Submitting a PET Drug Investigational New Drug (IND) Application

June 4, 2011

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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

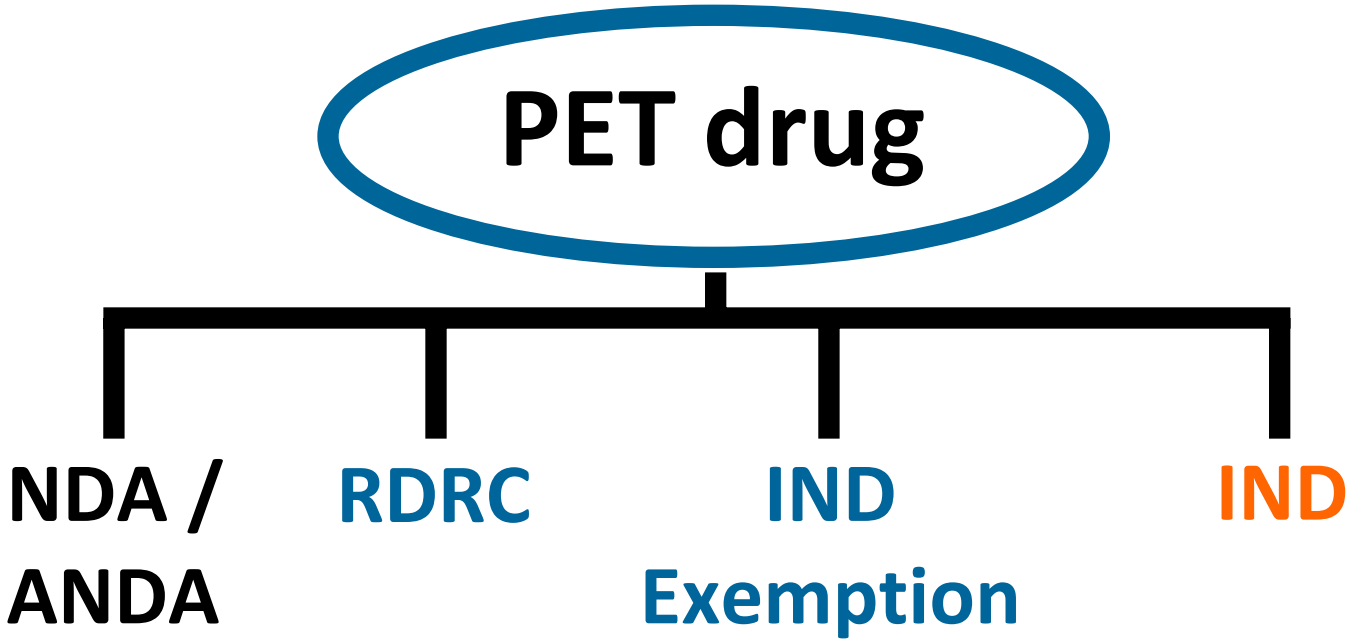
- **"investigational use" …**
  - **Drug administered within a clinical trial/study or other research project**
  - **IND or RDRC or exempt from IND**
- **"clinical use" …**
  - **Drug administered as part of clinical care**
  - **Drug approved under NDA/ANDA or otherwise legally marketed**

PET Drug Regulation

by Dec 12, 2011

NDA or ANDA must be submitted for any PET drug marketed for clinical use in the U.S.

Which submission is most appropriate?



