

Guidance and Procedures Number: 34
Title: FDA Requirements
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I. Overview

Research involving new drugs, biologics and devices is regulated primarily by the Food and Drug Administration (FDA) and provides a transition from promising basic or laboratory research to accepted therapeutic or diagnostic procedures for patients. Investigational drug, biologic and device products (also called test articles) include (1) products that are not generally recognized as being safe and effective for any use under the conditions prescribed, recommended, or suggested by the FDA and (2) products already approved by the FDA as safe and effective for specific indications, that are being studied for new indications (or doses, strengths, or frequency) other than those previously approved.

FDA requires IRB review and informed consent in much the same way as DHHS and other federal agencies that support research. However, FDA has several additional reporting conditions that involve investigators directly, as described below. FDA regulations [21 CFR parts 50 and 56] apply to all clinical investigations¹ and research involving products regulated by FDA, regardless of funding source.

II. Investigational New Drug Exemption (IND) and Investigational Device Exemption (IDE)

Federal law prohibits the distribution of new drugs, biologics, and medical devices until the FDA has reviewed clinical data and determined that a particular product is safe and effective for a specific use in human patients. In order to test a new drug, biologic, or device in a clinical trial, it is necessary to obtain an exemption from that law. Thus a drug or device sponsor is required to apply for an Investigational New Drug exemption (IND) or an Investigational Device Exemption (IDE) before tests with human subjects may begin.

(1) If an investigator (PI) is the developer of the drug or device or if no commercial manufacturer is involved, then either the PI or UCLA may be the sponsor for purposes of designing and organizing clinical trials. The sponsor is responsible for submitting an IND and IDE application to FDA and providing a copy of the FDA's response to the IRB. Sponsors also have important administrative and reporting requirements above and beyond those of investigators. Faculty contemplating the dual role of sponsor-PI should consult with OPRS staff about the additional responsibilities that entails.

(2) Specific requirements for protocol design are set forth at 21 CFR 312.23 (drugs) and 21 CFR 812.25 (devices).

¹ See [HRPP Guidance & Procedure # 2: Determining When Research Activities Require UCLA IRB/OPRS Review](#). for related definitions and information.

III. Investigational New Drug Application [IND]

- A. Use of investigational drugs and biologics in clinical trials is regulated by the FDA in 21 CFR 312.
- B. IRBs use a checklist for determining whether an IND should be required for a given study. The checklist is based on requirements outlined in 21 CFR 312.2(b) [see attached].
- C. IRB approval of all research for which the IRB determines that an active IND is required is contingent upon any one of the following. *Please note* that if the needed documentation is submitted to the IRB after approval (i.e., in response to a codicil on the IRB approval notice), the research may not begin until the IRB has acknowledged the documentation by issuing a revised approval notice and releasing stamped study documents.
 - 1. The IRB receives documentation of the IND number from an external sponsor that holds the IND.
 - a. Such documentation may be in the form of the external sponsor's protocol or other communication in which the IND number is printed.
 - b. Such documentation may not otherwise indicate that the FDA has placed the study on clinical hold.
 - 2. The IRB receives FDA documentation that the clinical investigation may begin.
 - 3. In the absence of explicit FDA permission to begin, the IRB receives documentation of an IND number issued to the UCLA sponsor-investigator by the FDA.
 - a. Such documentation must indicate that the FDA received the IND submission on a date at least 30 days prior to the date the sponsor-investigator submits the documentation to the IRB.
 - b. The sponsor-investigator must provide his or her written assurance that the FDA has not placed a clinical hold on the investigation.
 - 4. The IRB receives FDA documentation of exemption or waiver from the requirements to obtain an IND.

IV. Treatment IND

- A. In order to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible, and to obtain data on the drug's safety and effectiveness, the FDA allows treatment use of investigational drugs, where the following criteria are met:

1. The drug is intended to treat a serious or immediately life-threatening² disease.
 - a. In the case of a serious disease, a drug may be made available for treatment use during Phase III investigations or after all clinical trials are completed. In appropriate circumstances, a drug may be made available for treatment use during Phase II.
 - b. In the case of immediately life-threatening disease, a drug may be made available for treatment use earlier than Phase III, but ordinarily not earlier than Phase II.
 2. There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population.
 3. The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed.
- B. Investigators are required to submit a request for a Treatment IND directly to the FDA. Treatment use may begin 30 days after FDA receives the protocol or upon earlier notification by the FDA.
- C. All treatment IND protocols require IRB review and approval prior to implementation.
- D. All requirements for informed consent are applied to treatment IND protocols.

