HHS Public Access

Author manuscript

J Investig Med. Author manuscript; available in PMC 2015 May 18.

Published in final edited form as:

J Investig Med. 2009 August ; 57(6): 688–694. doi:10.231/JIM.0b013e3181afdb26.

Understanding FDA Regulatory Requirements for Investigational New Drug Applications for Sponsor-Investigators

M. E. Blair Holbein, PhD

Department of Clinical Sciences, the University of Texas Southwestern Medical Center at Dallas, TX

Abstract

Clinical investigators invoke a number of specific regulatory requirements if their study includes use of a pharmaceutical agent. Studies using a drug that has not been approved by the Food and Drug Administration (FDA) or for indications not in the approved labeling may require filing an Investigational New Drug (IND) application with the FDA. If a study meets specific regulatory exemption criteria, then an IND may not be needed. Individual investigators may meet the FDA definition of a sponsor-investigator, in which case the application process is generally less complicated than for commercial sponsors, and this review addresses only this circumstance. Filing an IND requires completion of 3 sets of forms: 1 detailing the study (FDA Form 1571), 1 providing information about the investigator and study site (FDA Form 1572), and 1 certifying that the study is registered in the national database of clinical trials (FDA Form 3674). If the IND is approved, the study may begin 30 days after the FDA acknowledges receipt and assigns an IND. If the FDA requires additional information or if the study is placed on a “clinical hold,” the study must not proceed. While the IND is active, the investigator must also continue to meet a set of regulations for monitoring the study and reporting to the FDA.

Keywords

food and drug administration; investigational new drug; sponsor-investigator; federal regulations; investigational drug studies

Clinical investigators initiating a drug study invoke a number of specific regulatory requirements beyond those mandated for protection of human subjects in clinical trials.[1] These regulatory requirements for drug studies address the safety and efficacy issues unique to the use of pharmaceuticals in the clinical research setting. The US Food and Drug Administration (FDA) is charged with the regulation of most drugs in addition to other products. This extends to regulatory authority over clinical research using these agents. Therefore, to conduct drug studies, an investigator must comply with FDA requirements. Failing to meet the FDA’s regulations can have legal and financial implications for the

Reprints: M. E. Blair Holbein, PhD, Department of Clinical Sciences, the University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Dallas, TX 75390-9066. Blair.Holbein@UTSouthwestern.edu.

The author declares no conflict of interest.

individuals conducting the research as well as the institutions associated with the research activities.

An initial part of the regulatory process involved for investigational drugs is notifying the FDA that a pharmaceutical agent will be used in an experimental way. This notification is called an Investigational New Drug (IND) application.[2] For drug trials conducted by the pharmaceutical industry or other commercial sponsors, individuals highly trained and expert in meeting the regulations address the regulatory requirements. However, for individual investigators who are not as familiar with the requirements and regulations, filing an IND can be intimidating and may be perceived as an impediment to conducting drug studies. It is interesting to note that the majority of IND submissions are noncommercial.[3] Thus, individual clinical investigators frequently meet the regulatory requirements necessary to conduct investigational drug studies. This review is intended to address the simplest scenario in which an individual investigator initiates and conducts a drug study that requires filing and maintaining an IND with the FDA. In addition, for the sake of simplicity, this review only addresses regulatory requirements for studies conducted at a single site. Figure 1 depicts the IND application process for a sponsor-investigator.

THE REGULATORY ENVIRONMENT AND FDA ROLE

The FDA is an agency in the US Department of Health and Human Services charged with assuring the safety, efficacy, and security of human as well as veterinary drugs in addition to other areas of regulatory authority. The agency is also responsible for facilitating advances in medications. The FDA is a large and rather complex federal agency with a number of centers, divisions, and offices located both centrally in the Washington Metropolitan Area as well as numerous regional offices in the United States. For the purposes of regulatory supervision of investigational drugs in human clinical trials, the centers primarily involved are the Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health, and the Center for Biologics Evaluation and Research (CBER). Within these centers are offices with regulatory, functional, or therapeutic focus. Most pharmaceutical drug products, both synthetic and biologic, fall under the regulatory supervision of CDER, including most drug studies. The CBER regulates biological and related products including blood, vaccines, allergenics, tissues, and cellular and gene therapies, so only a small number of specialized drug studies would come under CBER jurisdiction.[4] The FDA Web site publishes comprehensive organizational charts with the names and contact information of officials.[4–6]

