Investigational New Drugs: Application, Process, and Trial

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This is the fourth article in a four-part series of nuclear medicine updates. Upon completion of this article, the reader will have: (1) an understanding of the various phases involved in investigational new drugs (IND), (2) a reference for preparing an IND, and (3) an awareness of the common pitfalls associated with preparing and fulfilling the commitment of an IND.

An investigational new drug application (IND) is a request for Food and Drug Administration (FDA) authorization to administer an investigational drug or biological (serums, vaccines, antitoxins, antigens, etc...) 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 (NDA) (*1*), abbreviated new drug application (ANDA), or product license application (PLA).

Most INDs are filed by two groups: manufacturers (typically sponsors) and health practitioners (typically investigators). Individuals may, under certain circumstances, sponsor their own investigations. The commercial manufacturer should have little difficulty in knowing when or if it should file an IND. The health practitioner, on the other hand, does have some difficulty in deciding if the study he or she has planned (a) requires an IND, (b) falls under the practice of medicine and/or pharmacy, or (c) can be handled by internal committees (*2*).

This article, consequently, focuses on clarifying the role of the sponsor and/or investigator with regard to the IND process and familiarizing him with some of the nuances involved. At the outset, the reader should be aware that the regulations and requirements can be exhausting, and the submission, an exercise in word engineering. This is true for both the applicant and reviewer. To write a simple set of rules/regulations or guidelines which would cover every set of circumstances to protect the public health is no simple task. In fact, the regulations (Title 21 of the Code of Federal Regulations, Part 312 [21CFR312] (*3*) are a living document in that they are updated from time to time in order to make the IND process more effective. This article will additionally call attention to some of the highlights associated with the 1987 IND update, also known as the IND rewrite (*3*).

But why would anyone want to go to all this trouble to file an IND if the radiopharmaceutical agent will eventually become available anyway, or might turn out to be of no value at all? The answer is multidimensional:

1. Certain institutions have a research mission, such as university medical center hospitals.
2. Certain investigators simply enjoy working with and learning about new agents.
3. The use of investigational agents can enhance the prestige of an institution, department, or individual investigator (among peers or with the public).
4. Given today's competitive environment, the use of these IND agents can theoretically provide a competitive edge.
5. The newest agents can possibly bring the most advanced patient care to bear upon a particular medical problem.

It is interesting to observe that until recently new advances in nuclear medicine, including new radiopharmaceuticals, have, to a large extent, come from hospital- and university-based health practitioners. This is in sharp contrast to traditional pharmaceuticals, which have been developed predominantly by pharmaceutical manufactuers (*4,5*).

Whereas it has been argued that radiopharmaceuticals are indeed different from other classes of drugs, and that this difference has gone unrecognized by the FDA, examination of the guidelines for the clinical evaluation of radiopharmaceuticals (*6*) compared to the guidelines for the clinical evaluation of nonradioactive drugs (*7*) will quickly reveal that this difference has been acknowledged, even if this degree of acknowledgement has been subject to controversy (*1–7*). The guidelines are clear and relatively comprehensive in delineating expectations; it is the interpretation of these guidelines in specific circumstances that has often caused confusion.

The delineation of boundary in practice often gets blurred with the exercising of actual versus perceived authority. The FDA operates from the perspective of *public health*, its authority embedded in Federal law. The practice of medicine and pharmacy are geared toward care of the individual patient with authority garnered from State law. Recently, the Nuclear

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Regulatory Commission (NRC) has tread into the arena, but not without ruffling some feathers (*8*), in attempting to fill a "perceived" void at the interface between FDA regulations and the practice of medicine and pharmacy as they relate to investigational drugs.

CLINICAL TESTING FOR SAFE AND EFFECTIVE DRUGS: AN OVERVIEW OF THE PROCESS

Before 1962, the FDA did not require notification of drugs being tested on humans. The 1962 Kefauver-Harris amendment to the Federal Food, Drug, and Cosmetic Act greatly strengthened the government's authority over clinical (human) testing of new drugs. With this regulatory authority, the FDA has taken steps to:

1. Provide added safeguards for those on whom drugs are tested.
2. Improve reports by drug investigators.
3. Establish investigative procedures to supply substantial scientific evidence that a drug is safe and effective.

