# FDA Updates: Post <212> Deadline

January 27, 2012

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**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?

# History (page 1 of 2)

| | |
|---|---|
| **1997** | **Section 121 of Food Drug Administration Modernization Act:**<br>**FDA should establish for PET drugs**<br>• **Approval procedures and**<br>• **Current Good Manufacturing Practice (CGMP) requirements** |
| **2009**<br>**December 9** | **Procedures & requirements finalized**<br>• **Within 2 years, a NDA or ANDA must be submitted for any PET drug marketed for clinical use in the U.S.** |

# History (page 2 of 2)

| 2011<br>December 6 | Notice of FDA Exercise of Enforcement Discretion for PET Drugs<br>• FDA received requests to extend submission deadline<br>• FDA concerned about creating barrier to access in certain areas<br>• FDA yet to issue 2 guidances (IND, Q&As) |
|---|---|

- 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

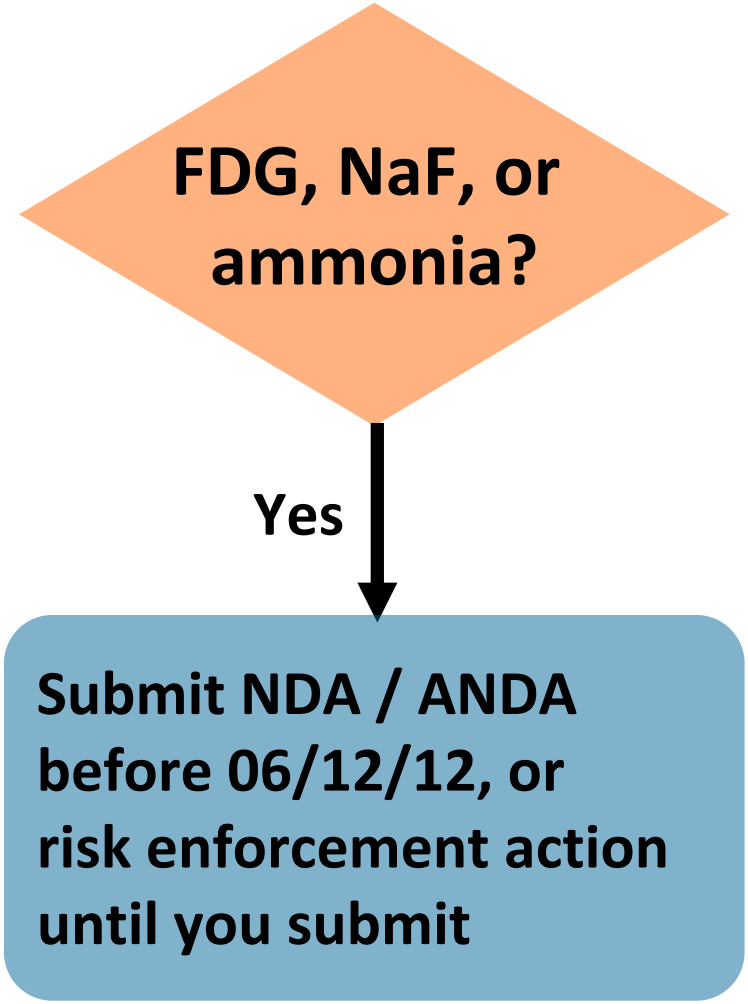
# Outline

- History
- Definitions
- Clinical Use
  - Submission options
  - Inspections
- 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?**

