FDA Updates: Post <212> Deadline

January 27, 2012

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Division of Medical Imaging Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
If a facility wishes to continue to produce PET drugs for *clinical use* after June 12, 2012, it must have submitted a

- new drug application (NDA) or
- abbreviated new drug application (ANDA) or
- investigational new drug (IND)

by June 12, 2012.
Outline

• History

• Definitions

• Clinical Use
  – Submission options
  – Inspections

• Research and Investigational Use
  – RDRC
  – IND exemption
  – PET drugs in therapeutic trials
Why June 12, 2012?
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>Section 121 of Food Drug Administration Modernization Act:</td>
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<tr>
<td></td>
<td>FDA should establish for PET drugs</td>
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<tr>
<td></td>
<td>• Approval procedures and</td>
</tr>
<tr>
<td></td>
<td>• Current Good Manufacturing Practice (CGMP) requirements</td>
</tr>
<tr>
<td>2009</td>
<td>Procedures &amp; requirements finalized</td>
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<tr>
<td></td>
<td>• Within 2 years, a NDA or ANDA must be submitted for any PET drug</td>
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<tr>
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<td>marketed for clinical use in the U.S.</td>
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## History (page 2 of 2)

<table>
<thead>
<tr>
<th>2011 December 6</th>
<th>Notice of FDA Exercise of Enforcement Discretion for PET Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• FDA received requests to extend submission deadline</td>
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<tr>
<td></td>
<td>• FDA concerned about creating barrier to access in certain areas</td>
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<tr>
<td></td>
<td>• FDA yet to issue 2 guidances (IND, Q&amp;As)</td>
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</tbody>
</table>

• FDA will not exercise enforcement discretion after **June 12, 2012**
  (so **submit** your NDA, ANDA, or IND!).

• All producers of PET drugs for clinical use must be operating under an **approved** NDA or ANDA, or **effective** IND, by **December 12, 2015**.


FDA Notice: PET Drugs

Exercise of Enforcement Discretion

www.fda.gov

Search: “Positron Emission Tomography”

-- 2nd result --
How does clinical use differ from investigational use and research use?
Definitions

Clinical use
- Using as a component of clinical care
- No intent to systematically study safety or effectiveness of the drug

Investigational use
- Use in a study to establish the safety or effectiveness of a new use of the drug to support approval
- Use of certain PET drugs for clinical purposes (expanded access IND)

Research use
- Use in a study of the drug for basic science research
- Not using for immediate therapeutic, diagnostic, or similar purpose
- No intent to determine safety or effectiveness for clinical use
Outline

• History

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• Research and Investigational Use
  – RDRC
  – IND exemption
  – PET drugs in therapeutic trials
I have been producing a PET drug for *clinical* use.

What should I submit to FDA to continue *clinical* use?
Submission Options if Currently (before 06/12/12) Producing for *Clinical* Use

FDG, NaF, or ammonia?

Yes

Submit NDA / ANDA before 06/12/12, or risk enforcement action until you submit
What if the PET drug I have been producing for *clinical* use is not FDG, NaF, or ammonia?

What should I submit to FDA to continue *clinical* use?
Submission Options if Currently (before 06/12/12) Producing for *Clinical* Use

FDG, NaF, or ammonia?  

- **Yes**  
  - Submit NDA / ANDA before 06/12/12, or risk enforcement action until you submit

- **No**  
  - Submit
  - NDA or
  - expanded access IND (if criteria are met)
  by 06/12/12, or risk enforcement action until you submit
Can you tell me more about expanded access IND?
Expanded Access

www.fda.gov

Search: “expanded access”
Expanded Access

3rd bullet
Expanded Access

**CRITERIA**

- Patient(s) with serious or immediately life-threatening disease / condition
- No satisfactory alternative “therapy”
- Potential patient benefit justifies potential risks of “treatment” use
- Provision of drug will not interfere with drug development
Expanded Access

**C R I T E R I A (in the context of PET drugs)**

- Patient(s) with serious or immediately life-threatening disease / condition
  - **Serious**: Associated with morbidity that has substantial impact on day-to-day functioning
  - **Life threatening**: Reasonable likelihood of death within months or premature death without treatment
  - **For a PET drug**: To help detect serious disease / condition in patients without active disease manifestation is considered use for a serious disease or condition
## Expanded Access

### CRITERIA (in the context of PET drugs)

- Patient(s) with serious or immediately life-threatening disease / condition
- No satisfactory alternative “therapy”
- Potential patient benefit justifies potential risks of “treatment” use
- Provision of drug will not interfere with drug development

