Approval of Radiotracers for Dementing Diseases
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Director of Nuclear Medicine
University of Utah School of Medicine

Director: Molecular Imaging Program
Huntsman Cancer Institute

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Diagnostic Imaging Agents

- Contrast Agents for CT of MRI
- US contrast agents
- Optical Imaging Agents
- Nuclear Medicine Imaging Agents
- PET Imaging Agents
The Imaging Agent Development Process


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Imaging Agent Development Process - Radiopharmaceuticals

Phase II studies → Phase III pivotal studies → NDA submitted

Phase I study → IND submitted

Animal Dosimetry studies → Pharm tox studies

Pre-clinical animal testing → Final Synthesis optimization

Target Identification → Synthesis of several candidate probes

Synthesis optimization → Lead candidate via in-vitro studies

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Medical imaging agents generally are governed by the same regulations as other drugs or biological products. However, because medical imaging agents are used solely to diagnose and monitor diseases or conditions as opposed to treat them, development programs for medical imaging agents can be tailored to reflect these particular uses.
FDA Guides the Process

• Specifically, the FDA has finalized three guidance documents which discuss and elaborate on recommendations on selecting and studying clinical indications for medical imaging agents administered in vivo.
The Design of Imaging Agent Clinical Trials

Guidance for Industry
Developing Medical Imaging Drug and Biological Products

Part 1: Conducting Safety Assessments

Part 2: Clinical Indications

Part 3: Design, Analysis, and Interpretation of Clinical Studies

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FDA Guides the Process

- These guidance documents are intended to assist developers of medical imaging drug and biological products (medical imaging agents) in planning and coordinating their clinical investigations and preparing and submitting investigational new drug applications (INDs), new drug applications (NDAs), biologics license applications (BLAs), abbreviated NDAs (ANDAs), and supplements to NDAs or BLAs.
Guidance for Industry:
New Contrast Imaging Indication
Considerations for Devices and Approved Drug and Biological Products

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products (OCP) in Office of Commissioner
Center for Devices and Radiological Health (CDRH)
Center for Drug Evaluation and Research (CDER)

September 2008

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• The Food and Drug Administration (FDA) issued regulations establishing the Current Good Manufacturing Practices (CGMP) for positron emission tomography (PET) drugs.

• The regulations in new 21 CFR Part 212 apply to the production, quality control, holding, and distribution of PET drugs. The regulations ensure that PET drugs are of the highest quality and will meet the requirements of the Federal Food, Drug, and Cosmetic Act (the Act) regarding safety, identity, strength, quality, and purity.

• In conjunction with the final rule, the FDA also announced the availability of a guidance entitled PET Drugs — Current Good Manufacturing Practice (CGMP). The guidance provides information about approaches to comply with the regulations.
PET CGMP Regulations 12/9/09

Guidance

PET Drugs — Current Good Manufacturing Practice (CGMP)


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The Imaging Agent Development Process

- Typically, during imaging agent development, several candidate molecules are generated in very small quantities with the goal of identifying the most promising candidates for further development.
- These molecules are generally related in some way, either as a single active ingredient with multiple salts or esters, or closely related active moieties.
The Imaging Agent Development Process

• Promising candidates are then selected using in vitro testing models that examine binding to receptors, effects on enzyme activities, toxic effects, or other in vitro pharmacological parameters.

• Candidates that are not rejected during these early tests are prepared in greater quantities for in vivo animal testing for safety and efficacy.

• Commonly, a single candidate is selected for an Investigational New Drug (IND) application and introduction into human subjects, often healthy volunteers.
Pre-clinical Animal studies

• Typically done in mice or rat model if available
• For many brain imaging compounds non-human primates are used
• Rules and regulations via local Institutional Animal Care and Use Committee (IACUC) – rules may vary
Pre-clinical Animal studies

- The Animal Welfare Act was signed into law in 1966
- It is the only Federal law in the United States that regulates the treatment of animals in research, exhibition, transport, and by dealers
- Other laws, policies, and guidelines may include additional species coverage or specifications for animal care and use, but all refer to the Animal Welfare Act as the minimum acceptable standard
- The Act was amended six times (1970, 1976, 1985, 1990, 2002, 2007) and is enforced by the USDA, APHIS, Animal Care agency

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Pre-clinical Animal studies

• The Institutional Animal Care and Use Committee (IACUC) oversees a university's animal care and use programs, facilities, and procedures ensuring the appropriate care, use and humane treatment of animals being used for research, testing and teaching.

