

Obtaining IND for Investigator-Initiated Study ...for the first time

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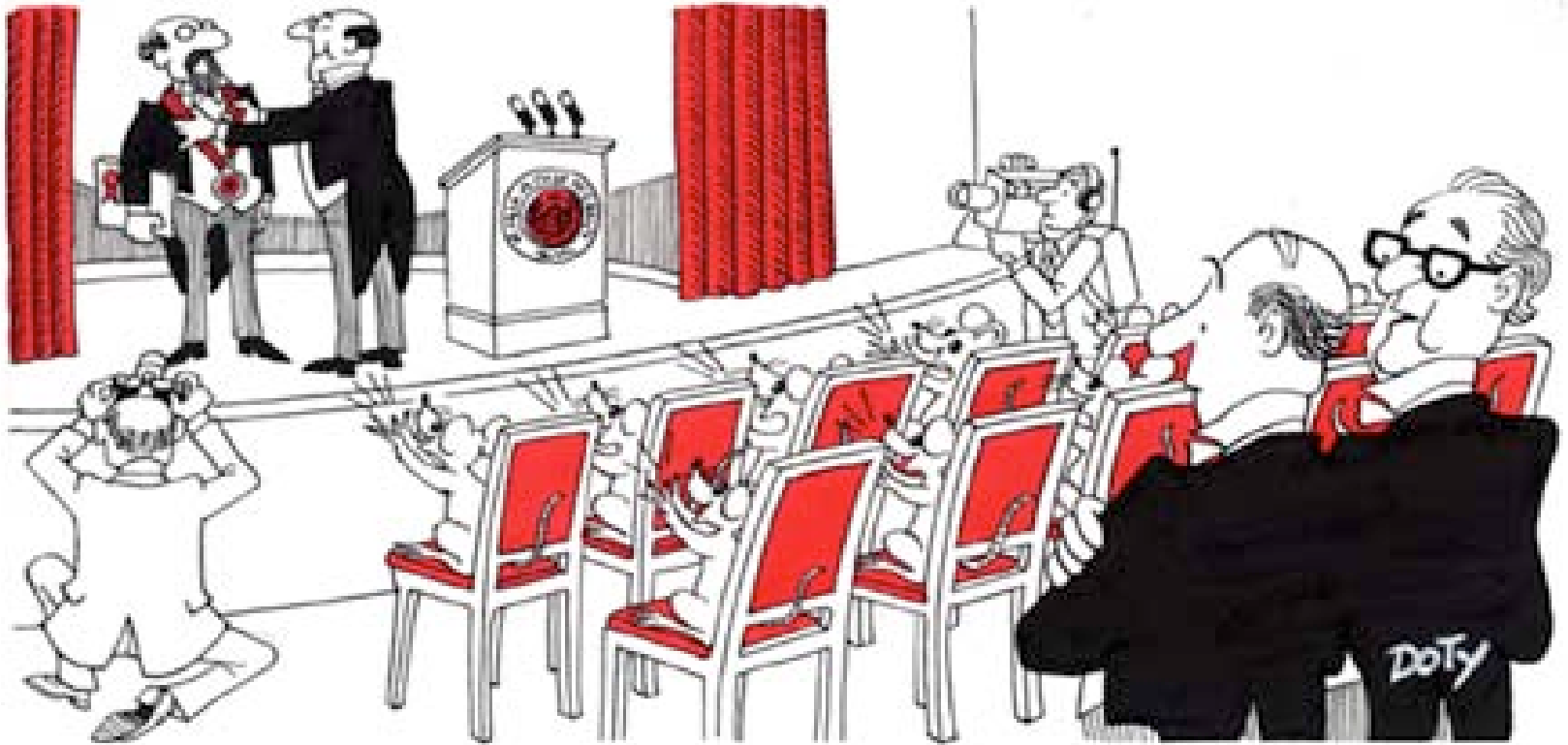
Clinical Research Center



Goldman School of Dental Medicine

New Product Development

When a product is identified as a viable candidate for further development by *in vitro* and *in-vivo* animal studies, the sponsor or investigator may want to test the diagnostic or therapeutic potential in humans.



