

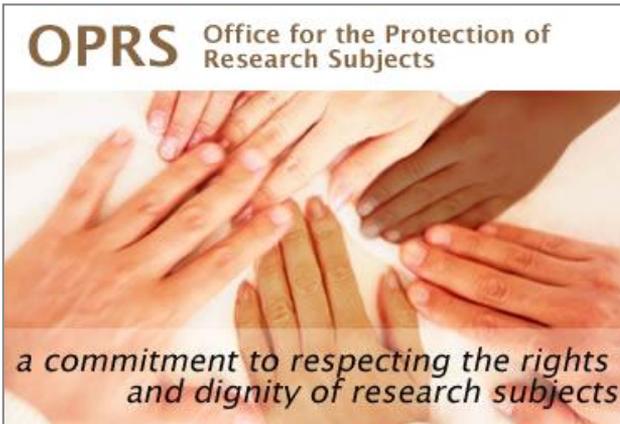
ARE YOU THE HOLDER OF AN IND OR IDE?

**...CONSIDER YOUR LEGAL
OBLIGATIONS**



**Office for the Protection of
Research Subjects (OPRS)**

This booklet was written to familiarize researchers with the responsibilities of IND/IDE holders. The booklet is also intended as a useful reference for investigators holding an IND or IDE and/or IRB staff who will be reviewing IND/IDE studies.



Booklet Prepared by OPRS

Susan Rose, Ph.D., Executive Director
Jennifer Hagemann, M.S., Program Director
Dalar Shahnazarian, M.S.W. candidate, IRB Student Mentor
Monica Aburto, B.A. Program Administrator

Acknowledgements

OPRS thanks...

*Professor Frances Richmond PhD, Director of Regulatory Science
Program USC School of Pharmacy,
and Sandra Jean M.S., CIP, Director of USC Health Sciences IRB for
review of this material.*

What Is An IND Application?

An Investigational New Drug (IND) application is the document submitted to the Food and Drug Administration (FDA) for permission to conduct a clinical study using a drug or biologic that is new or not approved for a given dosage, formulation or indication.

What Is An IDE?

An Investigational Device Exemption (IDE) application is the document submitted to FDA to allow for the conduct of a clinical study using a significant risk device that is new or not approved for a given use.

If you are the holder of an IND or IDE and you assume the responsibilities of both an investigator and a sponsor, all of the following are true:

1. You obtained an IND or IDE from FDA (you are the “holder”)
2. You are responsible for clinical testing of the drug or device (you are the “sponsor”)
3. You are conducting a clinical trial and dispensing or using the drug or device in human subjects (you are the “investigator”)

In order to conduct a clinical investigation of a drug, biologic, or device an IND or IDE application must be filed with FDA, unless the study is exempt from IND or IDE requirements.

These terms may also be used to describe IND/IDE holders:

- Sponsor-investigator*
- Investigator-initiated research
- IND/IDE Investigator
- Investigator-Sponsored IND/IDE
- Physician-Initiated Research

**the terms “sponsor-investigator” and “IND/IDE holder” are used interchangeably throughout this pamphlet, particularly when the investigator has not yet submitted the IND/IDE application to FDA*

When Do You Need An IND?

An IND is required when the investigation (21CFR 312.2):

- is for a product intended to be submitted to FDA by the “sponsor-investigator” in support of a new drug or a new indication for use or significant change in labeling of a marketed drug
- is for a product intended to support a significant change in advertising (i.e., for use in children as well as adults)
- involves a different route of administration or dosage level or use in a new, high-risk, and/or different patient population or other factor that significantly increases the risks associated with use of the product – or decreases the acceptability of the risks

Additionally, when an IND is required, the study must be conducted in compliance with 21 CFR 312.7 which deals with promotion and sale of investigational products.

What If Your Drug Study Is IND Exempt?

If the above do not apply to the investigation, the study is exempt from IND requirements.

Note: At USC, the investigator must select the exemption category in the IRB application Section 17.1.2 that demonstrates why the study is exempt.



IND exempt studies must comply with informed consent and IRB approval requirements (21 CFR 50 and 56, respectively). If a study does not require an IND per FDA, the investigator must be able to document this determination, and the Institutional Review Board (IRB) will verify documentation.

When Do You Need An IDE?

Significant vs. Non-significant Risk Devices

An IDE is required to study an investigational device (including new intended use of an approved device) posing *significant risk** and must be submitted to FDA before study initiation. If the investigation involves the use of a device that does not pose significant risk to humans (a non-significant risk* device), an IDE application to FDA is not required.