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

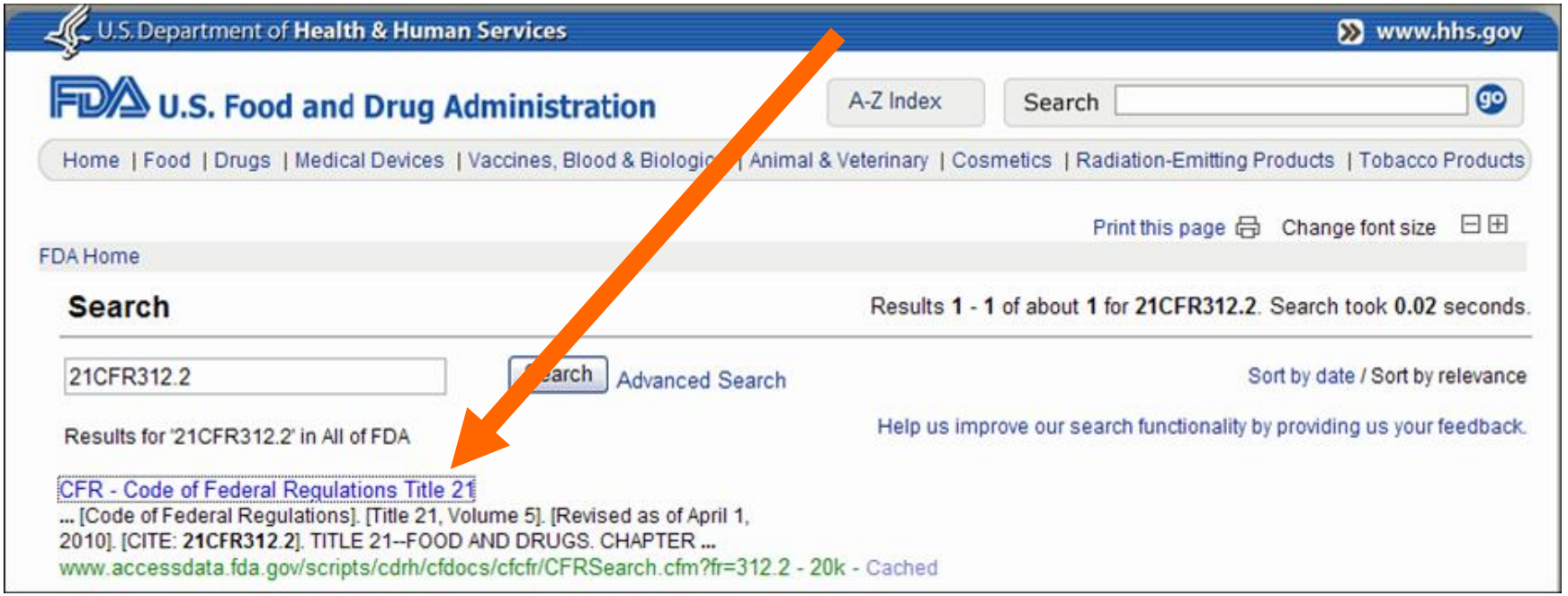
C R I T E R I A

- **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**

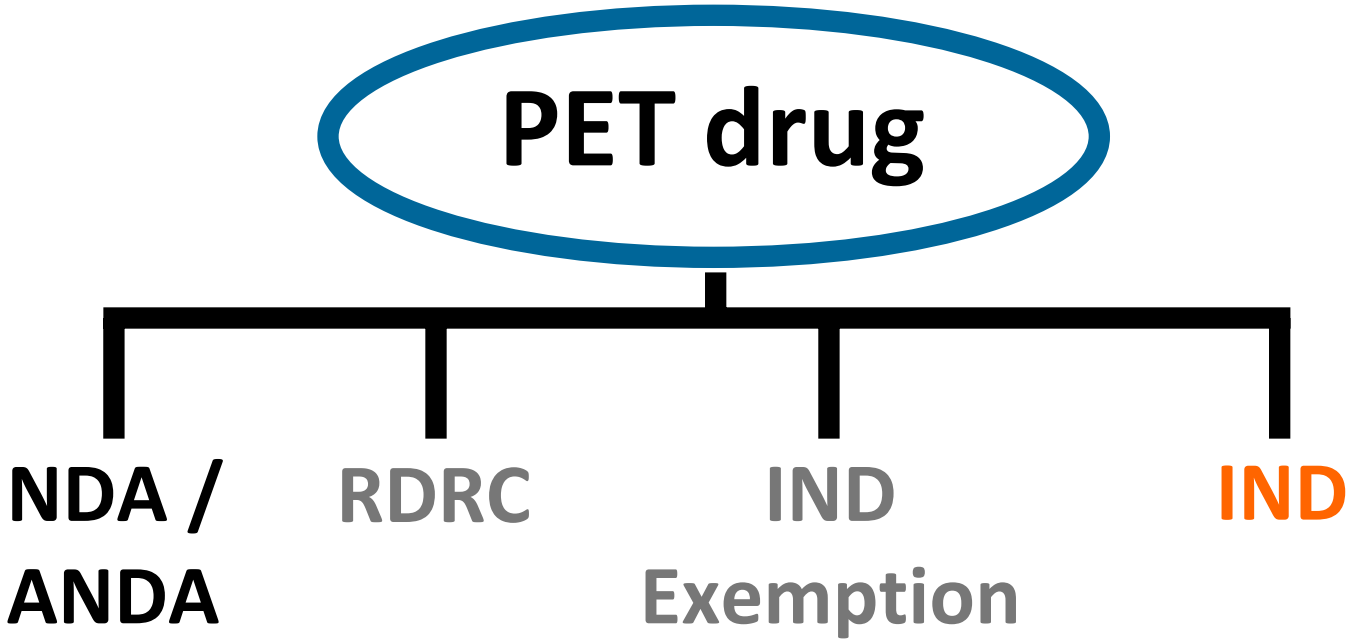
IND Exemption Info

www.fda.gov

