

The CDER Handbook

● Introduction.....	2
● New Drug Development and Review Process.....	3
● Generic Drug Review Process.....	29
● Over-The-Counter Drug Review Process.....	35
● Post Drug Approval Activities.....	41
● Communicating with CDER.....	68
● Other Activities.....	74
● People at CDER.....	84

Produced by:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Revised: 03/16/98

Introduction

The CDER Handbook was developed to provide a user-friendly resource on the World Wide Web for obtaining information on the Center's processes and activities of interest to regulated industry, health professionals, academia, and the general public.

The CDER Handbook is arranged according to the four major activities that the Center is involved in: New Drug Review, Generic Drug Review, Over-the-Counter Drug Review, and Post Drug Approval Activities. Two other categories, "Communicating with CDER" and "Other Topics" are included to describe the additional activities and topics of interest at the Center.

Each selection in the CDER Handbook contains a concise description of a particular process or activity and often provides resources or links to other sites for further information on a given subject.

In addition, the CDER Handbook provides an "Acronym List" to provide you with definitions of unfamiliar acronyms used in CDER. There is also a "People" section which provides links to information on how CDER is organized as well as to key points of contact within the Center.

Some documents in the CDER Handbook are in Portable Document Format (PDF) to retain the original format. To view or print these documents, you must use the Adobe Acrobat Reader. The Acrobat Reader is free and available directly from Adobe's website with full installation instructions.

The CDER Handbook was designed specifically with the Web user in mind, and it is our hope that you will find the information contained in this resource useful and easy to locate. We welcome your comments and suggestions on how this product can be improved. We hope you enjoy your visit!

New Drug Development and Review Process

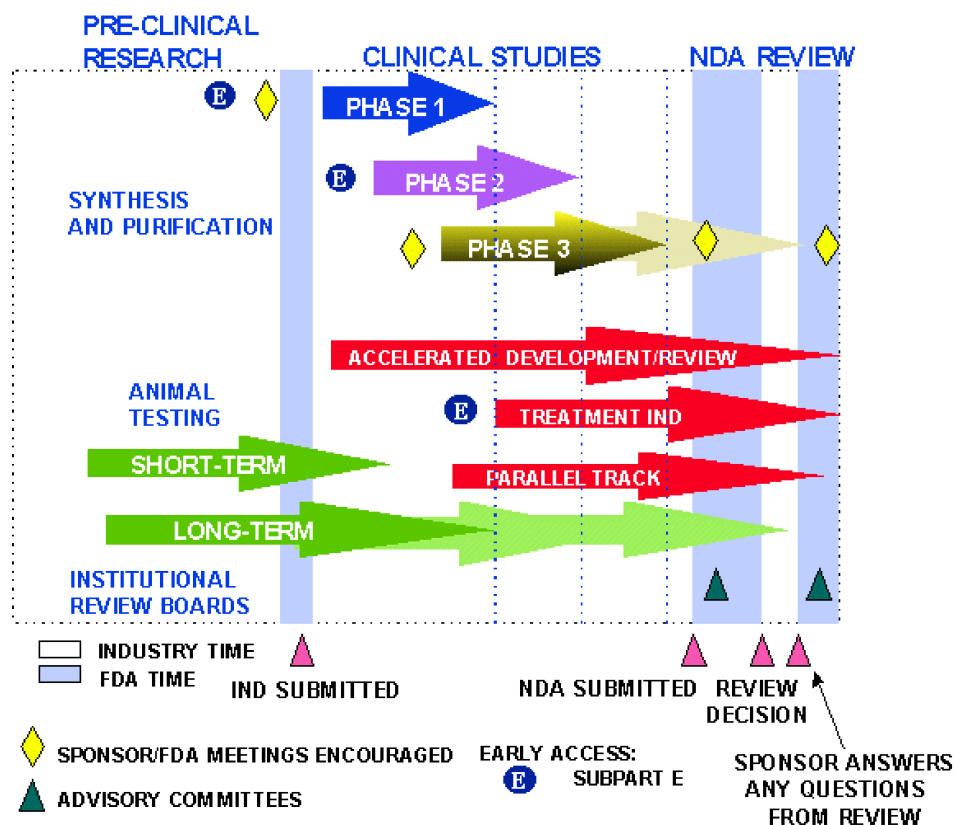


The mission of FDA's Center for Drug Evaluation and Research is to assure that safe and effective drugs are available to the American people. The information below provides an understanding of how CDER works to accomplish this mission as it relates to new drug development and review.

- New Drug Development Process- An interactive chart that provides an overview of the new drug development process, with an emphasis on preclinical research and clinical studies conducted by the drug's sponsor 4
- Investigational New Drug (IND) Review Process- An interactive chart that provides an overview of CDER's investigational new drug application process, including how CDER determines if the product is suitable for use in clinical trials. 13
- New Drug Application (NDA) Review Process- An interactive chart that provides an overview of CDER's new drug application review process, including how CDER determines the benefit:risk profile of a drug product prior to approval for marketing 19

The New Drug Development Process:

Steps from Test Tube to New Drug Application Review



Pre-Clinical Research

Under FDA requirements, a sponsor must first submit data showing that the drug is reasonably safe for use in initial, small-scale clinical studies. Depending on whether the compound has been studied or marketed previously, the sponsor may have several options for fulfilling this requirement: (1) compiling existing nonclinical data from past in vitro laboratory or animal studies on the compound; (2) compiling data from previous clinical testing or marketing of the drug in the United States or another country whose population is relevant to the U.S. population; or (3) undertaking new preclinical studies designed to provide the evidence necessary to support the safety of administering the compound to humans.

During preclinical drug development, a sponsor evaluates the drug's toxic and pharmacologic effects through in vitro and in vivo laboratory animal testing. Genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body. At the preclinical stage, the FDA will generally ask, at a minimum, that sponsors: (1) develop a pharmacological profile of the drug; (2) determine the acute toxicity of the drug in at least two species of animals, and (3) conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies.

Synthesis and Purification

The research process is complicated, time-consuming, and costly and the end result is never guaranteed. Literally hundreds and sometimes thousands of chemical compounds must be made and tested in an effort to find one that can achieve a desirable result.

FDA estimates that it takes approximately eight-and-a-half years to study and test a new drug before it can be approved for the general public. This estimate includes early laboratory and animal testing, as well as later clinical trials using human subjects.

There is no standard route through which drugs are developed. A pharmaceutical company may decide to develop a new drug aimed at a specific disease or medical condition. Sometimes, scientists choose to pursue an interesting or promising line of research. In other cases, new findings from university, government, or other laboratories may point the way for drug companies to follow with their own research.

New drug research starts with an understanding of how the body functions, both normally and abnormally, at its most basic levels. The questions raised by this research help determine a concept of how a drug might be used to prevent, cure, or treat a disease or medical condition. This provides the researcher with a target. Sometimes, scientists find the right compound quickly, but usually hundreds or thousands must be screened. In a series of test tube experiments called assays, compounds are added one at a time to enzymes, cell cultures, or cellular substances grown in a laboratory. The goal is to find which additions show some effect. This process may require testing hundreds of compounds since some may not work, but will indicate ways of

changing the compound's chemical structure to improve its performance.

Computers can be used to simulate a chemical compound and design chemical structures that might work against it. Enzymes attach to the correct site on a cell's membrane, which causes the disease. A computer can show scientists what the receptor site looks like and how one might tailor a compound to block an enzyme from attaching there. But even though computers give chemists clues as to which compounds to make, a substance must still be tested within a living being.

Another approach involves testing compounds made naturally by microscopic organisms. Candidates include fungi, viruses and molds, such as those that led to penicillin and other antibiotics. Scientists grow the microorganisms in what is known as a "fermentation broth," with one type of organism per broth. Sometimes, 100,000 or more broths are tested to see whether any compound made by a microorganism has a desirable effect.

Animal Testing

In animal testing, drug companies make every effort to use as few animals as possible and to ensure their humane and proper care. Generally, two or more species (one rodent, one non-rodent) are tested because a drug may affect one species differently from another. Animal testing is used to measure how much of a drug is absorbed into the blood, how it is broken down chemically in the body, the toxicity of the drug and its breakdown products (metabolites), and how quickly the drug and its metabolites are excreted from the body.

Short-Term Testing

Short-term testing in animals ranges in duration from 2 weeks to 3 months, depending on the proposed use of the substance.

Long-Term Testing

Long-term testing in animals ranges in duration from a few weeks to several years. Some animal testing continues after human tests begin to learn whether long-term use of a drug may cause cancer or birth defects. Much of this information is submitted to FDA when a sponsor requests to proceed with human clinical trials. The FDA reviews the preclinical research data and then makes a decision as to whether to allow the clinical trials to proceed (see Clinical Studies (Overview)).

Institutional Review Boards

Institutional Review Boards (IRB) are used to ensure the rights and welfare of people participating in clinical trials both before and during their trial participation. IRBs at hospitals and research institutions throughout the country make sure that participants are fully informed and have given their written consent before studies ever begin. IRBs are monitored by the FDA to protect and ensure the safety of participants in medical research.

An IRB must be composed of no less than five experts and lay people with varying backgrounds to ensure a complete and adequate review of activities commonly conducted by research institutions. In addition to possessing the professional competence needed to review specific activities, an IRB must be able to ascertain the acceptability of applications and proposals in terms of institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. Therefore, IRBs must be composed of people whose concerns are in relevant areas.

For more information, see the *IRB Operations and Clinical Requirements* list provided by FDA's Office of Health Affairs. This document is intended to help IRB's carry out their responsibilities for protection of research subjects. Also see the March 13, 1975, Federal Register, and the Technical Amendments concerning "Protection of Human Subjects" (45 CFR Part 46).

Clinical Studies (Overview)

The new drug application (NDA) is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale in the United States. To obtain this authorization, a drug manufacturer submits in an NDA nonclinical (animal) and clinical (human) test data and analyses, drug information, and descriptions of manufacturing procedures.

An NDA must provide sufficient information, data, and analyses to permit FDA reviewers to reach several key decisions, including:

- ▶ Whether the drug is safe and effective for its proposed use(s), and whether the benefits of the drug outweigh its risks.
- ▶ Whether the drug's proposed labeling is appropriate, and, if not, what the drug's labeling should contain.
- ▶ Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

The purpose of preclinical work--animal pharmacology/toxicology testing--is to develop adequate data to undergird a decision that it is reasonably safe to proceed with human trials of the drug. Clinical trials represent the ultimate premarket testing ground for unapproved drugs. During these trials, an investigational compound is administered to humans and is evaluated for its safety and effectiveness in treating, preventing, or diagnosing a specific disease or condition. The results of this testing will comprise the single most important factor in the approval or disapproval of a new drug.

Although the goal of clinical trials is to obtain safety and effectiveness data, the overriding consideration in these studies is the safety of those in the trials. CDER monitors the study design and conduct of clinical trials to ensure that people in the trials are not exposed to unnecessary risks.

Subject-Related CDER Guidances of Interest

- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs
- Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro

Phase 1 Clinical Studies

Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are closely monitored and may be conducted in patients, but are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolic 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.

Phase 1 studies also evaluate drug metabolism, structure-activity relationships, and the mechanism of action in humans. These studies also determine which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects included in Phase 1 studies varies with the drug, but is generally in the range of twenty to eighty.

In Phase 1 studies, CDER can impose a clinical hold (i.e., prohibit the study from proceeding or stop a trial that has started) for reasons of safety, or because of a sponsor's failure to accurately disclose the risk of study to investigators. Although CDER routinely provides advice in such cases, investigators may choose to ignore any advice regarding the design of Phase 1 studies in areas other than patient safety.

Phase 2 Clinical Studies

Phase 2 includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps 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 several hundred people.

Phase 3 Clinical Studies

Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained in Phase 2, 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. Phase 3 studies also provide an adequate

basis for extrapolating the results to the general population and transmitting that information in the physician labeling. Phase 3 studies usually include several hundred to several thousand people.

In both Phase 2 and 3, CDER can impose a clinical hold if a study is unsafe (as in Phase 1), or if the protocol is clearly deficient in design in meeting its stated objectives. Great care is taken to ensure that this determination is not made in isolation, but reflects current scientific knowledge, agency experience with the design of clinical trials, and experience with the class of drugs under investigation.

Accelerated Development/Review

Accelerated development/review (**Federal Register, April 15, 1992**) is a highly specialized mechanism for speeding the development of drugs that promise significant benefit over existing therapy for serious or life-threatening illnesses for which no therapy exists. This process incorporates several novel elements aimed at making sure that rapid development and review is balanced by safeguards to protect both the patients and the integrity of the regulatory process.

Accelerated development/review can be used under two special circumstances: when approval is based on evidence of the product's effect on a "surrogate endpoint," and when the FDA determines that safe use of a product depends on restricting its distribution or use. A surrogate endpoint is a laboratory finding or physical sign that may not be a direct measurement of how a patient feels, functions, or survives, but is still considered likely to predict therapeutic benefit for the patient.

The fundamental element of this process is that the manufacturers must continue testing after approval to demonstrate that the drug indeed provides therapeutic benefit to the patient. If not, the FDA can withdraw the product from the market more easily than usual.

Treatment IND

Treatment Investigational New Drugs (**Federal Register, May 22, 1987**) are used to make promising new drugs available to desperately ill patients as early in the drug development process as possible. FDA will permit an investigational drug to be used under a treatment IND if there is preliminary evidence of drug efficacy and the drug is intended to treat a serious or life-threatening disease, or if there is no comparable alternative drug or therapy available to treat that stage of the disease in the intended patient population. In addition, these patients are not eligible to be in the definitive clinical trials, which must be well underway, if not almost finished.

An immediately life-threatening disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. For example, advanced cases of AIDS, herpes simplex encephalitis, and subarachnoid hemorrhage are all considered to be immediately life-threatening diseases. Treatment INDs are made available to patients before general marketing begins, typically during Phase 3 studies. Treatment INDs also allow FDA to obtain additional data on the drug's safety

and effectiveness.

Parallel Track

Another mechanism to permit wider availability of experimental agents is the "parallel track" policy (*Federal Register, May 21, 1990*) developed by the U.S. Public Health Service in response to AIDS. Under this policy, patients with AIDS whose condition prevents them from participating in controlled clinical trials can receive investigational drugs shown in preliminary studies to be promising.

Subpart E

Subpart E in *Section 312 of the Code of Federal Regulations* establishes procedures to expedite the development, evaluation, and marketing of new therapies intended to treat people with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternatives exist (*Federal Register, October 21, 1988*).

Sponsor/FDA Meetings (Pre-IND)

Prior to clinical studies, the sponsor needs evidence that the compound is biologically active, and both the sponsor and the FDA need data showing that the drug is reasonably safe for initial administration to humans. Under FDA requirements, the sponsor usually must first submit data showing that the drug is reasonably safe for use in initial, small-scale clinical studies.

Pre-clinical meetings are conducted with the appropriate review division that would review the drug marketing application and these meetings are typically requested by the sponsor of a drug. Meetings at such an early stage in the process are useful opportunities for open discussion about testing phases, data requirements, and any scientific issues that may need to be resolved prior to IND submission. At these meetings, the sponsor and FDA discuss and agree upon the design of the animal studies needed to initiate human testing. (see CFR 312.47, and CFR 312.82).

Sponsor/FDA Meetings (End of Phase 2)

The primary focus of "end of Phase 2" meetings is to determine whether it is safe to begin Phase 3 testing. This is also the time to plan protocols for Phase 3 human studies and to discuss and identify any additional information that may be required to support the submission of a new drug application. It is also intended to establish an agreement between the Agency and the sponsor of the overall plan for Phase 3 and the objectives and design of particular studies. These meetings avoid unnecessary expenditures of time and money because data requirements have been clarified.

One month prior to the "end of the Phase 2" meeting, the sponsor should submit the background information and protocols for Phase 3 studies. This information should include data supporting the claim of the new drug product, chemistry data, animal data and proposed additional animal data, results of Phase 1 and 2 studies, statistical methods being used, specific protocols for Phase

3 studies, as well as a copy of the proposed labeling for a drug, if available. This summary provides the review team with information needed to prepare for a productive meeting.

