

Required Amendments and Reports to a FDA-Accepted Investigational New Drug (IND) Application

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A. Protocol Amendments- 21 CFR 312.30

Once an IND application has been accepted by the FDA, the Sponsor of the application shall amend it as needed to ensure that the IND is current with regard to (1) all clinical protocols being conducted under the application; and (2) the version of the clinical protocol(s) that is (are) currently active. This section sets forth the requirements and procedures for the submission of new protocols and changes in previously submitted protocols.

1. New Clinical Study Protocol

Whenever the Sponsor of the IND application intends to conduct a clinical study with the investigational drug that is not covered by a protocol already contained within the respective IND, the Sponsor shall submit to the IND application/FDA a Protocol Amendment to include the protocol for the new clinical study.

The Sponsor shall submit a Protocol Amendment for the new clinical study prior to its implementation.

Content and Format

The Protocol Amendment shall be prominently identified as a “Protocol Amendment: New Protocol” and shall contain the following:

- A copy of the new clinical study protocol and a brief description of the most clinically significant differences between it and previously submitted protocols
- Reference, if necessary, to specific technical information contained within the IND application or within a concurrently submitted Information Amendment to the IND that the Sponsor is relying on to support the new clinical protocol submission. If the reference is made to supporting information already present in the IND application, the Sponsor shall identify by name, reference number, volume, and page number the location of the information.

If the Sponsor desires the FDA to comment on the new clinical protocol submission, a request for such comment and the specific questions that the FDA’s response should address.

Initiation of the New Clinical Study

The new clinical study may be initiated provided that two conditions are met: (1) the Sponsor has submitted the respective Protocol Amendment to the FDA; and (2) the protocol for the new clinical study has been approved by an Institutional Review Board (IRB) that functions in accordance with the FDA regulations of [21 CFR Part 50](#) and [21 CFR Part 56](#). (The Sponsor may comply with these two conditions in either order.)

2. Changes to a Previously Submitted Protocol

Changes to a Phase 1 Protocol

The Sponsor of the IND application must submit prospectively (i.e., prior to actual implementation of the changes) a Protocol Amendment describing any change in a Phase 1 clinical protocol that significantly affects the safety of the research subjects.

Revisions to a Phase 1 clinical protocol that do not significantly affect the safety of the research subjects should be reported to the FDA in the Annual Report to the IND application. 21 CFR Sec. 312.23(a)(6)

Changes to Phase 2 and 3 Protocols

The Sponsor of the IND application must submit prospectively (i.e., prior to actual implementation of the changes) a Protocol Amendment describing any change to a Phase 2 or 3 protocol that significantly affects the safety of the research subjects, the scope of the investigation, or the scientific quality of the study.

Examples Protocol Amendments

Examples of protocol changes requiring the submission of a Protocol Amendment include:

- Revisions to a Phase 2 or 3 clinical protocol that do not significantly affect the safety of the research subjects, the scope of the investigation, or the scientific quality of the study should be reported to the FDA in the Annual Report to the IND application.
- Examples of protocol changes requiring the submission of a Protocol Amendment include, but are not limited to:
 - Any increase in drug dosage or duration of exposure of individual subjects to the investigational drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.
 - Any significant change in the design of the protocol (such as the addition or deletion of a control group).
 - The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor the safety of the investigational drug.

Content and Format

The Protocol Amendment shall be prominently identified as a “Protocol Amendment: Change in a Protocol” and shall contain the following:

- A brief description of the protocol change and reference (date and number) to the previous submission that contained the clinical protocol that is being revised.
- Reference, if necessary, to specific technical information contained within the IND application, or within a concurrently submitted Information Amendment to the IND, that the Sponsor is relying on to support any clinically significant change to the previously submitted protocol. If the reference is made to

supporting information already present in the IND application, the Sponsor shall identify by name, reference number, volume, and page number the location of the information.

- If the Sponsor desires the FDA to comment on the change to the previously submitted protocol, a request for such comment and the specific questions that the FDA's response should address.

Implementation of Changes to the Protocol

Changes to the clinical protocol may be implemented provided that two conditions are met: (1) the sponsor has submitted the respective Protocol Amendment to the IND application/FDA; and (2) the changes to the clinical protocol have been approved by the Institutional Review Board (IRB) that has responsibility for oversight of the initial protocol. (The Sponsor may comply with these two conditions in either order.)

