

## RESEARCH INVOLVING INVESTIGATIONAL DRUGS

### 1. Overview

Investigators and IRBs must ensure that research (i.e., clinical investigation) involving investigational drugs or biologics is conducted in accordance with applicable federal regulations. These regulations describe, among other things, requirements for Investigational New Drug Applications (INDs), drug accountability and record retention, and responsibilities of investigators, IRBs, and sponsors when research is conducted with investigational drugs.

The purpose of this policy is to describe the requirements for research involving investigational drugs or biologics, including the responsibilities of investigators, IRBs, and sponsors.

### 2. Definitions

**Biological product:** Also: **biologic.** A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of a disease or condition of human beings. *Note: Biological products also include immunoglobulin products, monoclonal antibodies, products containing cells or microorganisms, and most proteins intended for therapeutic use.*

**Clinical Investigation:** Also: **research, clinical research, clinical study.** Any experiment that involves a test article and one or more human subjects that either:

- Meets the requirements for prior submission to the FDA under sections 505(i) or 520(g) of the Food, Drug, and Cosmetic Act; or
- Need not meet the requirements for prior submission to the FDA under the sections noted above, but the results of which are intended to be later submitted to or held for inspection by the FDA as part of an application for a research or marketing permit.

*Note: Non-clinical laboratory studies are not considered to be clinical investigations. See the DHHS definition of research for DHHS-regulated research.*

**Drug:** Substance recognized in the United States Pharmacopoeia, Homeopathic Pharmacopoeia of the United States, or National Formulary (or any supplement to any of these), and is an article:

- Intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or intended to affect the structure or any function of the body (other than food), or
- Intended for use as a component of any substance described above.

**Investigational Drug:** Also: **investigational new drug.** A new drug or biologic (i.e., not approved for marketing by FDA) used in a clinical investigation, including a biological product used in vitro for diagnostic purposes.

**Investigational New Drug Application (IND):** An application that permits an investigational drug that would otherwise be required to have pre-market approval by FDA to be legally shipped for a clinical investigation.

**Sponsor-Investigator:** An individual who initiates (*i.e., obtains an IND or IDE*) and conducts an investigation and under whose immediate direction an investigational drug or device is administered, dispensed, or used. *Note: The regulatory requirements applicable to a sponsor-investigator include those applicable to both an investigator and a sponsor.*

### 3. General Information

- A. When human subjects research involves the use of drugs or biological products, FDA regulations apply. Investigators must provide sufficient information about the drug or biologic for the IRB to evaluate its associated risks and benefits, including the FDA approval status of the product (*i.e., approved for marketing or investigational*).
- B. An Investigational New Drug Application (IND) must be filed with FDA to test the safety and efficacy of a new (*i.e., investigational*) drug for marketing approval. Studies involving the “investigational/research use” of an *approved* drug also require an IND if the intent of the study is to generate data that will lead to a new clinical indication, formulation, or advertising claim, or the study includes a new dose, population, or other factor that significantly increases risk (or decreases acceptability of the risk).
- C. As described above, an IND is required for some research uses of a marketed drug or biologic; however, certain exemptions apply to the FDA requirements. For information about the FDA exemptions from the requirements for an IND for studies involving marketed drugs, see Attachment 1. Additional FDA guidance for studies of approved drugs for treating cancer is available; see [IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer](#).
- D. When an IND is required for the proposed use of a marketed drug or biologic in research, investigators must submit an application (Form FDA 1571) to FDA. An IND number will be assigned by FDA upon receipt of the application. Unless earlier notification is received, studies may be initiated 30 days after FDA’s receipt of the IND. For more information about obtaining an IND and forms and instructions, see [21 CFR 312 Subpart B - Investigational New Drug Application](#) and [Information for Sponsor-Investigators Submitting Investigational New Drug Applications \(INDs\)](#). Final IRB approval will not be given until a valid IND number is provided.
- E. An investigator obtaining an IND for the proposed use of a drug or biologic in research becomes a “sponsor-investigator,” and additional institutional requirements apply to assist investigators in complying with applicable FDA regulations (see “Additional Responsibilities of Sponsor-Investigators” below).