In search box, "21 CFR 312.2"



Should I Be Submitting An IND?



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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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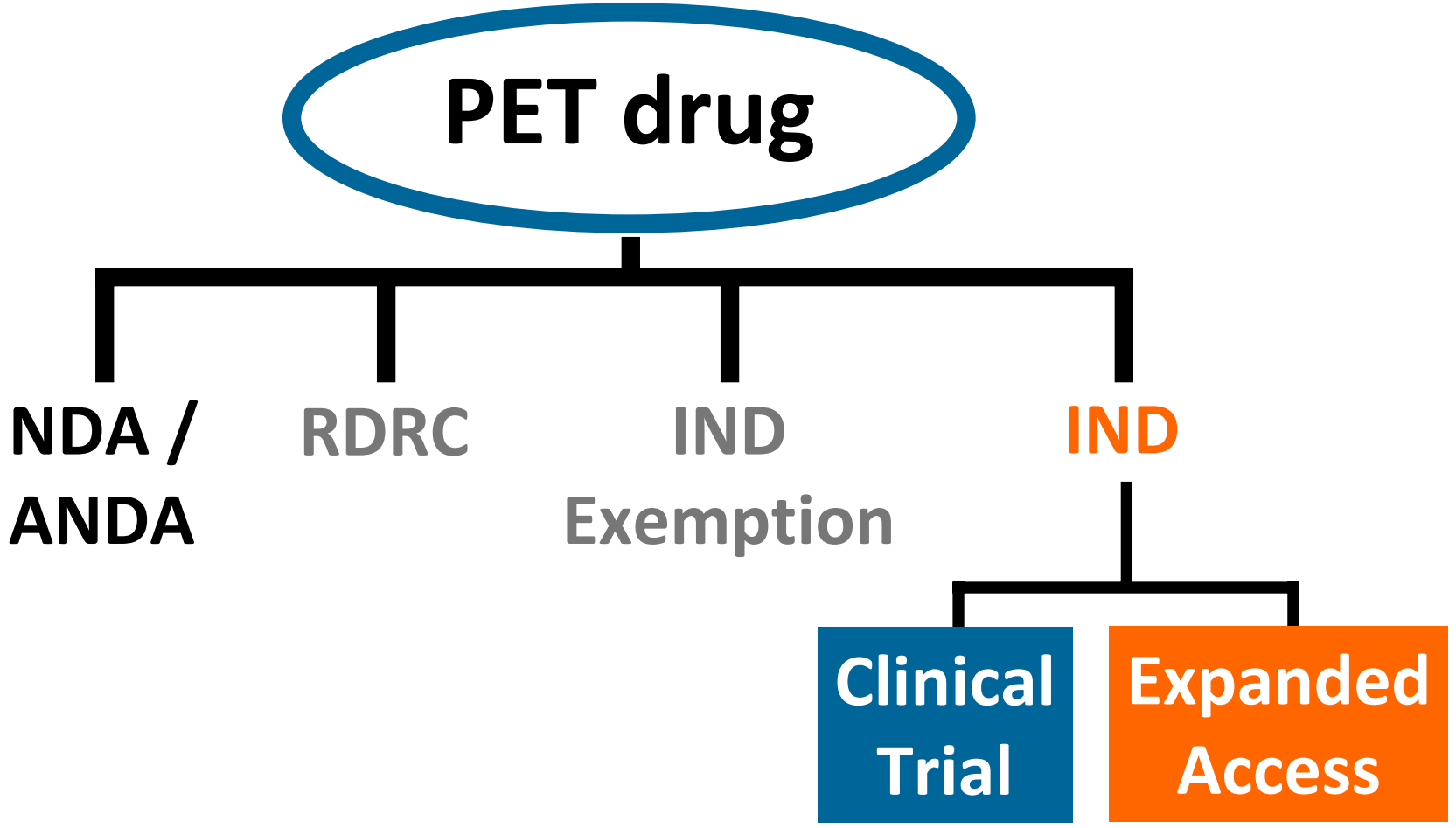
IND Options


