

SOP 15A v.2

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**HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL &  
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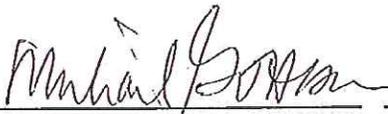
**OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS**

**SOP Number:** SOP 15A v.2

**SOP Title:** Research Regulated by the Food and Drug Administration (FDA):  
Information and Policies Specific to Research Involving Investigational New Drugs  
(Including Biological Products)

**Distribution:** Scientific Directors; Clinical Directors; Clinical Investigators, IRB  
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**SOP 15A RESEARCH REGULATED BY THE FOOD AND DRUG ADMINISTRATION  
(FDA): INFORMATION AND POLICIES SPECIFIC TO RESEARCH INVOLVING  
INVESTIGATIONAL NEW DRUGS (INCLUDING BIOLOGICAL PRODUCTS)**

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## **SOP 15A RESEARCH REGULATED BY THE FOOD AND DRUG ADMINISTRATION (FDA): INFORMATION AND POLICIES SPECIFIC TO RESEARCH INVOLVING INVESTIGATIONAL NEW DRUGS (INCLUDING BIOLOGICAL PRODUCTS)**

### **15A.1 DEFINITIONS AND LINKS TO WEBSITES**

Terms that first appear below in bold and with an asterisk are defined in **Appendix A - Definitions**. Links to websites are provided in **Appendix B – Links to Websites**.

### **15A.2 PURPOSE**

This SOP provides guidance for investigators engaged in research involving a **drug(s)\*** or **biological products\*** administered under a "Notice of Claimed Investigational Exemption for a New Drug", an investigational new drug (**IND\***) application (Ref: 21 CFR 312.3). Research undertaken consistent with this SOP must also, as applicable, comply with 45 CFR 46 and related HRPP SOPs.

### **15A.3 POLICY**

Investigations involving **investigational drugs\*** must be conducted in accordance with applicable FDA regulations, including the investigational new drug regulations at 21 CFR Part 312 (see Appendix B- Links to Websites). Such investigations should also be conducted consistent with GCP (Appendix B- Links to Websites) and with the policies contained in SOP 15 "Research Regulated by the Food and Drug Administration (FDA): General Procedures for IND and IDE Applications".

### **15A.4 EXEMPTIONS FROM FDA INVESTIGATIONAL NEW DRUG REGULATIONS**

21 CFR 312.2(b), (see **Appendix B- Links to Websites**) explains what criteria various kinds of clinical investigations must meet to be exempt from the requirements of 21 CFR part 312, including the requirement for an IND. The exemptions in 21 CFR 312.2(b) are as follows:

- A. A **clinical investigation\*** of a drug is exempt from the investigational new drug regulations (21 CFR part 312) if the drug is lawfully marketed in the United States and ALL of the following are true:

1. The investigation is not intended to be reported to the 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.
  2. 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.
  3. 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.
  4. The investigation is conducted in compliance with the requirements for institutional review set forth in 21 CFR part 56 (see also NIH SOP 7 “Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs)” and SOP 8 “Procedures and Required Documentation for Submission and Initial Review of Protocols”), and with the requirements for informed consent set forth in 21 CFR part 50 (for NIH policy see also SOP 12 “Requirements for Informed Consent from Research Subjects”).
  5. The investigation is conducted in compliance with the requirements regarding promotion of an investigational drug at 21 CFR 312.7.
- B. A clinical investigation involving one of the below-listed *in vitro* diagnostic biological products is exempt from the requirements of the investigational new drug regulations (21 CFR part 312) if the product is intended to be used in a diagnostic procedure that confirms the diagnosis made by another physician, and is shipped in compliance with 21 CFR 312.160 (see Appendix B-Links to websites). The biological products to which this exemption applies are the following:
1. Blood grouping serum
  2. Reagent red blood cells
  3. Anti-human globulin

- C. A drug intended solely for tests *in vitro* or in laboratory research animals is exempt from the requirements of 21 CFR part 312 if it is shipped in accordance with 312.160.
- D. A clinical investigation involving use of a placebo is exempt from the requirements of 21 CFR part 312 if the investigation does not otherwise require submission of an IND.

