Once approved, an applicant may then manufacture and market the generic equivalent as a safe, effective, low cost alternative to the innovator drug.

3.4 An **Over-the-Counter Drugs (OTC) Application** is specific to those drugs marketed and sold without a physician’s prescription. There are more than 80 therapeutic categories of over-the-counter drugs for which CDER is responsible to ensure they are properly labeled and the benefits of their use outweigh the risks.

3.5 The **Biologic License Application (BLA)** falls under the provisions of the Public Health Act and is used to manage the interstate commerce for drug products of a biological nature. This submission must contain specific information on the chemistry, pharmacology, clinical pharmacology, and the medical effects of the biologic product. A license is granted for products that meet the standards designed to insure continued safety, purity, and potency (efficacy) of the product.

4. **GXP REGULATIONS**

**Good laboratory Practice (GLP)** provides the framework for assuring the quality and integrity of safety data that is obtained from nonclinical laboratory studies intended to support applications to the Food and Drug Administration for research or approval of pharmaceutical drugs.

“**Good Clinical Practice (GCP)**” is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

Investigators should review and apply GCP guidelines to all aspects of clinical research involving drug development. Chapter 4 of the GCP guidelines outlines Investigator responsibilities, such as education and training, regulatory compliance, components of informed consent, and study subject participation and withdrawal. Additionally, investigators should ensure that any drug used in a feasibility or clinical research study for which they are responsible has been developed and manufactured under good manufacturing practices as outlined in the regulations.

**Good Manufacturing Practice (GMP)** provides the framework for assuring the quality systems are in place to document the manufacturing, processing, release criteria, testing, packaging, and labeling of a drug.
5. CODE OF FEDERAL REGULATIONS (CFR)

CFR Title 21 Part 312 and Part 314 are established for the presentation of FDA regulations and guidelines applicable to investigational new drugs. CFR Title 21 Part 601 addresses the product licensing for biologics. Other parts of Title 21 are applicable to clinical research in which investigational devices are used that apply to other types of studies as well. As an Investigator of a drug clinical trial, it is important to have a basic understanding of all applicable regulations and where to find them.

5.1 21 CFR Part 50

Part 50 includes FDA regulations for the protection of human subjects during the conduct of a clinical trial. Subject headings include Informed Consent for Human Subjects and Additional Safeguards for Children in Clinical Investigations.

5.2 21 CFR Part 54

Part 54 includes FDA regulations that address the requirements for an applicant whose submission relies in part on clinical data to disclose certain financial arrangements between sponsor(s) of the covered studies and the clinical investigators and certain interests of the clinical investigators in the product under study or in the sponsor of the covered study.

5.3 21 CFR Part 56

Part 56 establishes the regulations and guidelines that must be followed by Institutional Review Boards (IRBs). An Investigator should be familiar with the role of the IRB with respect to medical device risk assessments and exemptions.

5.4 21 CFR Part 58

Part 58 establishes the regulations for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing of medical devices for human use.

5.5 46 CFR Part 46

DHHS Protection of Human Subjects. Investigators are required to comply with the regulations if they are engaged in research involving human subjects that is conducted, supported by DHHS, unless the research is exempt under 45 CFR 46.101(b). It also includes research that is otherwise subject to regulation by any Federal department or agency that takes appropriate administrative action to make the policy applicable to such research.

5.6 21 CFR Part 312

Part 312 defines the procedures and requirements that support the use of an investigational new drug, including the submission requirements and review process.
5.7 21 CFR Part 314

Part 314\textsuperscript{13} includes FDA regulations for the procedures and requirements that support the application and abbreviated application to request approval to market a new drug in the United States.

5.8 21 CFR Part 316

Part 316\textsuperscript{14} includes FDA regulations for that provides procedures to encourage and facilitate the development of drugs for rare diseases or conditions, including biological products and antibiotics.

5.9 21 CFR Part 201

Part 201\textsuperscript{15} includes FDA regulations for the required contents of the labeling for a drug. Please note this section does not apply to biological drug products.

5.10 21 CFR Part 600

Part 600\textsuperscript{16} includes FDA regulations that provides procedures to address the licensing of products of a biological nature. These include drugs derived from biological material.