Note that a protocol deviation intended to eliminate an apparent *immediate hazard to a research subject or group of research subjects* may be implemented immediately provided that the responsible IRB is notified. Such deviations should be reported to the IND application/FDA at the time of the Annual Report to the IND application. If the deviation is to be implemented as a permanent change to the protocol, a corresponding Protocol Amendment should be submitted to the IND application/FDA in accordance with the criteria specified above and approval of the change should be obtained prospectively from the responsible IRB.

3. New Investigator

The Sponsor of the IND application shall submit a Protocol Amendment when a new Investigator (i.e., study site principal investigator) is added to carry out a previously submitted protocol.

Timeline

The Sponsor shall notify the IND application/FDA of the new investigator within 30 days of the investigator being added. Protocol Amendments to add a new investigator or to provide additional information about investigators may be grouped and submitted at 30-day intervals.

Content and Format

The Protocol Amendment shall be prominently identified as a "Protocol Amendment: New Investigator" and shall contain the Investigator's name; address; a statement of the Investigator's qualifications to conduct the protocol; the name of each Sub-investigator (e.g., other health professionals, research coordinators, research fellows, residents) participating in the conduct of the protocol under the supervision of the Investigator; the name and address of the respective research facilities being used by the Investigator; and the name and address of the Institutional Review Board that is responsible for approving the protocol for conduct at the Investigator's study site.

Initiating the Involvement of the New Investigator

Once the new Investigator is added to the protocol, the investigational drug may be

shipped to the Investigator and the Investigator may begin participating in the conduct of the study (i.e., provided that the responsible Institutional Review Board has approved the protocol to be conducted at the Investigator's study site).

B. Information Amendments- 21 CFR 312.31

The Sponsor of the IND application shall submit essential information related to the IND application that is not within the scope of a Protocol Amendment, IND Safety Report, or IND Annual Report in Information Amendments.

Examples Information Amendments

Examples of information requiring the submission of an Information Amendment include:

- New non-clinical toxicology, chemistry, or other technical information; or
- A report regarding the discontinuance of a clinical protocol included within the IND.

Content and Format

An Information Amendment is required to bear prominent identification of its contents (e.g., "Information Amendment: Chemistry, Manufacturing and Control"; or "Informational Amendment: Pharmacology/Toxicology"; or "Information Amendment: Clinical") and to contain the following:

- A statement of the nature and purpose of the Information Amendment
- An organized submission of the respective data in a format appropriate for scientific review
- If the Sponsor desires the FDA to comment on an Information Amendment, a request for such comment and the specific questions that the FDA's response should address

Frequency of Submission

Information Amendments to the IND application should be submitted as necessary but, to the extent feasible, not more than every 30 days.

C. IND Safety Reports- 21 CFR 312.32

1. Definitions

Adverse Event means any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related.

Adverse Reaction means any adverse event caused by a drug.

Suspected Adverse Reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction"

Reasonable Possibility means (for the purpose of IND safety reporting) there is evidence to suggest a causal relationship between the drug and the adverse event.

Life-threatening, suspected adverse reaction: A suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include a suspected adverse reaction that had it occurred in a more severe form, might have caused death.

Serious, suspected adverse reaction: A suspected adverse reaction is considered “serious” if, in the view of the Investigator (i.e., the study site principal investigator) or Sponsor, it results in any of the following outcomes: death, a life-threatening adverse reaction, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Important drug-related medical events that may not result in death, be life-threatening, or require hospitalization may be considered “serious” when, based upon appropriate medical judgment, they may jeopardize the research subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected, suspected adverse reaction: A suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current IND application.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents.

“Unexpected”, as used in this definition, also refers to suspected adverse reactions that are mentioned in the investigator’s brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

2. Review of Safety Information: Sponsor Responsibilities- 21 CFR 312.32(b)

The Sponsor of the IND application must promptly review all information relevant to the safety of the drug that is obtained or otherwise received by the Sponsor from foreign or domestic sources, including information derived from any clinical or

epidemiological investigations, animal or *in vitro* studies, reports in the scientific literature, and unpublished scientific papers; as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

NOTE! The requirements of the Sponsor for the reporting of suspected adverse drug reactions to the FDA (see below C “IND Safety Reports: Notification Requirements and Format”) differ from the requirements of the Investigator for the reporting of adverse events to the Sponsor (see Investigator Responsibilities). Sponsor-investigators of IND applications are subject to compliance with both the adverse reaction reporting requirements of the Sponsor and the adverse event reporting requirements of the Investigator.

