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SNMMI Clinical Trials Network (CTN) Research Series for Technologists: "Clinical Research Primer – Regulatory Process Part I: How and when Radiopharmaceuticals Can be Used"

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Abstract

The radiopharmaceutical development and approval process in the U.S. has changed dramatically over the past decade with the emergence of several new and exciting diagnostic and therapeutic drugs. This impressive expansion is a direct result of the symbiotic relationship that exists between drug development, clinical research, and improved regulatory guidance. The correlative increase in clinical research has introduced diverse opportunities for newcomers in medical and scientific professions. Knowing how to successfully navigate the clinical research process can be challenging for a novice. The pathway is highly regulated and, with the addition of radiopharmaceuticals, may be confusing and daunting. Moreover, very little clinical research education and training is provided in the typical collegiate curricula for these new initiates. This article will familiarize the reader with the U.S. regulatory process by providing basic definitions and understanding of how and when radiopharmaceuticals can be used in clinical research including those involving investigational new drug (IND) applications and radioactive drug research committees (RDRCs). A later article will expand the reader's clinical research knowledge by focusing on the identity and role of the institutional review board (IRB).

Key words: Radiopharmaceutical, clinical research, clinical trial, investigational new drug, investigational new drug application, radioactive drug research committee, RDRC, Food and Drug Administration, FDA

Introduction

Clinical research using both approved and investigational new drugs continues to augment scientific knowledge, direct the next wave of approved radiopharmaceuticals, and expand indications for currently approved drugs. Knowing the regulations for how and when radiopharmaceuticals can be used in the clinical research setting is a crucial component for ensuring safe and effective outcomes. The sheer volume and granularity of material on the subject is vast and, to many, time prohibitive. The intent of this article is to guide the reader through the expanse of radiopharmaceutical clinical research regulations to help build a solid base of knowledge.

Background

Radiopharmaceuticals are a sub-set of traditional pharmaceuticals. In the U.S., the primary requirements to establish safety and efficacy come from the United States Food and Drug Administration (FDA), an agency of the United States department of Health and Human Services. The regulations are identified in the Code of Federal Regulations (CFR) which is a compilation of rules and regulations formulated by the Federal Government. The CFR has 50 Titles, each Title is dedicated to a particular agency or branch of the Federal government. Title 21 is dedicated to Food and Drugs and is comprised of 3 chapters which are further divided into 1499 parts. These regulations may be referenced in clinical research documents, support materials, and in this article. For example, 21 CFR § 312 means:

1. Title number (21)
2. Abbreviated name of the source (Code of Federal Regulations)
3. Section number (312)

Additionally, the FDA publishes guidance documents on certain subjects. While guidance documents are not enforceable, they represent the FDA's current thinking on a subject and provide practical information.

As with most topics today, federal regulations and guidance documents are easily searched on the internet. To ensure the veracity of the information, one should use an official government website. The FDA federal regulations can be found through a variety of official online sources including:

- The Food and Drug administration website – https://www.fda.gov
- The Electronic Code of Federal Regulations (e-CFR) website – https://www.ecfr.gov
- Regulations.gov – www.regulations.gov
- U.S Department of Health & Human Services – https://www.HHS.gov

Definitions

Before we embark on a discussion of radiopharmaceutical clinical research, we need to review the following terms that are defined or referenced in Title 21 CFR or other research sources such as FDA guidance documents.

"Adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related".

"Case Report Form (CRF) A printed, optical, or electronic document designed to record all the protocol-required information to be recorded for the study or reported to the sponsor on each trial subject"*(1).*

"Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects". The terms 'clinical investigation', 'clinical study', 'clinical research', and 'clinical trial' are deemed to be synonymous for purposes of this article.

"Contract research organization (CRO) means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.

Current good manufacturing practices (cGMP) "The cGMP regulations for drugs contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product" *(2).* "

FDA approval of a drug means that data on the drug's effects have been reviewed and the drug is determined to provide benefits that outweigh its known and potential risks for the intended population *(3).*

Institutional Review Board (IRB) means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects.