V. Parallel Track

- A. Parallel Track is a mechanism by which FDA makes promising investigational drugs available as quickly as possible to persons with AIDS/HIV related diseases, while generating data on the safety and effectiveness of the drugs.
- B. All Parallel Track protocols require IRB review and approval prior to implementation.
- C. All requirements for informed consent are applied to Parallel Track protocols.

VI. Investigational Device Exemption [IDE]

- A. Use of investigational devices in clinical trials is regulated by the FDA in 21 CFR 812.
- B. IRBs use a checklist for determining whether an Investigational Device Exemption [IDE] should be required for a given study. The checklist is based on requirements outlined in 21 CFR 812.2(c) [see attached].
- C. The IRBs determine whether the use of a device poses significant risk³ (SR) or non-significant risk (NSR). An IDE is required and the study must follow all requirements in

² An “**immediately life-threatening**” disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment [21 CFR 312.34(b)].

21 CFR 812 if the proposed device is determined by the Board as SR. The risk determination is based on the proposed use of a device in an investigation, and not on the device alone. If the subject must undergo a procedure as part of the research, e.g., a surgical procedure, the IRB must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device. In order to make this determination, the Board may request:

1. Investigator's and/or sponsor's risk assessment, to include a rationale for their determination
 2. Consultation from FDA
- D. IRB approval of all research for which an IDE is required is contingent upon IRB's receipt and acknowledgement of an IDE number issued by the FDA or a letter of exemption from the FDA.
- E. If the IRB determines that a device poses non-significant risk and the overall study poses minimal risk⁴, the study may be considered for expedited review. Please refer to [HRPP Guidance & Procedure #8: IRB Review Process - Expedited Review](#) for details.
- F. If the IRB determines that a device poses non-significant risk, the study must follow the abbreviated requirements at 21 CFR 812.2(b).

VII. 510(k)

- A. A device with a 510(k) per section 510(k) of the Food, Drug and Cosmetic Act is one that the FDA has determined equivalent to a device already FDA approved and placed into one of the three classification categories.
- B. A device with a 510(k) may only be used in research in accordance with the labeling cleared by FDA. Investigation of an off-label use of a 510(k) product takes it outside this exemption. A device subject to 510(k) remains "investigational" until the 510(k) is cleared by FDA and the investigational use is subject to the requirements of IDE regulation.

VIII. Changes in Investigational Plan & Devices

³ **Significant Risk Device** means an investigational device that (a) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (b) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; (c) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (d) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject [21 CFR 812.3(m)].

⁴ **Minimal risk** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [45 CFR 46.102(i) and 21 CFR 50.3(k)].

- A. Per 21 CFR 812.35(a), IRBs require submission of prospective FDA approval of changes in a protocol or a device unless the changes meet the following criteria:
1. Developmental changes in the device which do not constitute a significant change in design or basic principles of operation and that are made in response to information gathered during the course of an investigation
 2. Changes in clinical protocols that do not affect (i) the validity of the data or information resulting from the completion of the approved protocol, or the relationship of the likely patient risk to benefit relied upon; (ii) the scientific soundness of the investigational plan; or (iii) the rights, safety, or welfare of the human subjects involved in the investigation.
 3. For the changes described in (a) and (b) above, investigator is advised by the IRBs to submit notification of changes to the FDA within 5 working days of making the changes.
- B. Regardless of whether prospective FDA approval is required, prospective IRB approval is required for all changes to an investigational plan and devices. See [HRPP Guidance & Procedure #11: IRB Review of Modifications to Previously Approved Research](#) for more details.

IX. Humanitarian Use Device

- A. Humanitarian Use Device [HUD] is a device which has received a Humanitarian Use Exemption [HDE] issued by the FDA, which exempts the device from the effectiveness requirements because it meets the following criteria:
1. The device is designed to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the United States.
 2. The device would not be available to a person with a disease or condition referred to in (a) above without an HDE and there is no comparable device.
 3. The device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available device or alternative forms of treatment.
- B. IRBs are required to review and approve the use of all Humanitarian Use Devices [HUD] at UCLA.
- C. FDA does not require informed consent from each patient if a HUD is being used for the limited purpose of benefiting the patients. However, this does not preempt any such requirement for informed consent imposed by the IRBs. As such, IRBs may require that patients provide documented informed consent.
- D. If a HUD is the subject of a clinical investigation, i.e. collection of safety and effectiveness data in support of a pre-market approval, the FDA and the UCLA IRBs require documented informed consent from subjects.