- F. The “off-label” use of a marketed drug (i.e., a use other than the indication(s) approved by FDA) by a physician for treatment purposes does not require an IND or IRB approval. When such uses meet the regulatory definitions of *research* or *clinical investigation*, IRB approval is required. An IND may also be required, unless the conditions for exemption (described in Attachment 1) are met.
- G. Additional requirements apply to the emergency use of an investigational drug or biologic and planned emergency research involving investigational drugs or biologics subject to FDA regulations. For more information, see OSU HRPP policies [[Emergency Use of Investigational Drugs, Biologics, or Devices](#)] and [[Planned Emergency Research](#)].
- H. In certain situations, an investigational drug intended to treat a serious or immediately life-threatening condition may be used under a Treatment IND. Such “treatment use” of an investigational drug requires IRB review and approval. For more information, see FDA guidance [Treatment Use of Investigational Drugs](#) or contact ORRP.

#### 4. Submission and Pre-Review Procedures

- A. To describe proposed uses of drugs or biologics in human subjects research, investigators will submit *Appendix F: Drugs or Biologics* with the *Initial Review of Human Subjects Research* application form and all applicable attachments. For more information about IRB submission requirements, see OSU HRPP policy [[IRB Submission and Pre-Review](#)].
- B. During the pre-review process, ORRP IRB Protocol Analysts are responsible for making an initial determination about whether an investigator’s proposed use of a drug or biologic involves the use of a marketed drug in the course of medical practice, requires an IND, or meets one of the FDA exemptions from the IND requirements. The IRBs will make the final determination. Note: For assistance in determining whether an IND is required in a specific situation, the FDA may be contacted directly. (For contact information, see FDA guidance ["Off-label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices](#).)
- C. When the research involves a drug or biologic with an IND, ORRP IRB Protocol Analysts will verify that the IND number provided by the investigator is valid. Protocol-specific confirmation (e.g., sponsor’s protocol cover sheet, FDA or sponsor correspondence, etc.) will be obtained. *Note: The investigator’s drug brochure is not a protocol-specific document.*

#### 5. IRB Review

- A. The convened IRBs will review proposed research involving investigational drugs or biologics considering the criteria for approval as described by regulations and OSU HRPP policy [[Review of Research by the Convened IRB](#)]. Note: Research involving a drug for which an IND is required is not eligible for expedited review.

B. When research involves the use of an investigational drug or biologic, to approve the research the IRBs will also require the following:

- Available clinical and non-clinical information on the investigational product that is adequate to support the proposed research
- A valid IND, unless the proposed use of the drug or biologic represents the use of a marketed product in the course of medical practice or meets one of the FDA exemptions from the IND requirements
- An adequate plan for monitoring data to ensure the safety of participants and for reporting adverse events and unanticipated problems involving risks to participants or others
- A plan for control, accountability, and storage of the investigational drug or biologic that ensures that the product will be used only in the approved research under the direction of the approved investigator(s)
- For sponsor-investigators, that they are knowledgeable about and will comply with the additional FDA requirements associated with conducting research for which an IND has been obtained.

## **6. Investigational Drug Control, Accountability, and Record Retention**

A. Investigational drugs used in OSU research must be appropriately controlled, administered, and stored in compliance with IRB and FDA requirements and applicable OSU policies. Such requirements include processes to ensure that investigational products are manufactured, handled, and stored in compliance with applicable good manufacturing practices; inventory and accountability records are maintained for investigational drug receipt, dispensing, and disposition; and investigational drugs are used only in accordance with available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information and the approved protocol.

B. Investigators may delegate accountability, storage, and recordkeeping responsibilities to the OSU Medical Center (OSUMC) Department of Pharmacy as described in OSU policy [Investigational Drug Service Policies and Procedures] (Attachment 3). For more information, contact the OSUMC Department of Pharmacy at 614-293-8470. Alternatively, an investigator may provide a plan to ensure that the investigational drug or biologic will be used according to the IRB-approved protocol, under the direction of the approved investigator(s), and in compliance with FDA and OSU requirements.