Sponsor/FDA Meetings (Pre-NDA)

The purpose of a Pre-NDA meeting is to discuss the presentation of data (both paper and electronic) in support of the application. The information provided at the meeting by the sponsor includes:

- ▶ A summary of clinical studies to be submitted in the NDA;
- ▶ the proposed format for organizing the submission, including methods for presenting the data; and
- ▶ other information needed to be discussed.

The meeting is conducted to uncover any major unresolved problems or issues, to identify studies the sponsor is relying on as adequate and well controlled in establishing the effectiveness of the drug, to help the reviewers to become acquainted with the general information to be submitted and to discuss the presentation of the data in the NDA to facilitate its review.

Once the NDA is filed, a meeting may also occur 90 days after the initial submission of the application in order to discuss issues that are uncovered in the initial review.

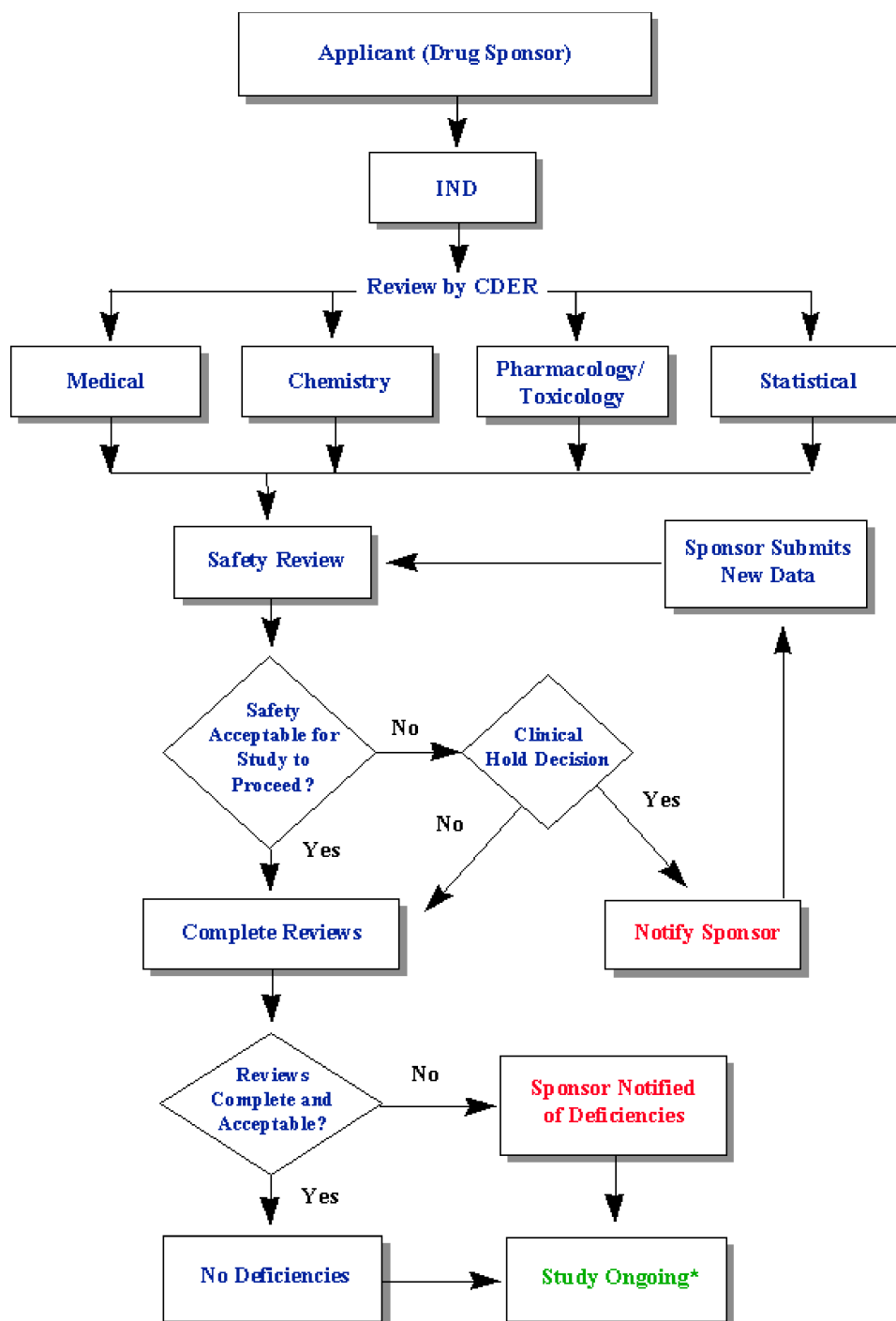
Advisory Committees

CDER uses advisory committees to obtain outside advice and opinions from expert advisors so that final agency decisions will have the benefit of wider national expert input. Committee recommendations are not binding on CDER, but the agency considers them carefully when deciding drug issues.

CDER may especially want a committee's opinion about a new drug, a major indication for an already approved drug, or a special regulatory requirement being considered, such as a boxed warning in a drug's labeling. Committees may also advise CDER on necessary labeling information, or help with guidelines for developing particular kinds of drugs. They may also consider questions such as whether a proposed study for an experimental drug should be conducted or whether the safety and effectiveness information submitted for a new drug are adequate for marketing approval.

For additional information about FDA advisory committee meetings, call 1-800-741-8138. In the metropolitan Washington, D.C. area, call (301)443-0572.

IND Review Process



*While sponsor answers any deficiencies

Applicant (Drug Sponsor)

An applicant, or drug sponsor, is the person or entity who assumes responsibility for the investigation of a new drug, including responsibility for compliance with applicable provisions of the Federal Food, Drug, and Cosmetic Act and related regulations. The "sponsor" is usually an individual, partnership, corporation, government agency, manufacturer or scientific institution.

Full application submissions under 21 CFR subpart 314.50 and 314.54 submitted for filing should be directed to:

Center for Drug Evaluation and Research
Food and Drug Administration
Document and Records Section
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

Correspondence not associated with a particular application should be addressed specifically to the intended office or division and to the person as follows:

Center for Drug Evaluation and Research
Food and Drug Administration
Attn: [insert name of person]
HFD-[insert mail code of office or division]
5600 Fishers Lane
Rockville, MD 20857

Investigational New Drug Application

In many ways, 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).

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.

Generally, this includes data and 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.
- ▶ **Manufacturing Information-** Information pertaining to the composition, manufacture,

stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed as to ensure 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.

The IND is not an application for marketing approval. Rather, it is a request for an exemption from the Federal statute that prohibits an unapproved drug from being shipped in interstate commerce. 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; however, its main purpose is to detail the data that provide documentation that it is indeed reasonable to proceed with certain human trials with the drug.

Types of INDs

"Commercial INDs" 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."

Subject-Related CDER Guidances of Interest

- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs
- Submitting Application Archival Copies in Electronic Format (DRAFT ONLY)
- Electronic Submission of Case Report Forms and Case Report Tabulations (DRAFT ONLY)
- Drug Master Files

Medical Review

Medical/clinical reviewers, often called medical officers, are almost exclusively physicians. In rare instances, non-physicians are used as medical officers to evaluate drug data. Medical reviewers are responsible for evaluating the clinical sections of submissions, such as the safety of the clinical protocols in an IND or the results of this testing as submitted in the NDA. Within most divisions, clinical reviewers take the lead role in the IND or NDA review, and are responsible for synthesizing the results of the animal toxicology, human pharmacology and clinical reviews to formulate the overall basis for a recommended agency action on the application.

During the IND review process, the medical reviewer evaluates the clinical trial protocol to determine: (1) if the participants will be protected from unnecessary risks; and (2) if the study design will provide data relevant to the safety and effectiveness of the drug. Under Federal regulations, proposed Phase 1 studies are evaluated almost exclusively for safety reasons. Since the late 1980's, FDA reviewers have been instructed to provide drug sponsors with greater freedom during Phase 1, as long as the investigations do not expose participants to undue risks. In evaluating Phase 2 and 3 investigations, however, FDA reviewers also must ensure that these studies are of sufficient scientific quality to be capable of yielding data that can support marketing approval.

Chemistry Review

Each review division employs a team of chemists responsible for reviewing the chemistry and manufacturing control sections of drug applications. In general terms, chemistry reviewers address issues related to drug identity, manufacturing control, and analysis. The reviewing chemist evaluates the manufacturing and processing procedures for a drug to ensure that the compound is adequately reproducible and stable. If the drug is either unstable or not reproducible, then the validity of any clinical testing would be undermined because one would not know what was really being used in the patients, and, more importantly, the studies may pose significant risks to participants.

At the beginning of the Chemistry and Manufacturing section, the drug sponsor should state whether it believes the chemistry of either the drug substance or the drug product, or the manufacturing of either the drug substance or the drug product, present any signals of potential human risk. If so, these signals should be discussed, with steps proposed to monitor for such risks.

In addition, sponsors should describe any chemistry and manufacturing differences between the drug product proposed for clinical use and the drug product used in the animal toxicology trials that formed the basis for the sponsor's conclusion that it was safe to proceed with the proposed clinical study. How these differences might affect the safety profile of the drug product should be discussed. If there are no differences in the products, that should be stated.

Pharmacology/ Toxicology Review

The pharmacology/toxicology review team is staffed by pharmacologists and toxicologists who evaluate the results of animal testing and attempt to relate animal drug effects to potential effects in humans.

Pharmacology and Drug Distribution (21 CFR 312.23(a)(8)(I)):

This section of the application should contain, if known: 1) a description of the pharmacologic effects and mechanism(s) of action of the drug in animals, and 2) information on the absorption, distribution, metabolism, and excretion of the drug. The regulations do not further describe the presentation of these data, in contrast to the more detailed description of how to submit toxicologic data. A summary report, without individual animal records or individual study results, usually suffices.

To the extent that such studies may be important to address safety issues, or to assist in the evaluation of toxicology data, they may be necessary; however, lack of this potential effectiveness should not generally be a reason for a Phase 1 IND to be placed on clinical hold.

Toxicology Data

Present regulations (21 CFR 312.23(a)(8)(ii)(a)) require an integrated summary of the toxicologic effects of the drug in animals and in vitro. The particular studies needed depend on the nature of the drug and the phase of human investigation. When species specificity, immunogenicity, or other considerations appear to make many or all toxicological models irrelevant, sponsors are encouraged to contact the agency to discuss toxicological testing.

Subject-Related CDER Guidance of Interest

- Single Dose Acute Toxicity Testing for Pharmaceuticals
- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs

Safety Review

Following review of an initial IND submission, CDER has 30 calendar days in which to decide if a clinical hold is necessary (i.e., if patients would be at an unacceptable risk or if CDER doesn't have the data to make such a determination). Generally, drug review divisions do not contact the sponsor if no concerns arise with drug safety and the proposed clinical trials. If the sponsor hears nothing from CDER, then on day 31 after submission of the IND, the study may proceed as submitted.

Clinical Hold Decision

A clinical hold is the mechanism that CDER uses when it does not believe, or cannot confirm, that the study can be conducted without unreasonable risk to the subjects/patients. If this occurs, the Center will contact the sponsor within the 30-day initial review period to stop the clinical trial. CDER may either delay the start of an early-phase trial on the basis of information submitted in the IND, or stop an ongoing study based on a review of newly submitted clinical protocols, safety reports, protocol amendments, or other information. When a clinical hold is issued, a sponsor must address the issue that is the basis of the hold before the order is removed.

CDER's authority concerning clinical holds is outlined in Federal regulations. The regulations specify the clinical hold criteria that CDER applies to various phases of clinical testing. In addition, all clinical holds are reviewed by upper management of CDER to assure consistency and scientific quality in the Center's clinical hold decisions.

Notify Sponsor

Once a clinical hold is placed on a commercial IND, the sponsor will be notified immediately by telephone by the division director. For both individual and commercial INDs, the division is required to send a letter within five working days following the telephone call. The letter should describe the reasons for the clinical hold, and must bear the signature of the division director (or acting division director).

The sponsor may then respond to CDER by sending an "IND CLINICAL HOLD RESPONSE" letter to the division. To expedite processing, the letter must be clearly identified as an "IND CLINICAL HOLD RESPONSE" letter.

The division then reviews the sponsor's response and decides within 30 days as to whether the hold should be lifted. If the division does not reply to the clinical hold response within 30 calendar days, the division director will telephone the sponsor and discuss what is being done to facilitate completion of the review.

If it is decided that the hold will not be lifted, the hold decision is automatically sent to the office director for review. The office director must decide within 14 calendar days whether or not to sustain the division's decision to maintain the clinical hold. If the decision is made to lift the hold, the division telephones the sponsor, informs them of the decision, and sends a letter confirming that the hold has been lifted. The letter will be sent within 5 working days of the telephone call. However, the trial may begin once the decision has been relayed to the sponsor by telephone.

For more information, see MAPP 6030.1, "*IND Process and Review Procedures*".

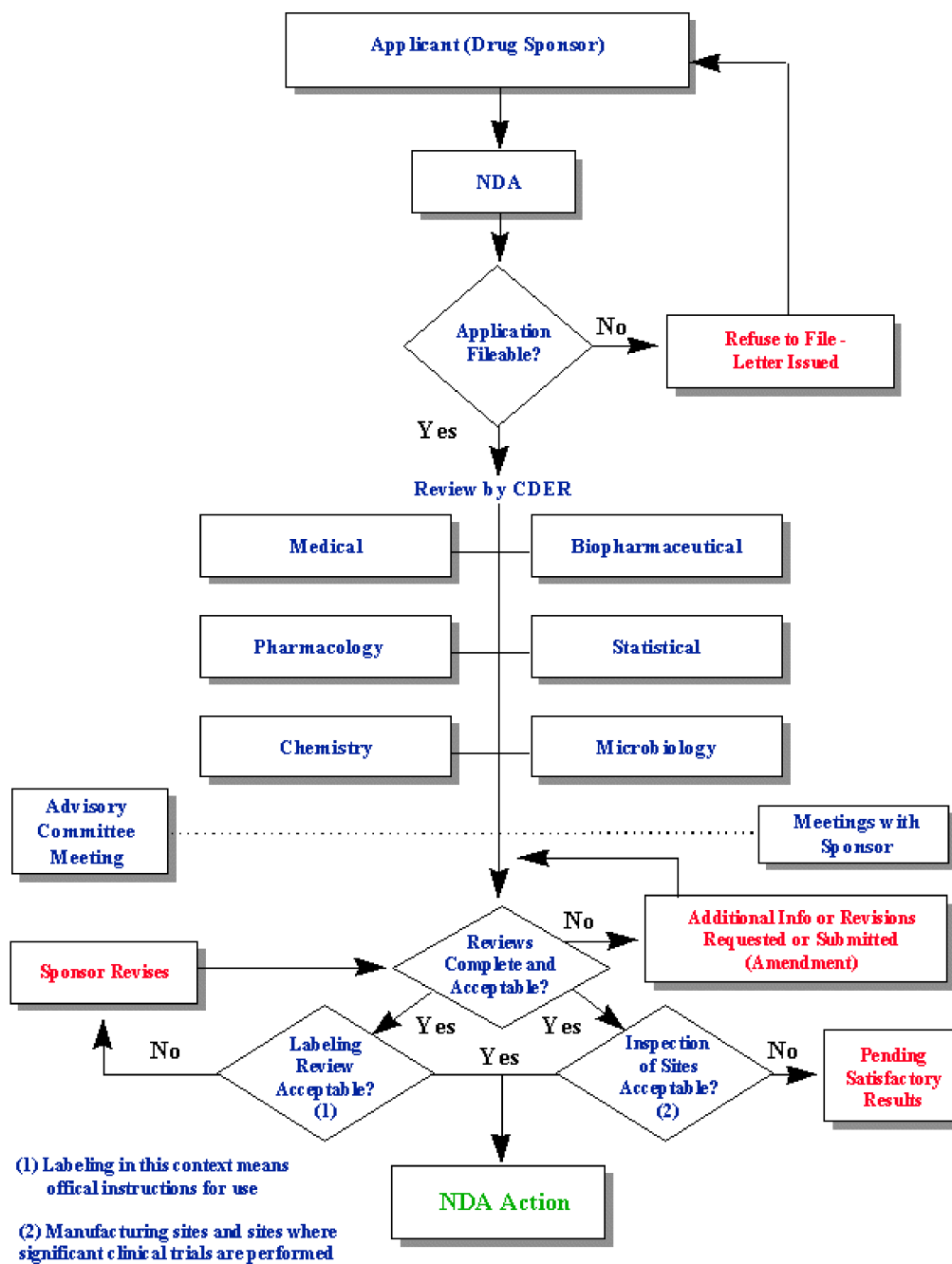
Sponsor Notified of Deficiencies

If other deficiencies are found in an IND that the review division determines are not serious enough to justify delaying clinical studies, the division may either telephone or forward a deficiency letter to the sponsor. In either case, the division informs the sponsor that it may proceed with the planned clinical trials, but that additional information is necessary to complete or correct the IND file, or that there are issues that need to be addressed prior to a marketing application (NDA) submission.