The primary set of federal laws establishing FDA authority as well as codification of the regulations is the Federal Food, Drug, and Cosmetic Act. The specific section of these laws covering an IND is in Part 312 of the Code of Federal Regulations (CFR). There are also other parts of the CFR that impact the conduct of clinical studies using pharmaceutical products. Table 1 lists the more important sections relevant to individual investigators. All of these regulations are readily accessible at the FDA Web site in a searchable format.[7] Finally, Federal law dictates that in order for a drug to be transported or distributed across state lines, it must have an approved marketing application. Because drugs to be used in most clinical trials will be shipped across state lines, the sponsor must seek an exemption

from that legal requirement. The name, “Notice of Claimed Investigational Exemption for a New Drug,” refers to this exemption. The more commonly used name is an “IND.”

The stated purpose of an IND is “to ensure that subjects will not face undue risk of harm” in a clinical investigation that involves the use of a drug.[8] Hence, to authorize a drug study in humans, the FDA requires sufficient information to assess the safety of the intended research study. The IND is the mechanism by which by the investigator or sponsor provides the requisite information to obtain authorization to administer an investigational agent to human subjects (or an approved drug used for a new indication or a new population of patients). All studies that use a drug not approved for marketing by the FDA will always require an IND. By a rather broad set of definitions for a “new drug,”[9] all studies using not only new molecular entities or unapproved pharmaceuticals but also approved drugs used in unapproved indications, in new formulations, in new dosages, in a patient population that would be put at increased risk require an IND. Under specific criteria, an exemption from this IND requirement may be met.

For regulatory purposes, clinical investigations involving drugs are initiated by a “sponsor” who takes responsibility for the conduct of the study. This term applies to a number of different entities. A sponsor can be an individual, a commercial entity such as a pharmaceutical company, an organization, or a governmental agency. Sponsors may conduct large multicenter trials with unapproved drugs in the anticipation of submitting the results of such investigations in support of a New Drug Application or a change in the official labeling for an approved drug. Investigational New Drug applications for studies of this nature require a comprehensive dossier of information including animal studies, pharmacokinetic analyses, toxicology studies, and manufacturing information (CFR 312.23). A description of this type of complex commercial submission is beyond the intended scope of this article.

The FDA defines an “investigator” to be the “individual who actually conducts a clinical investigation (ie, under whose immediate direction the drug is administered or dispensed to a subject).”[2] Investigators may conduct clinical studies for a sponsor. However, individual investigators who initiate and conduct a clinical study, as well as being directly accountable for the administration or dispensing of the investigational drug, are designated as a sponsor-investigator by the FDA. Clinical investigators at academic medical centers who are initiating clinical studies with a lawfully marketed drug to be used in a patient population or indication not within the official labeling often fit within this designation. Unlike a commercial sponsor initiating studies with an unapproved drug, often at multiple sites, a sponsor-investigator conducting an investigation at a single site will have a substantially less complicated filing requirement. The sponsor-investigator obtaining the IND would then be the “holder” of the IND and thus would be responsible for the associated regulatory requirements. This “simplest case” is the subject of this review.

WHEN IS AN IND NOT NEEDED FOR STUDIES INVOLVING MARKETED DRUGS?

The use of a placebo does not require an IND if the investigation does not otherwise require submission of an IND. Clinical trials that use an FDA-approved drug within the approved

labeling do not need an IND. However, clinical investigations initiated by sponsor-investigators frequently make use of FDA-approved drugs in populations or indications not addressed in the approved labeling. Clearly, such studies have a markedly different risk profile than a phase 1 or 2 study with a new molecular entity. Correspondingly, the FDA has a mechanism to bypass filing an IND if specific exemption criteria are met, which address the safety of the proposed study as well as stated limits on the noncommercial intent of the study. The exemption criteria only apply to studies using marketed pharmaceuticals commercially available in the United States. These criteria are listed in CFR 312.2 (b). Importantly, all studies must also be approved by an institutional review board (IRB), and informed consent procedures must be met as set forth in 21 CFR 50 and 56 in addition to meeting the exemption criteria. Note that studies involving an "exception from informed consent" all require an IND and cannot claim an exemption under these provisions.

