Use of Investigational Drugs or Biologic Products in Human Subjects Research

Content Applies To

Mayo Clinic Human Research Protection Program

Purpose

The purpose of this document is to direct and inform Investigators, IRB committee members and IRB staff of the requirements for human subject research when using FDA-regulated investigational drugs or biological products.

Key Terms

Drug:

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

Investigational or experimental drug: new drugs that have not yet been approved by the FDA or approved drugs that have not yet been approved for a new use, and are in the process of being tested for safety and effectiveness.

Biological Product (or *biologic*) is a medical product. Many biologics are made from a variety of natural sources (human, animal or microorganism). Like drugs, some biologics are intended to treat diseases and medical conditions. Other biologics are used to prevent or diagnose diseases. Examples of biological products include:

- vaccines
- blood and blood products for transfusion and/or manufacturing into other products
- allergenic extracts, which are used for both diagnosis and treatment (for example, allergy shots)
- human cells and tissues used for transplantation (for example, tendons, ligaments and bone)
- gene therapies
- cellular therapies
- tests to screen potential blood donors for infectious agents such as HIV

- In general, the term "drugs" includes therapeutic biological products.

IND (Investigational New Drug) Application: Means by which permission may be obtained to 1) ship an investigational drug, biologic or agent across state lines and 2) use in humans prior to FDA review of clinical data has determined a new drug, agent, or biologic is safe and effective for a specific use. Testing of an investigational product may proceed once a valid IND is in effect or an IND exemption has been granted.

Label: The FDA approved label is the official description of a drug or biologic product which includes indication (what the product is used for); who should take it; adverse events (side effects); instructions for uses in pregnancy, children, and other populations; and safety information for the patient. Labels are often found inside product packaging.

Policy

It is the policy of the Mayo Clinic Office for Human Research Protection IRB to require that investigators comply with all applicable regulations pertaining to investigational drugs and biologic products and that all proposed uses are reviewed and approved by the IRB as defined by Federal regulations.

A convened IRB will review the initial research application. Modifications and continuing review reports are reviewed using the criteria described in the documents *IRB Initial Approval of Research, Modifications to Previously Approved or Exempt Research* and *Continuing Review of Research Projects*.

An investigational new drug or biologic product may be used in a human subject research project if:

- The sponsor of the investigation receives an IND from the FDA, or
- An IND exemption is granted from the FDA, or
- The IRB agrees with the principal investigator assessment that the proposed use of the drug in the research project meets the IND exemption criteria, AND
- The research project has been approved by the convened IRB.

Research requiring an IND **must not** begin until a valid IND is in effect and IRB approval has been granted. Research activities include, but are not limited to, recruitment, consent, and screening of potential subjects.

FDA advises IND sponsors that research in humans may not begin until thirty days after the FDA receives the IND application. During that review period or any time thereafter a clinical hold may be imposed that could affect individual studies or the entire IND.

In certain emergency situations where IND submission and/or IRB approval is not possible, FDA may authorize shipment of an investigational drug or biologic product for a specified use in advance of the submission of an IND. For further details, refer to the IRB document *One-Time Emergency Use of an Investigational Device, Drug or Biologic Product.*

Investigator Responsibilities

1. The investigator must submit a complete and accurate IRB electronic application to request IRB approval for the use of an investigational drug or biologic product in a human subject research project. In the application, the investigator provides the following information:
    - When the research requires an IND, a copy of the FDA IND acknowledgement letter or confirmation from the sponsor of a valid IND including the IND number
    - A description of the drug or biologic product

- Reports of prior investigations with the drug or biologic product
- The investigational plan/protocol/research project proposal
- A description of subject selection criteria
- A description of planned monitoring procedures
- Consent form(s)
- Any other information that the IRB requires in order to conduct its review and make a determination

2. The investigator is responsible for ensuring the research project is conducted according to the IRB-approved application and in compliance with the requirements of this document and other applicable requirements and regulations.
3. The investigator is responsible for protecting the rights, safety and welfare of the subjects.
4. The investigator must report all unanticipated problems involving risk to human subjects or others (UPIRTSO) to the IRB. See IRB document *Reporting an Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO) to the IRB.*
5. The investigator is responsible for controlling the investigational drug or biologic product.
6. The investigator will not make changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
7. The Investigator must comply with IRB and regulatory requirements for the initial application, modification, and continuing review report submissions to the IRB for review and approval. See IRB documents *IRB Initial Approval of Research, Modifications to Previously Approved or Exempt Research and Continuing Review of Research Projects.*

Exemption from IND Requirement

According to Food and Drug Administration (FDA) regulations 21 CFR 312.2 - *Investigational New Drug Application*, the following studies of drugs and biologicals are exempt from requirements to submit an Investigational New Drug (IND) application to the FDA.