The applicability of 21 CFR part 312 to *in vivo* bioavailability studies is subject to the provisions in 21 CFR 320.31. See 21 CFR 312.2(c). Accordingly, NIH **investigators\*** and **sponsor-investigators\*** should refer to 21 CFR 320.31 to determine whether such studies are exempt from the requirements of 21 CFR part 312.

NIH investigators and sponsor-investigators should also be aware that “[a] clinical investigation involving an exception from informed consent under 50.24 of this chapter [exception from informed consent requirements for emergency research] is not exempt from the requirements of [the investigational new drug regulations at 21 CFR part 312]. See 21 CFR 312.2(b)(6).

## 15A.5 DETERMINATION OF WHETHER AN IND IS NEEDED

Under FDA regulations at 21 CFR 312.20, **sponsors\***, including sponsor-investigators, are required to submit an IND to the FDA if the sponsor intends to conduct an investigation that is subject to 21 CFR part 312. Consistent with this requirement, NIH sponsor-investigators will make a preliminary determination whether or not an IND is needed. All NIH investigators, including investigators who are not sponsor-investigators, will do the following:

- A. If the PI thinks that the FDA regulations at 21 CFR part 312 do not apply, or the sponsor has identified the investigation as not requiring an IND, the PI will provide to the IRB a rationale why an IND is not needed and appropriate written documentation of this determination.
- B. If FDA regulations at 21 CFR part 312 do apply, the PI will provide the IRB with IND documentation. Documentation of the IND in the form of a dated written communication from the FDA, issued at the time the IND number is assigned, should be submitted as an attachment to the initial protocol application. Research may not begin until a valid IND is in effect. The IND goes into effect 1) thirty days after FDA receives the IND, unless FDA notifies

the sponsor that the investigations described in the IND are subject to a clinical hold under 312.42; or 2) An earlier notification by FDA that the clinical investigations in the IND may begin. (21 CFR 312.40 (b))

- C. The IRB administrative staff, in collaboration with the IRB Chair, will review the documents provided by the PI and confirm whether the research requires an IND and that there is appropriate supporting documentation.

## **15A.6 RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR (PI)**

The responsibilities listed here relate specifically to FDA-regulated drug research conducted at NIH, and are in addition to those provided in SOP 19 “Investigator Responsibilities” and SOP 15 “Research Regulated by the Food and Drug Administration (FDA): “General Procedures for Both IND and IDE Applications.”

### **15A.6.1 RESPONSIBILITIES RELATED TO ACCOUNTABILITY, STORAGE AND USE OF INVESTIGATIONAL PRODUCTS**

- A. Accountability, storage and disposition of investigational products:  
Investigators’ general responsibilities under FDA regulations (21 CFR 312.60 and 812.100) include the responsibility for control of the drugs under investigation. Investigators’ specific responsibilities under FDA regulations (21 CFR 312.62(a) and 812.140(a)(2)) include keeping adequate records of the disposition of the drug or device. Responsibility for investigational product(s) at the trial site(s) ultimately rests with the PI. However some or all of the duties associated with this responsibility may be delegated to other appropriate individuals. For example, at the NIH, the CC Pharmacy Department is responsible for the receipt, storage, dispensing and disposition of all investigational drugs (see 15A.6.3, below).
- B. Use of the product: The PI will ensure that the investigational product(s) are used only in accordance with the approved protocol. In the case of drugs, PIs will maintain records that document that subjects were provided the doses specified by the protocol.
- C. Education of research participants about proper use of the product: The PI, or a person designated by the PI, will explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