Before a new drug may be tested on humans, the sponsor (usually a pharmaceutical firm, but sometimes a clinician-investigator) must give the FDA information formerly specified as a "Notice of Claimed Investigational Exemption for a New Drug," but now known as an IND. (As of the 1987 rewrite, FDA forms 1571, 1572, and 1573 have been replaced by new forms FDA 1571 and 1572 (Figs. 1–2). The current IND regulations became effective in June 1987. Copies of the regulations, further guidance regarding IND procedures, and additional forms are available from:

FDA Legislative, Professional, and
Consumer Affairs Branch (HFN-365)
5600 Fishers Lane
Rockville, Maryland 20857
Telephone: 301-295-8012.

When a clinical investigator intends to perform a study, for example, a clinical trial for a radiopharmaceutical manufacturer, he only needs to fill out FDA 1572 (Statement of Investigator) in which one certifies one's qualifications to conduct the study and makes a series of agreements with the sponsor and the FDA. The simplest way to handle this form is to attach a *curriculum vitae* (CV) rather than filling in the individual blanks. However, the sponsor or sponsor-investigator must still deal with FDA 1571 (Investigational New Drug Application). The sponsor of an IND can be anyone (e.g., physician, scientist, pharmacist, corporate executive, etc.), but for a study or phase of a study involving patients a physician must be, at least, a co-investigator.

Although much of the basic information requested on the form did not change with the rewrite, the organization of the form and the emphasis is somewhat different. Item 12 in Figure 1B lists various categorical contents such as statement; investigational plan; investigators brochure.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved: OMB No. 0910-0014 Expiration Date: November 30, 1987

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1 NAME OF SPONSOR

2 DATE OF SUBMISSION

3 ADDRESS *(Number, Street, City, State and Zip Code)*

4 TELEPHONE NUMBER *(Include Area Code)*

5 NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*

6 IND NUMBER *(If previously assigned)*

7 INDICATION(S) *(Covered by this submission)*

8. PHASE (S) OF CLINICAL INVESTIGATION TO BE CONDUCTED ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9 LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION

10 SERIAL NUMBER — — —

IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (i.e., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

11 THIS SUBMISSION CONTAINS THE FOLLOWING *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)

PROTOCOL AMENDMENT(S)
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S)
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ RESPONSE TO CLINICAL HOLD

☐ GENERAL CORRESPONDENCE ☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

Refer to the designated CFR citations before checking any of the following:

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED
		DIVISION ASSIGNMENT

FORM FDA 1571 (8/87) PREVIOUS EDITION IS OBSOLETE

12 **CONTENTS OF APPLICATION**

This application contains the following items: *(check all that apply)*

☐ 1. Form FDA 1571 *[21 CFR 312.23 (a) (1)]*
☐ 2. Table of contents *[21 CFR 312.23 (a) (2)]*
☐ 3. Introductory statement *[21 CFR 312.23 (a) (3)]*
☐ 4. General investigational plan *[21 CFR 312.23 (a) (3)]*
☐ 5. Investigator's brochure *[21 CFR 312.23 (a) (5)]*
6. Protocol(s) *[21 CFR 312.23 (a) (6)]*
  ☐ a. Study protocol(s) *[21 CFR 312.23 (a) (6)]*
  ☐ b. Investigator data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  ☐ c. Facilities data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  ☐ d. Institutional Review Board data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23 (a) (7)]*
  ☐ a. Environmental assessment or claim for exclusion *[21 CFR 312.23 (a) (7)(iv)(e)]*
☐ 8. Pharmacology and toxicology data *[21 CFR 312.23 (a) (8)]*
☐ 9. Previous human experience *[21 CFR 312.23 (a) (9)]*
☐ 10. Additional information *[21 CFR 312.23 (a) (10)]*

