

## THE CHILDREN'S MERCY HOSPITAL

**TITLE:** Research and Grants: Investigator Initiated Investigational New Drug (IND) Applications

**NUMBER:**

**EFFECTIVE:** June 2003

**REVISION DATE:**

**REVIEWED WITH NO CHANGES:** June 2006

**RETIRED:**

### **PURPOSE:**

To describe the procedure by which Hospital Staff Members (collectively "Staff") will prepare, submit, and update Investigational New Drug (IND) applications to the Food and Drug Administration (FDA).

### **POLICY:**

All Investigational New Drug (IND) applications made by a Staff member to the FDA must be reviewed and approved by Research and Grants Administration prior to being submitted to the FDA. All studies conducted under such Investigator-Initiated INDs must be performed in compliance with Federal Regulations and guidelines, in accordance with protocols as submitted to the FDA, and as approved by the CMH Pediatric Institutional Review Board (CMH IRB). Updates to Investigator-Initiated INDs must be made as described in this Policy and as required by Federal Regulations.

Studies conducted under an Investigator-Initiated IND are also governed by CMH IRB policies and procedures. Please consult the CMH IRB investigator handbook, "Information for Investigators", for additional information.

This policy does not apply to the "off label" therapeutic use of a marketed drug (i.e., therapeutic use in a population or for an indication not included in the drug's approved labeling).

### **DEFINITIONS:**

Emergency Use: the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval.

Hospital Staff Members: All administrative staff, managers, employees, Medical Staff, allied health professionals, and other individuals providing regular and ongoing on-site services.

Investigational New Drug (IND) Application: An Investigational New Drug (IND) application is a request for FDA authorization to administer an investigational drug to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug that is not the subject of an approved new drug application.

Investigational Drug: An investigational drug is defined by one of the following: (a) a drug in any of the clinical stages of evaluation which has not been released by the FDA for general use or cleared for sale in interstate commerce; (b) any commercially available drug proposed for a new use; (c) any commercially available drug proposed for a new dosage form or method of administration; (d) a commercially available drug which contains a new component such as an excipient or coating; (e) a new combination of two or more commercially available drugs; or (f) a combination of commercially available drugs in new proportions.

Investigator-Initiated IND: An IND application that is made by an individual Investigator instead of by a corporation. Investigators who initiate their own INDs are referred to as Sponsor-Investigators and must fulfill the responsibilities of both Investigators and Sponsors. This term is synonymous with Sponsor-Investigator IND.

Sponsor: A person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or a pharmaceutical company, governmental agency, academic institution, or other organization.

Treatment IND: A mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A Treatment IND will be granted only if the drug is already under investigation or trials have been completed and the trial sponsor is actively pursuing marketing approval. In addition, these patients are not eligible to be enrolled into the definitive clinical trials, which must be well underway, if not almost finished.

## **PROCEDURE:**

### **A. Approval of IND Application Prior to Submission to FDA**

1. Research involving investigational drugs or FDA-approved drugs being used in non-approved ways, or for non-approved populations, such as children, (i.e. off-label) may require the submission of an IND to the FDA. This submission may be made by an individual Investigator in which case the application is referred to as an Investigator-Initiated IND or a Sponsor-Investigator IND. In this situation, the Investigator initiates and conducts an investigation and directly oversees the administration and dispensing of the study drug. Such Investigators must comply with Federal Regulations in 21 CFR § 312 relating to Sponsors and Investigators. Contact Research & Grants Administration for a copy of the applicable regulations.

When an Investigator plans a study involving an investigational drug or use of an FDA-approved drug in a non-approved way, the Investigator must determine if submission of an Investigator-Initiated IND is warranted. This determination should be made based upon the IND Application Checklist (Appendix A). This step is not required in those situations where the supplier of the drug has indicated that an IND will be necessary. In this situation, an IND must be submitted.