- E. Investigators are required to submit the following materials to the IRB for review of the use of a HUD:
1. Completed applicable sections of Application to Involve Human Subjects in Research
 2. HDE number issued by the FDA
 3. Information submitted to FDA outlining the device is intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect or are manifested in fewer than 4,000 individuals in the USA per year
 4. Description of the patient population who will receive the device and the rare disease or condition for which the device is intended
 5. Scientific rationale for the use of the device in the specific patient population and why/how it may benefit the patients
 6. Documentation with authoritative references demonstrating why/how the possible benefits of the device outweigh the potential risks of injury or illness from its use
 7. Comparison of currently available devices or alternative forms of treatment to the proposed humanitarian use device, and an explanation of why the HUD is the preferred or a viable alternative form of treatment for the given population
 8. If patients will be charged for the cost of the device, a statement of how much patients will be charged and how the charge does not exceed the costs of the device's research and development, fabrication and distribution. This should be accompanied by the report filed with the FDA from the Certified Public Accountant for the HDE.
 9. Device manual to include a description of the device and outlining how the device should be used
 10. HUD submissions are subject to annual continuing review by the IRB. Please refer to policies and procedures for full Committee review for details regarding continuing review.
- F. If the HUD is being used for the limited purpose of benefiting the subjects, and if the UCLA IRB requires that patients give documented informed consent, investigators may use either (a) an informed consent form created using the Sample Consent Form for Medical Research [see attached] as a template, and deleting all references to "research," "investigator" and "subject"; or (b) FDA Patient Labeling. The informed consent document must receive IRB approval prior to implementation.
- G. If the HUD is the subject of a clinical investigation, UCLA investigators are required to develop a research informed consent using the Sample Consent Form for Medical Research as a template. The informed consent document must receive IRB approval prior to implementation.

X. Use of Dietary Supplements / Botanical Products

- A. An IND may be required when a dietary supplement / botanical product is studied for a drug use.⁵
- B. IRBs use a checklist for determining whether an IND should be required for a given study. The checklist is based on requirements outlined in 21 CFR 312.2(b) [see attached].
- C. In order to ensure the quality of a botanical product, IRBs may require the use of a single-source product by an identified manufacturer.
- D. In order for the IRB to review the contents and potential side effects of the product, IRBs may require submission of an informational brochure regarding the product from the manufacturer who will supply the product.

XI. Costs of Investigational Products

- A. As explained in Sections III and IV of [HRPP Guidance & Procedure #32: Financial Obligations](#), subjects may not be charged for investigational products without FDA permission.

XII. Qualifications of Study Personnel

- A. Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article 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 56.102(h)].
- B. The IRBs consider the qualifications and licensure of each investigator and all persons obtaining informed consent.
 - 1. IRBs ensure that only those individuals with appropriate qualifications and licensure carry out the research procedures.
 - 2. Only those individuals who are continuously involved in the research and are qualified to answer any questions regarding the nature of a subject's participation and explain the alternatives to participation are approved to obtain informed consent.
 - 3. For studies involving the use of investigational drugs or devices, the IRBs require that only IRB approved physician investigators obtain informed consent, unless justification for an exception provided by the Principal Investigator is approved by the IRB.

⁵ DRUG USE means the study of a marketed botanical product for its effects on diseases in a proposed investigation (i.e., to cure, treat, mitigate, prevent, or diagnose disease including its associated symptoms) [Center for Drug Evaluation & Research – Frequently Asked Questions on Botanical Drug Product Development: http://www.fda.gov/cder/Offices/ODE_V_BRT/faq.htm].

Regulations:

21 CFR 50
21 CFR 56
21 CFR 312.23
21 CFR 312.40
21 CFR 312.62
21 CFR 312.126
21 CFR 314.126
21 CFR 812.25
21 CFR 812.30
21 CFR 813
21 CFR 814
Federal Food, Drug and Cosmetic Act

References:

FDA Guidance for Industry Botanical Drug Products:
http://www.fda.gov/cder/guidance/4592fnl.htm#_Toc73174083

FDA IRB Information Sheets: <http://www.fda.gov/oc/ohrt/irbs/default.htm>