

Section 34: Investigator-held INDs

A trial sponsor may be a drug company/manufacturer or a single investigator. When an investigator holds his or her own IND, the FDA considers the investigator to be a sponsor-investigator. *This means that one individual is assuming all of the responsibilities of the study sponsor in addition to that of the overall principal investigator.* The additional responsibilities of a sponsor include:

- All of the regulatory reporting (FDA) requirements
- Responsibility for drug manufacturing and control issues, including proper labeling of the investigational product
- The assessment of safety
- Ensuring IRB approval prior to shipping clinical supplies to sites
- Communicating with and monitoring all participating investigators

In preparing and maintaining an IND application, sponsor-investigators may find the following documents developed by DF/HCC useful in the initial submission of the IND application and in the submission of periodic reports to the FDA.

- Biomedical Protocol Template
- Original IND Submission Transmittal Letter
- Original IND Application Template
- IND Amendment Transmittal Letter
- IND Safety Reporting Transmittal Letter
- IND Annual Report Transmittal Letter
- IND Annual Progress Report
- IND Withdrawal Transmittal Letter

These documents are available through the DF/HCC Clinical Investigator Toolkit or by contacting the Clinical Trials Education Office (cte@dfci.harvard.edu or 617-582-8480).

34.1 IND Overview

Before conducting a clinical trial with an investigational new drug (IND), the sponsor-investigator must submit an IND application to the FDA. The FDA reviews the application for both subject safety and the ability to satisfy the requirement for efficacy. FDA has 30 days from date of receipt of an IND to make a determination on whether it is safe for the sponsor-investigator to proceed. If no notice is received within the 30-day period, the IND is considered approved. The sponsor-investigator *should confirm* that the FDA did, in fact, receive the application and that they do not have any issues or concerns with the application

prior to enrolling participants to the trial.

In some cases it may not be obvious that an IND is required for a proposed trial. *DF/HCC strongly encourages the sponsor- investigator to request the FDA's assistance in making the determination. If it is a much safer path for the sponsor-investigator to file an IND application and have it deemed exempt than not to file and later be subject to a determination that an IND should have been requested.*

Preparing the IND application is a comprehensive process that must consider FDA as well as IRB and institutional requirements. The sponsor-investigator sponsoring the IND must abide by all processes that are in place for human participant research.

It is recommended that the sponsor- investigator be a practicing physician and that the trial be submitted sequentially for review to the FDA and IRB, unless IRB approval is necessary to secure funding.

34.2 General Principles of the IND Submission [21 CFR 312.22](#)

The FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to ensure the safety and rights of participants. In Phase II and Phase III trials, the FDA helps to ensure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, although the FDA's review of Phase I submissions will focus on assessing the safety of Phase 1 investigations, the FDA's review of Phases II and Phase III submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

The amount of information on a particular drug that must be submitted in an IND depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug. The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human trials. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of animal toxicology trials or other human trials as appropriate. Annual reports to the IND should serve as the focus for reporting the status of trials being conducted under the IND and should update the general investigational plan for the coming year.

34.3 IND Content and Format [21 CFR 312.23](#)

The IND format is described in the regulations in [21 CFR 312.23](#) and should be followed by the sponsor-investigator in the interest of fostering an efficient review of applications. The general format is described below. The investigator is expected to exercise considerable discretion, however, regarding the content of information submitted in each section, depending upon the kind of drug being studied and the nature of the available information.

Note: An investigator who uses, as a research tool, an IND that is already subject to a manufacturer's IND or marketing application should follow the same general format but ordinarily may, if authorized by the manufacturer, refer to the manufacturer's IND or marketing application in providing the technical information supporting the proposed clinical investigation. An investigator who uses an investigational drug not subject to a manufacturer's IND or marketing application is ordinarily required to submit all technical information supporting the IND, unless such information may be referenced from the scientific literature.