**Diagnose, monitor, or treat**

- No satisfactory alternative “therapy”
  
  - **Alternative therapy:** Specified in approved labeling
  
  - **For a PET drug:** Unique capability (e.g. assess metabolic activity or identify receptors) might satisfy criteria because information provided is of different nature from that provided by other imaging modalities
Expanded Access

CRITERIA (in the context of PET drugs)

- **Basis of determination:**
  - Available evidence to support treatment use
  - Population exposed (size, nature)
  - Relative seriousness of disease / condition

- **Potential patient benefit justifies potential risks of “treatment” use**

  - **For a PET drug:** FDA anticipates risks of diagnostic use not unreasonable in most patient populations when used to assist in diagnosis of serious conditions (relatively low mass dose & radiation dose)
**Expanded Access**

**CRITERIA (in the context of PET drugs)**

- **Patient(s) with serious or immediately life-threatening disease / condition**
- **No satisfactory alternative “therapy”**
- **Potential patient benefit justifies potential risks of “treatment” use**
- **Provision of drug will not interfere with drug development**

- **For a PET drug:** FDA anticipates expanded access INDs for PET drugs will generally be used in situations in which it is not feasible to develop the PET drug for marketing approval

- **Provision of drug will not interfere with drug development**
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

<table>
<thead>
<tr>
<th>Modernization Act (comply with USP monograph):</th>
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<tbody>
<tr>
<td>• Carbon monoxide C11</td>
</tr>
<tr>
<td>• Fluorodopa F18 injection</td>
</tr>
<tr>
<td>• Flumazanil C11 injection</td>
</tr>
<tr>
<td>• Mespiperione C11 injection</td>
</tr>
<tr>
<td>• Methionine C11 injection</td>
</tr>
<tr>
<td>• Raclopride C11 injection</td>
</tr>
<tr>
<td>• Sodium acetate C11 injection</td>
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<tr>
<td>• Water O15 injection</td>
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</table>

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) NDA**
Expanded Access IND Content

www.fda.gov

Search: “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
Expanded Access

IND Content (p2/4)

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
Expanded Access

IND Content (p3/4)

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)**

**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
Can I recover costs with an expanded access IND?
Request to Charge

www.fda.gov

Search: “charging for investigational drug”
Recoverable Costs with Expanded Access IND
(typically 1 year authorization)

- **Individual patient**
  - Only direct costs

- **Intermediate-size patient population**
  - Direct costs
  - Indirect administrative costs
    - Including costs associated with monitoring the IND, complying with IND reporting requirements
Request to Charge Submissions

- **Cover letter:**
  - Prominently highlight that IND submission is a “Request to Charge”

- **Submission:**
  - A component of an original IND application, or
  - An amendment to an existing IND

- **Questions?**

  Dr. Kaye Kang  
  kyong.kang@fda.hhs.gov  
  telephone: 301-796-2050  
  (Division of Medical Imaging Products)
Request to Charge Submission Content
(Expanded Access--intermediate-size patient population)

• Provide assurance that charging will not interfere with developing the drug for marketing approval
  – e.g. Limited use
  – e.g. on-site preparation or limited distribution region (short half-life)

• Define same number of patients for charging and for expanded access

• Describe proposed cost per patient & justification
  (consistent with 21 CFR 312.8(d)(1) and (d)(2))

• Provide statement by independent certified public accountant
I have NOT been producing a PET drug for clinical use, but I want to start.

What should I submit to FDA, and by when?
Submission Options if NOT Producing for *Clinical* Use Before 06/12/12

**FDG, NaF, or ammonia?**

**Yes**

- Submit NDA / ANDA before 06/12/12 and begin production
- If you submit after 06/12/12, wait until NDA/ANDA approval before starting production for clinical use
What if the PET drug I want to start producing for clinical use is not FDG, NaF, or ammonia?

What should I submit to FDA, and by when?
Submission Options if NOT Producing for Clinical Use Before 06/12/12

FDG, NaF, or ammonia?

Yes

• Submit NDA / ANDA before 06/12/12 and begin production
• If you submit after 06/12/12, wait until NDA/ANDA approval before starting production for clinical use

No

Obtain approved NDA or effective IND before you may begin production for clinical use
Can you summarize what you’ve said so far regarding submission requirements for *clinical* use of PET drugs?
See **APPENDIX A** in:

**Guidance**

**FDA Regulation of PET Drug Products**

**Questions and Answers**

[Date]
Procedural
I’ve submitted my NDA/ANDA. Any advice regarding inspections?