Submissions for non-significant risk devices are made directly to the IRB. The sponsor-investigator must explain to the IRB why the device does not pose a significant risk. If the IRB agrees with the non-significant risk determination, FDA considers the device to have an approved IDE. However, if the IRB determines that the device poses a significant risk to subjects, the sponsor-investigator must notify FDA within five working days.

Sponsor-investigators conducting non-significant risk device studies must comply with abbreviated IDE requirements listed in 21 CFR 812.2(b):

www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=812.2

What If Your Device Study is Exempt from IDE Requirements?

An approved IDE allows investigators to use an investigational device for the purpose of clinical testing. However, not all clinical trials using devices require permission from FDA to proceed. The investigator must select the IDE exemption category in the IRB application in Section 18.1.4 in order to demonstrate that the study device is exempt.

*Significant risk: presents a potential serious risk to the health, safety, or welfare of subjects (e.g., stents, sutures)

Exempt IDE Categories

The following categories of devices are exempt from IDE requirements:

- devices in commercial distribution before 5/28/76
- devices determined by FDA to be substantially equivalent to a device in commercial distribution before 5/28/76
- diagnostic devices that are noninvasive or do not require an invasive sampling procedure that presents significant risk, do not introduce energy into a subject or are not used as a diagnostic procedure without the confirmation of another medically established diagnostic product or procedure
- devices used for consumer preference testing or for any test that is not intended to determine safety or effectiveness and does not expose subjects to risk
- devices exclusively used for veterinary indications
- devices to be shipped exclusively for research on laboratory animals
- custom devices unless these are used to assess safety or effectiveness for commercial distribution

Device studies exempt from IDE requirements, generally still require IRB approval (21 CFR 56). Documentation of the IDE exemption category must be submitted to IRB (iStar section 18.1.4). Contact the IRB for further guidance.

What If You Need Help Submitting an IND to FDA?

Investigators may first consult with investigators or others on campus familiar with the IND submission process. Additionally, submitters of an IND can learn about the soundness of their study design and study acceptability from a Pre-IND consultation.

Through the Pre-IND consultation program, potential IND holders can consult with FDA and these meetings are encouraged by FDA. The focus of the meeting is to discuss preclinical studies needed to support clinical testing, to understand study product chemistry, manufacturing and control (CMC) issues and to preview the proposed clinical studies. Generally, only one pre-IND meeting is

granted by FDA per product claim; therefore, it is best to address any issues anticipated in the drug development process. It is important to be well-prepared to utilize this valuable opportunity to obtain FDA feedback and guidance.

To initiate a pre-IND meeting, submit a written request to FDA. An information package must be submitted to FDA at least 4 weeks prior to the meeting.

Detailed contents of the information to be included in the package are found in the “FDA Guidance for Industry Formal Meetings with Sponsors and Applicants for PDUFA Products”:

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

After the meeting takes place, FDA will issue written official minutes to the IND applicant within 30 days of the meeting.

What If You Need Help Submitting an IDE to FDA?

Investigators may first consult with investigators or others on campus familiar with the IDE submission process.



Additionally, FDA encourages prospective sponsors to communicate with the Office of Device Evaluation (ODE) prior to an IDE submission. Early communication with FDA is a valuable resource, particularly for new IDE holders or for studies with new technology. It can be used to increase understanding of FDA requirements and decrease delays in the process.

Preliminary information can be submitted to FDA in the form of a pre-IDE submission when the applicant requires IDE application guidance.

The submission is reviewed by FDA and the applicant receives a response within 60 days of submission. Pre-IDE submissions include correspondence between applicants and FDA that transpire before the IDE submission and include pre-IDE meetings.

Pre-IDE meetings are classified as either informal or formal IDE meetings. Informal meetings can be utilized to obtain guidance for pre-clinical data and investigational plan development. The meeting format can be through telephone or video conferences as well as face-to-face conversations.

Formal meeting requests are submitted in writing and take place within 30 days of request submission. Formal meetings are either agreement or determination meetings and the type of meeting must be specified in the request.

Agreement vs. Determination Meetings

A formal agreement meeting is for the applicant of an IDE and FDA to reach an agreement about the investigational plan. Meeting requests are submitted as pre-IDE submissions and must include a detailed description of the device and of the proposed conditions of use as well as the investigational plan and clinical protocol. If an agreement is made with FDA about the investigational plan details, these are written into the IDE administrative record by FDA.