For sponsor-investigators initiating a study with an approved drug, the exemption that most directly relates to safety issues is CFR 312.2 (b) (iii). This criterion addresses whether the study "significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product" specifically regarding a route of administration, dosage level, dosage form, new proportions, use in a patient population, or any other relevant study aspect that affects safety of drug use. For example, this might include an exemption for studying the use of a drug in a disease entity not in the approved labeling but is reasonably supported by the underlying pharmacology and without any anticipated increase in the risk of adverse effects from the drug for the study population.

The noncommercial context of the exemptions assures that the results will not be used to support a change in labeling for a new indication or a significant change in the advertising for the product. Such studies are typically undertaken by a pharmaceutical or device manufacturing company or other commercial entity. Analogously, there must be a compliance with the requirements that the study does not amount to a commercial distribution or marketing of a new drug. The provisions do allow for charging the subject for the drug under narrow specified circumstances, however.

Notably, the FDA has issued additional guidance for exemption from IND for drugs used to treat cancer.[10] Further provisions are made allowing exceptions for studies involving in vitro diagnostic biological products, blood grouping serum, reagent red blood cells, and anti–human globulin.

If a study does not meet the exemption criteria, then an IND may be required. If the sponsor-investigator has any question whether the study meets the exemption criteria, it is usually appropriate to contact the FDA to clarify the regulatory requirements. The local IRB may also be able to help the investigator determine whether the criteria for safety are adequately addressed in the study so as to avoid the need for an IND. Unless it is clear that an IND is required, contacting the FDA for clarification or discussion with the IRB can save a significant amount of time and effort. The organizational charts for CDER can be used to guide the initial telephone contact. A project manager in the relevant division can provide significant help not only in addressing exemption requirements but also in the IND

application process. Note that the FDA will not accept an application or review a study that is exempt under the stated provisions.

INVESTIGATIONAL NEW DRUG APPLICATION

There are different categories and types of IND. For individual sponsor-investigators, the IND will be categorized as a "research IND." The other category is "commercial IND." The FDA categorizes IND applications as "commercial" if the sponsor is either a corporate entity or one of the institutes of the National Institutes of Health or if it is clear that the drug may be eventually commercialized. The FDA has issued numerous Guidances regarding filing an IND. Most (80%) of the Guidances are addressed to industry (ie, commercial).[11]

Within the stated categories are a number of other designations. An "investigator IND" is a research IND submitted by an investigator who initiates and conducts the study including the immediate supervision of the use of the study drug. This would typify the studies conducted by sponsor-investigators. Additional IND types include an "emergency IND" that allows the FDA to authorize the use of an experimental drug in emergency situations that do not allow time for filing an IND or for patients who do not have access to the drug under protocol. Similarly, the "treatment IND" allows access for subjects in serious or life-threatening situations to experimental drugs that have shown promise in early clinical testing but before final FDA review. Lastly, an "exploratory IND" is conducted early in phase 1 studies of an agent. These studies involve limited human exposure and are designed without therapeutic intent (screening, microdosing, etc) and are preliminary to conducting more descriptive traditional safety and tolerance studies and allow for greater flexibility in the drug development process.[9]

In addition, for antimicrobial products, the FDA has a consultation program to facilitate communications between the sponsor and the FDA before filing an IND involving the treatment of bacterial, fungal, and viral infections, opportunistic infections, emerging infections (including naturally emerging diseases and potential biothreat agents), topical microbicides directed at prevention of HIV transmission, and transplant rejection.[12]

GENERAL PRINCIPLES

The general scheme for an IND includes providing information in general areas: animal pharmacology and toxicology studies, manufacturing information, and clinical protocols and investigator information. The intent is to provide the FDA information to allow a review that assures the safety of participants. For sponsor-investigators, typically, the IND will not require the same extensive information including preclinical studies or manufacturing and process information as would be required for a commercial sponsor applying for an IND for a yet unapproved drug, especially early in its development. To an extent, this is because the studies conducted by sponsor-investigators usually use FDA-approved pharmaceuticals. Note that a sponsor-investigator has responsibilities as both a sponsor and an investigator, and investigations conducted under this designation are frequently single-site studies.