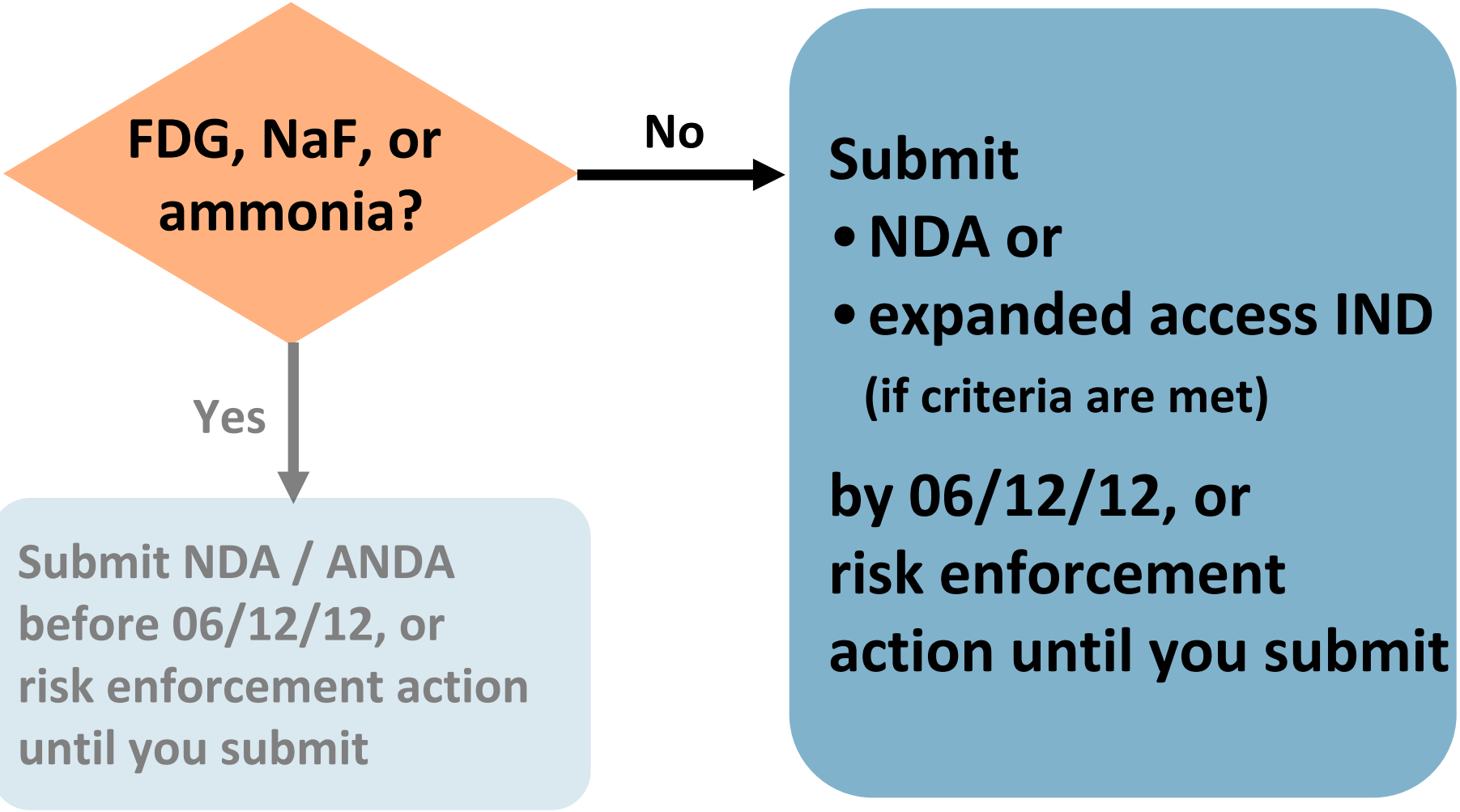
# Submission Options if Currently (before 06/12/12) Producing for *Clinical* Use