13 IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED

14 NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

15 NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND or on earlier notification by FDA. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16 NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17 SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
18 ADDRESS *(Number, Street, City, State and Zip Code)*	19 TELEPHONE NUMBER *(Include Area Code)*	20 DATE

WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

U.S. GPO: 1987-181-338/64452

FIG. 1. FDA form 1571, Investigational New Drug Application.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
STATEMENT OF INVESTIGATOR
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)
(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014
Expiration Date: November 30, 1987

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator. Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED:

☐ CURRICULUM VITAE ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES)

6. NAMES OF THE SUBINVESTIGATORS *(e.g., research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S)

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND IDENTIFYING THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR

FORM FDA 1572 (8/87) REPLACES PREVIOUS EDITIONS OF FDA 1572 AND FDA 1573

8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

☐ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED

☐ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMER TO BE EMPLOYED AS CONTROLS; IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY, AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED

9. COMMITMENTS:

I AGREE TO CONDUCT THE STUDY(IES) IN ACCORDANCE WITH THE RELEVANT, CURRENT PROTOCOL(S) AND WILL ONLY MAKE CHANGES IN A PROTOCOL AFTER NOTIFYING THE SPONSOR, EXCEPT WHEN NECESSARY TO PROTECT THE SAFETY, THE RIGHTS, OR WELFARE OF SUBJECTS.

I AGREE TO PERSONALLY CONDUCT OR SUPERVISE THE DESCRIBED INVESTIGATION(S).

I AGREE TO INFORM ANY PATIENTS, OR ANY PERSONS USED AS CONTROLS, THAT THE DRUGS ARE BEING USED FOR INVESTIGATIONAL PURPOSES AND I WILL ENSURE THAT THE REQUIREMENTS RELATING TO OBTAINING INFORMED CONSENT IN 21 CFR PART 50 AND INSTITUTIONAL REVIEW BOARD (IRB) REVIEW AND APPROVAL IN 21 CFR PART 56 ARE MET.

I AGREE TO REPORT TO THE SPONSOR ADVERSE EXPERIENCES THAT OCCUR IN THE COURSE OF THE INVESTIGATION(S) IN ACCORDANCE WITH 21 CFR 312.64.

I HAVE READ AND UNDERSTAND THE INFORMATION IN THE INVESTIGATOR'S BROCHURE, INCLUDING THE POTENTIAL RISKS AND SIDE EFFECTS OF THE DRUG.

I AGREE TO ENSURE THAT ALL ASSOCIATES, COLLEAGUES, AND EMPLOYEES ASSISTING IN THE CONDUCT OF THE STUDY(IES) ARE INFORMED ABOUT THEIR OBLIGATIONS IN MEETING THE ABOVE COMMITMENTS.

I AGREE TO MAINTAIN ADEQUATE AND ACCURATE RECORDS IN ACCORDANCE WITH 21 CFR 312.62 AND TO MAKE THOSE RECORDS AVAILABLE FOR INSPECTION IN ACCORDANCE WITH 21 CFR 312.68.

I WILL ENSURE THAT AN IRB THAT COMPLIES WITH THE REQUIREMENTS OF 21 CFR PART 56 WILL BE RESPONSIBLE FOR THE INITIAL AND CONTINUING REVIEW AND APPROVAL OF THE CLINICAL INVESTIGATION. I ALSO AGREE TO PROMPTLY REPORT TO THE IRB ALL CHANGES IN THE RESEARCH ACTIVITY AND ALL UNANTICIPATED PROBLEMS INVOLVING RISKS TO HUMAN SUBJECTS OR OTHERS. ADDITIONALLY, I WILL NOT MAKE ANY CHANGES IN THE RESEARCH WITHOUT IRB APPROVAL, EXCEPT WHERE NECESSARY TO ELIMINATE APPARENT IMMEDIATE HAZARDS TO HUMAN SUBJECTS.

