U.S. FDA Regulation of PET Drugs

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History of FDA Regulation of PET Drugs

- In 1997, US Food and Drug Administration Modernization Act directs FDA to establish appropriate approval procedures and CGMP requirements for PET drugs from traditional drugs (Part 211)
- FDA's CGMP regulation for PET drugs was finalized on December 10, 2009
- The regulation of 21 Code of Federal Regulations part 212 (21 CFR 212) became effective on June 12, 2012
- All PET drug producers must be operating under an approved NDA, ANDA or IND after December 12, 2015
- Search for FDA regulation of PET Drugs or related useful guidance: https://www.fda.gov/drugs/pharmaceutical-quality-resources/positron-emission-tomography-pet

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Glossary

- CGMP: Current Good Manufacturing Practices
- NDA: New Drug Application
- ANDA: Abbreviated New Drug Application
- IND: Investigational New Drug
- eIND: exploratory Investigational New Drug
- eaIND: expanded access Investigational New Drug
- RDRC: Radioactive Drug Research Committee

- Search for Drugs@FDA Glossary of Terms: https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms#RLD

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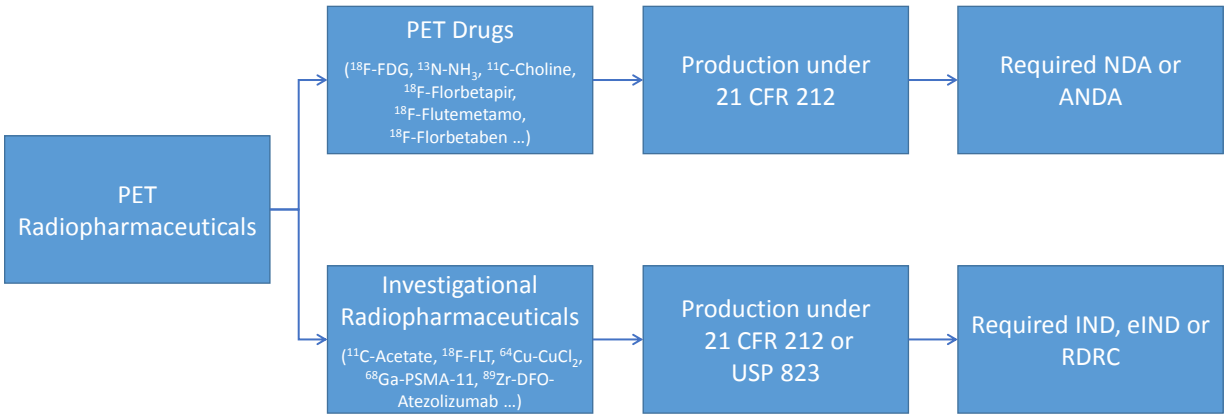
CGMP Manufacturing of PET Drugs



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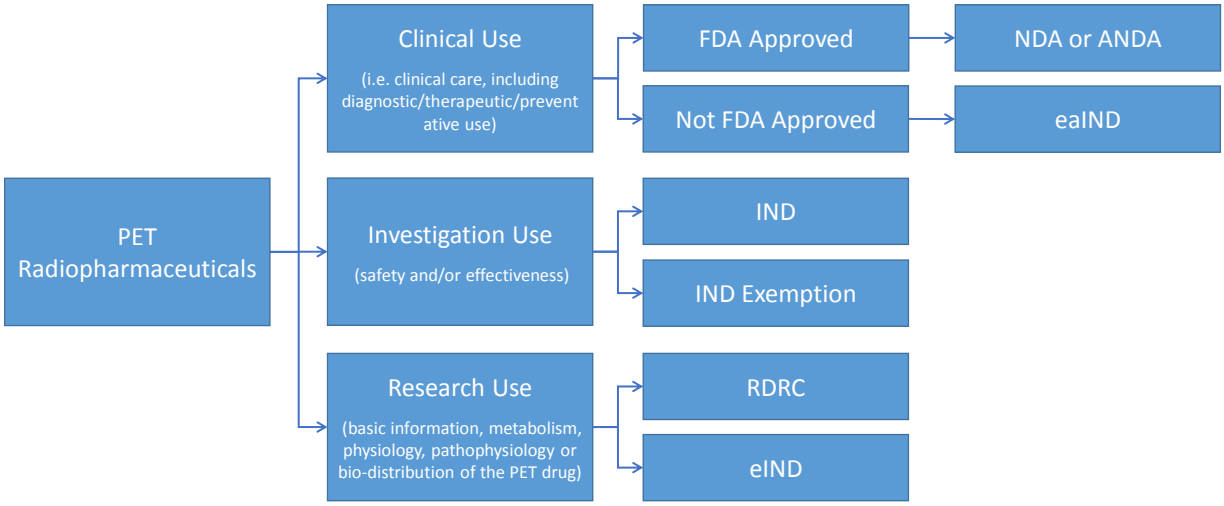
Clinical Use of PET Drugs