### **15A.6.2 ADHERENCE TO THE POLICIES AND PROCEDURES OF THE PHARMACY DEPARTMENT AT THE CLINICAL CENTER (CC)**

- A. PI adherence to CC Pharmacy policies for studies involving investigational drugs: The PI is required to state in the protocol that he/she will comply with the NIH Clinical Center Pharmacy's policies and the procedures, which are described in 15A.6.3, below.
- B. Information to be reported/disseminated to the NIH Pharmacy by the PI for research involving investigational new drugs:
  - 1. The PI must ensure that the protocol number is provided to the NIH/CC Pharmacy to document the IRB's initial approval of the research study.
  - 2. PIs must assure that the Pharmacy is notified of all changes in the approved protocol including suspensions, terminations, amendments or modifications in the use and handling of investigational drugs or other drugs specifically required by the protocol.
  - 3. The PI must inform the Pharmacy when a study involving investigational drugs has been discontinued or will not start.
- C. For studies involving investigational drugs that are conducted outside the Clinical Center, the PI will follow the site-specific policies and procedures of the Institute or Center (IC) where the investigational drug is stored.

### **15A.6.3 POLICIES AND PROCEDURES OF THE CC PHARMACY**

CC Pharmacy Policies: The Clinical Center Medical Administrative and Pharmacy Department policies related to the handling of investigational drugs are listed in **Appendix C - Policies of the Pharmacy Department at the Clinical Center.**

- A. CC Pharmacy Procedures and Duties: As explained above, under FDA regulations the investigator is ultimately responsible for the control and disposition of the investigational drug (see 21 CFR 312.60 and 312.62(a)). However, at the NIH, certain duties related to the control and disposition of the investigational drug are delegated to the CC Pharmacy Department. The CC Pharmacy Department manages the receipt, storage, dispensing and disposition of all investigational drugs. This includes, but is not limited to, the following:

1. Maintenance of the following records:
  - a. the product's delivery to the trial site,
  - b. the inventory at the site,
  - c. the use in each research participant, and
  - d. the return to the sponsor or alternative disposition of unused product(s).
2. Content of records:
  - a. dates,
  - b. quantities,
  - c. batch/serial numbers,
  - d. expiration dates (if applicable), and
  - e. the unique code numbers assigned to the
  - f. investigational product(s) and trial subjects.
3. Storage of the product: The investigational product(s) should be stored as specified by the sponsor and in accordance with the IRB-approved protocol.
4. Disposition and reconciliation of products: The CC pharmacy will destroy investigational product(s) or will return investigational products received from the sponsor to the sponsor.

#### **15A.6.4 REQUIRED REPORTS**

##### **A. IND Reports**

1. Investigator reporting: Under 21 CFR 312.64, investigators are required to provide progress, safety, final and financial disclosure reports to the sponsor.

2. Annual Reports: Sponsors including NIH sponsor-investigators are responsible for submitting annual reports to the FDA as required in FDA Regulations at 21 CFR 312.33 (see Appendix B-Links to websites). Under 21 CFR 312.33, a sponsor must submit to FDA, within 60 days of the anniversary date that the IND went into effect, a report of the progress of the investigation.
3. Safety Reports: Sponsors including NIH sponsor-investigators are responsible for submitting safety reports as required in FDA Regulations at 21 CFR 312.32. (See Appendix B-Links to websites). The requirements in 21 CFR 312.32 include, but are not limited to, the following:
  - a. The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, and
  - b. The sponsor must notify FDA and all participating investigators in writing as soon as possible but no more than 15 calendar days after the sponsor's determination of the need for reporting, any adverse experience associated with the drug that is both serious and unexpected, any findings from other studies that suggest a significant risk in humans exposed to the drug, any finding from tests in laboratory animals or experiments that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity or any increased rate of occurrence of serious suspected adverse reactions, based on information listed in the protocol or the **investigator's brochure**\*.
  - c. If the event is an unexpected fatal or life-threatening **suspected adverse reaction**\*, sponsors must submit a **serious adverse event (SAE)**\* report to the FDA within 7 days after the sponsor's initial receipt of the information.
  - d. Study endpoints, such as mortality or major morbidity, must be reported to FDA as described in the protocol and are not reported as a safety report unless a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (See CFR 21 312.32(c)(5))

- B. Other progress reports (See Appendix B-Links to websites ), **Guideline for Good Clinical Practice (GCP)\***: Consistent with GCP, NIH PIs will provide other written reports, as required by the IRB-approved protocol, to the sponsor, the IRB, and, when required, to the FDA on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.
  
