Guidance for Industry and Researchers

The Radioactive Drug Research Committee: Human Research Without An Investigational New Drug Application

U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

Guidance for Industry and Researchers[1]

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I. INTRODUCTION

This guidance is intended to provide information for those using radioactive drugs for certain research purposes to help determine whether research studies can be conducted under 21 CFR 361.1, Prescription Drugs for Human Use Generally Recognized as Safe and Effective and Not Misbranded: Drugs Used in Research, or whether research studies must be conducted under 21 CFR part 312, Investigational New Drug Application (IND).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

In 1963, the Commissioner of Food and Drugs issued an order exempting radioactive new drug and biological products for investigational use in humans from new drug requirements (part 312), as long as they were shipped consistent with regulations issued by the then Atomic Energy Commission (AEC) (28 FR 183; January 8, 1963).

On July 25, 1975 (40 FR 31298), FDA changed the conditions under which new radioactive drug and biological products could be used. First, the Agency terminated the 1963 order. The FDA and the AEC then agreed that all radioactive drugs and biological products should now become subject to the same requirements for investigational use as other new drugs under section 505 of

[1] This guidance has been prepared by the Office of New Drugs, Office of Drug Evaluation IV, Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER), at the Food and Drug Administration.

the Federal Food, Drug, and Cosmetic Act and section 351 of the Public Health Service Act. Simultaneously, the Agency issued regulations (21 CFR part 361) explaining when radioactive drugs for basic science and medical research in humans would be generally recognized as safe and effective, and would therefore not be subject to the same requirements for investigational use as other new drugs. Under 21 CFR part 361, basic science and certain medical research may be conducted without an IND if approved by a Radioactive Drug Research Committee (RDRC). The term *radioactive drug* as used in 21 CFR part 361, includes radioactive biological products labeled with a radionuclide (21 CFR 361.l(a), 21 CFR 310.3(n), and 21 CFR 600.3(ee)).

III. RESEARCH CONDUCTED UNDER AN RDRC

Under§ 361.1, human research using a radioactive drug or biological product may be conducted under an **RDRC** only (e.g., without an IND) when that research is basic science research, and not research that is 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). 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 (21 CFR 361.l(b)(1) and 21 CFR 361.1(c)(4)).

(2) The dose to be administered must be known not to cause any clinically detectable pharmacological effect in humans (21 CFR 361.l(b)(2)).

(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 (21 CFR 361.l(b)(3)).

The following sections of this guidance examine each of these requirements in more detail, and Appendices A through **D** to the guidance answer frequently asked questions about determining whether human research with a radioactive drug can be conducted under an **RDRC.** Appendix E sets out information on the membership and functions of the **RDRC,** and Appendix F provides a checklist of the minimum RDRC review criteria.

A. What Constitutes Basic Science Research?

Human research under an RDRC must be considered basic science research and must be done for the purpose of advancing scientific knowledge (21 CFR 361.1). As described in 21 CFR 361.l(a), this type ofresearch 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 (1) metabolism (including kinetics, distribution, dosimetry, and localization) of a radioactive drug or (2) 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.

Radioactive drugs are subject to§ 361.1, regardless of whether the compound to which the radionuclide is attached is a naturally occurring substance or a synthetic molecule.

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

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.

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:

(1) **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.

(2) **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.

(3) **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.

(4) **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.

(5) **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.

(6) **Multistep biochemical processes.** Many biochemical and molecular processes represent the net effect of a complex array of serial and parallel pathways. Radioactive drugs can be used as markers to study processes such as DNA synthesis, cellular proliferation, or apoptosis.

B. What Are the Study Criteria for Research Conducted Under an RDRC?

An FDA-approved **RDRC** is one that fulfills the requirements for membership, function, reporting, approval, and monitoring specified in§ 361.l(c)(l)-(c)(S), and has an application that FDA has accepted as meeting these criteria (see Appendix E for more details on submitting an application and on **RDRC** membership, functions, and reports).

For an **RDRC** to determine whether a study meets the conditions of§ 361.l(b) and does not need an IND, investigators should provide sufficient information to the RDRC to ensure that the research will include the following (see Appendix F, RDRC Review Criteria Checklist, for a working checklist of these items).

- Qualified study investigators (21 CFR 361.l(d)(3))
- Proper licensure to handle radioactive materials (21 CFR 361.l(d)(4))
- Appropriate selection and consent of research subjects (21 CFR 361.l(d)(S))
- Appropriate quality of radioactive drug administered (21 CFR 361.l(d)(6))
- Sound research protocol design (21 CFR 361.1(d)(7))
- Reporting of adverse events to the RDRC (21 CFR 361.l(d)(8))
- Approval by an appropriate institutional review board (IRB)2 (21 CFR 361.l(d)(9))

The RDRC should be provided with information on the following topics:

Radiation dose to subjects (see Appendix D of this guidance). To ensure that research subjects receive a radiation dose as low as practicable to perform the study and meet the criteria of § 361.l(b)(3), § 361.1(d)(l) requires that investigators:

(1) Provide radiation absorbed dose calculations based on biologic distribution data from published literature or from other valid studies.

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[2] While 21 CFR 361.l(d)(5) uses the term "institutional review committee," since the definition of"institutional review board" in both 21 CFR part 50 and 56 (50.3(i) and 56.102(g)) includes "any board, committee, or other group," we use the terms "institutional review committee" and "institutional review board" interchangeably in this guidance document.

(2) Provide an acceptable method of radioassay of the radioactive drug before its use to ensure that the radioactivity calculations actually reflect the administered activity.

(3) 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.

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

Pharmacological dose (see Appendix C of this guidance). Section 361.l(d)(2) requires that investigators 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.**

Qualifications of investigators. Section 361.1(d)(3) requires that investigators provide information about their training and experience to show they are qualified to conduct the proposed research studies.

License or authorization to handle radioactive materials. Section 361.l(d)(4) requires that the investigator or institution be licensed by the appropriate state, local, and/or Federal authorities. Investigators must (1) be licensed or authorized to possess and use the specific radionuclide for research use or (2) be a listed investigator under a broad license issued by the Nuclear Regulatory Commission or an Agreement State. We recommend you check with your state and local governments and relevant Federal agencies (e.g., Department of the Army) for their specific requirements.

Human research subjects. FDA regulations require investigators to provide the RDRC with certain information about the human research subjects, including the following:

(1) **Consent:** Section 361.l(d)(5) states that each investigator must select appropriate human subjects, obtain the review and approval of an IRB that conforms to the requirements of 21 CFR part 56, and obtain the consent of the subjects or their legal representatives in accordance with 21 CFR part 50.

(2) **Number of subjects:** The number ofresearch subjects enrolled in a protocol under an RDRC can vary. Of primary importance is that research with the radioactive drug is conducted for the purpose of advancing scientific knowledge and not for immediate therapeutic, diagnostic, or similar purposes in humans or to determine the safety and effectiveness of the drug in humans. FDA recommends that an RDRC protocol be approved for a ***finite number*** of subjects sufficient to gain basic information. In FDA's experience, many studies under an RDRC start with 30 research subjects or fewer. Recent RDRC studies have averaged 10 subjects annually per study.

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 in the format specified in § 361.l(c)(3).

The special summary should include a justification for continued subject enrollment to ensure that research is considered basic science and not moving towards immediate therapeutic or diagnostic purposes, or determining the safety and effectiveness of a drug in humans (i.e., carrying out a clinical trial for safety and efficacy). Reasons for increasing subject enrollment might include the study of the radioactive drug in different subpopulations related to age, sex, or disease types, such as subjects with impaired renal function or diabetes. Reasons such as statistical powering for non-basic research endpoints, grant requirements, or making decisions about patient treatment are not valid justifications for continued subject enrollment in RDRC studies. Contents of these special summary reports are available for public disclosure, unless confidentiality is requested by the investigator and it is adequately shown by the investigator that the report constitutes a trade secret or confidential commercial information as defined in 21 CFR 20.61.