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FDA Approved PET Radiopharmaceuticals

- ^{18}F Sodium Fluoride, 1972
- ^{82}Rb Rubidium Chloride, 1989
- ^{18}F Fludeoxyglucose, 1994
- ^{13}N Ammonia, 2000
- ^{18}F Florbetapir (Amyvid), 2012
- ^{11}C Choline, 2012
- ^{18}F Flutemetamol (Vizamyl), 2013
- ^{18}F Florbetaben (Nuraceq), 2014
- ^{18}F Fluciclovine (Axumine), 2016
- ^{68}Ga DOTATATE (Netspot), 2016
- ^{68}Ga DOTATOC, 2019
- ^{18}F Fluorodopa, 2019
- ^{18}F Flortaucipir (Tauvid), 2020
- ^{18}F Fluoroestradiol (Cerianna), 2020

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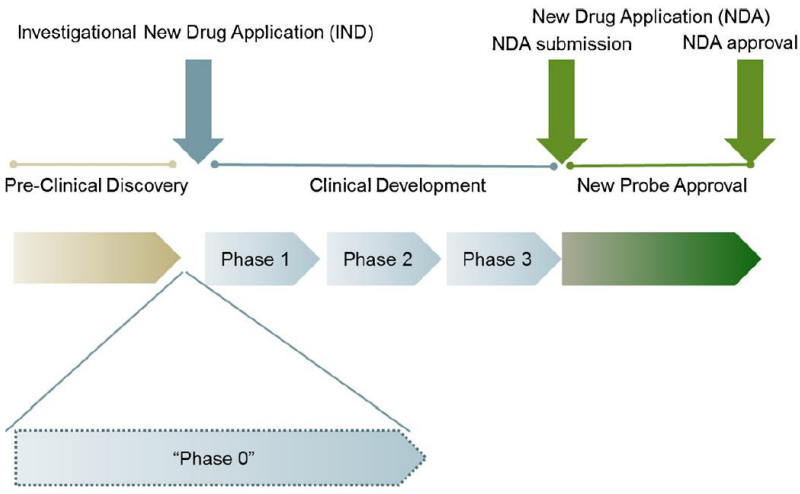
FDA Approval Process for PET Drugs



- RDRC: Radioactive Drug Research Committee approval
  or
- eIND: Exploratory Investigational New Drug Application