2. If, after completing this checklist, there is uncertainty as to whether an IND is required, or if any of the questions are answered “yes”, the FDA will be consulted in accordance to “Investigator Inquiry Regarding the Need for an Investigational New Drug Application (IND) to Conduct a Clinical Study” (Appendix B).
3. If the FDA confirms that an IND is required, then the Investigator must notify the Director of Clinical Trials Administration of his or her plans to submit an IND application.
4. If it is determined that an IND is not required, **CMH IRB approval still must be obtained before the study is initiated or continued at CMH.**
5. Federal Form 1571 must be completed in accordance with Instructions for the Completion of IND Application. Both of these documents can be obtained from Research and Grants Administration. The Director of Clinical Trials Administration will be available to assist in the completion of this application.

A significant part of the IND application is the clinical protocol. It is recommended that the protocol be reviewed by the Director of Clinical Trials Administration and the Office for Research Integrity for comments prior to submission to the FDA.

6. In the event the research is being conducted with an investigational drug, the Investigator must have a written agreement from the manufacturer that they will supply the investigational drug and that their IND application to the FDA may be referenced as a part of the submission.
7. Once the application has been completed, it will be submitted to Research and Grants Administration for review and approval in accordance with the Research and Grants - Administrative Approval of Proposals policy. In the event reviewers express concerns or have questions, the Director of Clinical Trials Administration or the reviewer will work with the Investigator to revise the application.
8. Once final Administrative Approval has been obtained by Research and Grants Administration, the Sponsor-Investigator will be notified that the application may be submitted to the FDA by the Investigator to addresses listed below. A copy of the application will be forwarded to Research and Grants Administration for their records.

For a drug:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

For a biologic:

CDER Therapeutic Biological Products  
Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
12229 Wilkins Avenue  
Rockville, MD 20852

9. Upon receipt of the IND by the FDA, an IND number will be assigned, and the application will be forwarded to the appropriate reviewing division. The reviewing division will send a letter to the Sponsor-Investigator providing notification of the IND number assigned, date of receipt of the original application, address where future submissions to the IND should be sent, and the name and telephone number of the FDA representative to whom questions about the application should be directed. A copy of all such correspondence must be forwarded to Research and Grants Administration.

Upon receipt of the IND number and prior to initiation of the protocol, the Investigator is required to receive training on the responsibilities associated with holding an IND from either the Director of Clinical Trials Administration or the Manager of Research Compliance.

The study may begin 30 days following documented receipt of the IND by the FDA unless the FDA notifies the Sponsor-Investigator that the investigation described in the IND is subject to a clinical hold. **In addition, all such studies must be reviewed by the CMH IRB in accordance with their policies and procedures prior to initiation.**

10. When submitting such a study to the CMH IRB for review, the Investigator will include as part of the submission, a copy of the Investigator-Initiated IND application. The Investigator will also provide a copy of the FDA letter providing notification of the IND number assignment when received. The CMH IRB must be notified that the study is being conducted under an Investigator-Initiated IND.
11. After submitting an Investigator-Initiated IND, the Sponsor-Investigator is responsible for providing additional information to the FDA as required by law. (Refer to 21 CFR § 312 for specific details.) These FDA reporting requirements include, but are not limited to, the following:
  - a. When a Sponsor-Investigator intends to conduct a study that is not already contained in the IND, the Sponsor-Investigator must submit the new protocol to the FDA;
  - b. When there is a protocol amendment describing any change in a Phase 1 protocol or when there is a protocol amendment describing any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. All such amendments must be submitted to the FDA and to the IRB prior to implementation unless such changes are necessary in order to eliminate an apparent immediate hazard to subjects. In such a case, the FDA must be notified as soon as possible after the change is made. All other amendments must be reported as specified in the Federal Regulations

- c. Addition of new Investigators or changes to Federal Form 1572;
- d. Any adverse experience associated with the use of the drug that is both serious and unexpected or any findings from tests in laboratory animals that suggests a significant risk for human subjects. Such reports must be made within 15 calendar days after initial receipt of information, or within 7 calendar days after initial receipt of the information if the event is fatal or life-threatening;
- e. Annual reports that summarize the status of the study and other summary information;
- f. Any new information that is not within the scope of a protocol amendment, IND safety report, or annual report;
- g. Final report;

Copies of all such reports submitted to the FDA must be forwarded to the Director of Clinical Trials Administration and the CMH IRB for their records.