(3) **Women of childbearing potential:** Section 361.l(d)(S) 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.** FDA recommends that the absence of pregnancy be confirmed by a pregnancy test. Lack of pregnancy in women of childbearing potential is usually confirmed by a negative urine pregnancy test. Postmenopausal or surgically sterile women are not regarded as having childbearing potential. Postmenopausal is defined as 12 months of spontaneous amenorrhea, 6 months of spontaneous amenorrhea with serum FSH levels >40 mIU/mL, or 6 weeks postsurgical bilateral oopherectomy with or without hysterectomy.3 FDA recommends that women of childbearing potential use a reliable form of contraception, such as an IUD, hormonal contraception, tubal ligation, partner's vasectomy, latex condom, diaphragm, or cervical cap throughout the at-risk period. FDA recommends that IUD use and hormonal contraception begin at least 1 month before radioactive drug administration.

FDA recommends that women not become pregnant after exposure to a radioactive drug until the potential fetal dose from remaining radionuclide(s) is< 1 mSv (<100 mrem).

(4) **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.

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[3] See the Agency's draft guidance for industry on *Estrogen and Estrogen/Progestzn Drug Products to Treat Vasomotor Symptoms and Vu/var and Vaginal Atrophy Symptoms - Recommendatzons for Clznzcal Evaluatzon.* Once finalized, this guidance will represent the Agency's thinking on this topic.

Section 361.l(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 (see discussion under **Risk assessment** below).

As with adult studies under an RDRC, § 361.l(d)(5) requires that studies in pediatric subjects comply with the requirements for informed consent in accordance with 21 CFR part 50, Protection of Human Subjects, and with the requirements for review and approval by an IRB in accordance with 21 CFR part 56, Institutional Review Boards. In addition, when some or all of the study subjects are children, § 56.109(h), IRB Review of Research, requires IRBs to determine that the research is in compliance with 21 CFR part 50, subpart **D** (Additional Safeguards for Children in Clinical Investigations).

Section 361.l(d)(5) requires that studies in pediatric subjects be supported with review by qualified pediatric consultants to the **RDRC.** In addition,§ 361.l(b)(3)(ii) requires that the radiation dose in pediatric subjects must not exceed 10 percent of that for adult subjects as specified in § 361.l(b)(3)(i). The radiation dose limit includes the radiation dose of the radioactive drug to be administered as well as the radiation dose from all sources that are part of the entire research study, including follow-up studies (e.g., x-ray procedures, transmission scans, CT scans, x-ray absorptiometry) (§ 361.l(b)(3)(iii)).

If an **RDRC** approves a study involving one or more pediatric subjects, a special summary of information must immediately, but no later than 7 calendar days, be submitted to FDA in the format specified in§ 361.l(c)(3). Contents of these special summary reports are available for public disclosure, unless confidentiality is requested by the investigator and it is adequately shown by the investigator that the report constitutes a trade secret or confidential commercial information as defined in 21 CFR 20.61.

Pharmacological effect. Sections 361.l(b)(2) and (d)(l)(i) require that the dose to be administered must be known not to cause any clinically detectable pharmacological effect based on data available from published literature or other valid human studies. When research is proposed in pediatric subjects, the RDRC should consider data from a similar pediatric age group for evidence that the dose to be administered does not cause any clinically detectable pharmacological effect.

Risk assessment. Section 361.l(d)(5) refers to pediatric research that is "without significant risk." In 2001, FDA adopted 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations, as an interim final rule. These regulations do not use the term "without significant risk," but rather refer to "minimal risk" and "greater than minimal risk." Minimal risk is defined in§ 50.3(k) as "the probability and magnitude of harm or discomfort

anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

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. FDA recommends that risk assessment of proposed pediatric studies include consideration of the magnitude, probability, and duration of each protocol intervention, the age-related changes in risk profile, and factors such as the use of venipuncture (both the frequency and total blood volume needed for the study), the use of enclosed or confining equipment, the length of any proposed immobilization (including the possibility that the immobilization may be prolonged), concomitant medications, any additional protocol interventions, and the need for sedation (if any).

Quality of radioactive drug. In accordance with§ 361.l(d)(6), all radioactive drugs (PET and non-PET drugs) produced under an **RDRC** are required to" ... meet appropriate 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." Radioactive materials for parenteral use are required to be "prepared in sterile and pyrogen-free form."

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, by December 12, 2011, when CGMP regulations for PET drugs are adopted.

Because drugs produced under an **RDRC** are on a research scale, usually involve exposure of a limited number of subjects, are not used for purposes of defining the drug's safety or effectiveness, and are not used for patient management purposes, for non-PET drugs, manufacturers should comply with increasingly rigorous production requirements as more batches are produced for a greater number of subjects being exposed. This is consistent with the Agency's approach to CGMP compliance that mandates compliance with CGMPs that are appropriate for the product's stage of development. [4] For PET drugs, the Agency has proposed that a drug studied under an RDRC may be produced either in accordance with the requirements in the PET CGMP regulations or with the standards in USP Chapter <823> (70 FR 55038, September 20, 2005).

The RDRC is responsible for determining the appropriate production standards for meeting CGMP requirements and satisfying the requirements of§ 361.l(d)(6). FDA recommends that in making such determinations both the investigator and the RDRC use scientifically sound judgment and reference the relevant USP monographs for the performance of various operations and tests (e.g., USP <823>, USP <621> Chromatography, USP <821>

[4] The Agency has issued guidance for phase 1 CGMPs for non-PET drugs (http://www.fda.gov/downloads/Dmgs/GuidanceComplianceRegulat01ylnformation/Guidances/ucm070273.pqf).

Radioactivity, USP <71> Sterility Tests, USP <85> Bacterial Endotoxin Tests). For example, for the production ofRDRC research drugs where only one batch is produced, FDA recommends that a written procedure for the production be available and that a record on how the batch is produced, including the end-product testing results, be maintained. The analytical equipment should be calibrated to ensure reliability of the test results and the production should be conducted in an environment suitable for the intended use of the drugs. For a facility producing multiple research drugs, there should be procedures in place to prevent cross-contamination or other unintended consequences. State regulations may require specific controls over preparation of drugs containing radioactive material. The investigator and the institution are responsible for ensuring conformance to applicable state regulations.

Research protocol. Section 361.l(d)(7) requires that no study be conducted under§ 361.1 unless the RDRC concludes that scientific knowledge and benefit is likely to result from that study. Therefore, the investigator must:

- Provide a rationale for the research derived from appropriate animal studies or published literature.

- Provide a design of the study that will result in information of scientific value.

- Confirm that the radiation dose to research subjects is sufficient and no greater than necessary to obtain valid measurement.

- Verify that the number of research subjects is sufficient and no greater than necessary for the purpose of the study. The number of subjects must be limited to a number needed for basic research and not for immediate therapeutic, diagnostic, or similar purposes, or to carry out a clinical trial to determine the safety and effectiveness of the drug.

Adverse reactions. Section 361.l(d)(8) requires that the investigator immediately, but 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. That is, the RDRC need not confirm a causal relationship between the drug and the event, but a likelihood that the event and the use of the drug were related.

Approval by an IRB. Section 361. l(d)(9) requires that the investigator obtain IRB approval of the study protocol. IRBs are required to conduct continuing review ofresearch at intervals appropriate to the degree ofrisk, but not less than once a year(§ 56.109 (f)).