Institutional Review Board (IRB) approval means the determination of the IRB that the clinical investigation has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

"Investigational new drug (IND) means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes". The terms 'investigational drug' and 'investigational new drug' are deemed to be synonymous for purposes of this article.

"*Investigational new drug application* is a request from a clinical study sponsor to obtain authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans."

"Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the study is conducted or the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team". The lay terms principal or primary investigator (PI) is often used for the investigator.

Investigator's Brochure (IB) is a comprehensive document summarizing the information about an investigational product obtained during a drug trial.

"Multi-site (or multicenter) clinical trial involves the implementation of the same clinical protocol at two or more independent investigational sites where participants are seen for an intervention and/or outcomes assessment. In a multi-site trial, investigational sites are typically administratively or corporately distinct from each other" *(4)*.

"New Drug Application (NDA) is the vehicle through which a drug sponsor formally propose that the FDA approve a new pharmaceutical for sale in the United States. To obtain this authorization, a drug manufacturer submits in an NDA nonclinical (animal) and clinical (human) test data and analyses, drug information, and descriptions of manufacturing procedures*."*

Single-site clinical trial, on the other hand, utilizes one investigational site to conduct and coordinate the protocol. While a single-site clinical trial may enroll participants from multiple locations, those participants will receive an intervention and/or undergo outcome assessments under the direction and oversight of one research team located at one investigational site" *(4)*.

Site Initiation Visit (SIV) is part of a sponsor's monitoring plan to ensure that participating sites comply with protocol requirements and conduct the study appropriately. An initiation visit takes place after the sponsor has selected the site for participating in a clinical trial, and typically prior to patient enrollment.

"Sponsor means an entity who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual, pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator". The terms sponsor and sponsor-investigator are deemed to be synonymous for purposes of this article.

"Sponsor-Investigator means 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". The terms sponsor and sponsor-investigator are deemed to be synonymous for purposes of this article.

"Subject means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease".

Overview of Radiopharmaceutical Clinical Research Processes

Title 21 CFR allows pharmaceutical products to be administered to human patients/subjects under the following five conditions:

1. A U.S. lawfully marketed drug administered under clinical care. These are drugs which have been studied in IND clinical trial process. All data gathered during the clinical trial is submitted by the sponsor to the FDA in an NDA application. If the FDA determines the NDA application

meets all requirements including, but not limited to, proving safety and efficacy, the drug will be approved and may be marketed and sold in the US.

2. Emergency Use Authorization (EUA). An FDA EUA is a temporary permit to allow a drug to be administered to human patients without the requirement of clinical trials being completed and prior to an NDA application being approved. EUAs are approved to respond to designated chemical, biological, radiological, and nuclear emergencies. For example, COVID-19 vaccines were approved under an EUA in the US prior to their eventual approval by the FDA.

3. U.S. lawfully marketed drug administered within a clinical trial or other research project. Generally, regulations in 21 CFR § 312 require sponsors who wish to study a drug or biological product in humans to submit an IND application to the Agency. However, these regulations also provide for the exemption of some studies from the requirement to submit and IND application if they meet certain criteria. *(5)*

4. Investigational new drug administered within a clinical trial/study or other research project under an authorized IND application.

5. U.S. lawfully marketed (i.e., FDA approved) or investigational drug administered for basic research within research study/project under a radioactive drug research committee (RDRC) (21 CFR § 361).

The remainder of this article will focus on details for options 3-5 above.

IND Application for Marketed Drugs

Determining if an IND application is needed to conduct a clinical investigation of a marketed (i.e., FDA approved) drug primarily depends on the intent of the investigation and the degree of risk associated with the use of the drug in the investigation. A clinical investigation of a marketed drug is exempt from the IND application requirements if *all* of the following criteria are met:

- The drug product is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product.
- The investigation is conducted in compliance with the requirements for review by an IRB and with the requirements for informed consent.
- The investigation is conducted in compliance with the requirements of 21 CFR § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

The potential sponsor of a planned clinical investigation using an approved drug is responsible for determining whether the investigation meets the criteria for an exemption. If there is uncertainty about whether the exemption criteria are met, the potential sponsor can seek advice from FDA on the applicability of the IND regulations *(5)*.