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

Why is the IND Process Important for PET drugs?

- **Drug development** — **Clinical Trial**
- **Patient access to:** — **Expanded Access**
  - **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

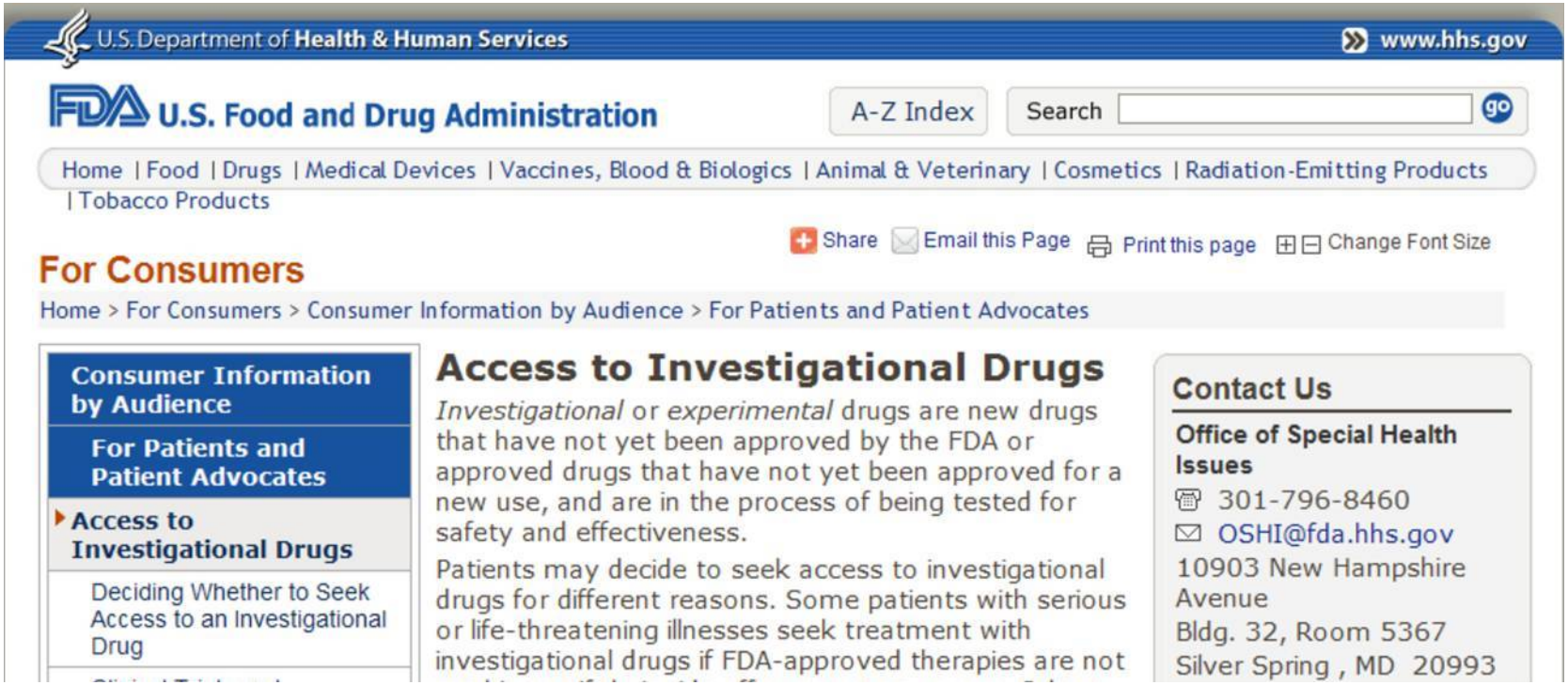
Expanded Access