“It’s an award for a cancer cure, but it only works on mice.”



FDA's Role in Testing New Compounds as a Potential Drug

FDA's role in the development of a new drug begins

- ...when the product's sponsor (usually the manufacturer or potential marketer) or Investigator who has screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans through clinical investigations.
- The molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.



Definitions by the FDA

Clinical Investigation...

- any experiment in which a drug is administered or dispensed to one or more human subjects

Investigator...

- an individual under whose immediate direction the drug is administered or dispensed to a subject

Sponsor...

- a person who takes responsibility for and initiates a clinical investigation

Sponsor-Investigator...

- an individual who both initiates and conducts an investigation and under whose immediate direction the investigational drug is administered or dispensed

FDA Regulations for Investigational Drug

- **21 CFR 312 (drugs)** and **21 CFR 601 (biologics)** contain procedures and requirements governing the use of investigational new drugs and biologics
- All clinical research projects involving drugs or biologics which are not FDA-approved for marketing must be reviewed by the FDA
- This is done by filing an Investigational New Drug Application (IND)

What is an IND?

- is an Investigational New Drug application
- It is a request to the FDA to allow the administration of investigational drugs to humans
- Is a request for an exemption from the Federal statute that prohibits an unapproved drug from being shipped in interstate commerce

*******Is not an application for marketing approval*******

When is an IND Required?

A clinical study is required for an IND if it is intended to support a:

- ✓ New indication
- ✓ Change in the approved route of administration or dosage level
- ✓ Change in the approved patient population (e.g. pediatric) or a population at greater or increase of risk (elderly, HIV positive, immunocompromised)
- ✓ Significant change in the promotion of an approved drug

Determining if an IND Application is Needed

Ask yourself:

- Will human subjects receive an unapproved drug?
- Will human subjects receive an approved drug for an unapproved use?
- If you answered 'yes' to either question then most likely an IND application is needed.

Do I need to submit an IND for an approved product?

According to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does NOT require submission of an IND if all six of the following conditions are met:

- ✓ It is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug
- ✓ It is not intended to support a significant change in the advertising for the product
- ✓ 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
- ✓ It is conducted in compliance with the requirements for IRB review and informed consent [21 *CFR* parts 56 and 50, respectively]
- ✓ It is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 *CFR* 312.7]
- ✓ It does not intend to invoke 21 *CFR* 50.24

Application Categories

➤ Sponsor-Initiated (Commercial) IND

Submitted by a sponsor that intends to market the product upon FDA approval

➤ Investigator-Initiated (Non-commercial) IND

Submitted by a physician who both initiates and conducts an investigation

• Emergency Use IND

Allow the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.23 or Sec. 312.34. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist

• Treatment IND

Submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place



“These studies always remind me of an ant colony I had as a kid!”

Timing of the IND Submission

Pre-IND Advice

Investigators considering submitting an IND application to the FDA should consult the FDA's [Office of Drug Evaluation IV \(ODE IV\) Pre-IND Consultation Program](#) before submitting an IND application

IND Submission

To the FDA and the IRB application should be initiated at the same time. The FDA has 30 days to review the IND application. Likewise, the IRB typically reviews an application within a 30-day window, but it may take longer to secure approval