Similarly, determination meetings are utilized to determine the type of valid scientific data necessary in a study for IDE applicants planning to submit a Pre-Market Approval (PMA). Premarket approval (PMA) is an FDA scientific and regulatory review process to evaluate the safety and effectiveness of Class III medical devices (e.g., devices that sustain human life).

Meeting requests are submitted along with summary information and FDA provides a written determination within 30 days of the meeting.

How Do You Submit an IND?

What Forms Are Required?

To submit an IND application to FDA, the following are required ([21 CFR 312.23](#)):

- Form FDA 1571 (IND Application) (or a dossier addressing all of the elements outlined in Form 1571) is submitted by the sponsor (or sponsor-investigator).
- Form FDA 1572 (Statement of Investigator)

Form FDA 3674 (Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank)

Elements required in an IND Submission Dossier

1. Investigational New Drug Application
 - a. Table of Contents
 - b. Introductory Statement
 - c. General Investigational Plan
 - d. Investigator's Brochure
 - e. Protocol
 - i. Study protocol
 - ii. Investigator data or completed Form FDA 1572
 - iii. Facilities data or completed Form FDA 1572
 - iv. Institutional Review Board data or Form 1572
 - f. Chemistry, manufacturing, and control data
 - g. Pharmacology and toxicology data
 - h. Previous human experience
 - i. Additional information
2. Statement of Investigator (Form FDA 1572)
3. Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank (Form FDA 3674)

How Do You Submit an IDE?

What Does FDA Want?

The IDE application to FDA must include the items listed below. Three copies of the signed IDE application must be submitted to FDA with the following ([812.20](#)):

Required Items for IDE Application*

1. The IDE holder's name and address
2. A report with all prior investigations of the device and a summary of the investigational plan. The complete investigational plan must be submitted to FDA if no IRB has reviewed the investigational plan and report of prior investigations, if FDA determines the IRB review is inadequate or if FDA requests them.
3. A description of methods, facilities and controls used in the manufacture, processing, packing, storage, and, if applicable, installation of the device. The description will be used to assess quality control and good manufacturing practices, therefore, the level of detail should reflect the complexity of the process.
4. An example of the agreement to be signed by the investigators and a list of the names and addresses of all investigators.
5. A statement certifying that all investigators participating in the study will sign the agreement and that no investigator will take part in the study before signing the agreement.
6. An IRB list with the name, address and chairperson of each IRB that will review the investigation and a certification of IRB study-related action. Also, the name and address of any institution in which part of the study may be conducted but not yet identified in the application.
7. If the device will be sold, the amount to be charged for the device and a rationale of how its sale does not amount to commercialization of the device.

Note: FDA regulations allow for sponsors to sell a device and often the cost is passed onto participants.

8. Note: a categorical exclusion claim as listed under 21 CFR 25.30 or 25.34 or an environmental assessment as required by 21 CFR 25.40 is no longer required.
9. Copies of all device labeling
10. Copies of all informational material to be presented to subjects in the informed consent process
11. Any other information requested by FDA for inclusion in the IDE application

**Form FDA 3674 (Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank) must also be submitted to FDA*

FDA website provides additional guidance on the IDE application including required elements, suggested content and format, and common problems submitting IDEs. Refer to:

www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046706.htm

USC Educational Requirements

In addition to federal and state requirements, USC IND or IDE holders must comply with applicable USC educational training requirements.



1. Human Subjects Education On-line

All investigators and key personnel conducting human subjects research at USC, whether IND/IDE holders or not, must complete the CITI human subjects education. The mandatory training is a condition of IRB study approval. The education is available online. For CITI access, FAQs:

<https://oprs.usc.edu/education/citi/>.

2. Good Clinical Practice (GCP)

Good Clinical Practice training is required for all principal investigators and key personnel conducting full board clinical trials (not applicable to personnel who conduct expedited or

exempt studies exclusively). More information can be found at: <https://oprs.usc.edu/education/citi/>.

3. HIPAA

All USC faculty, staff, employees, students, volunteers and agents with access to patient protected health information (PHI) from USC providers must complete the online HIPAA compliance program: <http://ooc.usc.edu/hipaa-privacy-regulations>.

USC Sponsor-Investigator Agreement in iStar

All investigators must read and agree to the *Principal Investigator's Assurance* in iStar, which requires acceptance of all Principal Investigator (PI) responsibilities before submitting a completed application for IRB review.