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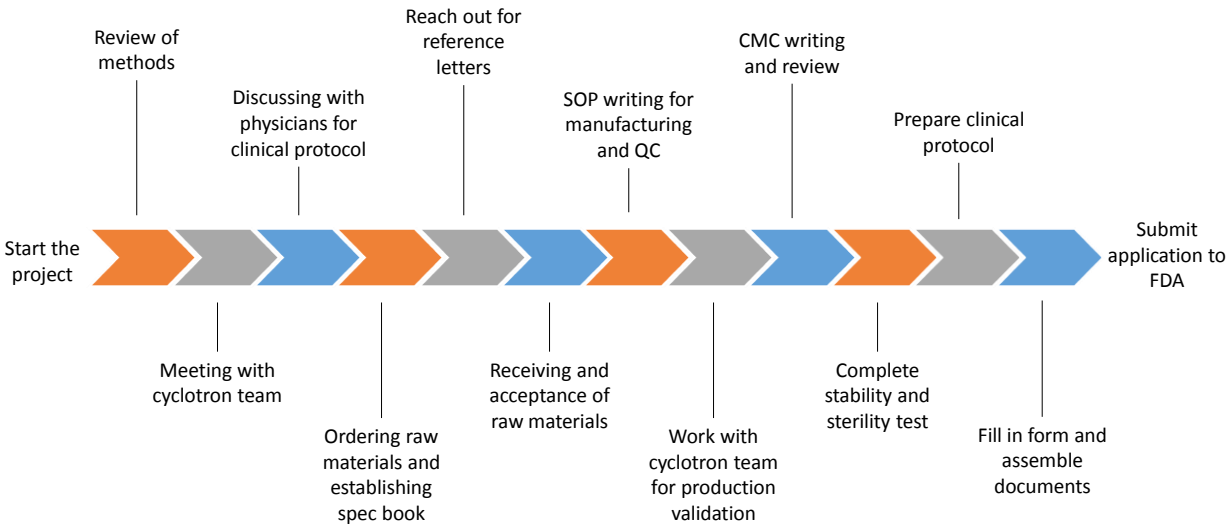
Regulatory Affairs Process for PET Drugs Application



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Facility Registration

- A facility must register as PET drug manufacturer if approved PET drugs are produced and used in clinical diagnosis:
  - Use in the same facility's PET imaging suites
  - Offered for sale to another facility for clinical imaging purposes
- Registered facilities must fully comply with 21 CFR part 212 and submit NDAs or ANDAs to cover the approved PET drugs that are manufactured for clinical use
- Registration must renew annually
- Registration and listing must be done electronically
- DOES NOT need to be registered if the facility is producing radiotracers for use in clinical research only under IND or RDRC application

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New Drug Application (NDA)

- NDA is the approval pathway for new drugs (not the same as an already approved product) that are to be marketed and sold in the US
- New molecular entity or indication not already FDA-approved
- Required data for application:
  - From animal studies
  - From IND trials
  - Manufacture
  - Quality control
- Guidance document: https://www.fda.gov/media/72271/download

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Abbreviated New Drug Application (ANDA)

- An ANDA is usually submitted for a drug product that is the same as an already approved drug and it is the approval pathway for generic drug (already on the market, ex. ^{18}F-FDG, ^{13}N-NH_3, ^{18}F-NaF) that are to be marketed and sold in the US
- Required data for application:
  - Comparable to a Reference Listed Drug (RLD) in: characteristics, dosage, formulation, intended use, quality, administration, strength
- DOES NOT required data for application:
  - Animal studies
  - Clinical studies
- Guidance document: https://www.fda.gov/media/72271/download

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Reference Listed Drugs (RLD)

- A Reference Listed Drug (RLD) is defined as the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application. FDA listed approved drugs that may be referenced in an ANDA in the ORANGE BOOK
- Generic drug that has the identical active ingredient(s), dosage form, strength, route of administration, and (with certain exceptions) conditions of use as its RLD
- Search for RLD: https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm

Fludeoxyglucose F 18 Injection (NDA 20-306)

Active ingredient	2-Deoxy-2[^{18}F]fluoro-D-glucose
Inactive ingredients	Sodium chloride injection, USP (9 mg/mL sodium chloride in water for injection (WFI))
Dosage form	Injection
Specific activity	No-carrier added
Strength (radioconcentration)	4 - 90 mCi/mL at EOS (end of synthesis)
Osmolality	Isotonic
pH	5.5 - 7.5
Route of administration	Intravenous

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Drug Master Files (DMF)

- A Drug Master File (DMF) is a composite of proprietary information about materials used in the preparation of a drug product
- A DMF is a submission to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs products. It reduces the burden of information to be provided as part of an NDA or ANDA
- For example: for FDG DMFs required:
  - ^{18}O-H_2O
  - FDG cassette
  - 30 mL sterile vials
- Search for DMF and Holder: https://www.fda.gov/drugs/drug-master-files-dmfs/list-drug-master-files-dmfs

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Drug Master Files (DMF) (Continued)

- DMF subtypes:
  - Type 1: plant information
  - Type 2: drug substances, intermediates, drug products, or supplies used in the preparation of the drug product
  - Type 3: packaging materials
  - Type 4: additives, including excipients, colorants, flavors, essences, or components or intermediates used in the additive production
  - Type 5: reference information. For example, a type V DMF related to the PET field might include detailed information about a proprietary automated radiotracer synthesis unit.

