

FDA-REGULATED RESEARCH

This guidance document is intended for investigators planning to conduct research that involves the use of drugs and/or medical devices. Should you need additional assistance, please contact OPHS at 510-642-7461 or ophs@berkeley.edu.

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A. Introduction

Research is governed by Food and Drug Administration (FDA) regulations when the research involves a human subject and an FDA-regulated test article, or human subjects research data will be submitted to or held for inspection by the FDA. In these instances, the research must follow both Department of Health and Human Services (DHHS) and FDA human subjects research regulations, which have [different provisions](#). This guidance is provided to assist University of California, Berkeley (UCB) investigators in understanding FDA regulatory requirements when conducting research involving drugs or medical devices.

B. Definitions and Important Concepts

1. **Clinical investigation** means any experiment that involves a *test article* and one or more *human subjects*, and that either: a) must meet the requirements for prior submission to the Food and Drug Administration; or b) the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The terms *research*, *clinical research*, *clinical study*, *study*, and *clinical investigation* are deemed to be synonymous. Note: The DHHS regulatory definition of [research](#) is different.

2. **Human subject**, under FDA regulations, means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient. For device studies, this includes *an individual on whom or on whose specimen an investigational device is used*. Note: The DHHS regulatory definition of a [human subject](#) is different.

3. **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 or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

4. A **Drug** is defined as:

- 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; or
- A substance intended for use as a component of a medicine but not a device or a component, part, or accessory of a device.

Note: [Biological products](#) (e.g., vaccine, virus, or blood) 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.)

5. **Investigational New Drug** or **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. The terms “investigational drug” and “investigational new drug” are deemed to be synonymous.

6. A **Medical Device** is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- Recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them;
- Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in human or other animals; or
- Intended to affect the structure or any function of the body of human or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of human or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

7. **Investigational device** means a device, including a transitional device, that is the object of an investigation.

8. **Investigator** means an individual who actually conducts the research (e.g., principal investigator, study coordinator, research associate).

9. **Sponsor** means the entity who initiates, but who does not actually conduct, the research (e.g., a pharmaceutical company). The sponsor may or may not also be the entity that is funding the research.

10. **Sponsor-investigator** means an individual who both initiates and actually conducts the research. A sponsor-investigator must meet the requirements and obligations of both the investigator and the sponsor described in FDA regulations. Most FDA-regulated research conducted at UCB is sponsor-investigator research.

C. Research Involving Drugs

Research Requiring an IND: An *Investigational New Drug Application* (IND) refers to an application that is submitted to the FDA. An IND is a request for authorization from the FDA to administer an investigational drug or biological product to humans.

FDA's IND regulations require that human subjects research studies be conducted under an IND if all of the following conditions exist:

- The research involves a *drug* as that term is defined in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) ([21 U.S.C. 321\(g\)\(1\)](#));
- The research is a *clinical investigation* as defined in the IND regulations, [21 CFR 312.3](#); and
- The clinical investigation is not otherwise *exempt* from the IND requirements

Definition of Clinical Investigation: In the context of research involving drugs, “clinical investigation” refers to 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 a drug except for the use of a marketed drug in the course of medical practice.

Research Involving Drugs Exempt from IND Requirements: A clinical investigation of a marketed drug (i.e., an FDA-approved drug) is exempt from the IND requirements if all of the criteria for an exemption are met:

- The drug product is lawfully marketed in the United States (i.e., FDA approved);
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug;
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug;
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product ([21 CFR 312.2\(b\)\(1\)\(iii\)](#));
- The investigation is conducted in compliance with the requirements for review by an IRB ([21 CFR part 56](#)) and with the requirements for informed consent ([21 CFR part 50](#)); and
- The investigation is conducted in compliance with the requirements of [21 CFR 312.7](#) (i.e., the investigation is not intended to promote or commercialize the drug product).

In Vitro Diagnostic Biologics ([21 CFR 312.2\(b\)\(2\)](#)): A clinical investigation involving an *in vitro* diagnostic biological product (blood grouping serum, reagent red blood cells, and anti-human globulin) is exempt from the requirements if:

- It is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and
- It is shipped in compliance with 312.160.

Unapproved Drugs: There are certain currently marketed drug ingredients that were first marketed before Congress passed the FD&C Act of 1938 (requiring demonstration of safety before marketing) or before it passed the 1962 amendments to the FD&C Act (requiring demonstration of effectiveness and safety before marketing). This means that there are commercially available drugs that have not been approved by the FDA for any use (e.g. treatment or diagnosis). Sponsor-investigators planning to conduct research using products with these drug ingredients should consult with FDA to determine whether the ingredient is “lawfully marketed.” Investigators who are unsure whether a drug falls under this category should also consult with the FDA. If the ingredient is not lawfully marketed, an IND is required.