Additionally, when the study is an investigator-initiated drug, biologic or device study, and the PI is the IND/IDE holder, the investigator must upload a signed *USC Sponsor-Investigator Agreement form* on the iStar application (Question 9.5). By signing this form, the investigator agrees to comply with both sponsor and investigator responsibilities and assure compliance with regulations. A copy of the *USC Sponsor-Investigator Agreement form* can be found at: <https://oprs.usc.edu/hsirb/hsirb-forms/>.

How to Monitor Your Study

In studies sponsored by a pharmaceutical or device company, study monitors provided by the sponsor regularly visit the sites to ensure regulatory compliance. However, when investigators are also sponsors, they normally do not have study monitors to verify that the study is conducted in compliance with the protocol, IRB application, and applicable regulations. IND/IDE holders must ensure that all federal, state and institutional regulations are being met.

In order to encourage and understand self-monitoring, the relevant excerpts from FDA guidance and regulations are provided at: http://oprs.usc.edu/files/2013/01/IND_IDE_monitoring.pdf

A self-audit checklist is also provided:

http://oprs.usc.edu/files/2013/01/Audit_Checklist_42010_HSIRB.pdf

Products Manufactured in California

If an IND or IDE product is manufactured in California, the following requirements must be met:

1. License and Inspection

A license application (one per place of manufacture) must be submitted to the Food and Drug Branch (FDB) of the California Department of Health Care Services for IND/IDE products manufactured in California. The license depends on a successful audit from Good Manufacturing Practice (GMP) facilities to determine ownership, adequacy, and personnel qualifications for the product in question, and will be effective for two years from date of issue unless it is revoked.

Thereafter, renewal depends on an audit every two years. A license renewal application should be filed before its expiration date to maintain compliance and avoid penalties.

2. Drug or Device Manufacturing Requirements

When a drug or device is manufactured in the state of California, IND/IDE holders must abide by additional requirements according to the CA Sherman Food, Drug, and Cosmetic Law, click here:

www.cdph.ca.gov/services/Documents/fdbSFDCAL.pdf

Reporting Requirements

1. IND Reporting Requirements

Protocol Amendments (21 CFR 312.30)

- New protocols or changes to existing protocols must be submitted to FDA for review as well as to the reviewing Institutional Review Board (IRB) for approval before the new protocol or change is implemented.

IND Safety Reports (21 CFR 312.32)

- Adverse events that are **unexpected and fatal or life-threatening** whether or not they can be causally associated with a drug or placebo must be reported to FDA within 7 calendar days after an IND holder is notified of the event
- Adverse events **associated with use of the drug that are both serious and unexpected** or any **finding from tests in laboratory animals that suggests a significant risk for human subjects** must be reported to FDA within 15 calendar days after the IND holder is informed of the incident.
- Follow up information to safety reports should be submitted as soon as the information is available.

Annual Reports (21 CFR 312.33)

Submit to FDA within 60 days of the IND anniversary date.

2. IDE Reporting Requirements

Changes to Investigational Plan (21 CFR 812.35)

- Holders of IDE must notify FDA within 5 working days of implementing the change to the plan

Unanticipated Adverse Device Effects (UADE) (21 CFR 812.3)

- UADE refers to any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
- Evaluations of UADEs must be submitted to FDA and to all reviewing IRBs and participating investigators within 10 working days after the IDE holder receives notice of the effect.

Progress Reports or Annual Reports (21 CFR 812.150(b)(s), 812.35(a)(4))

- Must be submitted at least once a year to reviewing IRB and FDA

Study Completion or Termination (21 CFR 812.150(b)(7))

- Holders of an IDE must notify FDA of the completion or termination of a study of a significant risk device within 30 working days of termination and submit a final report to FDA and all reviewing IRBs within 6 months after completion or termination.

Potential Conflicts of Interest



The University of Southern California defines Conflict of Interest (COI) as “a situation in which financial or other personal considerations compromise, or have the appearance of compromising an individual’s professional judgment in proposing, conducting, supervising or reporting research” (USC Conflict of Interest in Research: Policy and Procedure). See <http://ooc.usc.edu/conflict-interest>

Investigators must disclose Conflicts of Interest in the iStar application (Question 39).