CDER Pre-IND Consultation Contacts

Office of Drug Evaluation I	Office of Drug Evaluation II	Office of Drug Evaluation III	Office of Antimicrobial Products	Office of Oncology Drug Products	Office of Non-Prescription Products
Division of Cardiovascular and Renal Products Edward Fromm 301-796-2240 FAX 301-796-9841	Division of Anesthesia, Analgesic, and Rheumatology Products Parinda Jani 301-796-1232 Sara Stradley 301-796-1298 FAX 301-796-9722	Division of Gastroenterology Products Julie Dubeau Brian Strongin 301-796-2120 FAX 301-796-	Division of Anti-Infective and Ophthalmology Products Frances LeSane 301-796-1400 FAX 301-796-9881	Division of Drug Oncology Products Dorothy Pease 301-796-1434 FAX 301-796-9867	Division of Nonprescription Clinical Evaluation Leah Christl 301-796-0869 Fax: 301-796-9899
Division of Neurology Products Robbin Nighswander 301-796-1126 FAX 301-796-9842	Division of Metabolism and Endocrinology Products Enid Galliers 301-796-1211 Katie Johnson 301-796-1234 FAX 301-796-9712	Division of Dermatology and Dental Products Suzanne Childs 301-796-0867 FAX 301-796-9895	Division of Anti-Viral Products Kenny Shade 301-796-0807 Karen Winestock 301-796-0834 Topical Microbicides and other Anti-Viral Diseases FAX 301-796-9883	Division of Medical Imaging and Hematology Products Kyong Kang 301-796-2050 FAX 301-796-9848	
Division of Psychiatry Products Steve Hardeman 301-796-1081 FAX 301-796-9838	Division of Pulmonary and Allergy Products Sandy Barnes 301-796-1174 FAX 301-796-9728	Division of Reproductive and Urologic Products Jennifer Mercier 301-796-0957 Margie Kober 301-796-0937 FAX 301-796-9897	Division of Special Pathogens and Transplant Products Dianna Willard 301-796-1600 FAX 301-796-9880	Division of Biological Oncology Products Karen Jones 301-796-1377 FAX 301-796-9849	

Compiling an IND Application

IND Application Format:

The IND/IDE Assistance Program will help in compiling an IND application if all the necessary documents are provided:

- Form FDA 1571: The Investigational New Drug Application Form with application number 0000
- Assistance in completing FDA-1571
- Form FDA 1572: Statement of Investigator Form
- Cover Letter
- Study Protocol: A written protocol describing the methodology to be used and an analysis of the protocol demonstrating its scientific soundness.
- Monitoring Procedures: written out Standard Operating Procedures including name, address and qualifications of the monitor
- Monitoring Plan
- FDA Guidance for Monitoring of Clinical Investigators found at: http://www.fda.gov/ora/compliance_ref/bimo/clinguid.html
- Case Report forms: is a form used to collect various forms of data for your research
- Additional Documents needed to compile an IND

Three Main Sections of IND Application

➤ Animal Pharmacology and Toxicology Studies

- Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans
- any previous experience with the drug in humans (often foreign use).

➤ Manufacturing Information

- Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product

➤ Clinical Protocols and Investigator Information

- Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks.
- information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfill their clinical trial duties
- commitments to obtain informed consent from the research subjects, review of the study by an IRB, and to adhere to the investigational new drug regulations

Where to Send The Application

- The initial IND submission and each subsequent submission to the IND should be accompanied by a Form FDA 1571 and must be submitted in triplicate (the original and two photocopies are acceptable).