Other Substances: Sponsor-investigators of human subjects research involving radioactive isotopes, cold isotopes, endogenous compounds, live organisms, cosmetics, foods, or dietary supplements (e.g. vitamins, minerals, or herbs) should review the FDA guidance [Investigational New Drug Applications \(INDs\) – Determining Whether Human Research Studies Can Be Conducted Without an IND](#) to determine whether their research may be conducted without an IND.

D. Research Involving Medical Devices

The Investigational Device Exemption (IDE) regulations describe three types of device investigations:

- Exempt Device Studies
- Nonsignificant Risk (NSR) Device Studies
- Significant Risk (SR) Device Studies

Definition of Clinical Investigation: In the context of devices studies, a “clinical investigation” refers to research involving one or more subjects to determine the safety or effectiveness of a device.

All clinical investigations of devices must have an approved IDE (i.e., IDE application has been submitted to the FDA or an NSR determination has been made by the reviewing Institutional Review Board or the FDA) or be exempt from the IDE regulations.

Exempt Device Studies: The FDA’s IDE regulations do not apply to “[IDE Exempt Investigations](#)” defined in the IDE regulations ([21 CFR 812.2\(c\)](#)). Studies exempt from the IDE regulations include clinical investigations of:

- A legally marketed device when used in accordance with its labeling.
- A diagnostic device if it complies with the FDA’s labeling requirements in [21 CFR 809.10\(c\)](#) and if the testing:
 - 1) Is noninvasive;
 - 2) Does not require an invasive sampling procedure that presents significant risk;
 - 3) Does not by design or intention introduce energy into a subject; and
 - 4) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

Note: This document only describes the criteria for “exempt device studies” that most commonly apply to human subjects research at UCB. Investigators should refer to the [FDA’s website](#) or [regulations](#) for the full list of criteria.

In-vitro diagnostic device studies involving de-identified samples: The FDA intends to exercise enforcement discretion as to the informed consent requirements for clinical investigators, sponsors, and Institutional Review Boards, if an in-vitro diagnostic device investigation is conducted using de-identified samples and the investigation meets all the criteria described in [Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable](#).

Nonsignificant Risk (NSR) Device Studies: An NSR device study is one that does not meet the definition for an SR device study. NSR studies must follow the [abbreviated requirements](#) described in the IDE regulations ([21 CFR 812.2\(b\)](#)).

Significant Risk (SR) Device Studies: Significant risk device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is purported or represented to be for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- 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
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

An IDE application must be submitted to the FDA if the device involved in the research is determined to be significant risk.

Note: Refer to [Part E](#) of this document for information on Committee for Protection of Human Subjects (CPHS) determination of SR vs NSR.

E. Protocol Submission and Informed Consent Considerations

Studies involving drugs and medical devices should be submitted through [eProtocol](#) on a *Biomedical Non-Exempt* application form. Research conducted under an IND or research involving medical devices (except for exempt device studies) will be reviewed by the full-committee CPHS at initial submission. Sponsor-initiated research applications should include the protocol document supplied by the sponsor as an attachment.

CPHS Review of Drug Studies: For studies conducted under an IND, the IND Acknowledgement Letter should be attached to the protocol. All drugs should be listed in the protocol with, at minimum, the drug name, source of the drug, and dosage. Human subjects research involving drugs that are exempt from the FDA's IND requirements still require review and approval by CPHS.

CPHS Review of Device Studies and SR or NSR Determinations: The study sponsor (or sponsor-investigator) is responsible for making the initial risk assessment (SR or NSR). Investigators should note that CPHS' determination of SR or NSR (a judgment based on the proposed use of a device in an investigation the nature of the harm that may result) is different and separate from the CPHS' determination of minimal risk or greater than minimal risk (a determination based on the study's risk-benefit assessment). Investigational devices should be

listed in the protocol along with their initial risk assessment (SR or NSR) and the sponsor or sponsor-investigator's rationale.

Nonsignificant Risk Device Studies: If CPHS concurs with the initial NSR assessment presented in the investigator's protocol and approves the study with an NSR determination, the study will be considered to have an approved IDE (i.e., no IDE application needs to be filed with the FDA).

Significant Risk Device Studies: If the protocol is determined to be an SR device study, the sponsor (or sponsor-investigator) must submit an *investigational device exemption* (IDE) application to the FDA in addition to submitting the protocol application to CPHS.

Human subjects research involving medical devices that are exempt from the FDA's IDE requirements still require review and approval by CPHS.

Screening and Inclusion/Exclusion Criteria: When conducting research involving drugs or devices, exclusion of certain populations (e.g., pregnant women, nursing mothers, geriatric populations, or pediatric populations) may be appropriate and should be incorporated into the protocol application. The subject population that should be excluded may depend on the specific drug or device.

Informed consent must be obtained prior to screening. Investigators may provide a separate screening consent form or include screening information in the consent document for the entire study.