- C. Final Report(s) and Submission of Data by the PI. Upon completion or termination of the trial, the PI will provide the sponsor with all required reports and data; the IRB with a summary of the trial's outcome, and provide any final reports to the sponsor and/or the FDA required by applicable laws and regulations.

## **15A.7 EXCEPTION FROM INFORMED CONSENT REQUIREMENTS FOR EMERGENCY RESEARCH**

These requirements are found in 21 CFR 50.24 (see Appendix B-Links to websites). FDA regulations related to exception from informed consent for emergency research (21 CFR 50.24.) are located in Appendix D. This research must also comply with the requirements of 45 CFR 46, if applicable.

## **15A.8 EXPANDED ACCESS TO INVESTIGATIONAL DRUGS FOR TREATMENT USE, INCLUDING EMERGENCY IND**

### **15A.8.1 GENERAL CONSIDERATIONS AND DEFINITIONS**

- A. General Considerations: FDA's regulations at 21 CFR 312.300-312.320 (see Appendix B-Links to websites) contain the requirements for the use of investigational new drugs (and approved drugs where availability is limited by a risk evaluation and mitigation strategy (REMS) when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition.<sup>1</sup> The aim of these regulations is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or

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<sup>1</sup> Generally expanded access activities, including expanded access program activity for emergency uses, are for treatment purposes only and therefore are not considered human subjects research under 45 CFR 46. If an expanded access activity, including an emergency use, also involves research, then the human subjects protections rules (45 CFR 46) apply. FDA generally requires that data from expanded access uses be reported to it.

condition. These regulations contain criteria, submission requirements, and safeguards applicable:

1. to all expanded access uses (21 CFR 312.305),
  2. when an investigational drug is to be used for the treatment of an individual patient, including for **emergency uses\*** (21 CFR 312.310),
  3. when an investigational drug is to be used in the treatment of an “intermediate-size” patient population (21 CFR 312.315), and
  4. when an investigational drug is to be used for widespread treatment use (21 CFR 312.320).
- B. Definitions: For the purposes of the regulations regarding expanded access to investigational drugs (21 CFR 312.300-320), the following definitions apply:
1. Immediately life-threatening disease or condition means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment, 21 CFR 312.300(b).
  2. Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one, 21 CFR 312.300(b).

#### **15A.8.2 CRITERIA AND SAFEGUARDS APPLICABLE TO ALL EXPANDED ACCESS USES**

- A. Under 21 CFR 312.305(a), for any expanded access use, including emergency uses, FDA must determine that:
1. The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or

satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

2. The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and
  3. Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.
- B. 21 CFR 312.305(c) also provides various safeguards for all expanded access uses, including that investigators are responsible for ensuring that expanded access protocols are conducted in accordance with 21 CFR part 50 (FDA's informed consent regulations) and 21 CFR part 56 (FDA's IRB regulations).

### **15A.8.3 EMERGENCY USE IND FOR NON-RESEARCH PURPOSES**

- A. FDA Regulations in general: Under 21 CFR 312.310(d), if there is an emergency that requires that an individual patient be treated before a written IND submission to the FDA (also known as an Emergency IND) can be made in accordance with 21 CFR 312.310(b) and 312.305(b), the FDA may authorize the Emergency use IND expanded access use by telephone, facsimile or other means of electronic submission (for more information see **Appendix B**-Links to websites). In such a case, the licensed physician or sponsor must explain how the expanded access use will meet the requirements of 312.305 and 312.310 and must agree to submit an expanded access submission within 15 working days of the FDA's authorization of the use.