# 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

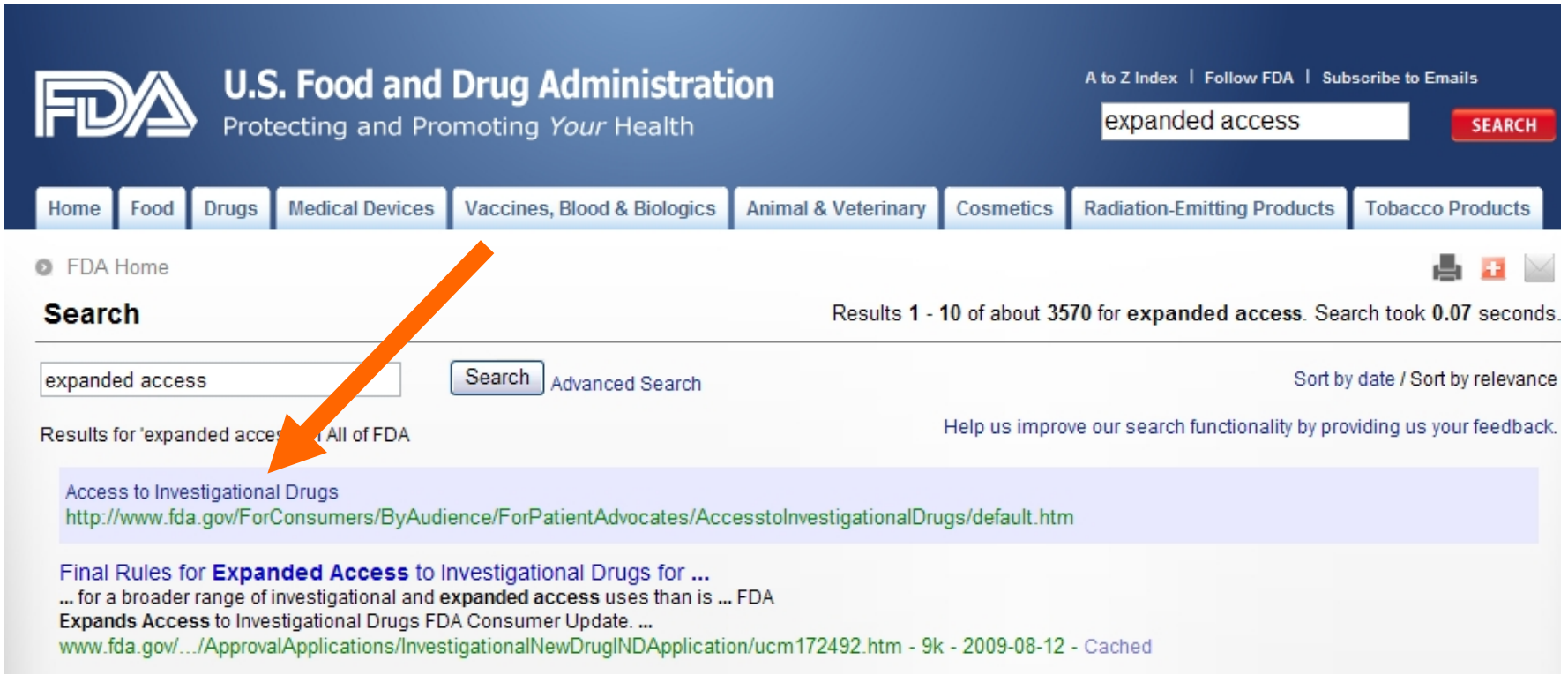


# Can you tell me more about expanded access IND?

# Expanded Access

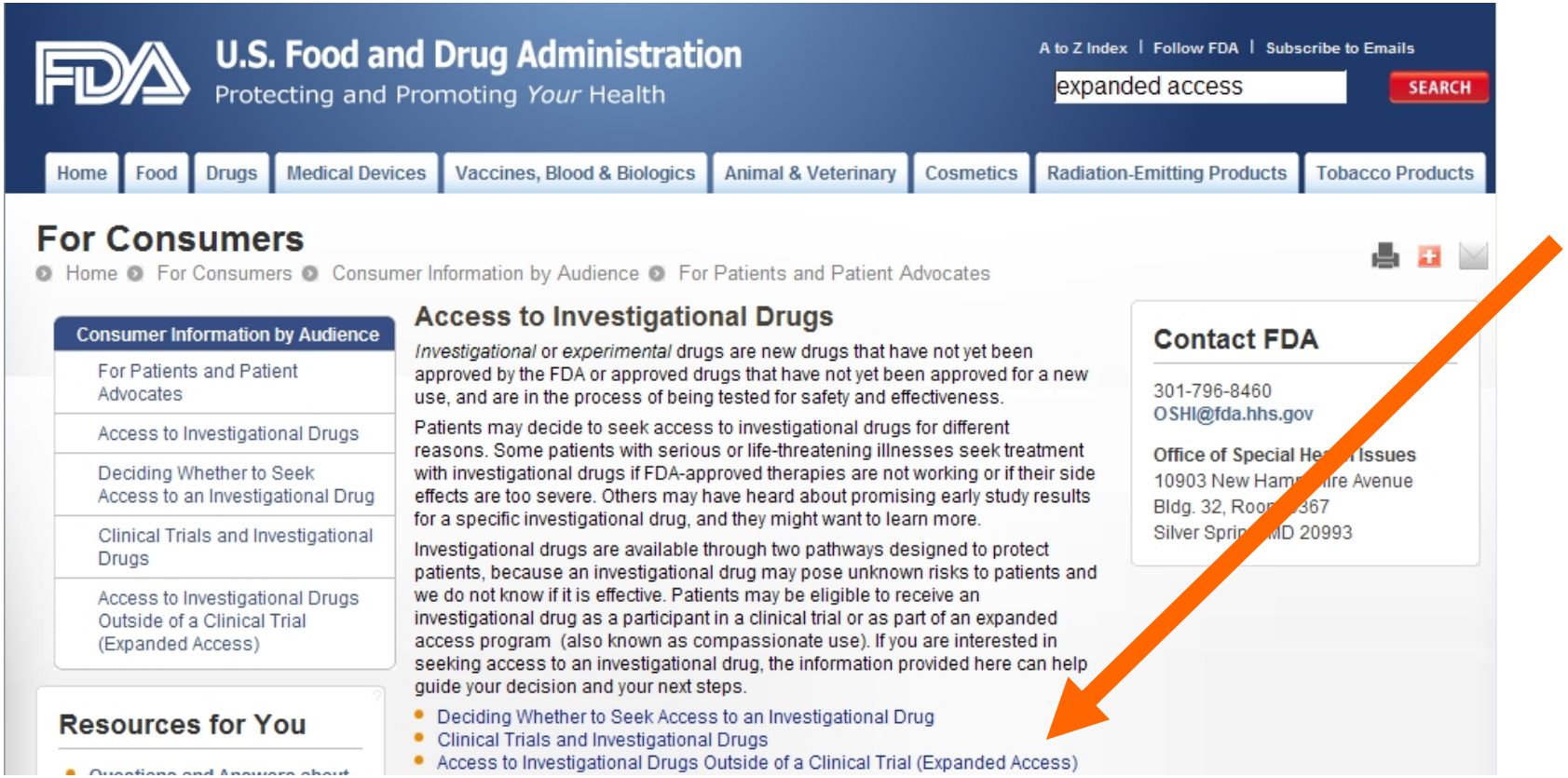
**www.fda.gov**

**Search: "expanded access"**



# Expanded Access

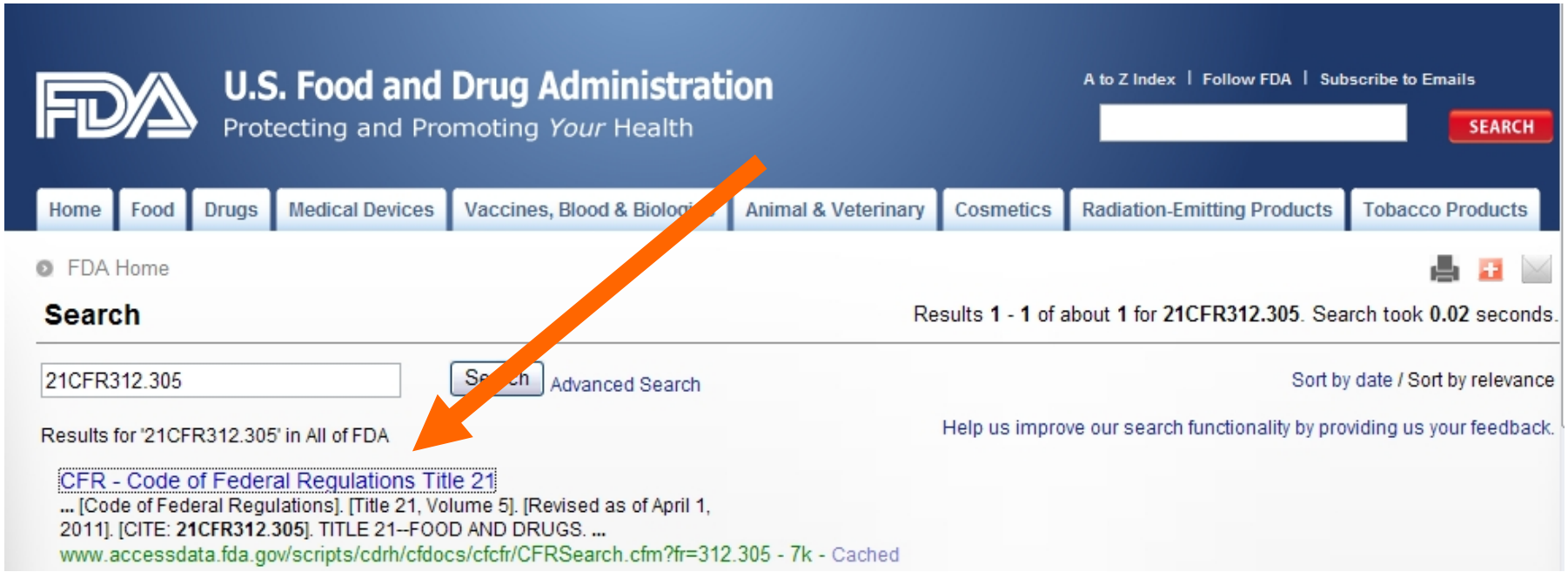
## 3rd bullet



# Expanded Access Criteria

**www.fda.gov**

**Search: "21 CFR 312.305"**



# Expanded Access

## C R I T E R I A

- 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 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

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

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

## C R I T E R I A *(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

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

- **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**

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

- Carbon monoxide C11
- Fluorodopa F18 injection
- Flumazanil 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**