Answer:

1. Links on Exercise of Enforcement Discretion webpage
2. Info in Q&As Guidance
3. Links on FDA Compliance and Enforcement Actions webpage
Advice on Inspections

1. Links on Exercise of Enforcement Discretion webpage

2. Info in Q&As Guidance

3. Links on FDA Compliance and Enforcement Actions webpage
FDA Notice: PET Drugs
Exercise of Enforcement Discretion

www.fda.gov

Search: “Positron Emission Tomography”
-- 2nd result --

And scroll down...
Middle of the page...

1a

1b

2

3

**CGMP for PET Drugs**
- Small Entity Compliance Guide: PET Drugs - Current Good Manufacturing Practice (CGMP) (PDF - 228KB)
- Federal Register Notice: Final Rule - CGMP for PET Drugs
- PET Drug Products - Current Good Manufacturing Practice (CGMP) (PDF - 399KB)
  Guidance document issued 12/9/2009
- Positron Emission Tomography (PET): Questions and Answers about CGMP Regulations for PET Drugs (12/9/2009)
- Positron Emission Tomography (PET): Additional Questions and Answers Based on December 9, 2009 Stakeholder Call (4/8/2010)

**Compliance Program Guidance Manual**
FDA has posted the Compliance Program Guidance Manual for PET CGMP drug inspections. FDA’s Compliance Programs provide instructions to FDA personnel for inspecting facilities, sampling and analyzing FDA-regulated products, and initiating and implementing regulatory follow up, when appropriate. FDA personnel who will be involved in evaluating PET production facilities are being trained to use the PET Compliance Program, to know the PET CGMP regulations and guidance, and to understand the unique aspects of PET production. FDA will offer webinars to the PET community to explain this program and provide general information about FDA inspection practices beginning in 2012.
- CPGM: PET CGMP Drug Process and Pre-approval Inspections/Investigations (PDF - 182KB)

**Historical Information**
- Historical Information on Positron Emission Tomography (PET)

**Contact Us**
For more information contact the PET working group, by e-mail at: PETDrugs@fda.hhs.gov.

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**Public Meeting Information**
- Preparing NDAs or ANDAs for fludeoxyglucose (FDG) 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection used in PET imaging; Public Meeting
- Webinar on CGMP for PET Drugs
Guidance

PET Drugs — Current Good Manufacturing Practice (CGMP)

(Small Entity Compliance Guide)

August 2011
Compliance
Guidance

PET Drugs — Current Good Manufacturing Practice (CGMP)

December 2009
Compliance
# CHAPTER 56 - DRUG QUALITY ASSURANCE

**SUBJECT:**
- POSITRON EMISSION TOMOGRAPHY (PET)
- CGMP DRUG PROCESS AND PRE-APPROVAL INSPECTIONS/INVESTIGATIONS

**REF:** 7356.002 (2/01/2002) and 7346.832 (5/10/2010)

**IMPLEMENTATION DATE:**
- 12/12/2011

**COMPLETION DATE:**
- 12/11/2014

**DATA REPORTING**

<table>
<thead>
<tr>
<th>PRODUCT CODES</th>
<th>PROGRAM ASSIGNMENT CODES</th>
</tr>
</thead>
<tbody>
<tr>
<td>All PET Drugs</td>
<td>56002P Drug Process Inspections (PET)</td>
</tr>
<tr>
<td>Industry code: 65</td>
<td>46832P Positron Emission Tomography (PET) Pre-Approval Inspections/Investigations (NDA)</td>
</tr>
<tr>
<td>Profile Class code: PET</td>
<td>52832P Positron Emission Tomography (PET) Pre-Approval Inspections/Investigations (ANDA)</td>
</tr>
</tbody>
</table>

**10/5/2011**
# Webinar on CGMP for PET Drugs

FDA is presenting a webinar on CGMPs for PET Drugs.

**Date:** January 19, 2012

**Time:** 1:00 p.m. - 3:00 p.m. EST

**Link:** [https://collaboration.fda.gov/cderpet/](https://collaboration.fda.gov/cderpet/)

**Conference number:** (866) 771-2454, and participant code: 84786087
Advice on Inspections

1. Links on Exercise of Enforcement Discretion webpage

2. Info in Q&As Guidance

3. Links on FDA Compliance and Enforcement Actions webpage
See General Questions & Inspections in:

Guidance

FDA Regulation of PET Drug Products

Questions and Answers

[Date]
Procedural
Are inspections required before continuing production at a site included in an NDA / ANDA submitted by 06/12/12?