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Pre ANDA Checklist

- ✓ Obtain materials and equipment
- ✓ IOQ/PQ equipment and keep record
- ✓ Write, print and sign SOPs and Specification Book (SB)
- ✓ Check in materials with correct SB and suppliers
- ✓ Have Certificates of Analysis (COA)
- ✓ Obtain National Drug Code (NDC) number
- ✓ Have DUNS (Data Universal Numbering System) number with associated facility name/address from DUNS database
- ✓ Have FEI (Facility Establishment Identifier) number: https://www.accessdata.fda.gov/scripts/cder/drls/default.cfm
- ✓ Have data from 3 consecutive runs including stability
- ✓ Data for Growth Promotion/Inhibition Test
- ✓ Data from Media Fill simulation
- ✓ Obtain letters of Authorization with DMF numbers

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Administrative Requirements

- Completed, signed From FDA 356h: https://www.fda.gov/media/72649/download
  - Applicant information
  - Product description
  - Application description
  - Establishment information
  - Cross reference
  - Individual item based on regulations
  - Certification
  - Signature of responsible official

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Administrative Requirements (Continued)

- Individual items in the application
  - Table of contents
  - Basis for ANDA submission (RLD)
  - Patent certification & exclusivity statements
  - Comparison of RLD to generic drugs
  - Labeling
  - Bioequivalence
  - Chemistry section (CMC): https://www.fda.gov/media/72278/download
  - Financial disclosure
  - Debarment certification
  - Field copy certification
  - User fees

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FDA Audits and Inspections

- FDA audits of PET manufacturers fall into 3 categories:

1. Preapproval inspection (new site, new molecular entity or new sponsor within an NDA or ANDA)
   - Observation of actual productions and practices
   - Qualification of equipment and processes
   - Review of procedure and records
2. Routine CGMP (surveillance) inspection (within 2 years of filling an NDA or ANDA)
   - Verify CGMP compliance
3. For-cause (compliance) inspection
   - Follow-up for deficiencies in previous inspections
   - External complaint brought to FDA

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FDA Inspections and Annual Reporting

- FDA inspections follow a set protocol
  - Written notice of inspection (Form FDA 482)
  - Explain the purpose of inspection and how it will proceed
  - Perform the inspection
  - Notify the facility of inspectional observation (Form FDA 483)
- Reporting
  - Any significant changes to the submitted application (before approval)
  - *Guidance for Industry: CMC Postapproval Manufacturing Change To Be Documented in Annual Reports* https://www.fda.gov/media/79182/download
  - A serious and unexpected adverse event (within 15 days)
  - Sterility and labeling defects (within 3 days)
  - Quarterly safety reports for the 3 first years and annually thereafter: Guidance for safety reports: https://www.fda.gov/media/83280/download

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Expanded Access Investigational New Drug (eaIND)

- An eaIND refers to a range of investigational new drug (IND) mechanisms intended to provide access to investigational drugs outside of traditional clinical investigation
- Type of eaIND
  - Individual patient
  - Intermediate-size patient population (10-20 patients)
  - Widespread use under a treatment IND or treatment protocol
- General Criteria
  - Patient with **serious or immediately life-threatening** disease/condition
  - **No** comparable/satisfactory **alternative "therapy"**
  - Potential benefit justifies the potential risk of the clinical use
  - Provision of drug will not interfere with drug development for market approval

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Clinical Investigation and Research

- IND (Investigational New Drug)
  - Approval by FDA (21 CFR part 312) and IRB
- IND Exemption (Investigational New Drug Exemption)
  - Approval by FDA (21 CFR part 312.2(b)) and IRB
- RDRC (Radioactive Drug Research Committee)
  - Approval by RDRC (21 CFR part 361.1) and IRB
- eIND (Exploratory Investigational New Drug)
  - Approval by FDA (21 CFR part 312) and IRB

