# The Study of Radioactive Drugs in Human Subjects

Radioactive Drug Research Committee (RDRC)
versus
Investigational New Drug (IND)

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# PRESENTATION OUTLINE

- State the Objective of Overview
- Discuss the Research Pathways
- Identify 21 CFR Regulations
- Compare the Requirements of the Research Pathways
- Provide Closing Remarks
- List FDA Program Contacts

# OBJECTIVE OF PRESENTATION

Provide an overview of the regulatory pathways available in the U.S. to study radioactive drugs in human subjects and compare the regulatory requirements

# RESEACH PATHWAYS
# RDRC OR IND

**Radioactive Drug Research Committee (RDRC) Program**

- Established by July 25, 1975 FR to regulate **ALL** radioactive drugs under the FDA that are ***Generally Recognized as Safe and Effective (GRAS/E)***

- Allows for ***basic research*** of radioactive drugs in human subjects without an IND if certain conditions are met under a FDA approved RDRC

**Investigational New Drug (IND) Program**

- Established under the FD&C Act to regulate new drug research

- Allows for the ***clinical investigation*** of radioactive drugs in human subjects, under an IND application

Currently-ALL radioactive drug research is now subject to **IND** or **RDRC** regulations as established by Federal Register Notice (Vol. 40, No. 144; July 25, 1975)

# REGULATORY CODE

- **21 CFR 312** Investigational New Drug Application (IND)

- **21 CFR 361** Prescription Drugs For Human Use Generally Recognized as Safe and Effective and not Misbranded: Drugs Used in Research

***361.1 Radioactive drugs for basic research***

# RDRC RESEARCH PATHWAY

***Basic research*** for the purpose of advancing scientific knowledge

- The research is intended to obtain ***basic*** information regarding **the metabolism** of radioactive drugs including kinetics, distribution, dosimetry, and localization

  **or**

- obtain ***basic*** information regarding **human physiology, pathophysiology, and biochemistry** of radioactive drugs

- The research is ***not*** intended to determine the safety and effectiveness of a radioactive drug in human subjects as a therapy, diagnostic, or preventive medical product

- The research is ***not*** intended for the immediate therapeutic, diagnostic, or preventive benefit to the human study subjects

# IND RESEARCH PATHWAY

- Research is ***not restricted*** to basic research for the purpose of conducting clinical investigations and can include:
  - Research involving therapeutic, diagnostic, or preventive benefits to human subjects
  - Research to study safety and efficacy (i.e., clinical trials)
  - Basic research that *does not* meet the requirements of 361.1
  - Basic research that meets requirements of 361.1 however the investigator *chooses the IND Pathway*

    *Note: If the investigator chooses the IND pathway simultaneous reporting to the RDRC is not required*

# INSTITUTIONAL REVIEW BOARD (IRB) REVIEW AND APPROVAL

**Institutional Review Board (IRB)-**primary function is to review and monitor biomedical research involving human subjects to assure protection of their rights and welfare

- **IRB that approves FDA regulated research must comply with 21 CFR 56**

- **IRB Responsibilities include:**
  - Review of initial research and subsequent changes
    - Authority to approve, require modification in, or disapprove research activities.
    - Authority to suspend or terminate approval of research
    - Approval must be obtained prior to implementation
  - Continuing review of ongoing research

- **IRB Approves Research Study Protocols if the following Criteria are demonstrated:**
  - Minimization of risks to subjects; risks are reasonable in relation to anticipated benefits
  - Equitable selection of subjects
  - Compliance with the informed consent requirements of 21 CFR 50, including subpart D if some subjects are children
  - Adequate provision for monitoring data to ensure safety of subjects
  - Protection of rights and welfare of vulnerable subjects
  - Adequate provisions to protect privacy and confidentiality

# COMPARISON
# REVIEW AND MONITORING

## RDRC

Radioactive Drug Research Committee

- Monitors the basic research
- Responsible for ensuring that the requirements of 361.1 are met:
  - Qualified study investigators
  - Proper licensure for radioactive materials
  - Appropriate selection and consent of research subjects
  - Appropriate quality of radioactive drug administered
  - Sound research protocol design
  - Reporting of adverse events
  - Approval by IRB
  - Labeling