Answer: The facility does not need to be inspected before production of PET drugs can continue.
Can academic sites schedule the initial FDA inspection in advance?

**Answer:**
Yes.

**Note:** For-cause inspections are not scheduled in advance.
For an NDA / ANDA submitted before 06/12/12, can the production method be changed before the initial inspection of the facility?

Answer:
Yes. Submit an amendment to the application. Include:

- supporting data;
- description of all changes & controls required;
- assessment of effect on identity, strength, purity, & quality
For Changes in Equipment or Facilities, See **APPENDIX B** in:

**Guidance**

**FDA Regulation of PET Drug Products**

**Questions and Answers**

[Date]
Procedural
Advice on Inspections

1. Links on Exercise of Enforcement Discretion webpage

2. Info in Q&As Guidance

3. Links on FDA Compliance and Enforcement Actions webpage
FDA Compliance and Enforcement Actions

Search: “FDA compliance and enforcement actions”

Lower down, see link to “Warning letters” (section III.A.)
Switch Gears

From: Clinical Use

To: Research & Investigational Use
Outline

• History

• Definitions

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  – Submission options
  – Inspections

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  – RDRC
  – IND exemption
  – PET drugs in therapeutic trials
Definitions

Clinical use
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- Use in a study to establish the safety or effectiveness of a new use of the drug to support approval
- Use of certain PET drugs for clinical purposes (expanded access IND)

Research use
- Use in a study of the drug for basic science research
- Not using for immediate therapeutic, diagnostic, or similar purpose
- No intent to determine safety or effectiveness for clinical use
I’m administering PET drugs to humans, but *NOT* for a *clinical* use/purpose.

What should I submit to FDA, and by when?
Submission Options for PET Drug Uses Other Than *Clinical* Use / Purpose

- **Meet RDRC criteria?**
  - Yes: Obtain RDRC approval
  - No: Meet IND exemption criteria?
    - Yes: Submit nothing
    - No: Submit traditional IND
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 pharmacologic effect
- Radiation dose within specific limits
In search box, “RDRC”
Submission Options for PET Drug Uses Other Than *Clinical* Use / Purpose

- **Meet RDRC criteria?**
  - Yes: Obtain RDRC approval
  - No: Continue to the next step

- **Meet IND exemption criteria?**
  - Yes: Submit nothing
  - No: Submit traditional IND

- **RDRC criteria?**
  - Yes: Obtain RDRC approval
  - No: Continue to the next step

- **IND exemption criteria?**
  - Yes: Submit nothing
  - No: Submit traditional IND
IND Exemption Info

www.fda.gov
In search box, “21 CFR 312.2”
IND Exemption

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

**Criteria**

- Drug is lawfully marketed
- 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

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

**C R I T E R I A**

- Drug is lawfully marketed

Before 12/12/2015
- PET drug used in the trial is made at a facility included in NDA/ANDA submission

After 12/12/2015
- Approved NDA/ANDA
IND Exemption

Before December 12, 2015

C R I T E R I A

• PET drug used in the trial is made at a facility included in a submitted NDA/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

After December 12, 2015

CRITERIA

• PET drug used in the trial is included in an approved NDA/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
Is a drug with a USP monograph exempt from IND?

Answer: No.
By when should I submit my IND application (if not exempt from IND)?

Answer: By June 12, 2012
Anticipated Guidance

Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs

[Date]
Clinical/Medical
See INDs in:

Guidance

FDA Regulation of PET Drug Products

Questions and Answers

[Date]
Procedural
If an approved PET drug is used in an investigational therapeutic trial, does there need to be an IND for the PET drug \textit{and} an IND for the therapeutic drug?

\textbf{Answer:}

No. The therapeutic IND should provide documentation that the PET drug is sourced from a facility with an approved NDA or ANDA.
For a PET drug that has not been approved, do I need to submit CMC info to an IND in effect for a therapeutic drug?

**Answer:**

Before Dec 12, 2015:
No, as long as the PET drug is manufactured at a facility named in an NDA/ANDA submission.

After Dec 12, 2015:
Yes, if the PET drug is not manufactured at a facility named in an approved NDA/ANDA.
Thank you!
Additional questions?
Contact us at: PETDrugs@fda.hhs.gov