3. IND Safety Reports: Notification Requirements and Format

Requirements for Written IND Safety Reports

The Sponsor of the IND application shall submit a written IND Safety Report to the FDA and all participating Investigators (i.e., all study site principal investigators to whom the Sponsor is providing drug under the Sponsor’s IND) for:

Serious and Unexpected Suspected Adverse Reactions

The Sponsor of the IND application must report any suspected adverse reaction that is both serious and unexpected. The Sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event; such as: (a) a single occurrence of an adverse event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); (b) one or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture); and (c) an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates that those events occur more frequently than in a concurrent or historical control group.

NOTE! The Sponsor of an IND application involving a clinical study of a marketed drug for an off-label indication is required to submit Safety Reports for serious and unexpected suspected adverse reactions that are observed in the clinical study. The Sponsor is not, however, required to submit a Safety Report for any adverse reaction that occurs as a result of the use of the marketed drug outside of the respective clinical study. 21 CFR 312.32(c) (4)

Reporting study endpoints: Study endpoints (e.g., mortality or major morbidity) must be reported to the FDA by the Sponsor as described in the IND application/clinical protocol and ordinarily would not be reported as a serious and unexpected suspected adverse reaction. However, if a serious and unexpected adverse event occurs for which there is evidence supporting a causal relationship between the drug and the event (e.g., death

from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

Findings from Other Clinical Studies

The Sponsor of the IND application must report any findings from epidemiological studies, pooled analysis of multiple studies, or other clinical studies involving the use or evaluation of the investigational drug (i.e., whether or not conducted under an IND and whether or not conducted by the Sponsor) which suggest a new (i.e., not previously addressed in the investigator's brochure or protocol) significant risk to humans exposed to the investigational drug.

Ordinarily such a finding would necessitate a safety-related change in the clinical protocol(s), informed consent form(s), investigator brochure (if applicable), or other aspects of the overall conduct of the clinical investigation.

Findings from Animal or In Vitro Testing

The Sponsor must report in an Information Amendment to the IND application any findings from animal or *in vitro* testing, whether or not conducted by the Sponsor, brochure or protocol) significant that suggest a new (i.e., not previously addressed in the investigator's risk to humans exposed to the drug; such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure.

Ordinarily such a finding would necessitate a safety-related change in the clinical protocol(s), informed consent form(s), investigator brochure (if applicable), or other aspects of the overall conduct of the clinical investigation.

Increased Rate of Occurrence of Serious Suspected Adverse Reactions

The Sponsor of the IND application must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the investigator brochure or clinical protocol(s).

NOTE! Each written IND Safety Report shall be made as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting in accordance with the above criteria.

Unexpected Fatal or Life-Threatening Suspected Adverse Reaction Reports

The Sponsor of the IND application must also notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 days after the Sponsor's initial receipt of the information.

The Sponsor of the IND application must submit each serious and unexpected suspected adverse reaction on a FDA Form 3500A. (The Sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences [CIOMS] I Form instead of a FDA Form 3500 A.) Reports of overall findings or pooled analyses from published or unpublished *in vitro*, animal, epidemiological, or clinical studies must be submitted in a narrative format.

- Each written IND Safety Report shall bear prominent identification of its contents; i.e., “IND Safety Report”.
- Each written IND Safety Report shall be submitted to the review division in the FDA’s Center for Drug Evaluation and Research (CDER) or in the FDA’s Center for Biologics Evaluation and Research that has responsibility for review of the respective IND application.
- In each IND Safety Report, the Sponsor must identify all IND Safety Reports previously submitted to the FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of the previous, similar reports or any other relevant information.

Follow-up to submitted IND Safety Reports- 21 CFR Sec. 312.32 (d)

The Sponsor of the IND application must promptly investigate all additional information related to a submitted IND Safety Report.

Relevant follow-up information to an IND Safety Report must be submitted to the applicable review division of the FDA as soon as the information is available and must be identified as such, i.e., “Follow-up IND Safety Report”.

If the results of a Sponsor’s investigation show that an adverse event not initially determined to be reportable does, in fact, meet the requirements for reporting; the Sponsor shall submit a written IND Safety Report as soon as possible, but in no case later than 15 calendar days after the determination is made.