Primary purpose is to diagnose or monitor patient's disease / condition

Expanded Access

www.fda.gov

In search box, "expanded access"



Expanded Access

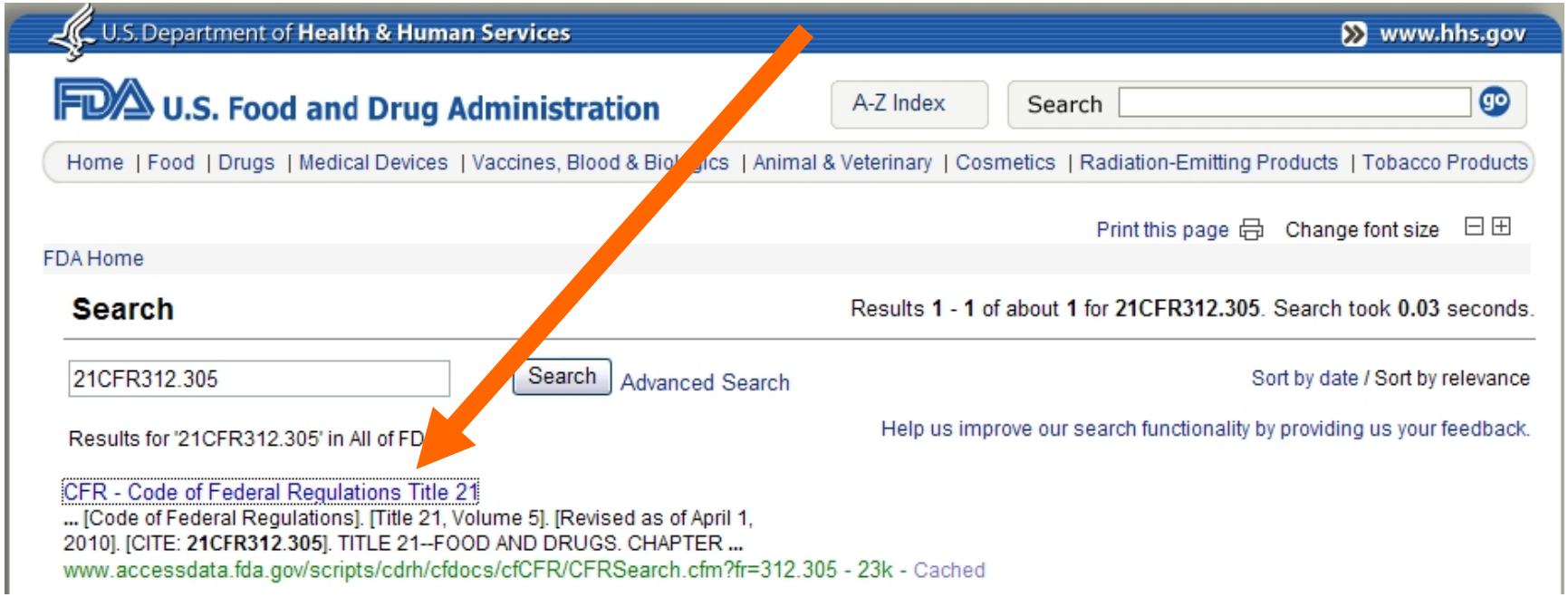
C R I T E R I A

- 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 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
- 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)**