6. IND APPLICATION PROCESS\textsuperscript{11}

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 compound for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the compound 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. This is the point in which further testing requires an IND application to the FDA for approval to continue use in Phase I clinical trials and beyond.

6.1 General Principles of the IND Submission

An IND is submitted for a specific drug and may incorporate multiple clinical protocols to address the various phases of testing to determine the drug’s safety and effectiveness.

An IND is required for a clinical study designed to obtain/support

- New indications for an already approved drug,
- Changes in the dosage or approved route in which it is administered to patients,
- Changes to the population for which the drug is currently indicated for use, and/or
- Significant changes to the promotional claims of an already approved/marketed drug
The FDA’s primary objective in reviewing an IND in all phases of the clinical investigation is to assure the safety and rights of the patients. However, the later phases of the trials are also evaluated for the scientific quality of the investigation and the potential for yielding data capable of supporting market approval of the drug. It is important to remember these objectives when preparing the initial IND and subsequent amendments throughout the investigational process. All communications with the FDA with regard to the drug should focus on providing data and trial status in support of these objectives.

6.2 Phases of the Drug Development

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

Phase 1 trials are designed to introduce the new drug into humans.

Phase 2 trials focus on the determination of side effects and risks associated with use of the drug for the intended use in the defined patient population.

Phase 3 trials focus on obtaining data in support of the product labeling claims and to further establish the benefit to risk profile for the overall drug approval.

6.3 FDA Communications and Actions

The FDA encourages communications via email, teleconference, meetings, and written communications. However, the regulations require certain communications and even establish the timelines for those activities. These communications include end of phase meetings and Pre-IND and Pre-NDA meetings.

Investigators are strongly encouraged to engage the FDA early into the planning stages and at a minimum for a Pre-IND formal meeting. This meeting is designed to discuss things like problems with the drug substance, drug product, or formulation intended for human use, adequacy of preclinical toxicology studies, issues with dosing schedules, known/unknown metabolites, novel dose-escalation schematics, as well as the proposed overall clinical investigation plan. Any comments or suggestions FDA provides at the Pre-IND meeting should be addressed in the actual IND submission package. If given the opportunity to provide materials for a preliminary review prior to the official submission, it is strongly advised to agree to this action and follow up promptly. These types of
communication will in most cases drive the process to a positive outcome much faster and serve to educate the participants on both sides of the table.

Once an IND is submitted to FDA a series of formal communications are initiated and will continue throughout the IND’s existence.

The first notice comes to the sponsor in writing of the date the FDA received the IND. This is important because the IND goes into effect thirty days after the FDA acknowledges receipt, unless the sponsor is notified of a clinical hold. Alternatively, the FDA may notify the Sponsor earlier than thirty days that the investigation may begin. An investigator may not administer an investigational drug to human subjects until the IND goes into effect.

A clinical hold may be ordered via a telephone call or other means of rapid communication or in writing. This comes from FDA to delay a proposed clinical investigation or to suspend an ongoing investigation. If a hold is applied to a proposed study, subjects may not be given the investigational drug. If a hold is applied to an ongoing study, no new subjects may be recruited to the study or given the investigational drug. The Director of the FDA Division with responsibility for the review of the IND will provide the Sponsor with a written explanation of the basis for the hold within thirty days of the imposed hold.

A written response from the Sponsor should be sent to FDA addressing the issues for which a hold was imposed and formally requesting the hold be lifted. No study can resume without a formal notification from FDA that the hold has been lifted. If a study remains on clinical hold for 1 year or more, the IND may be placed on inactive status by FDA.

In the event FDA concludes there are issues with a drug’s trial such that a termination is merited, a proposal to terminate and an opportunity for the sponsor to respond will be communicated prior to formal notice of termination. This process does not apply to conditions in which the FDA concludes continuation of the studies under the IND present an immediate or substantial danger to the health of the human subjects.

An IND may be placed on inactive status by either the FDA or the Sponsor if no subjects are entered into the study for a period of 2 years or more or the IND remains on clinical hold for 1 year or more. To resume an IND placed on inactive status, the Sponsor must submit a protocol amendment containing the general investigational plan for the coming year and/or any additional information via an informational amendment to the FDA for reconsideration.