Pregnancy: Investigators must consider provisions to exclude pregnant women through pregnancy testing/screening especially when conducting research involving drugs that fall under an FDA pregnancy category as described in the FDAs' [labeling requirements](#). If the study involves multiple sessions, repeated pregnancy tests may need to be conducted throughout the subjects' participation in the study.

Nursing Mothers: Exclusion of nursing mothers must be considered if there are potential risks for the infant of nursing mothers (e.g., the product labeling states that the drug is known to be excreted in human milk or the information on excretion in human milk is unknown).

Risks and Discomforts: Information pertaining to risks/discomforts associated with the drug or device must be submitted with the protocol. This information is often found in package inserts, product labels, or Investigator's Brochures. Consistent information must be presented to subjects (in lay language) within the informed consent document(s).

Confidentiality: The protocol application and informed consent document(s) should clearly communicate how identifiable data, including screening data, will be handled and how long this information will be retained. Plans to maintain identifiable data for future analysis or to re-contact individuals for future studies must be discussed in the protocol application and consent document(s).

FDA Inspection of Records: For FDA-regulated research, the investigator must state in the informed consent document(s) and in the confidentiality section of the protocol application that the FDA may inspect the research records. Investigators should refer to the [CPHS consent templates](#) for recommended language.

FDA Record Retention Requirements: The FDA’s recordkeeping and record retention requirements are specified at 21 CFR [312.57](#), [312.62](#), and [812.140](#), and are summarized on [this CPHS webpage](#). In addition to these requirements, investigators are encouraged to include record retention flexibility language in their CPHS protocol and corresponding consent form(s) to allow for future data sharing and data use. For example, the protocol and consent form(s) may state that data will be retained “indefinitely” and that collected data may be used for future research purposes by the investigators or by others.

Investigators who leave UCB must make arrangements to ensure that research records continue to be retained at UCB as required by applicable regulations, policies, and requirements (e.g., [UC policies and funding agency requirements](#)).

Clinical Trial Registration and Reporting: In accordance with Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801), the *responsible party* for a clinical trial must register an *applicable clinical trial* and submit results information to [clinicaltrials.gov](#).

“Applicable clinical trials” include:

- *Trials of drugs and biologics:* Controlled clinical investigations, other than phase 1 clinical investigations, of drugs or biological products subject to Food and Drug Administration (FDA) regulation.
- *Trials of devices:* 1) Controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and 2) pediatric postmarket surveillance required by FDA.

In most cases, the *responsible party* is the sponsor or sponsor-investigator. Investigators should refer to [FDAAA 801 Requirements](#) for additional information and definitions.

Investigators submitting a protocol application to CPHS must [determine whether the study is an applicable clinical trial](#). If the study is an applicable clinical trial, the following statement must be included in the informed consent document(s) submitted to CPHS:

“A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.”

Waiver of Documentation of Informed Consent (i.e., Unsigned Consent): For FDA-regulated research CPHS may, for some or all subjects, waive the requirement that the subject (or the subject's legally authorized representative) sign a written consent form *only* if CPHS finds that *the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context.*

This means that investigators are still required to obtain informed consent but the requirement to obtain a written signature is waived. A waiver of documentation may apply to screening procedures (e.g., screening surveys conducted over the phone to determine eligibility).

Waiver of Elements of Informed Consent (i.e., Altered Consent or Consent Waiver):

Currently, FDA regulations allow exception from the general requirements for informed consent only under very limited circumstances (e.g., emergency research). However, as stated in [July 2017 guidance](#), the FDA intends to revise its informed consent regulations to add a waiver of informed consent for certain minimal risk clinical investigations. Until the revised regulations are issued, the FDA does not intend to object to a waiver or alteration of informed consent provided that:

- The clinical investigation involves no more than minimal risk to the subjects;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- The clinical investigation could not practicably be carried out without the waiver or alteration; and
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Training: According to the [CPHS Training and Education](#) policy, all UCB investigators and key personnel who will be conducting FDA-regulated research must complete and pass the online biomedical course sequence of the basic human subjects research CITI course. Additional training in Good Clinical Practice (GCP) is needed for research involving clinical trials or investigations of devices.

F. Additional Information

[21 CFR 50 - Protection of Human Subjects](#)

[21 CFR 56 - Institutional Review Boards](#)

[21 CFR 312 - Investigational New Drug Application](#)

[21 CFR 812 - Investigational Device Exemptions](#)

[Frequently Asked Questions About Medical Devices](#)

[ICH E6: Good Clinical Practice](#)

[IDE Approval Process](#)

[In Vitro Diagnostic \(IVD\) Device Studies – Frequently Asked Questions](#)

[Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens That Are Not Individually Identifiable](#)

[Investigational New Drug Applications \(INDs\) – Determining Whether Human Research Studies Can Be Conducted Without an IND](#)

[IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and Determination of Whether an IND/IDE Is Needed](#)

[Is the Product a Medical Device?](#)

[Mobile Medical Applications](#)

[Significant Risk and Nonsignificant Risk Medical Device Studies](#)