The necessary documents needed to compile an IND include:

1. A **cover letter**
2. [FDA form 1571](#): The Investigational New Drug Application Form
3. [FDA form 1572](#): The Statement of Investigator Form
4. A **table of contents**
5. An **introductory statement** or background information intended to place the development plan for the drug into perspective and help the FDA understand that study hypothesis.
6. A **general investigational plan** describing the general steps that will be carried out in order to perform the study.
7. An **investigator's brochure**, if required under [21 CFR 312.55](#).
8. The **study protocol(s)** describing the methodology to be used and an analysis of the protocol demonstrating its scientific soundness.
9. The **informed consent document** explaining the study, procedures, risks, benefits, alternative treatment, compensation and confidentiality measures.
10. **Chemistry, manufacturing, and control data** sufficient to assure the proper identification, quality, purity, and strength of the investigational drug. If the drug is legally marketed in the U.S., this should be stated.
11. **Investigational drug labeling** with a warning stating "caution new drug for investigational use only."
12. **Environmental assessment** indicating whether or not the research or study will affect the environment. For more information, refer to a claim for categorical exclusion under [21 CFR 25.30](#) or [21 CFR 25.31](#) or an environmental assessment under [21 CFR 25.40](#).
13. **Pharmacology and toxicology data** that describes the mechanism of action of the drug, its toxicological effect and its pharmacological effects (absorption, distribution, metabolism and excretion) in animal and *in vitro*.
14. **Previous human experience with the investigational drug**
15. **Articles cited in the study protocol**

34.4 Submission of the IND application to the FDA

IND applications are submitted to one of two centers within the FDA, the Center for Biologics Evaluation and Research (CBER) or the Center for Drug Evaluation and Research (CDER). The decision governing which center is appropriate is dependent on the nature of the experimental agent described in the IND. Generally, the CBER oversees vaccine and blood-related products, while the CDER has oversight responsibilities for drugs and biologics. Questions about the appropriate center for submission can be directed to the:

- CBER Ombudsman at (301) 827-0379 or cberombudsman@fda.hhs.gov
- CDER Ombudsman at (301) 796-3436 or cderombudsman@fda.hhs.gov

General Submission Information

If the sponsor-investigation involves an exception from informed consent under [21 CFR 50.24](#), the sponsor-investigator should prominently identify in the cover letter that the investigation is subject to the requirements in 21 CFR 50.24 of the regulations.

The submission must be broken down into volumes, each page paginated (numbering of each page in sequence in the submission, regardless of the page number already on it).

The original IND and all subsequent amendments must be submitted in triplicate (one original and two copies, [per 21 CFR 312.23](#)). Processing may be delayed if insufficient copies are submitted.

Typically each submission relating to an IND should be numbered serially. The initial IND is numbered 0000; each subsequent submission (e.g., amendment, report, correspondence) is numbered chronologically.

Submissions should be sent to the appropriate division within the FDA as outlined below.

Biologics	Center for Drug Evaluation and Research (CDER)
Drugs	Center for Drug Evaluation and Research (CDER)
Vaccines/gene therapy	Center for Biologics Evaluation and Research (CBER)

34.5 IND Application Approval Process

FDA will respond within 30 days with an acknowledgment letter and an IND number.

Note: This means the IND has been successfully filed, however, the research can not begin until 30 days after the IND has been received by the FDA, unless earlier notification by FDA is received stating that the research may begin.

After the acknowledgment the FDA may respond in one of two ways.

1. The FDA may request additional information and may place clinical holds on the research. The research cannot begin until all concerns raised by the FDA have been responded to their satisfaction.
2. The FDA may conclude that the research is exempt. An exemption means that the research may be conducted without filing an IND application or subsequent information to the FDA.

Note: An IND exemption does not release a sponsor-investigator from his/her submission and/or reporting requirements to the IRB.

34.6 IND Post-Approval

After approval of an IND, the sponsor-investigator is subject to conditions set forth by the FDA. The following sections outline these conditions and the responsibilities of an IND sponsor-investigator.

34.7 IND Protocol Amendments [21 CFR 312.30](#)

If any change is made to the research protocol, the amendment must be submitted to FDA to ensure that

the clinical investigations are conducted according to protocol included in the application. Changes include:

- New protocol(s) under an existing IND
- Changes to the existing protocol(s)
- Addition of a new investigator to an existing protocol

New Protocol(s)

A new protocol may begin only after the IND protocol amendment has been submitted to the FDA for review and the protocol has been approved by the IRB of record.

Changes in Existing Protocols

A sponsor-investigator should submit a protocol amendment for any change that significantly affects the safety of participants, or any change in a Phase 2 or 3 protocol that significantly affects the safety of participants, the scope of the investigation, or the scientific quality of the study as outlined in 21 CFR 312.30.

Protocol changes are made only after the protocol amendment has been submitted to the FDA for review and the protocol amendment has been approved by the IRB.

New investigator

A protocol amendment should be submitted when a new investigator is added to a previously submitted protocol. An amendment is not required when a licensed practitioner is added to a treatment (single-patient IND) protocol per [21 CFR 312.34](#).