INVESTIGATIONAL NEW DRUG GUIDANCE AND PLANNING

For commercial sponsors, the drug development is a far more complex and involved process compared with sponsor-investigator. Analogously, the pre-IND process is more formalized and often entails scheduled meetings or a teleconference. For sponsor-investigator, most questions are typically less complicated. Nonetheless, individual investigators can and should make use of the agency resources. The FDA Web site has downloadable forms, descriptions of the IND application process, and listings of guidance on the completion of the forms and clerical requirements.[13] The FDA has issued a Guidance that addresses the IND submission process specifically for sponsor-investigators.[14] An extensive information for sponsors to guide preclinical and phase 1 studies and pre-IND consultations is also listed. The FDA makes contact information for both CDER and CBER officials available on the FDA Web site. Questions about the IND process can be directed to the appropriate office or division, generally by telephone or email.

FDA FORM 1571

The IND application, FDA Form 1571, provides the structure to present the information about the proposed research. By definition, the sponsor is the single individual initiating and taking responsibility for the study. Hence, an individual investigator who initiates (eg, designs, obtains funding) and conducts the trial meets the criteria of a sponsor-investigator. Note especially, even if a pharmaceutical company will supply drugs or placebos, the individual investigator is still the named sponsor. For sponsor-investigators, parts of the information required on the 1571 overlap and are covered by the FDA Form 1572.

Form 1571 is used by all applicants, commercial or research investigators, and there are several sections that do not apply to a sponsor-investigator. Likewise, because the IND from the sponsor-investigator involves the use of an FDA-approved drug, several responses in the 1571 are abbreviated, amended, or even omitted compared with a pharmaceutical industry sponsor. Specifically, no designation is needed for Phase of Study (section 8), IND Number (section 6) is left blank with initial application, Contract Research Organization (section 13) should be marked “no,” and contact information for sponsor representative (sections 18 and 19) are left blank. Finally, the serial number is “0000” with the initial application (section 10). Subsequent IND amendments increase the serial number by 1 in the order of submission.

Because the study drug is a commercially available product, the information required by the FDA will be modified for a sponsor-investigator compared with an industrial sponsor. If the marketed drug will be used “without modification to its approved packaging,” the 1571 should contain the trade name, generic name, dosage form, strength, and lot number. Drug Master Files (21 CFR 314.42), Product License Applications (21 CFR Part 601), or the Investigator’s Brochure are generally not required.

If a product will be provided in a nonapproved form, then manufacturing and controls information, pharmacology and toxicology data, or data from prior human studies will be required, unless that information has previously been submitted to FDA. If this is the case, then a means for the FDA to reference the previous information will be needed. Typically,

this can be done via a letter from the original sponsor that authorizes access and includes the file identification (IND/Drug Master File/New Drug Application) number. If the dosage form will be modified by the investigator, then manufacturing and controls information, pharmacology and toxicology data, or data from prior human studies may be required. Discussion with the FDA can help clarify what additional information is needed.

The section entitled. “Contents of the Application” (section 12), is likewise abbreviated for most sponsor-investigator submissions. For this section, items 2, 3, and 4 (Table of Contents, Introductory Statement, and General Investigational Plan, respectively) may be addressed in the cover letter. The information detail is not dissimilar from information required by most local IRBs. Projects using commercially available pharmaceutical products that will be used without modification can be adequately described by reference to their standard identifiers (names, dosage forms, and strength). The “Environmental Assessment” (section 7) can be addressed with a categorical exclusion statement, “I claim categorical exclusion (under 21 CFR 25.31[e]) for the study(ies) under this IND. To my knowledge, no extraordinary circumstances exist.” However, if the pharmaceutical agent is modified in any way, additional information may be required. All manufacturing (or compounding) information should be submitted. Likewise, if the agent has the potential for drug dependence or abuse, if it is radioactive, or if it will be used in pediatric studies, additional information may be needed. A more detailed description of the information required is contained in 21 CFR 312.23.

For all forms in the IND application, the sponsor-investigator is the single person responsible for the conduct, progress, review, and evaluation of safety associated with the trial. It is important to provide complete and consistent contact information for all forms and correspondence. The correspondence address and the telephone number listed should also indicate the most effective contact information for the individual sponsor-investigator, including a daytime telephone number.

There are slight differences in completing and submitting the 1571 for CBER than for CDER.[15] Owing to the highly specialized nature of CBER studies, investigators should consult CBER directly for guidance.