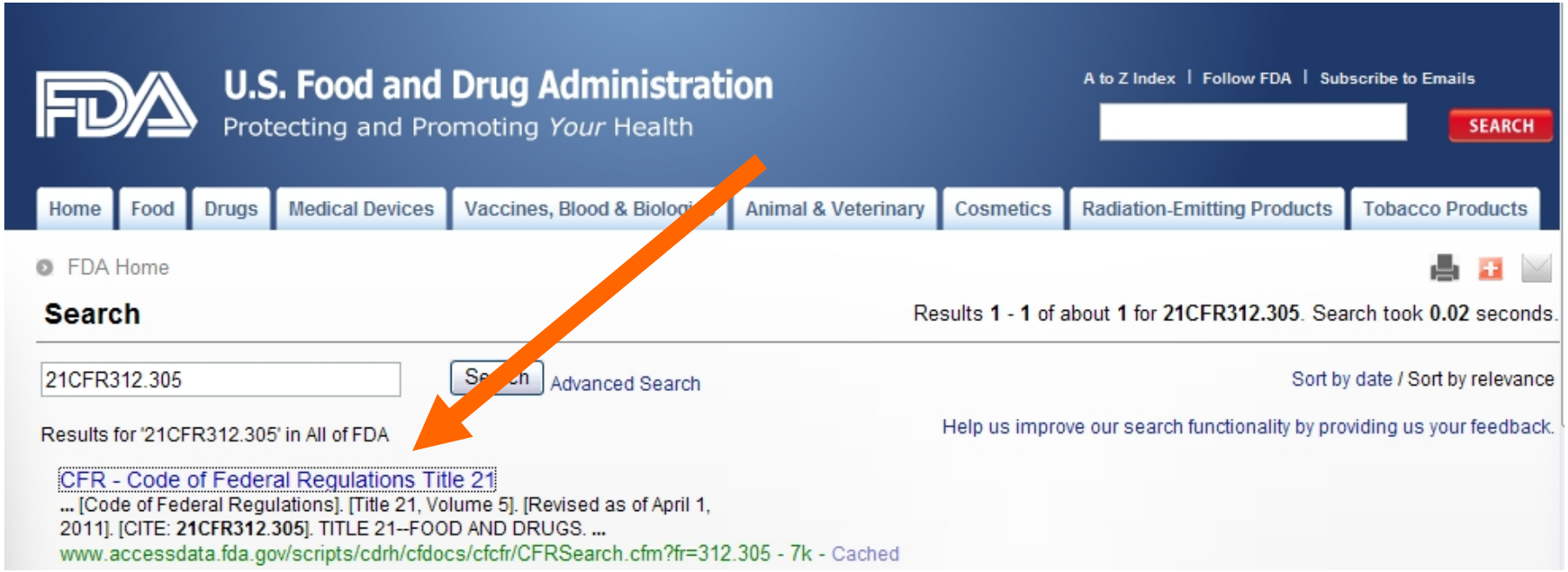
**OR**

- **505(b)(2) 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)

### 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**

# 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?**

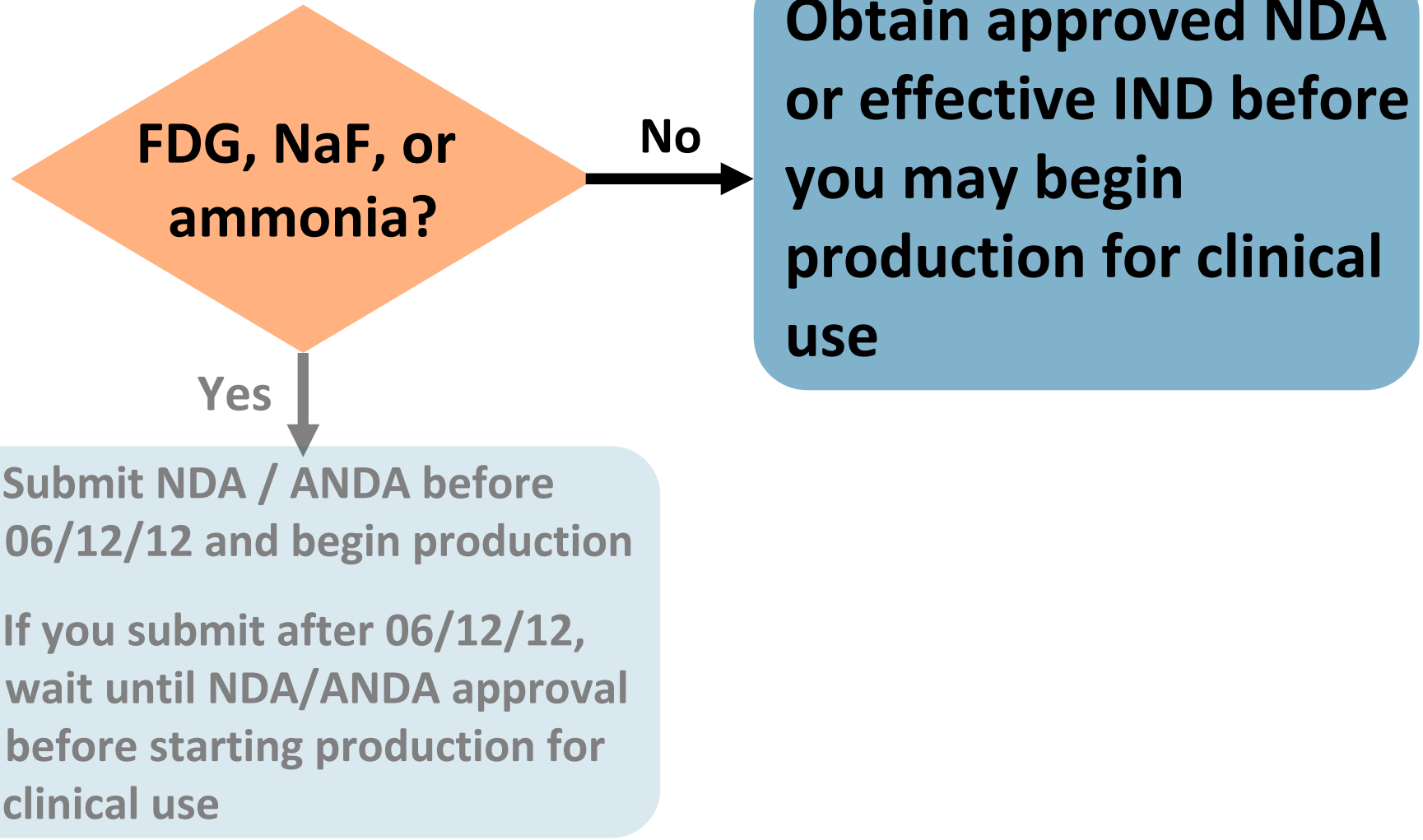
# Submission Options if NOT Producing for *Clinical* Use Before 06/12/12


- 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



# 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 →

**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

1b →

- 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)