Study Ongoing

Once CDER's 30-day initial review period expires, clinical studies can be initiated, unless a clinical hold has been placed. Beyond the 30-day review period for an IND, subsequent clinical trials may begin immediately upon submission of the clinical protocol to the IND (i.e., there is no 30-day waiting period for subsequent clinical trials after the submission of the first clinical trial protocol). If the sponsor was notified of deficiencies that were not serious enough to warrant a clinical hold, the sponsor addresses these deficiencies while the study proceeds.

NDA Review Process



Applicant (Drug Sponsor)

An applicant, or drug sponsor, is the person or entity who assumes responsibility for the marketing of a new drug, including responsibility for compliance with applicable provisions of the Federal Food, Drug, and Cosmetic Act and related regulations. The "sponsor" is usually an individual, partnership, corporation, government agency, manufacturer or scientific institution.

Full drug marketing application submissions under 21 CFR subpart 314.50 and 314.54 should be directed to:

Center for Drug Evaluation and Research
Food and Drug Administration
Document and Records Section
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

Correspondence not associated with a particular application should be addressed specifically to the intended office or division and to the person as follows:

Center for Drug Evaluation and Research
Food and Drug Administration
Attn: [insert name of person]
HFD-[insert mail code of office or division]
5600 Fishers Lane
Rockville, MD 20857

New Drug Application

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) become part of the NDA.

The NDA has evolved considerably during its history. 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 expedite FDA reviews.

Fundamentals of NDA Submissions

Although the quantity of information and data submitted in NDAs can vary significantly, the components of NDAs are more uniform. The components of any NDA are, in part, a function of the nature of the subject drug and the information available to the applicant at the time of 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, Methods 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

Although the exact requirements are a function of the nature of a specific drug, the 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). Below is a partial list of some newer Guidances of interest. See DIB's Guidance Documents (at <http://www.fda.gov/cder/guidance/index.htm>) for a complete list of available guidelines online and instructions on how to obtain them.

Subject-Related CDER Guidances of Interest (examples)

- Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (03/97)
- Archiving Submissions in Electronic Format- NDAs (09/97)
- Drug Master Files (09/89)

NDA Classifications

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:

- 1- New Molecular Entity
- 2- New Salt of Previously Approved Drug (not a new molecular entity)
- 3- New Formulation of Previously Approved Drug (not a new salt OR a new molecular entity)
- 4- New Combination of Two or More Drugs
- 5- Already Marketed Drug Product - Duplication (i.e., new manufacturer)
- 6- New Indication (claim) for Already Marketed Drug (includes switch in marketing status from prescription to OTC)
- 7- 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.

Application Fileable?

After a New Drug Application (NDA) is received by the agency, it undergoes a technical screening generally referred to as a completeness review. This evaluation ensures that sufficient data and information have been submitted in each area to justify "filing" the application--that is, justifying initiating CDER's formal review of the NDA.

Refuse-to-File Letter Issued

New Drug Applications that are incomplete become the subject of a formal "refuse-to-file" action. In such cases, the applicant receives a letter detailing the decision and the deficiencies that form its basis. This decision must be forwarded within 60 calendar days after the NDA is initially received by CDER.

Medical Review

Medical/clinical reviewers, often called medical officers, are almost exclusively physicians. Medical reviewers are responsible for evaluating the clinical sections of submissions, such as the safety of the clinical protocols in an IND or the results of this testing as submitted in the NDA. Within most divisions, clinical reviewers take the lead role in the IND or NDA review, and are responsible for synthesizing the results of the animal toxicology, human pharmacology and clinical reviews to formulate the overall basis for a recommended Agency action on the application.

Biopharmaceutical Review

Pharmacokineticists evaluate the rate and extent to which the drug's active ingredient is made available to the body and the way it is distributed in, metabolized by, and eliminated from the human body.

Statistical Review

Statisticians evaluate the statistical relevance of the data in the NDA with the main tasks of evaluating the methods used to conduct studies and the various methods used to analyze the data. The purpose of these evaluations is to give the medical officers a better idea of the power of the findings to be extrapolated to the larger patient population in the country.

Microbiology Review

The Clinical Microbiology information is required only in NDAs for anti-infective drugs. Since these drugs affect microbial, rather than human physiology, reports on the drug's in vivo and in vitro effects on the target microorganisms are critical for establishing product effectiveness.

An NDA's Microbiology section usually includes data describing:

- the biochemical basis of the drug's action on microbial physiology;
- the drug's antimicrobial spectra, including results of in vitro preclinical studies demonstrating concentrations of the drug required for effective use;
- any known mechanisms of resistance to the drug, including results of any known epidemiologic studies demonstrating prevalence of resistance factors; and
- clinical microbiology laboratory methods needed to evaluate the effective use of the drug.

More specific guidance on developing the microbiology component of the NDA is available from the FDA's ***Guideline for the Format and Content of the Microbiology Section of an Application (February 1987)***.

Advisory Committees

CDER uses advisory committees to obtain outside advice and opinions from expert advisors so that final agency decisions will have the benefit of wider national expert input. Committee recommendations are not binding on CDER, but the agency considers them carefully when deciding drug issues.

CDER may especially want a committee's opinion about a new drug, a major indication for an already approved drug, or a special regulatory requirement being considered, such as a boxed warning in a drug's labeling. Committees may also advise CDER on necessary labeling information, or help with guidelines for developing particular kinds of drugs. They may also consider questions such as whether a proposed study for an experimental drug should be conducted or whether the safety and effectiveness information submitted for a new drug are adequate for marketing approval.

For additional information about FDA advisory committee meetings, call 1-800-741-8138. In the metropolitan Washington, D.C. area, call (301)443-0572.

Meetings with Sponsor

During the course of reviewing an application, CDER usually communicates often with sponsors about scientific, medical, and procedural issues that arise during the review process. Communications may take the form of telephone conversations, letters, faxes or meetings (either face-to-face or via videoconferencing).

Notification of Easily Correctable Deficiencies

CDER makes every effort to communicate promptly to applicants easily correctable deficiencies found during the review of an application. CDER also informs applicants of the need for more data or information, or for technical changes in the application needed to facilitate the agency's review. This type of early communication would not ordinarily apply to major scientific issues, which require consideration of the entire pending application by agency final decision makers as well as by reviewing staff. Instead, major scientific issues are usually addressed in an action letter at the end of the initial review process.

End of Review Conference

At the conclusion of CDER's review of an application, there are three possible action letters that can be sent to the sponsor:

- Not Approvable Letter Lists the deficiencies in the application and explains why the application cannot be approved.
- Approvable Letter Signals that, ultimately, the drug can be approved. Lists minor deficiencies that can be corrected, often involves labeling changes, and possibly requests commitment to do post-approval studies.
- Approval Letter States that the drug is approved. May follow an approvable letter, but can also be issued directly.

If the action taken is either an approvable or a not approvable action (as opposed to an approval action), CDER provides applicants with an opportunity to meet with Agency officials and discuss the deficiencies. The purpose of the meeting is to discuss what further steps are necessary before the application can be approved. This meeting is available on all applications, with priority given

to applications for priority review drugs and major new indications for marketed drugs. Requests for such meetings are directed to the director of the division responsible for reviewing the application.

Other Meetings

Other meetings between CDER and applicants may be held to discuss scientific, medical, and other issues that arise during the review process. CDER makes every effort to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times.

For more information on meetings between CDER and applicants, see MAPP 4512.1, *"Formal Meetings Between CDER and CDER's External Constituents"*.

Reviews Complete and Acceptable?

Much of the primary review process involves reviewer attempts to confirm and validate the sponsor's conclusion that a drug is safe and effective for its proposed use. The review is likely to involve a reanalysis or an extension of the analyses performed by the sponsor and presented in the NDA. For example, the medical reviewer may seek to reanalyze a drug's effectiveness in a particular patient subpopulation not analyzed in the original submission. Similarly, the reviewer may disagree with the sponsor's assessment of evaluable patients and seek to retest effectiveness claims based on the reviewer-defined patient populations.

There is also extensive communication between review team members. If a medical reviewer's reanalysis of clinical data produces results different from those of the sponsor, for example, the reviewer is likely to forward this information to the statistical reviewer with a request for a statistical reanalysis of the data. Likewise, the pharmacology reviewer may work closely with the statistical reviewer in evaluating the statistical significance of potential cancer-causing effects of the drug in long-term animal studies.

When the technical reviews are completed, each reviewer develops a written evaluation of the NDA that presents their conclusions and their recommendations on the application. The division director or office director then evaluates the reviews and recommendations and decides the action that the division will take on the application. The result is an action letter that provides an approval, approvable or non-approvable decision and a justification for that recommendation.

Additional Information (Amendment)

In some cases, an applicant may seek to augment the information provided in the original NDA during the review process. For example, the applicant may submit a new analysis of previously submitted data, or information needed to address a deficiency in the drug application.

Any such information provided for an unapproved application is considered an NDA amendment. The submission of a significant amendment may result in an extension of FDA's time line for application review.

Labeling Review Acceptable?

Each statement proposed for drug labeling must be justified by data and results submitted in the NDA. The Code of Federal Regulations (CFR) describes labeling requirements in *21 CFR Part 201- Labeling*. The labeling is organized in the following sections:

- Description

Proprietary and established name of drug; dosage form; ingredients; chemical name; and structural formula.

- Clinical Pharmacology.

Summary of the actions of the drug in humans; in vitro and in vivo actions in animals if pertinent to human therapeutics; pharmacokinetics

- Indications and Usage

Description of use of drug in the treatment, prevention, or diagnosis of recognized disease or condition.

- Contra-Indications

Description of situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit.

- Warnings

Description of serious adverse reactions and potential safety hazards, subsequent limitation in use, and steps that should be taken if they occur.

- Precautions

Information regarding any special care to be exercised for the safe and effective use of the drug. Includes general precautions and information for patients on drug interactions, carcinogenesis/mutagenesis, pregnancy rating, labor and delivery, nursing mothers, and pediatric use.

- Adverse Reactions

Description of undesirable effect(s) reasonably associated with the proper use of the drug.

- Drug Abuse/Dependence

Description of types of abuse that can occur with the drug and the adverse reactions pertinent to them.

- Overdosage

Description of the signs, symptoms, and laboratory findings of acute overdosage and the general principles of treatment.

- Dosage/Administration

Recommendation for usage dose, usual dosage range, and, if appropriate, upper limit beyond which safety and effectiveness have not been established.

- How Supplied

Information on the available dosage forms to which the labeling applies.

Sponsor Revises

When an NDA nears approval, agency reviewers evaluate draft package labeling for accuracy and consistency with the regulatory requirements for applicable prescription or over-the-counter drugs. Each element of the proposed labeling, including indications, use instructions, and warnings, is evaluated in terms of conclusions drawn from animal and human testing. All claims, instructions, and precautions must accurately reflect submitted clinical results.

If CDER has concerns about the draft labeling, the Center will contact the sponsor detailing suggested revisions. CDER comments can relate to almost any aspect of the proposed labeling. For example, CDER can comment upon drug indications and warnings, or suggest general changes in wording and format.

The labeling "negotiation process," through which a drug's final approved labeling is agreed upon, can take a few weeks to many months. The length of the process depends upon the number of agency comments and an applicant's willingness to reach agreement. Sometimes a sponsor will submit several revisions of labeling before agreement with FDA on the labeling can be reached.

Inspection Acceptable?

A division's decision to file an NDA begins the review process and, when needed, initiates a request for a preapproval inspection of the sponsor's manufacturing facilities and clinical trial sites. During such inspections, FDA investigators audit manufacturing-related statements and commitments made in the NDA against the sponsor's manufacturing practices. More specifically, the FDA conducts inspections to:

- ▶ verify the accuracy and completeness of the manufacturing-related information submitted in the NDA;

- ▶ evaluate the manufacturing controls for the preapproval batches upon which information provided in the NDA is based;
- ▶ evaluate the manufacturer's compliance with Current Good Manufacturing Practices (CGMPs) and manufacturing-related commitments made in the NDA; and
- ▶ collect a variety of drug samples for analysis by FDA field and CDER laboratories. These samples may be subjected to several analyses, including methods validation, methods verification, and forensic screening for substitution.

According to CDER policy, product-specific preapproval inspections generally are conducted for products: (1) that are new chemical or molecular entities; (2) that have narrow therapeutic ranges; (3) that represent the first approval for the applicant; or (4) that are sponsored by a company with a history of CGMP problems or that has not been the subject of a CGMP inspection over a considerable period. More specific guidance on CDER's preapproval inspection program is available from CDER's *Compliance Program Guide 7346.832*.

The results of the preapproval inspection may also affect the final approval decision. When such inspections discover significant CGMP problems or other issues, the reviewing division may withhold approval until these issues are addressed and corrected. The division's response to such deficiencies is likely to depend on several factors, including the nature of the problem, the prognosis for the problem's correction, and the potential effect of the problem on the safety and efficacy of the drug.

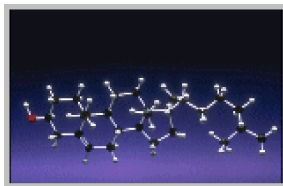
NDA Actions

Once an approval, approvable, or non-approvable recommendation is reached by the reviewers and their supervisors, the decision must be evaluated and agreed to by the director of the applicable drug review division or office. For the director's review, the consumer safety officer assembles an "action package" that contains the action letter and any data, CDER reviews and memos, and other information supporting the reviewers' recommendation.

Following his/her review of the action package, the division director may begin a dialogue with the reviewers and their supervisors. The division director generally serves as the final FDA ruling. In this sense, the division director is said to have "sign-off" authority for such drugs. The level of "sign-off" authority needed is determined by the classification of the drug under consideration. Class 1 drugs, for example, cannot be "signed off" by division directors; they require office level "sign-off" on action letters.

Once the division director (or office director, as appropriate) signs an approval action letter, the product can be legally marketed starting that day in the United States.