FDA FORM 1572

This form comprises the “Statement of Investigator.” The information requested regarding the investigator’s qualifications and contact information can often be met by an academic curriculum vitae, noting on the form that the information is contained in the attachment. Note also that sponsor-investigator sections of the FDA Form 1572 satisfy the information requirements for specific sections of the FDA Form 1571.

FDA FORM 3674

The IND application must be accompanied by a certification that the requirements of section 402(j) of the Public Health Service Act have been met. United States Public Law 110-85 (FDA Amendments Act of 2007), Title VIII, Section 801, requires registration of “applicable clinical trials.”[16] All controlled clinical investigations that use a drug regulated

by the FDA must be registered with the exception of phase 1 studies. The intent of the legislation requiring that applicable clinical studies be registered is to ensure that the public has access to information about certain clinical trials that are being conducted, including access and results. This registration process is done via filing trial information with the Protocol Registration System of clinical trials run by the US National Library of Medicine at the National Institutes of Health.[17] Form 3674 certification requires the appropriate ClinicalTrials.gov identifiers (NCT numbers) that are obtained from registration. The FDA has issued draft guidance on the certification process.[18]

For a sponsor-investigator filing an IND, the responsibility for registration rests with the investigator. For most sponsor-investigators, the institution with the regulatory oversight for the conduct of the study is probably already a registered research entity with a registration account, and the investigator will not need to create a separate registration account.

SUBMITTING AN IND

A cover letter should accompany the IND submission. Include identification of the sponsor-investigator, a clear indication that this is an initial IND submission, and ensure that the contact information is clear and complete. Because this is the initial IND submission, there is no IND number. Each sequential correspondence regarding an IND should carry a sequential identifying serial number, which, in this initial submission, would be “0000.” Clearly indicate the title of the study. Take care that the contact information exactly matches that in 1571 and 1572 to avoid any delays in communications. Because this process is time-sensitive, delays due to communications errors can have significant consequences. Send the submission to the attention of the division that oversees the therapeutic area for the study drug. If there has been a discussion with an individual at CDER or CBER, they may direct the submission to a specific recipient. The IND should be submitted in triplicate, namely, 1 original and 2 copies. No special binders or packaging is required.

Submission addresses:

IND submissions to CDER:	Food and Drug Administration
For a Drug:	Center for Drug Evaluation and Research Central Document Room 5901-B Ammendale Rd Beltsville, MD 20705-1266
IND submissions to CDER:	Food and Drug Administration
For a Therapeutic Biological Product:	Center for Drug Evaluation and Research Therapeutic Biological Products Document Room 5901-B Ammendale Rd Beltsville, MD 20705-1266
IND submissions to CBER:	Center for Biologics Evaluation and Research
For a Biological Product:	HFM-99, Room 200N 1401 Rockville Pike Rockville, MD 20852-1448

FOLLOWING RECEIPT OF IND BY THE FDA

The IND will be routed to the appropriate division for review. A letter of acknowledgment will be sent to the sponsor-investigator. This letter provides the assigned IND number, date received, and the name and telephone number of the FDA project manager to whom questions about the application and further correspondence should be directed. The IND becomes effective 30 days after the stated FDA receipt date unless the FDA sends notification otherwise. The FDA generally does not send a letter notifying the sponsor-investigator of approval. Studies may begin after the 30-day interval, if the FDA does not notify the investigator otherwise. If the FDA requests further information or clarification, the 30-day window is not affected unless the FDA gives an indication that the study is placed on a complete or partial clinical hold. A partial hold will allow a specific part of the study to begin while the other part cannot be started. A clinical hold explicitly means that the study may not begin.

RESPONDING TO A CLINICAL HOLD

A clinical hold occurs when the FDA contacts the sponsor-investigator and indicates that the study cannot start pending resolution of questions or concerns. The specific questions that the agency has are conveyed to the investigator, typically by telephone followed by a detailed letter. Upon receipt of the list of FDA concerns, the sponsor-investigator should respond to the issues cited in the letter in their entirety. The cover letter that accompanies the response should clearly indicate the response with a heading, “Clinical Hold Complete Response.” Likewise, the accompanying FDA Form 1571 should indicate by serial number and checkbox that it is a response to a clinical hold. The “clock” on the review process does not begin until all issues have been addressed and the responses have been received and acknowledged by the FDA.

