

## FDA GUIDANCE

### BACKGROUND

Food and Drug Administration (FDA) regulations impose specific requirements regarding the protection of human subjects, some of which vary from the Health and Human Services (HHS) regulations. This guidance summarizes pertinent FDA regulations and distinctions which should be considered in addition to the HHS regulations when research at JHSPH involves products regulated by the FDA.

This guidance covers the following topics:

- the scope of FDA regulations
- informed consent
- emergency use of a test article
- research involving an investigational new drug (IND)
- required reports to the FDA
- adverse drug experience reporting
- research involving devices
- unanticipated adverse device effect reports
- record retention
- Good Clinical Practice (GCP)

This guidance **does not** provide information about **JHSPH institutional policies and procedures** regarding FDA-regulated research. For questions about JHSPH institutional policies regarding research, please contact the JHSPH IRB Office.

### GUIDANCE

#### Scope of FDA Regulations

The FDA regulations apply to all studies of test articles where the results will be submitted to FDA. If research falls within the purview of FDA, then the Federal Regulations governing food, drugs, devices, and cosmetics, as well as all of the other federal regulations governing human subjects research, must be taken into account.

All studies with FDA regulated products involving human subjects must undergo IRB approval even if they are exempt from IND/IDE filing, except for the following categories of studies, which are exempt from IRB review:

- The emergency use of a test article is exempt from IRB review if that use is reported to the IRB within 5 working days. (21 CFR §56.104(c)). Any subsequent use of the test article at the institution is subject to IRB review. (21 CFR §56.104(c)). Emergency use is defined 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)). Test articles include any drug, biological product or medical device for human use, as well as human food additive, color additive, electronic product, or other article subject to FDA regulation. (21 CFR §56.102(l)).
- Test and food quality evaluations and consumer acceptance studies are exempt from IRB review, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. (21 CFR 46.104(d)).

### Informed Consent

FDA regulations impose special requirements on informed consent for FDA regulated research. The provisions for confidentiality must inform subjects that their medical records may be subject to review by the IRB, agents of the FDA and, in some cases, by agents of the industrial sponsor (21 CFR 50.25(a)(5)). Study participants do not have the option of keeping their records from being reviewed by FDA. In addition, the informed consent forms must be dated and signed (21 CFR 50.27(a)). While FDA regulations do not require the subject's copy of the form to be signed, a photocopy of the informed consent form with the subject's signature is preferred. FDA regulations include an exception from the informed consent requirements in emergency situations (21 CFR 50.23), while HHS regulations provide for waiving or altering elements of informed consent if certain conditions are met (45 CFR 46.116(c) & (d)).

### Emergency Use of a Test Article

Emergency use is defined in the FDA regulations 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)). In general, the use of an investigational drug, device, or biologic requires IRB approval. The emergency use provision in the FDA regulations is an exemption from prior review and approval by the IRB (21 CFR 56.104(c)). While the FDA regulations specifically note this exemption, the HHS regulations simply note that they are not intended to limit the provision of emergency medical care (see 45 CFR 46.116(f)). According to the FDA regulations, the emergency use exemption can only be used if all of the following exist:

- There is a life-threatening or severely debilitating situation calling for the use of the investigational drug, biologic or device;
- No standard acceptable treatment is available; and
- There is not sufficient time to obtain approval from IRB.

The exemption allows for one emergency use of a test article without prospective IRB approval. If an investigator determines that a proposed use meets all of the elements of emergency use, she should contact the manufacturer of the drug/biologic to determine if it can be provided under an existing IND, ask the manufacturer if they have an Emergency IND, or contact the FDA for an Emergency IND. The IRB must be notified of any planned emergency use. Within five days of the emergency use, the investigator must file a report with the IRB (21 CFR 56.104(c)). Any subsequent use of the test article at the institution is subject to IRB review (21 CFR 56.104(c)), except when the only problem is lack of time for the IRB to convene, review the use and give approval.

Investigators are still required to obtain informed consent from the patient or the patient's legally authorized representative in an emergency situation. However the investigator does not need to obtain informed consent from the patient or the patient's legally authorized representative if the investigator and an independent physician both certify in writing all of the following (21 CFR 50.23(a)):

- The subject has a life-threatening or severely debilitating situation which requires the use of the investigational drug or biologic;
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
- There is not sufficient time to obtain consent from the subject's legal representative; and
- There is no standard acceptable treatment available.

## Research Involving an Investigational New Drug

### *Investigational New Drug Application*

When a test article has not been approved by FDA for commercial distribution for use in humans, FDA regulations will govern the protocol. First, investigators must determine whether an IND is required for the particular study. There are two options for obtaining an opinion from the FDA about the need for an IND. The first option is to submit the following information in writing:

- The investigator's name, address, phone number, fax number, e-mail address, and affiliation.
- The name and a brief description of the substance to be administered, the source (e.g., animal, synthetic, etc.), dosage form, sterility (if applicable), and supplier.
- A brief summary of the study including the purpose, hypothesis, number of subjects, patient population, condition or disease (if applicable), dose, route, and duration of substance administration.
- A brief explanation of why the investigator considers the substance safe for administration to human subjects under the conditions of the study (append references, if necessary).