- B. Informed consent for emergency use:

For an emergency use and documentation, as with all expanded access uses, the investigator is required to obtain informed consent from the subject or the subject's legally authorized representative in accordance with FDA regulations at 21 CFR part 50 (see 21 CFR 312.305(c)(4))  
Circumstances will dictate which one of the following two courses of action will be taken with regard to exception of informed consent for emergency use. 21 CFR 50.23 provides exceptions to the general informed consent

requirement for the emergency use of a **test article**\* in a single patient (see Appendix B-Links to websites), including as follows:

1. Informed consent is not required if both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing that all of the following conditions are met:
  - a. The subject is confronted by a life-threatening situation necessitating the use of the test article.
  - b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
  - c. Time is not sufficient to obtain consent from the subject's legal representative.
  - d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.
  
2. If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and time is not sufficient to obtain an independent physician's determination that the four conditions above apply in advance of using the test article, the clinical investigator should make the determination. In this circumstance, within 5 working days after the use of the article, the investigator must have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

The documentation required in paragraph (2) or (3) above shall be submitted to the IRB within 5 working days after the use of the test article (see 21 CFR 50.23(c)). The IRB will review these reports to determine if the circumstances met FDA regulations.

For more information refer to 21 CFR part 50 (see Appendix B-Links to websites).

### C. FDA Requirements for IRB Review of Emergency Use INDs

For an Emergency use IND, as with all expanded access uses, an investigator is responsible for ensuring that IRB review is obtained in a manner consistent with the requirements of 21 CFR part 56 (see 21 CFR 312.305(c)(4)). Emergency use of an investigational drug in accordance with 21 CFR 312.310 is exempt from the requirement for prospective IRB review and approval, provided that such use is reported to the IRB within 5 working days (21 CFR 56.104(c)). NIH researchers should also be aware that:

1. FDA regulations require that any subsequent use of the investigational product at the institution be subject to IRB review (21 CFR 56.104(c)).
2. The FDA regulations do not provide for expedited IRB approval in emergency situations (see 21 CFR 56.110).

#### **15A.8.4 NIH REQUIREMENTS FOR EMERGENCY INDS**

In addition to the FDA requirements for Emergency IND usage above, the NIH has the following requirements:

- A. NIH requires that the IRB Chair/designee and the IC Clinical Director/designee sign the “Notification Form: Emergency IND” form before the NIH investigator may seek approval from the FDA. For more information and to obtain NIH approval for emergency use of an investigational drug, use **Attachment 1** “Notification Form: Emergency IND”.
- B. When emergency treatment has ended, the investigator will submit a completion report to the IRB.

#### **15A.8.5 REQUIREMENTS SPECIFIC TO EXPANDED ACCESS TO INDIVIDUAL PATIENTS (FOR NON-EMERGENCY USE), INTERMEDIATE-SIZE POPULATIONS, AND WIDESPREAD USE**

Refer to 21 CFR 312.310, 312.315, and 312.320, respectively (see Appendix B-Links to websites).

## **LIST OF APPENDICES**

Appendix A – Definitions

Appendix B – Links to web sites

Appendix C - Policies of the Pharmacy Department at the Clinical Center

Appendix D: FDA Regulations Regarding Exception from Informed Consent  
Requirements for Emergency research (21 CFR SEC. 50.24)

## **LIST OF ATTACHMENTS**

Attachment 1 – Notification Form: Emergency IND

## APPENDIX A: DEFINITIONS

Except where noted otherwise, the definitions listed below are for the purpose of this SOP and are not necessarily found in the Federal Food, Drug, and Cosmetic Act (FDCA), the Public Health Service Act, FDA regulations, or other applicable laws and regulations.