Annual reports must be submitted by the Sponsor to FDA annually for any IND study in an active state. The requirements for this report are clearly defined in the regulations.
6.4 IND Application Content

The content and format of an IND application are defined in the regulations and a variety of guidance documents in order to ensure a consistent process for FDA to efficiently review submissions. There are obvious redundancies in some sections and although recognized, should not be dismissed or abbreviated as this is done intentionally to facilitate multiple FDA reviewers in different disciplines working independently. Sponsors are encouraged to use their own discretion in how they wish to address specific section content. However, a sponsor-investigator who wishes to study an already approved drug or one that has an existing IND, should follow the same general format as the original submission. It is also suggested that the investigator obtain in writing from the sponsor/manufacturer permission to reference their submission in order to facilitate this application process.

An Initial IND Application should include the items in the specific order noted in Appendix A.12

6.5 Roles and Responsibilities of the Sponsor/Investigator holding an IND

A Sponsor of a clinical trial may be an individual, company, or institution that takes responsibility for the initiation, financing, and/or management of a clinical trial. The investigator initiates and conducts, either with others or alone, a clinical trial and directs the investigational products administration to patients/subjects.

The primary responsibility of the Sponsor and investigator, whether one in the same or separate is to protect the rights and safety of all study participants. This is done by ensuring the clinical investigation is performed by qualified investigators in a manner consistent with an IRB approved protocol, the investigator agreements, and all applicable rules and regulations.

Administratively the role of the Sponsor is to maintain an effective IND, ensure all sites are adequately monitored and are performing to expectations, investigators are provided timely information regarding adverse events or risks with respect to the drug, and that FDA receives all expected reports and records in the time frames specified by the regulations. This includes adverse event reporting, significant changes to the protocol or study investigational process, and the annual report of all activities associated with the investigational studies to name a few.

Various duties associated with these roles may be delegated to other individuals but the Sponsor’s role is accountable and responsible for the overall conduct of the trial and its outcomes.

7. NDA APPLICATION PROCESS

The basis for an NDA approval is demonstration of efficacy with acceptable safety in adequate and well controlled studies. Additionally, this process gains approval for
the product labeling that defines an appropriate patient population for treatment with the drug and adequate information to enable safe and effective use of the drug.4

7.1 General Principles of the NDA Process11

The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA.

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.

7.2 Pre-NDA Meeting

The purpose of a Pre-NDA meeting is to discuss filing and format issues that could impact the FDA’s ability to effectively review the submission and/or negatively impact the submission’s objective to get the new drug approved. This is a critical meeting in which the Sponsor should be prepared to provide a brief summary of the trial results, discuss the statistical analysis plan and how the data will be presented and formatted, and to address any major unresolved problems that will impact the submission. If effective, this meeting will provide an assurance that all facilities utilized in the manufacturing, testing, and packaging of the drug will be ready for inspection at the time of the submission, stability data as agreed upon in earlier meetings is or will be complete and included in the package, and all previously identified issues in prior (end of phases) meetings have been addressed with supporting data in the NDA.

It is recommended this meeting be planned at least six months prior to the actual planned NDA submission date in order to provide adequate time and resources to prepare and plan for information obtained during the pre-NDA meeting.

7.3 New Drug Application (NDA) Content12, 13

The NDA process includes the materials submitted in the IND and builds on that story with the additional testing and statistical analysis from the clinical trial data. There are numerous guidance documents and specific regulations that dictate the content of the package and format in which it should be produced. Three copies of the completed application package are required to be submitted. These should be identified as a review copy, archive copy, and a field copy.

The archive copy is maintained by FDA during the review of the application as a reference copy to permit individual reviewers of sections of the application access
to other sections, for additional personnel to access for official business, and to ensure the agency has a complete copy on file.

The review copy contains several common elements of the complete submission (the application form and a copy of the summary) but additionally has the expectation that the technical sections be bound separately.

The field copy is similar to the review copy but must also have a certification that the technical content is the same as that found in the archive and review copies of the submissions.