For a Drug

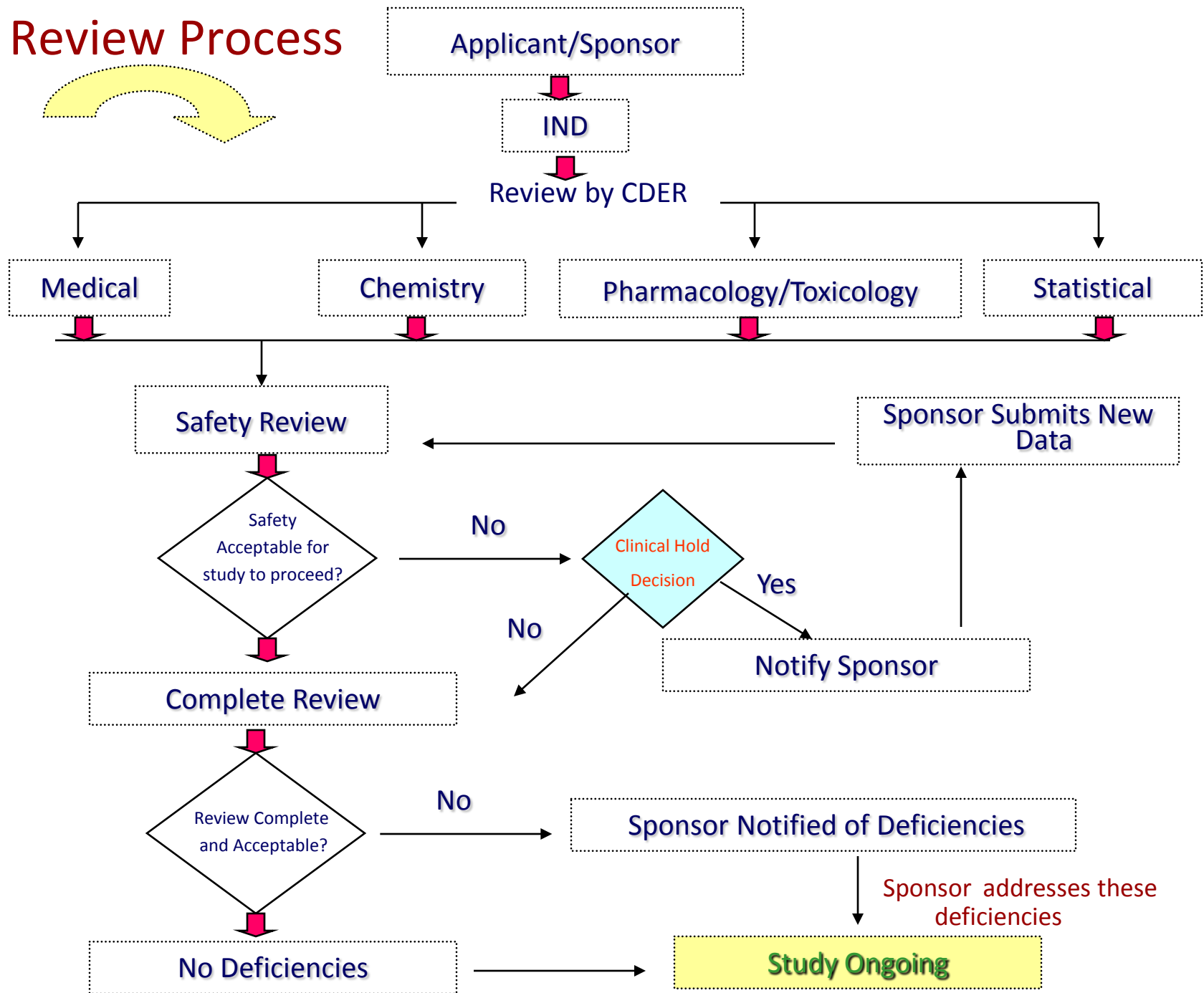
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

For a Therapeutic Biological Product:

(<http://www.fda.gov/cber/transfer/transfer.htm>)

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

IND Review Process

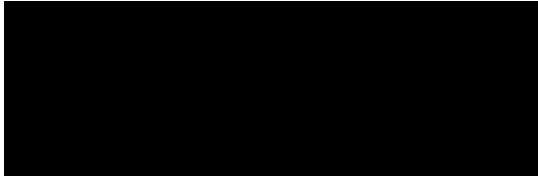


FDA Receipt of the IND

- Upon receipt of the IND by 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 person to whom questions about the application should be directed.
- Studies shall not be initiated until 30 days after the date of receipt of the IND by FDA unless you receive earlier notification by FDA that studies may begin.



IND 79,635

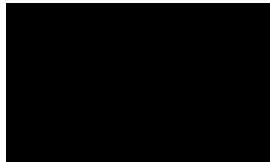


IND ACKNOWLEDGEMENT

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND NUMBER ASSIGNED: 79,635

SPONSOR:



PRODUCT NAMES:

DATE OF SUBMISSION:

DATE OF RECEIPT: October 29, 2007

You may not initiate studies in humans until 30 days after the date of receipt shown above unless we notify you sooner that you may proceed. If, on or before November 28, 2007, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will immediately notify you verbally or in writing that (1) clinical studies may not be initiated under this IND ("clinical hold") or (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). If we place your human studies on clinical hold, you will be notified in writing of the reasons and the information necessary to correct the deficiencies. In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have subsequently notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold

Submitting an Exempt Request

Re: Investigator Inquiry Regarding the need for an IND application to conduct a clinical study

1. Name, address, phone, fax, e-mail and affiliation
2. Name and brief description of substance to be administered, source, dosage, sterility, supplier/manufacturer (marketed or special preparation)
3. A brief summary of the study including, purpose, hypothesis, number of subjects, patient population, dose route, duration, endpoints, references, etc.
4. Title of the study
5. A brief explanation why the product is consider to be safe to humans
6. State whether the manufacturer will use the study data to change labeling, or advertising, whether you will charge the study patients for the drug.

