Regulation of PET Radiopharmaceuticals

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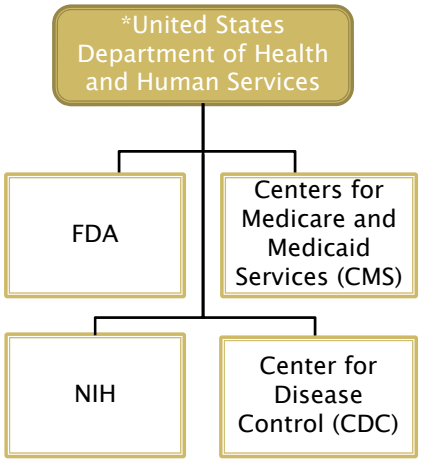
May 8th, 2013

Learning Objectives

- A. Understand the role and structure of FDA.
- B. Learn how to use available resources to find answers to regulatory questions.
- C. Understand drug/PET probe regulatory approval process.

A. FDA- Food and Drug Administration

- FDA is an agency within the US Dept. of Health and Human Services.



*This is not a comprehensive list of agencies associated with Dept of Health and Human Services

What is FDA's responsibility?

- Protecting the public health by assuring that foods are **safe, wholesome, sanitary and properly labeled**; human and veterinary drugs, and vaccines and other biological products and medical devices intended for human use are **safe and effective**
- Protecting the public from electronic product radiation
- Assuring cosmetics and dietary supplements are safe and properly labeled
- Regulating tobacco products
- Advancing the public health by helping to speed product innovations
- Helping the public get the accurate science-based information they need to use medicines, devices, and foods to improve their health

Legislation

- The Federal Food, Drug, and Cosmetic Act of 1938 was passed after a legally marketed toxic elixir Sulfanilamide killed 107 people, including many children.
  - The FD&C Act completely overhauled the public health system. Among other provisions, the law authorized the evidence of safety for new drugs, issue standard conduct factory inspections.
- The Kefauver-Harris Amendments of 1962,
  - Inspired by the thalidomide tragedy in Europe (a vigilance that prevented the drug's marketing in States), strengthened the rules for drug safety a manufacturers to prove their drugs' effectiveness
- The Medical Device Amendments of 1976 f Senate finding that faulty medical devices h 10,000 injuries, including 731 deaths.
  - The law applied safety and effectiveness safegua devices.

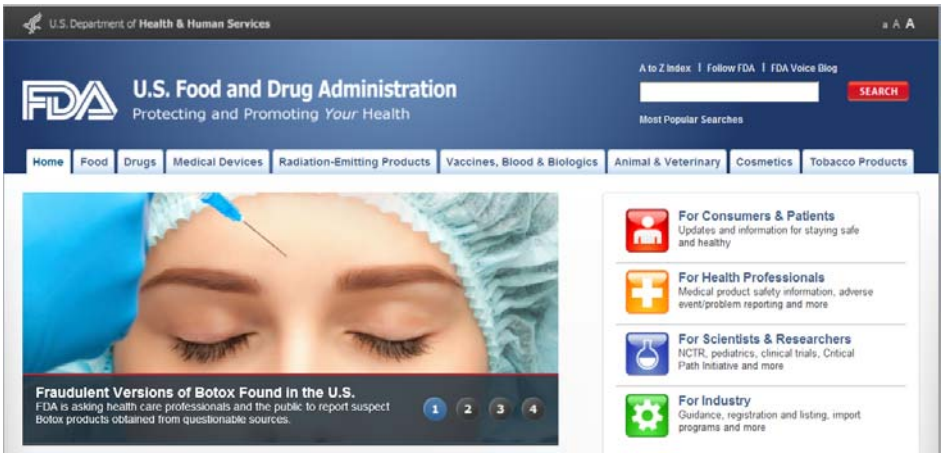
What does FDA regulate?

- **Foods**
  - safety of all food products (except for most meat and poultry products, which are regulated by the U.S. Department of Agriculture)
  - labeling
  - bottled water
  - food additives
  - infant formulas
- **Dietary Supplements**
- **Human Drugs**
  - product approvals
  - OTC and prescription drug labeling
  - drug manufacturing standards
- **Medical Devices**
- **Cosmetics**
  - safety
  - labeling
- **Electronic Products**
  - products that give off radiation, such as microwave ovens and X-ray equipment
- **Vaccines, Blood Products, and Other Biologics**
  - product and manufacturing establishment licensing
  - safety of the nation's blood supply
- **Veterinary Products**
  - livestock feeds
  - pet foods
  - veterinary drugs and devices
  - veterinary biologics not regulated by USDA are considered new animal drugs
- **Tobacco Products**

B. How to find answers to your regulatory questions?

1. Look up information on the FDA website.
2. Ask the FDA.

FDA website



Important Regulatory Documents on the FDA website

2 types of important regulatory documents:

1. Code of Federal Regulations (CFR)
2. Guidances

1. Code of Federal Regulations

- The Code of Federal Regulations (CFR) is the codification of the general and permanent rules published in the Federal Register by the departments and agencies of the Federal Government.
- These are referred to as Requirements and Rules
- Total of 50 titles:
- Title 21 governs food and drugs in the US for FDA.