Investigational New Drug Applications

"During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies."*(6)*

Unless exempted, the sponsor for a clinical study must obtain authorization from the FDA for conducting the study by submitting an IND application. Such authorization must be secured prior to interstate shipment and administration of any new drug that is not the subject of an approved NDA. *(6)*

IND Application Categories

The FDA recognizes 2 main IND application categories:

1. Commercial IND application - is one for which the sponsor (usually a corporate entity) intends to commercialize the product by eventually submitting a marketing application.

2. Research (non-commercial) IND application - is one for which the sponsor (generally an individual investigator, academic institution, or non-profit entity) does not intend to later commercialize the product. *(6)*

There are 3 main types of IND applications as described below. Note that the emergency use and expanded access IND applications have some overlapping similarities.

1. Investigator IND application (sometimes referred to as investigator-initiated IND) - An Investigator IND application is submitted by a physician who both initiates and conducts an investigation (i.e., they are the sponsor-investigator), and under whose immediate direction the

investigational drug is administered or dispensed. A physician might submit a research IND application to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.

2. Emergency Use IND application – An emergency use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND application in accordance with 21 CFR § 312.23 or 21 CFR § 312.20. 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.
3. Treatment or Expanded access IND application – Sometimes called "compassionate use", this type of IND application is used 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. It is the use of investigational new drug products outside of clinical trials to diagnose, monitor or treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. Under FDA's current regulations, there are three categories of expanded access:
    - Expanded access for individual patients, including for emergency use. This differs from an Emergency Use application because it is based on a single patient.
    - Expanded access for intermediate-size patient populations (generally smaller than those typical of a treatment IND or treatment protocol — a treatment protocol is submitted as a protocol to an existing IND by the sponsor of the existing IND).
    - Expanded access for widespread treatment use through a treatment IND or treatment protocol (designed for use in larger patient populations) *(7)*

The distinction between administering an investigational drug in the setting of a 'traditional' clinical trial versus emergency use or an expanded access IND lies in the intended use. In a traditional clinical trial, the intention is to understand the safety and effectiveness of the investigational drug; in expanded access and emergency use the intention is treatment *(7).* Emergency use and expanded access IND applications are not part of the clinical research pathway and are therefore beyond the scope of this article.

IND Application Submission Pathway

Investigational new drugs progress through several FDA regulated, clinical research phases:

1. Exploratory IND (sometimes referred to as phase "0" studies or eIND)- This is a clinical trial that is conducted early in phase 1, involves very limited human exposure, and has no therapeutic or diagnostic intent (e.g., screening studies, microdose studies) *(8).*
    - This is not a required phase but is a useful option in certain circumstances.
    - Depending on the study, the informational requirements for exploratory IND studies are more flexible than for traditional IND studies.
    - Is filed separately from a traditional IND application submission
2. Traditional IND phases
    - Phase 1 - primary goal is to assess safety of drug
    - Phase 2 - primary goal is to assess efficacy, safety, and dose determination
    - Phase 3 - primary goal is to assess efficacy and monitoring of adverse effects
    - Phase 4 - post marketing surveillance

IND application process

The IND application requirements and processes for commercial vs non-commercial (i.e., research) INDs differ with respect to the route of filing. All commercial IND applications must be filed electronically whereas non-commercial IND applications can be filed by electronic or paper options *(9).*

Sponsors of IND applications may obtain advice and guidance from FDA at any stage of IND development. Before filing an IND application, the sponsor may have questions regarding key components such as protocol design, drug specifics or pharmacology and toxicology information. In these cases, FDA allows the IND sponsor to request a pre-IND meeting *(9).* If granted, questions are provided to FDA in advance of the scheduled meeting. After the meeting, the FDA provides formal responses to help guide critical decisions for the IND application submission.