4. IND Annual Reports- 21 CFR 312.33

The Sponsor of the IND application must annually submit, within 60 days of the anniversary date that the IND application was accepted by the FDA, a brief report of the progress of the evaluation of the investigational drug. The IND Annual Report shall include:

Individual Clinical Study Information; to include a brief summary of the status of each clinical study in progress and each study completed during the previous year. The summary is required to include the following information for each study:

- The **title of the study** (with any appropriate study identifiers such as a protocol number);
- The **purpose of the study**;
- A brief statement identifying the **patient population**;
- A statement as to whether the **study is ongoing or completed**;
- The **total number of subjects initially planned for inclusion in the study**;
- The **total number of subjects entered into the study to date**, tabulated by age group, gender, and race;
- The **number of subjects for whom participation in the study was completed as**

planned;

- The **number of subjects who dropped out of the study early for any reason;** and
- If the study has been completed, or if interim results are known, a **brief description of any available study results.**

Summary Investigational Drug Information; to include a summary of information about the investigational drug obtained during the previous year's clinical and nonclinical investigations; including:

- A narrative or tabular **summary documenting the most frequent and most serious adverse reactions by body system;**
- A **summary of all IND Safety Reports submitted during the previous year;**
- A **list of subjects who died during participation in the investigation** (i.e., inclusive of all studies conducted under the IND) whether or not thought to be related to the investigational drug, **with the cause of death listed for each subject;**
- A **list of subjects who dropped out during the course of the investigation** (i.e., inclusive of all studies conducted under the IND) in association with any adverse experience (co-listed), whether or not thought to be related to the investigational drug;
- A **brief description of what information, if any, was obtained that is pertinent to an understanding of the drug's actions;** including, for example, information about dose response, information from controlled trials, and information about bioavailability;
- A **list of the non-clinical studies** (including *in-vitro* and animal studies) **completed or in progress during the past year and a summary of the major non-clinical study findings;** and
- A **summary of any significant manufacturing or microbiological changes made during the past year.**

General Investigational Plan; to include a description of the general investigational plan for the coming year (i.e., to replace the general investigational plan submitted the previous year). The general investigational plan shall contain the following information:

- The **rationale for the drug or the research study);**
- The **indication(s) to be studied;**
- The **general approach to be followed in evaluating the drug;**
- The **nature of the clinical studies to be conducted in the following year** (if plans are not developed for the entire year, the sponsor should so indicate);
- The **estimated number of patients or subjects to be given the investigational drug in those studies;** and
- Any **risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans** with the investigational drug or related drugs.

Investigator Brochure Revisions

If the investigator brochure (if applicable) has been revised, include a description of the revision and a copy of the new brochure.

Protocol Modifications; to include a description of any Phase 1, Phase 2 or Phase 3 protocol modifications made during the previous year and not previously reported to the IND in a Protocol Amendment.

Foreign Market Developments; to include a brief summary, if applicable, of significant foreign market developments with the investigational drug during the past year; such as approval of marketing in any country or withdrawal or suspension from marketing in any country.

Outstanding FDA Business

If desired by the Sponsor, include a log of any outstanding business with respect to the IND for which the Sponsor requests or expects a reply, comment or meeting from or with the FDA.

5. IND Withdrawal or Discontinuation Notice- 21 CFR 312.38

At any time, the Sponsor may withdraw an effective IND without prejudice.

A. Notification Requirements: General

If an IND is withdrawn by the Sponsor, the Sponsor shall so notify the FDA, all current participating Investigators (i.e., study site principal investigators), and all reviewing Institutional Review Boards (IRBs).

All clinical studies being conducted under the IND shall be terminated.

All stocks of the investigational drug shall be returned to the Sponsor of the IND application or otherwise disposed of at the request of, and in accordance with the procedures specified by, the Sponsor

B. Notification Requirements: Safety Issues

If an IND is withdrawn because of a safety reason, the Sponsor of the IND application shall promptly so notify the FDA, all (current and past) participating Investigators (i.e., study site principal investigators), and all reviewing Institutional Review Boards (IRBs); to include notification of the specific safety issue(s) leading to the decision to withdraw the IND.

All clinical studies being conducted under the IND shall be terminated. All stocks of the investigational drug shall be returned to the Sponsor of the IND application or otherwise disposed of at the request of, and in accordance with the procedures specified by, the Sponsor.