12. In addition to the above-mentioned obligations, the Sponsor-Investigator must also comply with all Investigator responsibilities as outlined in Federal and State Regulations, including necessary review, approval and reporting to the CMH IRB (Refer to 21 CFR § 50, 54, 56, and 312 for specific details.) A copy of these regulations can be accessed through the CMH website under “Researchers/Resources for Researchers/Code of Federal Regulations”. The Sponsor-Investigator must also comply with all CMH policies and procedures, including IRB policies and procedures. For example, unless necessary to address an immediate safety issue, no changes to the protocol may be implemented until reviewed and approved by the CMH IRB.
13. In certain circumstances, an Investigator may desire access to an investigational drug in order to treat serious or immediately life-threatening illnesses. In order to obtain access to such investigational drugs, the Investigator must contact the manufacturer to determine if there is an “open label” or treatment IND protocol available for the Investigator’s participation. If not, the Investigator can apply to the FDA for sponsorship of a treatment IND. The process for obtaining such an IND is the same as that noted above. Treatment IND studies require prospective IRB review and informed consent.
14. Sponsor-Investigators will maintain all records relating to their INDs for the time period required by Federal Regulations. Research and Grants Administration will also maintain a project folder on each IND. Examples of records that must be maintained include, but are not limited to, signed informed consent documents, patient records, submissions to regulatory agencies, correspondence with the IRB, correspondence with investigators, drug accountability, and data forms.

## **B. Procedure for Emergency INDs**

1. The need for an Investigational Drug may arise in an emergency situation that does not allow time for submission of an IND in the usual manner. Again, the Investigator must contact the manufacturer to determine if there is an FDA approved protocol under which the subject could be enrolled. If the manufacturer has no such protocol, the Investigator must contact the FDA in order to obtain FDA permission for use of the drug in this manner. In such cases the FDA may authorize shipment of the drug for a specified one-time use. Such authorization is usually conditioned upon the Sponsor-Investigator filing an appropriate application as soon as practicable after drug shipment. Prospective IRB review is required unless the conditions for exemption are met [21 CFR 56.104(c) and 56.102(d)]. For instance, prior IRB review and approval for the emergency use of a test article is exempted provided that (1) the emergency use is reported to the IRB within 5 working days; and (2) any subsequent use of the test article at the institution is subject to prior IRB review and approval. Informed consent is required unless the conditions for exception are met [21 CFR 50.23]. In either situation, refer to CMH IRB Policies for specific information related to Emergency Use situations. In the event an Investigator-Initiated IND must be completed, the process outlined in this policy will be followed as soon as possible after shipment of drug.

### **RELATED POLICIES:**

Research and Grants - Administrative Approval of Proposals  
CMH Pediatric IRB Information for Investigators

### **REFERENCES:**

Title 21, Code of Federal Regulations, Part 312  
Title 21, Code of Federal Regulations, Part 56  
Title 21, Code of Federal Regulations, Part 54  
Title 21, Code of Federal Regulations, Part 50  
Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators

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### **REVIEW PERIOD:**

Per Hospital policy

**APPROVED:**

Research Council	06/16/03
Medical Staff Executive Committee	06/04/03
Administrative Council	06/26/03

_____	<u>06/30/03</u>
Ralph Kauffman, MD	Date
Chair, Research Council	

_____	<u>06/30/03</u>
Michele Kilo, MD	Date
Medical Staff President	

_____	<u>07/01/03</u>
Randall L. O'Donnell, Ph.D.	Date
President/Chief Executive Officer	

Appendix A

**IND APPLICATION CHECKLIST**

This checklist is intended for use by Investigators as a test of whether an IND application needs to be submitted to the FDA for particular research. If any question is answered "yes", an IND application may need to be submitted to the FDA. If the answers to all questions are "no", then the study may meet the criteria for an exemption from an IND. Please contact Research and Grants Administration for assistance or the FDA consumer safety officer for confirmation.