## **7. Additional Responsibilities of Sponsor-Investigators**

A. Investigators obtaining an IND to initiate and conduct research must also fulfill the federal requirements of sponsors. These requirements include (but are not limited to) additional FDA reporting (e.g., annual progress reports), data monitoring, and recordkeeping obligations. Institutional requirements for “sponsor-investigators” conducting research with investigational drugs or biologics also apply, as described below.

- B. When an OSU investigator obtains an IND to perform human subjects research, a representative from the College of Medicine Office of Research (COM/OR) will meet with the PI (and research staff, as applicable) to review the FDA responsibilities of investigators and sponsors. The COM/OR works with the IRBs and Office of Research Compliance to assure investigator and institutional compliance with IRB and FDA requirements. The COM/OR will assist investigators with information on FDA requirements, submission of required FDA reporting, and drug accountability and recordkeeping procedures.
- C. College of Medicine Office of Research review is required for first-time IND holders performing human subjects research (regardless of College/Department affiliation). Experienced sponsor-investigators will not require COM/OR review, at the discretion of the IRB. Final IRB approval will not be given until documentation of COM/OR review (as applicable) is provided.
- D. In addition to FDA regulations for the protection of human subjects (21 CFR Parts 50, and 56) and use of investigational drugs (21 CFR 312), additional regulations may apply to sponsor-investigators, depending on the nature of the research. These regulations include:
- [Electronic Records; Electronic Signatures \(21 CFR 11\)](#)
  - [Financial Disclosure by Clinical Investigators \(21 CFR 54\)](#)
  - [Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs \(21 CFR 210\)](#)
  - [Current Good Manufacturing Practice for Finished Pharmaceuticals \(21 CFR 211\)](#)
  - [Applications for FDA Approval to Market a New Drug \(21 CFR 314\)](#)
  - [Bioavailability and Bioequivalence Requirements \(21 CFR 320\)](#)
  - [Over-the-Counter Human Drugs Which are Generally Recognized as Safe and Effective and Not Misbranded \(21 CFR 330\)](#)
  - [Applications for FDA Approval of a Biologic License \(21 CFR 601\)](#).
- E. For more information describing the FDA requirements for sponsors and investigators when research is initiated and conducted with investigational drugs or biologics, see Attachment 2. Additional guidance describing the international standards for good clinical practices in human subjects research (“ICH/GCP”) is available at [ICH E6: Good Clinical Practice: Consolidated Guidance](#).

## 8. Applicable Regulations/Guidance

21 CFR 50; 21 CFR 56; 21 CFR 312; 21 CFR 600; FDA Guidance “E6: Good Clinical Practice: Consolidated Guidance” (04/96); FDA Information Sheets: “Frequently Asked Questions,” “‘Off-label’ and Investigational Use of Marketed Drugs, Biologics and Medical



Devices,” and “Treatment Use of Investigational Drugs”; OSU “Investigational Drug Service Policies and Procedures” (08/16/02)

## Attachment 1.

### Investigational New Drug Application (21 CFR 312) Subpart A – General Provisions

#### *Applicability*

Except as provided in this section, this part applies to all clinical investigations of products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201et seq.)).

#### *Exemptions*

1. The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:
  - i. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
  - ii. If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
  - iii. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
  - iv. The investigation is conducted in compliance with the requirements for institutional review set forth in 21 CFR part 56 and with the requirements for informed consent set forth in part 50; and
  - v. The investigation is conducted in compliance with the requirements of 312.7.
2. (i) A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (ii) of this section is exempt from the requirements of this part if:
  - a. It is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and
  - b. It is shipped in compliance with 312.160.(ii) In accordance with paragraph (i) of this section, the following products are exempt from the requirements of this part:
  - a. Blood grouping serum;
  - b. Reagent red blood cells; and
  - c. Anti-human globulin.
3. A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with 312.160.
4. FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (1) of this section.
5. A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.



