

Trials and Tribulations

A Primer on Successfully Navigating the Waters of the Food and Drug Administration

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Conducting clinical trials in a regulated environment constitutes unfamiliar territory for most physicians. There exists no formal training in this subject, so many clinicians lack even a basic understanding of the procedures required by the Federal Food, Drug, and Cosmetic Act and their implications vis-à-vis clinical practice. The authors distill drug regulation to relevant applications and elucidate the rationale and procedures for submitting an Investigational New Drug application by providing a user-friendly road map of the process. *Ophthalmology* 2004;111:1801–1806 © 2004 by the American Academy of Ophthalmology.

The practice of clinical trials has matured from an unstructured and often anecdotal exercise into a rigorous, evidence-based science. Increasingly, physician–investigators are generating more meaningful data by conducting clinical studies that incorporate randomized, well-controlled, and masked designs. Unfortunately, as the validity of these preferred standards has become universally accepted, the acquisition of concurrent regulatory knowledge and proficiency has lagged. Not surprisingly, this disconnect has contributed to inefficiencies in clinical development, and delays have fed misperceptions that the Food and Drug Administration (FDA) is at least partly to blame. So while the general public continues to entrust the FDA with safeguarding and promoting the public health, there are some in the medical (and corporate) community who bemoan the FDA as an albatross impeding the kinetic march of scientific advancement. It is instructive, therefore, not only to provide the physician with a practical field guide to regulatory procedures in the medical arena, but also to explain the method to the FDA's apparent madness.

FDA Basics

A brief overview of the FDA's organization, workings, and purpose provides a context for understanding the regulatory requirements it imposes. In short, the FDA is a scientific, regulatory, and public health agency whose mission is to

promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner. The FDA regulates but does not conduct clinical trials.

Within the agency are several centers; of those most relevant to clinicians, the Center for Drug Evaluation and Research regulates drug products and certain therapeutic biologic products, the Center for Devices and Radiologic Health regulates medical devices, and the Center for Biologic Evaluation and Research regulates blood, blood products, vaccines, etc., as well as some associated devices. Within each center are offices and reviewing divisions that are subdivided roughly by medical discipline. Currently, the Division of Antiinflammatory, Analgesic, and Ophthalmologic Drug Products (in the Center for Drug Evaluation and Research), the Division of Ophthalmic and Ear, Nose and Throat Devices (in the Center for Devices and Radiologic Health), and the Center for Biologic Evaluation and Research regulate ophthalmic applications.

The FDA receives its legal authority from the Federal Food, Drug, and Cosmetic Act, which prohibits the interstate commerce of misbranded or adulterated products that fall under its purview. As a practical matter, this means that a drug must be the subject of an approved New Drug Application or the subject of an old drug monograph (i.e., an over-the-counter product that is generally recognized as safe and efficacious) to be sold.

Interstate commerce includes the shipment of not only domestic products, but also those that originate outside of the country and are tested or used in the United States. In theory, commerce entirely confined within a specific state would not be subject to federal law. However, any visions of legally evading the FDA would require the intrastate manufacture and sale of every component of a drug product or device and would preclude cross-state movement of patients, which is usually an impractical and undesirable proposition.

Thus, a new drug must be the subject of an approved

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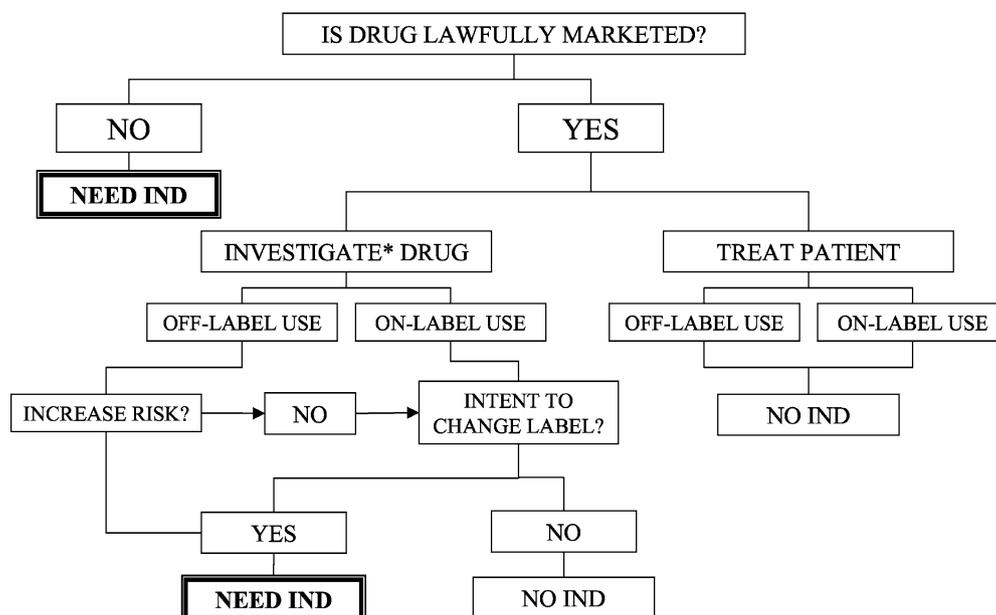