• The IACUC is also responsible for reviewing all requests for approval to use vertebrate animals, ensuring compliance with federal regulations.
Pre-clinical Animal studies

• The IACUC also performs inspections of all areas and laboratories where animals are housed and used, and oversees training and educational programs.

• The IACUC serves as a resource to faculty, investigators, technicians, students, staff, and administrators, providing guidance in fulfilling the obligation to plan and conduct all animal use procedures with the highest scientific, humane, and ethical principles.
The Imaging Agent Development Process

• Before the human studies can begin, an Investigational New Drug (IND) application must be submitted to the FDA containing, among other things, information on any risks anticipated based on the results of pharmacological and toxicological data collected during studies of the drug in animals (21 CFR 312.23(a)(8)). (This is mandated by regulation)
The Imaging Agent Development Process

- These basic safety tests *(toxicology and pharmacology)* are most often performed in rats and dogs.
- The studies are designed to permit the selection of a safe starting dose for humans, to gain an understanding of which organs may be the targets of toxicity, to estimate the margin of safety between a clinical and a toxic dose, and to predict pharmacokinetic and pharmacodynamic parameters.
- In imaging however the dose may be set by radiation exposure issues or other factors.

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The Imaging Agent Development Process

- These early safety tests are usually resource intensive, requiring significant investment in product synthesis, animal use, laboratory analyses, and time.
- Many resources are invested in, and thus wasted on, candidates (including imaging agents) that may eventually be found to have unacceptable profiles when evaluated in humans.

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The Imaging Agent Development Process

- Fewer than 10 percent of INDs for new molecular entities (NME) progress beyond the investigational stage.
- In addition, animal testing does not always predict performance in humans, and potentially effective candidates may not be developed because of resource constraints.
The Imaging Agent Development Process

- Existing regulations allow a great deal of flexibility in terms of the amount of data that need to be submitted with any IND application, depending on the goals of an investigation, the specific human testing being proposed, and the expected risks.

- The FDA believes that sponsors have not taken full advantage of that flexibility.

- The FDA actually feels that developers often provide a more extensive preclinical database than is actually required by regulation.
The Imaging Agent Development Process

• As a result, the FDA has developed a guidance document to clarify what preclinical and clinical approaches (including chemistry, manufacturing, and controls) should be considered when planning exploratory IND studies in humans, including studies of closely related drugs or therapeutic biological products, under an investigational new drug (IND) application (21 CFR 312).
Guidance for Industry, Investigators, and Reviewers Exploratory IND Studies

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
January 2006

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Exploratory IND

• This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic

• Alternative approaches can be used if the approach satisfies the requirements of the applicable statutes and regulations

• Discussions of an alternative approaches can be scheduled by contacting the FDA staff responsible for implementing this guidance
Exploratory IND

• The guidance clarifies what preclinical and clinical approaches (including chemistry, manufacturing, and controls) should be considered when planning exploratory IND studies in humans, including studies of closely related drugs or therapeutic biological products, under an investigational new drug (IND) application (21 CFR 312)
Exploratory IND

• For the purposes of the guidance, the phrase exploratory IND study is intended to describe a clinical trial that occurs very early in phase 1, involves very limited human exposure, and has no therapeutic intent (e.g., screening studies, micro-dose studies).

• Such exploratory IND studies are conducted prior to the traditional dose escalation, safety, and tolerance studies that ordinarily initiate a clinical drug development program.
Exploratory IND

• The duration of dosing in an exploratory IND study is expected to be limited (e.g., 7 days).

• The guidance applies to early phase 1 clinical studies involving investigational new drug and biological products that assess feasibility for further development of a drug (an imaging agent for example) or biological product.

• Ideally suited for imaging agent development

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Exploratory IND

- Specifically, the guidance is limited to drug and certain well-characterized therapeutic biological products (e.g., recombinant therapeutic proteins and monoclonal antibodies) regulated by CDER.
- The guidance does not apply to human cell or tissue products, blood and blood proteins, vaccines, or to products regulated as devices.
Investigational New Drug Application (IND)

• 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.
Investigational New Drug Application (IND)

• FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer) having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans.