Labeling. The packaging, label, and labeling of the radioactive drug must be in compliance with Federal, state, and local laws on radioactive materials(§ 361.l(f)). The label of the immediate container and the shielded container, if any, must bear the following:

- The statement "Rx only"
- The statement "To be administered in compliance with the requirements of Federal regulations regarding radioactive drugs for research use (21 CFR 361.1)"
- The established name of the drug, if any
- The established name and quantity of each active ingredient
- The name and half-life of the radionuclide, total quantity of radioactivity in the drug product's immediate container, and amount of radioactivity per unit volume or unit mass at a designated referenced time
- The route of administration, if it is for other than oral use
- The net quantity of contents
- An identifying lot or control number from which it is possible to determine the complete manufacturing history of the package of the drug
- The name and address of the manufacturer, packer, or distributor
- The expiration date, if any
- If the drug is intended for parenteral use, a statement as to whether the contents are sterile
- If the drug is for other than oral use, the name of all inactive ingredients, except that trace amounts of harmless substances added solely for individual product identification need not be named
- If the drug is intended for parenteral use, the quantity or proportion of all inactive ingredients, except that those ingredients added to adjust pH or to make the drug isotonic may be declared by name with a statement of their effect. If the vehicle is water for injection, it need not be named.
- In the case of containers too small or otherwise unable to accommodate a label with sufficient space to bear all such information, the information required by paragraphs (f)(l) and (12) of this section may be placed on the shielded container only.

C. What Are the Pharmacological Dose Limits?

One of the conditions for research to be conducted under an **RDRC** is that the dose of the radioactive drug to be administered is not known to cause any clinical detectable pharmacological effect (§ 361.1(b)(2)). Although the term *clinically detectable pharmacological effect* is not defined under § 361.1, FDA's current recommendation is that a drug be considered to have a clinically detectable pharmacologic effect if any of the following occur:

- After the drug is administered, research subjects report symptoms in response to questions about how they are feeling.
- An adverse event occurs.
- A change outside the range of normal variation from baseline vital signs is observed (e.g., change in baseline systolic blood pressure, diastolic blood pressure, heart rate, temperature, mental status, or respiratory rate).
- Targeted monitoring based on the drug's pharmacology, such as blood testing, urine analysis, papillary reactions, or an EKG reveals a pharmacologic effect.

FDA does not regard effects such as changes in receptor binding visualized on PET scanning, with no associated changes to the above parameters, as clinically detectable pharmacological effects. The term No Observed Effect Level (NOEL) is sometimes used by pharmacologists to define that level below which there are no observed short-term pharmacological effects. Pharmacological doses below this NOEL are usually considered acceptable for **RDRC** research.

D. What Are the Radiation Dose Limits?

Under§ 361.l(b)(3)(i), Limit on radiation dose, the radiation dose to an adult research subject from a single study or cumulatively from a number of studies conducted within 1 year may not be generally recognized as safe if such dose exceeds the following:

Table 1: Limits on Radiation Dose for Adults

Organ or System	Single Dose Sieverts (Rems)	Annual and Total Dose Sieverts (Rems)
Whole body	0.03 (3)	0.05 (5)
Active blood-forming oreans	0.03 (3)	0.05 (5)
Lens of the eye	0.03 (3)	0.05 (5)
Gonads	0.03 (3)	0.05 (5)
Other organs	0.05 (5)	0.15 (15)

Individual Subjects. The radiation dose to an individual subject consists of the sum total of all sources of radiation associated with the research protocol including the following (§ 361.l(b)(3)(iii)):

- The radiation absorbed dose from the radioactive drug, which consists of the dose from the radionuclide associated with the drug and any significant contaminant or impurity;
- The radiation absorbed dose from any associated x-ray procedures (related procedures such as PET transmission scans, CT scans, and dual energy x-ray absorptiometry (DEXA) should also be included); and
- The radiation from any follow-up studies.

Pediatric Subjects. Section 21 CFR 361.l(b)(3)(ii) requires that the radiation limits for a research subject under 18 years of age at his or her last birthday not exceed 10 percent of the radiation values given above in Table 1, "Limits on Radiation Dose for Adults."

Studies with any purpose other than basic research, or basic research studies that do not meet the specified conditions listed in section III of this guidance, must be conducted under an IND (21 CFR part 312) unless they meet the conditions for IND exemption (21 CFR § 361.l(a)).

The questions and answers in Appendices A-D to this guidance are designed to provide more information about the requirements applicable to human research with radioactive drugs conducted under an RDRC.

IV. MONITORING

The Food and Drug Administration shall conduct periodic reviews of approved committees. Monitoring of the activities of these committee shall be conducted through reviews of committees' annual reports, through review of minutes and full protocols for certain studies, and through on-site inspections.

V. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). This guidance refers to previously approved collections of information found in FDA regulations. The collections of information for RDRC in 21 CFR 361.1 have been approved under OMB control number 0910-0053.

> An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0053. The current expiration date is available at https://www.reginfo.gov (search ICR and enter OMB control number).

APPENDIX A

BASIC SCIENCE RESEARCH USING RADIOACTIVE DRUGS

FREQUENTLY ASKED QUESTIONS

The recommendations in this appendix are based on§ 361.l(a), which states in part:

> Radioactive drugs ... are generally recognized as safe and effective when administered ... to human research subjects during the course of a research project intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes . . . Certain basic research studies ... may have eventual therapeutic or diagnostic implications, but the initial studies are considered to be basic research within the meaning of this section.

1. Is a separate IND needed to use a radioactive drug as a research tool in studies being conducted under an existing IND for therapeutic drug development? For example, could a radioactive drug be used to image a nonradioactive therapeutic drug's effects on an organ?

No, a separate IND is not needed for the radioactive drug if there is an existing IND and that IND is amended to label the drug with a radionuclide. This may be preferred because the IND already exists.

An alternative approach would be to conduct the study using the subject drug separately under the oversight of an RDRC if the data to be collected are basic science information and the study meets all of the conditions of§ 361.1. However, this assumes no pharmacologic effect for the study drug, and monitoring a therapy drug would most probably involve using a therapeutic dose, which would disqualify this from an **RDRC** study. If the RDRC conditions were met, and the studies were conducted under RDRC review, the results of the radioactive drug studies should be included in the IND of the nonradioactive drug that is being developed.

2. Is an IND needed if research using a radioactive drug starts out as basic science but then changes to clinical research?

Yes, an IND would be needed when research goals change to study the clinical safety or effectiveness of the radioactive drug. For example, the initial investigations to demonstrate the localization of a radioactive drug to a particular organ or fluid space and to determine the kinetics of that localization could be considered basic research. If all other conditions of§ 361.1 were met, those investigations could be conducted under an **RDRC.** If and when the basic science research evolves into a more formal clinical trial that expands beyond the conditions of § 361.1, it would have to be conducted under an IND. The IND could be submitted at the time that the basic research of the radioactive drug begins under§ 361.1.

3. I am not sure whether my research will evolve into drug development for use in a clinical setting. Should I submit an IND?

Yes. While early research objectives may be basic research and may or may not evolve into a formal clinical trial for safety and/or efficacy, if there is doubt as to whether the research is still basic science research, FDA recommends that the drug be studied under an IND.

4. If basic research with a radioactive drug does not meet RDRC conditions for pharmacological activity and/or radiation dose limits, but the radioactive drug is a simple, commonly used compound, is an IND needed?