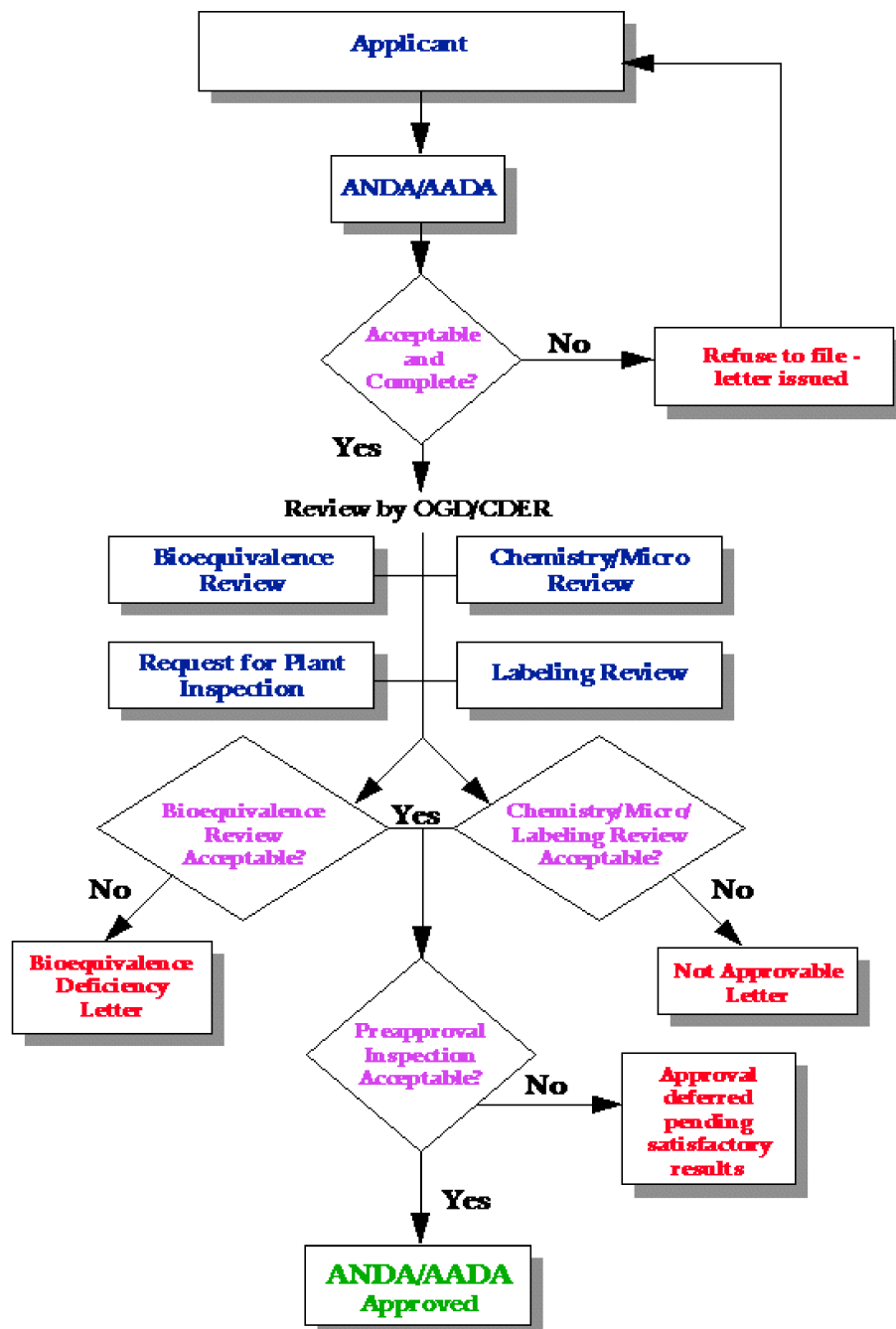
Generic Drug Review Process



An important part of CDER's mission is to assure that safe and effective generic drugs are available to the American people. This work is accomplished in CDER's Office of Generic Drugs (OGD). The information below provides an understanding of how CDER works to assure the safety and effectiveness of generic drug products.

- Generic Drug Review Process- An interactive chart that provides an overview of CDER's abbreviated new drug application (ANDA) and abbreviated antibiotic drug application (AADA) review process, and how CDER determines the safety and bioequivalence of generic drug products prior to approval for marketing..... 30
- OGD Home Page- For further information on CDER's generic drug program, visit the Office of Generic Drugs home page at <http://www.fda.gov/cder/ogd/index.htm>.

Generic Drug (ANDA/AADA) Review Process



Applicant

An applicant is any person (usually a firm) who submits an abbreviated new drug application (ANDA) or an abbreviated antibiotic drug application (AADA) to obtain FDA approval to market a generic drug product and any person who owns an approved application or abbreviated application.

Abbreviated new drug applications under 21 CFR subpart 314.94, and amendments, supplements, and resubmissions; and Abbreviated antibiotic drug application submissions, as well as items sent by parcel post or overnight courier service to the Office of Generic Drugs, should be directed to:

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

ANDA/AADA

A generic drug product is one that is comparable to an innovator drug product (also known as the reference listed drug (RLD) product as identified in the FDA's ***list of Approved Drug Products with Therapeutic Equivalence Evaluations***) in dosage form, strength, route of administration, quality, performance characteristics and intended use.

Abbreviated new drug applications (ANDA's) and abbreviated antibiotic drug applications (AADA's) are submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs for review and approval. Once approved an applicant may manufacture and market the generic drug product provided all patent protection and exclusivity associated with the RLD have expired.

Generic drug applications are termed "abbreviated" in that they are not required to provide clinical data to establish safety and efficacy, since these parameters have already been established by the approval of the innovator drug product (first approved version of the drug product marketed under a brand name).

Subject-Related CDER Guidances of Interest

- Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application
- Submitting Application Archival Copies in Electronic Format (DRAFT ONLY)

- Drug Master Files

Acceptable and Complete?

An application must contain sufficient information to allow a review to be conducted in an efficient and timely manner. An initial assessment of completeness and acceptability is performed by the project manager. This initial review documents that the application contains all the necessary components and is, therefore, acceptable for filing and review.

Refuse to File Letter Issued

If the application is missing one or more essential components, a Refuse to File letter is issued to the applicant. The letter identifies the missing component(s) and informs the applicant that the application will not be filed until it is complete.

Bioequivalence Review

FDA requires an applicant to provide information to establish bioequivalency. Such information may include:

- ▶ a formulation comparison for products whose bioavailability is self evident, for example, oral solutions, injectables, or ophthalmic solutions where the formulations are identical;
- ▶ comparative dissolution testing where there is a known correlation between in vitro and in vivo effects;
- ▶ in vivo bioequivalence testing comparing the rate and extent of absorption of the generic to the reference product; and
- ▶ for non-classically absorbed products, a head-to-head evaluation of comparative effectiveness based upon clinical endpoints.

Chemistry/Microbiology Review

The Chemistry/Microbiology review provides assurance that the generic drug will be manufactured in a controlled consistent manner. Areas such as manufacturing procedures, raw material specifications and controls, sterilization processes and validation, container and closure systems, and stability are reviewed to assure that the drug will perform in an acceptable manner.

Request for Plant Inspection

Upon filing an ANDA/AADA an establishment evaluation request is forwarded to CDER's Office of Compliance to determine whether the product manufacturer, the bulk drug substance manufacturer, and any outside testing or packaging facilities are operating in compliance with current Good Manufacturing Practice regulations as outlined in *21 CFR 211*. Furthermore, a preapproval product specific inspection may be performed on certain applications to assure data integrity.

Labeling Review

The labeling review ensures that the proposed generic drug labeling is identical to that of the reference listed drug except for differences due to a change in manufacturer, patent or exclusivity issues, or if approval is based upon a suitability petition. Furthermore, the labeling review serves to identify and resolve issues of confused or mistaken identity that may arise in drug labeling in an effort to avoid drug mix-ups and prevent medication errors.

Bioequivalence Review Acceptable?

If the Bioequivalence Review determines that there are deficiencies in the Bioequivalence portion of the application, then a Bioequivalence deficiency letter is issued to the applicant. The deficiency letter will detail the deficiencies and request information and data to resolve the deficiencies. If the review determines the bioequivalence portion of the application is acceptable, a letter indicating that there are no further questions at that time will be issued.

Chemistry/Micro/Labeling Review Acceptable?

If there are deficiencies involved in the Chemistry/Manufacturing/Controls, Microbiology or Labeling portions of the application, these deficiencies are communicated to the applicant in a not approvable letter. The letter instructs the applicant to provide information and data to address the deficiencies and provides regulatory direction on how to amend their application. If the above sections are found to be acceptable, as well as the preapproval inspection and bioequivalence portion of the application, then the application moves to approval and an approval or tentative approval letter is issued.

Preapproval Inspection Acceptable?

A satisfactory recommendation from the Office of Compliance based upon an acceptable preapproval inspection is required prior to approval. If an unsatisfactory recommendation is received, a not approvable letter may be issued. In such a case, approval of the generic drug product will be deferred pending a satisfactory re-inspection and recommendation.

ANDA/AADA Approved

After all components of the application are found to be acceptable, an approval or tentative letter is issued to the applicant detailing the conditions of the approval and providing them with the ability to market the generic drug product. If the approval occurs prior to the expiration of any patents or exclusivities accorded to the reference listed drug product, a tentative approval letter is issued to the applicant which details the tentative approval of the generic drug product until the patent/exclusivity condition has expired. A tentative approval does not allow the applicant to market the generic drug product.

Over-the-Counter Drug Review Process



Over-the-counter (OTC) drugs play an increasingly vital role in America's health care system. Today, six out of every ten medications bought by consumers are OTC drugs. Much of the work of reviewing these products is accomplished in CDER's Division of OTC Drug Products. The information below provides an understanding of how CDER works to assure the safety and efficacy of OTC drug products.

- Introduction..... 36
- OTC Drug Review Process- An interactive chart that provides an overview of CDER's over-the-counter drug review process, and how CDER determines the safety and efficacy of OTC drug products..... 37
- Division of OTC Drug Products Home Page- For further information about non-prescription drugs, visit the Division of OTC Drug Products home page (<http://www.fda.gov/cder/otc>). This page also contains documents that are frequently requested of the Division.

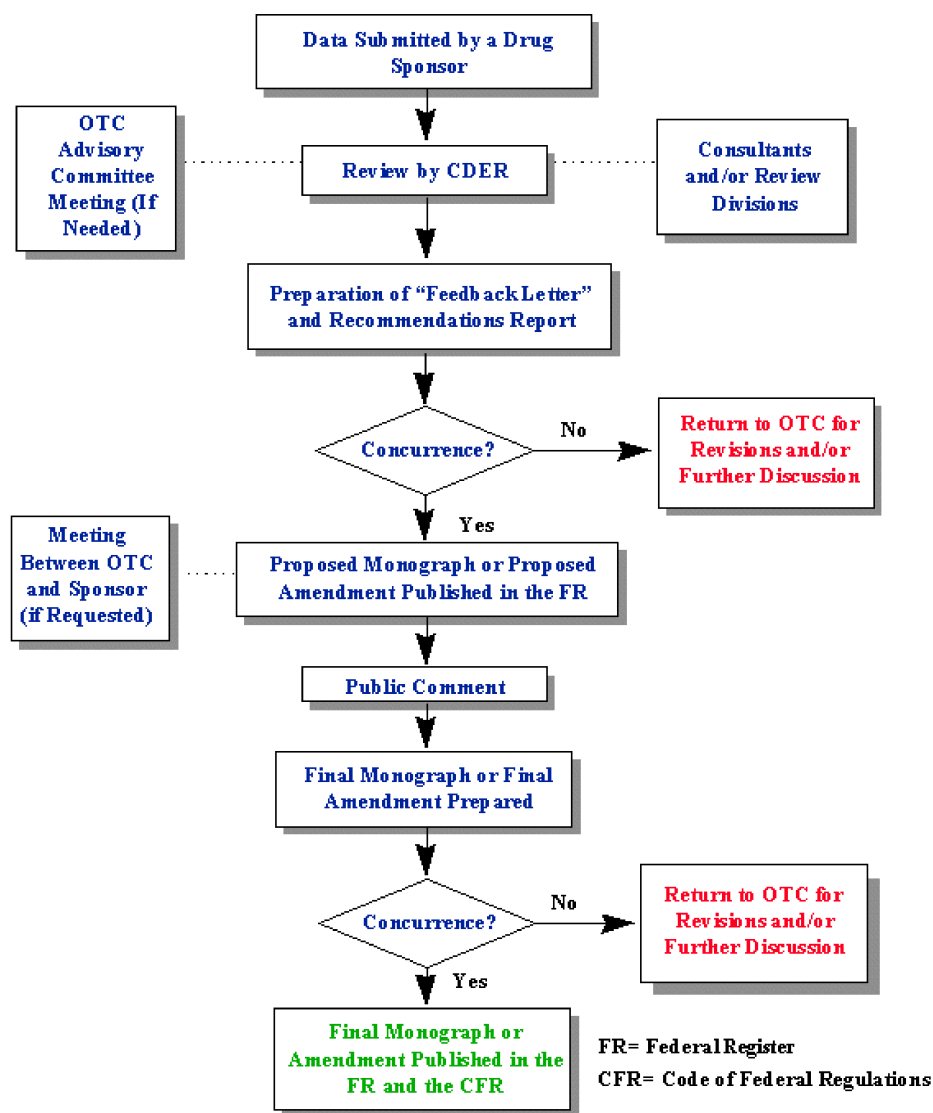
Over-the-Counter Drug Products

Over-the-Counter (OTC) drug products are those drugs that are available to consumers without a prescription. There are more than 80 classes (therapeutic categories) of OTC drugs, ranging from acne drug products to weight control drug products. As with prescription drugs, CDER oversees OTC drugs to ensure that they are properly labeled and that their benefits outweigh their risks.

OTC drugs play an increasingly vital role in America's health care system by providing easy access to certain drugs that can be used safely without the help of a health care practitioner. This enables consumers to take control of their own health care in many situations. There are more than 100,000 OTC drug products marketed, encompassing about 800 significant active ingredients. Most OTC drug products have been marketed for many years, prior to the laws that require proof of safety and effectiveness before marketing. For this reason, FDA has been evaluating the ingredients and labeling of these products as part of "The OTC Drug Review Program." The goal of this program is to establish OTC drug monographs for each class of products. OTC drug monographs are a kind of "recipe book" covering acceptable ingredients, doses, formulations, and labeling. Monographs will continually be updated adding additional ingredients and labeling as needed. Products conforming to a monograph may be marketed without further FDA clearance, while those that do not, must undergo separate review and approval through the "New Drug Approval System." The NDA system--and not the monograph system--is also used for new ingredients entering the OTC marketplace for the first time. For example, the newer OTC products [previously available only by prescription] are first approved through the NDA system and their "switch" to OTC status is approved via the NDA system.

FDA's review of OTC drugs is primarily handled by CDER's Division of Over-the-Counter Drug Products in the Office of Drug Evaluation V. However, scientists and regulators throughout CDER, the Office of General Counsel, and other Centers within FDA are routinely asked to assist in this massive effort. There is also an advisory committee, "The Nonprescription Drug Advisory Committee," which meets regularly to assist the agency in evaluating issues surrounding these products.

OTC Drug Monograph Review Process



Data Submitted by a Drug Sponsor

Data regarding OTC monographs can be submitted by anyone- such as a drug company, health professional, consumer, or citizen's group. If the submission is a request to amend an existing drug monograph or is an opinion regarding a drug monograph, it needs to be submitted in the form of a citizen petition or as correspondence to an established monograph docket. However, if no monograph exists, data must be submitted in the format as outlined in the Code of Federal Regulations (CFR) section 330.1.

Data is submitted to the Dockets Management Branch where it is logged in and a copy is made for the public files. The data is then forwarded to the Division of Over-the-Counter Drug Products for review and action.

Review by CDER

When the package is received in the Division of OTC Drug Products, a project manager conducts an initial review to determine the type of drug being referenced and then forwards the package to the appropriate team for a more detailed review. The team leader determines if the package will need to be reviewed by other discipline areas in the review divisions, such as chemists or statisticians, or by other consultants, such as from other centers or agency offices. The package is then forwarded to a team member to review.

If the data submitted is a comment or opinion on a specific rule or monograph, there is no deadline established for CDER to respond. However, if the data is a petition or request to amend a monograph, or request to have a drug approved based on an existing monograph, the OTC division has 180 days to review the data and respond to the sponsor.

When the data is reviewed, the drug is categorized through the monograph rulemaking process as follows:

- Category I - generally recognized as safe and effective and not misbranded.
- Category II - not generally recognized as safe and effective or is misbranded.
- Category III - insufficient data available to permit classification. This category allows a manufacturer an opportunity to show that the ingredients in a product are effective, and, if they are not, to reformulate or appropriately relabel the product.