An IND/IDE holder must disclose COIs as a sponsor and as an investigator. If the IND/IDE holder does not have an identifiable disclosable financial arrangement to report, an [FDA 3454 Form](#) (Certification: Financial Interests and Arrangements of Clinical Investigators) must be completed and submitted to FDA. However, if an identifiable disclosable financial arrangement will be reported, an [FDA 3455 Form](#) (Disclosure: Financial Interest and Arrangement of Clinical Investigators) must be submitted to disclose the financial arrangement.

Note: if the IND/IDE holder is the only investigator for the study, only one form is submitted to FDA. If other investigators are involved in the study, the IND/IDE holder can attach a list of all investigators without a disclosable financial arrangement to report to FDA 3454 Form. However, an individual FDA 3455 Form must be

completed by each investigator in the study reporting a disclosable financial arrangement

Federal Resources

Food and Drug Administration

IND Application:

www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm

www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm

Draft Guidance on IND Applications:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm229175.pdf>

Regulations for Clinical Trial and GCP:

www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm

Guidance on Formal Meetings with Sponsors and Applicants for PDUFA Products:

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

Clinical Trials Registry www.clinicaltrials.gov

Office of Human Research Protections (OHRP)

www.hhs.gov/ohrp/

State Resources

California Dept of Health for Manufacturers, Processors, and Distributors

www.cdph.ca.gov/certlic/manfprocdistrib/Pages/default.aspx

California Food and Drug Branch

www.cdph.ca.gov/programs/Pages/FDB%20Food%20and%20Drug%20Branch.aspx

Additional Resources at Other Institutions

University of Michigan

Michigan Investigator Assistance Program (MIAP) provides IRB regulatory support and guidance and education to holders of INDs and IDEs. For more information, go to:

<http://michr.umich.edu/services/regulatorysupport/miap>

Partners Research Management

Provides various comprehensive checklists including the “FDA Sponsor & Investigator Responsibility Checklist” to ensure that all IND/INDE responsibilities have been fulfilled. They also offer a personalized study binder to achieve and maintain regulatory compliance. For more information, go to:

www.partners.org/phsqi/ToolsPage.htm

University of Minnesota

IND /IDE programs provide assistance with determination of product classification (i.e. drug, device, biologic), applicability of an IND or IDE, preparation, coordination, facilitation, and attendance at FDA meetings, preparation for and regulatory support during FDA inspections of investigator-sponsored clinical trials, and regulatory support for IRB applications. This information can be found at:

www.policy.umn.edu/Policies/Research/INDIDE.html

University of Cincinnati

IND/IDE Assistance program provides support to all University of Cincinnati faculty members who need to file either an IND or IDE. They also provide regulatory assistance to the sponsor-investigator of the clinical investigation:

<http://researchcompliance.uc.edu/HSR/FDA/Overview.aspx>

University of Pennsylvania

IND website includes an “IND Decision tool”, a self-guided questionnaire to assist PIs in determining if IND is necessary for their study. IND application templates are also available on the website. For more information, go to:

www.med.upenn.edu/ohr/ind/index.html

Whom to Contact at USC

Office for the Protection of Research Subjects (OPRS)

3720 South Flower Street, Third Floor

Los Angeles, CA 90089-0706

Tel: (213) 821.1154 Fax: (213) 740.9299 E-mail: oprs@usc.edu

Web: <https://oprs.usc.edu/>

Health Sciences Institutional Review Board

General Hospital, Suite 4700

1200 North State Street

Los Angeles, CA 90033

Tel: (323) 223.2340 Fax: (323) 224.8389 E-mail: irb@usc.edu

Web: <https://oprs.usc.edu/hsirb/>

University Park Campus Institutional Review Board

Credit Union Building (CUB), Suite 301

3720 S. Flower Street

Los Angeles, CA 90089 Tel: (213) 821.5272 E-mail: upirb@usc.edu

Web: <https://oprs.usc.edu/upirb/>

Office of Compliance

University Gardens Building, Room 105

3500 Figueroa Street

Los Angeles, CA 90089-8007

Tel: (213) 740.8258 E-mail: complian@usc.edu

Web: www.usc.edu/compliance/

USC Clinical Research Organization (formerly HRA)

1640 Marengo St 7th floor

Los Angeles, CA 90033

Tel: (323)223-4091 Web:

http://keck.usc.edu/About/Administrative_Offices/Clinical_Research_Organization.aspx

iStar Helpdesk: istar@usc.edu (323)276-2238

CITI Helpdesk: citi@usc.edu (213)821-5272