Yes. If basic research with a radioactive drug does not meet ***all*** the conditions under§ 361.1, including limits on the pharmacological and radiation doses, the research may not be conducted under an **RDRC** and is subject to the IND regulations. However, some clinical investigations of a drug product that is lawfully marketed in the United States may be exempt from IND requirements under certain conditions (see § 312.2 (b), Exemptions).

5. *If research is being conducted to identify a radioactive drug to eventually be used in human therapy, diagnosis, or prevention trials, should the investigator begin by submitting an IND, or should an IND be submitted at the conclusion of the basic science studies?*

For the initial basic science studies meeting requirements of§ 361.1, the investigator has the choice of conducting the studies under the RDRC or under an IND. However, after these initial basic science studies are complete, an IND must be submitted to conduct clinical trials to determine the safety and effectiveness of the radioactive drug. One type of IND that is intended to be simpler than the traditional IND, the exploratory IND,[5] involves limited human exposure and may require less preclinical support than traditional IND studies.

6. Can I use a radioactive biological product as a radioactive drug under an RDRC?

Yes. The term *radioactive drug* includes radioactive biological products labeled with a radionuclide (21 CFR 310.3(n) and 600.3(ee)). Therefore, basic research studies with a radioactive biological product may be conducted under RDRC review if they meet all the requirements set forth in § 361.1. However, biological products (e.g., monoclonal antibodies and therapeutic proteins such as cytokine, interferon, interleukin, and enzymes) that are immunogenic proteins could potentially produce an antigenic response. Therefore, we recommend that only basic research with radioactive biological products that have been shown to have no immune response be conducted under § 361.1.

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[5] See the guidance for industry, investigators, and reviewers on Exploratory IND Studies (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulat01yinformation/Guidances/ucm078933.pc[). Please note that the Exploratory IND guidance does not apply to all drugs regulated by CDER and does not apply to CBER regulated drugs.

7. ***Where can I get information about submitting an IND?***

Information about the IND application process, including application forms, regulations, and guidance documents, is available online at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm or http://www.fda.gov/cber/manufacturer.htm. You can also call CDER's Division of Drug Information at 301-796-3400 or CBER's Office of Communication, Outreach, and Development, 301-827-2000 or 800-835-4709.

8. Does an existing IND for a nonradioactive investigational drug need to be amended if the drug is labeled with a radionuclide?

It would be preferable for an existing IND to be amended if the drug is labeled with a radionuclide, but this may not be required under certain circumstances. It would not be necessary to amend an existing IND if the investigator wanted to conduct the research under an **RDRC,** the radioactive form of the investigational drug met all conditions of§ 361.1, and the research was reviewed and approved by the **RDRC.** The results of the research should be submitted to the IND. If the RDRC requirements were not met (e.g., the research was not basic science in nature, or the pharmacological or radiation doses were not within the limits specified in § 361.1), an IND would be required. In that case, to use the radioactive form of the investigational drug, the existing IND would have to be amended, or a new IND submitted.

*9. **I have an unapproved radioactive drug that I want to use to monitor the progress of therapy in patients who are given various therapeutic drugs. Do I need to submit an IND?***

Yes. Because the imaging results from the radioactive drug will provide immediate diagnostic information about patients, this is not considered basic research and you will need an IND.

10. Should studies of radioactive diagnostic drugs be conducted under§ 361.1 (RDRC) or under§ 312 (IND)?

If the intent of the studies is to develop a diagnostic drug, an IND is appropriate. One of the requirements of§ 361.1 is that the research is not intended to determine the safety and effectiveness of the radioactive drug in humans as a therapeutic, diagnostic, or preventive medical product. This does not mean that initial basic research studies could not be done under an RDRC if they meet the requirements in § 361.1. However, once you intend to perform clinical trials to determine the safety and effectiveness of the drug for purposes of diagnosis, an IND will be required.

11. Is an IND needed for phase 1 and phase 2 clinical trials of a radioactive drug, even if the drug used is a labeled endogenous substance given in extremely low amounts?

Studies that explore the safety and effectiveness of a radioactive drug may not be conducted under RDRC review and must be conducted under an IND(§ 361.l(a)), even with compounds

endogenous to the body. The purpose of traditional phase 1 studies is to investigate safety parameters of a drug with respect to the dose, repeat doses, and escalating doses, while the main purpose of phase 2 studies is generally to demonstrate efficacy. Although most radioactive diagnostic drugs are considered safe because of their very low pharmacologic doses, they are not exempt from the IND requirements. Phase 1 trials for radioactive drugs are much simpler than traditional phase 1 trials, where determining drug toxicity is a major objective of the study.

An IND may not be necessary if the criteria for IND exemption (§ 312.2(b)) are met, or if all of the criteria of§ 361.1 are met. The research must be basic science in nature, and the endogenous substance, even if given in extremely low amounts, must show no clinically detectable pharmacological effect.

12. Can I use an unapproved radioactive drug if I use it for an occasional patient who may be difficult to diagnose, and I'm exploring whether this test is useful?

This type of study requires an IND because you cannot use an unapproved radioactive drug for diagnosis on humans without an IND.

13. Can I do research on radiolabeled endogenous peptides, such as neuropeptides, without an IND?

Yes, if the research is basic in nature, such as the studies of metabolism of a peptide, or its role in physiology, pathophysiology, or biochemistry, and conditions of§ 361.1 for pharmacologic dose and radiation are met. However, if the RDRC has doubts about the safety of doses being proposed for the study, or if the hypothesis is related to treatment, diagnosis, or prevention of a disease in patients, an IND is needed.

*14. **I have an unapproved drug, compound X, which could eventually be an antidepressant drug. I want to radiolabel compound X (for example, with 1-123, C-11, or F-18) to study its basic biodistribution, metabolism, receptor occupancy, and pharmacokinetic profile in normal human volunteers. Do I need to submit an/ND?***

Yes. If the study is intended to develop a diagnostic or therapeutic drug, the research must be conducted under an IND.

However, if the research is truly basic science research, it can still be initially investigated under an RDRC if all of the requirements of§ 361.1 are met. If previous human data regarding the pharmacologic dose of the unapproved drug are available, basic research involving isotopic substitution can be conducted under the RDRC mechanism. However, because the potential attachment of a non-isotopic radionuclide to this unapproved drug may change the biodistribution and other biological properties in humans, you will need to establish that the known pharmacological dose will not produce any clinically detectable pharmacological effect in humans(§ 361.l(b)(2)). This will require an IND, unless such information for this specific radiolabeled drug is already available.

15. I want to radiolabel an approved anti-tumor drug for imaging studies either by isotopically substituting a radioactive element for the nonradioactive element (e.g., radioactive F-18 is substituted for the nonradioactive F-19) or by adding a radionuclide that was not part of the original chemical structure. Can I use the RDRC mechanism, or do I need an IND to image tumors or to monitor the progress of therapy in humans?

This proposed investigation would probably require an IND. First, the dose of an approved anti-tumor drug will probably have a pharmacological effect, disqualifying it from **RDRC** research. If, however, low doses will be administered which are known to have no pharmacological effect, the RDRC mechanism could be used.

The second issue is with the actual chemical structure of the tested drug. Basic science research involving isotopic substitution can be conducted under the RDRC mechanism, where one substitutes an isotope of the same element for another isotope without altering its chemical structure. Substituting one element for another, however, will change the chemical structure of the drug, and may result in differences in the biodistribution and other biological properties from the original drug in humans. You will therefore need to establish that the known pharmacological dose of this new radiolabeled drug does not produce any clinically detectable pharmacological effect in humans. If previous human data based on information available from published literature or from other valid human studies is not available, you must conduct the research under an IND.

