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RESEARCH ARTICLE

NEW APPROACH OF INVESTIGATIONAL NEW DRUG APPLICATION FOR SPONSER- INVESTIGATOR IN PHARMACEUTICAL INDUSTRY AS PER FDA GUIDELINES

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A B S T R A C T

Investigation of new drug is a submission to food and drug administration (FDA) requesting permission to initiate a clinical study of new drug products. 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. The purpose of this article is to assist sponsor-investigators in preparing and submitting complete investigational new drug applications (INDs) to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA). Sponsor-investigators seeking to do clinical research often do not have the regulatory knowledge or the resources to hire experts to help them with the IND submission process. Although not an exhaustive step-by-step instruction manual, this article highlights certain elements of this process to facilitate a sponsor-investigator's successful submission of an IND. This article also discusses the IND review process and general responsibilities of sponsor-investigators related to clinical investigations.

INTRODUCTION

Clinical investigators initiating a drug study invoke a number of specific regulatory requirements beyond those mandated for protection of human subjects in clinical trials. 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 (USFDA) 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 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. 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. 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.

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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 Guidance's regarding filing an IND. Most (80%) of the Guidance's are addressed to industry (i.e., commercial).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. 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), and topical microbicides directed at prevention of HIV transmission, and transplant rejection.

Guidelines for investigational new drug applications prepared and submission method by sponsor investigator

The purpose of this guidance is to assist sponsor-investigators in preparing and submitting complete investigational new drug applications (INDs) to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA). Sponsor-investigators seeking to do clinical research often do not have the regulatory knowledge or the resources to hire experts to help them with the IND submission process. Although not an exhaustive step-by-step instruction manual, this guidance highlights certain elements of this process to facilitate a sponsor-investigator's successful submission of an IND. This guidance also discusses the IND review process and general responsibilities of sponsor-investigators related to clinical investigations. It is important to note that this guidance does not include discussions of all of the requirements that apply to the IND submission and review process or to conducting clinical research. Sponsor-investigators should review in full these requirements, which are described in the Code of Federal Regulations (CFR).Many sections of the regulations that apply to INDs are described or referred to in this guidance (e.g., 21 CFR parts 50, 56, and 312).

Details of the informational content of an IND as well as information needed to complete required forms also are provided throughout this guidance. In addition, the guidance provides useful references to other IND-related information resources. This guidance is directed primarily at those sponsor-investigators who are seeking to evaluate a drug that is either currently approved or is being investigated under an existing IND for a different indication. This guidance is not intended for sponsor-investigators who are developing a drug for commercial purposes (i.e., seeking market approval or licensure) and thus does not focus on certain regulatory requirements that involve exchange of information or materials between a sponsor and investigator. This guidance does not apply to clinical trials that do not need to be conducted under an IND (i.e., that qualify for an IND exemption).This guidance also is not intended to address expanded access INDs or biologic devices. Sponsor-investigators should refer to available FDA regulations and guidances and/or contact the relevant CDER or CBER review division to discuss and obtain additional information for preparing INDs not covered by this guidance (if necessary). In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidance's means that something is suggested or recommended, but not required.

Background

Generally, FDA regulations require sponsors, including sponsor-investigators, who wish to evaluate a drug or biological product in humans to submit an IND to the FDA (21 CFR part 61312).The FDA's primary objectives in reviewing an IND are to help protect the rights and safety of subjects and, in phases 2 and 3, to help ensure that the quality of the clinical trial is adequate to evaluate the drug's effectiveness and safety. Sponsor-investigators who are seeking to evaluate a marketed unapproved new drug (i.e., a drug marketed in the United States that does not have the required FDA approval for marketing) in a clinical trial should contact the relevant CDER or CBER review division. For information about whether a trial has to be conducted under an IND, see 21 CFR 312.2, and the guidance for clinical investigators, sponsors, and IRBs Investigational New Drug Applications (INDs)-Determining Whether Human Research Studies Can Be Conducted Without an IND. When final, this guidance will represent the FDA's current thinking on this topic. 6 Part 312 applies, with certain exceptions, to all clinical investigations of drugs and biological products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 et seq.)). An investigational new drug, for which an IND that complies with part 312 is in effect, is exempt from the premarketing approval requirements that would otherwise apply to new drugs and may be shipped lawfully for the purpose of conducting clinical investigations of that drug.

A sponsor takes responsibility for and initiates a clinical investigation. A sponsor can be an individual or Pharmaceutical company, governmental agency, academic institution, private organization, or other organization. An investigator is the individual who actually conducts the investigation (i.e., under whose immediate direction the investigational drug is administered or dispensed to a subject). A sponsor-investigator is an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term, as defined in FDA regulations, does not include any entity other than an individual. As the name

suggests, a sponsor-investigator assumes the responsibilities of, and must comply with, FDA regulations applicable to both a sponsor and an investigator. These responsibilities include the submission and maintenance of an IND.