The FDA should reply within 30 days of the receipt of the complete response from the sponsor-investigator. The agency will issue a letter that lifts the clinical hold (the study may proceed), places the study on partial hold (specific restrictions), or that the study continues to be on hold pending resolution of continuing questions. Until the FDA indicates that a hold has been removed, a study must not proceed.

REGULATORY REQUIREMENTS FOR AN IND DURING STUDY AND AT COMPLETION

Submission of an IND begins the regulatory process under which a study progresses. There are ongoing obligations that the sponsor-investigator agrees to with the signature of the FDA Form 1571. In brief, the sponsor-investigator agrees to keep the IND current, to notify the FDA about any safety issues, to file annual reports, and to notify the FDA when the study ends for any reason. Any amendment to the IND must be filed with the FDA.

Protocol Amendments (21 CFR 312.30)

Provisions in this section allow for the filing of a new protocol, changes to protocol, or the addition of a new investigator. Changes can include any increase or decrease in drug

exposure by way of dose or duration, a change in the subject population's inclusion or exclusion, or a change in monitoring for safety. The IRB with oversight responsibility must likewise be notified and give approval. The amended protocols must be submitted before implementation with the exception of a protocol change intended to eliminate an apparent immediate hazard to subjects. In this case, the IRB is notified in accordance to regulations and the FDA subsequently notified.

Information Amendments (21 CFR 312.31)

Similar to amendments in the research protocol, changes in the essential information regarding the IND that are not within other reports are added via an "information amendment." This can include changes in toxicology, chemistry, or other technical information. All amendments should be clearly labeled as to the contents (eg, "Information Amendment: Pharmacology- Toxicology"). These amendments should not be issued more frequently than 30-day intervals.

Safety Reports (21 CFR 312.32)

Sponsor-investigators are responsible for investigating all safety concerns brought to their attention. They must notify the FDA, all participating investigators, and the local IRB of any adverse experience associated with the use of the drug that is both serious and unexpected in a written IND safety report. This equally applies to any finding that suggests a significant risk for human subjects. The time frame for reporting is no later than 15 calendar days after the sponsor's initial receipt of the information. The report should be made via FDA Form 3500A (MedWatch) or in a narrative format. The report should be clearly labeled "IND Safety Report." The sponsor-investigator is responsible for analyzing the significance of the report in context of other safety reports.

In the case of either death or life-threatening experience associated with the study drug, notification of the FDA must be made no later than 7 calendar days after the sponsor-investigator's initial receipt of the information. This should be done either by telephone report or by facsimile transmission. The local IRB should likewise be informed.

Annual Reports (21 CFR 312.33)

Annual reports must be filed by the sponsor-investigator. The filing deadline is within 60 days of annual date of the IND. If there are multiple protocols under a single IND, each should be identified by title and have a summary report. The investigator should include the status of each study still in progress and each study completed during the previous year. The progress of enrollment should be tallied including total number of subjects planned, number entered to date (by age, sex, and race), the number of subjects whose participation in the study was completed as planned; and the number who dropped out of the study for any reason. If the study has been completed, or if interim results are known, a brief report of results should be included. A summary of all IND safety reports submitted during the past year should be included. A summary of any significant changes in the pharmacology, toxicology, or technical information should be included. Lastly, the plan for the coming year should be stated.

WITHDRAWAL, TERMINATION, AND INACTIVATION

A sponsor may withdraw an IND at any time. The FDA and all investigators should be notified and all drug stocks accounted for. If the withdrawal is for safety reasons, the notification must provide a report of the reasons. In this case, the reviewing IRB must also receive notification. When a study ends, the sponsor-investigator must notify the FDA.

The FDA may terminate an IND. This is usually done in cooperation with the sponsor but may be unilateral. The sponsor is allowed a response to an FDA-initiated termination, but the time frame is quite limited.

A study may be placed on “inactive status” by the sponsor or the FDA. This may be due to a number of reasons such as delays in implementation, insufficient enrollment, failure to file annual reports, or failure to respond to FDA inquiries. An IND that remains in inactive status for 5 or more years may be terminated.

MONITORING RESPONSIBILITIES FOR SPONSOR-INVESTIGATORS

Monitoring of the study is an ongoing responsibility. The regulations explicitly charge the sponsor-investigator with accountability. Sponsors must monitor and assure that human subjects are adequately protected, that all reported clinical data are accurate and complete, and that the conduct of the trial is in compliance with the protocol and regulations. Unique to drug studies is the added responsibility for drug accountability. Investigators must also correct any problems that occur during the study or terminate the study and notify their IRB, the FDA, and other investigators.