6. A clinical investigation involving an exception from informed consent under 21 CFR 50.24 of this chapter is not exempt from the requirements of this part.

## **Attachment 2.**

### **Investigational New Drug Application (21 CFR 312) Subpart D – Responsibilities of Investigators and Sponsors**

#### ***312.50 General responsibilities of sponsors***

Sponsors are responsible for selecting qualified investigators, providing them with the information they need 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 FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described elsewhere in this part.

#### ***312.52 Transfer of obligations to a contract research organization***

- a. A sponsor may transfer responsibility for any or all of the obligations set forth in this part to a contract research organization. Any such transfer shall be described in writing. If not all obligations are transferred the writing is required to describe each of the obligations being assumed by the contract research organization. If all obligations are transferred, a general statement that all obligations have been transferred is acceptable. Any obligation not covered by the written description shall be deemed not to have been transferred.
- b. A contract research organization that assumes any obligation of a sponsor shall comply with the specific regulations in this chapter applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations. Thus, all references to "sponsor" in this part apply to a contract research organization to the extent that it assumes one or more obligations of the sponsor.

#### ***312.53 Selecting investigators and monitors***

- a. Selecting investigators. A sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug.
- b. Control of drug. A sponsor shall ship investigational new drugs only to investigators participating in the investigation.
- c. Obtaining information from the investigator. Before permitting an investigator to begin participation in an investigation, the sponsor shall obtain the following:
  1. A signed investigator statement (Form FDA-1572) containing:
    - i. The name and address of the investigator;
    - ii. The name and code number, if any, of the protocol(s) in the IND identifying the study(ies) to be conducted by the investigator;
    - iii. The name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted;
    - iv. The name and address of any clinical laboratory facilities to be used in the study;
    - v. The name and address of the IRB that is responsible for review and approval of the study(ies);
    - vi. A commitment by the investigator that he or she:

- a. Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects;
  - b. Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part;
  - c. Will personally conduct or supervise the described investigation(s);
  - d. Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;
  - e. Will report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 312.64;
  - f. Has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug; and
  - g. Will ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.
- vii. A commitment by the investigator that, for an investigation subject to an institutional review requirement under part 56, an IRB that complies with the requirements of that part will be responsible for the initial and continuing review and approval of the clinical investigation and that the investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.
- viii. A list of the names of the subinvestigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s).
2. Curriculum vitae. A curriculum vitae 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. Clinical protocol.
    - i. For Phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.
    - ii. For Phase 2 or 3 investigations, an outline of the study 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 study; and copies or a description of case report forms to be used.
  4. Financial disclosure information. Sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

- d. Selecting monitors. A sponsor shall select a monitor qualified by training and experience to monitor the progress of the investigation.

#### ***312.54 Emergency research under 50.24 of this chapter***

- a. The sponsor shall monitor the progress of all investigations involving an exception from informed consent under 50.24 of this chapter. When the sponsor receives from the IRB information concerning the public disclosures required by 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter, the sponsor promptly shall submit to the IND file and to Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, copies of the information that was disclosed, identified by the IND number.
- b. The sponsor also shall monitor such investigations to identify when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in 50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA, investigators who are asked to participate in this or a substantially equivalent clinical investigation, and other IRB's that are asked to review this or a substantially equivalent investigation.

#### ***312.55 Informing investigators***

- a. Before the investigation begins, a sponsor (other than a sponsor-investigator) shall give each participating clinical investigator an investigator brochure containing the information described in 312.23(a)(5).
- b. The sponsor shall, as the overall investigation proceeds, keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use. Such information may be distributed to investigators by means of periodically revised investigator brochures, reprints or published studies, reports or letters to clinical investigators, or other appropriate means. Important safety information is required to be relayed to investigators in accordance with 312.32.