Clinical trial protocol

A detailed description of the intended investigation, depending on the drug development phase.

Chemistry, manufacturing, and control information

Sufficient information that ensures the proper identification, quality, purity, and strength of the investigational drug.

Pharmacology and toxicology information

A summary of nonclinical (in vitro or 99 animals) data that is intended to support the safety of the proposed clinical trial.

Summary of Previous Human Experience

If applicable, a summary of all clinical trial results intended to support the safety of the proposed clinical trial. A sponsor-investigator may not be required to submit an IND for, for example, a study of a lawfully marketed drug if the criteria for an IND exemption are met. Furthermore, in some circumstances, even if a sponsor-investigator is required to submit an IND, the IND may not need to include all of the information listed above. For example, if a sponsor-investigator is proposing to evaluate a drug that is the subject of an existing IND, a sponsor-investigator can seek a letter of cross-reference authorization from the sponsor of that IND (called the commercial sponsor) that permits the sponsor-investigator to refer the FDA to the information contained in the commercial sponsor's IND. If the sponsor-investigator is studying an FDA-approved prescription or nonprescription drug, even if an IND is required, some of the information needed for an IND submission can be found in the FDA-approved labeling.

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.

Certain information required for an ind submission:

Required forms for ind submission

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. The FDA has issued a Guidance that addresses the IND submission process specifically for sponsor investigators. 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 FDAWeb site. Questions about the IND process can be directed to the appropriate office or division, generally by telephone or email.

Form fda 1571 investigational new drug application

A signed Form FDA 1571 is required for the submission of an IND to the FDA. A signed Form FDA 1571 documents the sponsor-investigator's agreement to refrain from beginning a clinical trial until 30 days after the official date that the FDA receives the IND (or unless the sponsor investigator receives earlier notification from the FDA that the trial may begin), to refrain from beginning or continuing a clinical trial covered by the IND if that trial is placed on clinical hold, to ensure that an institutional review board (IRB) in compliance with FDA regulations will be responsible for the initial and continuing review and approval of each proposed trial, and to conduct the trial in accordance with all other applicable regulations. This form is largely self explanatory and contains a brief series of fill-in-the-blanks and check boxes that describe and catalog the contents of the application. As such, it can serve as a road map for the sponsor investigator, a checklist, and as a cover sheet for the initial IND submission.

Form FDA 1572 Statement of Investigator

Before permitting an investigator to begin participation in an investigation, a sponsor is required to obtain a signed investigator statement, Form FDA 1572 Statement of Investigator (Form FDA 1572). As an investigator, a sponsor-investigator is also required to sign Form FDA 1572. By signing Form FDA 1572, the sponsor-investigator agrees to, among other things, conduct the trial in accordance with the protocol, ensure that the requirements relating to obtaining informed consent and IRB review are met, and comply with all requirements regarding the obligations of clinical investigators (e.g., recordkeeping, reporting adverse experiences).

Form F da 3674

The Food and Drug Administration Amendments Act of 2007 (FDAAA) was enacted on September 27, 2007. Title VIII of FDAAA added new section 402(j) to the Public Health Service Act (PHS Act) (42 U.S.C. 282(j)) and expanded the current National Institutes of Health (NIH) data bank known as ClinicalTrials.gov. FDAAA requires the responsible party, who could be the sponsor, or in certain instances, the principal investigator of particular clinical trials of human drugs, biological products, and devices (referred to in FDAAA as applicable clinical trials), to register the trials and to submit results information for inclusion in the Clinical Trials.

Introductory statement and general investigational plan

The introductory statement must include the investigational drug's name and all of its active ingredients, pharmacologic class, structural formula (if known), formulation of the dosage form to be used, the route of administration, and the broad objectives of the proposed clinical trial. There also must be a brief summary of previous human experience with the investigational drug including any investigational and marketing experience in other countries. For an investigational drug under commercial development, this information can be obtained from the commercial sponsor, and is most commonly submitted through a letter of cross-reference authorization to the commercial IND. For an FDA-approved prescription drug, the sponsor-investigator should be able to obtain all or most of this information from the drug's FDA-approved labeling, but additional information may be needed if the sponsor-investigator is studying an unapproved use or dose of the drug.

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 B0000. [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 copy. No special binders or packaging is required.