CDER also oversees OTC drug labeling because the safety and effectiveness of OTC drug products depend not only on the ingredients but also on clear and truthful labeling that can be understood by consumers.

When the initial review is complete and other consult requests have been received, a "Feedback Letter" is prepared for the sponsor outlining CDER's recommendations. The recommendations will vary depending on the type of data submitted. For example, a response based on a request to

amend a monograph may contain explanations approving or disapproving the amendment.

If the sponsor is not satisfied with the recommendations made by the division, the applicant may request a meeting to discuss any concerns.

OTC Advisory Committee Meeting

Advisory Committee meetings are usually held to discuss specific safety or efficacy concerns, or the appropriateness of a switch from prescription to OTC marketing status for a product. Usually the OTC advisory committee meets jointly with the advisory committee having specific expertise in the use of the product.

Consultants Review

Depending on the kind of data submitted, the OTC team may request that the information be reviewed by consultants from the other review divisions, i.e., chemists or statisticians; or by experts in other Centers or agency offices; or by advisory committee members (for their specific scientific expertise on a critical issue).

When the consultants complete their review of the data, their comments are returned to the OTC review team.

Preparation of "Feedback Letter"

After the OTC reviewers complete their review, a feedback letter explaining CDER's actions or recommendations will be prepared. This letter will be forwarded to the sponsor. A copy will remain on file at FDA's Dockets Management Branch.

Proposed Monograph/Amendment Published in FR

If CDER supports the recommendation of the sponsor to either amend an existing monograph or to create a new monograph, a notice is published in the Federal Register (FR). If CDER does not support the recommendation, a letter is sent to the sponsor explaining the decision to not accept the petition.

Meeting Between OTC Division and Sponsor

If the sponsor is not satisfied with the recommendations described in the feedback letter, a meeting can be requested with the division to discuss it, i.e., to provide more information, respond to any concerns of the Center, etc.

Public Comment

After the proposal is published in the Federal Register, the public has usually 30-90 days to

respond to it. This deadline depends on the controversial nature of the notice and can be extended if a request to do so is made [anyone can request an extension]. All comments are sent to the Dockets Management Branch and then are forwarded to the Division of Over-the-Counter Drug Products. The comments are reviewed/evaluated by the appropriate team and, if needed, are sent to other discipline areas for further review.

Final Monograph or Final Amendment Prepared

After the public comments have been reviewed, the final monograph is prepared. The final monograph is a kind of "recipe book" and sets final standards that specify ingredients, dosage, indications for use, and certain labeling.

Concurrence?

The final monograph is sent out for clearance through the appropriate channels, i.e., Division, Office, Center, Office of General Counsel, Deputy Commissioner for Policy, Regulations Editorial Staff.

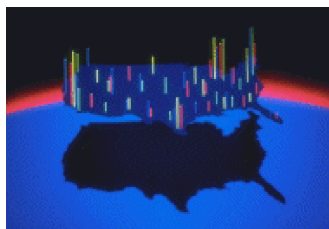
Return to OTC for Revisions/Further Discussion

If any office does not concur, the package is returned to the Division of Over-the-Counter Drug Products for revision and is then rerouted to the appropriate sources.

Final Monograph/Amendment Published in the FR and CFR

Once all revisions are made and the package receives all the appropriate final concurrences, it is published in the Federal Register (FR). All final monographs and amendments that have been published in the Federal Register are forwarded to the Regulations Editorial Staff for publication in the Code of Federal Regulations (CFR).

Post Drug Approval Activities



A vital part of CDER's mission is to monitor the safety and effectiveness of drugs that are currently available to the American people. The topics listed below provide an understanding of how CDER works to assure the ongoing safety and effectiveness of drug products currently marketed in the United States.

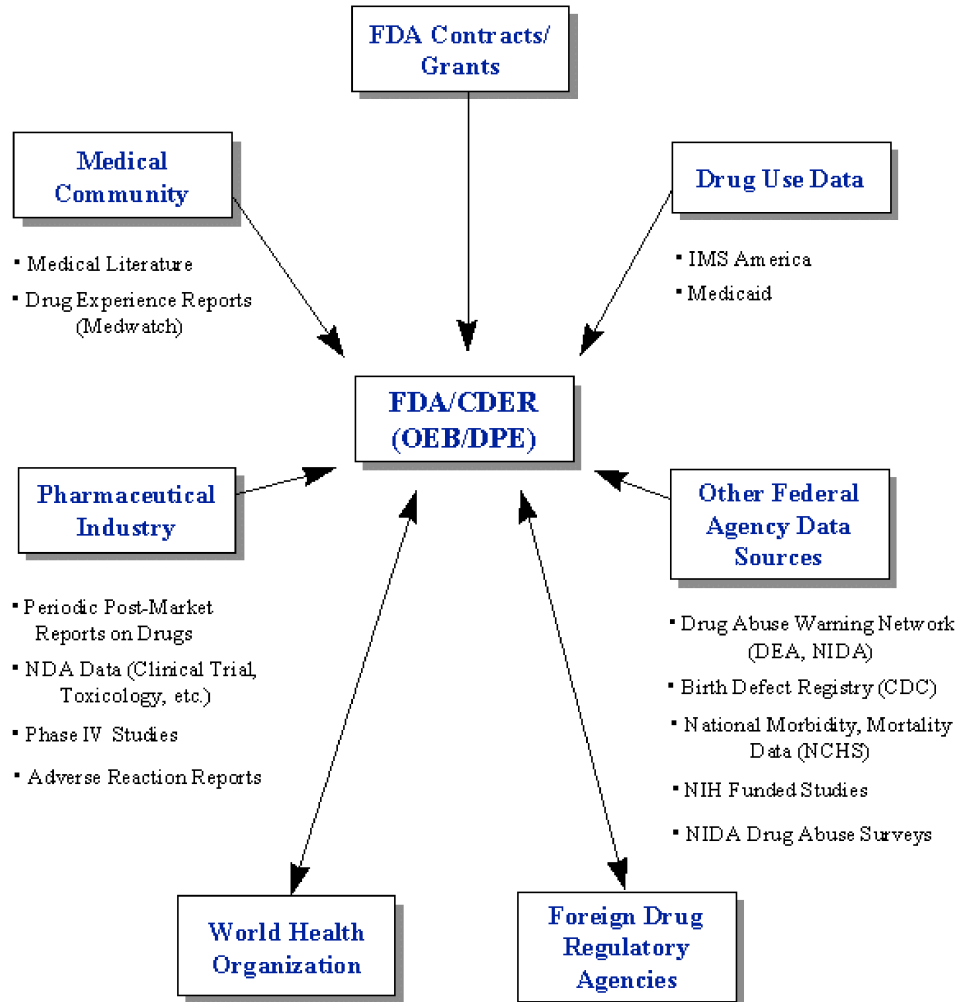
● Post-Marketing Surveillance.....	42
● Prescription Drug Advertising and Promotional Labeling.....	49
● Pharmaceutical Industry Surveillance.....	62
● Medication Errors.....	64
● Drug Shortages.....	66
● Therapeutic Inequivalence Reporting.....	67

Post-Marketing Surveillance

The goal of CDER's Post-Marketing Surveillance (PMS) system is to monitor the ongoing safety of marketed drugs. This is accomplished by reassessing drug risks based on new data learned after the drug is marketed, and recommending ways of trying to most appropriately manage that risk. This is done through a variety of activities and tools that are outlined below. This work is accomplished primarily through CDER's Division of Pharmacovigilance and Epidemiology.

- PMS Information Sources Chart- Provides an overview of the various drug experience and epidemiologic sources available to CDER in conducting surveillance and risk assessment of marketed drugs..... 43
- MEDWatch- a description of FDA's medical product reporting program..... 44
- Spontaneous Reporting System- For monitoring Adverse Drug Reaction Reports..... 45
- Pharmacoepidemiology- Efforts of CDER's epidemiology staff in monitoring drug safety..... 47
- Contracts/Cooperative Agreements- These provide important drug safety data on a national level..... 48

Drug Experience/Epidemiologic Sources Available to FDA (For Post-Marketing Surveillance and Risk Assessment)



MEDWatch Program

Even the large, well-designed Phase 3 clinical studies that are conducted by drug manufacturers cannot uncover every problem that can come to light once a product is widely used. To capture more of this critical data, especially serious adverse event data, CDER receives expedited and periodic reports of new information from the drug's manufacturer. The manufacturers are required by regulation to make such reports. In addition, to promote and facilitate voluntary reporting of serious adverse events and product problems with drugs by health care practitioners, FDA initiated a new medical products reporting program called "MEDWatch." MEDWatch has been in effect since June 1993.

MEDWatch has four goals:

- Make it easier for healthcare providers to report serious events.
- Make it clearer to healthcare providers what types of adverse events FDA is interested in receiving.
- More widely disseminate information on the FDA's actions that have resulted from adverse event and product problem reporting.
- Increase healthcare providers' understanding and awareness of drug and device-induced disease.

The MEDWatch program makes it easy for healthcare professionals to report serious adverse events to FDA. It requires a single form that may be sent via postage-prepaid mail, fax or computer modem or uses a special call-in phone number to verbally report.

FDA is interested in learning of serious events that follow drug use. Serious events are generally defined as those that involve death, a life-threatening condition, hospitalization, disability, a congenital anomaly or intervention to one of these serious outcomes.

In return, FDA keeps healthcare professionals informed about new safety discoveries. To date, a quarterly insert in the FDA Medical Bulletin and a quarterly MEDWatch update capture the most current safety information on a routine basis. More acute information is relayed via the Internet, letters, roundtable telecon briefings with MEDWatch partners, etc.

To learn more about FDA's MEDWatch program, visit FDA's [MEDWatch home page](#) [Notice: This link will take you outside the CDER web site].

Spontaneous Reporting System

CDER's Division of Pharmacovigilance and Epidemiology (DES) maintains a Spontaneous Reporting System (SRS) which contains the adverse drug reaction reports from hospitals, health care providers and lay persons that are sent either directly to the Agency (via MEDWatch) or first to the drug manufacturer, and then, by regulation, to the Agency by the manufacturer.

In the near future, SRS will be replaced by an expanded system called the Adverse Events Reporting System (AERS), currently under development. AERS is the result of efforts to implement many agreements from the International Conference for Harmonisation (ICH) as well as new regulations and pharmacovigilance processes of the FDA to increase the efficiency with which CDER receives, files, and analyzes these reports. To learn more about AERS, visit CDER's AERS home page.

These reports are triaged through the MEDWatch program, then forwarded to the appropriate Center (Drugs, Biologics, Foods or Veterinary). Adverse Drug Reaction Reports are also sent directly from the sponsors of the New Drug Application (NDA) to the Division. When either of these types of reports are received, they are entered into the computerized SRS.

The SRS is maintained and used by DPE's data processing, epidemiology and statistic staff. Their efforts are aimed at actively analyzing the data through recognition of Adverse Drug Reaction (ADR) patterns that might indicate a public health problem (a "signal"). Improving access to the data facilitates our timely evaluation of aggregates of Adverse Drug Event (ADE) reports, which are often the first signals of a potential problem. The individual reports of serious adverse events are then critically and individually reviewed by staff trained in the analysis of these data and signal generation. DPE receives approximately 250,000 adverse experience reports possibly associated with drug use annually. Approximately 25% of the reports received by CDER are reports of serious and unlabelled (or 15-day) and/or Direct Reports.

The primary focus of DPE's reviews are to detect serious unlabeled reactions. Adverse experience reports are reviewed and analyzed to generate signals of serious, yet unrecognized, drug-associated events. These signals are communicated within DPE to staff epidemiologists and to the relevant review division via written summaries and safety conferences.

When DPE suspects that manufacturers have not been reporting ADRs as required, DPE prepares summaries of adverse drug experience reporting deficiencies and forwards this information to CDER's Office of Compliance, Division of Prescription Drug Compliance and Surveillance (DPDCS). Based on such information, DPDCS issues inspectional assignments to FDA field offices to follow-up these deficiencies at the pertinent firm. DPDCS evaluates the information provided by DPE along with the inspectional findings and makes a determination if further regulatory action is indicated.

In addition, DPE represents the Office of Epidemiology and Biostatistics on the Therapeutic Inequivalency Action Coordinating Committee (TIACC). DPE's representative assists in the

investigation and resolution of claims of alleged drug bioinequivalency. In this way, CDER works to prevent injury from drugs that are super-potent or sub-potent because of manufacturing errors.

Pharmacoepidemiology Efforts

CDER's Division of Pharmacovigilance and Epidemiology (DPE) also carries out an epidemiological function in the monitoring of drug safety. This function is performed by a multi-disciplinary professional staff of physicians and Ph.D. epidemiologists, pharmacists and program/project managers. The primary work is directed towards the evaluation and risk assessment of drugs in the postmarketing environment, using the tools of epidemiology.

Epidemiologists integrate the medical/clinical details of the underlying disease being treated with the influence of patient factors, concomitant diseases and medications, as well as the clinical pharmacology of the specific product under study.

DPE's Epidemiology staff work closely with the Post-Marketing Safety Reviewers to provide clinical and epidemiologic case-series reviews of spontaneous adverse event reports submitted to FDA. These data are used in a variety of ways to develop and further refine and investigate signals of clinical importance related to drug safety. As a complement, drug-use data are used frequently to estimate the size and characterize the demographic composition of the population exposed to a given prescription product.

Additionally, epidemiologists are involved in the design and critique of Phase IV protocols for safety studies performed by industry, and in the review of study findings. They also design, execute and help to analyze data from epidemiologic studies performed through the mechanism of the DPE's cooperative agreement program which provides the Center with access to several large record-linked databases.

The reports produced by DES are integral to the ongoing risk assessment and risk management performed by CDER review divisions of a product's risk vs. benefit profile. In addition, DPE epidemiologists are called upon to meet with industry over important safety issues or to present their work before FDA advisory committees.

Contracts/Cooperative Agreements

Externally, the Agency uses a mix of contracts and cooperative agreements (an interactive form of a grant) to address a variety of drug exposure and risk issues. Each of these cooperative agreements and contracts have a distinct purpose that is vital to the surveillance and evaluation of drug safety issues on a national level. The contracts are used to gain access to databases to help obtain answers to questions that the FDA has regarding particular drugs. The Agency defines a specific need, generates a request or a protocol, and the contractor makes a delivery of data or a report.



CDER's Division of Pharmacovigilance and Epidemiology (DPE) has several contracts used for pharmacoepidemiologic and drug safety evaluation. One such contract is a drug marketing database used for describing and estimating use of many drugs. The database also provides various patient demographics.

Cooperative agreements are extensions of the federal grants process that allows federal scientists to work with scientists in academia and the private sector. These agreements create a mechanism for the government to participate in inquiries and research on issues of adverse drug reactions with scientists and databases that would otherwise be beyond the resources of the Agency if they were to be funded as contracts.





DPE is able to work with several grantees who have a variety of data and scientific resources at their disposal and for which each grantee is an expert. For instance, one grantee might have a large elderly population, while another will have strength such as the ability to link mothers and their drug usage during pregnancy to pregnancy outcomes.

