AAH RSPP GUIDANCE
Investigational Drug and Biologic Research Studies

PURPOSE
The purpose of this guidance is to provide the reader with information on investigational drug and biologic studies, and IRB review. There are instances where investigational drugs/biologics are used in treatment situations – these are cases of Expanded Access/’compassionate use’. In expanded access of investigational drugs, prospective convened IRB review must be completed before the drug/biologic may be used at AAH. Emergency use situations may allow for a waiver of prospective IRB review, but then require a report made to the IRB within 5 working days. Information on these instances can be found in RSPP SOP 1 and 2, as well as RSPP guidance documents: Expanded Access, and Emergency Use.

The US FDA Investigational New Drug (IND) program is the means by which an entity or investigator obtains permission to administer an investigational drug or biologic to human subjects (or an approved drug used for a new indication or new population of patients) (21 CFR 312).

The FDA has two primary objectives in reviewing an IND: 1) to assure the safety and rights of subjects in all phases of an investigation, and 2) in phases 2 and 3, to help assure that the quality of the scientific evaluation of the drug is adequate to permit an evaluation of the drug’s effectiveness and safety.

NOTE that when a physician uses a legally marketed drug outside its labeling to treat a patient and no research is being done, IRB review is not required.

Definitions of italicized words can be found in the AAH RSPP Glossary.

GUIDANCE
What kind of drug studies require an IND?
The following ‘new drug’ studies require an IND:

- Studies that use a drug or pharmaceutical that is not approved for marketing by the FDA
- Studies that use approved drugs in unapproved indications
- Studies that use new formulations, new dosages, or in a new patient population that would be put at increased risk

An exemption from the IND requirement may be met under specific criteria (discussed later).

It should be noted that INDs may also be required for research introducing food or food-derived products, spices/herbs or dietary supplements.
What kind of INDs/IND research studies are there?
There are several different kinds of INDs issued for use of investigational drugs/biologics in research studies. Research studies done under these types of IND require prospective convened IRB review and subject informed consent.

**Commercial INDs** are filed by companies to obtain marketing approval for a new drug.

**Research or Investigator INDs** are non-commercial INDs filed by researchers to study an unapproved drug or to study an approved drug for a new indication, different route of administration, new dose level, or new patient population.

**Open Label INDs** are used in uncontrolled studies, carried out to obtain additional safety data (Phase 3 studies). They are typically used when the controlled trial has ended and treatment is continued so that the subjects and the controls may continue to receive the benefits of the investigational drug until marketing approval is obtained.

Which research studies are exempt from needing an IND?
FDA regulations describe two categories of clinical investigations that are exempt from the IND requirements provided the criteria for exemption are met:

1. Research Involving Marketed Drug Products
   A clinical investigation of a marketed drug is exempt from the IND requirements if all of the criteria for an exemption in 21 CFR 312.2(b) are met:
   - The drug product is lawfully marketed in the United States.
   - 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.
   - The investigation is conducted in compliance with the requirements for review by an IRB and with the requirements for informed consent.
   - The investigation is not intended to promote or commercialize the drug product.

2. Bioavailability or Bioequivalence Studies in Humans
   FDA regulations describe criteria under which bioavailability or bioequivalence (BA/BE) studies using unapproved versions of approved drug products can be conducted without submission of an IND (21 CFR 320.31(b) and (d)). A BA/BE study in humans does not require an IND if all of the following conditions are met:
• The drug product does not contain a new chemical entity, is not radioactively labeled, and is not cytotoxic.
• The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product.
• The investigation is conducted in compliance with the requirements for review by an IRB and with the requirements for informed consent.
• The sponsor meets the requirements for retention of test article samples and safety reporting.

Is IRB oversight required when using investigational drugs and biologics in human subject research?

IRB review and approval is generally required before a study can be initiated under an Investigational New Drug Application (IND). Under 21 CFR 56.105, FDA may waive IRB review requirements for specific research activities or for classes of research activities otherwise covered by the IRB regulation. However FDA believes that this waiver provision should be used only when alternative mechanisms for ensuring protection of the rights and welfare of human subjects are acceptable.