Regarding your proposed trial of an FDA-approved drug:

1. Does the study involve a different route of administration of the marketed drug than currently appears in the FDA approved labeling?  YES  NO
2. Does the study involve the administration of different drug dosage levels that could significantly increase risk or decrease the acceptability of risk to study subjects?  YES  NO
3. Does the study involve the administration of the drug to a patient population not named in the current FDA approved product label for whom there may be increased risk or decreased acceptability of risk?  YES  NO
4. Does the study entail any other factor that significantly increases the risk or decreases the acceptability of risk to study subjects?  YES  NO
5. Are the results of the study intended to be reported to the FDA in support of any significant change in labeling or advertising for the drug (e.g., corporate sponsored studies)?  YES  NO
6. Is the Investigator seeking exception from informed consent requirements for emergency research?  YES  NO
7. Drug name \_\_\_\_\_ Manufacturer/Supplier of Drug \_\_\_\_\_
8. If any of the answers to the above questions are "yes", complete the name and telephone number of the consumer safety officer that you contacted at the FDA and the date of the discussion. Please attach written documentation of the outcome of such discussions. If you are granted an IND Exemption, please provide a copy of that document as well.

\_\_\_\_\_  
Name of Consumer Safety Officer Telephone #

\_\_\_\_\_  
Date of Discussion

\_\_\_\_\_  
Signature of Investigator

Date \_\_\_\_\_

Appendix B

**INVESTIGATOR INQUIRY REGARDING THE NEED FOR AN INVESTIGATIONAL NEW DRUG APPLICATION (IND) TO CONDUCT A CLINICAL STUDY**

If, after completing the IND Application Checklist, there is uncertainty as to whether an IND is required, or if any of the questions in the checklist are answered “yes”, the FDA will be consulted. The Investigator will contact the appropriate review division within the FDA for determination of the need for an IND (see contact list below).

It is useful to have the following information available to provide to the reviewer during such a discussion. They may take the information over the phone, or request that the information be submitted in writing. The approach taken will depend upon the FDA reviewing division.

1. 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.
2. 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.
3. A brief explanation of why you consider the substance safe for administration to human subjects under the conditions of the study.

**If an IND is required, follow the process outlined in “Investigator Initiated Investigational New Drug (IND) Applications” Policy.**

**If an IND is not required, request that the FDA provide you with an IND Exemption in writing.**

Division of Cardio-Renal Drug Products.....	301/594-5300
Division of Neuropharmacological Drug Products.....	301/594-2850
Division of Oncology Drug Products .....	301/594-2473
Division of Metabolic and Endocrine Drug Products .....	301/827-6430
Division of Pulmonary and Allergy Drug Products .....	301/827-1050
Division of Anesthetic, Critical Care and Addiction Drug Products .....	301/827-7410
Division of Medical Imaging and Radiopharmaceutical Drug Products .....	301/827-7510
Division of Reproductive and Urologic Drug Products .....	301/827-4260
Division of Gastrointestinal and Coagulation Drug Products.....	301/827-7310
Division of Anti-Infective Drug Products.....	301/827-2132
Division of Anti-Viral Drug Products.....	301/827-2339
Division of Special Pathogen and Immunologic Drug Products.....	301/827-2366
Division of Dermatologic and Dental Drug Products .....	301/827-2021
Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products.....	301/827-2040
Division of Over-The-Counter Drug Products.....	301/827-2264

**Instructions for the Completion of IND Application**

The following instructions address only the administrative aspects of preparing and submitting an IND.

**FILLING OUT THE FORM FDA 1571:** (The numbers below correspond to the numbered boxes on the Form FDA 1571.)

1. The sponsor is the person who takes responsibility for and initiates a clinical investigation. The sponsor may be a pharmaceutical company, a private or academic organization, or an individual. **A Sponsor-Investigator is an individual who both initiates and conducts a clinical investigation and under whose immediate direction the investigational drug is being administered or dispensed.** For administrative reasons, only one individual should be designated as sponsor.

If a pharmaceutical company will be supplying the drug, but will not itself be submitting the IND, the company is not the sponsor.