These nuances are important because failure to comply with these specifics can create confusion and extensive delays in the review and ultimate approval process. The general elements found in common for most submissions include a signed application form (see Appendix B), a summary of the content, technical sections, patient data, drug samples, and proposed text for the drug labeling. Each of these sections are well defined in the regulations with respect to the minimal content that must be included.

7.4 Financial Disclosures

Since 1998, the FDA has required a formal documentation of any financial interests or arrangements made with Principal Investigators and Sponsors that could affect the reliability of data submitted in support of new drugs, devices, or biologics approvals. Specifically for NDAs, the applicant must certify that no financial arrangements exist with the investigator that are impacted by the outcome of the clinical studies. Additionally, the investigator must certify that he/she does not own a significant equity interest or proprietary interest in the tested product and has not received significant payments of other sorts. If special arrangements exist, it is the Applicant’s responsibility to disclose the nature of the arrangements and the value associated with those arrangements. Failure to disclose this information will significantly impact the submission and potential approval.

7.5 User Fees

In 1992, congress enacted the laws that require a fee be paid to FDA that is designed to cover the cost of the review and approval process for new products. This was done to fund resources needed to address an overwhelming complaint that approvals took too long and delays were impacting the health and welfare of individuals who needed the new drugs, biologics, and medical devices for which these fees were designated to cover. Each year a new cost structure is published for the following fiscal year. The one applicable to the NDA process is called the Prescription Drug User Fee Act. As a point of reference, the PDUFA rates for FY 2015 were published via the Federal Register as follows;
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Fee category | Fee rates for FY 2015
---|---
Applications: | |
Requiring clinical data | $2,335,200 |
Not requiring clinical data | $1,167,600 |
Supplements requiring clinical data | $1,167,600 |
Establishments | $ 569,200 |
Products | $ 110,370 |

7.6 NDA Review Process

The official review process for a new drug is the time it take somewhere between 20 and 3000 FDA experts (medical doctors, chemists, statisticians, microbiologists, pharmacologists, and others) to review the submission package and issue an action letter. This begins approximately 60 days after receipt at FDA and only after the submission is deemed acceptable for review.

The action letter is the official statement informing the applicant of the agency’s decision to approve for marketing in the US (approval letter) or that there exist problems with the NDA and more information is necessary to make that determination (complete response letter). Reasons for a complete response letter include such issues as failure to adequately demonstrate the drug’s effectiveness and safety or a poor inspection of the GMP manufacturing facility associated with the drug’s manufacturing. In these cases the Sponsor may need to conduct additional testing under different circumstances to alleviate the FDA’s concerns or address the deficiencies noted in the inspectional findings of the manufacturing facility before further actions will be taken.

The timeline for completion of a standard NDA review is targeted for ten months from acceptance, which is twelve months from submission. It is important to note this timeline is under the best of circumstances and is not binding for the FDA. Expedited or abbreviated reviews are targeted to be completed in six months but these are exceptional circumstances.

7.7 Drug Approval Timeline

Timelines to complete the scope of work defined for the development and testing needed to support an NDA submission are dependent on numerous factors. Below is a general timeline to be used for planning purposes only. This provides an example of what can be expected in the process. It is important to note that the quantity of subjects/patients in a trial for each phase and thus the time to complete phases of the testing can vary tremendously and require FDA’s agreement. Additionally, factors that impact the results of the trials can prolong the testing and even increase the kinds of patients/subjects needed to establish the risk profile for a drug based on data.
8. SUMMARY AND RECOMMENDATIONS

8.1 Summary

In order to have a clear path to a new drug’s approval, it is recommended the investigator consider the regulatory process early in the research stage of drug development as this process is actually initiated with the laboratory and animal testing results in which one discovers how the drug works and whether it’s likely to be safe and effective in humans. If this documentation is sound and supportive, the next steps to initiate a series of tests in people becomes more easily defendable. The clinical trials will then produce the results needed to substantiate the drug is safe when used to treat a disease and that it provides a real health benefit.