• At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

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There are three types of INDs:
1. An **Investigator IND** is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication, or in a new patient population.
2. Emergency Use IND (compassionate use) allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR ,Sec 312.23 or Sec 312.34. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist (compassionate use)
Investigational New Drug Application (IND)

3. **Treatment IND** is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.
There are two IND categories

• Commercial

• Research (non-commercial)
The IND application must contain information in three broad areas:
Investigational New Drug Application (IND)

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.
Investigational New Drug Application (IND)

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/sponsor can adequately produce and supply consistent batches of the drug.
Investigational New Drug Application (IND)

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 institutional review board (IRB), and to adhere to the investigational new drug regulations.

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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.
Investigational New Drug Application (IND)

Applicant (Drug Sponsor) → IND

Review by CDER

Medical → Safety Review

Chemistry

Pharmacology/Toxicology

Statistical

Sponsor Submits New Data

Safety Acceptable for Study to Proceed?

Yes

Complete Reviews

No

Clinical Hold Decision

Yes

Notify Sponsor

No
Investigational New Drug Application (IND)

- Complete Reviews
  - Yes: No Deficiencies
  - No: Reviews Complete and Acceptable?
    - No: Sponsor Notified of Deficiencies
    - Yes: Study Ongoing*

Notify Sponsor

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Investigational New Drug Application (IND)

1. Form 1571 (Application)
   Letter from company allowing cross-reference to their IND
2. Table of Contents of Application
3. Introductory Statement
4. General Investigational Plan
5. Investigators’ Brochure
6. Protocol
   Study Protocol- complete as approved by IRB
   Investigator Data –
     Physician’s Form 1572
     Physician’s CV
   Institutional Review Board approval Letter

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Investigational New Drug Application (IND)

7. Chemistry, Manufacturing, and Control Data
8. Pharmacology and Toxicology Data
9. Previous Human Experience
10. Additional Information.
   - Letter from company allowing cross-reference to their IND
   - Site/NCI Approved Data and Safety Monitoring Plan
Investigational New Drug Application (IND)

<table>
<thead>
<tr>
<th>Field</th>
<th>Description</th>
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<tbody>
<tr>
<td>IND Number</td>
<td>FDA 1571</td>
</tr>
<tr>
<td>Investigator</td>
<td>[Contact Information]</td>
</tr>
<tr>
<td>Investigator's Institution</td>
<td>[Institution Name]</td>
</tr>
<tr>
<td>Phase of Clinical Investigation</td>
<td>[Phase]</td>
</tr>
<tr>
<td>Study Number</td>
<td>[Number]</td>
</tr>
<tr>
<td>Protocol Number</td>
<td>[Number]</td>
</tr>
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</table>

**Certification Statement:**

Certification statement must be submitted with application for any check box below. Refer to the IND Regulations for Partner Notification.

- [ ] Treatment Protocol 31 CFR 312.3(b)
- [ ] Treatment Protocol 31 CFR 312.3(c)
- [ ] Charge for Reimbursement 31 CFR 312.3(c)

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### Investigational New Drug Application (IND)

#### Contents of Application

- Form FDA 1571 (21 CFR 312.21(a)(1))
- Table of Contents (21 CFR 312.21(a)(1))
- Investigator's statement (21 CFR 312.22(a)(1))
- Investigative plan (21 CFR 312.22(a)(3))
- Investigator's brochure (21 CFR 312.22(b)(5))
- Protocol (21 CFR 312.23(a)(8))
  - a. Study protocol (21 CFR 312.23(a)(8)(i))
  - b. Investigator data (21 CFR 312.23(a)(7)(i)(II))
  - c. Facilities data (21 CFR 312.23(a)(7)(i)(IV))
- Institutional Review Board data (21 CFR 312.22(b)(2)(ii))
- Chemistry, manufacturing, and control data (21 CFR 312.23(a)(7)(iv))
- Pharmacology and toxicology data (21 CFR 312.23(a)(8))
- Previous human experience (21 CFR 312.23(a)(9))
- Additional information (21 CFR 312.23(a)(10))

#### Any portion of the IND to be conducted by a contract research organization?

- Yes: [ ]
- No: [ ]

#### Any of the IND activities transferred to the contract research organization?

- Yes: [ ]
- No: [ ]