I AGREE TO COMPLY WITH ALL OTHER REQUIREMENTS REGARDING THE OBLIGATIONS OF CLINICAL INVESTIGATORS AND ALL OTHER PERTINENT REQUIREMENTS IN 21 CFR PART 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.

2. Attach curriculum vitae or other statement of qualifications as described in Section 2.

3. Attach protocol outline as described in Section 8.

4. Sign and date below.

5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR.
The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

10. SIGNATURE OF INVESTIGATOR | 11. DATE

FIG. 2. FDA form 1572, Statement of Investigator.

The IND should include the following specific information:

1. Complete composition of the drug, its source, and manufacturing data, to show that there are appropriate standards to ensure its safe use. Note: It is not 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), *if* that information has previously been submitted to the FDA, and *if* the sponsor of the file containing that information is willing to provide a letter to the FDA authorizing reference to the information.
2. Results of all pre-clinical (pre-human) investigations, including animal studies. Initially, these should be directed toward defining the drug's safety rather than its efficacy. The data must demonstrate that there will not be unreasonable hazard in initiating studies in humans. Further animal studies may be conducted concurrently with clinical (human) studies. The Center for Drug Evaluation and Research or the Center for Biologic Evaluation and Research will, on request, comment on the adequacy of the proposed animal studies. Generally, the FDA minimally requires that: (a) there be a pharmacologic profile; (b) acute toxicity be determined in several species of animals and that the route of administration will be the same in the animal trials, and (c) there be short-term studies ranging from 2 wk to 3 mo, depending on the proposed use, to evaluate toxicity. Additional animal studies frequently are necessary.
3. A detailed outline (protocol) of the planned investigation including anticipated or postulated changes to the protocols based upon study findings.
4. Information regarding the training and experience of the investigators. Investigators are responsible for and are required to submit to the sponsor (not the FDA) Form 1572 for clinical trials.
5. Copies of all informational material supplied to each investigator. This type of material is listed in Form FDA 1571. Additionally, a letter from the investigator's institutional review board (IRB) stating that it approves of and will monitor the study.
6. An agreement from the sponsor to notify the FDA and all investigators of any adverse effects that may arise during either animal or human tests.
7. The investigator's agreement to obtain informed consent from the study participants before the test is performed.
8. Agreement to submit annual progress reports and commitments regarding disposal of the drug when studies are discontinued.
9. Agreement not to initiate any part of a study for 30 days after submission of the IND in order to allow the FDA to review the submission for safety.

SELECTED HIGHLIGHTS AND SHIFTS IN ATTITUDE ASSOCIATED WITH THE IND REWRITE

The IND rewrite reflects both a fine-tuning of the regulatory process as well as of a change in attitude on the part the FDA.

The agency carefully reviewed more than 50 comments received from pharmaceutical manufacturers, trade associations, health professionals, professional societies and consumer organizations. In addition, agency managers met with a congressionally-sponsored commission in part responsible for improving the process. Thus, virtually all groups with an interest in the IND process got to speak their piece. A review of the comments section in the final ruling (*3*) suggests that these comments were carefully considered in that two major shifts in policy occurred: (a) focusing attention during the early phase of the IND process (clinical research) on protecting the safety of human test subjects and (b) giving sponsors greater freedom to design, revise, and implement clinical research studies, while providing greater assistance to the applicants.

Policy Shifts

Continuing Dialogue. Accordingly, the regulations codify a series of four standard conferences targeted at key stages of the drug approval process between FDA staff and sponsor/applicants. Another provision provides for conferences on an as needed basis. Additionally, there is a strong commitment to resolve disputes in a timely manner.

Assistance. Whereas the responsibilities of the sponsors and clinical investigators are substantially the same, the FDA has significantly expanded the use of guidelines on how to fulfill certain technical requirements in order to provide greater guidance to applicants.

Highlights

Selected highlights from the IND rewrite include the following items.