Prescription Drug Advertising and Promotional Labeling

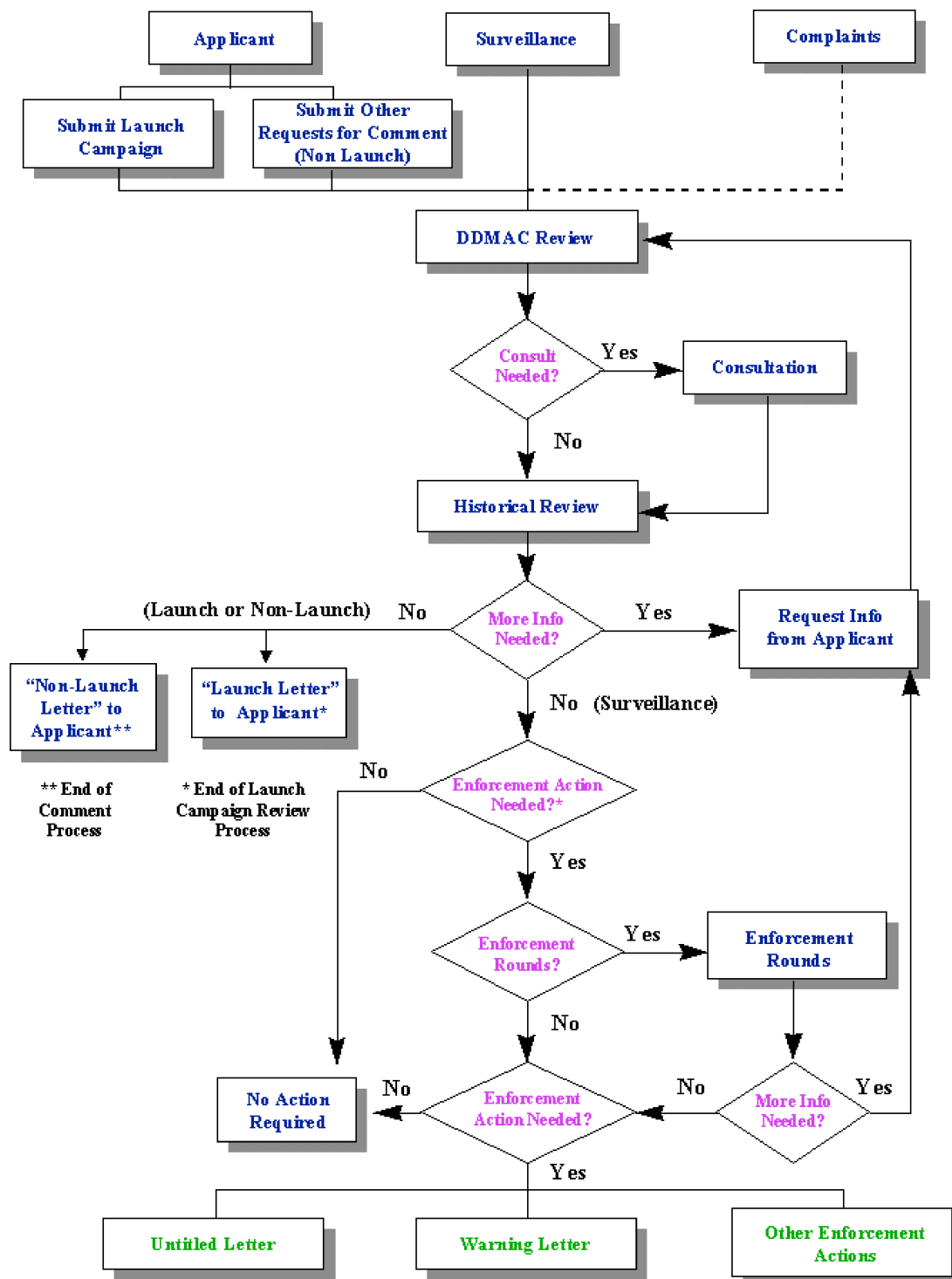
Part of CDER's mission is to assure that prescription drug information provided by drug firms is truthful, balanced, and accurately communicated. This is accomplished through a comprehensive surveillance, enforcement, and education program, and by fostering better communications of labeling and promotional information to both health professionals and consumers. This work is accomplished primarily through CDER's Division of Drug Marketing, Advertising and Communications (DDMAC).

-  [Promotional Materials Review Process](#)- An interactive chart that provides an overview of CDER's process for reviewing and monitoring prescription drug advertising and promotional labeling provided by drug firms..... 50
-  [DDMAC Home Page](#)- Click here for further information on CDER's Division of Drug Marketing, Advertising and Communications.

Also...

-  Advertising/Labeling Definitions..... 56
-  Labeling Research..... 58
-  Patient Information/Education..... 59
-  Policy Development and Guidance to Industry..... 61

Promotional Material Review Process



Applicant

A company with an approved new drug application (NDA), abbreviated new drug application (ANDA), or abbreviated antibiotic drug application (AADA) that submits one or more promotional pieces.

Submit Launch Campaign

Launch campaigns are introductory promotional campaigns for a new drug or for a new indication or dosage for an already marketed drug. The campaigns usually contain a variety of promotional pieces, such as detail aids, monographs, advertisements, and press kits.

DDMAC advises the pharmaceutical industry on proposed advertising and promotional labeling, as specified in 21 CFR 202.1(j)(4). DDMAC has requested in guidance to industry that launch campaigns be submitted voluntarily to DDMAC for comment before dissemination. Launch campaigns are DDMAC's highest review priority, because these campaigns create the initial and often lasting impression to prescribers regarding the product's safety and efficacy. Reviewers generally respond to applicants within 2 to 3 weeks after the product is cleared for marketing or after the labeling issues have been negotiated.

Submit Other Requests for Comment

Under 21 CFR 10.85, companies may request an advisory opinion on promotional pieces before the pieces are used by the company. DDMAC will provide comments on these pieces as time permits and based on the division's work priorities.

Surveillance

DDMAC monitors prescription drug promotion for compliance with the law. Promotion cannot be false or misleading and must be presented with fair balance. Types of promotion include, but are not limited to, detail aids, sales aids, journal ads, direct-to-consumer ads, product information on the Internet, and radio and TV advertisements.

DDMAC conducts surveillance in a variety of ways:

1. Submissions from drug applicants:

FDA's regulations at 21 CFR 314.81(b)(3)(I) require drug applicants to:

. . . submit specimens of mailing pieces and any other labeling devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. . . . Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling.

DDMAC reviews these pieces to determine if they meet the requirements of the Act and the regulations.

To obtain Form FDA 2253, write to the following address:

PHS Forms and Publications Distribution Center
12100 Parklawn Drive
Rockville, MD 20857

2. Conferences: DDMAC staff attend medical professional conferences where they observe company exhibition booths and collect promotional materials to review.

DDMAC Review

Launch campaigns, Form FDA-2253 submissions, materials obtained through surveillance activities, and complaints are assigned to the DDMAC reviewer responsible for that drug or product class. Reviewers evaluate whether the materials meet the requirements for advertising or promotional labeling. Complaints follow a slightly different review process.

See [Advertising/Labeling Definitions](#) section for an understanding of what constitutes prescription drug advertising and promotional labeling.

Consultation

When necessary, there are a variety of different consults that are obtained within the Center regarding prescription drug advertising and promotional labeling issues:

- **Direct-to-Consumer Advertising Consult**

Advertising directed to consumers must meet the same requirements as promotion directed to health professionals. Drug application reviewers may send direct-to-consumer (DTC) advertising pieces to the DDMAC consultant on DTC issues to ensure consistency in applying the regulations to this type of advertising. DTC advertisements are often printed in popular magazines and journals that are read by a broad audience.

- **Pharmacoeconomics/Managed Care Consult**

Consults for pharmacoeconomic and managed care issues may be sent to the epidemiologist in DDMAC to determine whether related claims meet the requirements of the regulations. Pharmacoeconomics refers to the measurement of the costs and effects of pharmaceuticals in terms of price, cost-effectiveness and other cost ratios, and quality of life.

- **Medical Consult**

DDMAC reviewers work closely with medical review staff when evaluating scientific claims

used in promotional materials and contact the medical staff regarding scientific questions about products.

- Statistical Consult

DDMAC reviewers may ask CDER statisticians to provide a consult on issues requiring statistical interpretation.

Historical Review

DDMAC reviewers review the files for a product's previous promotional pieces and for competing products in the same therapeutic class.

"Launch Letter" to Applicant

A "launch letter" is a letter in response to an applicant's launch campaign submission. DDMAC reviewers provide the applicant with comments about the proposed launch campaign. Letters are reviewed by and receive the concurrence of appropriate managers.

Enforcement Rounds?

Reviewer decides whether issue needs to be discussed at "enforcement rounds" meeting. This is a weekly DDMAC meeting devoted to discussing regulatory concerns, complaints, enforcement options, and status of actions.

Enforcement Rounds

"Enforcement rounds" is a weekly DDMAC meeting devoted to discussing regulatory concerns, complaints, enforcement options, and status of actions regarding advertising under review in the division.

Untitled Letter

Untitled letters address promotion violations that are less serious than those addressed in warning letters. A reviewer's untitled letter is peer-reviewed and has the concurrence of the branch chief. In such letters, DDMAC usually requests that a company take specific action to bring the company into compliance within a certain amount of time, usually 10 working days. There is no requirement that the agency take enforcement action, although the letters may serve as a basis for additional regulatory action.

Warning Letter

Warning letters are written communications from FDA, in this case DDMAC, to a company notifying the company that DDMAC considers one or more promotional pieces or practices to be

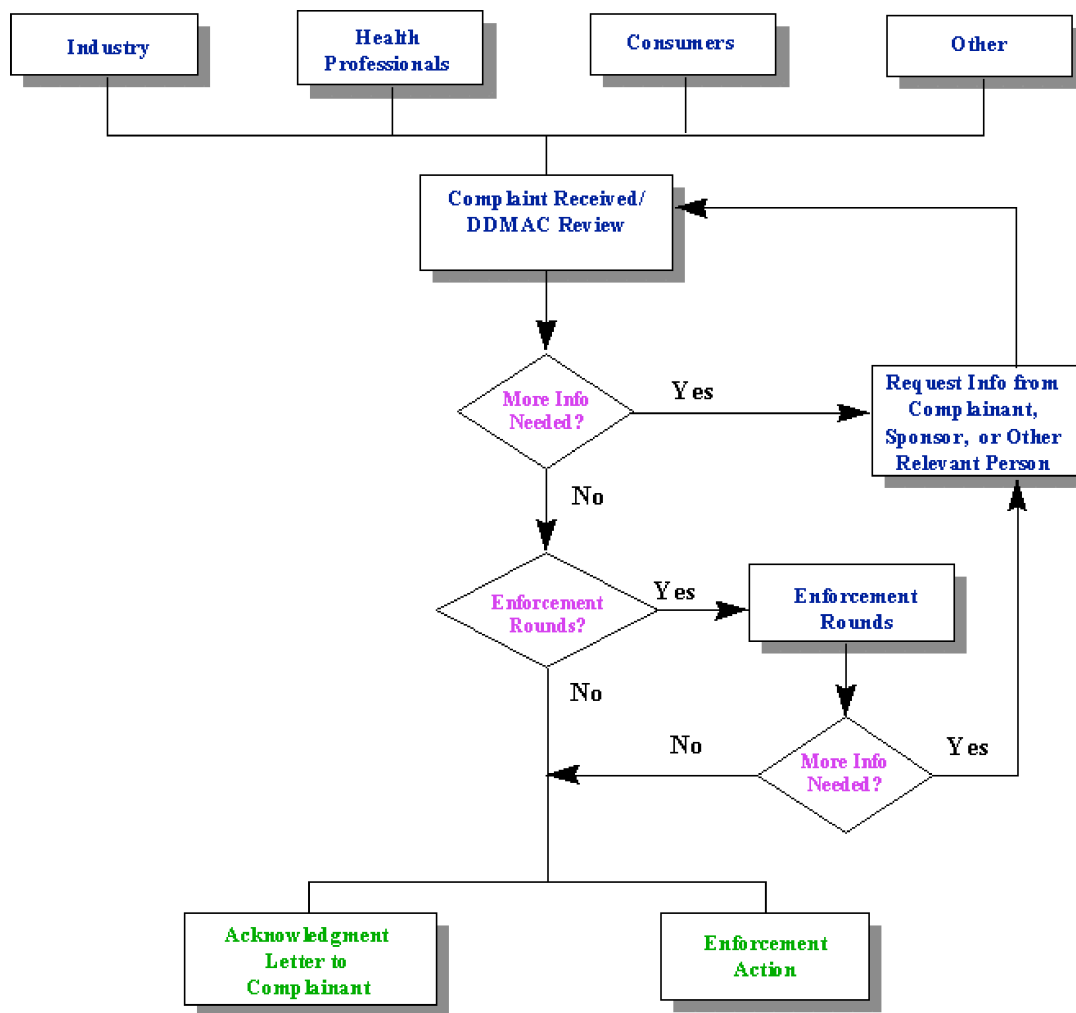
in violation of the law. If the company does not take appropriate and prompt action, as requested in the warning letter, to correct the violation, there may be further enforcement action without further notice.

Warning letters are issued by the DDMAC Division Director and receive concurrence from appropriate officials in the Center for Drug Evaluation and Research. Companies have 15 working days to respond to the warning letter. Warning letters are put on display at the time of issuance in FDA's Freedom of Information office.

Other Enforcement Actions

Other possible enforcement actions include recalls, seizures, injunctions, administrative detention, and criminal prosecution.

Promotional Material Review Process (Complaints)



Advertising/Labeling Definitions

Q. What is prescription drug advertising?

21 CFR 202.1(l)1 states that advertisements subject to Section 502(n) of the Food, Drug, and Cosmetic Act (FD&C Act) include advertisements published in journals, magazines, other periodicals, and newspapers; and broadcast through media such as radio, television, and telephone communications systems. This is not a comprehensive list of advertising media subject to regulation. For example, FDA also regulates advertising conducted by sales representatives, on computer programs, through fax machines, or on electronic bulletin boards.

Q. What must a prescription drug advertisement include?

Under section 502(n) of the FD&C Act, advertisements must include: the established name, the brand name (if any), the formula showing quantitatively each ingredient, and information in brief summary which discusses side effects, contraindications, and effectiveness. The brief summary is further discussed in 21 CFR 202.1(e)(1).

Q. Are there exceptions to the advertising regulations?

Yes, there are a few exceptions but only to the requirement to provide a true statement of information in brief summary as required under 21 CFR 202.1(e)(1). 21 CFR 202.1(e)(2) describes which ads are exempt:

1. Reminder advertisements - advertisements which call attention to the name of the drug product but do not include indications or dosage recommendations for use of the product, or any other representation. Reminder ads contain the proprietary name of the drug and the established name of each active ingredient. They may also contain additional limited information, such as the name of the company, price, or dosage form.

The exception does not apply to products with black box warnings in their approved product labeling.

2. Advertisements of Bulk-sale drugs - promote sale of the drug in bulk packages to be processed, manufactured, labeled, or repackaged and that contain no claims for the therapeutic safety or effectiveness of the drug.

3. Advertisements of prescription-compounding drugs - promote sale of a drug for use as a prescription chemical or other compound for use by registered pharmacists.

Q. What is labeling?

Section 201(m) of the FD&C Act states labeling ". . . means all labels and other written, printed, or graphic matter . . . accompanying such article."

The regulations provide examples of labeling under 21 CFR 202.1(1)(2):

"Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio or visual matter descriptive of a drug and references published (for example, the Physician's Desk Reference) for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor are hereby determined to be labeling as defined in section 201(m) of the FD&C Act."

Q. What must labeling include?

Labeling must include the established name, proprietary name (if any), adequate directions for use, and adequate warnings. The agency considers the approved product labeling, sometimes called the full prescribing information, to be adequate directions for use and adequate warning.

Q. Are there exceptions to the requirements for labeling?

Yes. Reminder labeling is exempt from the requirements for adequate directions for use and adequate warnings. Reminder labeling, as defined in 21 CFR 201.100(f), is exempted. Reminder labeling calls attention to the name of the drug product but does not include indications or dosage recommendations for use. Reminder labeling may contain only the proprietary name of the drug, the established name of each active ingredient, and optionally, information relating to quantitative ingredient statements, dosage form, quantity of package contents, price, and other limited information.

The exemption does not apply to products with black box warnings in their approved product labeling.

Labeling Research Activities

CDER's Division of Drug Marketing, Advertising and Communications (DDMAC) conducts research to improve the design and format of labeling for prescription and over-the-counter drugs.

- In cooperation with CDER's Office of the Center Director, DDMAC is examining how to improve communication of prescribing information through the revision of professional labeling format.
- DDMAC is working with CDER's Division of Over-The-Counter (OTC) Drug Products to develop and test formats for OTC labels (the information that is on the box or container).