#### Any change in the IND to be conducted by the contract research organization?

- Yes: [ ]
- No: [ ]

#### Keywords and terms of the person responsible for adequate evaluation of information relevant to the safety of the drug

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the study may begin. I also agree not to begin or continue clinical investigations covered by the IND if these studies are planned on a multidose basis. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 U.S.C. 355 and its regulations shall be responsible for initial and continuing review and approval of such studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

#### Number of Investigators/Study Coordinators/Auxiliary Personnel

<table>
<thead>
<tr>
<th>12. Address:</th>
<th>13. Telephone Number (Local Area Code):</th>
<th>14. Date:</th>
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#### Publicly Available Data

- [ ]

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<tr>
<th>FDA 1571</th>
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<tr>
<td><strong>DEPARTMENT OF HEALTH AND HUMAN SERVICES</strong></td>
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<tr>
<td><strong>FOOD AND DRUG ADMINISTRATION</strong></td>
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<tr>
<td>(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)</td>
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<tr>
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<tbody>
<tr>
<td>1. NAME AND ADDRESS OF INVESTIGATOR</td>
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<tr>
<td>2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AND REQUIRED FOR CLINICAL INVESTIGATION OF THE MEDICINE:</td>
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<tr>
<td><strong>CURRICULUM VITAE</strong></td>
<td><strong>OTHER STATEMENT OF QUALIFICATIONS</strong></td>
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<tbody>
<tr>
<td>3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATIONS WILL BE CONDUCTED.</td>
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<td>4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.</td>
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<tr>
<td>5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).</td>
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<tr>
<td>7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.</td>
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</tbody>
</table>

**FDA 1572**
Investigational New Drug Application (IND)

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 6.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).

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

FDA 1572
Investigational New Drug Application (IND)

The Radioactive Drug Research Committee (RDRC) program began when the Food and Drug Administration (FDA) published a Federal Register notice on July 25, 1975 classifying all radioactive drugs as either new drugs requiring an Investigational New Drug Application (IND) for investigational use (21 CFR 312) or as generally recognized as safe and effective when administered under the conditions specified in the RDRC regulations (21 CFR 361.1).

Revised April 1, 2009
The RDRC program under 21 CFR 361 permits basic research using radioactive drugs in humans without an IND when the drug is administered under the following conditions:
The research is considered basic science research and is done for the purpose of advancing scientific knowledge. This type of research is:

- intended to obtain basic information regarding the metabolism (including kinetics, distribution, dosimetry, and localization) of a radioactive drug or regarding human physiology, pathophysiology, or biochemistry,
- not intended for immediate therapeutic, diagnostic or similar purposes (e.g. preventive benefit to the study subject from the research), and
- not intended to determine the safety and effectiveness of a radioactive drug in humans.

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Radioactive Drug Research Committee (RDRC)

The research study is approved by an FDA-approved RDRC 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 Institutional Review Board (IRB)

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The dose of the radioactive drug to be administered is not known to cause any clinically detectable pharmacologic effect in humans.
The radiation dose to be administered is justified by the quality of the study being undertaken and the importance of the information it seeks to obtain [21 CFR 361.1(b)(1)(iii)] and is within the limits specified in 21 CFR 361.1(b)(3)
For adult subjects: Radiation dose from a single study or cumulatively from a number of studies conducted within 1 year does not exceed the following:

<table>
<thead>
<tr>
<th>Organ or System</th>
<th>Single Dose Sieverts (Rems)</th>
<th>Annual and Total Dose Sieverts (Rems)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole body</td>
<td>0.03 (3)</td>
<td>0.05 (5)</td>
</tr>
<tr>
<td>Active blood-forming organs</td>
<td>0.03 (3)</td>
<td>0.05 (5)</td>
</tr>
<tr>
<td>Lens of the eye</td>
<td>0.03 (3)</td>
<td>0.05 (5)</td>
</tr>
<tr>
<td>Gonads</td>
<td>0.03 (3)</td>
<td>0.05 (5)</td>
</tr>
<tr>
<td>Other organs</td>
<td>0.05 (5)</td>
<td>0.15 (15)</td>
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</tbody>
</table>

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Radioactive Drug Research Committee (RDRC)

For subjects under 18 years of age:

Radiation dose does not exceed 10 percent of dose set forth for adults.
Radioactive Drug Research Committee (RDRC)

RDRC PROTOCOL REVIEW CHECKLIST: Criteria for the Evaluation of the Appropriateness of Research Studies under a RDRC

To approve a proposed research study, the RDRC must consider the following:

<table>
<thead>
<tr>
<th>1. Is the pharmacological dose within the following limits?</th>
<th>YES</th>
<th>NO</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. The amount of active ingredient or combination of active ingredients shall be known to not cause any clinically detectable pharmacological effect in humans.</td>
<td></td>
<td></td>
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<tr>
<td>* Sufficient documentation provided.</td>
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<tr>
<td>B. If the same active ingredients (exclusive of the radionuclide) are to be administered simultaneously (e.g., under an IND or for a therapeutic use), the total amount of active ingredients including the radionuclide shall be known not to exceed the dose limitations applicable to the separate administration of the active ingredient excluding the radionuclide.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Sufficient documentation provided.</td>
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<td></td>
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<tr>
<td>2. Were pharmacological dose calculations based on data available from published literature or from other valid studies?</td>
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<tr>
<td>3. Is the radiation dose within the following limits?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Subject must receive the smallest radiation dose practical to perform the study.</td>
<td></td>
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<tr>
<td>* Absorbed dose calculations based on biologic distribution data available from published literature or from other valid studies was provided.</td>
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<tr>
<td>* An acceptable method of radioassay of the radioactive drug prior to its use was provided.</td>
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<tr>
<td>* Adequate and appropriate instrumentation for the detection and measurement of the specific radionuclide will be utilized.</td>
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</table>

Protocol Review Checklist
### Protocol Review Checklist

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. The radioactive drug has the combination of half-life, type of radiation, radiation energy, metabolism, and chemical properties that results in the lowest dose to the whole body or specific organs which is possible to obtain the necessary information.</td>
<td></td>
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<tr>
<td>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:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single dose</td>
<td>3 Rems</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Annual &amp; total dose</td>
<td>5 Rems</td>
<td></td>
</tr>
<tr>
<td></td>
<td>* Other organs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single dose</td>
<td>5 Rems</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Annual &amp; Total Dose</td>
<td>15 Rems</td>
<td></td>
</tr>
<tr>
<td>C. For subject under 10 years of age: Radiation dose may not exceed 10 percent of dose set forth above.</td>
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<tr>
<td>D. When determining total radiation doses and dose commitments must consider:</td>
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<tr>
<td></td>
<td>* All radioactive material included in drug either as essential material or as significant contaminant or impurity.</td>
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<tr>
<td></td>
<td>* X-ray procedures that are part of the research study.</td>
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<tr>
<td></td>
<td>* Possibility of follow-up studies.</td>
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</tr>
<tr>
<td>E. Are the numerical definitions of dose based on absorbed fraction method of radiation absorbed dose calculation (e.g., system set forth by Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine or by the International Commission on Radiological Protection)?</td>
<td></td>
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<tr>
<td></td>
<td>*Sufficient documentation provided.</td>
<td></td>
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<tr>
<td>4. Is the radiation exposure justified by the quality of the study being undertaken and the importance of the information it seeks to obtain?</td>
<td></td>
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</tr>
</tbody>
</table>
## Protocol Review Checklist

<table>
<thead>
<tr>
<th>Protocol Item</th>
<th>YES</th>
<th>NO</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Is each investigator qualified by training and experience to conduct the proposed research studies?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6. Is the investigator’s or institution’s license to handle radioactive materials appropriate? Does the investigator meet the following requirements?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. For reactor-produced isotopes: The investigator or institution shall be licensed by the Nuclear Regulatory Commission or Agreement State to possess and use the specific radionuclides for research use or be a listed investigator under a broad license.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. For non-reactor-produced isotopes: The investigator or institution shall be licensed by either appropriate State or local authorities, when required by state or local law.</td>
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</tr>
<tr>
<td>7. Is the use of human subjects appropriate and does it meet the following requirements?</td>
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<td></td>
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</tr>
<tr>
<td>A. Number of subjects should not exceed 30.</td>
<td></td>
<td></td>
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<tr>
<td>B. Research must be reviewed and approved by an institutional review board and consent must be obtained from the subjects or legal representatives.</td>
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<tr>
<td>C. Research subjects must be at least 18 years of age and legally competent.</td>
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<tr>
<td>D. Exceptions to preceding requirement only permitted if:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>Investigator can demonstrate that: 1) the study presents a unique opportunity to gain information not currently available; 2) requires use of subjects less than 18 years of age; 3) is without significant risk to subjects.</em></td>
<td></td>
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<tr>
<td><em>RDRC review is supported with review by qualified pediatric consultant.</em></td>
<td></td>
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<tr>
<td>E. Female subjects of childbearing potential must: 1) state in writing that they are not pregnant or 2) on basis of pregnancy test be confirmed as not pregnant.</td>
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</tr>
</tbody>
</table>

