Department: **UAMS Institutional Review Board**
Policy Number: **18.1**
Section: **Drugs and Devices**
Effective Date: **July 31, 2002**
Revision Dates: **February 8, 2005; April 15, 2004**

SUBJECT: Review of Investigational New Drug (IND) Studies

Definitions:

Food and Drug Administration(FDA): The U S. Food and Drug Administration is a scientific, regulatory, and public health agency that oversees human and animal drugs, therapeutic agents of biological origin, medical devices, radiation-emitting products for consumer, medical, and occupational use, cosmetics, and animal feed. FDA scientists evaluate applications for new human drugs and biologics, complex medical devices, food and color additives, infant formulas, and animal drugs. It also monitors the manufacture, import, transport, storage, and sale of the aforementioned products as well as inspects facilities for compliance with regulations.

FDA Acknowledgment Letter: This letter typically comes 1-2 weeks after the FDA receipt of an IND submission. This letter assigns the IND number, gives the date of receipt, and reminds the sponsor-investigator of their obligations under the IND. This is NOT an approval to begin clinical trials. Clinical trails may not begin until 30 days after the IND receipt date or later if the IND is placed on clinical hold. The Sponsor-Investigator may or may not receive a letter permitting them to proceed with their trial. If a clinical hold is placed on the IND, the FDA should issue a letter detailing the IND deficiencies.

Good Clinical Practices (GCP): International ethical and scientific quality standards for designing, conducting, monitoring, recording, auditing, analyzing, and reporting studies. Insures that the data reported is credible and accurate and that subject's rights and confidentiality are protected.

Current Good Manufacturing Practices (cGMP): The minimum requirements for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug or biologic to assure that such drug meets the requirements of the Food, Drug, and Cosmetic Act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

Current Good Tissue Practice (cGTP): The minimum requirements for methods to be used in, and the facilities or controls to be used for, the manufacture of human cell, tissue, and cellular and tissue-based products (HCT/P); recordkeeping; and the establishment of a quality program. (Effective May 25, 2005)

Investigational Agents: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial. This includes products with marketing authorization when they are formulated, packaged, or administered in a way different from the approved form, products used for off-label use, or products used to gain further information about an approved use (such as an unapproved population).

Investigational drugs/investigational biologics: A new drug or biological drug that is used in a clinical investigation. It also includes a biological product that is used *in vitro* for diagnostic purposed. Investigational drugs or biologics may include products that are not generally recognized as being safe and effective by the FDA or products already approved by the FDA as safe and effective for specific indications but are being studied for new indications, doses, strengths, dosing frequency, or in new populations. This latter description is known as off-label use.

Investigational New Drug (IND): Current Federal law requires that a drug be the subject of an approved New Drug Application (NDA) before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in other states, a sponsor must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

Sponsor-Investigator: This is an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

Standard Operating Procedures (SOPs): Detailed, written procedures for the uniform performance of a function. These are the standard procedures that trained study personnel must follow to ensure the quality and integrity of the work performed during a study.

Waiver: A request to FDA to waive applicable requirements under 21 CFR 312 – Investigational New Drug Application.

Policy:

It is the policy of the University of Arkansas for Medical Sciences (UAMS) Institutional Review Board (IRB) that all studies involving investigational drugs, agents, and/or biologics be reviewed and approved for use in accordance with Federal regulations and Institutional policies.

Criteria for Investigational New Drug (IND) Exemption for Sponsor-Investigators

I. IRB Responsibilities

The IRB has the responsibility to evaluate all studies submitted by a Sponsor-Investigator, which involve the use of a drug substance, for compliance with 21 CFR 312, Investigational New Drug Application. There are at least three possible scenarios:

A. The Sponsor-Investigator already has applied for and/or received an IND under 21 CFR 312;
B. The Sponsor-Investigator has obtained a waiver of IND requirements from the FDA under 21 CFR 312.10; or
C. The Sponsor-Investigator has not determined the need for an IND for the study.

A. If the Sponsor-Investigator already has an IND, the FDA acknowledgment letter informing the Sponsor-Investigator of their obligations under 21 CFR 312 must be submitted to the IRB. (NOTE: This is a letter assigning the IND number which comes approximately 1-2 weeks after the FDA receipt of the IND. This is not an approval letter for the IND and does not give the Sponsor-Investigator permission to proceed with the study.) If this letter is not submitted with the original filing in ARIA, a contingency will be issued by the IRB and an approval letter for the study will not be issued until the Sponsor-Investigator has satisfied the contingency.

B. If the Sponsor-Investigator has obtained a waiver for the requirements of 21 CFR 312, this must be stated in the original submission to the IRB and a copy of this letter submitted to the IRB. If this letter is not submitted with the original filing in ARIA, a contingency will be issued and an approval letter for the study will not be issued until the Sponsor-Investigator has satisfied the contingency.

