

Overview:

Whenever the Lawrence Livermore National Laboratory (LLNL) is conducting Food and Drug Administration (FDA)-regulated research, the conduct of the research and the IRB review of such research must comply with FDA regulations.

The purpose of this document is to describe how the IRB will apply FDA regulatory requirements to the review of research involving investigational drugs, devices, biologics, or diagnostic tests.

Any Principal Investigator (PI) and key personnel of the research team involved in biomedical research must complete the CITI module for Human Subjects Protection for Biomedical Research. Any PI and key personnel who is also involved in FDA regulated research (i.e., research with an investigational drug, device, biologic, or diagnostic test) must also complete CITI Good Clinical Practice module and the CITI module on FDA-regulated research.

Procedures

Research with Investigational Devices

For studies involving the evaluation of the safety and effectiveness of a non-FDA approved device, or an FDA-approved device used outside of its approved indication (i.e., off-label), the IRB will ensure that an Investigational Device Exemption (IDE) application has been approved by FDA, unless **the requirement for an IDE is exempt** from FDA regulations in accordance with 21 CFR 812.2(c) **or** the use of the device in the study **is determined to be a non-significant risk (NSR) device** (and the abbreviated IDE requirements are satisfied in accordance with 21 CFR 812.2(b)).

The IRB Program Manager or designee will help the IRB ensure the appropriate regulatory status of any device whose safety and effectiveness is being evaluated in the research. During the IRB pre-review process, IRB staff will check that the regulatory status of the device as used in the proposed research is clearly documented in the materials submitted for IRB review. The IRB staff may also consult with the FDA database for approved devices on the FDA website at: <http://www.fda.gov/MedicalDevices/default.htm>. Alternatively, one can submit questions regarding whether an IDE is needed by contacting the FDA's Center for Devices and Radiological Health (CDRH) [Division of Industry and Consumer Education (DICE)] by sending an email to DICE@fda.hhs.gov or by calling 1-800-638-2041 or 301-796-7100.

For FDA-approved devices (that will be used for an off-label or new use) or investigational devices, the device manual will be required. In addition, for research involving an investigational device one of the following will be required:

- 1) An approved IDE#, appearing on the sponsor's protocol, the Device Brochure, and/or the IDE letter from FDA.
- 2) The sponsor's or investigator's (in an investigator-initiated study) letter to the FDA for submission of an IDE application. Regarding this option, final approval of a study cannot be granted by the IRB until 30 days have passed from the date of submission to the FDA, and there has been no notice from FDA of a hold placed on the device.

- 3) An explanation and justification from the sponsor/investigator as to why the device may be exempt from the IDE requirements in accordance with [21 CFR 812.2\(c\)](#).
- 4) An explanation and justification from the sponsor/investigator that an IDE is not required (investigators are strongly encouraged to consult with FDA for an official determination).

If the regulatory status is not clear, the IRB Chair will determine whether the use of an investigational device in the study satisfies the exemption criteria in accordance with 21 CFR 812.2(c).

If the investigational device is determined to not meet the exemption criteria (and again the research involves the evaluation of the safety and effectiveness of the device), the convened IRB must review the study and determine whether the device is considered to be an NSR device in accordance with 21 CFR 812 and FDA's guidance, "[Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies](#)." If the convened IRB determines that the device is a significant risk (SR) device, then an IDE must be approved by the FDA before the IRB may proceed with approval of the study (or at least approval of the portion of the study that will involve the device). If an IDE must be approved by the FDA, the PI will be informed in writing and instructed to inform the sponsor of the SR determination (if applicable).

The review of the device by the convened IRB and the determination of either a SR or NSR device will be documented in the minutes. These determinations will be made in addition to the overall risk determination of the protocol of minimal risk or greater than minimal risk. If the IRB determines the device to be an NSR device and the overall risk in the study to be minimal risk, the convened IRB may determine whether the continuing review may be done by expedited review. If such a determination is made, it will be documented in the meeting minutes.

The IRB will also review the investigator's plan on how the device (whether investigational or FDA-approved) will be supplied, stored, utilized in the study, and whether any special handling of the device is required. The plan must ensure that the integrity, quality, and sterility of the device will not be compromised during the storage process. For example, if temperature controls are needed to maintain the stability of the device, the plan must document how the device will be stored accordingly. The plan should also describe how device accountability will be maintained (who will be responsible for the storage, distribution and record-keeping of the device). If the device is implanted, or otherwise requires sterilization, and does not come in a sterilized package, the autoclaving of the device (or other sterilization technique that will be used) should be described in the plan.

