Submitting a PET Drug Investigational New Drug (IND) Application

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Division of Medical Imaging Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Outline

• Introduction

• When IND Submission Is Not Required

• When IND Submission Is Appropriate

• IND For Clinical Trial vs. Expanded Access

• IND Content

• IND Process
Uses of PET Drugs

• “investigational use” ...
  - Drug administered within a clinical trial/study or other research project
  - IND or RDRC or exempt from IND

• “clinical use” ...
  - Drug administered as part of clinical care
  - Drug approved under NDA/ANDA or otherwise legally marketed
PET Drug Regulation

by Dec 12, 2011

NDA or ANDA must be submitted for clinical use in the U.S.
Which submission is most appropriate?

- NDA / ANDA
- RDRC
- IND Exemption
- IND
**RDRC**

**IND not needed if study is approved by a Radioactive Drug Research Committee (RDRC)**

**RDRC research limited to:**

- Basic science
- Not for diagnostic or therapeutic purpose
- Not an evaluation of drug’s safety/efficacy
- Dose known not to cause any pharm effect
- Radiation dose within specific limits
RDRC Info

www.fda.gov

In search box, “RDRC”
IND Exemption

Sponsor or Sponsor Investigator (SI) determines whether study/trial is exempt

**CRITERIA**

- Drug used has approved NDA or ANDA
- No intent to support new indication, labeling change, or advertising change
- No intent to promote/commercialize the drug
- No significant risk increase (e.g. dose, route of administration, patient population)
- Compliant with IRB/consent process
IND Exemption Info

www.fda.gov

In search box, “21 CFR 312.2”
Should I Be Submitting An IND?

PET drug

- NDA / ANDA
- RDRC
- IND Exemption
- IND
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What is an IND?

An IND Application is a request for authorization from FDA to:

- Administer an investigational drug to humans
- Be exempt from premarket approval requirements
- Ship lawfully
Why is the IND Process Important for PET drugs?

- Drug development & clinical research

- Patient access to:
  - Investigational PET drugs
  - PET drugs already in clinical use and uncommon usage does not justify submission of NDA/ANDA

- IND process active now and continues beyond Dec 12, 2011
**IND Information**

www.fda.gov

In search box, “IND”
IND Webpage Information

- Pre-IND consultation/meeting program
- Guidance documents
- Emergency IND options
- Multiple related aspects (forms, contacts)
- Content and format of IND submissions
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IND Options

PET drug

- NDA / ANDA
- RDRC
- IND Exemption
- IND
  - Clinical Trial
  - Expanded Access
Why is the **IND** Process Important for **PET** drugs?

- **Drug development**
- **Patient access to:**
  - Investigational PET drugs
  - PET drugs already in clinical use and uncommon usage does not justify submission of NDA/ANDA
- **IND process active now and continues beyond Dec 12, 2011**
“Access” to Investigational PET Drugs Via:

Clinical Trial
Primary purpose is to study the drug

Expanded Access
Primary purpose is to diagnose or monitor patient’s disease / condition
Expanded Access

www.fda.gov

In search box, “expanded access”
# Expanded Access

<table>
<thead>
<tr>
<th>C R I T E R I A</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patient(s) with serious or immediately life-threatening disease / condition</td>
</tr>
<tr>
<td>• No satisfactory alternative “therapy”</td>
</tr>
<tr>
<td>• Potential patient benefit justifies potential risks of “treatment” use</td>
</tr>
<tr>
<td>• Provision of drug will not interfere with drug development</td>
</tr>
</tbody>
</table>
Expanded Access Criteria

www.fda.gov

In search box, “21 CFR 312.305”
Expanded Access

Good Clinical Practice

- Informed consent
- IRB approval
- Safety reports & annual reports
- Provide Investigator’s Brochure if exists
- Adherence to expanded access protocol
  - Criteria for patient selection
  - Safety monitoring
Drugs That May Qualify For Expanded Access

Low usage may not justify submission of NDA

**Modernization Act (comply with USP monograph):**

- Carbon monoxide C11 injection
- Fluorodopa F18 injection
- Flumazenil C11 injection
- Mespiperione C11 injection
- Methionine C11 injection
- Raclopride C11 injection
- Sodium acetate C11 injection
- Water O15 injection

But other PET drugs could potentially qualify.
## Drugs That **DO NOT** Qualify For Expanded Access

### Approved PET drugs

- Ammonia N13
- Fludeoxyglucose F18
- Sodium fluoride F18
- Rubidium chloride Rb82

### SUBMIT

- **ANDA** using the NDA product as the reference product

OR

- **505(b)(2)**
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**IND Sponsor, Investigator, Spon.-Invest. (SI)**

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submits IND</td>
<td>Conducts clinical investigation</td>
</tr>
<tr>
<td>Responsible for and initiates clinical investigation</td>
<td></td>
</tr>
<tr>
<td>Individual, institution, or company</td>
<td>Individual</td>
</tr>
</tbody>
</table>