Regulation of the Early Phase of Research. Greater emphasis on safety for human subjects and greater flexibility to modify protocols without prior FDA notification. Also, there is the proposed use of nongovernmental Outside Review Boards (ORBs). However, this may probably never occur.

Format for IND Submission. A new organization of the form 1571 to facilitate agency review for much of the same data required, but with a modified time frame for the components, so that they can be viewed in light of the proposed clinical investigations.

IND Safety Reports. Unexpected or life-threatening reports are to be made by telephone in three working days and in writing in ten working days. This requires prompt review, evaluating, and reporting on the part of the sponsor.

Amendment Procedures. Amendments are divided into three categories with individual reporting intervals: (a) protocol amendments, (b) information (data) amendments, and (c) safety reports. The annual report provides an overview of the progress to date and future plans.

Meetings Between FDA and Drug Sponsors. Periodic meetings are codified as a matter of policy to facilitate appropriate data submission.

Clinical Hold Procedures. A clinical hold is an order from the FDA to the sponsor either not to begin or to discontinue a study. The final rule limits clinical holds in Phase I studies to situations where there is an unreasonable and significant risk to human subjects. Phase II and III studies can be held for serious defects in study design.

Exemption for Certain Studies on Marketed Drugs. This exemption is designed to foster research and will most likely be emphatic with respect to academic institutions. Most IND requirements would be exempted except for safety reasons. This situation applies to marketed drugs in which dose, route of administration and patient population with the approved labeling are similar to that for which the drug was originally approved.

Dispute Resolution. This process relies on *informal* communication to resolve differences between the FDA and sponsors. An ombudsman's function would be to facilitate timely and equitable resolutions of administration and managerial disagreements about INDs. Outside consultants can be used and the informal process supersedes the formal appeals process.

Economic Analysis. Additionally, an economic analysis of clinical trials can result in further savings by the elimination of poorly designed or unnecessary clinical studies, e.g., avoiding the need to redo it.

THE PHYSICIAN-SPONSORED IND

When a physician and/or a clinical investigator wishes to act as a sponsor for the use of a drug solely as a research tool or for early clinical investigation of a drug for its therapeutic or diagnostic potential (clinical pharmacology, Phases I and II), a simpler abbreviated form of submission is acceptable. An example would be the study of a drug that no manufacturer is interested in sponsoring. An outline of such a study should provide the following information:

1. The identity of the compound or compounds together with facts that satisfy the investigator that the agent maybe justifiably administered to a human as intended.
2. The purpose of the use and the general protocol.
3. Appropriate background information including a brief statement of the investigator's scientific training and experience and the nature of the facilities available to him/her. The clinical investigator sponsoring this type of IND deals directly with the FDA. The FDA has no authority over the practice of medicine and cannot require a physician to prescribe or not to prescribe a drug for a particular illness. Investigator sponsors are encouraged to submit an IND, when they use a drug for purposes other than those approved by the FDA. This enables the FDA to accumulate data on the safety and efficacy of the drug for that kind of treatment and to share this information with other physicians and health care professionals. At a recent program session of the American Pharmaceutical Association, FDA representatives and program panelists acknowledged that they recognize the difference between having clinical responsibility for a patient's care during an investigational study versus initiating and having responsibility for conducting and analyzing a particular investigational study.

This is relevant since only a single Principal Investigator is designated on FDA 1571 or 1572 (*9*).

If the sponsor does not perform the manufacturing and control operations for the new drug substance or final dosage form himself, this information (which is required on Form FDA 1571) can be furnished on behalf of the sponsor by the supplier who performs these operations. Similarly, a supplier may provide the pre-clinical or clinical study data. The sponsor may forward such supporting information or arrange to have it transmitted directly to the FDA. In practice, the manufacturer usually maintains a Drug Master File (DMF) containing manufacturing information with the FDA and, on the request of an investigator or sponsor and with permission of the DMF holder, this information can be used to satisfy certain requirements. The sponsor rarely, if ever, reviews the contents of the DMF under these circumstances. It remains his or her responsibility, however, to see that the items in the DMF meet the requirements.