The IND application must contain information in three broad areas:

- Animal Pharmacology and Toxicology Studies - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (can include use in countries outside the US).

- Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.

- Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, 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. Finally, commitments to obtain informed consent

from the research subjects, to obtain review of the study by an IRB, and to adhere to the IND regulations in 21 CFR § 312. *(6)*

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk *(6).* During or at the end of the 30-day review, FDA may either accept the IND application, allowing the clinical research to go into effect, or it may place the IND on clinical hold. It should be noted that the FDA does not "approve" an IND application but will provide authorization through a "Study May Proceed" letter or communication.

Clinical Hold

A clinical hold is an order issued by FDA to the sponsor of an IND application to delay a proposed clinical investigation or to suspend an ongoing investigation. All or some of the investigations conducted under an IND application may be placed on clinical hold. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and given the investigational drug; patients already in the study are expected to be taken off therapy involving the investigational drug unless treatment continuation is specifically permitted by FDA in the interest of patient safety. Within 30 days of the clinical hold, FDA will provide a written explanation of the basis for the hold to the applicant *(10).*

The IND sponsor is expected to address the cited deficiencies in writing and submit a complete response to the issue(s) identified in the clinical hold letter in a separate submission. Once the complete response to all of the clinical hold deficiencies has been received, FDA will review the submission within 30 calendar days and determine whether the applicant's response to clinical hold satisfactorily addresses the issues. The investigation may resume after FDA has notified the applicant that the investigation may proceed *(10).*

If an IND applicant disagrees with the reasons cited for the clinical hold, the applicant may request reconsideration of the decision through the Ombudsman and in accordance with Dispute Resolution procedures *(10).* If all investigations covered by an IND application remain on clinical hold for 1 year or longer, the IND application may be considered by FDA for Inactive Status (21 CFR § 312.42).

Active INDs

Once an IND application is authorized (active), a drug manufacturer may legally ship or provide the investigational drug to the investigator(s) named in the application. An investigator may not administer an investigational drug to human subjects until the IND application goes into effect and the protocol and informed consent form has been approved by the IRB of record.

IND Management

Sponsors of active INDs are required to provide oversight to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality of the clinical trial data submitted to FDA. To meet these requirements, sponsors are responsible for monitoring the trial and sending periodic updates, any necessary amendments, and reports related to their applications to FDA *(6).*

A sponsor may transfer responsibility for any or all obligations to a contract research organization (CRO). Any such transfer shall be described in writing. If not all obligations are transferred, the writing is required to describe each of the obligations being assumed by the CRO. If all obligations are transferred, a general statement that all obligations have been transferred is acceptable. Any obligation not covered by the written description shall be deemed not to have been transferred.

While the sponsor's responsibilities for a research IND versus a commercial IND do not differ, the monitoring plan may vary significantly due to intent and complexity of the IND. The monitoring plan should focus on preventing or mitigating important and likely risks to critical data and processes.

Regulations are not specific about how sponsors are to conduct such monitoring and are therefore compatible with the complexities of the IND and allow for a range of approaches to monitoring that will vary depending on multiple factors.

1. Monitoring - While the methods may differ, the following approaches may be used:
    - On-site Monitoring:
        - On-site monitoring is an in-person evaluation carried out by sponsor personnel or representatives at the sites at which the clinical investigation is being conducted. On-site monitoring can identify data entry errors (e.g., discrepancies between source records and case report forms (CRFs)) and missing data in source records or CRFs; provide assurance that study documentation exists; assess the familiarity of the site's study staff with the protocol and required procedures; and assess compliance with the protocol and investigational product accountability. On-site monitoring can also provide a sense of the quality of the overall conduct of the trial at a site (e.g., attention to detail, thoroughness of study documentation, appropriate delegation of study tasks, appropriate clinical investigator supervision of site staff performing critical study functions). On-site monitoring can therefore be particularly helpful early in a study, especially if the protocol is complex and includes novel procedures with which clinical investigators may be unfamiliar. Findings at the site may lead to training efforts at both the site visited and elsewhere.
        - This approach is used typically for research INDs but can also be used for commercial INDs.
    - Centralized Monitoring
        - Centralized monitoring is a remote evaluation carried out by sponsor personnel or representatives (e.g., clinical monitors, data management personnel, or