- A. Adverse event:** means any untoward medical occurrence temporally associated with the use of a drug in humans, whether or not considered drug related.
- B. Biological products:** see definition of “Test Article”
- C. Case Report Form (CRF):** is a protocol-specific form designed by the Principal Investigator or sponsor to enable the sponsor to collect data from each participating site and on each patient participating in a clinical trial.
- D. Clinical investigation:** FDA regulations define a clinical investigation as any experiment that involves a test article (e.g., drug or medical device-see definition of “test article”) and one or more human subjects (see definition of “human subjects”) that is subject to requirements for prior submission to the FDA or is intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit. (see 21 CFR 50.3(c) and 56.102(c)). The terms research, clinical research, clinical study, study and clinical investigation are synonymous for the purposes of this SOP.
- E. For drugs,** a clinical investigation is “any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects . . . an experiment is any use of the a drug except for the use of a marketed [approved] drug in the course of medical practice.” 21 CFR 312.3(b).
- F. Color Additive:** 21 CFR 70.3(f): Any material, not exempted under section 201(t) of the act, that is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal, mineral, or other source and that, when added or applied to a food, drug, or cosmetic or to the human body or any part thereof, is capable (alone or through reaction with another substance) of imparting a color thereto. Substances capable of imparting a color to a container for foods, drugs, or cosmetics are not color additives unless the customary or reasonably foreseeable handling or use of the container may reasonably be expected to result in the transmittal of the color to the contents of

the package or any part thereof. Food ingredients such as cherries, green or red peppers, chocolate, and orange juice which contribute their own natural color when mixed with other foods are not regarded as color additives ; but where a food substance such as beet juice is deliberately used as a color, as in pink lemonade, it is a color additive. Food ingredients as authorized by a definitions and standard of identity prescribed by regulations pursuant to section 401 of the act are color additives, where the ingredients are specifically designated in the definitions and standards of identity as permitted for use for coloring purposes. An ingredient of an animal feed whose intended function is to impart, through the biological processes of the animal, a color to the meat, milk, or eggs of the animal is a color additive and is not exempt from the requirements of the statute. This definition shall apply whether or not such ingredient has nutritive or other functions in addition to the property of imparting color. An ingested drug the intended function of which is to impart color to the human body is a color additive. For the purposes of this part, the term color includes black, white, and intermediate grays, but substances including migrants from packaging materials which do not contribute any color apparent to the naked eye are not color additives (See Appendix B- Links to websites).

**G. Drug:**

- A substance recognized by an official pharmacopoeia or formulary
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease
- A substance (other than food) intended to affect the structure or any function of the body
- A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device
- Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process).

**H. Emergency use:** FDA regulations define emergency use as “the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.” 21 CFR 56.102(d).

**I. Food Additives:** 21 CFR 170.3 (e)(1): Food additives include all substances not exempted by section 201(s) of the act, the intended use of which results or may reasonably be expected to result, directly or indirectly, either in their becoming a component of food or otherwise affecting the characteristics of food. A material

used in the production of containers and packages is subject to the definition if it may reasonably be expected to become a component, or to affect the characteristics, directly or indirectly, of food packed in the container. “Affecting the characteristics of food” does not include such physical effects, as protecting contents of packages, preserving shape, and preventing moisture loss. If there is no migration of a packaging component from the package to the food, it does not become a component of the food and thus is not a food additive. A substance that does not become a component of food, but that is used, for example, in preparing an ingredient of the food to give a different flavor, texture, or other characteristic in the food, may be a food additive (see Appendix B- Links to websites).

- J. The Guideline for Good Clinical Practice (GCP):** GCP is an international ethical and scientific standard developed by the International Conference on Harmonisation (ICH) for designing, conducting, recording and reporting trials involving the participation of human subjects consistent with the principles of the Declaration of Helsinki. FDA published this guidance in the Federal Register on May 9, 1997 (62 FR 25692) (see Appendix B- Links to websites.)
- K. Human subject:** FDA regulations define a human subject as “an individual who is or becomes a participant in research, either as a recipient of the test article [see definition of “test article”] or as a control. A subject may be either a healthy human or a patient.” 21 CFR 50.3(g); see also 21 CFR 56.102(e).
- a. **For drugs,** a subject “means a human who participates in an investigation, either as a recipient of the investigational new drug [see definition of “investigational drug”] as a control. A subject may be a healthy human or a patient with a disease.” 21 CFR 312.3(b).
  - b. **For medical devices,** a subject “means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device [see definition of “investigational device”] is used or as a control. A subject may be in normal health or may have a medical condition or disease.” 21 CFR 812.3(p).
- L. Investigational device:** “means a device, including a transitional device that is the object of an investigation”, 21 CFR 812.3(g).
- M. Investigational drug:** “means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes.” 21 CFR 312.3(b).