Once added to the study the new investigator may receive shipments of investigational drug and may begin participating in the study. The overall PI should submit the protocol amendment to report the addition of a new investigator within 30 days of the addition.

Content and Format of an IND Protocol Amendment

The specific purpose of the protocol amendment should be prominently identified (i.e., Protocol Amendment: New Protocol, Protocol Amendment: Change in Protocol, Protocol Amendment: New Investigator), and include the following:

1. **New protocol:** A copy of the new protocol along with a brief description of the most clinically significant differences between it and the previous protocol(s).
2. **Protocol Change:** A brief description of the change and reference (i.e., date and number) to the submission that contained the protocol.
3. **New Investigator:** The investigator's name and address, qualifications to conduct the investigation (i.e., CV), the name and address of the research facility used by the investigator, the name of each co-investigator (i.e., fellow, resident, etc.) working under the supervision of the investigator; the name and address of the investigator's IRB, and a reference (i.e., date and number) to the submission containing the previously submitted protocol to which the investigator

is being added.

4. **Reference:** Identify specific information either in the existing IND or in a concurrently submitted IND amendment that is necessary to support any clinically significant change. References to existing INDs include the reference number, volume number, and page number of the specific information being referenced.

34.8 IND Safety Reports for Investigator-Held INDs [21 CFR 312.32](#)

The sponsor-investigator is responsible for submitting safety reports to the FDA. This section describes the FDA's expectations. The sponsor-investigator should be aware that IRB requirements are slightly different than FDA requirements. The sponsor-investigator is responsible for being familiar with and meeting expectations of both sets of requirements. Additionally, if the trial involves recombinant DNA, there may be additional reporting requirements to the OBA and/or the NIH and/or the OHRP. The sponsor-investigator is responsible for being familiar with these requirements as well as meeting these requirements.

Definitions

Associated with the use of the drug: There is a reasonable possibility that the experience may have been caused by the drug.

Disability: A substantial disruption of a person's ability to perform normal life functions.

Life-threatening adverse drug experience: Any adverse drug experience that places the participant at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death).

Serious adverse drug experience: Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the participant 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 an 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 adverse drug experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Review of Safety Information

The sponsor-investigator should promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor-investigator from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the FDA by the sponsor-investigator.

IND Safety Reports

Written reports are used by the sponsor-investigator to notify the FDA as well as all participating investigators of:

1. Any adverse experience associated with the use of the drug that is both serious and unexpected.
2. Any finding from tests in laboratory animals that suggests a significant risk for human participants including reports of mutagenicity, teratogenicity, or carcinogenicity.

Each notification should be made as soon as possible and in no event later than 15 calendar days after the sponsor-investigator is initially notified of the event.

Each written notification may be submitted on [FDA form 3500A](#) or in a narrative format (foreign events may be submitted either on an FDA form 3500A or, if preferred, on a CIOMS I form; reports from animal or epidemiological trials should be submitted in a narrative format) and should bear prominent identification of its contents (i.e., IND Safety Report).

Each written notification to the FDA should be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND

In each written IND safety report, the sponsor-investigator should identify all safety reports previously filed with the IND concerning a similar adverse experience, and should analyze the significance of the adverse experience in light of the previous, similar reports.

Telephone and facsimile transmission safety reports are utilized by the sponsor-investigator to notify FDA of any unexpected and fatal/life-threatening adverse drug experiences that are associated with use of the experimental drug.

The sponsor-investigator should notify the FDA by telephone or fax of any **unexpected** and **fatal or life-threatening** experience **associated with the use of the drug** as soon as possible but in no event later than 7 calendar days after the sponsor-investigator is initially notified of the event.

Each telephone call or fax to the FDA should be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND.

Reporting format or frequency. The FDA may request that the sponsor-investigator submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor-investigator may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the new drug review division in the Center for Drug Evaluation and

Research or the director of the products review division in the Center for Biologics Evaluation and Research that is responsible for review of the IND.

Marketed Drug: The sponsor-investigator of a clinical trial of a marketed drug is not required to make a safety report for any adverse experience associated with use of the drug that is not from the clinical trial itself.

Follow-up Action to an IND Safety Report

The sponsor-investigator is obligated to promptly investigate any follow-up information received about the adverse drug experience.

All follow-up information to an IND Safety Report should be submitted to the FDA as soon as the relevant information is available.

In studies using marketed drug(s), the sponsor-investigator should follow-up on reports only for those drugs in connection with the adverse experience that derive from the use of the drug as a result of the study.