Under an **RDRC,** you may investigate whether there are changes in the distribution of the radioactive drug before and after therapy. However, if you plan to use the imaging results to make decisions on initiating or modifying therapy in the patients who are being imaged, those studies must also be conducted under an IND, unless they meet the conditions for IND exemption.

16. The compound that I want to radiolabel is an approved drug or endogenous substance. I want to investigate the potential use of this compound for imaging tumors by attaching to the molecule a radionuclide for which there is no corresponding nonradioactive atom of the same element (e.g., adding F-18 to estradiol). Can I use the RDRC mechanism, or do I need an IND?

To be eligible for **RDRC** review, the total pharmacologic dose administered, labeled and unlabeled, must be known not to cause any clinically detectable effect in humans. Therapeutic doses cannot be used.

Basic research involving isotopic substitution can be conducted under the RDRC mechanism; however, the attachment of a non-isotopic radionuclide (i.e., a different element) to the drug may change the biodistribution and other biological properties of the original substance in humans. Consequently, to conduct the study under the **RDRC,** you will need to establish that the known pharmacological dose of the specific substituted radiolabeled drug does not produce any clinically detectable pharmacological effect in humans. Knowledge of no clinically detectable pharmacological effect must be based on prior data available from published literature or from

other valid human studies(§ 361.l(d)(2)). ***If previous human data are not available, you must first conduct this human research under an IND.***

If you are studying the basic distribution of the radioactive drug to the tumor site, then the RDRC would be an appropriate mechanism, assuming that other conditions under § 361.1 are met. When you are ready to evaluate the use of imaging with this radioactive drug to guide therapy, you must conduct the study under an IND.

17. Can research using cold isotopes (nonradioactive, stable isotopes such as deuterium and 13-Carbon) be conducted under§ 361.1?

No, § 361.1 does not apply to nonradioactive drugs.

18. Do positron emission tomography (PEI) drugs need INDs?

If your PET drug meets all criteria of§ 361.1, you do not need an IND. Drugs labeled with positron emitting radionuclides are not treated any differently than drugs labeled with any other radionuclides, as long as the requirements in§ 361.1 are met.

APPENDIXB

RADIOACTIVE DRUG RESEARCH COMMITTEE

FREQUENTLY ASKED QUESTIONS

The guidance in this appendix is based on§ 361.l(b)(l), which states in part:

> A Radioactive Drug Research Committee, composed and approved by the Food and Drug Administration ... has determined ... that the pharmacologic dose is within (specified) limits ... the radiation dose is within [specified] limits ... the study meets the other requirements ... regarding qualifications of the investigator, proper licensure for handling radioactive materials, selection and consent ofresearch subjects, quality of radioactive drugs used, research protocol design, reporting of adverse reactions, and approval by an appropriate Institutional Review Committee ... [and] the use of the radioactive drug in human subjects has the approval of the Radioactive Drug Research Committee.

1. How can I find out whether my institution has an FDA-approved RDRC?

Your **IRB** may know if your institution has an FDA-approved **RDRC.** You can also consult CDER's Division of Medical Imaging (ODE IV) or CBER's Office of Communication, Outreach, and Development, CBER, 301-827-2000 or 800-835-4709.

*2. Can my **RDRC approve basic research studies conducted at another medical institution?***

Your RDRC may review and approve RDRC studies conducted at another medical institution if that institution is affiliated with your medical institution or if your RDRC is an FDA-approved joint RDRC involving the two medical institutions. Under§ 361.l(c)(l), joint RDRCs involving more than one medical institution are acceptable in order to achieve a high level and diversity of expenence.

3. How do I establish a joint RDRC?

The process for establishing a joint RDRC is the same as that for a single **RDRC** (i.e., an application must be submitted to and approved by FDA). The joint RDRC functions as a single **RDRC** and is responsible for approving and monitoring all RDRC studies conducted at either institution, holding joint quarterly meetings, and submitting joint reports to FDA (see Appendix E for more details on submitting an application and on **RDRC** responsibilities).

4. What is the difference between an RDRC and a Radiation Safety Committee?

A Radiation Safety Committee **(RSC)** is mandated by various Federal, state, and local agencies for the purpose of ensuring the safety of an institution's overall program for the use of radioactive materials and radiation producing equipment.

An **RDRC** is mandated and approved only by FDA for the specific purpose of approving and monitoring basic human research studies using radioactive drugs under the conditions set forth in § 361.1. A medical institution may involve its RDRC in other matters, such as the review of institutional radiation safety issues or the review of research conducted under an IND, but FDA regulations do not require that **RDRCs** perform such activities.

5. *Do I have to be physically present at the required quarterly meetings of the RDRC?*

Section 361.l(c)(2) requires that a quorum consisting of more than 50 percent of the RDRC members be present at the quarterly meetings, with appropriate representation of the required fields of specialization. If **RDRC** members are unable to be physically present at these meetings, members can attend via teleconference or videoconference.

6. How long will it take the RDRC to review my study?

This depends entirely on your local RDRC's administrative procedures. We recommend that you check with your **RDRC** about this.

7. *Will my study need to be approved by both my RDRC and IRB?*

Yes. Section 361.l(d)(9) requires that all research on human subjects under an **RDRC** also have **IRB** approval.

8. If my study meets all the requirements in§ 361.1, do I need an IND?

If your study meets the requirements of§ 361.1 as determined by your **RDRC,** this means your study does not need an IND. However, your **RDRC** may prefer that your study be conducted under an IND for a variety of medical, ethical, or legal reasons, and may not approve your study under the RDRC authority.

9. If the RDRC does not approve my study, do I need an IND?

If your study does not meet the requirements of § 361.1 as determined by your **RDRC,** your study must be conducted under an IND unless it meets the conditions for IND exemption (§ 312.2(b)).

10. How many subjects can I enroll in my study under an RDRC?

Please refer to section **111.B,** What Are the Study Criteria for Research Conducted Under an **RDRC,** Human Research Subjects, (2) Number of subjects, for additional information.

11. Can I enroll pregnant women in my study for my basic research under an RDRC?

No. For a more detailed discussion please see section **111.B,** What Are the Study Criteria for Research Conducted Under an **RDRC,** Human Research Subjects, (3) Women of childbearing potential, for additional information.

12. Are studies involving pediatric subjects appropriate under an RDRC?

Although RDRC research subjects generally must be 18 years of age or older, exceptions are permitted in special situations. Please refer to section **111. B,** What Are the Study Criteria for Research Conducted Under an **RDRC,** Human Research Subjects, (4) Pediatric subjects, for additional information.

13. What type of quality standards should be considered for the production of radioactive drugs under RDRC?

Please refer to section **111.B,** What Are the Study Criteria for Research Conducted Under an **RDRC,** Quality of Radioactive Drug, for additional information.

14. How does FDA determine that the RDRC is in compliance with§ 361.1?

FDA's review of the RDRC annual reports and FDA inspections are two ways FDA reviews an RDRC's compliance with the regulations specified in § 361.1. RDRCs are required to submit annual reports to the FDA on or before January 31 of each year(§ 361.1(c)(3)). The report must contain a description of each study conducted during the previous year. This report must be signed by the investigator and the Chair of the RDRC. FDA's review of the reports will help to determine the RDRC's compliance with the regulations. If significant discrepancies are noted during this review, FDA can request additional information from the RDRC, such as copies of meeting minutes or a specific research protocol.

FDA can also conduct an on-site inspection of the RDRC's operations(§ 361.l(c)(S)). The inspection may be done as part of routine surveillance or conducted secondary to a concern (i.e. "for-cause" inspection). This inspection will include an assessment of the RDRC's compliance with the regulatory requirements under § 361.1.