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Investigational New Drug (IND)

- Purposes
  - For clinical investigation of radiolabeled probes
  - For therapeutic, diagnostic and preventative use
  - For determining safety and efficacy
- Requirements
  - Good Laboratory Practice (GLP) compliant
    https://www.fda.gov/media/75866/download
  - Clinical protocol
  - Manufacturing under USP 823 or CFR 212 guidelines
  - Rodent dosimetry data
  - Safety pharmacology and toxicology studies in 2 species
  - Genotoxicity studies
- Limitations
  - No limit (number of subjects, duration etc.)

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IND Components

- Form FDA 1571 (cover sheet): https://www.fda.gov/media/116608/download
- Form FDA 3674 (www.ClinicalTrials.gov): https://www.fda.gov/media/105405/download (for clinical trials data bank)
- Table of contents
- Introductory statement, description of clinical investigation
- Investigator brochure
- **Clinical protocol**
- **Background information**

- Guidance document: https://www.fda.gov/media/83077/download

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IND Components (Continued)

- Clinical protocol
  - Phase 1: safety, PK, human radiation dosimetry
  - Phase 2: safety, selective binding to target (diagnostic or therapeutic)
  - Phase 3: efficacy (sensitivity, specificity)

- Background information
  - Chemistry, Manufacturing, and Control (CMC)
  - Pharmacology – toxicology
  - Previous human experience
  - Estimate of radiation-absorbed dose

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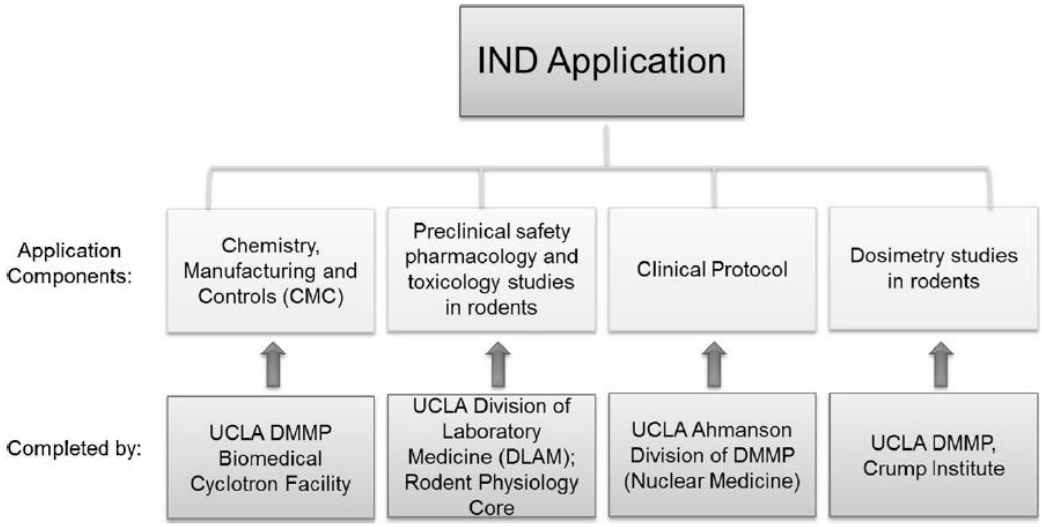
PET Probe IND Application Components (UCLA Experience)



