

## **SECTION 8: USE OF DRUGS IN INVESTIGATIONAL ACTIVITIES**

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### **SECTION 8.1 APPLICABILITY**

This policy applies to ALL use of a drug in an investigational setting, whether FDA-approved or not, and whether used for clinical or research purposes.

The FDA (21 CFR 312.3) defines a clinical investigation as “any experiment in which a drug is administered to, or used involving, one or more human subjects.” Based on this definition, there are no exceptions to the requirement that any drug used in research with humans must be reviewed by the IRB and, in addition, is subject to FDA regulation.

This includes both Drugs and Biologic products.

### **SECTION 8.2 IND (INVESTIGATING NEW DRUG) APPLICATION**

All drug use in research must include submission of an IND. The **ONLY** exception is if the marketed drug or biologic product meets **ALL six** of the following conditions:

- i) It is not intended to be reported to the FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
- ii) It is not intended to support a significant change in the advertising for the product;
- iii) It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- iv) It is conducted in compliance with the requirements for IRB review and informed consent (21 CFR parts 56 and 50, respectively);
- v) It is conducted in compliance with the requirements concerning the promotion and sale of drugs (21 CFR 312.7); and
- vi) It does not intend to invoke 21 CFR 50.24 (this has to do with waiver of informed consent in an emergency room setting).

If your study does not meet **ALL** six of these conditions, or is an unapproved drug or unapproved use of a new drug, you must submit and IND, or provide written evidence from the FDA that an IND is not required. Because of the potential risk involved, the IRB will require an IND submission if there is any doubt that your study meets these six criteria.

Refer to the FDA website for instructions.

Currently, we have two contact numbers available.

A Food and Drug Administration  
Division of Drug Information, HFD-240  
5600 Fishers Lane, Rockville, MD 20857  
Fax number: 301-827-4577  
Email: [druginfo@cder.fda.gov](mailto:druginfo@cder.fda.gov)  
Contact at the FDA: Barry Poole at 301-827-4570

Send:

- ☒ Your name, address, phone number, fax number, Email address, and affiliation.
- ☒ The name and a brief description of the substance to be administered, the source ( e.g., animal, synthetic, etc.), dosage form, sterility (if applicable) and supplier
- ☒ A brief summary of the study including the purpose, hypothesis, number of subjects, patient population, condition or disease (if applicable), dose, route, and duration of substance administration.
- ☒ A brief explanation of why you consider the substance safe for administration to human subjects under the conditions of the study (append references, if necessary).

B. The FDA has also established a Pre-IND consultation Program that you may contact for guidance and instructions:

U.S. Food and Drug Administration  
Office of Drug Evaluation IV (HFD-104)  
Pre-IND Consultation Program  
ATN: Sylvia D. Lynche, PharmD  
9201 Corporate Blvd, 4<sup>th</sup> Floor  
Rockville, MD 20850  
Phone: 301-827-2335

### **SECTION 8.3 RESEARCH INVOLVING AN FDA-APPROVED USE**

If the proposed use of a drug in a study is fully within the guidelines for use approved by the FDA, and meets the six criteria listed in Section 8.2, then an IND is not required.

However, the protocol submission should contain a summary of known risks and precautions associated with the drug, including any new data that has emerged the drug or biologic received FDA approval.

### **SECTION 8.4 RESEARCH INVOLVING AN OFF-LABEL USE OF AN APPROVED DRUG.**

An off-label use of a drug in experimental setting will generally require submission of an IND. Again, refer to section 8.2. **THIS IS TRUE EVEN IF THE DRUG IS COMMONLY USED IN A CLINICAL SETTING FOR THE “OFF LABEL” CONDITION OR DOSAGE.**

Purely clinical, non-research use of a drug in an off-label manner is outside the jurisdiction of the IRB and is covered by other regulations of the UNTHSC and the

physician's license.

### **SECTION 8.5 RESEARCH INVOLVING A NEW OR UNAPPROVED DRUG**

Any investigation involving the use of a new drug, or any drug that does not have formal FDA approval, will require an IND. **NO EXCEPTION** will be made without written documentation from the FDA.

### **SECTION 8.6 SUBMISSION AND REVIEW PROCEDURES**

**IN ADDITION** to the requirements of the IRB contained in other policies and procedures, the following procedures apply.

A. For **ON-LABEL**, approved use:

Submit the study protocol as usual, but include:

1. Information supporting your use as an approved use
2. Updated safety and efficacy information. You are responsible for conducting a current literature review as outlined in section 8.6.