#### ***312.56 Review of ongoing investigations***

- a. The sponsor shall monitor the progress of all clinical investigations being conducted under its IND.
- b. A sponsor who discovers that an investigator is not complying with the signed agreement (Form FDA-1572), the general investigational plan, or the requirements of this part or other applicable parts shall promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation. If the investigator's participation in the investigation is ended, the sponsor shall require that the investigator dispose of or return the investigational drug in accordance with the requirements of 312.59 and shall notify FDA.
- c. The sponsor shall review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator. The sponsors shall make such reports to FDA regarding information relevant to the safety of the drug as are required under 312.32. The sponsor shall make annual reports on the progress of the investigation in accordance with 312.33.
- d. A sponsor who determines that its investigational drug presents an unreasonable and significant risk to subjects shall discontinue those investigations that present the risk, notify FDA, all institutional review boards, and all 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 by 312.59, and furnish FDA with a full report of the sponsor's actions. The sponsor shall 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, FDA will confer with a sponsor on the need to discontinue an investigation.

### ***312.57 Recordkeeping and record retention***

- a. A sponsor shall maintain 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 investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.
- b. A sponsor shall maintain complete and accurate records showing any financial interest in 54.4(a)(3)(i), (a)(3)(ii), (a)(3)(iii), and (a)(3)(iv) of this chapter paid to clinical investigators by the sponsor of the covered study. A sponsor shall also maintain complete and accurate records concerning all other financial interests of investigators subject to part 54 of this chapter.
- c. A sponsor shall retain the 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 FDA has been so notified.
- d. A sponsor shall retain reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies described in, 320.38 or 320.63 of this chapter, and release the reserve samples to FDA upon request, in accordance with, and for the period specified in 320.38.

### ***312.58 Inspection of sponsor's records and reports***

- a. FDA inspection. A sponsor shall upon request from any properly authorized officer or employee of the Food and Drug Administration, 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 part. Upon written request by FDA, the sponsor shall submit the records or reports (or copies of them) to FDA. The sponsor shall discontinue shipments of the drug to any investigator who has failed to maintain or make available records or reports of the investigation as required by this part.
- b. Controlled substances. If an investigational new drug is a substance listed in any schedule of the Controlled Substances Act (21 U.S.C. 801; 21 CFR part 1308), records concerning shipment, delivery, receipt, and disposition of the drug, which are required to be kept under this part or other applicable parts of this chapter shall, upon the request of a properly authorized employee of the Drug Enforcement Administration of the U.S. Department of Justice, be made available by the investigator or sponsor to whom the request is made, for inspection and copying. In addition, the sponsor shall assure that adequate precautions are taken, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

### ***312.59 Disposition of unused supply of investigational drug***

The sponsor shall assure the return of all unused supplies of the investigational drug from each individual investigator whose participation in the investigation is discontinued or terminated. The sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug. The sponsor shall maintain written records of any disposition of the drug in accordance with 312.57.

### ***312.60 General responsibilities of investigators***

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights,

safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. An investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered, except as provided in 50.23 or 50.24 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

### ***312.61 Control of the investigational drug***

An investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it.

### ***312.62 Investigator recordkeeping and record retention***

- a. Disposition of drug. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 312.59.
- b. (b) Case histories. An 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 shall document that informed consent was obtained prior to participation in the study.
- c. Record retention. An investigator shall retain records required to be maintained under this part 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 FDA is notified.

### ***312.64 Investigator reports***

- a. Progress reports. The investigator shall furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. The sponsor is required under 312.33 to submit annual reports to FDA on the progress of the clinical investigations.
- b. Safety reports. An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately.
- c. Final report. An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.
- d. Financial disclosure reports. The clinical investigator shall provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under part 54 of this chapter. The clinical investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

### ***312.66 Assurance of IRB review***

An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research

activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

### ***312.68 Inspection of investigator's records and reports***

An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to 312.62. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