Patient Information and Education Activities

CDER's Division of Drug Marketing, Advertising and Communications conducts and monitors research on factors that may influence or improve drug use by consumers, patients, and health care professionals.

- Objective 12.8 of Healthy People 2000: This objective reads: "Increase to at least 75% the proportion of people who receive useful information verbally and in writing for new prescriptions from prescribers or dispensers." Two approaches undertaken by FDA to influence private sector initiatives are: (1) the development of performance goals for the quantity as well as the quality of distributed information and (2) research and development activities to better understand how to communicate prescription drug information to patients.
- Medication Guides: A proposed rule for Medication Guide requirements was published on August 24, 1995. The proposed rule was intended to increase the dissemination of useful written prescription drug information to patients who receive prescription drugs on an outpatient basis. FDA believes that such information must be widely distributed and be of sufficient quality to promote the proper use of prescription drugs. The agency proposed goals (performance standards) that would define acceptable levels of information distribution and quality. To meet the performance standards for distribution of patient information, the agency proposed that by the year 2000, at least 75% of people receiving new prescriptions receive useful written information. This goal was adapted from the Public Health Service's "Healthy People 2000" report. In addition, the agency proposed that by the year 2000, at least 95% of the people who receive new prescription drugs receive useful written information.

A public meeting was held in February 1996 to discuss standards for Medication Guides. In August 1996, Congress passed a law requiring that the private sector be given the opportunity to develop a plan, acceptable to the Department of Health and Human Services (DHHS), to reach the goals specified in the proposed Medication Guide rule. On December 13, 1996, the private sector steering committee submitted its plan to reach these goals. The Secretary of DHHS accepted the plan on January 13, 1997. FDA will continue to assess progress toward the goals and to assist the private sector to achieve them in the specified time frames.

- Prescription Drug Counseling Surveys: Trends in providing prescription drug information have been followed through periodic surveys of people who recently obtained a new prescription at a retail pharmacy. Nationwide surveys have been undertaken in 1982, 1984, 1992, and 1994. Data from the surveys have been used to support proposed regulations and private sector initiatives in improving the quality and quantity of drug information. Data collection from the 1996 survey has recently been completed and analysis is under way.
- Women's Health: A study is being undertaken to investigate gender differences in consumer understanding of and response to the presentation of risk and benefit information about medications. A questionnaire to assess men's and women's understanding of risk and benefit

communications was recently approved by the Office of Management and Budget (OMB). Research funds are being sought from the Office of Women's Health. By examining gender differences in processing benefit and risk information, the goal is to develop ways of presenting labeling for patients that are useful and meaningful to all patients.

- Over-the-Counter (OTC) Labeling: Studies to evaluate newly proposed formats and labeling language for OTC drugs are being designed. Focus group testing is currently under way.

Policy Development and Guidance to Industry

CDER's Division of Drug Marketing, Advertising and Communications (DDMAC) develops guidances to the industry on prescription drug advertising and promotional labeling issues. In addition, the division holds meetings with the regulated industry and other involved parties to discuss emerging issues, such as broadcast, direct-to-consumer, and Internet advertising, and use of cost effectiveness and quality of life claims in promotion. DDMAC communicates its interpretations of the regulations to the industry through guidance documents that are published in the Federal Register and made available to the public on the World Wide Web or from the Drug Information Branch, Division of Communications Management, HFD-210, CDER.

For guidance specific to a drug or therapeutic class, DDMAC works with the appropriate new drug review division to ensure that division's concerns are adequately addressed in the guidance.

Some of the Policies and Guidances Currently Under Development

- ***Revision of Previous Guidances***- DDMAC is revising all guidances it has issued since 1970 to determine if they are obsolete or need revision. A series of Federal Register notices will explain the changes and give the public an opportunity to comment.
- ***Direct-to-consumer advertising and promotion***- With other FDA offices, DDMAC is examining whether the current advertising and labeling regulations should continue to apply to promotion directed to consumers, or whether there should be changes made in the requirements for this type of promotion.
- ***Promotion on the Internet***- As part of an FDA working group, DDMAC is developing an agency-wide policy to address how advertising and promotion of FDA-regulated products will be regulated on the Internet.
- ***Promotion to managed care organizations***- DDMAC is developing a policy regarding pharmaceutical marketing, pharmacoeconomic claims, and information exchange in managed care environments.
- ***Quality of Life Claims***- DDMAC is developing a policy regarding the claims made in labeling and advertising about the impact of pharmaceuticals on the quality of life.

Pharmaceutical Industry Surveillance

Government oversight of the pharmaceutical industry is usually classified into preapproval and post-approval categories. Most of the therapeutically significant compounds marketed today are the subject of new drug applications (NDAs) and abbreviated new drug applications (ANDAs). Preapproval activities, based on these detailed applications, are used to assure the drug is safe and effective before marketing. The Center for Drug Evaluation and Research (CDER) is the FDA organization responsible for drug evaluation and approval. Before approval, the FDA may inspect and audit the development facilities, planned production facilities, clinical trials, institutional review boards, and laboratory facilities in which the drug was tested in animals.

After the drug is approved and marketed, the FDA uses different mechanisms for assuring that firms adhere to the terms and conditions of approval described in the application and that the drug is manufactured in a consistent and controlled manner. This is done by periodic unannounced inspections of drug production and control facilities by FDA's field investigators and analysts. These professionals are organized under FDA's Office of Regulatory Affairs (ORA), which has twenty-one district offices and many more resident posts throughout the country.

The Federal Food, Drug, and Cosmetic Act (FD&C Act) provides legal authority for inspections and access to factories, vehicles, equipment, records, processes, and controls necessary to determine that drugs are being produced in conformance with regulations that have the force of law. These regulations, Current Good Manufacturing Practice for Finished Pharmaceuticals, are contained in Part 211 of Title 21 of the U.S. Code of Federal Regulations. These regulations contain requirements for: Organization and Personnel; Buildings and Facilities; Equipment; Components, Containers, and Closures; Production and Process Control; Packaging and Labeling; Distribution; Laboratory; and Reports and Records.

The regulations are general enough to be applied to a wide variety of dosage form drugs from topical ointments and creams to sterile injectables and ophthalmics. Yet, they are specific enough to require: testing of every batch for conformance with specifications before release, manufacture according to a specific master formula and process, validation of all manufacturing and control processes, investigation of complaints and failures, annual evaluation of products, testing program to assure stability of product throughout its labeled life, and testing of components and ingredients.

FDA investigators often use additional information from a variety of market surveillance systems to assist them in identifying a manufacturing or control problem. Consumer complaints, MedWatch submissions, NDA Field Alerts, Drug Quality Reporting System, and Adverse Drug Experience Reports are some of the systems used to identify drug problems by FDA's epidemiological units. FDA investigators also have access to a large variety of state-of-the-art analytical facilities throughout the country. These laboratories confirm suspected chemical, physical, and microbiological problems with pharmaceuticals; verify and develop analytical methods; and conduct research.

This system of regulation has grown with the pharmaceutical industry through many crises and challenges. The FDA welcomes dialogue with other regulatory bodies, industry organizations, Congress, and the public to improve the efficiency of its regulatory and administrative processes.

For more information, contact the Office of Compliance, Division of Manufacturing and Product Quality (DMPQ) at (301)594-0093, or contact FDA's Office of the Commissioner, Office of Regulatory Affairs at (301)443-6230. You can also visit DMPQ's [CGMP Web Page](#) or see the Office of Compliance FY 1996 Annual Report.

Subject-Related CDER Guidances of Interest

- [General Principles of Process Validation](#)
- [Manufacture, Processing or Holding of Active Pharmaceutical Ingredients](#)
- [Drug Master Files](#)

Other Subject-Related Documents of Interest

- [Sections 505, 501\(a\)\(2\)\(B\), and 704 of the Federal Food, Drug, and Cosmetic Act as Amended](#)
- [21 CFR Part 211- Current Good Manufacturing Practice for Finished Pharmaceuticals](#)
- [CDER Manual of Policies and Procedures 4732.1- The Establishment Evaluation Process \(draft\)](#)
- [Compliance Program Guidance Manual 7346.832, 7346.843, 7356.002, 7356.020](#)

Medication Errors

Medication errors cause at least one death every day and injure approximately 1.3 million people annually in the United States. Medication mishaps can occur anywhere in the distribution system:

- prescribing,
- repackaging,
- dispensing,
- administering, or
- monitoring.

Common causes of such errors include:

- poor communication,
- ambiguities in product names, directions for use, medical abbreviations or writing,
- poor procedures or techniques, or
- patient misuse because of poor understanding of the directions for use of the product.

In addition, job stress, lack of product knowledge or training, or similar labeling or packaging of a product may be the cause of, or contribute to, an actual or potential error.

CDER began receiving reports of medication errors in January 1992, when the U.S. Pharmacopeia began forwarding reports to the FDA. To evaluate and recommend appropriate action on these reports, the Medication Errors Subcommittee was formed in June 1992. In November 1993, the Agency began evaluating and coding MedWatch reports for medication errors and publicly stated that physicians and other health care professionals could report medication errors directly to the FDA through the MedWatch program.

CDER responsibilities are not completed when the safety and effectiveness of a drug product are determined. The Center also has the responsibility for helping to ensure the safe use of the drugs it approves by identifying and avoiding proprietary names that contribute to problems in the prescribing, dispensing, or administration of the product. Because early identification of a potential confusing proprietary name is crucial, CDER reviews these proposed names, prior to approval of a new drug application, by means of the Labeling and Nomenclature Committee.

CDER's approach to medication errors is as follows:

- Prevent medication errors prior to a drug's approval;
- After approval, evaluate, monitor, and take appropriate action on reports of medication errors;
- Educate and provide feedback to health professionals; and
- Share information with outside organizations involved in preventing medication errors.

For more information, see:

- Federal Food, Drug and Cosmetic Act, as Amended Section 502 (e)
- Code of Federal Regulations 21 CFR 201.10 (c); 201.56(b); and 299.4
- American Society of Health System Pharmacists (ASHP) guidelines on the prevention of medication errors, 1993

Drug Shortages

It is FDA's policy to attempt to prevent or alleviate shortages of medically necessary products. Patient "inconvenience" alone is an insufficient basis to classify a product as a medical necessity. However, a drug shortage situation can result from or may involve:

- changes in production, marketing decisions, and changing or increased use patterns for old drug products, and other factors;
- production changes leading to a drug shortage can result from voluntary recalls or FDA regulatory activities;
- shortage of raw materials (foreign as well as domestic), unpredicted or unanticipated disease outbreaks as well as shifts in product demand;
- single source products or circumstances where one manufacturer has a majority of market share;
- an actual or a potential shortage of a drug product; and
- a product is considered to be medically necessary or a medical necessity, if it is used to treat or prevent a serious disease or medical condition, and there is no other available source of that product or alternative drug that is determined by medical staff to be an adequate substitute.

The Center has established procedures for the evaluation of drug shortage situations in order that appropriate measures may be promptly activated. The purpose of the procedure is to develop the capability to evaluate potential drug shortage problems, assess the potential public health impact, and propose a plan to resolve the issue.

Reporting Drug Shortages

External reports on drug shortages are received in CDER through a variety of means. One such means is the Drug Shortage System which is maintained by the Center's Drug Quality Reporting System (DQRS). DQRS is the preferred entry point for consumer reports of drug shortages. Other sources of drug shortage information include FDA's Office of Health Affairs, which is a focal point for drug shortage reports from health professionals.

When drug shortage reports are received, the involved manufacturer(s), supplier(s), FDA's field organization, and appropriate Center staff are contacted to determine whether the shortage is caused by production or distribution problems. Most of the complaints received are simple distribution problems that are easily resolved. FDA personnel have been instrumental in identifying and meeting specific shortages of significant tuberculosis drugs, critical antibiotics, antihypertensives, as well as insulin products.

For more information on the Drug Shortage System, contact the Division of Prescription Drug Compliance and Surveillance, Office of Compliance at 594-0101 or see the Office of Compliance FY 1995 Annual Report.

Therapeutic Inequivalence Reporting

In the past 10 years, FDA's Center for Drug Evaluation and Research has received more and more reports of drug products that fail to work in patients because the product simply has no effect or is toxic. These problems are usually attributed to switching brands of drugs.

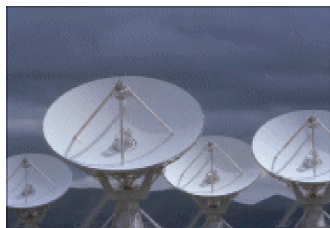
As a result, on Sept. 14, 1988, FDA created in CDER the Therapeutic Inequivalence Action Coordinating Committee (TIACC) to identify and evaluate reports of therapeutic failures and toxicity that could indicate that one product is not equivalent to another similar product. The committee also provides a mechanism for timely follow-up on reports of therapeutic inequivalence and, when, appropriate, conducts a full-scale investigation of these issues.

Once an inequivalent product is identified, TIACC can take a number of actions. These include:

- Removing inequivalent products from the market;
- Evaluating and changing the therapeutic equivalence rating of a product;
- Recommending that a grandfathered product submit a new drug application and require approved generics;
- Testing and evaluating the relationship of dissolution to bioequivalence;
- Recommending appropriate dissolution specifications for narrow therapeutic drugs; and
- Evaluating the toxicity profile of injectables and mandate appropriate controls.

For more information, see Federal Register, Sept. 14, 1988, No. 88N-0254.

Communicating with CDER



One of CDER's primary goals is to work collaboratively and cooperatively with industry, academia, and others to improve the drug development and review process. CDER also strives to provide consumers and health care providers with drug information that is vital to improving the public health. The topics listed below provide an overview of the various means of communicating with CDER.

● Consumer/Industry Inquiries.....	69
● Regulatory Correspondence.....	71
● Videoconferencing.....	72
● CDER Ombudsman.....	73

Consumer/Industry Inquiries

The Food and Drug Administration's Center for Drug Evaluation and Research is dedicated to ensuring that all persons involved in, or who depend upon, drug regulation excellence have the information needed to develop, review, market, dispense, prescribe or use drugs safely and effectively.

To enhance the communications aspect of this process, the Center created the Office of Training and Communications' Division of Communications Management (DCM). This division enhances information exchange, strategic communications planning, and the development of communications products and initiatives.

DCM works to ensure that pharmaceutical industry representatives, health care professionals, government officials, and consumers have easy and open access to information, and are educated about the drug regulation process and the benefits and risks of drugs.

Any of these individuals or groups may request information on specific drugs, guidance documents, publications, or general information such as a description of the drug approval process.

There are a number of ways consumers and industry representatives can communicate with or get reliable, current, and up-to-date information from the Center.

- The newest, and easiest, method for getting information is the Center's World Wide Web home page at <http://www.fda.gov/cder> .
- Another easy method is the Center's Fax-on-Demand system which contains literally hundreds of documents for consumers, industry, Federal, state, and local agencies, and foreign government representatives. The number is 1-800-342-2722.
- For more specific or complex drug inquiries, telephone the Drug Information Branch at (301) 827-4573 or click [here](#) to send them an electronic mail message at dib@cderr.fda.gov.
- For specific inquiries from industry, telephone CDER's Compendia Operations at (301) 594-0104.

Other sources of information include:

- the FDA Office of Public Affairs, at (301) 443-1130.

In addition, consumers and industry representatives can contact:

- CDER Ombudsman, Jim Morrison, (301) 594-5443;
- FDA Freedom of Information Staff, (301) 827-6567;
- FDA MedWatch Office at 1-800-FDA-1088;
- AIDS Clinical Trials Information Service, 1-800-TRIALS-A or on the World Wide Web at <http://www.actis.org>. [Notice: This link will take you outside the CDER web site].

Regulatory Correspondence

There are a number of ways that regulated industry can formally or informally communicate with or get information from the Center.

The Center is making available large amounts of information to regulated industry on CDER's World Wide Web home page at <http://www.fda.gov/cder>.