B. For **ALL** other uses, the submission should include:

1. The IND number and name of the sponsor (if different than the investigator)
2. The generic, chemical, and trade name of the drug and its structural formula.
3. An abstract of the available information concerning the animal pharmacology and toxicology.
4. A summary of previous clinical studies. This should include any adverse effects or toxicity. Pertinent references should be included. See Section 8.6 for guidelines.
5. A specific indication of the Phase (i.e., I, II, III, or post-marketing surveillance) should be included.

C. The UNTHSC-IRB will review the project in two parts.

1. Upon submission for full-board review, the chair will assign the protocol to a member of the board who has specific training in pharmacology; if an appropriate member is not available, it will be assigned to an outside consultant.
2. The reviewer will conduct a Pharmacy and Therapeutics (P&T) review to evaluate the protocol and drug for safety for the proposed use, and make one of three recommendations: approval, modification, or disapproval. If the reviewer recommends modifications or disapproval, the investigator must satisfy the recommendations of the reviewer. **NO STUDY** will be approved until cleared for approval by the pharmacy and therapeutics reviewer.
3. The IRB will then conduct a full board review.

D. Since the UNTHSC does not have a separate pharmacy and therapeutics committee, there is no time estimate for this review process. Since the study cannot go forward until cleared, the investigator is strongly advised to submit the study as early as possible.

### **SECTION 8.7 DOCUMENTATION GUIDELINES**

The following guidelines are adapted from those in place at Johns Hopkins University.

When a study involving a drug or biologic is submitted for review, the IRB must have access to sufficient information to determine if the drug is sufficiently safe to use in the subjects of the study. The standard the investigator must reach has been raised in recent years due to situations where negligent documentation by investigators and negligent review by IRBs have resulted in the death of otherwise healthy research subjects. The investigator should strive to provide more than the minimum data and be prepared for careful scrutiny of any use of drugs or biologics with humans.

This means the investigator must conduct and provide evidence of a thorough review of the literature for safety of the proposed agent. What this means in practice will vary widely. For example, sponsored drug trials are usually presented to the local investigator with extensive, current documentation, so that the local investigator's obligation will be to be familiar with the data, be prepared to report to the IRB (and sponsor) any additional safety data, and transmit the materials to the IRB for review. This is normally also a requirement by the sponsor. A study involving an established, approved use of an approved drug will also require a simple updated literature review to supplement that available from the drug manufacturer. At the other extreme, an agent that has not been approved by the FDA for any use will require an extensive and comprehensive review of the literature. If the study is investigator-initiated, then the **ENTIRE** responsibility for that documentation falls to the investigator.

The standards given here apply to the latter case, that is, where the study is of an off-label or unapproved use or use of an unapproved drug. However, the IRB and the P&T reviewer have the responsibility of assessing whether the submitted documentation is adequate and have the obligation to request additional documentation if, in their judgment, the provided documentation is inadequate or incomplete. The IRB members and the P&T reviewer also have the option to conduct an independent literature review.

The investigator should conduct a thorough and complete review of the literature. It is **NOT SUFFICIENT** to simply order a computerized search. The search may include reviews, textbooks, abstracts, meeting notes, meeting synopses, and advertisements but are not sufficient. It should also include primary peer reviewed publications.

The investigator should also remember that a substantial amount of information may be unpublished, and other information may predate the years covered by an automated search. The investigator is responsible for showing that an active effort was made to search out those sources. For example, a published paper may not contain all the data from a study, and direct contact with the study authors might reveal information affecting subject safety. Investigators have been cited when auditors believed that the investigator knew or should have known about such unpublished data.

The investigator should provide three sets of information:

- A. A summary of the literature review, detailing the findings regarding the safety and toxicity of the agent, including data from both human and animal studies.
- B. A Literature Search Log showing the information sources used as well as the search

paths that have led to that information. The search log should include information showing:

1. Date search conducted
2. Name of database
3. Host
4. Latest update available
5. Years searched
6. Print-out of your search strategy (not a retyped form, but rather the original strategy)

### C. Bibliography

Johns Hopkins recommends the following search strategy be used as a general guideline:

1. Identify the drug
2. Check for alternate names of the drug
3. Define the research setting in which the drug will be used
4. Consult reference or tertiary sources as a starting point
5. Consult secondary sources (abstracting and indexing services) for comprehensiveness and quality assurance.
6. Choose the most appropriate sources of evidence of safety/adverse effects
7. Create a bibliography