statisticians) at a location other than the sites at which the clinical investigation is being conducted. Centralized monitoring processes can provide many of the capabilities of on-site monitoring as well as additional capabilities.

- One notable type of monitoring is the site initiation or site initiation visit (SIV). The SIV is a critical study activity occurring prior to study recruitment and often involves sponsor personnel from a range of disciplines, including monitors.
    - Key components of site initiation include ensuring the clinical investigator and site staff understand their responsibilities:
        - applicable regulatory requirements,
        - study processes and procedures,
        - the sponsor's processes for monitoring the investigation *(11)*.

2. IND Amendments - For any given IND application, FDA may receive the following categories of amendments:

    - Protocol Amendments - Once an IND application is in effect; the sponsor may amend the application as needed to ensure that the clinical investigations are conducted according to protocols included in the IND application. Sponsors are expected to submit protocol amendments for new protocols or changes to existing protocols before implementation of the respective changes. However, protocol changes intended to eliminate an apparent immediate hazard to human subjects may be implemented immediately, provided that FDA is subsequently notified by protocol amendment and the reviewing IRB is also notified. New studies may begin when the sponsor has submitted the change to FDA for its review and the new protocol or changes to the existing protocol have been approved by the IRB with the responsibility for review and approval of the studies. The general types of protocol amendments are:

- New protocol
- Change in protocol
- New investigator

- Information Amendments – An Information Amendment is any amendment to an IND application with information essential to the investigational product that is not within the scope of protocol amendments, safety reports, or annual reports. For example, information amendments to IND applications may include new toxicology, chemistry, or other technical information or a report regarding discontinuance of a clinical or non-clinical investigation.

3. IND Reports – The following reports are required, at minimum.

- IND Safety Reports - IND application sponsors/applicants are required to notify FDA in a written safety report of:
  - 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 suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, and carcinogenicity *(12)*.
- IND Annual Reports - IND sponsors/applicants are expected to submit brief reports of the progress of the investigations conducted under their respective IND application within 60 days of the anniversary date that the application went into effect. The information listed below is expected to be included in an IND Application Annual Report:
  - Individual study information - there may be several protocols or studies submitted under one IND, information must be provided for each study.
  - Summary information – for each protocol/study

- Update to the General Investigational Plan – for each protocol/study
- Update to Investigator's Brochure – if applicable
- Significant protocol updates – for each protocol/study
- Update on foreign marketing developments
- A log of outstanding business *(13)*

Radioactive Drug Research Committee

Under 21CFR § 361.1, human research using a radioactive drug or biological product may be conducted under an RDRC and without an IND when that research is basic science research and is not intended for immediate therapeutic, diagnostic, or similar purposes, or to determine the safety and effectiveness of the radioactive drug or biological product for such purposes (i.e., the research cannot constitute a clinical trial for the product).

Each RDRC must obtain FDA approval before it may approve research studies. Approval of a RDRC will remain in effect unless and until FDA withdraws such approval. Approval of a RDRC may be withdrawn at any time for failure of the RDRC to comply with the requirements.