2 →

**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.

## 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

3 →

# 1a

# Guidance

## PET Drugs — Current Good Manufacturing Practice (CGMP)

*(Small Entity Compliance Guide)*

**August 2011**
**Compliance**

# 1b

# Guidance

## PET Drugs — Current Good Manufacturing Practice (CGMP)

**December 2009**
**Compliance**

2

**FOOD AND DRUG ADMINISTRATION**
**COMPLIANCE PROGRAM GUIDANCE MANUAL**

PROGRAM 7356.002P

## CHAPTER 56 - DRUG QUALITY ASSURANCE

| SUBJECT: | IMPLEMENTATION DATE |
|---|---|
| POSITRON EMISSION TOMOGRAPHY (PET)<br>CGMP DRUG PROCESS AND PRE-APPROVAL INSPECTIONS/INVESTIGATIONS | 12/12/2011 |
| REF: 7356.002 (2/01/2002) and 7346.832 (5/10/2010) | COMPLETION DATE<br>12/11/2014 |

| DATA REPORTING | |
|---|---|
| PRODUCT CODES | PROGRAM ASSIGNMENT CODES |
| All PET Drugs<br>Industry code: 65<br>Profile Class code: PET | 56002P Drug Process Inspections (PET)<br>46832P Positron Emission Tomography (PET) Pre-Approval Inspections/Investigations (NDA)<br>52832P Positron Emission Tomography (PET) Pre-Approval Inspections/Investigations (ANDA) |

**10/5/2011**

# 3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Protecting and Promoting Your Health
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Manufacturing
Development & Approval Process (Drugs)
Manufacturing
Drug Applications and Current Good Manufacturing Practice (CGMP) Regulations
Positron Emission Tomography (PET)
Questions and Answers on Current Good Manufacturing Practices (CGMP) for Drugs
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/
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:*

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# Guidance

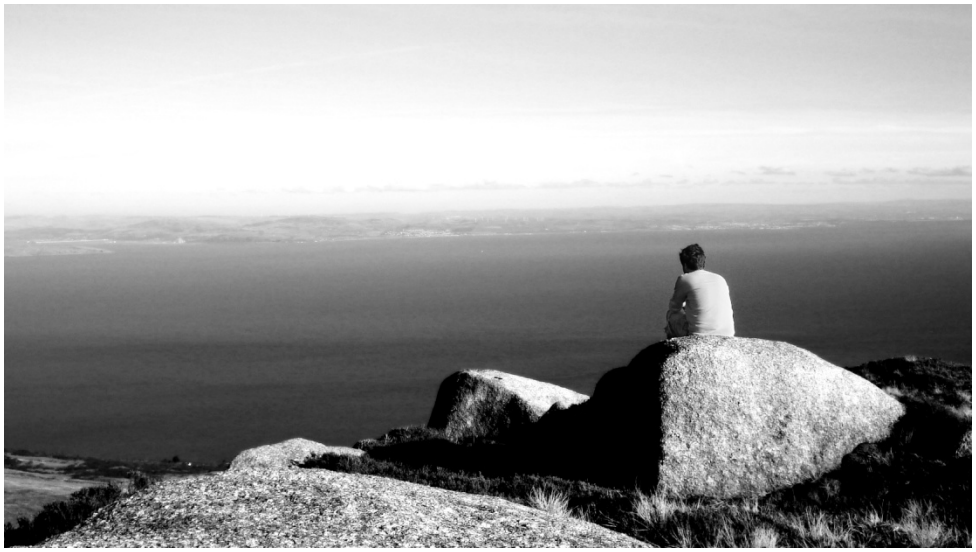
## FDA Regulation of PET Drug Products

## 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.**

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**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

## www.fda.gov

**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
- Clinical Use
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- Research and Investigational Use
  - RDRC
  - IND exemption
  - PET drugs in therapeutic trials