The role of the CDER physicians, statisticians, chemists, pharmacologists, and other scientists is to provide an unbiased review of the documentation submitted in support of a drug approval to ensure the data supports a drug’s health benefits outweigh its known risks. Working effectively with those individuals along the way can help both parties (FDA reviewers and the Sponsor/Investigator) to accomplish the task of determining risk benefits of a new drug in the most effective manner.

8.2 Recommendation for Sponsors/Investigators

- Familiarize yourself with all applicable rules and regulations at the onset of the activity. Ensure all participants of your investigation understand and follow the applicable rules and regulations throughout the trial.
• Ensure adequate time and resources are allocated for the IND and NDA processes at the onset of the trial planning phase once the objectives of the study have been defined.

• Request and plan for FDA meetings at each key juncture of the process and make sure all documentation for those meetings is sent to the FDA 4–6 weeks before the date of any meeting.

• Evaluate all site monitoring activities and reports to ensure appropriate actions are taken and significant issues that might impact the overall study results and/or safety and welfare of the subjects are addressed in a timely manner.

9. RESOURCES

9.1 Government Resources
• NHLBI, Children and Clinical Studies: https://www.nhlbi.nih.gov/childrenandclinicalstudies/index.php
• Patient Recruitment for Studies Conducted by the NHLBI/NIH: http://patientrecruitment.nhlbi.nih.gov/
• Guidance and Implementation for Monitoring Adequacy of Accrual of Participants to NHLBI Supported Human Subjects Research: http://www.nhlbi.nih.gov/funding/policies/accrual_guidelines.htm
• Centers for Disease Control and Prevention: http://www.cdc.gov/
• Clinical Trials.gov website: https://clinicaltrials.gov/
• Food and Drug Administration website: https://www.fda.gov/

9.2 Professional/Medical Resources
• Drug Information Association: http://www.diaglobal.org/en-US.aspx
• Regulatory Affairs Professionals Society (RAPS): http://www.RAPS.org
• PhRMA, the Pharmaceutical Research and Manufacturers of America: http://www.phrma.org
• Pharmaceutical Education and Research Institute: http://www.peri.org/
REFERENCES


APPENDIX A: INITIAL IND APPLICATION CONTENT AND FORMAT

THE ORDER TO BE PREPARED FOR SUBMISSION IS;

1. A completed Form FDA 1571
2. Table of Contents
3. Introductory Statement and General Investigational Plan
   a. Provide the name of the drug and all active ingredients, the drugs’ pharmacological class, structural formula of the drug, formulation of the dosage to be used, route of administration, and the broad objectives and duration of the clinical investigation.
   b. Summary of previous human experiences with the drug, reference to other INDs if pertinent, and to investigational or marketing experience in other countries that may be relevant to the safety profile.
   c. If the drug has been withdrawn from investigation or marketing in any other country for any reason related to safety or effectiveness, identify the country and the reasons for withdrawal.
   d. An overall description of the investigational plan for the first year.
      i. Rational for the drug or the study
      ii. Indications to be studied
      iii. General approach to be followed in evaluating the drug
      iv. Kinds of clinical trials to be conducted
      v. Estimated number of subjects to be given the drug
      vi. Any risks of particular severity or seriousness anticipated based on the toxicology data in animals or prior studies in humans with the drug or related drugs.
4. Investigator’s Brochure (not required for sponsor investigator IND applications but recommended)
   a. Description of the active drug substance and the drug product formulation.
   b. Summary of the pharmacological and toxicological effects of the drug in animals and (to the extent known) in humans.
   c. Summary of information relating to the safety and effectiveness of the drug in humans obtained from prior clinical studies.
   d. Description of possible risks and side effects to be anticipated
5. Clinical Protocol (There should be a separate clinical protocol for each planned study of the investigational drug product. If not all of the phases protocols are available for the initial submission, they must be submitted as a protocol amendment at a later date.)
   a. General Principles
i. Phase 1 studies
ii. Phase 2 and 3 studies
b. Protocol content and format
   i. Statement of the objective and purpose of the study
   ii. Name and address and statement of qualifications of each investigator; names of each sub-investigator working under the investigator, name and address of the research facilities to be used, and the name and address of each IRB.
   iii. Criteria for research subject selection and exclusion and estimated number of subjects to be studied.
   iv. Description of the study design, including control group to be used, a description of the methods to be used to randomize subjects, minimize bias of investigators and data analysts.
   v. Method to determine the dose to be administered and planned maximum dosage and duration of individual human subject exposure to the drug.
   vi. Description of the observations and measurements to be made.
   vii. Description of the clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