2. The date of submission is the date that the application is mailed to FDA.

3. The address is the address to which written correspondence from FDA should be directed. If this address is a post office box number, a street address must also be provided.

4. The telephone number is the number where the sponsor is usually available during normal working hours. A telephone number must be provided.

5. For name(s) of drug, list the generic name(s) and trade name, if available. Also, state the dosage form(s).

6. If an emergency IND number was previously assigned by FDA, or the Form FDA 1571 is being included with an amendment to the original IND, then that IND number should be entered here; otherwise, the space should be left blank.

7. Self-explanatory.

8. This section is to be completed by pharmaceutical firms that are conducting clinical studies in support of a marketing application. Sponsor-Investigators need not complete this section.

9. It is necessary for the sponsor to submit certain information with an IND (such as manufacturing and controls information, pharmacology and toxicology data, or data from prior human studies) unless that information has previously been submitted to FDA by another sponsor ("Previous Sponsor"), AND the Previous Sponsor provides a letter authorizing FDA to refer to the information. In this case, the letter of authorization including the file identification (IND/DMF/NDA number) must be: 1) submitted to the application of the Initial Sponsor and, 2) included in the initial submission of the new sponsor's IND. The sole exception to this requirement is when a marketed drug is used in the study, without modification to its approved packaging, in which case the marketed drug product must be identified by trade name, established name, dosage form, strength, and lot number.

10. Numbering of submissions is primarily intended for pharmaceutical firms. Sponsor-Investigators do not have to complete this section.

11. For an original IND submission, only the "Initial Investigational New Drug Application (IND)" box should be checked. For subsequent submissions, check ALL the boxes that apply since the submission may contain more than one type of information.

Requests to charge and Treatment Protocols must be submitted separately. Treatment INDs and Treatment Protocols are special cases and are not intended for single patient use. Before checking either of these boxes, the sponsor should be thoroughly familiar with the cited regulations and contact the appropriate FDA reviewing division to discuss the proposed treatment use.

12. For a Sponsor-Investigator IND, items 2, 3, and 4 may be briefly addressed in the cover letter or in a summary.

Where the investigational drug is obtained from a supplier in a final dosage form, items 5, 7, 8, and 9 may be referenced if authorization is given by the supplier (see explanation in section 9 above). If the investigational drug is prepared or altered in any way after shipment by the supplier, complete manufacturing (or compounding) and controls information, including information on sterility and pyrogenicity testing for parenteral drugs, must be submitted for that process in Item 7.

Item 6 requires that the protocol be submitted, along with information on the Investigators, facilities, and Institutional Review Board (copies of the completed Form FDA 1572 with attachments would suffice for 6 b-d).

Item 7 also requires submission of either a claim of categorical exclusion from the requirement to submit an environmental assessment or an environmental assessment (21 CFR 25.15[a]). When claiming a categorical exclusion, the sponsor should include the following statements: "I claim categorical exclusion (under 21 CFR 25.31[e]) for the study(ies) under this IND. To my knowledge, no extraordinary circumstances exist."

13. This section does not pertain to a Sponsor-Investigator.

14-15. For a pharmaceutical firm, the name of the person responsible for monitoring the conduct of the clinical investigation, and reviewing and evaluating safety information, should be entered. For Sponsor-Investigator INDs, the Investigator has this responsibility.

Certain important commitments that the IND sponsor makes by signing the form FDA 1571 are listed below box 15.

16-17. For an IND sponsored by a pharmaceutical firm or research organization, the name of the sponsor's authorizing representative would be entered and that individual must sign the form. For a Sponsor-Investigator IND, the Sponsor-Investigator should be named and must sign the form.

18-19. Box 18 and 19 need not be completed if they duplicate boxes 3 and 4.

20. The date here is the date the form is signed by the sponsor.

#### **FORM FDA 1572:**

Copies of Form FDA 1572 with its attachments may be sent by the Sponsor-Investigator to FDA to satisfy Form FDA 1571, box 12, item 6 b-d. Information can be supplied in the form of attachments (such as a curriculum vitae) rather than entering that information directly onto the form, but this should be so noted under the relevant section numbers.