CONCLUSIONS

Meeting the regulatory requirements for conducting drug studies is an essential part of doing clinical research. Filing and maintaining an IND may seem intimidating. But a sponsor-investigator, working with the FDA, can meet the regulatory obligations and can proceed with their research study with minimal delay. The FDA makes it easy to contact the officers who are responsible for handling the IND. The guidance for filing the necessary documents is comprehensive and readily available from the FDA Web site. Filing and maintaining an IND should not be regarded as an impediment to doing clinical drug research.

ACKNOWLEDGMENT

The author thanks Rafia Bhore, PhD, for her helpful comments during the preparation of the manuscript.

Supported in part by National Institutes of Health Clinical and Transitional Science Award Grant UL1 RR024982.

REFERENCES

1. Federal Food. Drug, and Cosmetic Act.
2. CFR Title 21 Part 312. Investigational New Drug Application.
3. [Accessed June 16, 2009] CDER Original INDs Received, Calendar Years 1986–2006. 2007 Jan 29. Available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/UCM165257.pdf.

4. [Accessed June 16, 2009] Center for Biologics Evaluation and Research Organization. 2009 May 28. Available at: http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135943.htm.
5. Center for Drug Evaluation and Research Organization. [Accessed June 16, 2009] 2009 May 28. Available at: http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135674.htm.
6. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. [Accessed June 16, 2009] Available at: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OrganizationCharts/UCM144011.pdf.
7. [Accessed May 14, 2009] CFR Title 21 Database Search. 2008 Apr 1. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312.
8. Guidance for Industry, Investigators, and Reviewers, Exploratory IND Studies. [Accessed June 16, 2009] Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078933.pdf.
9. Code of Federal Regulations Title 21 Part 310. New Drugs.
10. Guidance for Industry. [Accessed June 16, 2009] IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071717.pdf.
11. Investigational New Drug (IND) Guidances. [Accessed June 16, 2009] 2009 Apr 30. Available at: http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/InvestigationalNewDrugINDorDeviceExemptionIDEProcess/ucm094297.htm.
12. Division of Antiviral Products—ODE IV Pre-IND Consultation Program. [Accessed June 16, 2009] Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/ucm077776.htm.
13. Investigational New Drug (IND) Application. [Accessed June 16, 2009] 2009 Jun 2. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ default.htm.
14. Information for Sponsor-Investigators Submitting Investigational New Drug Applications (INDs). [Accessed June 16, 2009] 2009 Apr 30. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm071098.htm.
15. Investigational New Drug (IND) or Device Exemption (IDE) Process (CBER). [Accessed June 16, 2009] 2009 Jun 15. Available at: http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/InvestigationalNewDrugINDorDeviceExemptionIDEProcess/default.htm.
16. US Public Law 110-85 (Food and Drug Administration Amendments Act of 2007), Title VIII, Section 801.
17. Protocol Registration System Information. [Accessed May 14, 2009] Available at: https://register.clinicaltrials.gov/.
18. Guidance for Sponsors, Industry, Researchers, Investigators, and Food and Drug Administration Staff. [Accessed June 16, 2009] Certifications to Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance With Section 402(j) of the Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007. 2009 Jun 8. Available at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm125335.htm.