Decisions

- If the FDA determines that an IND is not necessary, it will provide an exemption letter. A copy of this letter should be provided to the IRB.
- If the FDA determines that an IND is required, a complete IND application must be submitted to the FDA for review.
- Upon completion of review, the FDA will send the investigator a letter. The IRB will withhold approval of the study until the investigator provides a copy of either the FDA determination letter or the IND number provided by the FDA.

Sample of FDA response

- Upon review of information contained in your submission, we conclude that your study meets all of the requisites set forth at 21 CFR 312 (b)(1), and accordingly that is exempt from the requirements of part 312 of the IND regulations and IND is not required.

“Hold Clinical Decision”

- Is the mechanism that CDER uses when it does not believe, or cannot confirm, that the study can be conducted without unreasonable risk to the subjects/patients.
- Center contacts the sponsor within the 30-day initial review period to stop the clinical trial.
- CDER may either delay the start of an early-phase trial on the basis of information submitted in the IND, or stop an ongoing study based on a review of newly submitted clinical protocols, safety reports, protocol amendments, or other information.
- When a clinical hold is issued, a sponsor must address the issue that is the basis of the hold before the order is removed.
- CDER's authority concerning clinical holds is outlined in Federal regulations. The regulations specify the clinical hold criteria that CDER applies to various phases of clinical testing. In addition, all clinical holds are reviewed by upper management of CDER to assure consistency and scientific quality in the Center's clinical hold decisions.



Learned from Experiences

- Even when there is no immediate intent to change product labeling or advertising, investigators who are planning rigorous, carefully controlled clinical investigations of an off-label uses of approved drugs or biologics should obtain an IND for the study.
- **Example 1:** An investigator proposes a small pilot study of an approved drug for a novel use and states that an IND is not needed because the data will not be submitted to the FDA. The investigator explains that if the pilot data looks promising a larger trial will be submitted with an IND. The IRB is likely to approve the pilot study without an IND because a small pilot study is an appropriate first step in determining whether a change in labeling should be sought. FDA will also grant this study with exemption.
- **Example 2:** An investigator proposes a multicenter randomized trial of an approved drug for a novel use and states that an IND is not needed because the data will not be submitted to the FDA. The IRB is not likely to approve the study without an IND because the data could be important and should be considered by the FDA.

Advice

- ✓ Usually, they don't really respond to you! Just submit the IND application, and they will get back to you with questions and requests for clarification

For Questions

- For DRUG PRODUCTS contact: Drug Information Branch (HFD-210)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane; Rockville, Maryland 20857; 301-827-4573
- For a BIOLOGICAL BLOOD product, contact: Office of Blood Research and Review (HFM-300)
Center for Biologic Evaluation and Research
Food and Drug Administration
1401 Rockville Pike; Rockville, Maryland 20852; 301-827-3518
- For a BIOLOGICAL VACCINE product, contact: Office of Vaccines Research and Review (HFM-400); Food and Drug Administration
8800 Rockville Pike; Bethesda, Maryland 20892-0001; 301-827-0648
- For a BIOLOGICAL THERAPEUTIC product, contact: Office of Therapeutics Research and Review (HFM-500); Food and Drug Administration
1451 Rockville Pike; Rockville, Maryland 20852-1420; 301-594-2860
- For a MEDICAL DEVICE product, contact: Program Operations Staff (HFZ-403)
Office of Device Evaluation ; Center for Devices and Radiological Health
Food and Drug Administration; 9200 Corporate Blvd.
Rockville, Maryland 20850;301-594-1190

Thank you!