Figure 1. Investigational New Drug application (IND) flowchart. *All studies are considered investigations.

marketing application before it is transported across state lines for use in humans. How, then, can an unapproved new drug be tested to demonstrate that it is safe and effective? The answer is that there is an exemption from the law for this very purpose. The sponsor of a study to investigate an unapproved product can request an exemption from the law by filing an Investigational New Drug (IND) application, officially a “Notice of Claimed Investigational Exemption for a New Drug,” or an Investigational Device Exemption (IDE) with the FDA. The IND or IDE application can sometimes lead to a New Drug Application (required to market a drug) or a Premarket Approval Application (marketing application for a device). New Drug Applications and Premarket Approval Applications typically are submitted by industry and are therefore not the subject of this article.

Is an Investigational New Drug Application Required?

As mentioned, any new drug that is not lawfully marketed requires an IND application before use in humans (devices and the IDE follow a somewhat different set of rules; note that because it is more common for a clinician–investigator to sponsor an IND than an IDE, the remainder of this article focuses on the IND application). Conversely, when physicians treat patients with approved drugs in unapproved uses (i.e., off-label), things become slightly more complicated.

The term *off-label* is deeply embedded in the medical vernacular, which is particularly ironic in a health care world where drug product labels rarely get unfolded, let alone read. However, the oft-ignored label is of critical importance (the FDA presently is reorganizing the label format to improve its accessibility). It serves not only as a reference text to educate prescribers, but also as a legal

document that limits the product’s promotional materials, which must be consistent with the label to avoid misbranding. The label describes and defines the specific medical indication, dose, dosage form, route of administration, etc. for which the product has been approved; any deviation from the label (literally, off-label) qualifies as an unapproved use. So, are ophthalmologists who prescribe a topical aminoglycoside for a corneal ulcer breaking the law? Don’t physicians retain the ability to use their discretion in determining patient care without receiving regulatory blessing?

The answer to both questions is a definitive “it depends” (Fig 1). In fact, the determination of on- or off-label use has little bearing on whether an IND application or IDE is required. Rather, the *intent to change* the label, the risk associated with a study, and the seemingly semantic distinction between treating a patient and investigating a product in a patient are the things that have profound regulatory implications.

Physicians retain the ability to treat a patient according to their best judgment, provided they are not conducting an investigation. Here, *investigation* is broadly defined as any use of a drug in people other than use of a lawfully marketed drug to *treat* a patient. *Treating* generally implies that the physician is using a product based on a scientific rationale and on sound medical evidence, in the patient’s best interest. Every study, therefore, is an investigation, and no study is ever considered treating.

Again, physicians can use lawfully marketed products without filing with the FDA when they are treating the patient according to their best judgment, regardless of whether the product is being used in a way that is consistent with the approved labeling (on/off-label). Thus, in the preceding example with the corneal ulcer, if the ophthalmolo-

gist's intent is the practice of medicine, it does not invoke FDA regulatory oversight.

Does this mean that every investigation of an approved drug requires an IND application submission? No. The physician is obligated to file an IND application before initiating an investigation of an approved drug in 2 circumstances: if the principal intent is to develop information about the drug product's safety or efficacy and to change the label, or if the conditions of the study will change the risk profile for the drug product. Most investigations meet at least one of these criteria. For example, a physician who wishes to conduct a study to assess the safety and efficacy of intravitreal corticosteroid injections in patients with macular edema must submit an IND application, because intravitreal use increases the risk profile. For similar reasons, an IND application would be required to investigate the potential benefit of a topical nonsteroidal anti-inflammatory drug for an indication with 6-month dosing (e.g., cystoid macular edema), because topical nonsteroidal anti-inflammatory drugs currently are approved for dosing up to 2 weeks.