C. If the Sponsor-Investigator has not obtained an IND or a waiver of IND requirements, the IRB will refer the study to the Office of Research Compliance (ORC) for IND determination. The ORC will work with the Sponsor-Investigator to develop an IND.

Prior to an IND study approval, the IRB must determine that:

1. An IND exists for the drugs under study, if applicable.
2. The drug is labeled according to the appropriate IND regulations.
3. The study staff has been appropriately informed of their obligations and responsibilities under the Federal and institutional regulations and policies.
4. There is adequate control and handling of the drug.
5. The drug/dosage form is manufactured according to the appropriate Federal regulations.

II. Office of Research Compliance (ORC) Responsibilities

The ORC will utilize a decision tree, based upon 21 CFR 312.2 to determine the applicability of the IND requirements. (Attachment 1) This decision tree will be available to the IRB in case of disagreement with the ORC determination, but not in the case of FDA determination.

If the ORC cannot make an unequivocal determination regarding the need for an IND, they will contact the appropriate FDA Division, in consultation with the Sponsor-Investigator, for advice and/or request a waiver under 21 CFR 312.10. Alternatively, the ORC will assist the Sponsor-Investigator in directly filing a request for waiver from the IND regulations as outlined below.

III. Possible Determinations of the ORC and Resultant Actions

A. <u>IND not required</u>
If the ORC determines that there is no regulatory requirement for an IND, a letter will be issued to the IRB and the Sponsor-Investigator outlining the rationale for the decision.

B. IND waiver under 21 CFR 312.10
If the ORC determines that IND requirements might be waived, the ORC will apply for this waiver under ORC Standard Operating Procedure 209.2, IND Exemption Request Under 21 CFR 312.10. A copy of the letter requesting the IND waiver will be sent to the IRB.

C. IND required
If an IND is required under the regulations, the ORC will notify the IRB of their determination. The following will then occur:
1. The ORC will meet with the Sponsor-Investigator and issue a copy of the ORC IND Packet for Sponsor-Investigators. The ORC will work with the Sponsor-Investigator, and affiliated compliance offices as necessary, to develop and submit the IND to the FDA.
2. The ORC will review the responsibilities of a Sponsor-Investigator under 21 CFR 312 using the attached "Summary FDA Requirements for Investigations Who Are Also Considered Sponsors of New Drugs." (Attachment 2)
3. The ORC will review with the Sponsor-Investigator the Good Clinical Practice guidelines as adopted by the International Conference on Harmonisation and the FDA.
4. If the IND requires that the Sponsor-Investigator manufacture either the drug substance or the dosage form, the ORC will review the responsibilities of a Sponsor-Investigator under 21 CFR 210 & 211 as well as the Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (ICH Q7A).
5. The Sponsor-Investigator will be given a copy of the ORC Monitoring Packet for Sponsor-Investigators and will write and submit a monitoring plan for IRB review and approval. (See IRB Policy 7.8 Data and Safety Monitoring and ORC SOP 207.01 Review of Monitoring Plans)

IV. Sponsor-Investigator Responsibilities

A. IND Is Not Required
No further documentation is required of the Sponsor-Investigator; the ORC will issue a letter to the IRB.

B. IND Waiver
If the Sponsor-Investigator has already obtained a Waiver for 21 CFR 312, the FDA letter granting the waiver must be submitted to the IRB. If they have not yet applied for a waiver,they must inform the IRB of their intent and submit the letter granting or denying the waiver to the IRB. If the waiver is denied, the Sponsor-Investigator must either apply for an IND as outlined in this document or withdraw the protocol from consideration by the IRB.

C. IND Required
1. The Investigator will work with the ORC to develop an IND for submission to the FDA.
2. The Sponsor-Investigator will provide the IRB with a copy of the FDA Acknowledgement Letter when received.
3. The Sponsor-Investigator will notify the IRB and ORC when the 30-day waiting period is completed or if an FDA clinical hold has been placed on the IND.

4. The Sponsor-Investigator will develop and institute Standard Operating Procedures (SOPs) for the conduct of the clinical investigation. Assurance will be given to the ORC that these SOPs are in place and an index of said SOPs will be submitted to the ORC.
5. The Sponsor-Investigator will develop an IND monitoring plan (IRB Policy 7.8) and submit it to the IRB for their review and approval.
6. The Sponsor-Investigator will consult with the Research Pharmacist to develop a cost impact statement, dispensing, control, and handling of the drug.
7. The Sponsor-Investigator will consult with the ORC regarding the cGMPs and/or the cGTPs where applicable, and the GCPs.