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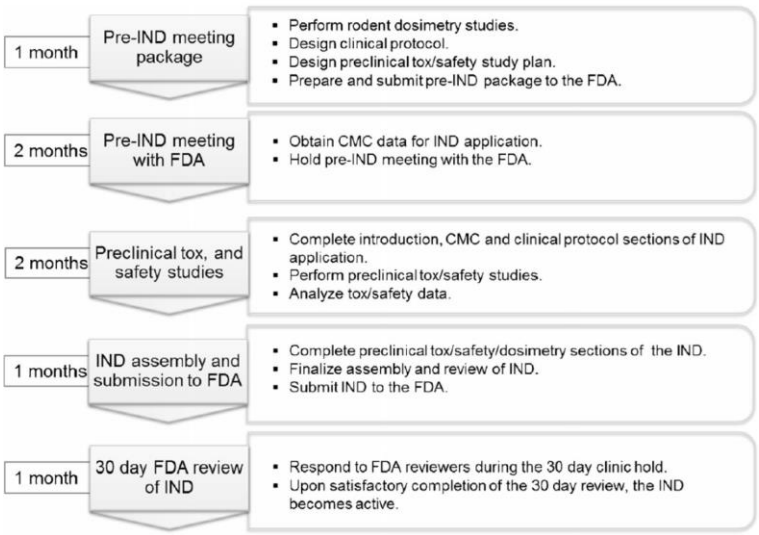
IND Submission Timeline for PET Drugs (UCLA Experience)



Note: The costs to obtain data in support of the IND application are around $50 K to $100 K per imaging probe.

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Shared INDs

- "Shared" INDs – The approach that uses right of reference letters to existing INDs or drug master files (DMFs) that are already active at the FDA. The IND itself is not shared.
- Requirement for IND application:
  - Site specific information: CMC, clinical protocol
  - Common information: pharmacology, toxicology, dosimetry
- Resource for shared INDs
  - NCI's Cancer Imaging Program and SNMMI-CTN
  - [^{18}F] FMISO, [^{18}F] FLT, [^{18}F] FES, [^{18}F] DCFBC, [^{89}Zr] Panitumumab …
  - https://imaging.cancer.gov/clinical_trials/resources.htm

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IND Review and Maintenance

- IND is reviewed by multiple disciplines
  - Chemistry, pharmacology, toxicology, microbiology, clinical etc.
- Submit protocol revision or new protocols before initiating them
- Report serious and unexpected adverse events
- Submit annual progress reports
- Can I administer the PET drug while my IND is being reviewed?
  - No, need to wait
  - If unsure, ask FDA

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IND Exemptions

- IND involving marketed drug product can be exempted if all of following criteria are met in accordance with 21 CFR 312.2(b):
  - Drug product lawfully marketed in the US
  - Not intended to support new indication or changing in the labeling of the drug
  - Not intended to support changing in the advertising for the drug
  - Does not involve a route of administration, dose, patient population, or other factor increasing the risk associated with the used of the drug
  - In compliance with the IRB review and informed consent
  - In compliance with the requirements of 21 CFR 312. (i.e. the sponsor does not intend to promote or commercialize the drug product)
- An IND exemption is permissible (only for producer who has submitted NDAs or ANDAs) for each of the FDA-approved PET drugs (i.e., ^{13}N-NH_3, ^{18}F-FDG, ^{18}F-NaF …) as long as the others criteria as stated above are met

Radioactive Drug Research Committee (RDRC)

- Purposes
  - Only for basic science research
  - No diagnostic/therapeutic intent
  - Not to determine safety and effectiveness
- Requirements
  - Clinical protocol
  - Manufacturing under USP 823 or CFR 212 guidelines
  - Dosimetry studies in rodents
  - Limited safety/tox studies in rodents (determined by RDRC)
- Limitations
  - Up to 30 subsects
  - **Not for first-in-human study**
  - Total amount of radiation administered must be the **smallest dose**
  - The dose mustn't cause any detectable pharmacological effect in humans

RDRC Components

- Qualified study investigators
- Proper licensure to handle radioactive materials (Cyclotron and Physicians)
- Appropriate selection and consent of research subjects (Physicians)
- Appropriate quality of radioactive drug administered (Cyclotron)
  - Compliance with 21 CFR part 212 or USP 823
- Sound research protocol design (Physicians)
- Reporting of adverse events to the RDRC
- Approval by an appropriate IRB
- Evaluation of radiation dose to subjects (Medical Physics)
- Labeling (Cyclotron)
- Pharmacology/Toxicology information
  - Limited preclinical data defined by RDRC
- Guidance document: https://www.fda.gov/media/76286/download

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Post Approval Requirements – Annual Reporting