It might come as a surprise that even on-label drug use occasionally warrants IND application submission. For instance, a head-to-head trial comparing 2 approved intraocular pressure (IOP)-lowering medications in glaucoma patients might need an IND application, even if both products are administered in accordance with the label, if study results are intended to support a significant change in labeling. To be sure, it is prudent for the investigator to consult the label or contact the FDA when contemplating such studies.

In sum, a clinical investigator must file an IND application with the FDA when (1) using any never-approved drug product or (2) conducting an *investigation* that is intended to support a change in the label or will change the risk profile for the drug. Note that these regulations apply to any use of a drug product in subjects within the United States, even if the drug product originates outside the country.

The Investigational New Drug Application, Step by Step

Once a physician has determined that an IND application is required for a study, the next step is to retrieve the relevant application form from the Internet.¹ This form contains requests for the applicant to provide supporting data demonstrating that it is reasonable to begin testing a drug in humans.

The IND application (form 1571) is largely self-explanatory and contains a brief series of fill-in-the-blank and checkoff boxes to describe and catalogue the contents of the application. As such, it serves as a road map for the applicant and as a coversheet for the submitted IND application dossier.

Generally, a first-time IND application for a new drug product provides data in 3 broad areas. Animal pharmacology and toxicology studies (in regulatory-speak, the pharm/tox section) demonstrate that the product is reasonably safe for initial testing in humans and should help the applicant select and justify an acceptable starting dose range. Chem-

Table 1. Common Clinical Protocol Sections

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1. Study objective
 2. Number of subjects
 3. Description of the study population, with specific inclusion/exclusion criteria
 4. Study design
 5. Time points of each visit
 6. Procedures at each visit
 7. Efficacy and safety end points
 8. Statistical methods of analysis
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istry, manufacturing, and controls information (the CMC section) describes the drug product's composition (i.e., what is in it), its stability (i.e., expected shelf life), and the controls used in manufacturing it; these data demonstrate that the drug product can be reliably produced and supplied in consistent batches. Last, the clinical section outlines the rationale and intended plan for administering the drug to subjects.

An acceptable clinical protocol demonstrates that the investigator has anticipated the potential risks and, for efficacy studies, has designed a protocol that will adequately test the proposed hypothesis. The FDA will assess the expected risk associated with administering the drug to the proposed subject population and, for efficacy studies, the likelihood that the study will meet its objectives. Although a treatise on sound clinical trial design is outside the scope of this article, in general, a double-masked, controlled, randomized protocol that tests multiple doses is preferred where possible. The format is variable, but common sections are listed in Table 1.

In addition, the clinical package should contain an investigator's brochure to characterize the drug product's expected pharmacological effects and to describe the rationale for the investigation.

Traditionally, initial (phase I) clinical studies assess safety, early pharmacokinetic properties, and preliminary efficacy trends for the drug in healthy volunteers or in patients when appropriate. The protocols are designed to support later studies, not to form the basis for marketing approval, and should focus on elements of the study that are critical to subject safety. Unlike studies further along in drug development (sometimes designated phase II, III, or IV), these small, early studies usually do not have efficacy end points, so such matters as primary end point selection and statistical methods of analysis are not an issue. An IND application might be required for clinical trials in any phase.

Each investigator must be qualified by education and training to carry out the intended investigation. Investigators who have repeatedly or deliberately failed to comply with regulatory requirements and those who have submitted false or misleading data can be disqualified. Therefore, every investigator who intends to participate in the trial must either complete another brief form—the Statement of Investigator (form 1572)—or submit a curriculum vitae (or other statement of qualifications), clinical facility data, and the name of the institutional review board (IRB).

At first glance, an investigator unfamiliar with the IND application might be puzzled by the presence of numerous

references to “21 CFR Part . . .” located throughout the application form. Briefly, the Code of Federal Regulations (CFR) represents the various federal agencies’ working details of the respective laws and is reprinted at least once each calendar year. The CFR is divided into 50 titles, each of which is subdivided into chapters. For instance, title 21 is Food and Drugs, and chapter 1 is the Food and Drug Administration, Department of Health and Human Services. Title 21 is composed of 9 volumes, which are further divided into parts. Part 312 contains the IND regulations (21 CFR 312). Though not exactly riveting prose, the CFR is a useful reference tool, and the entire text is available online.²

The sponsor of the IND is responsible for submitting the application to the FDA, and may be the clinical investigator, a research institution, or a company. A clinical investigator who assumes the role of sponsor (the sponsor–investigator) often receives the study drug from a company. In this case, particularly when the study drug is already the subject of a previously submitted IND application from the company, the company usually provides the investigator with a letter referencing the active application. This letter is submitted along with the IND application and saves the investigator from submitting duplicate data that are already on file with the FDA, such as the chemistry/manufacturing data, animal data, and previous human experience data (items 5 and 7–9 of section 12 on IND form 1571). Even simpler, if the company sponsors the IND, the investigator may be responsible for completing only the Statement of Investigator form.