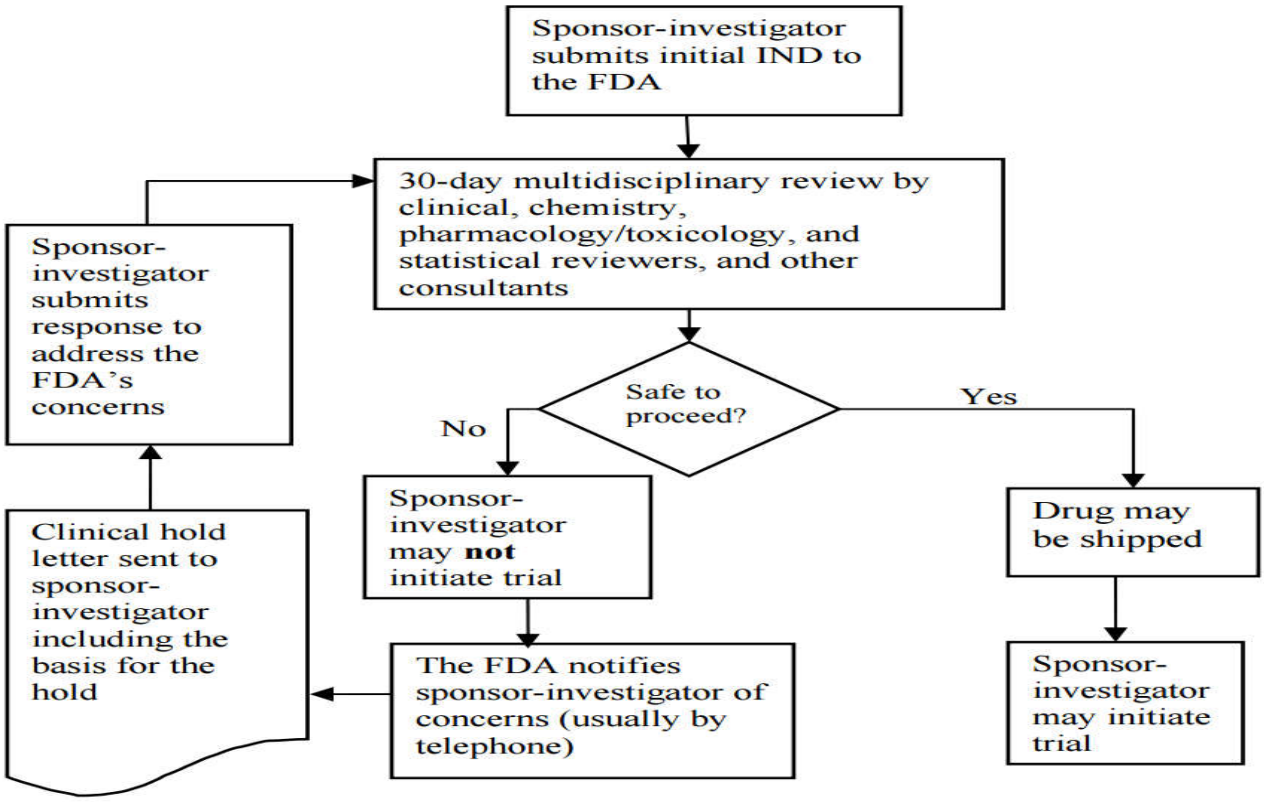

Figure 1 The ind review process

The general investigational plan must summarize the rationale supporting the proposed clinical trial (including the dose, schedule, and patient population), the indications to be investigated, the general approach to evaluating the investigational drug, the planned trial duration, any trial plans for the following year (along with an estimated number of subjects to be given the investigational drug in the trial), and any risks of particular severity or seriousness anticipated on the basis of toxicology. When the IND is for a single trial, the information should be directed at supporting and describing that trial.

The Ind Process And Review Procedure

After the FDA receives the IND, an IND Acknowledgement Letter will be sent to the sponsor investigator. The letter includes important information such as the assigned review division, IND number, division contact, and the official FDA date of receipt. The latter is important because by regulation the proposed trial may not be initiated until 30 calendar days after official FDA receipt. This time period allows the division's multidisciplinary review team, comprised of clinical reviewers, chemists, toxicologists, clinical pharmacologists, and project managers (along with a microbiologist and/or statistician depending on the indication and development phase), to review the proposed clinical trial

materials. This review generally includes, for example, the proposed investigational drug's formulation, toxicity, nonclinical pharmacology and toxicology, and any previous human experience information provided. In addition, many teams also may consider other proprietary studies and clinical trials in similar drugs and may perform literature searches. By the end of this 30-day review period, if the division makes the determination that it is safe to proceed with the clinical trial, the FDA may (e.g., to convey any comments regarding the submission) or may not contact the sponsor-investigator about its determination. Unless notified by the FDA within 30 days that a clinical hold has been placed, the trial can proceed as long as IRB approval has been obtained. If the division makes the determination within the 30-day review period that the trial should be placed on clinical hold, the FDA will notify the sponsor investigator as soon as possible after making that determination (usually by telephone) to not initiate the trial. Likewise, the sponsor-investigator will be notified promptly if the FDA makes the determination that a trial that has been initiated needs to be suspended, as further described in Figure 1, The IND Review Process, and section VI.A., Clinical Holds and Requests for Modifications.