CLINICAL INVESTIGATION: OBTAINING THE EVIDENCE

The type and the extent of investigational drug tests are crucial for producing the substantive scientific evidence of safety and effectiveness needed to approve the drug for marketing. This evidence is obtained in three phases.

Phase I

Pharmacology studies are used to determine toxicity, metabolism, absorption, elimination and other pharmacologic actions, preferred route of administration, and safe dosage range. These studies involve a small number of subjects and are conducted under carefully controlled circumstances by people trained in clinical pharmacology.

Phase II

Initial trials are conducted on a limited number of patients for a specific disease treatment or prevention. Additional pharmacologic studies performed concurrently on animals may be necessary to indicate safety.

Phase III

Proposals for Phase III of the clinical investigation, which involve extensive clinical trials, are in order if the information

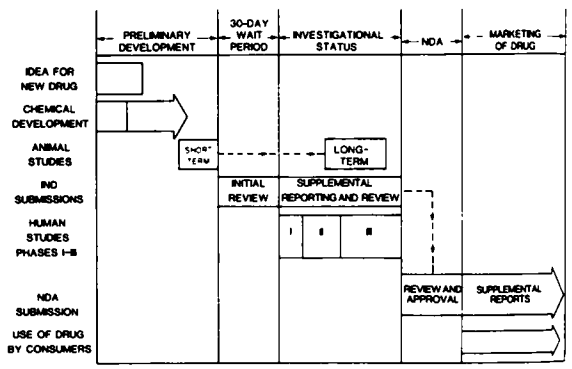

FIG. 3. Schematic rendering of the new drug development process.

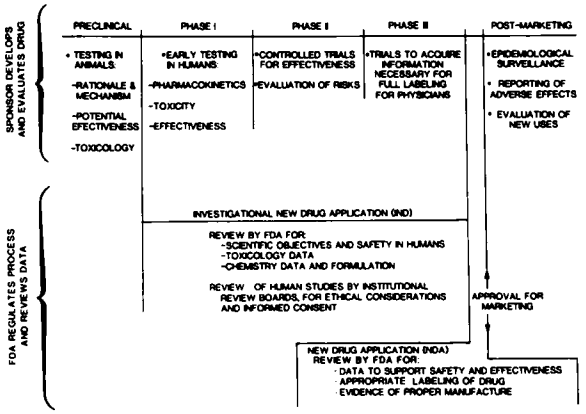

FIG. 4. Schematic outline showing regulatory monitoring of drug development and evaluation.

obtained in the first two phases demonstrates reasonable assurance of safety and effectiveness or suggests that the drug may have a potential value outweighing possible hazards. Phase III studies are intended to assess the drug's safety, effectiveness, and most desirable dosage in the treatment of a specific disease in a large group of subjects. The studies, no matter how extensive, should be carefully monitored.

The FDA continually receives reports on the progress of each phase. If the continuation of the studies appears to present an unwarranted hazard to the patients, the sponsor may be requested to modify or discontinue clinical testing until further preclinical work has been completed (*2,10*).

A schematic outline of the new drug development process is presented in Figure 3. In Figure 4, the development and regulation of drugs, including radiopharmaceuticals, are further described.

INSURANCE AGAINST UNNECESSARY DELAYS: TIPS FOR SPONSORS AND INVESTIGATORS OF INDS

Instructions for the preparation and submission of FDA-1571 are available from the FDA (*1*), yet, we have reviewed or assisted in the preparation of INDs in which the directions had never been consulted. Thus, just as with income tax forms or any unfamiliar application, the individual clinical investigator has a choice between a relatively painless exercise or one fraught with futility.

It is important to understand that the FDA is made up of individuals, with numerous responsibilities. They are few in number when compared to the vast variety of products and procedures being investigated. Your submission must clearly state the goal of the study as well as the sponsor/investigator's competency in carrying out the task.