Open Communication at the FDA

The FDA encourages open communication with the sponsor as an effective means of expediting the regulatory process; any confusion that can be clarified in advance translates to real savings in time and resources for everyone involved. For questions or issues, the sponsor may request a pre-IND application meeting with the FDA to review whether the preclinical database will likely support the proposed human trial or whether any obvious deficiencies exist (this option is utilized more often by industry than by clinicians). Alternatively, if specific questions exist that do not necessarily warrant a formal meeting, the sponsor can contact the FDA at any time via telephone, and the project manager or other team member is usually willing to help. Every effort is made to provide the sponsor with clear and consistent advice; the intent is to resolve problems in a collaborative, iterative process rather than to delay or place studies on hold.

The Fate of an Investigational New Drug Application

The sponsor should submit the IND application in triplicate, as several individuals will simultaneously review it. On receipt, the FDA assigns a number to the IND application and the reviewing division (Division) sends a letter to the sponsor providing specific contact information for future correspondence. A team of specialists representing various disciplines reviews the application. For instance, a chemist

reviews the manufacturing section, a pharmacologist reviews the animal studies, and a biostatistician might review the statistical analysis plan. A medical officer (an ophthalmologist reviews an ophthalmic application) serves as the focal point for the review team, synthesizing the comments provided by the various disciplines, critically reviewing the proposed clinical protocol, and creating a document that summarizes the entire submission. The medical officer then generates a composite list of deficiencies and recommendations to be communicated to the sponsor; no news is good news . . . if the Division does not communicate a deficiency list within 30 days, the sponsor is permitted to begin clinical work.

If the Division determines that the deficiencies confer risks to the study subjects that outweigh the potential benefits, or if the sponsor has submitted insufficient information for the team to make that determination, the IND application is placed on clinical hold status. The sponsor is prohibited from all clinical work requested under the IND application, but can submit a response to the deficiencies in an amendment to the application (all amendments or other correspondence to the IND application are submitted with another form 1571, referencing the original IND application number). Often, the Division sends comments to the sponsor without officially placing the application on clinical hold. The purpose of these comments is to improve the proposed study.

The Emergency Investigational New Drug Application

Not uncommonly, a patient presents to a physician–investigator with a medical condition that requires an urgent investigational intervention. In these situations it might not be appropriate to wait the usual 30 days before initiating therapy. For instance, delaying administration of an investigational treatment in a patient with endophthalmitis might qualify as unacceptably risky. In such cases, the investigator contacts the Division via telephone or other rapid means of communication to obtain verbal authorization for an agreed-upon use—this is an Emergency IND application. Note that even a study under the Emergency IND application provision requires IRB approval.

Under these circumstances, the investigator receives an IND number and remains obligated to submit a complete IND application (including form 1571) as soon as practicable after receiving an acknowledgment letter from the FDA. However, contrary to the formal protocol submitted with a traditional research IND application, a descriptive case history for the patient and a brief explanation to justify use of the study drug might suffice for an Emergency IND application. Importantly, the Division expects submission of follow-up clinical information from subsequent patient visits as it becomes available.

Based on clinical practice trends, the investigator might anticipate seeing more than one patient with a similar, urgent condition for which an investigational drug is potentially available. In this case, rather than make repeated individual requests under an Emergency IND application,

the investigator contacts the Division for one IND application to cover a small series of patients who meet prespecified enrollment criteria (e.g., “the next 5 patients with endophthalmitis”).

No News Is Good News! . . . Now What?

As mentioned, if the sponsor hears nothing for 30 days after the FDA has received the IND application, the study may proceed. If at any time the sponsor wishes to make changes to the IND application (e.g., transfer to a new manufacturing plant, modify a clinical protocol, add a new clinical trial, even add a new investigator) an amendment to the IND application is required. Contrary to the original IND application submission, however, the sponsor may implement those changes immediately after sending the amendment to the FDA, without waiting 30 days (though protocol changes do require prior IRB approval). Note that the FDA reserves the right to suspend an ongoing investigation at any time if warranted, even after the protocol has started.