# 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)

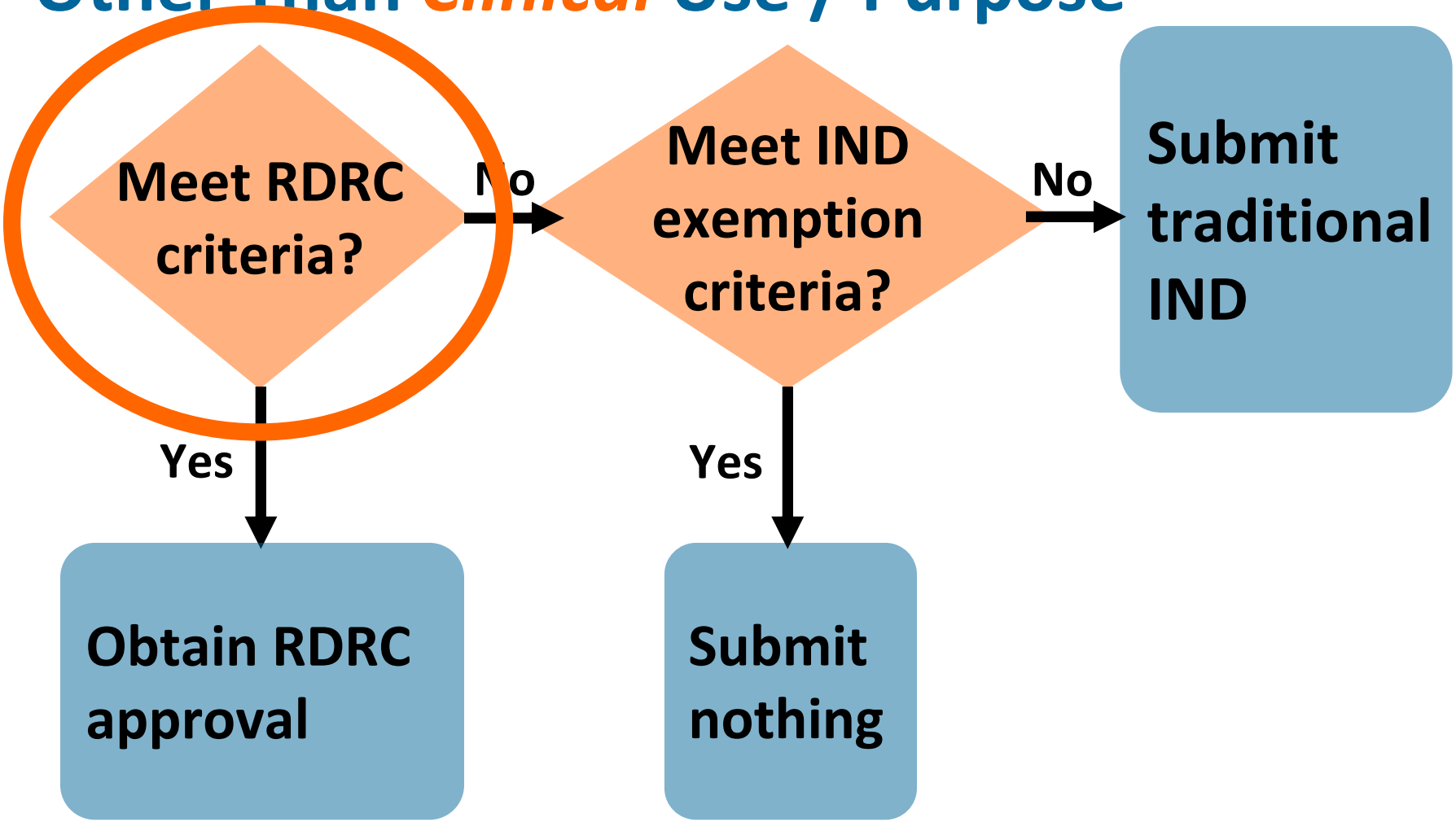
## Research use

- 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

# 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



# RDRC

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

### *RDRC research limited to:*

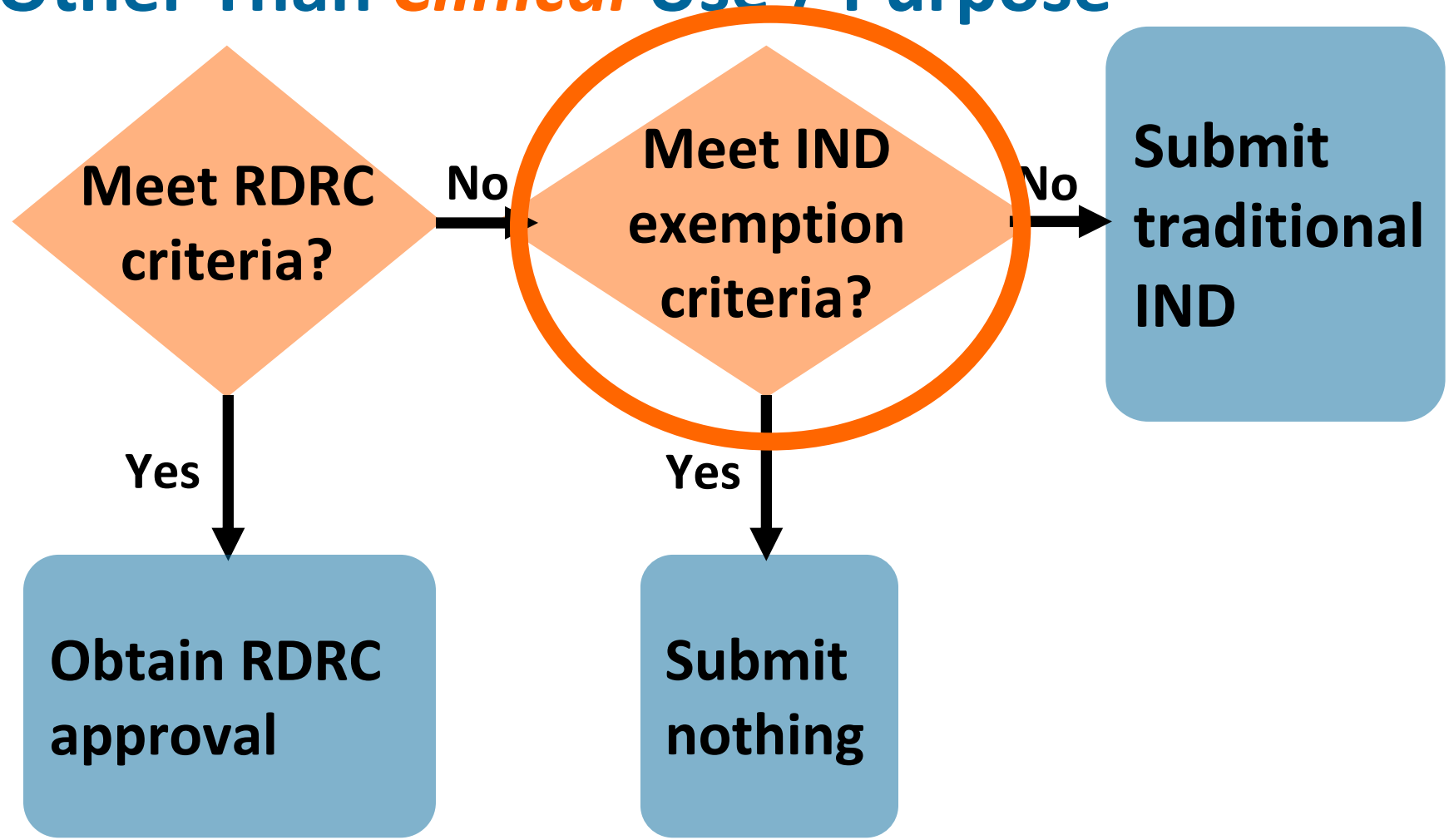
- **Basic science**
- **Not for diagnostic or therapeutic purpose**
- **Not an evaluation of drug's safety/efficacy**
- **Dose known not to cause any pharmacologic effect**
- **Radiation dose within specific limits**