If the sponsor-investigator's review shows that an adverse drug experience not initially determined to be reportable under the previous part of this section is so reportable, the sponsor-investigator should report such experience in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made.

The sponsor-investigator should report the results of other safety information, as appropriate, in either an information amendment or annual report.

34.9 IND Annual Report [21 CFR 312.33](#)

The purpose and focus of the annual reports is to keep FDA informed of the progress of the clinical study during the year and the investigational plan for the upcoming year. A system should be put in place at the beginning of the IND process to routinely collect information that will need to be submitted in the annual report.

An annual report is due within 60 days (+/-) of the anniversary date that the IND went into effect. **DF/HCC strongly encourages the sponsor-investigator to submit the annual progress report to FDA at the time he/she files a continuing review form with the DFCI IRB.** An annual report should comprise a brief progress report of the investigation. The content of the IND Annual Report is as follows:

1. **Individual study information** summarizing all studies under the IND
2. **Summary information** of the year's clinical and non-clinical results.
3. **General investigational plan** for the coming year as per [21 CFR 312.23 \(3\)](#). The content must be distinct from and replace the plan submitted for the previous year.
4. A description of any **revisions to the investigator's brochure**. A copy of the newly revised brochure must be included with the annual report.
5. A description of any significant **protocol modification** made during the previous year and not previously reported to FDA as an IND protocol amendment.

6. A brief summary of any **significant events in foreign marketing of the drug during the past year** including marketing approval as well as withdrawal/suspension of marketing privileges in any foreign country.
7. Any **outstanding IND related business** to which a reply, comment or scheduled meeting with FDA is expected or requested.

Note: Submission of the IND Annual Report does not preclude the sponsor-investigator's responsibility to submit Continuing Review/Progress Reports to the reviewing IRB.

34.10 Final Study Reports

A final report should be written and submitted for all IND applications. The final report should be submitted as soon as the clinical studies have concluded or within six months of study completion.

34.11 Withdrawal of an IND Application [21 CFR 312.38](#)

A sponsor-investigator may choose to withdraw an effective IND at any time without prejudice, however the withdrawn IND cannot be reactivated nor can it continue to be referenced in other IND applications.

When an IND is withdrawn the sponsor-investigator must complete these steps:

1. Cease conducting all clinical investigations under the IND.
2. Notify all participating investigators that the IND has been withdrawn.
3. Request the return of all unused stocks of drug and dispose of them in a manner that does not put anyone at risk per [21 CFR 312.59](#).
4. Notify the FDA in writing that the IND is being withdrawn with the reason the IND is being withdrawn.

Note: The sponsor-investigator must promptly notify the FDA, all participating investigators, and all reviewing IRBs when an IND is withdrawn because of safety concerns. A reason for the withdrawal should be given.

34.12 General Responsibilities of the Sponsor-Investigator

According to [21 CFR 312.50](#) the sponsor-investigator is responsible for selecting qualified investigators, providing them with the information necessary to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that the FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

34.13 Selecting Participating Investigators and Monitors

The investigator has the following obligations as outlined in [21 CFR 312.53](#).

Selecting Investigators

The sponsor-investigator should select only investigators qualified by training and experience as appropriate experts to investigate the drug.

Control of Drug

The sponsor-investigator must ship investigational new drugs only to investigators participating in the investigation.

Obtaining information from the Participating Investigator(s)

Before permitting a participating investigator to begin participation in an investigation, the sponsor-investigator should:

1. Obtain a **signed investigator statement** ([FDA form 1572](#))
2. Obtain a **curriculum vitae** (CV) or other statement of qualifications of the investigator showing the education, training, and experience that qualifies the investigator as an expert in the clinical investigation of the drug for the use under investigation.
3. Provide the participating investigator a copy of the **protocol**: For Phase I investigations, a general outline of the planned investigation including the estimated duration of the trial and the maximum number of subjects that will be involved. For Phase II or Phase III investigations, an outline of the trial protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the trial; and copies or a description of case report forms to be used.

Selecting Monitors

The sponsor-investigator should select a monitor qualified by training and experience to monitor the progress of the investigation.

34.14 Informing Participating Investigators of New Observations

Before the investigation begins, the sponsor-investigator should give each participating investigator an investigator brochure containing the information described in [21 CFR 312.23 \(a\)\(5\)](#) if and when such a document exists.