### ***312.69 Handling of controlled substances***

If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

### ***312.70 Disqualification of a clinical investigator***

- a. If FDA has information indicating that an investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has submitted to FDA or to the sponsor false information in any required report, the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research will furnish the investigator written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered but not accepted by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research, the investigator will be given an opportunity for a regulatory hearing under part 16 on the question of whether the investigator is entitled to receive investigational new drugs.
- b. After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has deliberately or repeatedly submitted false information to FDA or to the sponsor in any required report, the Commissioner will notify the investigator and the sponsor of any investigation in which the investigator has been named as a participant that the investigator is not entitled to receive investigational drugs. The notification will provide a statement of basis for such determination.
- c. Each IND and each approved application submitted under part 314 containing data reported by an investigator who has been determined to be ineligible to receive investigational drugs will be examined to determine whether the investigator has submitted unreliable data that are essential to the continuation of the investigation or essential to the approval of any marketing application.
- d. If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor who shall have an opportunity for a regulatory hearing under part 16. If a danger to the public health exists, however, the Commissioner shall terminate the IND immediately and notify the sponsor of the determination. In such case, the sponsor shall have an opportunity for a regulatory hearing before FDA under part 16 on the question of whether the IND should be reinstated.

- e. If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued approval of the drug product for which the data were submitted cannot be justified, the Commissioner will proceed to withdraw approval of the drug product in accordance with the applicable provisions of the act.
- f. An investigator who has been determined to be ineligible to receive investigational drugs may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ investigational drugs solely in compliance with the provisions of this part and of parts 50 and 56.



**Attachment 3.**

Effective Date 08/16/02

Revision Date \_\_\_\_\_

Page 1 of 3

**THE OHIO STATE UNIVERSITY MEDICAL CENTER**

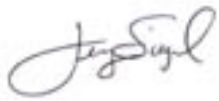
**DEPARTMENT OF PHARMACY  
POLICY AND PROCEDURE**

---

**Title: Investigational Drug Service Policy and Procedures**

---

Prepared by: Department of Pharmacy

Authorized by:   
Jerry Siegel, Senior Director

**POLICY STATEMENT:**

The pharmacists and pharmacy technicians of the Investigational Drug Service (IDS) are responsible for coordinating investigational/clinical drug studies approved by the Biomedical Sciences Institutional Review Board (IRB), James Cancer Institutional Review Board or an external IRB. Investigational drug supplies are handled and dispensed in accordance with applicable legal, institutional, professional, and sponsor requirements.

**PROCEDURES**

**1.0 Investigational Drug Protocol Review**

Pharmacists of the Investigational Drug Service are responsible for reviewing proposed investigational/clinical drug studies as members of or consultants to the Biomedical Sciences IRB, James Cancer IRB, Clinical Scientific Review Committee (The James Cancer Hospital and Solove Research Institute) and other committees, as applicable. Protocol review is also performed by an IDS pharmacist prior to Department of Pharmacy participation in an investigational/clinical drug study (see below, "2.00 Establishment of an Investigational Drug Study"). An IRB approval must be obtained by investigators prior to initiation of research.

**2.0 Establishment of an Investigational Drug Study**

Proposed investigational/clinical drug studies are reviewed by an investigational drug pharmacist for feasibility, compliance with applicable institutional and professional standards, and cost considerations prior to the involvement of the Department of Pharmacy. Pharmacy participation procedures (including randomization and blinding, if applicable), drug data sheets, and inservice materials are developed and utilized, as necessary. Copies of investigational drug protocols are maintained in the participating dispensing area(s) and the Investigational Drug Service office. Initial drug supplies may be obtained by a principal investigator or the investigational drug technicians, or can be provided by the sponsor. Packaging, labeling, and storage requirements; inventory records; computer entries; and pharmacy reimbursement procedures are established.

### **3.0 Investigational Drug Inventory/Recordkeeping**

Investigational drug supplies are inventoried on a regular basis by the investigational drug technicians. Separate dispensing records and perpetual inventories are maintained for each drug, strength, dosage form, and research protocol. Recordkeeping may include both OSU Investigational Drug Records and individual sponsor record forms (e.g., NCI Drug Accountability Records). Additional records, such as drug disposition forms or return drug lists, may be required at the completion of a study.