The regulations list three additional requirements for human subject research that may be conducted under an RDRC:

1. The research must be approved by an RDRC that is approved by FDA based on the following requirements:
   - qualified study investigators
   - properly licensed medical facility to possess and handle radioactive materials
   - appropriate selection and consent of research subjects

- appropriate quality assurance of radioactive drug administered
- sound research protocol design
- reporting of adverse events by the investigator to the RDRC
- approval by an appropriate IRB

2. The pharmacologic dose of the radioactive drug to be administered is known not to cause any clinically detectable pharmacologic effect in humans.
    - Investigators must provide pharmacological dose calculations based on clinical data in the published literature or from other valid human studies to show that the radioactive drug has no clinically detectable pharmacological effect. This requirement means that RDRC protocols cannot include the use of drugs that have no documented previous human experience.
3. The total amount of radiation to be administered as part of the study must be the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study and must be within specified limits. Investigators must:
    - Provide radiation absorbed dose calculations based on biologic distribution data from published literature or from other valid studies.
    - Provide an acceptable method of radioassay of the radioactive drug before its use to ensure that the radioactivity calculations actually reflect the administered activity.
    - Provide information demonstrating that the radioactive drug chosen for the study has the half-life, types of radiation emitted, radiation energy, metabolism, and chemical properties that result in the lowest dose to the whole body or specific organs with which it is possible to obtain necessary information.

- Identify adequate and appropriate instruments for the detection and measurement of the specific radioactive drug *(14)*.

Human research under an RDRC must be considered basic science research and must be done for the purpose of advancing scientific knowledge. As described in 21 CFR § 361.1(a), this type of research differs from a clinical trial to determine safety and efficacy under an IND in the following ways:

- It is intended to obtain basic information on
    - metabolism (including kinetics, distribution, dosimetry, and localization) of a radioactive drug or
    - human physiology, pathophysiology, or biochemistry.
- It is not intended for immediate therapeutic, diagnostic, or similar purposes to the study subject.
- It is not intended to determine the safety and effectiveness of a radioactive drug in humans as a therapeutic, diagnostic, or similar type of medical product.

<u>Types of studies appropriate for RDRC approval</u>

The following are examples of types of basic science research that would be appropriate to conduct under an RDRC without an IND:

1. Metabolism and excretion studies: These studies usually employ non-imaging radionuclides. Following administration of the radioactive drug, samples can be obtained at various times from blood, urine, feces, accessible fluid or tissues, and expired gas. Samples can be analyzed to determine the amount, structure, and persistence of the parent molecule and various metabolites formed. Separate studies of metabolism or excretion can be conducted. A

combined study is commonly known as a *Mass Balance study*. Carbon-14 and H-3 are most commonly used for these studies, but other radionuclides can also be used, including gamma emitting radionuclides that can be imaged.

2. Noninvasive functional imaging/molecular imaging studies: For most other types of research studies, the radioactive drug is usually selected for its imaging properties (i.e., positron emission tomography (PET), single photon emission computed tomography (SPECT), or gamma scintigraphy). The terms *noninvasive functional imaging* and *molecular imaging* are widely used to describe this category of studies, including the following:

    - Biodistribution - Investigation of the time course for delivery, uptake, and retention of a radioactive drug at various tissue sites in the body. The goal is to determine whether there are any sites in the body in which the radioactive drug is excluded or in which the radioactive drug preferentially accumulates. An understanding of the variation of these processes within the population is often the main objective.
    - Pathophysiology - Studies to determine whether the presence or absence of pathophysiological conditions (e.g., preferential uptake or exclusion by tumors compared with adjacent tissues) influences the distribution and persistence of the radioactive drug.
    - Receptor binding or occupancy - Characterization of the kinetics between the radioactive drug and receptors or other binding sites throughout the body, and characterization of the radioactive drug binding affinity to these receptors. The primary objective is to determine whether localization is specific or nonspecific. In some cases, the observed variation within the population or among populations is a major endpoint. In other studies, the goal may be to develop hypotheses related to disease states, receptor polymorphisms, or therapeutic interventions.