For general drug information, contact the Center's Drug Information Branch by mail at CDER, Drug Information Branch (HFD-210), 5600 Fishers Lane, Rockville, MD 20857; telephone (301) 827-4573; electronic mail dib@cder.fda.gov.

Specific comments or suggestions on CDER operations may be sent to CDER's Ombudsman, James C. Morrison, at CDER Ombudsman (HFD-1), 5600 Fishers Lane, Rockville, MD 20857; telephone (301) 594-5443; FAX (301) 594-5298 or 594-6197.

Additional expert sources may be found in CDER's *Quick Index to General Subjects of Interest Related to Drug Regulation*.

Videoconferencing

The Food and Drug Administration's Center for Drug Evaluation and Research has installed state-of-the-art videoconferencing technology for communicating with employees inside the organization as well as with industry representatives, consumers, healthcare professionals, academia, and other government agencies.

CDER's videoconferencing enhances face-to-face meetings by allowing participants the opportunity to listen, watch and participate "live" in a normal two-way conversation.

Videoconferencing can be used for such diverse purposes as:

- delivering a speech to an overseas audience from CDER facilities;
- "attending" a committee meeting being held in another city;
- interviewing prospective new employees;
- "attending" a training session being held in another city;
- holding a product review meeting with a division located in another CDER building.

CDER currently has videoconferencing capabilities in the Parklawn building, Woodmont Office Complex II, and Corporate Boulevard building.

For more information on the Center's videoconferencing capabilities or to schedule an event, telephone CDER's Office of Training and Communications at (301) 827-1243.

CDER Ombudsman

The Center for Drug Evaluation and Research's Ombudsman is responsible for receiving complaints, investigating and acting on them, mediating disputes, and attending to problems involving interpersonal working relationships. In addition, the ombudsman is responsible for getting feedback from inside and outside the Center about the effectiveness of programs and about problems that impede the performance of CDER's mission or conflict with its values/operating principles. The ombudsman also advises the Center Director on ways to correct such problems.

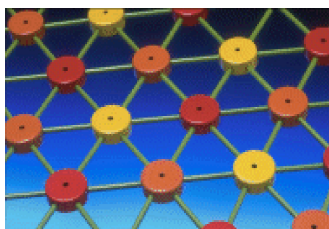
For more information, visit the [CDER Ombudsman](#) home page.

To speak with the CDER Ombudsman, James C. Morrison, phone (301) 594-5443 or fax (301) 594-5298 or (301) 594-6197.

In addition, you can send correspondence to him at:

CDER Ombudsman (HFD-1)
5600 Fishers Lane
Rockville, MD 20857

Other Activities



There are many other activities that CDER is involved in that contribute to its mission of assuring that safe and effective drugs are available to the American people. The topics listed below highlight some of these major activities.

● Orphan Drugs.....	75
● Drug Registration and Listing System.....	76
● Environmental Assessments.....	78
● Women's Health Issues.....	79
● CDER Pediatric Initiatives.....	81
● International Conference on Harmonisation.....	83

Orphan Drugs

The term "orphan drug" refers to a product that treats a rare disease affecting fewer than 200,000 Americans. The Orphan Drug Act was signed into law on January 4, 1983. Since the Orphan Drug Act passed, over 100 orphan drugs and biological products have been brought to market.

The intent of the Orphan Drug Act is to stimulate the research, development, and approval of products that treat rare diseases. This mission is accomplished through several mechanisms:

- Sponsors are granted seven years of marketing exclusivity after approval of its orphan drug product.
- Sponsors also are granted tax incentives for clinical research they have undertaken.
- FDA's [Office of Orphan Products Development](#) coordinates research study design assistance for sponsors of drugs for rare diseases [[Notice](#): This link will take you outside the CDER web site].
- The Office of Orphan Products Development also encourages sponsors to conduct open protocols, allowing patients to be added to ongoing studies.
- Grant funding is available to defray costs of qualified clinical testing expenses incurred in connection with the development of orphan products.

Drug Registration and Listing System

FDA attempted a comprehensive drug inventory for drug listings by establishing two voluntary programs. However, these two *voluntary* programs were unsuccessful. In order to make these efforts mandatory, FDA instituted the Drug Listing Act of 1972, this regulatory policy is in the **21 Code of Federal Regulations (CFR) Part 207**. The **21 CFR Part 207** addresses definitions, drug registration requirements, and drug listing requirements by FDA. This Act amended Section 510 of the Federal Food, Drug, and Cosmetic Act and defines the applicable following terms:

- The term *Firm* refers to a company engaged in the manufacture, preparation, propagation, compounding, or processing of a drug product.
- The term *Drug Products* refers to human drugs, veterinary drugs, and medicated animal feed premixes which includes biological products, but does not include blood and blood components.
- The term *Manufacturing and Processing* refers to repackaging or otherwise changing the container, wrapper, or labeling of any drug product package in the distribution process from the original "maker" to the ultimate consumer.

Registration Requirements

A firm must register all drug products (Domestic Manufacturers, Domestic Repackers, Domestic Labelers, and submissions for New Human Drug Application, New Animal Drug Application, Medicated Feed Application, Antibiotic Drug Application, and Establishment License Application to Manufacture Biological Products) whether or not they enter interstate commerce. All domestic distributors and foreign firms importing drug products into the United States must obtain a labeler code and list all of their products.

Listing Requirements

All firms, unless exempted by the Act, are requested to list their commercially marketed drug products with FDA within 5 days after the beginning of operation. They are required to list/update their drug products listing twice a year (June and December). The initial listing and updates of a product is done on a form FDA 2657. Manufactures are allowed to list the products for distributors on form FDA 2658. In order to assist the firms with the mandatory update in June, the Product Information Management Branch mails a Compliance Verification Report (CVR) to the firms. The CVR goes to all firms which have at least one prescription product listed with FDA. The firm is required to update the CVR and mail it back within 30 days.

Registration Exemptions

Pharmacies, hospitals, and clinics that dispense drug products at retail; licensed physicians who use drug products solely for purposes related to their professional practice; and/or persons using drug products solely for their professional needs and are not for sale are exempt from registration. [See **21 CFR 207**]

Registration Process

Firms can register by obtaining a Registration of Drug Establishment Form, FDA 2656 within 5 days after the beginning of operation or submission of an application. Firms are required to re-register annually by returning an Annual Registration of Drug Establishment Form, FDA 2656E, within 30 days after receiving it from the Product Information Management Branch.

For More Information:

For further information, or to obtain copies of Forms FDA 2656, FDA 2656E, FDA 2657, FDA 2658 or the Drug Registration and Listing Instruction Booklet (May 1996), contact CDER's Product Information Management Branch, Division of Database Management, HFD-58 at (301)594-1086.

Environmental Assessments

Under the National Environmental Policy Act of 1969 (NEPA), all Federal agencies are required to assess the environmental impact of their actions and to ensure that the interested and affected public is informed of the environmental analyses. CDER's ***Guidance for Industry for the Submission of an Environmental Assessment*** provides detailed information on a variety of topics related to preparing and filing environmental assessments (EAs).

In CDER, adherence to NEPA is demonstrated by the EA portion of the drug application. This section focuses on the environmental implications of consumer use and disposal from use of the candidate drug. However, because approval of many drugs are unlikely to have significant environmental effects, CDER has provisions for submission of abbreviated EAs rather than full EAs under certain circumstances or has categorically excluded certain classes of actions. FDA has reevaluated its NEPA regulations found in **21 CFR Part 25** and has proposed to improve its efficiency in the implementation of NEPA and reduce the number of EAs by increasing the number of applicable categorical exclusions. The notice of proposed rule making was posted in the Federal Register on April 3, 1996.

Women's Health Issues

CDER strongly supports activities on women's health issues through the Women's Health Subcommittee of the CDER Medical Policy Coordinating Committee.

Primary among these projects is the FDA Pregnancy Labeling Task Force which CDER co-chairs and manages. This task force was organized to review pregnancy labeling and to explore how the category information could be presented to clinicians, reviewers and other interested parties in the most effective manner in order to provide the greatest possible usefulness to the public. The long term goal is to determine how animal toxicology information contributes to clinically meaningful information. A major task of this group will be the reassessment of Category "C". Because of the traditional approach the FDA has taken, most drugs have been placed in this category. This has resulted in the erroneous appearance that there are few drugs which can be safely given to women of childbearing potential.

Other women's health projects in which CDER is participating are the Pregnancy Registry Working Group, the Pregnancy Drug Use Survey, rewriting of the Institutional Review Board regulations to foster studies in which women of child-bearing potential are included, and gender-related bioequivalence issues.

The FDA Consumer magazine, an official publication of the FDA, featured the Office of Women's Health in an article in the October 1996 issue entitled, "***InsideFDA: Office of Women's Health***." The FDA Office of Women's Health itself has established and maintains a Web site containing information on a broad range of issues related to women's health. [Notice: These two links will take you outside the CDER web site]. In addition, the page is linked to a variety of other sources inside and outside of FDA which provide information on topics of related interest.

Pregnancy "Category C" Labeling

An FDA Pregnancy Labeling Task Force was organized to review drug labeling information on pregnancy and fetal risks and to explore how the information could be presented to clinicians, reviewers and other interested parties in the most effective manner, in order to provide the greatest possible usefulness to the public. The long term goal is to determine how animal toxicology information contributes to clinically meaningful information. A major task of this group is the reassessment of category "C." Specific requirements on content and format of labeling for human prescription drugs states the following:

Pregnancy Category C: If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling shall state: "Pregnancy Category C. (Name of drug) has been shown to be

teratogenic (or to have an embryocidal effect or other adverse effect) in (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. (Name of drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." The labeling shall contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling shall state: "Pregnancy Category C. Animal reproduction studies have not been conducted with (name of drug). It is also not known whether (name of drug) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (Name of drug) should be given to a pregnant woman only if clearly needed." The labeling shall contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

CDER Pediatric Initiatives

CDER is actively involved in initiatives related to the improvement of children's health. This is accomplished primarily through CDER's Pediatric Subcommittee of the Medical Policy Coordinating Committee. The Pediatric Subcommittee has been charged with providing expert advice and promoting the development of medicines in the pediatric population. Following is a list of initiatives of the Pediatric Subcommittee.

Pediatric Use Regulations

- On December 12, 1994, FDA published a final rule revising the current pediatric use subsection of the professional labeling requirements for prescription drugs to broaden the basis on which information about use of a drug in the pediatric population may be included. The new regulation allows evidence of effectiveness in adults to be used as a basis for concluding that a drug is effective in the pediatric population if the course of the disease and effects of the drug are sufficiently similar in adults and the pediatric population to permit such extrapolation. Additional information supporting the pediatric use (e.g., pharmacokinetics data, safety data, pharmacodynamics data) should also usually be submitted to determine the appropriate pediatric dose.
- On August 15, 1997, FDA published a proposed rule that would require manufacturers to assess the safety and effectiveness of new drugs and biologics in pediatric patients. The 1994 regulation simplified the required pediatric data in order to encourage drug manufacturers to submit these data voluntarily for review. However, many new drugs are still being approved without information on how they should be used in children. In addition to new drugs, the proposed rule would also apply to many drugs already approved and being used. For drugs that are already marketed, this regulation would codify FDA's authority to require, in compelling circumstances, that manufacturers conduct studies to support pediatric-use labeling for the approved indications.

Guidance for Industry- In March 1996, FDA published the guidance for industry *The Content and Format for Pediatric Use Supplements*. This guidance provides information on the content and format of pediatric use supplements submitted in response to the December 1994 final rule.

Pediatric Drug Use Survey- CDER has obtained information on those approved drugs most frequently used in the outpatient pediatric population without adequate pediatric labeling and has sent letters to those commercial sponsors identified in this survey requesting that the sponsor contact the agency regarding their intention to submit a pediatric use labeling supplement.

Communication with Industry- CDER has begun focusing on the pediatric population throughout the clinical drug development. CDER has identified key opportunities for discussing with commercial sponsors the plan for pediatric development of a drug:

- Pre-IND and pre-IND submission meetings
- Initial IND submission
- IND annual report
- End of phase 2 meeting
- Presentation of IND to an FDA drug advisory committee
- Pre-NDA meeting
- NDA submission and FDA's 45-day filing meeting
- Presentation of NDA to an FDA drug advisory committee

Pediatric Page- CDER and the Center for Biologics Evaluation and Research (CBER) have revised the pediatric page and will extend its use to all NDAs/PLAs/PMAs/efficacy supplements for all action letters. The pediatric page summarizes the state of pediatric studies at the time an action is taken on an application. It is currently used only for approvals of new molecular entities. CDER is currently in the process of implementing a tracking system for the pediatric page.

Revised Pediatric Guidelines- CDER will be revising the 1977 guidance *General Consideration for the Clinical Evaluation of Drugs in Infants and Children* to reflect changes in drug development by focusing on earlier consideration of the pediatric population during the clinical evaluation of pharmaceuticals and extrapolation of adult data.

Pediatric Pharmacology Research Units (PPRU)- CDER collaborates with PPRU's regarding the development and conduct of clinical and pharmacokinetic studies of drugs in the pediatric population. CDER has proposed clinical trials on specific drugs or pediatric formulations without commercial sponsorship.

Pharmacokinetic Guidance- CDER and CBER have drafted a guidance for industry, *General Considerations for Pediatric Pharmacokinetic Studies*. The document provides guidance to those researchers interested in conducting pharmacokinetic studies in the pediatric population. The document is currently under review within the Center.

Pediatric Rapid Response Team- A team has been established to assist reviewers on pediatric issues on a day-to-day basis. The team consists of 4-5 rotating members from the Pediatric Subcommittee. Rotating members volunteer for 3 months at a time. The team will provide expert advice to reviewers on issues related to pediatric drug development. The team will strive to answer questions in a timely fashion (1-2 week turnaround time).

NDA Periodic Pediatric Use Report- CDER is in the process of modifying the regulations for the postmarketing periodic reports of adverse events to include information regarding the age of the patient and the diagnosis for which the drug was prescribed, with special emphasis on the pediatric population (21 CFR 314.80) as well as the NDA annual reports. This proposal will be harmonized with the International Conference on Harmonisation efficacy guidance *Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* to prevent any overlap or duplication of requirements.

“International Conference on Harmonisation”

As a Center within FDA, CDER, along with the Center for Biologics Evaluation and Research (CBER), is an active participant in the "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use" (ICH).

This unique undertaking is a cooperative effort between the drug regulatory authorities and the innovator pharmaceutical company professional organizations in the European Union, Japan and the United States to reduce the need to duplicate the testing conducted during the research and development of new medicines.

Through harmonization of the technical guidelines and requirements under which drugs for human use are approved within the participating nations, ICH members seek more economical use of human, animal and material resources and the elimination of delay in availability of new drugs, while maintaining the quality, safety and effectiveness of regulated medicines.

Information on this international initiative is available through the official [ICH Home Page](#) on the World Wide Web [Notice: This link will take you outside the CDER web site]. The ICH Secretariat maintains this web site and is responsible for the accuracy of the information it contains. In addition, CDER's Office of Training and Communications, through its Drug Information Branch, makes available a current list of [ICH guidance documents](#). If you access this page, scroll down to the section entitled ***International Conference on Harmonisation***. Also, information regarding many of FDA's international activities will soon be available via the FDA web site.







People at CDER



The Center for Drug Evaluation and Research is a dedicated community of scientists, professionals and support staff who work to assure that safe and effective drugs are available to the American people. Listed below are links to information (in PDF format) on how CDER is organized as well as to key points of contact within the Center.

- Office of the Center Director
- Office of Review Management
- Office of Pharmaceutical Science

Also..

-  [CDER Organization Chart](#)
-  [Quick Index to General Subjects of Interest Related to Drug Regulation-](#)
Contacts for specific IND/NDA topics.
-  [CDER Key Officials List](#)
-  [CDER Employee Directory](#) (Alphabetical)
-  [DHHS Employee Directory](#) (maintained by DHHS)
-  [CDER Fax Directory](#)