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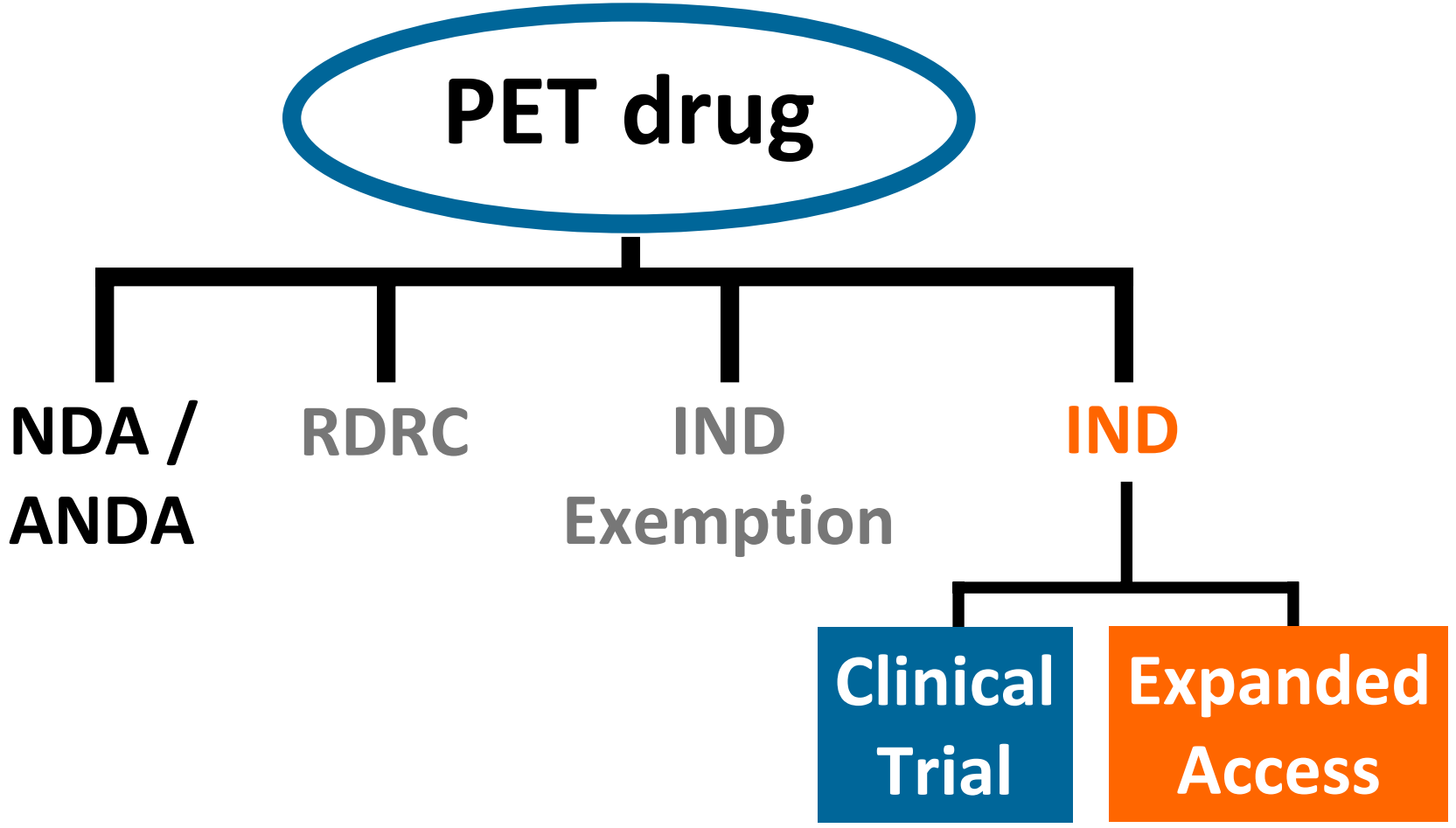
IND Sponsor, Investigator, Spon.-Invest. (SI)