Attachment I

21CFR312: Part 312 Investigational New Drug (IND) Application

EXEMPTIONS FROM INDs

1. Is the drug lawfully marketed in the US: **NO** → Need IND

↓ **YES**

a. Are the results of study to be reported to FDA in support of a new indication? **YES** → Need IND

↓ **NO**

b. Are they to be used to support any significant change in the labeling? **YES** → Need IND
(i.e. is the study intended to support a change in the advertising)

↓ **NO**

c. Does the study involve any of the following that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product: **YES** → Need IND

- a route of administration or
- dosage level or
- use in a patient population or
- other factor

↓ **NO**

d. The study is conducted in compliance with the requirements:

- for informed consent and institutional review set forth in 21 CFR part 50 (protection of human subjects) and part 56 (IRB)

↓ **AND** **NO** → Need IND

- of section 21CFR 312.7 (promotion and charging for investigational drugs)

↓ **YES**

EXEMPT FROM IND UNDER PROVISION 1

EXEMPTIONS FROM INDs (cont'd)

2. Does the study involve any of the following *in vitro* diagnostic biological products?

   a. blood grouping serum
   b. reagent red blood cells
   c. anti-human globulin

AND

(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 Section 312.160 (21 CFR Subpart G, 312.60 Drugs for Investigational Use in Laboratory Research Animals or *in vitro* Test)

EXEMPT FROM IND UNDER PROVISION 2

OTHER PROVISIONS FOR EXEMPTIONS

3. A **drug** intended solely for tests *in vitro* or in laboratory research animals is exempt from the requirements of 21CFR312.2 if shipped in accordance with Section 312.160. (This is similar to provision 2 except that it applies to drugs rather than *in vitro* diagnostic biologicals.)

4. FDA will not accept an application for an investigation that is exempt under the provisions of Paragraph 312.2(b)(1) of this Section.

5. A clinical investigation involving the use of a placebo is exempt from the requirements of 21CFR312 if the investigation does not otherwise require the submission of an IND.

6. A clinical investigation involving an exception from informed consent under 21CFR50.24 ("Exemption from informed consent requirements for emergency use") of this chapter is not exempt from the requirements of 21CFR312.

Attachment 2

Summary FDA Requirements for Investigations Who Are Also Considered Sponsors of New Drugs

This is an overview of the Food and Drug Administration (FDA) requirements for Sponsors with Investigational New Drugs (INDs). **Please review the federal regulations before performing any sponsor's duties. If you are the sponsor and the investigator for the drug, you must meet the requirements for the sponsor and the investigator.** Additional information can be found on the FDA's web Site: http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfr312_00.html

Major Responsibilities of Sponsors with IND Studies

1. Submit IND application form 1571 and other required documents to FDA. (21 CFR 312.23)
2. Label the investigational drug in accordance with FDA regulations. (21 CFR 312.6)
3. Promote and distribute the drug in accordance with FDA regulations. (21 CFR 312.7)

21 CFR 312.53:
4. Select qualified investigators based on training and experience.
5. Ship investigational drugs only to investigator(s) participating in the investigation.
6. Obtain FDA Form 1572 from the investigator(s).
7. Obtain a written statement that the investigator(s) will conduct the study as outlined in the protocol.
8. Obtain relevant financial information from the investigator(s).
9. Select a monitor to oversee the progress of the investigation.
10. Comply with FDA regulations regarding emergency use. (21 CFR 312.54)
11. Keep investigator(s) informed on the safety and effectiveness of the drug. (21 CFR 312.55)

21 CFR 312.56:
12. Monitor the progress of all IND investigations.
13. Terminate investigator(s) participation when investigator(s) fails to follow protocol.
14. Review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from each investigator(s).
15. Discontinue the study if the investigational drug presents an unreasonable and significant risk to subjects.
16. Notify the FDA, IRB, and the investigator(s) if the study is discontinued.
17. Send safety reports to FDA. (21 CFR 312.32)

21 CFR 312.57:

18. Maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug.
19. Maintain complete and accurate records of payments made to clinical investigator(s).
20. Assure that investigator(s) return all unused investigational drugs. (21 CFR 312.59)

21 CFR 312.62:
21. Require investigator(s) to maintain adequate drug records.

22. Require investigator(s) to keep case histories on each individual administered the investigational drug or employed as a control in the investigation.
23. Require investigator(s) to meet local IRB requirements. (21 CFR 312.66)
24. Collect reports (financial, progress, safety, and final report) from investigator(s). (21 CFR 312.64)
25. Require investigator(s) to store the investigational drug in a secure area. (21 CFR 312.69)

Attachment 2: Prepared by Joe Brown, University of Kentucky Office of Research Integrity and review by the FDA.