Another important point is that the FDA is the only game in town when it comes to utilizing investigative products. They may not always be as expert as you presume. The sponsor should present information in a form that the FDA can understand. Although the investigator fully understands what he is trying to accomplish, it is often not presented in

such a fashion to the FDA. It is your task to ensure that the study's principal contact communicates well (in writing and orally). Frequently, an investigator lets his/her temper or frustration cause a study either to be placed on hold or delayed from having to answer questions that may have been unnecessary if one had just been tactful. One can be stubborn but it will not pay off in the long run. Persuasion is far more effective.

A number of simple, common sense, administrative problems immediately evident to the reviewer can, if not handled properly, result in unnecessary delays. Paying close attention to detail and to instructions for filling out the IND is important. These obvious oversights are mentioned here because they occur so often. Information about how the IND is processed inside the FDA is presented to aid the sponsor and/or investigator.

1. IND Form FDA-1571 must be signed.
2. The application must be submitted in triplicate. Many of the applications are held up for this reason. INDs are initially sent to a Central Record Room where they are given a number as they are received (INDs are *not* numbered by category). The IND is then reviewed by three disciplines (pharmacology, chemistry, clinical medicine) and others as required.
3. On receipt, the FDA has 30 days to evaluate the IND for safety (safety only, not effectiveness). It is valuable to send the IND by certified or registered mail so that you have proof that the IND was received in order to validate the 30-day safety period.
4. Be sure to answer each question and do so in the proper sequence. It is a tedious job to search through piles of paper to find the answer to a question.
5. If the IND document contains many pages, paginate.
6. Recognize that INDs are of two major types: (a) commercially-sponsored INDs in which a large population will be put at risk, and (b) individually-sponsored INDs, in which a smaller population will be placed at risk. The IND will address two primary situations: (a) one in which the drug has already been approved, perhaps for another indication, and (b) one in which there is a new clinical entity, i.e., a new drug. In the former situation, the safety may have already been established and literature can be cited. A photocopy of a few articles attached to the back of the IND as an appendix aids the process. If nothing else, it saves duplicate trips to the library.
7. When calculations of dosimetry are indicated, (a) "walk" the reviewer through the calculations, since he or she cannot make assumptions, and (b) include the total radiation dose to the patient from all modalities.
8. The CV of the primary investigator and co-investigators (if any) is used to ascertain whether their training in the handling and administration of radioactive drugs is adequate. If the sponsor of the IND is not one of the investigators, his CV is important to submit, too, since it is necessary to demonstrate that this person can administratively handle the IND function. The CV of the person(s) preparing the radiopharmaceutical is also important (pharmacist, technologist). The IND must state whether the preparation of the radiopharmaceutical will be under the supervision of a physician or pharmacist (practice of medicine or pharmacy) or be prepared by a drug manufacturing firm (and, thus, be regulated by Good Manufacturing Practices).
9. The 30-day safety period can be waived on request, i.e., on an IND for an already-approved drug (because there would probably be no safety problem). When an IND is filed for what is really the practice of medicine and pharmacy, the FDA does not really find it necessary to review the study, nor does it want to. It will, however, do so as a courtesy at the present time.
10. There are no FDA-required limits on dosage. Each case is examined on its own merit, but consider the following when submitting an IND: Is the risk to be taken worthwhile for the information to be gained? Does the patient benefit or will the information more likely be of benefit to mankind? Clearly, the FDA wants the user to administer the smallest dose possible to obtain the desired effect.

One final point. Do not hesistate to phone the FDA. This agency will do its best to help. The answer to your question may not always be the one you want, but at least you will not have spent time and resources needlessly.