**“Sponsor-investigator”** is an individual who immediately directs the investigational drug administration.

21CFR312 (sections 3, 50 – 70)
**IND Options**

- PET drug
  - NDA / ANDA
  - RDRC
  - IND Exemption
    - Clinical Trial
    - Expanded Access
Trial IND Content

www.fda.gov

In search box, “21 CFR 312.23”

Click on 2nd link
IND Content (p1/2)

1. Form FDA-1571 (cover sheet)
2. Form FDA-3674 (Clinical trials.gov info)
3. Table of contents
4. Introductory statement, including description of clinical investigation
5. Investigator brochure... *not needed for SI*
6. Clinical protocol
7. Informed Consent
8. Background information... *see next slide*
7. Background information... (continued)

a. Chemistry, manufacturing & control (CMC) info

b. Animal and/or clinical pharmacology-toxicology information that supports safety of study/trial

c. Summary of previous PET drug clinical experience

d. Estimate of radiation-absorbed dose to body and critical organs, with justification
Expanded Access IND Content

www.fda.gov

In search box, “21 CFR 312.305”
Expanded Access

**IND Content (p1/4)**

**Identify category in IND submission:**

- Individual patient
- **Intermediate-size patient population**
- Widespread use (treatment IND)
  - Actively pursuing marketing approval
  - Has on-going or completed clinical trials
1. Form FDA-1571 (cover sheet)

2. “Protocol”
   - Title, protocol #
   - Rationale for intended use
   - Criteria for patient selection
   - Drug dose, # of doses, route of administration
   - Safety monitoring
   - Drug production site

3. Estimate of radiation-absorbed dose to body and critical organs, with justification
4. Chemistry, manufacturing & control (CMC)

5. Pharmacology & toxicology to justify dose and duration of use

6. Satisfaction of Expanded Access criteria
   - Serious, life threatening condition
   - No alternative diagnostic agent
   - Potential benefit justifies risks
   - Use will not interfere with trials for marketing approval
Expanded Access

**IND Content (p4/4)**

### Additional Information Required If

**Intermediate-size Population:**

- Is drug under development for marketing approval?
  - Explain why drug cannot be developed OR
  - Explain why patients cannot be enrolled in clinical study

- Planned size of patient population

- Sufficient evidence for safety of drug at proposed dose and duration to justify # of patients

- Preliminary evidence of effectiveness
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IND Submission Logistics

- Paper or electronic
- If paper, supply 3 copies
- Electronic submission similar to pathway for NDA / ANDA
- Contact (email) esub@fda.hhs.gov for questions re: electronic submission
Electronic Submission Info

www.fda.gov

In search box, “CDER Electronic Submission”

Electronic Regulatory Submission and Review

This page provides information about the electronic submission of regulatory information to the Center and the review of it by CDER staff. Additional guidance documents, when available in draft or final form, will be added to these pages.

- Electronic Common Technical Document (eCTD)
- All CDER Guidances on Electronic Submissions
- Requesting a Pre-Assigned Application Number
- Guidance for Formal Meetings with Sponsors and Applicants (PDF - 30KB)
- Submission Addresses
- General Considerations
- Abbreviated New Drug Applications (ANDAs)
- Drug Master Files (DMFs)
IND Submission Logistics

Mail paper submission to:

US Food and Drug Administration
Central Document Room
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

For more info, telephone: 301-796-2050
(Division of Medical Imaging Products)
**IND Process**

- Submission of IND application to FDA by sponsor or Sponsor-Investigator (SI)
- FDA assigns IND number and issues acknowledgement letter
- Clinical trial/study cannot be initiated until 30 days after date of IND receipt, unless otherwise notified by FDA
- FDA will notify sponsor or SI of any deficiencies within the 30 day review period
Can I Administer The PET Drug While My IND Is Being Reviewed?

• Yes, if can provide documentation about current clinical use AND adequate drug quality (e.g. reference USP monograph)

• No, if not in current clinical use

• If unsure, ask FDA
### IND Review and Maintenance

- IND is reviewed by multiple disciplines
  - Project manager, chemistry, pharmacology / toxicology, microbiology, clinical pharmacology, clinical, statistics if appropriate

- Discussion of IND submissions weekly

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**ONCE THE STUDY MAY PROCEED…**

- Submit protocol revisions and new protocols BEFORE initiating them
- Report serious and unexpected adverse events
- Submit annual progress reports
Questions after SNM???

Dr. Kaye Kang

kyong.kang@fda.hhs.gov
telephone: 301-796-2050

Division of Medical Imaging Products
Specific Websites (p1/3)

Electronic Submission:

IND Overview:
**Specific Websites (p2/3)**

**IND Exemption:**
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.2

**Expanded Access:**
http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccessoInvestigationalDrugs/default.htm
Specific Websites (p3/3)

Clinical Trial IND Content:

Expanded Access IND Content:
Register With FDA

Required for:
• Domestic and foreign establishments that produce, repack, or re-label drug products in U.S. (or import / offer import drug products)

New since Jun 1, 2009:
• Must register electronically (next slide)

When must I register?
• Now!
Drug Registration and Listing System

www.fda.gov

In search box, “DRLS”

Business Operation Code
(PET Drug Production) → C91403
Structured Product Labeling

www.fda.gov

In search box, “PET SPL”