### **4.0 Investigational Drug Ordering/Disposition**

Drug supplies are ordered, inventoried, and maintained by the investigational drug technicians, in cooperation with principal investigators, research protocol personnel, and sponsors. Specialized forms and procedures are utilized, as necessary. Outdated clinical supplies or unused stock remaining at the end of the study period are returned or destroyed by the investigational drug technicians, in accordance with appropriate legal, investigator, and sponsor requirements. Used drug containers are routinely disposed of at the time of use. Transport and incineration of study supplies to be destroyed is performed by a bonded, licensed hazardous waste contractor, according to departmental and institutional policies established for handling hazardous waste. Records of drug ordering, receipt, and disposition are maintained.

### **5.0 Investigational Drug Dispensing**

All drugs to be used for investigational purposes must be stored in and dispensed from the Department of Pharmacy, unless an exemption is requested. Investigational drugs are dispensed through routine distribution systems, upon authorized verbal or written order or prescription, in compliance with applicable legal, institutional, and professional standards. Drug dispensing records, including both OSU Investigational Drug Records and individual sponsor record forms, are maintained. Additionally, verification of patient eligibility and informed consent, special packaging and/or labeling, and other distributive and/or clinical activities (e.g., adverse reaction reporting) are performed on a 24-hour basis, as required. Dispensing fees may be charged to patients or principal investigators, depending on the nature of the research protocol.

### **6.0 Investigational Drugs from Another Institution**

When a subject in a research study conducted by other than OSU faculty becomes a patient of The Ohio State University Hospitals and Clinics or the James Cancer Hospital and Solove Research Institute, and the OSU physician has determined that it is appropriate to continue study participation, the following must be obtained:

1. A copy of the research protocol (including description of treatment procedures, drug preparation, adverse events, etc.),
2. A copy of the originating institution's IRB approval, and
3. A copy of the subject's (now patient's) signed informed consent document.

The investigator at the originating institution remains responsible for the investigational drug administration and follow-up and should be informed of the hospitalization. Note: since Ohio State is not participating as a "research site", OSU IRB approval is not required. The Investigational Drug Service should be contacted for assistance when investigational drugs are brought into the institution. Once the appropriate contacts and documentation have been obtained, as above, administration of the investigational drug(s) may proceed as in the Department of Pharmacy Policy and Procedure Manual, "Handling of Patients' Own Medications."

### **7.0 Emergency Use of Investigational Drugs**

To obtain an investigational drug/biologic for "emergency use" (i.e., use of a test article on a human subject in a life threatening situation for which no standard acceptable treatment is available), a physician must contact the sponsor or the FDA with specific information about the proposed circumstances for use. The clinical investigator is required to obtain informed consent from the subject or the subject's legally

authorized representative (except in certain situations), and an IND (Investigational New Drug Application) for the drug's use is also necessary. Investigational drugs for emergency use should be shipped directly to the Department of Pharmacy, in care of the Investigational Drug Service; the IDS should be contacted prior to the expected arrival of the drug. The Investigational Drug Service and Department of Pharmacy are responsible for the proper storage, labeling, dosage preparation, dispensing, and accountability of all investigational drugs and for ensuring that adequate information about the drug is available to pharmacy and nursing staffs. Physicians should notify the IDS as soon as possible if additional drug supplies will be needed following the initial treatment course. Emergency use of an investigational drug or biologic is exempt from FDA requirements for IRB review if the emergency use is reported by the physician to the IRB within five working days. Approval is limited to the single emergency use of the investigational drug for the treatment of one subject by one clinical investigator. The Department of Pharmacy will obtain verification of informed consent (or its waiver) prior to initial dispensing of the investigational drug. The clinical investigator is responsible for completing all sponsor documentation of the investigational drug's use; drug accountability records can be completed by the Department of Pharmacy, as applicable.

Note: for additional information, see the FDA Information Sheet "Emergency Use of an Investigational Drug or Biologic" at:

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm117832.htm#emergency>.