APPENDIXC

LIMITS ON THE PHARMACOLOGICAL DOSE

FREQUENTLY ASKED QUESTIONS

The guidance in this appendix is based on§ 361.l(b)(2), Limit on pharmacological dose which states in part:

> Limit on pharmacological dose. The amount of active ingredient or combination of active ingredients to be administered shall be known not to cause any clinically detectable pharmacological effect in human beings.

1. ***If I use an approved drug in doses stated in the drug package insert's Dosage and Administration section, and radiolabel it for clinical research on diseases other than those stated in the Indications and Uses section of the insert, do I need an IND?***

Yes, because an approved drug may likely cause a clinically detectable pharmacological effect, an IND would probably be needed, unless your study meets the conditions for IND exemption (§ 312.2(b)) or the requirements for research under an **RDRC** as defined in§ 361.1.

You can refer to http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucml84426.htm or contact FDA's Office of New Drugs (OND) for referral to the appropriate drug product division within CDER, or you can refer to http://www.fda.gov/AboutFDA/CentersOffices/CBER/default.htm or contact the Office of Communication, Outreach, and Development (OCOD) for referral to the applications division of the appropriate review office in CBER, based on the new indication, to discuss your research proposal.

2. ***If I use an approved diagnostic radioactive drug in doses stated in the drug package insert's Dosage and Administration section for research on biodistribution to obtain basic information on diseases other than those stated in the Indications and Uses section of the insert, do I need an IND?***

No. If the mass dose stated on the package insert does not elicit a clinically detectable pharmacological effect, often the case for diagnostic radioactive drugs, an IND is not needed, as long as you meet all the other conditions under§ 361.1. However, if the mass dose indicated on the package insert does elicit a pharmacological effect, then for qualification under § 361.1 a mass dose that does not elicit a pharmacological would have to be used.

3. ***Under what circumstances can I use doses of a radioactive drug that have a pharmacological effect for studies of basic research, metabolism, and pharmacokinetics, and not need an IND for the radionuclide study?***

There are no such circumstances. If your radioactive drug has a clinically detectable pharmacologic effect, your studies will not meet the requirements of§ 361.1, and you will need an IND.

4. If the mass dose of the unapproved radioactive drug I'm planning to study has a pharmacological effect, what should I do?

You will need to submit an IND. You can contact OND for referral to the appropriate drug product division within CDER, or OCOD for referral to the applications division of the appropriate review office in CBER to discuss your research proposal.

5. *Must I conduct dose-response studies to support no clinically detectable pharmacological effect?*

No, there is no requirement for a formal dose-response study to define the lower threshold for a clinically detectable pharmacological effect. For example, if the circulating blood levels or excretion rates of endogenously produced substances are well known, it may be possible for the **RDRC** to conclude that some small fraction of these levels or rates of administration (e.g., administration over a given interval of a low percentage of amount of a substance that is produced endogenously during the same interval) represents an amount without detectable pharmacological effect. Or, if large amounts of substances such as amino acids or sugar are regularly consumed as foodstuffs, it may be possible for the RDRC to conclude that a small amount of it (e.g., a small percentage of the amount usually consumed during a meal), at least by the oral route, would be without detectable pharmacological activity.

APPENDIXD

LIMITS ON THE RADIATION DOSE

FREQUENTLY ASKED QUESTIONS

The guidance in this appendix is based on§ 361.l(b)(3), Limit on radiation dose, which states in part:

> Limit on radiation dose. The amount of radioactive material to be administered shall be such that the subject receives the smallest radiation dose with which it is practical to perform the study without jeopardizing the benefits to be obtained from the study.

1. How do I determine the actual radiation dose for each individual subject?

In many cases, the actual individual radiation dose can only be estimated using standard adult and child reference models published by organizations such as the Society of Nuclear Medicine's **(SNM)** Medical Internal Radiation Dosimetry **(MIRD)** Committee, the British Health Protection Agency (formerly the National Radiological Protection Board **(NRPB))** for x-ray sources, including CT, and the FDA for conventional x-ray.

FDA believes that the determination of radiation dose to specific tissue or organs using currently accepted methods, such as the system set forth by the MIRD Committee, or the system set forth by the International Commission on Radiological Protection **(ICRP),** is sufficiently accurate for estimating radiation risk from radiolabeled drugs used in RDRC research. Although there are inherent limitations because of differences between standard reference models and actual human subject size and organ geometries, the risks associated with these low radiation doses are sufficiently low that the uncertainty associated with these estimates is acceptable for **RDRC** research. ***However, these methods alone are insufficient for the determination of radiation doses for radiotherapeutic purposes. The variation and uncertainty in patient specific anatomies, and the complexity of the pharmacokinetics and dosimetries, preclude using such standard models for radiotherapeutic purposes.***

2. Where can I find the reference documents and software for determining radiation dose?

Major organizations that have generated original organ dose tables are listed below.

Radioactive drugs

The MIRD Committee has developed and compiled methods for calculating internal radiation dosimetry of distributed radionuclides in humans including agents used for radiotherapy. This committee has published and continues to publish a series of publications available at http://interactive.snm.org/index.cfm?PageID=2l99&RPID=l372.

The ICRP has published a series ofreports numbered 53, 62, 80, and 106, on organ doses from radioactive drugs. These reports are periodically updated and available in the journal, *Annals of the ICRP*. The ICRP also publishes drafts of future reports for review and comment by the public. The ICRP Web site address is http://www.icrp.org and the ICRP publications are available at http://www.icrp.org/intrep.asp.

Associated procedures (X-ray and computed tomography)

The Food and Drug Administration has published a series of six handbooks on organ doses from x-ray plus a software program available at http://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/Medicallmaging/MedicalX-Rays/ucml 17898.htm

The British Health Protection Agency now includes organizationally what was formerly the NRPB. The Health Protection Agency has published a series of publications and related software for the determination of radiation dose from x-ray and computed tomography (CT). These are available either free or for a nominal charge. The Web site address is http://www.hpa.org.uk/radiation/. The related software to calculate radiation doses from x-ray and CT for adult and pediatric subjects is located at: http://www.hpa.org.uk/radiation/publications/software/index.htm and http://www.impactscan.org/ctdosimetry.htm.
The German National Research Center for Environment and Health (Gesellschaft for Strahlen-und-Umweltforschung, GSF) has published a series of radiation organ dose publications and is actively involved in research in development of a variety of human voxel phantoms for Monte Carlo organ dose calculations for the ICRP. The GSF Web site address is

http://www.helmholtz-muenchen.de/en/start/index.html

The Finnish Radiation and Nuclear Safety Authority (STUK) has also published a report and has available a Monte Carlo based program, PCXMC, for calculating organ doses from medical x-ray examinations. The Web site is:

http://www.stuk.fi/en_GB/

Other sources
There continues to be active research in this area, including university and commercially available services, publications, and software. Because research in this area is ongoing, it is the responsibility of the RDRC to verify that the methods and references used are current, relevant, and scientifically credible.

In the past, Oak Ridge Associated Universities had a program for dosimetry from medical isotopes, but that program ceased to exist several years ago due to lack of funding. However, two Web sites that are excellent gateways to the most current research and information in this area are the **Radiation Dose Assessment Resource (RADAR) site, located at:**

http://www.doseinfo-radar.com/RADARphan.html

and the Consortium of Computational Human Phantoms (CCHP), located at:

http://www.virtualphantoms.org/

3. What if there are no published reference data for calculating organ doses for the radioactive drug I am using?

When there is no published reference literature, you may provide a specific reference to unpublished data, along with a listing of your assumptions for your specific study in the annual report to FDA

If there is insufficient human biodistribution or pharmacokinetic data, absorbed dose calculations may be based upon animal data extrapolated to humans to approve the proposed research study. However, FDA recommends that the RDRC require investigators to verify this information in humans by carrying out dosimetry calculations on the first 5-10 subjects enrolled in the proposed research study and begin using the human biodistribution data for subsequent calculations. FDA prefers clinical data.