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## Protocol Review Checklist

<table>
<thead>
<tr>
<th>8. Does the radioactive drug meet appropriate chemical, pharmaceutical, radiochemical, and radionuclidic standards of identity, strength, quality and purity?</th>
<th>YES</th>
<th>NO</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Is the research design appropriate in that:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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;</td>
<td></td>
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</tr>
<tr>
<td>B. Scientific knowledge and benefit should be of sound design such that information of scientific value may result.</td>
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</tr>
<tr>
<td>C. Will the radiation dose be sufficient and no greater than necessary for purpose of the study?</td>
<td></td>
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</tr>
<tr>
<td>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.</td>
<td></td>
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</tr>
<tr>
<td>10. Is the packaging, label, and labeling of the radioactive drug in compliance with Federal, State, and local law regarding radioactive materials?</td>
<td>YES</td>
<td>NO</td>
<td>N/A</td>
</tr>
<tr>
<td>Is the label of the immediate container and shielded container, if any, in compliance with RDRC requirements?</td>
<td></td>
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</tr>
</tbody>
</table>

Revised: 10/03

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<table>
<thead>
<tr>
<th>RDRC Membership</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMMITTEE CHAIR</td>
<td></td>
</tr>
<tr>
<td>NON-CONFIDENTIAL</td>
<td></td>
</tr>
</tbody>
</table>

**FDA 2914**

RDRC Membership

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Radioactive Drug Research Committee (RDRC)

<table>
<thead>
<tr>
<th>Department of Health and Human Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA 2915</td>
</tr>
<tr>
<td>RDRC Annual Report</td>
</tr>
</tbody>
</table>

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Radioactive Drug Research Committee (RDRC)

### Slides are not to be reproduced without permission of author.
### Radioactive Drug Research Committee (RDRC)

#### Radiation Absorbed Dose - Summary

<table>
<thead>
<tr>
<th></th>
<th>a</th>
<th>b</th>
<th>c</th>
</tr>
</thead>
<tbody>
<tr>
<td>aDose</td>
<td>Activity Associated with Administration</td>
<td>Absorbed Dose</td>
<td>Total Dose</td>
</tr>
<tr>
<td>Dose</td>
<td>Activity</td>
<td>Absorbed Dose</td>
<td></td>
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</tbody>
</table>

#### Number of Research Subjects

1. Number of research subjects at the time of the report
2. Number of research subjects who received radiation exposure
3. Number of research subjects for whom the protocol was approved
4. Number of research subjects involved in the study

#### Clarity of Confidentiality

- Check the box for the confidentiality status.

#### Return Protocol Form

- Name of Investigator
- Signature of Investigator
- Name of Chairperson of Radioactive Drug Research Committee

#### FDA 2915
RDRC Annual Report

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*SNM 2010 SNM Compact Mid-Winter Meetings*
## Radioactive Drug Research Committee (RDRC)

<table>
<thead>
<tr>
<th>SEX</th>
<th>AGE</th>
<th>Activity &amp; Radionuclide/Administration</th>
<th>Absorbed Dose Per Single Administration</th>
<th>Total Dose Per Organ/Per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mR/whole body</td>
<td>mR/lens of eye</td>
<td>mR/whole body</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mR/lens of eye</td>
<td>mR/gonads</td>
<td>mR/lens of eye</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mR/gonads</td>
<td>(critical organ)</td>
<td>mR/gonads</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(blood forming organ)</td>
<td>(critical organ)</td>
<td></td>
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Radioactive Drug Research Committee (RDRC)

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Oncology/ucm093322.htm


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