- N. IND:** An IND means an Investigational New Drug application in accordance with 21 CFR Part 312.
- O. Investigator:** “[A]n individual who conducts a clinical investigation, i.e., under whose immediate direction the test article [see #25] is administered or dispensed to, or used involving a subject, or, in the event of an investigation conducted by a team of individuals, is the **responsible leader of that team.**” 21 CFR 50.3(d).
- P. Investigator’s Brochure.** “A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) on human subjects.” See the Guideline for Good Clinical Practice at section 6 (see Appendix B- Links to websites).
- Q. Non-Therapeutic Trial:** In the Guideline for Good Clinical Practice (GCP), FDA describes this as a trial in which there is no anticipated direct clinical benefit to the subject. See GCP at sections 4.8.13 and 4.8.14 (see Appendix B- Links to websites).
- R. Serious adverse event:** An adverse event or suspected adverse reaction is considered “serious” if, in the view of the investigator or sponsor, it 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 substantial disruption of the ability to conduct normal life functions, 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 medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- S. Sponsor:** A person (or other entity) “who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article [see #20] is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A[n] [entity] other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct a clinical investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.” 21 CFR 50.3(e); see also 21 CFR 56.102(j).

- T. Sponsor-investigator:** An “individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency” (see 21 CFR 312.3 and 21 CFR parts 50.3(f) and 56.102(k).)
- U. Suspected adverse reaction** (21 CFR 312.32(a)) means any adverse event for which there is a reasonable possibility that the drug caused the adverse event.
- V. Test article:** “Means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act [FDCA] or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).” See **Appendix B** - Links to websites: 21 CFR 50.3(j); see also 21 CFR 56.102(l). The definitions of the various examples of test articles are as follows:
1. Medical devices: A device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory which is-- (1) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes" Section 201(h) of the FDCA (see **Appendix B** - Link to websites).
  2. Biological products: Under the Public Health Service Act (42 USC 262(i)), the term “biological product” “means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings” (see **Appendix B**- Link to websites).

## APPENDIX B: LINKS TO WEB SITES

- A. FDA Form 1572:  
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf>
- B. Guideline for Good Clinical Practice (GCP):  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf>
- C. Information for Sponsor-Investigators Submitting Investigational New Drug Applications (INDs):  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm>
- D. FDA regulations -- IND annual reports (21 CFR 312.33):  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=312.33>
- E. FDA regulations -- IND safety reports (21 CFR 312.32):  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=312.32>
- F. FDA IND regulations 21 CFR part 312 (exemptions from these regulations provided at 312.2):  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312>
- G. FDA regulations -- Expanded Access to investigational Drugs for Treatment Use (21 CFR 312.300-312.320):  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.9>
- H. FDA Regulations -- "Protection of Human Subjects" (21 CFR part 50):  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50>
- I. Comparison of FDA's regulations at 21 CFR parts 50 and 56 and HHS Human Subject Protection Regulations:

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/EducationalMaterials/ucm112910.htm>

J. Test Article, 21 CFR 50.3(j):

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50&showFR=1&subpartNode=21:1.0.1.1.19.1>

K. Medical devices:

[http://www.fda.gov/RegulatoryInformation/Guidances/ucm258946.htm#\\_Toc294261435](http://www.fda.gov/RegulatoryInformation/Guidances/ucm258946.htm#_Toc294261435)