Research with Investigational Drugs

When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an Investigational New Drug (IND) application may be required. For studies involving an investigational drug, or an FDA-approved drug used outside of its approved indication (i.e., off-label), the IRB will ensure that an IND application has been approved by FDA, unless the requirement for an IND is exempt from FDA regulations in accordance with [21 CFR 312\(b\)](#).

The IRB Program Manager or designee will help the IRB ensure the appropriate regulatory status of any drug used in the research. During the IRB pre-review process, IRB staff will check that the regulatory status of the drug as used in the proposed research is clearly documented in the materials submitted for IRB review.

For FDA-approved drugs (that will be used for an off-label or new use), the package insert will be required. For an investigational drug, one of the following will be required:

- 1) An explanation and justification from the sponsor/investigator that an IND is not required (investigators are strongly encouraged to consult with FDA for an official determination).
- 2) An explanation and justification from the sponsor/investigator as to why the drug may be exempt from the IND requirements in accordance with [21 CFR 312.2\(b\)](#). If the drug is indicated for oncology, the IRB may rely on the FDA Guidance titled, *Investigational New Drug (IND) or Device Exemption (IDE) Process*, <https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/investigational-new-drug-ind-or-device-exemption-ide-process-cber>
- 3) An approved IND#, appearing on the sponsor's protocol, the Investigator's Brochure, and/or the IND letter from FDA.
- 4) The sponsor's or investigator's (in an investigator-initiated study) letter to the FDA for submission of an IND application. Regarding this option, final approval of a study cannot be granted by the IRB until 30 days have passed from the date of submission to the FDA, and there has been no notice from FDA of a hold placed on the drug.

If adequate documentation has not been obtained that an investigational drug has an IND# or that a determination has been made by FDA that an IND is not needed for the study, the IRB will determine in a convened meeting whether an IND is needed and document its determination in the minutes. The IRB or an investigator can find information regarding drug approvals and the drug approval process at <http://www.fda.gov/Drugs/default.htm>. Alternatively, one can submit questions regarding whether an IND is needed by contacting the FDA's Center for Drug Evaluation (CDER) (Human Drug Information, Division of Drug Information) by sending an email to druginfo@fda.hhs.gov or by calling (855) 543-3784 or (301) 796-3400.

The IRB will also review the investigator's plan on how the drug (whether investigational or FDA-approved) will be supplied, stored, dispensed and administered to subjects, and whether any special handling of the drug is required. The plan must ensure that the integrity and quality of the drug will not be compromised during the storage process. For example, if temperature controls are needed to maintain the stability of the drug, the plan must document how the drug will be stored accordingly. The plan should also describe how drug accountability will be maintained (who will be responsible for the storage, distribution and record-keeping of the drug; e.g., research pharmacy or research team, and if the latter which member of the research team).

If there is a known antidote for the drug in case of overdose or over-administration resulting in toxicity, the investigator's plan for management and storage of the drug should also include that the antidote, its availability and potential use, will be clearly communicated to research staff members.

If there is specific information regarding birth control measures that should be taken by subjects with reproductive capacity, the IRB will ensure during its review of the informed consent document(s) that that information is included in the Risks section.

Research with Biologics

For studies involving an investigational biologic, or an FDA-approved biologic used outside of its approved indication (i.e., off-label), the IRB will ensure that an Investigational Biologic-Based IND (BB-IND) application has been approved by FDA, unless the requirement for an IND is exempt from FDA regulations, and follow the IRB procedures in the Section B (Research with Investigational Drugs) above.

Compliance with Good Clinical Practice (GCP)

All FDA regulated research and NIH-supported clinical trials involving investigational drugs, devices, or biologics must comply with the International Conference for Harmonization <https://www.ich.org/> to the extent that the GCP standards apply to the research study. Additionally, it is recommended that all biomedical research complies with these GCP standards to the extent that the standards apply to the research.

In accordance with this guidance, the IRB should obtain the following documents: Trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB may require to fulfil its responsibilities.

References

21 CFR 50
21 CFR 56
21 CFR 54
21 CFR 312
21 CFR 600
21 CFR 812

Document Review History

Revision Number	Date	Author	Summary of Changes
01	November 2019	IRB Office	New
02	October 2020	Ann-Marie Dake	Revisions and updates