ON-SITE OVERSIGHT AND RESPONSIBILITY

Given a process that can be complex in terms of its components, establishing a protocol once an investigation is underway is relevant so that "the ball, so to speak, doesn't get dropped between the cracks." For example, at our institution, we are performing clinical trials using radiolabeled monoclonal antibodies (MAbs) for imaging. The MAb is supplied (manufactured) by a commercial pharmaceutical firm (sponsor). The final dosage form is prepared in the nuclear pharmacy and the dose is administered by a nuclear medicine technologist in the out-patient facility under oncology nursing and physician supervision. The technologist later images the patient. The nuclear medicine physician interprets the study and a protocol nurse-data manger collates the data. All the personnel involved fill out the case report forms. Who then is responsible for what?

21CFR 50.25 Requires an Informed Consent. It is the responsibility of the IRB to officially approve the informed consent document. The sponsor of the IND need only say that an informed consent will be obtained. A copy of the informed consent need not be submitted with the application. However, if submitted, reviewers can be quite helpful in pointing out deficiencies in the investigator-prepared informed consent forms; this clearly being to the investigator's advantage. The investigator often relies heavily upon the sponsor in preparing the informed consent.

The Radiation Safety Committee Oversees Radiation Safety. If the trial is a Phase I (a metabolism and kinetic study), then the Radioactive Drug Research Subcommittee (RDRC) is responsible; if it is a Phase II or III study, then the Human Use Subcommittee is responsible. In any event, the radiation dose to the patient from all facets of the study is considered, not just the drug in question, e.g., preliminary and confirmatory computed tomography scans.

Scientific Merit. At our institution, the scientific merit of cancer-related projects is reviewed by the Scientific Review Committee. This may also be done at the school department (Radiology) or hospital level research committee and at other levels.

Funding. At our institution, funding is handled by the Protocol Development Committee. It also may be done at the school department (Radiology) and hospital department (Nuclear Medicine) levels.

Patient Care. This is the responsibility of the physician; in our case, nuclear medicine or oncologist, in the event of an adverse reaction, since the physician is best qualified to treat a patient.

Sponsor Liasion. It is the responsibility of the principal investigator to coordinate and integrate the program as well as to serve as the liasion with the sponsor.

Peer Review. It should be noted that other areas of clinical investigation could be examined by other nuclear medicine professionals. These areas include: (a) new indications for an existing radiopharmaceutical; (b) new routes of administration for existing radiopharmaceuticals; (c) new dosage forms; (d) evaluating new salts of existing agents; (e) animal studies using new or existing agents; and (f) new ways of processing imaging data using computer programs.

EXAMPLES OF WHEN AN IND IS (AND IS NOT) REQUIRED

Example 1

A hospital-based nuclear medicine physician is consulted by a pediatrician, whose patient is depleted of lymphocytes. The pediatrician suspects that the lymphoma in the patient's cheek is trapping the lymphocytes. The nuclear medicine physician suggests an indium-111- (^{111}In) labeled lymphocyte scan.

Is an IND required? No, it is not. A specific patient is being treated (diagnosed) under the practice of medicine and pharmacy. The lymphocytes are a component of an already approved radiopharmaceutical, autologous ^{111}In-radiolabeled leukocytes.

Is informed consent required? No, not from the FDA's point of view. If an IND is not required, neither is informed consent.

Is it necessary to have the approval of RDRC if there is one? No.

What if this is the first time this treatment has performed on a patient? The treatment is still the practice of medicine and pharmacy. The patient (or his parents acting for him) can choose whether or not to receive the prescribed treatment.

Example 2

A nuclear medicine physician and a pediatrician decide to collaborate and compare ^{111}In-oxine labeled lymphocyte scans in one group of patients with lymphoma to iodine-123- (^{123}I) labeled lymphocyte scans in another group of patients with lymphoma. The ^{123}I radiolabeling methodology has not been approved.

Is an IND required before the administration of ^{111}In-lymphocytes under these circumstances? This apparently is a bona fide research study in which the findings from two groups of patients are compared. The patient has no choice as to which group he or she is entered into. Reference 2 provides a large series of illustrative examples of this type.

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NOTE

The views expressed in this article do not officially represent the views of the FDA.

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