The sponsor-investigator should, as the overall investigation proceeds, keep each participating investigator informed of new observations discovered by or reported to the sponsor-investigator on the drug, particularly with respect to adverse effects and safe use. Such information may be distributed to participating investigators by means of periodically revised investigator brochures, reprints or published

trials, reports or letters, or other appropriate means. Important safety information should also be relayed to participating investigators in accordance with [21 CFR 312.32](#).

34.15 Review of Ongoing Investigations [21 CFR 312.56](#)

The sponsor-investigator should monitor the progress of all clinical investigations being conducted under the IND.

A sponsor-investigator who discovers that a participating investigator is not complying with the signed agreement (FDA form 1572), the general investigational plan, or the requirements of the trial, should promptly either secure compliance or discontinue shipments of the IND to the participating investigator and end the participating investigator's involvement in the investigation. If the participating investigator's involvement in the investigation is ended, the sponsor-investigator should require that the participating investigator dispose of or return the investigational drug in accordance with the requirements of the protocol. These actions should be reported to the FDA.

The sponsor-investigator should review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the participating investigator. The investigator should make such reports to the FDA regarding information relevant to the safety of the drug as are required by the regulations. The investigator should make annual reports on the progress of the investigation.

A sponsor-investigator who determines that the investigational drug presents an unreasonable and significant risk to participants should discontinue those investigations that present the risk, notify the FDA, all IRBs, and all participating investigators who have at any time participated in the investigation of the discontinuance, assure the disposition of all stocks of the drug outstanding as required, and furnish the FDA with a full report of the actions. The sponsor-investigator should discontinue the investigation as soon as possible, and in no event later than 5 working days after making the determination that the investigation should be discontinued. Upon request, the FDA will confer with the investigator on the need to discontinue an investigation.

34.16 Record Keeping and Record Retention [21 CFR 312.57](#)

A sponsor-investigator should maintain and/or retain the following:

1. Adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the participating investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.
2. Records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified.
3. Reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability trials, and release the reserve samples to the FDA upon request, in accordance with, and for the period specified in [21 CFR 320.38](#).

34.17 Inspection of Records and Reports [21 CFR 312.58](#)

FDA Inspection

The sponsor-investigator should upon request from any properly authorized officer or employee of the

FDA, at reasonable times, permit such officer or employee to have access to and copy and verify any records and reports relating to a clinical investigation conducted under this IND. Upon written request by the FDA, the sponsor-investigator should submit the records or reports (or copies of them) to the FDA. The sponsor-investigator should discontinue shipments of the drug to any participating investigator who has failed to maintain or make available records or reports of the investigation as required.

34.18 Disposition of Unused Investigational Drug [21 CFR 312.59](#)

The sponsor-investigator should assure the return of all unused supplies of the participating investigators.

34.19 General Responsibilities of Participating Investigators

A participating investigator is responsible for ensuring that the investigation at his or her institution is conducted according to the signed investigator statement ([FDA form 1572](#)), the investigational plan and applicable regulations; for protecting the rights, safety, and welfare of participants under the participating investigator's care; and for the control of drugs under investigation at his or her institution. A participating investigator should, in accordance with the provisions of [21 CFR Part 50](#), obtain the informed consent of each human participant to whom the drug is administered. Participating investigators must also comply with all regulations set forth in [21 CFR Part 56](#), and [45 CFR Part 46](#).

34.20 Control of the Investigational Drug [21 CFR 312.61](#)

Participating investigators should administer the drug only to participants under their personal supervision or under the supervision of a sub-investigator responsible to them. Participating investigators should not supply the investigational drug to any person not authorized to receive it.

34.21 Participating Investigator Record Keeping and Record Retention

Disposition of Drug

A participating investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by participants. If the investigation is terminated, suspended, discontinued, or completed, the participating investigator should return the unused supplies of the drug to the sponsor-investigator, or otherwise provide for disposition of the unused supplies of the drug.

Case Histories

A participating investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual should document that informed consent was obtained prior to participation in the trial.

Record Retention

A participating investigator should retain records required to be maintained for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the FDA is notified.

34.22 Participating Investigator Reports

Progress Reports

Participating investigators should furnish all data and/or requested by the sponsor-investigator. The sponsor-investigator is required to collect and evaluate the results obtained and to submit annual reports to the FDA on the progress of the clinical investigations.

Safety Reports

A participating investigator should promptly report to the sponsor-investigator any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the participating investigator should report the adverse effect *immediately*.

Final Report

A participating investigator should provide the sponsor-investigator with an adequate report shortly after completion of the participating investigator's involvement in the investigation.