## IND

FDA-Office of New Drug Research (OND)

- Monitors Sponsors IND Activity
- Reviews initial applications and amendments to include:
  - Protocols, protocol changes
  - Study investigators
  - CMC, Pharm/Tox, PK
- Primary objectives of review:
  - To assure the safety and rights of subjects
  - To assess the scientific quality of the clinical investigations
- Assesses the safety of Studies:
  - Within First 30 days study Initiated or placed on **HOLD**

# COMPARISON
# REPORTING, MONITORING AND ENFORCEMENT

| | RDRC | IND |
|---|---|---|
| Reporting to FDA | Annual report<br>•Study Summary<br>•Membership Summary<br>Special Summary<br>Adverse events<br>If requested:<br>•Minutes<br>•Full protocols | Annual report<br>New protocols<br>Protocol changes<br>New investigators<br>Information amendment<br>Adverse events |
| Monitoring by FDA | FDA monitors the activities of the approved RDRCs | FDA monitors the Sponsors Research |
| FDA enforcement | On-site inspections<br>Notification of deficiencies<br>Withdrawal of approval of RDRC | On-site inspections<br>Full or partial clinical hold,<br>Termination of IND Application |

# COMPARISON DOSING

| | RDRC | IND |
|---|---|---|
| Pharmacological dose | Stated limits | No stated limits |
| | Amount of active ingredient must be known not to cause any clinically detectable pharmacological effect in humans, based on published literature or other valid human studies | Evaluated for safety on a case-by-case basis<br><br>Initial dose can be chosen based on animal and/or human data |
| Radiation dose | Stated limits | No stated limits |
| | Smallest dose with which it is practical to perform the study without jeopardizing the benefits to be obtained from the study<br><br>Single dose and annual/total dose limits | Evaluated for safety on a case-by-case basis |

# COMPARISON STUDY SUBJECTS

| | RDRC | IND |
|---|---|---|
| Informed Consent (21 CFR 50) | Required | Required |
| Number of subjects | Sufficient but no greater than necessary for the purpose of the study (usually <30)<br><br>Should reflect that the study is intended to obtain *basic research* information | No limit |
| Subjects < 18 years of age | Permitted only in special situations | Permitted, if accepted in IND protocol |
| Women of child bearing potential | Must state in writing that she is not pregnant, or be confirmed as not pregnant | Permitted, if accepted in IND protocol |

# COMPARISON
# ADVERSE EVENT (AE) REPORTING

**RDRC**

- **Investigator** must immediately report to RDRC all AEs associated with use of the radioactive drug in the research study
  - Serious- FDA recommends 2 business days
  - All others- FDA recommends 5 business days
- RDRC must immediately report to FDA all adverse events probably attributable to use of the radioactive drug in the research study
  - Serious
    - FDA recommends 7 business days
  - All others
    - FDA recommends 15 business days

**IND**

- **Sponsor** must notify FDA and all investigators of any AEs in a written Safety Reports
  - Serious/unexpected within 15 days of receipt
  - Unexpected fatal or life-threatening within 7 days of receipt
- Included in Annual reports
- **Sponsor** must promptly review and report to FDA all information relevant to the safety of the drug from any source, foreign or domestic including information derived from clinical trials, literature, animal studies, commercial marketing, unpublished papers, and reports from foreign regulatory authorities

# CLOSING

## RDRC

- Pathway available to conduct *basic research* of radioactive drugs in human subjects

## IND

- Pathway available to conduct research involving:
  - Therapeutic, diagnostic, or preventive benefits to human subjects
  - Safety and efficacy (i.e., clinical trials)
  - Basic research that *does not* meet the requirements of 361.1 and Basic research that *does* meet the requirements of 361.1

# WHEN IN DOUBT?

# SUBMIT AN IND!

# FDA CONTACTS

**RDRC FDA Contact:**

**Richard Fejka, M.S., BCNP**
**Senior Manager**
**(301) 796-2050**

**IND FDA CONTACT:**

**Kaye Kang, Pharm.D.**
**Chief Project Manager**
**(301) 796-2050**