- Special summary for subject <18 years old
- Request approval when number of subjects exceeds 30
- Immediately report adverse events
- RDRC annual report submitted each January
  - Form FDA 2914: membership summary
  - Form FDA 2915: study summary (special summary or annual report)
- FDA inspections
  - RDRC meeting minutes
  - Study reviews
  - Records

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Exploratory Investigational New Drug (eIND) (Phase 0)

- Purposes
  - Only for basic science research and can be **first-in-human studies**
  - Allow to **screen 2-5 probes simultaneously** under one application
  - **No diagnostic/therapeutic intent** and for **micro-dose studies**
- Requirements
  - Clinical protocol
  - Manufacturing under USP 823 or CFR 212 guidelines
  - Dosimetry studies in rodents
  - Toxicology studies in 1 species (both sexes)
  - No safety pharmacology and genotoxicity studies
- Limitations
  - Up to 30 subsects
  - Limited human exposure
  - When complete, must withdraw and transition to an IND

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eIND Components

- Clinical Development Plan (Physicians)
  - Pharmacokinetics/biodistribution
  - Human radiation dosimetry
- Chemistry, Manufacturing and Control (Cyclotron)
  - Compliance with USP 823 or 21 CRF 212 guidelines
- Pharmacology/Toxicology Information
- Previous human experience (if any)
- Guidance document: https://www.fda.gov/media/72325/download

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Differences Between RDRC and eIND

- Differences
  - RDRC is specifically for radioactive drugs, whereas eIND is not
  - eIND can be first-in-human study, whereas RDRC study cannot
  - eIND can screen 2-5 probes simultaneously, whereas RDRC cannot
  - Toxicity studies in a one species are required for eIND submission, whereas it is not necessary for RDRC protocol
  - RDRC involves 30 or more subjects and there is no limitation in completion time, whereas eIND is expected to be limited
  - FDA directly approves the eIND, whereas these responsibilities are delegated to the local RDRC by the FDA
  - RDRC needs to submit report to FDA if subjects of age are < 18 and/or the number of subjects are > 30, whereas eIND doesn't
  - RDRC limits the radiation exposure to human, whereas eIND doesn't

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Summary

	NDA	ANDA	IND	RDRC	eIND
Purpose	FDA approved new drug or new drug application	FDA approved generic drugs	Investigational drugs, phase 1, 2, 3 clinical trials	Basic Research	Basic Research
Requirements	Data from: animal studies, human trials, manufacture, quality control	Manufacture, quality control	Clinical protocol, dosimetry in rodents, toxicology in 2 species, pharmacology in 2 species, genotoxicity	Clinical protocol, dosimetry in rodents, limited toxicology in rodents	Clinical protocol, dosimetry in rodents, toxicology (1 species)
Limitations		Match Reference Listed Drug (RLD)		NOT first in human, up to 30 subjects, limited pharmacological and radiation dose	Up to 30 subjects, limited pharmacological and radiation dose

References

1. Marianna Dakanali. CRP Training Session – Regulatory Requirements or Use of PET Drugs. Cyclotron & Radiochemistry Program, UT Southwestern Medical Center. July 13, 2020
2. Joseph C. Hung. Bringing New PET Drugs to Clinical Practice – A Regulatory Perspective. Theranostics. 2013;3:885-893
3. Sherly Mosessian et al,. INDs for PET Molecular Imaging Probes - Approach by an Academic Institution. Mol Imaging Biol. 2014;16:441-448
4. Sally W. Schwarz et al,. Regulatory Requirements for PET Drug Production. J Nucl Med. 2014;55:1132-1137
5. Guidance: PET Drugs – Current Good Manufacturing Practice (CGMP). FDA, December 2009
6. Guidance: PET Drug Applications — Content and Format for NDAs and ANDAs. FDA, August 2011
7. Guidance: Investigational New Drug Application for Positron Emission Tomography (PET). FDA, December 2012
8. Guidance for Industry and Researchers: The Radioactive Drug Research Committee: Human Research Without An Investigational New Drug Application. FDA, August 2010
9. Guidance for Industry, Investigators and Reviewers: Exploratory IND Studies. FDA, January 2006

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Any Questions

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Thank you