This information should be sent to the Food and Drug Administration, Division of Drug Information, HFD-240, 5600 Fishers Lane, Rockville, MD 20857, or by facsimile to 301-827-4577, or by email to [druginfo@cder.fda.gov](mailto:druginfo@cder.fda.gov).

The second option is to utilize the Center for Drug Evaluation and Research Pre-Investigational New Drug Application Consultation Program. The contact information for review divisions, which are organized along therapeutic class, can be found at <http://www.fda.gov/cder/regulatory/applications/Pre-INDConsultationList.pdf>.

If the FDA notifies the investigator that an IND is not required, he or she must first obtain IRB approval before initiating the study. If FDA notifies the investigator that an IND is required, or if the industrial sponsor of a study involving drugs determines that an IND is required, an Investigational New Drug (IND) application must be filed with FDA. The IND application includes information about the nature of the drug; indications for the use of the compound; pre-clinical results; chemistry, manufacturing, and control information about the drug; and the research plan (21 CFR 312.23). Once the initial application for an IND is submitted, FDA has 30 days to review the application and place the study on “hold” if there are apparent reasons why the proposed study should not be conducted. Thirty days after submission, if FDA does not place the study on hold, the study may begin with IRB approval (21 CFR 312.40(b)). An IND may be submitted for one or more phases of an investigation.

Drug studies exempt from the IND requirement include (21 CFR §312.2(b)(1)):

- Studies which are not intended to support FDA approval of a new indication or a significant change in the product labeling;
- Studies not intended to support a significant change in the advertising for the product
- The investigation does not involve a route of administration or dosage level or use in a patient population or other risk factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product
- The study is conducted in compliance with IRB and informed consent criteria set forth in 21 CFR 56 and 50.
- The study is conducted in compliance with 312.7 (promotional and charging for investigational drugs).  
<http://www.fda.gov/cder/guidance/6036fnl.pdf>

### Required Reports to FDA

Within 60 days of the annual anniversary date that an IND went into effect, the sponsor must submit a progress report of the investigation to FDA (21 CFR 312.33).

The sponsor must notify FDA and all participating investigators in a written IND safety report of any serious and unexpected adverse experiences associated with the drug or any finding from test results in animals that suggests a significant risk for human subjects. The

safety report must be made as soon as possible and no later than 15 calendar days after the applicant's receipt of the information (21 CFR 312.32(c)).

If there is a change in protocol in a Phase 1 study with an IND, the sponsor must submit a protocol amendment to FDA describing any change that significantly affects the safety of subjects. In Phase 2 or Phase 3 studies with INDs, sponsors must submit protocol amendments to FDA when there is any change in a protocol that significantly affects the safety of the subjects, the scope of the investigation, or the scientific quality of the study (21 CFR 312.30(b)). Except when a licensed practitioner is added to a treatment protocol, a protocol amendment must also be submitted when a new investigator is added to a previously submitted protocol (21 CFR 312.30(c)).

### Adverse Drug Experience Reporting

Investigators are required to report all adverse experiences of drugs and biologics occurring during the course of a study to the sponsor (21 CFR 312.64(b)). Investigators must report any adverse experience that may reasonably be caused by or probably caused by the drug *promptly* to their sponsor (21 CFR 312.64(b)). Investigators must report alarming adverse experiences *immediately* to the sponsor (21 CFR 312.64(b)).

Investigators should report serious and unexpected and/or fatal or life threatening adverse experiences to the sponsor and the IRB.

### Research Involving Devices

An investigational device is a medical device which is the subject of a clinical study designed to evaluate the effectiveness or safety of the device. If a research protocol involves an investigational device, an investigator must first determine whether an Investigational Device Exemption (IDE) is required. Similar to requesting opinions on INDs, investigators may request advice from the FDA about IDEs. For general questions about the requirements of the IDE regulation, investigators may contact Division of Small Manufacturers, International and Consumer Assistance (HFZ-220), Center for Devices and Radiological Health, 1350 Piccard Drive, Rockville, MD 20850-4314. The phone number is 301- 443-6597 or 800-638-2041, the fax number is 301-443-8818, and the email address is [dsma@cdrh.fda.gov](mailto:dsma@cdrh.fda.gov). For specific questions regarding IDE policies or procedures for the review of IDE applications, contact IDE Staff, Investigational Device Exemptions Program (HFZ-403), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Boulevard, Rockville, MD 20850-3223. The phone number is 301-594-1190.

All significant risk devices require an IDE. Therefore, to determine whether an IDE is required, the device must be classified as a significant-risk device or a non-significant risk device. A significant risk device has the potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; (2) is used in supporting or sustaining human life; (3) is of substantial importance in diagnosing, curing, mitigating or treating disease; or (4) otherwise prevents impairment of human health; or otherwise presents a potential for serious risk to the health, safety, or welfare of a subject (21 CFR 812.3(m)).