- Transport processes - Many transport proteins regulate the extracellular and intracellular distribution of ions and other endogenous compounds in the body, as well as exogenous molecules, such as drugs. Radioactive drugs can be used to determine the relative abundance and specificity of such transporters in various tissues.
- Enzyme activity - Enzymes help to control the concentrations of critical signaling molecules. Radioactive drugs can serve as molecular probes to determine rates of synthesis or degradation of signaling molecules through enzymes.
- Multistep biochemical processes - Many biochemical and molecular processes represent the net effect of a complex array of serial and parallel pathways *(14).*

What information must be submitted to the RDRC for review and approval?

Investigators should provide sufficient information to the RDRC so they can determine whether a study meets the conditions of 21 CFR § 361.1(b) and does not need an IND. The RDRC should be provided with information on the following topics:

1. Radiation dose to subjects: Limits are provided under 21 CFR § 361.1(b)(3)(i).
2. Pharmacological dose: Investigators must provide pharmacological dose calculations based on clinical data in the published literature or from other valid human studies to show that the radioactive drug has no clinically detectable pharmacological effect.
3. Consent: Each investigator must select appropriate human subjects, obtain the review and approval of an IRB that conforms to the requirements of 21 CFR § 56.
4. Number of subjects: The number of research subjects enrolled in a protocol under an RDRC can vary. Many studies under an RDRC start with 30 research subjects or fewer. At the time a research proposal is approved by an RDRC to allow the exposure of more than 30 subjects

the RDRC must submit a special summary of information immediately, but no later than 7 calendar days, to the FDA.

5. Women of childbearing potential: 21 CFR § 361.1(d)(5) requires that a woman of childbearing potential state in writing that she is not pregnant, or, on the basis of a pregnancy test, be confirmed as not pregnant, before she may participate in a study under an RDRC.
6. Pediatric subjects: Although studies involving pediatric subjects are permissible in special circumstances under §361.1, few pediatric studies have been conducted in recent years under the RDRC mechanism. Section 361.1(d)(5) requires that for studies under an RDRC, subjects shall be at least 18 years of age and legally competent. Exceptions to this rule are permitted only when it can be demonstrated to the RDRC that:
    - The study represents a unique opportunity to gain information not currently available;
    - The study requires the use of research subjects less than 18 years of age; and
    - The study is without significant risk to the subject
    - When reviewing proposed pediatric studies under an RDRC, the IRB must approve only those studies that meet the criteria in, and satisfy all other requirements of 21 CFR part 50 subpart D.
7. Quality of radioactive drug: All radioactive drugs (PET and non-PET drugs) produced under an RDRC are required to meet appropriate sterility, endotoxin, chemical, pharmaceutical, radiochemical, and radionuclidic standards of identity, strength, quality, and purity as needed for safety and be of such uniform and reproducible quality as to give significance to the research study conducted. To ensure product quality, non-PET radioactive drugs studied under an RDRC must comply with the Current Good Manufacturing Practice (CGMP)

regulations in 21 CFR parts 210 and 211. PET radioactive drugs must be produced in accordance with the standards under USP Chapter <823>, Radiopharmaceuticals for Positron Emission Tomography—Compounding.

8. Research protocol: The investigator must provide sufficient information for the RDRC to conclude that scientific knowledge and benefit is likely to result from the study.
9. Adverse reactions: The investigator must immediately, and no later than 7 calendar days, report to the RDRC all adverse effects associated with the use of the radioactive drug in the research study. The RDRC must report immediately, but no later than 7 calendar days, to FDA all adverse reactions probably attributable to the use of the radioactive drug in the research study.
10. Approval by an IRB: The investigator must obtain IRB approval of the study protocol. Once obtained, proof of IRB approval must be provided to the RDRC. IRBs are required to conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once a year.
11. Labeling: The packaging, label, and labeling of the radioactive drug must be compliant with federal, state, and local laws on radioactive materials *(14)*.

Conclusion

While clinical research using radiopharmaceuticals may seem daunting to newcomers, one need not be overwhelmed. As this article has shown, a basic knowledge of applicable clinical research regulations, terms, and processes can equip the reader with the necessary resources to ensure safe and effective outcomes.

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