# RDRC Info

## www.fda.gov

## In search box, "RDRC"

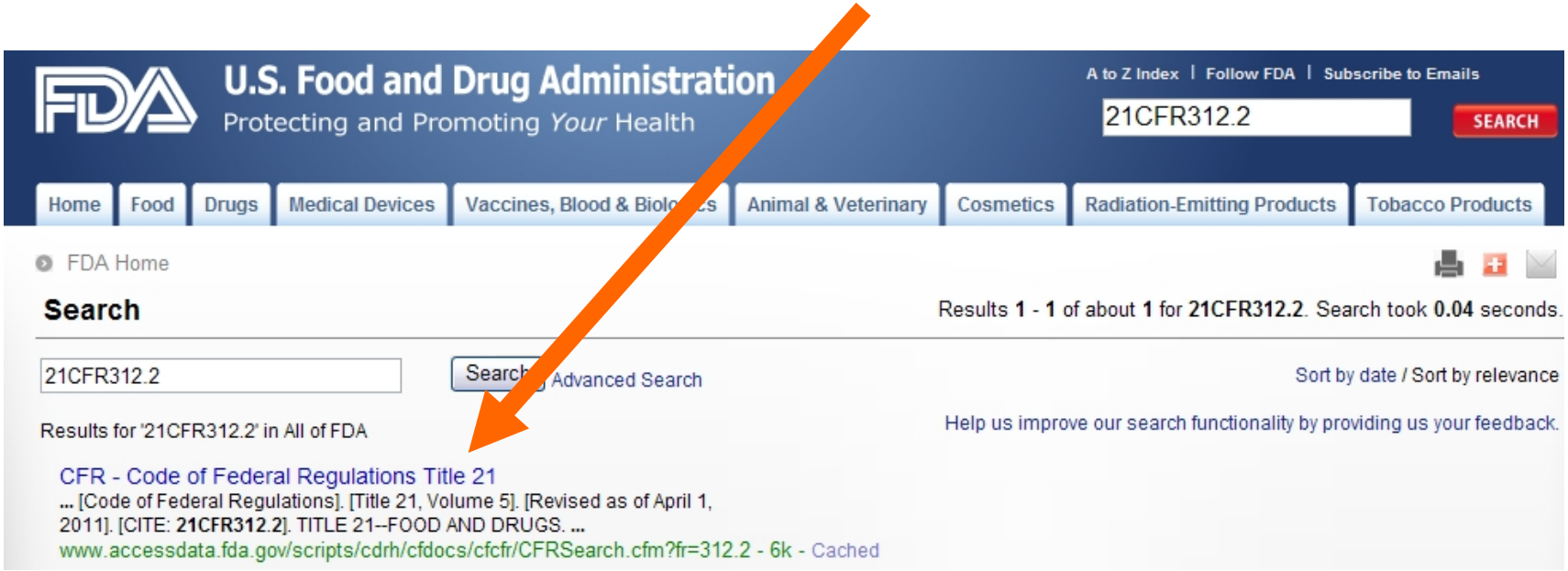
# Submission Options for PET Drug Uses Other Than *Clinical* Use / Purpose



# 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*

### C R I T E R I A

- **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

### C R I T E R I A

- **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

## 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 *and* an IND for the therapeutic drug?

**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