6. Chemistry, Manufacturing, and Control (CMC) Information
7. Labeling
8. Pharmacology and Toxicology Information
9. Previous Human Experience with the Investigational Drug
10. Additional Information
11. FDA-Requested Relevant Information
APPENDIX B: FDA GUIDANCE DOCUMENTS AND FORMS FOR IND AND NDA SUBMISSIONS FOUND AT HTTP://WWW.FDA.GOV.

1.0 Guidance documents to help prepare INDs include:

- **Safety Reporting Requirements for INDs and BE/BA Studies** (9/28/2010)
- **Enforcement of Safety Reporting Requirements for INDs and BA/BE Studies** (PDF - 41KB) (6/6/2011)
- **CGMP for Phase 1 Investigational Drugs** (PDF - 132KB) (7/2008)
- **Exploratory IND Studies** (PDF - 220KB) (1/12/2006)
- **Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well Characterized, Therapeutic, Biotechnology-Derived Products** (PDF - 42KB). Provides description of required sections of an application. (Issued 11/1995)
- **Q & A - Content and Format of INDs for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products** (PDF - 14KB). 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. (Issued 10/2000)
- **Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations** (PDF - 268KB). (Issued 10/2000, Posted 10/27/2000). 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.
- **IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer** (PDF - 188KB). (1/2004)
- **Guideline for Drug Master Files.** A Drug Master File (DMF) is a submission to 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.**
- **Immunotoxicology Evaluation of Investigational New Drugs** (PDF - 100KB) (Issued 10/2002, Posted 10/31/2002). This guidance makes recommendations to sponsors
of 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.

2.0 Guidance documents to help prepare NDAs include:

- Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (Issued 10/2000, Posted 10/27/2000). 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.

- Changes to an Approved NDA or ANDA (PDF) (Issued 11/1999, Posted 11/19/1999)

- Changes to an Approved NDA or ANDA: Questions and Answers (PDF) (Issued 1/2001, Posted 1/22/2001)


- Format and Content of the Chemistry, Manufacturing and Controls Section of an Application. (Withdrawn as per FR notice, 6/1/2006)

- Format and Content of the Microbiology Section of an Application.


- Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances.
• Submitting Documentation for the Stability of Human Drugs and Biologics. (Withdrawn as per FR notice, 6/1/2006)

• Submitting Samples and Analytical Data for Methods Validation.

• Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Products.


• Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application. (Issued 2/1987, Posted 3/2/1998)

• Format and Content of the Nonclinical Pharmacology/Toxicology Section of an Application. (Posted 3/2/1998)

• Providing 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 - Content and Format for NDAs and ANDAs (PDF) (Issued 3/7/2000, Posted 3/7/2000)

• Refusal to File. (Issued 7/12/1993, Posted 11/26/99) Clarifies CDER’s decisions to refuse to file an incomplete application.
3.0 Investigational New Drug Forms (IND) Forms

- FDA 1571 (pdf) Investigational New Drug Application
- FDA 1572 (pdf) Statement of Investigator
- Instructions for completing FDA forms 1571 and 1572
- FDA Form Distributions Page. includes links to:
  - Certification: Financial Interest and Arrangements of Clinical Investigators
  - Disclosure: Financial Interest and Arrangements of Clinical Investigators
  - MedWatch: FDA Medical Product Reporting Program - Voluntary
  - MedWatch: FDA Medical Products Reporting Program - Mandatory

4.0 New Drug Applications (NDA) Forms

- Form FDA-356h. Application to Market a New Drug, Biologic, or An Antibiotic Drug For Human Use
- Form FDA-356h instructions
- Form FDA-3397. User Fee Cover Sheet
- Form FDA-3331. New Drug Application Field Report