Sponsor	Investigator
Submits IND	
Responsible for and initiates clinical investigation	Conducts clinical investigation
Individual, institution, or company	Individual

"Sponsor-investigator" is an individual who immediately directs the investigational drug administration

21CFR312 (sections 3, 50 – 70)

IND Options


PET drug
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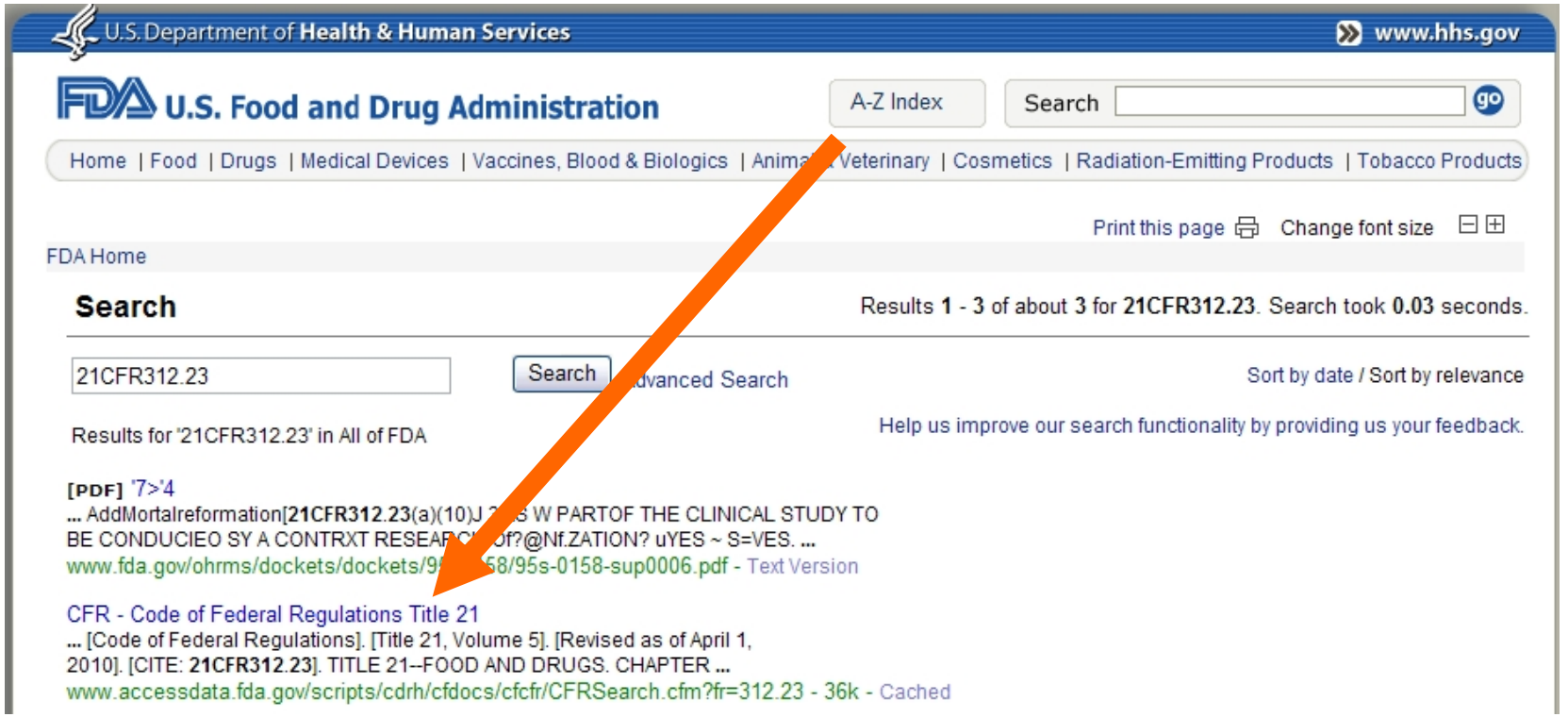
Trial IND Content