4. How do I report the radiation dose for each individual subject in my annual report to FDA?

Radiation dose must be reported as the organ dose for select organs and as a whole body dose, as specified in§ 361.l(b)(3)(i) (see Table 1, Limits on Radiation Dose for Adults, of this guidance). Since the promulgation of§ 361.1 in 1975, the ICRP has defined effective dose (E) to equate partial body doses to a whole body dose. Therefore, the whole body dose may be reported as E in the annual report to FDA using the most current tissue weighting factors published by the ICRP. However, individual organ doses must still be reported. Administered radioactivity is not radiation absorbed dose.

5. *What units should I use/or reporting radiation dose in my annual report to FDA?*

FDA prefers that radiation be reported using the International System of Units **(SI),** Becquerels for radioactivity, Gray for the physical concept of dose, and Sieverts for the biologically equivalent dose.

Units of Radioactivity

Becquerel (Bq) = 1 disintegration per second
Curie= 3.7×10^{10} disintegrations per second= 3.7×10^{10} Bq
1 mCi = 37 MBq

Units of Physical Absorbed Dose

Gray (Gy) = **1** joule of energy absorbed per **1** kilogram of mass
Gray = 100 rads
mGy = 100 mrads

Units of Biologically Equivalent Dose

Sievert (Sv), the biologically equivalent dose, obtained when the physical dose, in Gray, is modified by a radiation weighting factor, WR, previously known as a quality factor, which varies depending on the type and energy of the radiation. This is usually **1** for gamma, x-ray, and electron energies, but varies significantly for some particulate radiations such as alpha and neutron radiations.

Sievert= 100 rems
mSv = 100 mrem

Since the radiation weighting factor, WR, is usually **1** for gamma and x-ray photons, typically the primary types of radiation used in medicine, the terms are often used interchangeably. A 10 mGy **(1** rad) x-ray or gamma ray dose is sometimes referred to as a 10 mSv **(1** rem) dose. A 10 mGy **(1** rad) dose of alpha or neutron radiation will result in a much higher equivalent dose, depending on the quantity ofwR. If WR is 10, then the corresponding equivalent dose will be 10 times the absorbed dose in Gy (rads) (e.g., **1** Gy (100 rad)= 10 Sv (1000 rem)).

APPENDIXE

THE RADIOACTIVE DRUG RESEARCH COMMITTEE (RDRC):

MEMBERSHIP, FUNCTIONS, REPORTS, AND MONITORING

A. Approval by FDA

An FDA-approved **RDRC** is one that fulfills the requirements for membership, function, reporting, is subject to monitoring by FDA as specified in§ 361.l(c)(l)-(5), and has submitted an application that FDA has determined has met these criteria.

Under§ 361.l(c)(4), Approval, an application must be submitted to and approved by FDA before an **RDRC** may approve research studies under § 361.1. The application must include:

- The names and qualifications of the proposed **RDRC** members (see Form FDA 2914 -Radioactive Drug Research Committee **(RDRC)** Report on Research Use of Radioactive Drugs--Membership Summary)

  and

- A statement that the RDRC agrees to comply with the requirements set forth in § 361.1

The application should include a current and dated curriculum vitae (CV) for each proposed member and a brief summary statement describing each member's specific training and experience relative to one of the three required committee positions. The specific training and experience suggested for each committee position is described in the **Membership** section below.

Approval is based upon an assessment of the qualifications of the members of the RDRC and the assurance that all necessary fields of expertise are covered. Approval will remain in effect unless and until FDA withdraws such approval. Approval of an **RDRC** may be withdrawn at any time for failure of the RDRC to comply with the requirements in§ 361.1.

B. Membership

An RDRC must consist of at least **five individuals(§** 361.l(c)(l)). These five members must include:

(1) **A physician recognized as a specialist in nuclear medicine.** This requirement should be met by a physician with substantial training and experience in nuclear medicine or certification by the American Board of Nuclear Medicine or certification or eligibility for board certification by the American Board of Radiology, the American Board of Pathology, or the American Board of Internal Medicine, and appropriate additional training and experience in nuclear medicine.

(2) **A person qualified by training and experience to formulate radioactive drugs.** The requirement could be met by a board certified nuclear pharmacist or a pharmacist with special training and 2 years' experience in the formulation and quality control of radioactive drugs, or a chemist holding a graduate degree who can adequately demonstrate an association with a clinical medical program and who has 2 years' experience in the formulation and quality control of radioactive drugs.

(3) **A person with special competence in radiation safety and radiation dosimetry.** This requirement should be met by a medical physicist or scientist with training in radiation safety and substantial experience in calculating organ doses from radiopharmaceuticals and x-ray sources.

(4) **Individuals qualified in various disciplines pertinent to the field of nuclear medicine** (e.g., radiology, internal medicine, clinical pathology, hematology, endocrinology, radiation therapy, radiation physics, radiation biophysics, and radiopharmacy). We recommend that a clinical pharmacologist be a member of the **RDRC.**

Other considerations:

Under§ 361.l(c)(l), membership must be sufficiently diverse to permit expert review of technical and scientific aspects of protocols. Although one individual may have expertise in more than one category, an individual should only represent one category for the review of protocols. The addition of consultants in pertinent medical disciplines may help to provide oversight for specific studies (e.g., pediatric specialist). Administrative or management personnel may be included as non-voting members of the **RDRC.** These members should be listed in the "Non-Voting Members" section of Form FDA 2914.

C. Functions

Approval of Research Studies

The RDRC is responsible for the review of basic science research protocols subject to§ 361.1, Radioactive drugs for certain research uses. Approval of a research study by the RDRC is based upon consideration of the following requirements and the assurance that each is met.

Under§ 361.l(a), research conducted under an **RDRC** must be basic science research that is:

(1) Intended to obtain basic information about the metabolism (including kinetics, distribution, dosimetry, and localization) of the radioactive drug or about human physiology, pathophysiology, or biochemistry

(2) **Not** intended for immediate therapeutic, diagnostic, or similar benefit to the research subject from the research

(3) **Not** intended to determine the safety and effectiveness of the radioactive drug in humans for such purposes

- To be approved, the research protocol must meet the following requirements:

(1) Radiation dosimetry parameters are as low as practicable to perform the study and meet the criteria of§ 361.l(b)(3) (§ 361.l(d)(l)).

(2) The amount of active ingredient is known not to cause a clinical detectable pharmacological effect based on published data from human studies cited in the protocol(§ 361.l(d)(2)), or from other valid human studies.

(3) The study investigators are qualified by training and experience to conduct the study (§ 361.l(d)(3)).

(4) The medical facility is properly licensed to possess and handle radioactive materials (§ 361.l(d)(4)).

(5) The selection and consent ofresearch subjects is appropriate (i.e., age limitations and pregnancy exclusion)(§ 361.l(d)(S)).
- Research in subjects less than 18 years of age is permitted if the study presents a unique opportunity to gain information not currently available, requires the use of research subjects less than 18 years of age, and is without significant risk to the subjects. The radiation dose limit for subjects less than 18 years is 10 percent of that specified for adults (§ 361.l(b)(3)(ii)).
- Female research subjects of childbearing potential must state in writing that they are not pregnant, or pregnancy must be ruled out by a pregnancy test. We recommend the latter.

(6) The quality of the radioactive drug to be administered meets appropriate standards (i.e., pyrogen and sterility testing, radiochemical and radionuclidic purity), as needed for safety, and be of such uniform and reproducible quality as to give significance to the research study conducted(§ 361.l(d)(6)).