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm>

L. Biological Product, 21 CFR 600.3(h):

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=600.3>

M. Investigational new Drug Applications for Clinical Treatment with Investigational Drugs in Emergency Situations:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm343022.htm>

N. Color Additive: 21 CFR 70.3 (f):

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=70.3&SearchTerm=color%20additive>

O. Food Additives: 21 CFR 170.3 (e)(1):

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=170.3&SearchTerm=170%2E3>

P. OPRR Dear Colleague letter: Emergency Medical Care”

<http://www.hhs.gov/ohrp/policy/hcdc91-01.html>

## **APPENDIX C: POLICIES OF THE PHARMACY DEPARTMENT AT THE CLINICAL CENTER**

- A. M80-3 (rev.) The Use of Investigational or New Drugs In Patient Care (11/24/2009):<http://cc-internal.cc.nih.gov/policies/PDF/M80-3.pdf>
- B. M87-6 (rev.) Policy on Use of Investigational Drugs (FDA-approved IND) Brought into the Clinical Center by Patients for Therapeutic Use (12/31/2008):<http://cc-internal.cc.nih.gov/policies/PDF/M87-6.pdf>
- C. M82-5 (rev.) The Use of Foreign Drugs (Unlicensed In the U.S.A.) Brought into the Clinical Center by Patients for Therapeutic and Not Research Use (3/6/2009):  
<http://cc-internal.cc.nih.gov/policies/PDF/M82-5.pdf>
- D. M05-3 (rev.) Medication Management in the Clinical Center (11/7/2007): <http://cc-internal.cc.nih.gov/policies/PDF/M05-3.pdf>
- E. 118.00.00 Investigational Drugs Dispensing (Access limited to NIH Intranet users): [http://intranet.cc.nih.gov/pharm/pdf/policies/118-Investigational Drugs Dispensing-OP and Pass or discharg.pdf](http://intranet.cc.nih.gov/pharm/pdf/policies/118-Investigational%20Drugs%20Dispensing-OP%20and%20Pass%20or%20discharg.pdf)
- F. 950.01.00 Handling Unit Dose Investigational Drugs (Access limited to NIH Intranet users):  
<http://intranet.cc.nih.gov/pharm/pdf/policies/950.01.00%20Handling%20Unit%20Dose%20Investigational%20Drugs.pdf>
- G. 950.02.00 Logging Investigational Drugs in Unit Dose (Access limited to NIH Intranet users):<http://intranet.cc.nih.gov/pharm/pdf/policies/950.02.00%20Logging%20Investigational%20Drugs%20in%20Unit%20Dose.pdf>
- H. 950.03.00 Ordering and Inventory Control of Investigational Medications (Access limited to NIH Intranet users):  
<http://intranet.cc.nih.gov/pharm/pdf/policies/950.03.00%20Ordering%20and%20Inventory%20Control%20of%20Investigational%20.pdf>

## **APPENDIX D: FDA REGULATIONS REGARDING EXCEPTION FROM INFORMED CONSENT REQUIREMENTS FOR EMERGENCY RESEARCH (21 CFR SEC. 50.24)**

TITLE 21--FOOD AND DRUGS  
CHAPTER I--FOOD AND DRUG ADMINISTRATION  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
SUBCHAPTER A--GENERAL

### PART 50 -- PROTECTION OF HUMAN SUBJECTS

#### Subpart B--Informed Consent of Human Subjects

#### Sec. 50.24 Exception from informed consent requirements for emergency research.

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

- (1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
- (2) Obtaining informed consent is not feasible because:
  - (i) The subjects will not be able to give their informed consent as a result of their medical condition;
  - (ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
  - (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.
- (3) Participation in the research holds out the prospect of direct benefit to the subjects because:
  - (i) Subjects are facing a life-threatening situation that necessitates intervention;
  - (ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual

- subjects; and
- (iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
- (4) The clinical investigation could not practicably be carried out without the waiver.
- (5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.
- (6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.
- (7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:
- (i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
  - (ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
  - (iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
  - (iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

[61 FR 51528, Oct. 2, 1996]