21 CFR 312.2 (b) (1) IND Exemptions

1. The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the IND requirements if all the following apply:
    i. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug; and
    ii. If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product; and
    iii. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that

significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product; and

iv. The investigation is conducted in compliance with the requirements for institutional review set forth in 21 CFR 56 *Institutional Review Boards* and with the requirements for informed consent set forth in part 21 CFR 50 *Protection of Human Subjects*; and

v. The investigation is conducted in compliance with the requirements of 21 CFR 312.7 - *Promotion of Investigational Drugs*.

2. (i) A clinical investigation involving an in vitro diagnostic biological product is exempt from the requirements of Part 312 - *Investigational New Drug Application* if (a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (b) it is shipped in compliance with 21 CFR 312.160 - *Drugs for investigational use in laboratory research animals or in vitro tests*.

   (ii) The following products are exempt from the requirements of Part 312 - *Investigational New Drug Application*: (a) blood grouping serum; (b) reagent red blood cells; and (c) anti-human globulin.

3. A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of Part 312 - *Investigational New Drug Application* if shipped in accordance with 312.160 - *Drugs for investigational use in laboratory research animals or in vitro tests*.

4. FDA will not accept an application for an investigation that is exempt under the provisions of 21 CFR 312.2 (b) (1) - *IND Exemptions*.

5. A clinical investigation involving use of a placebo is exempt from IND requirements if the investigation does not *otherwise* require submission of an IND.

Convened IRB Responsibilities

- A Convened IRB will review all initial applications for a human research study that includes the use of an investigational drug or biologic.
- If there is a question as to whether an IND is required, the IRB may require, as part of the review and approval process, that an investigator contact the FDA to discuss the proposed research in an effort to help determine if an IND application is required. The IRB may also direct the investigator to submit a formal IND application to the FDA in cases where it is not clear whether an IND is required, or there is not enough evidence to support an IND exemption determination.
- The IRB will review and determine if the drug or biologic is exempt from IND requirements and will specify the category of exemption.

Emergency Use

An emergency use of an investigational drug or biologic product by a clinician without prior IRB review and approval is permitted under 21 CFR 56.104(c). See IRB document *One-Time Emergency Use of an Investigational Device, Drug or Biologic Product.*

Sponsor-Investigator Resources

The Mayo Clinic Office of Research Regulatory Support (ORRS) provides assistance to Mayo Clinic investigators working on FDA regulated research involving drugs, biologics,

devices or other test articles. It is a centralized resource for information, expertise, and support related to the conduct of clinical research under investigator-initiated INDs or IDEs. See IRB document *Reporting Requirements for Sponsor-Investigators Conducting Investigational New Drug (IND) or Investigational Device Exemption (IDE) Research Policy.*

Related Documents

IRB Initial Approval of Research

Modifications to Previously Approved or Exempt Research

Continuing Review of Research Projects

One-Time Emergency Use of an Investigational Device, Drug or Biologic Product

Reporting an Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO) to the IRB

References

Reporting Requirements for Sponsor-Investigators Conducting Investigational New Drug (IND) or Investigational Device Exemption (IDE) Research

Guidance for Industry: Investigational New Drugs

Guidance for Industry: IND Exemptions

21 CFR 312 Investigational New Drug Applications

21 CFR 50 Protection of Human Subjects

21 CFR 56 Institutional Review Boards

21 CFR 56.104(c) - Emergency Use of a Test Article

Drugs@FDA Glossary of Terms

HHS Guidance: Waiver of IRB Requirements for Drug and Biologic Product Studies