What is the Advocate Aurora IRB’s review process for investigational drug/biologic protocols used in human subject research?

Submission requirements

If the research study uses a drug or biologic, except those used in the course of medical practice, and that drug/biologic is being tested for safety and/or efficacy, the investigator/sponsor must ensure that the protocol has an IND associated with it prior to submission to the IRB, OR that the drug(s) used in the protocol all qualify for an IND exemption per 21 CFR 312(b). The investigator/sponsor may reach out to the FDA for guidance on whether an IND is required in the research protocol. At times, the IRB may ask the investigator/sponsor to discuss their intended use of investigational drug/biologic with the FDA.

If a drug/biologic has been issued an IND by the FDA, the printed protocol should reference the FDA issued IND number(s). If the protocol does not include a reference to the IND number(s) communication from the FDA or the investigator/sponsor indicating that the IND number(s) provided are the right ones for the protocol must be provided.

If the investigator/sponsor has submitted an IND application to the FDA, but has not yet received an IND number, the study team may submit an IRB application to the Advocate Aurora IRB with the IND number as pending. However the IRB will not consider the study until the FDA has issued their decision.

The AAH IRB submission application asks questions about the use of the investigational drug/biologic in the research study, the storage, maintenance, and control of the investigational agent(s), as well as the name/title of the individual responsible at each research location for
investigational product control. The IRB submission application also asks whether the submitter has contacted the Investigational Drug Service (IDS) department of the AAH Pharmacy. AAH Pharmacy has a system policy (Investigational Drugs Policy) that requires individuals involved in human subject research studies using investigational pharmaceutical agents to discuss the study with the IDS team prior to submission of the study to the IRB.

Review Checklist

The RCA/Primary Reviewer will complete a Reviewer Drug Checklist. This checklist documents one of the following:

- the existence of IND(s) for the study (confirmed in the sponsor’s protocol or via documentation from the sponsor or the FDA);
- an FDA-issued IND exemption for the study; or
- the sponsor’s determination that the drug/biologic qualifies for an IND exemption.

If completed by the RCA, the document will be provided to the Primary Reviewer in his/her consideration of drug/biologic risk level.

IRB Review

It is the responsibility of the IRB to consider the risks and benefits of the investigational drug/biologic as part of their review of the research study. The IRB will consider whether the study may be approved using the regulatory criteria for approval (21 CFR 56.111) as the basis for their decision.

If the sponsor’s protocol indicates that the investigational drug/biologic(s) are exempt from IND(s), the IRB will review that rationale and determine if appropriate.

Some studies involving investigational drug/biologic(s) in which the investigational drug regulations (21 CFR 312) do not apply may be considered minimal risk studies and may be reviewed through the expedited review procedure. However, research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.

Studies in which an IND has been issued will require convened IRB review.

- For studies reviewed via expedited review procedures, the Reviewer Drug checklist will be retained in the study file to document IDE exemption status.
- For studies reviewed at a convened IRB meeting, the Primary Reviewer will use the Drug checklist in his/her presentation to the IRB. The IND status of the study and any IRB discussion of the matter will be documented in the meeting minutes. The checklist does not need to be retained in the study file.
REQUIREMENTS

- FDA Regulations: 21 CFR 312; 21 CFR 46.111; 21 CFR 56.105; 21 CFR 320.31
- FDA guidance: "Off-Label" and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices; Treatment Use of Investigational Drugs; Waiver of IRB Requirements for Drug and Biological Product Studies; Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers; Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND; IND Application Procedures: Exemptions from IND Requirements
- AAHRPP Accreditation Standards/Elements: I.7.A
- RSPP SOPs 1, 2
- RSPP guidance: Expanded Access; Emergency Use.
- AAH system policy: Investigational Drugs Policy and Procedure #62777