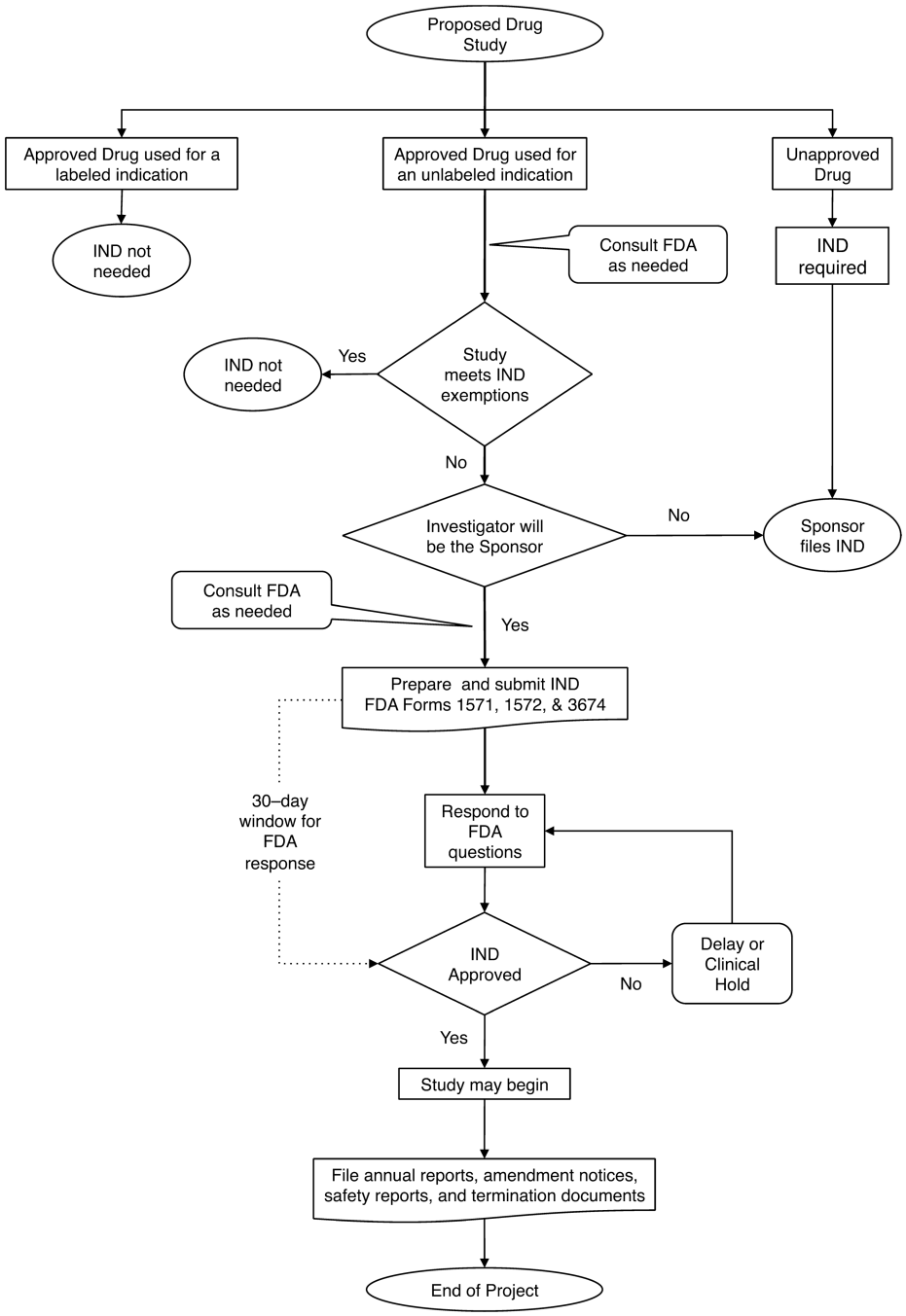

FIGURE 1.

Flowchart for a clinical drug study that may require an IND application for an investigator-sponsor.

TABLE 1

Federal Regulations That Apply to the IND Application Process

Code of Federal Regulations Title 21 Food and Drugs	
21 CFR Part 312	IND application
Subparts and sections discussed in text	
312.2	Applicability (exemptions listed in (b))
312.23	IND content and format
312.30	Protocol amendments (reporting requirements)
312.31	Information amendments (reporting requirements)
312.32	IND safety reports (reporting requirements)
312.33	Annual reports (reporting requirements)
312.38	Withdrawal of an IND
312.42	Clinical holds and requests for modification.
312.44	Termination
312.45	Inactive status
312.50	Responsibilities of sponsors
312.60	General responsibilities of Investigators
312.61	Control of the investigational drug
312.62	Investigator recordkeeping and record retention
312.64	Investigator reports
312.66	Assurance of IRB review
312.68	Inspection of investigator’s records and reports
312.69	Handling of controlled substances
312.70	Disqualification of a clinical investigator
Other relevant regulations	
21 CFR Part 314	IND and NDA applications for FDA approval to market a new drug (new drug approval)
21 CFR Part 316	Orphan drugs
21 CFR Part 50	Protection of human subjects
21 CFR Part 56	IRBs
21 CFR Part 201	Drug labeling
21 CFR Part 54	Financial disclosure by clinical investigators