A sponsor is responsible for abiding by specific standards in study conduct. The study drug package label must caution the reader that the bottle contains an investigational drug. Promoting or charging for the study drug is forbidden, except in rare circumstances, and then only with prior written approval by the FDA. The sponsor is expected to conduct investigations according to Good Clinical Practice,³ an international ethical and scientific quality standard for studies in human subjects. Further, the FDA expects careful recordkeeping and retention of case report forms, completed consent forms, and medical records. Records of drug disposition, such as the dates, quantity, use by subjects, and locations of the unused drug must also be retained and cataloged. The FDA may periodically inspect trial sites to ensure that the investigator is properly capturing and storing the required data.

If serious and unexpected adverse drug experiences occur that are associated with the use of the study drug, or if findings from new animal tests suggest significant risks to human subjects, the sponsor must submit a written safety report to the Division within 15 calendar days. The CFR explicitly defines the terms *serious* and *unexpected*. For example, uncontrolled, severe IOP elevation requiring surgical intervention would be serious and unexpected for a new corticosteroid eyedrop if the investigator’s brochure only referred to mild increases in IOP. Further, the sponsor is required to alert the Division by telephone or fax of any unexpected fatal or life- or sight-threatening experience associated with the use of the study drug within 7 days.

Last, the sponsor is required to submit a comprehensive annual report within 60 days of the yearly date of the IND application. The annual report contains numerous data points and is intended to update the Division as to all relevant developments over the preceding year. This includes individual study progress (e.g., enrollment, drop-outs), with study results, if completed; a tabulation of the adverse events by body system; all IND safety reports submitted during the previous year; and a list of subjects who dropped out due to adverse events. The report includes,

if available, new information regarding the drug’s actions, completed preclinical studies, and chemistry/manufacturing changes. It also contains a general investigational plan for the coming year, foreign marketing developments, and any other information not previously reported in sporadic amendments throughout the year.

It’s Over

The sponsor may choose to withdraw or inactivate an IND application at any time (e.g., after the trial has completed) by notifying the Division. A withdrawal indicates that all investigations have ended and stocks of the drug have been returned or otherwise disposed of. If the sponsor is withdrawing the IND application for safety reasons, the Division and the IRB should be promptly informed.

Alternatively, the sponsor can request that the IND application be placed on inactive status. In contrast with an IND application withdrawal, a sponsor can resume the investigation by filing a protocol amendment containing the proposed investigational plan etc., requesting to reactivate the inactive IND application, and waiting 30 days. Inactive status has the benefit of relinquishing the sponsor from the obligation to file annual reports.

FDA as Facilitator

Most clinicians become familiar with regulatory procedures only by necessity, but the merits of enduring the application process are manifold.

Clinical investigators are usually competent and well intentioned, but similar to the seasoned entrepreneur who still engages in the disciplined exercise of preparing a business plan for each new venture, even the most experienced clinical trialist benefits from the structured practice of formally developing a complete proposal. Though it initially may seem burdensome or exhaustive (perhaps even exhausting), the process has proven reliable as a quality assurance mechanism. Often, simply by obliging investigators to defend the study’s scientific rationale and by sobering them to the gravity of a drug’s potential risks in human trials, flaws in the development plan are revealed. Moreover, because FDA reviewers are privy to and have critiqued myriad applications, their ability to foresee potential problems and to offer preemptive remedies further improves the quality of the proposed study and can be a real value-added resource for sponsors.

Beyond its direct impact on the integrity of drug development, the FDA’s fastidious reputation confers a less tangible but more pervasive effect on the health care system at large by engendering a public trust in available drugs and devices. Because an information imbalance between physician and patient is intrinsic to any health care system, trust is the gold standard that underpins the free flow of care; in short, the public needs to trust physicians and the tools of their trade (e.g., drugs, devices), or the social contract collapses. Although important checks on providers include state and federal licensing bodies, trial lawyers, and insur-

ance oversight, the public's confidence in available drugs and devices hinges on an effective FDA that provides impeccable quality assurance.

The medical community and the FDA share a common goal—advancing scientific discovery for the betterment of the public health. To that end, the FDA has assumed a proactive posture in maintaining transparency by educating and fostering collaboration to facilitate sound clinical development. It is hoped that as physician–investigators gain even a superficial understanding of the inner workings behind the veil of the FDA, their next trip through the regulatory dance will be more tolerable. Perhaps they may take solace in knowing that the process, though cumbersome at times, is the cornerstone of a drug regulatory system that is the most trusted and whose decisions are the most respected in the world.

Resources

The litany of rules and regulations may seem onerous, and because many have caveats that are beyond the scope of this

article, questions almost always arise. To address some of the more common issues, the FDA has created numerous guidance documents that are available on the FDA website. Other resources include 21 CFR 312.22 and 312.23, or the agency may be contacted directly.

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