(7) The research protocol design has scientific worth and is based on a sound rationale (§ 361.l(d)(7)).

(8) The protocol includes provisions for the reporting of adverse events to the RDRC and then immediately, but no later than 7 calendar days, to FDA(§ 361.l(d)(8)).

(9) The protocol receives concurrent approval by an appropriate institutional review board **(IRB)** (§ 361.l(d)(9)).

Administrative Functions(§ 361.l(c)(2))

Chairperson

The members of the RDRC select a chairperson. The chairperson signs all applications, minutes, and reports of the RDRC.

Meetings

Meetings must be held by the RDRC at least once in each quarter in which research activity has been authorized or conducted.

(1) A quorum consisting of more than 50 percent of the members must be present at the meetings, with appropriate representation of the three required fields of specialization. If **RDRC** members are unable to be physically present at the meetings, attendance can be accomplished through teleconference or videoconference.

(2) No **RDRC** member may vote on a protocol in which he/she is an investigator.

(3) In addition to discussion of new protocols, meetings should include discussion of ongoing studies to ensure that they do not evolve into research projects that no longer meet the criteria for approval under an **RDRC.**

(4) The quarterly meeting may be canceled if in the quarter all of the following conditions have been met:

- No subjects have been admitted to any of the approved studies.
- No progress reports have been received on ongoing studies.
- No reports of adverse reactions have been submitted.
- No protocol amendments have been submitted for approval.
- No responses are due on committee recommendations or questions concerning pending research protocols.
- No new protocols have been submitted.

The RDRC records should document the reason for cancellation.

Minutes

The RDRC must keep minutes, which must include the numerical results of votes on new protocols involving human subjects(§ 361.l(c)(2)). Minutes should also identify abstentions and record the reasons for abstaining or for non-approval of new protocols.

Minutes should include discussion of the criteria for the evaluation of new protocols.

Reports

Annual Report(§ 361.l(c)(3)). The RDRC must submit an annual report to FDA on or before **January 31st** of each year. The annual report includes:

- The names and qualifications of the members of the RDRC and of any consultants used by the RDRC (Form FDA 2914) and
- A summary of study information for each study conducted during the preceding year (see Form FDA 2915 - Radioactive Drug Research Committee **(RDRC)** Report on Research Use of Radioactive Drugs--Study Summary)

A current and dated CV for each member and consultant listed on Form FDA 2914 should be included. If there are no changes to the CV from a previous submission, reference to the date the CV was previously submitted can be provided.

Information for each research study conducted during the reporting period should be provided on a separate Form FDA 2915.

Special Summary(§ 361.l(c)(3))

The RDRC must immediately, but no later than 7 calendar days, submit a special summary (using Form FDA 2915) to FDA at the time a proposal is approved that involves:

- More than 30 research subjects (or when a previously approved protocol is expanded to include more than 30 subjects)
  or
- Exposure to a research subject less than 18 years of age.

The special summary should include a justification for the number of subjects or for the inclusion of subjects less than 18 years of age. Studies involving minors are subject to dose limitations as specified in§ 361.l(b)(3) and must be supported with review by a qualified pediatric consultant to the RDRC (§ 361.l(d)(5)).

The special summary should be submitted immediately, but no later than 7 calendar days, of the approval to FDA by the **RDRC.**

Changes in Membership(§ 361.l(c)(4)). Changes in membership and applications for new members (Form FDA 2914) must be submitted to FDA as soon as, or before, vacancies occur and new members are appointed to the RDRC. The chair should notify FDA before new members assume Committee responsibilities so that FDA can review the qualifications of the members. If the RDRC membership has not been approved by FDA, the RDRC cannot function in accordance with 21 CFR 361.1

APPENDIXF

RDRC REVIEW CRITERIA CHECKLIST

To approve a proposed research study, the RDRC must, at a minimum, consider the following: Note: This checklist is not intended to be a substitute for consideration of each provision of 21 CFR 361.1 and all other applicable regulatory provisions.

	YES	NO	*NIA*
1. Is the pharmacological dose within the following limits?			
The amount of active ingredient or combination of active ingredients shall be known not to cause any clinically detectable pharmacological effect in humans.			
Sufficient documentation provided.			
2. Were pharmacological dose calculations based on data available from published literature or from other valid human studies?			
3. Is the radiation dose within the following limits?			
A Subject must receive the smallest radiation dose practical to perform the study.			
Absorbed dose calculations based on biologic distribution data available from published literature or from other valid studies was provided.			
An acceptable method of radioassay of the radioactive drug prior to its use provided.			

Adequate and appropriate instrumentation for the detection and measurement of the specific radionuclide will be used.			
The radioactive drug has the combination of half-life, type of radiation, radiation energy, metabolism, and chemical properties that result in the lowest dose to the whole body or specific organs sufficient to obtain the necessary information.			
B. For adult subject: Under no circumstances may radiation dose from a single study or cumulatively from a number of studies conducted within 1 year exceed:			
Whole body, active blood-forming organs, lens of eye, and gonads:			
Single dose 30 mSv (3 Rems)			
Annual & total dose 50 mSv *(5* Rems)			
Other organs:			
Single dose 50 mSv (5 Rems)			
Annual & Total Dose 150 mSv (15 Rems)			
C. For subject under 18 years of age: Radiation dose may not exceed 10 percent of dose set forth above.			
D. When determining total radiation doses and dose commitments must consider:			
All radioactive material included in drug, either as essential material or as significant contaminant or impurity.			
X-ray procedures that are part of the research study.			
Possibility of follow-up studies.			
Sufficient documentation provided.			
4. Is the radiation exposure justified by the quality of the study being undertaken and the importance of the information it seeks to obtain?			

5. Is the investigator's or institution's license to handle radioactive materials appropriate? Does the investigator meet the following requirements?			
The investigator or institution shall be licensed by the Nuclear Regulatory Commission, an Agreement State, or other appropriate authorities to possess and use the specific radionuclides for research use, or the investigator shall be listed as an authorized user under an institutional broad license.			
6. Is the use of human subjects appropriate and does it meet the following requirements?			
A Number of subjects should not exceed 30.			
B. Research must be reviewed and approved by an institutional review board and consent must be obtained from the subjects or their legal representatives.			
C. Research subjects must be at least 18 years of age and legally competent.			
D. Exceptions to preceding requirement only permitted if:			
Investigator can demonstrate that the study (1) presents a unique opportunity to gain information not currently available, (2) requires use of subjects less than 18 years of age, and (3) is without significant risk to subjects.			
RDRC review is supported with review by qualified pediatric consultant.			
E. Female subjects of childbearing potential must (1) state in writing that they are not pregnant or (2) be confirmed as not pregnant on the basis of a pregnancy test.			
7 **. Were the radioactive materials for parenteral use prepared in sterile and pyrogen-free form?**			

8. Is the research design appropriate in that:			
A Scientific knowledge and benefit is likely to result from the study and the research shall be based upon sound rationale derived from appropriate animal studies or published literature.			
B. Scientific knowledge and benefit are of sound design, so that information of scientific value may result.			
C. The radiation dose will be sufficient and no greater than necessary for purpose of the study.			
D. The projected number of subjects shall be sufficient and no greater than necessary and should reflect the fact that the study is intended to obtain basic research information and not intended for other purposes.			
9. **Is the packaging, label, and labeling of the radioactive drug in compliance with Federal, State, and local law regarding radioactive materials?**			
10. Is the label of the immediate container and shielded container, if any, in compliance with the requirements for drugs studied under RDRC review?			