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.

Ind Amendments

After the initial IND is submitted and is in effect, a sponsor-investigator must make changes to the IND as needed to ensure that the clinical investigations are conducted according to protocols included in the application. Sponsor-investigators also need to provide essential information on the IND that is not within the scope of any protocol amendment, IND safety report, or annual report. All these written communications to the FDA are called amendments to the IND. The division will review these amendments as they are received. It is important to identify in the amendment whether a reply from the FDA is expected. If the sponsor-investigator wants the FDA to comment on the submission, the amendment must include a request for an FDA reply (e.g., a specific request to review new information and respond by a certain proposed date), which can be included in a cover letter of an amendment. In addition to including this request in the amendment, the sponsor-investigator can also contact the review division directly (e.g., for an informal discussion or to request a teleconference). In contrast to the initial IND submission, if the IND is not on clinical hold, the sponsor investigator may implement changes to the IND immediately after sending the amendment to the FDA, without waiting 30 days (though new protocols and protocol changes to ongoing trials still require prior approval by an IRB unless the change to the protocol is necessary to eliminate apparent immediate hazards to human subjects). Note that the FDA reserves the right to suspend an ongoing trial (by placing it on clinical hold, as noted in section VI.A. Clinical Holds and Requests for Modifications) at any time a suspension is warranted. In some situations, it may be unclear whether a change to an existing protocol or a new protocol should be communicated as an amendment to an existing IND or under a new IND, or if a new 30-day review period at the FDA is warranted. In such situations, the sponsor-investigator should seek case-by-case guidance from the relevant CDER or CBER review division to minimize the chance of an unexpected clinical hold.

Safety reports

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 (Med Watch) or in a narrative format. The report should be clearly labeled BIND 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.

Ind Annual Reports

Within 60 days of the anniversary date that an IND went into effect, a sponsor-investigator must submit a brief annual report of the progress of the trial. The annual report is intended to update the review division as to all relevant developments over the preceding year. This annual report must contain certain information, including, but not limited to, the following:

- Individual trial progress (i.e., enrollment, dropouts) with results, if the trial has been completed or if interim results are known
- A narrative or tabular summary showing the most frequent and most serious adverse events by body system
- A summary of all IND safety reports submitted during the previous year
- A list of subjects who dropped out because of adverse events and a description of the adverse events
- New information regarding the investigational drug's actions (e.g., dose response), completed nonclinical studies, and any CMC changes, if available

- A general investigational plan for the coming year, significant foreign marketing developments

If a trial is completed, the final report should be submitted to the FDA, as should a list of any publications that result from the clinical trial. In addition to the submissions to the FDA, the sponsor-investigator should consider any responsibilities under Title VIII of FDAAA related to submission of data for applicable clinical trials to the NIH ClinicalTrials.gov data bank. Responsible parties have a statutory obligation to update clinical trial registration information on ClinicalTrials.gov (42 U.S.C. 282(j) (4) (C)). In addition, for certain applicable clinical trials that have been completed, summary trial results must be submitted (42 U.S.C. 282(j) (3)).

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. In contrast to a withdrawal, the sponsor-investigator can seek to reactivate the inactive IND by submitting a request to reactivate the inactive IND including a protocol amendment containing the proposed general investigational plan for the coming year and appropriate protocols with IRB approval. If the protocol amendment relies on information previously submitted, the plan should reference such information. Additional information supporting the proposed investigation, if any, should be submitted in an information amendment. The submitted information will be subject to a new 30-day safety review as described in section VI. The IND Process and Review Procedures. A trial under an IND on inactive status can only proceed 30 days after the FDA receives the protocol amendment.

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.

RESULT AND CONCLUSION

This article is mainly focused in recent activities in investigational of new drug application for sponsor-investigator in Pharmaceutical industry as per FDA guidelines, recently FDA published a draft guidance entitled "Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators: Guidance for Industry", which offers an alternative to benefit non-commercial individual investigators who prepare and submit an IND. This article offers sponsor-investigator with step-by-step information for INDs. Meeting the regulatory requirements for conducting drug studies is an essential part of doing clinical research. Filing and maintaining an IND may seen intimidating. But a sponsor instigator, working with 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 FDAWeb site. Filing and maintaining an IND should not be regarded as an impediment to doing clinical drug research.

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