The initial assessment of the risk level of a device should be made by the sponsor/investigator. The IRB is responsible for determining whether this assessment is appropriate (21 CFR §812.2(b)(1)(ii)). When determining whether a device is a

significant-risk device, the IRB should consider whether the device meets the above definition in addition to the seriousness of the harm which may result from the device. Also, the proposed use of the device should be taken into account in addition to the device itself. The minutes of IRB meeting should note the rationale for the risk classifications as well as the approval process. If the IRB determines that an investigation presented for approval as a non-significant risk device involves a significant risk device, it must notify the investigator, and, where appropriate, the sponsor (21 CFR 312.66). If the device is classified as a significant-risk device, an IDE application must then be submitted to FDA (21 CFR 312.20). The IDE application must be approved by FDA before the research can take place.

If the device is classified as a non-significant risk device, the study must comply with the abbreviated requirements of the IDE regulations, such as the requirements for IRB approval and informed consent, recordkeeping, labeling, promotion, and study monitoring (21 CFR 312.2(b)).

### Unanticipated Adverse Device Effect Reports

Investigators must submit reports of unanticipated adverse device effects to IRB and the sponsor of the study within 10 working days of learning of the effect (21 CFR 312.150(a)(1)). Once the sponsor learns of the effect, an immediate evaluation of any unanticipated adverse device effect is required (21 CFR 312.46(b)(1)). Within 10 working days after first receiving notice of the effect, the sponsor must report the results of the evaluation to FDA, IRB, and all participating investigators (21 CFR 312.150(b)(1)). The sponsor must terminate all investigations as soon as possible if the effect causes an unreasonable risk to subjects (21 CFR 312.46(b)(2)). The termination must occur within five working days after the determination of unreasonable risk has been made and within fifteen working days of when the sponsor was notified of the adverse effect (21 CFR 312.46(b)(2)). Finally, terminated studies may not be resumed without FDA and IRB approval (21 CFR 312.46(c)).

### Record Retention

Investigators must retain the study records for at least two years after notification from the sponsor that the drug/device has been approved for the indication that was investigated. If the drug/device is not approved, the investigator must keep the study records for at least two years after the investigation is completed or discontinued and FDA has been notified by the sponsor (21 CFR 312.57(c), 21 CFR 312.140(d)).

If an application or supplemental application is approved, reserve samples of any test article and reference standard identified in, and used in bioequivalence or bioavailability studies must be retained for at least 5 years after the date of approval. If no application is approved, the sample must be retained for at least 5 years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained was used (21 CFR 320.38(e)). The reserve samples must be released to FDA upon request (21 CFR 312.57(d)).

### Good Clinical Practice (GCP)

In 1997, FDA published a guideline on Good Clinical Practice (ICH GCP), which was prepared with the support of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. The ICH GCP provides a standard for designing, conducting, recording, and reporting trials that involve human subjects. It defines the responsibilities and roles of the Institutional Review Board (ICH GCP 3), investigators (ICH GCP 4, 8), and sponsors (ICH GCP 5, 8). In addition, the ICH GCP provides information on clinical trial protocols and protocol amendments (ICH GCP 6) and what should be included in the Investigator's Brochure (ICH GCP 7). Also, the ICH GCP provides guidance on the types of documents and records that investigators and sponsors should keep when they are engaged in human subjects research (ICH GCP 8). The ICH GCP can be accessed at [www.fda.gov/cder/guidance/iche6.htm](http://www.fda.gov/cder/guidance/iche6.htm). Investigators engaged in trials involving human subjects are encouraged to reference the ICH GCP to confirm that they are conducting their study in accordance with Good Clinical Practice.

## **DEFINITIONS**

**Applicant:** Any person who submits or plans to submit an application to the Food and Drug Administration for premarket review.

**Device:** An instrument, apparatus, implant, or machine which cures, mitigates, prevents, or diagnoses diseases or other conditions.

**Emergency use:** 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)].

**Investigational Device Exemption:** Mechanism for the clinical testing of devices.

**Investigational New Drug:** 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.

**Life-threatening:** Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

**Serious Adverse Drug Experience:** Any adverse experience occurring at any dose that results in any of the following outcomes: death; a life-threatening adverse experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity; or a congenital anomaly/birth defect [21 CFR 312.32]

**Test Article:** Any drug for human use, 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 FDCA or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

**Severely debilitating:** Diseases or conditions that cause major irreversible morbidity.

**Sponsor:** A person, including an individual, pharmaceutical company, governmental agency, academic institution, private organization, or other organization who is responsible for and initiates a clinical investigation. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

**Unanticipated Adverse Drug Experiences:** Any adverse experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended [21 CFR 312.32]

## **RESOURCES & REFERENCES**

21 CFR 50

21 CFR 56

21 CFR 312

21 CFR 807

21 CFR 812

International Conference on Harmonisation; Good Clinical Practice: Consolidated Guideline. 62 Federal Register, 25691-25709 (May 9, 1997).

*OHRP Requirement* \_\_\_\_\_  
*FDA Requirement* \_\_\_\_\_  
*AAHRPP Element* \_\_\_\_\_