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

IND Content (p2/2)

7. Background information… *(continued)*

   a. Chemistry, manufacturing & control (CMC) info

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

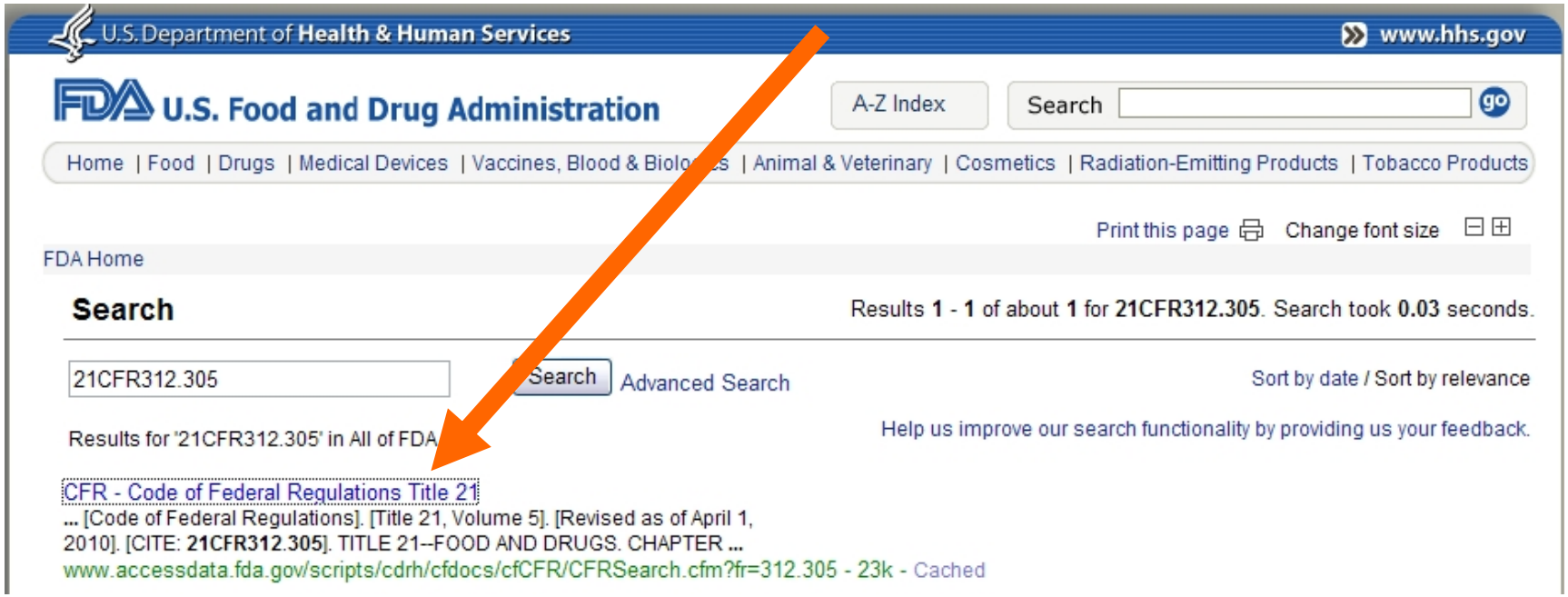
   c. Summary of previous PET drug clinical experience

   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

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**

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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"

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**

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???

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Division of Medical Imaging Products

Specific Websites (p1/3)

Electronic Submission:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm

IND Overview:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm

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/AccesstoInvestigationalDrugs/default.htm

Specific Websites (p3/3)

Clinical Trial IND Content:

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.23

Expanded Access IND Content:

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=312.305

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"


Center for Drug Evaluation and Research
FDA