1. CFR example

New Search | Help | More About 21CFR

[Code of Federal Regulations]
[Title 21, Volume 5]
[Revised as of April 1, 2012]
[CITE: 21CFR312.82]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D--DRUGS FOR HUMAN USE

PART 312 -- INVESTIGATIONAL NEW DRUG APPLICATION
Subpart E--Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses

Sec. 312.82 Early consultation.

For products intended to treat life-threatening or severely-debilitating illnesses, sponsors may request to meet with FDA-reviewing officials early in the drug development process to review and reach agreement on the design of necessary preclinical and clinical studies. Where appropriate, FDA will invite to such meetings one or more outside expert scientific consultants or advisory committee members. To the extent FDA resources permit, agency reviewing officials will honor requests for such meetings

(a) *Pre-investigational new drug (IND) meetings.* Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing. The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND.

(b) *End-of-phase 1 meetings.* When data from phase 1 clinical testing are available, the sponsor may again request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing, and to discuss the need for, as well as the design and timing of, studies of the drug in pediatric patients. For drugs for life-threatening diseases, FDA will provide its best judgment, at that time, whether pediatric studies will be required and whether their submission will be deferred until after approval. The procedures outlined in 312.47(b)(1) with respect to end-of-phase 2 conferences, including documentation of agreements reached, would also be used for end-of-phase 1 meetings.

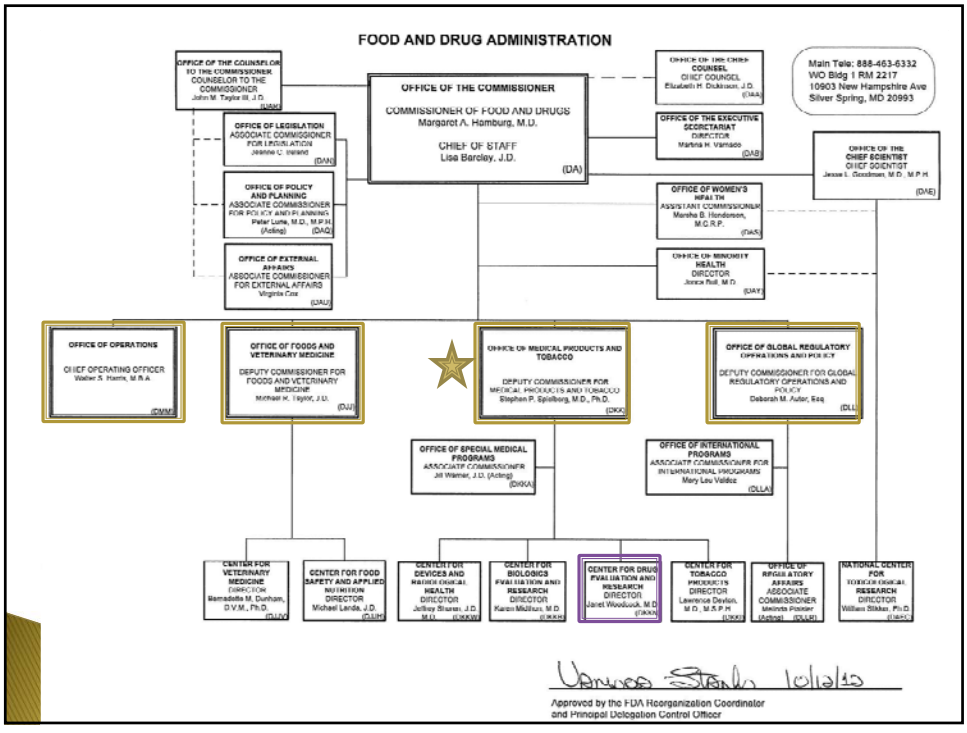
[53 FR 41523, Oct. 21, 1988, as amended at 63 FR 66669, Dec. 2, 1998]

2. Guidances

- Guidance documents represent FDA's current thinking on a topic. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations.
- These are referred to as recommendations.
- These documents are easier to read and they provide detail information on how the CRF 212 requirements can be satisfied.

Ask the FDA

- Email addresses available for different FDA offices on the FDA website.
- For questions related to PET, contact: PETDrugs@fda.hhs.gov
- A list of FDA employees and their contact info is available here: www.FDAzilla.com



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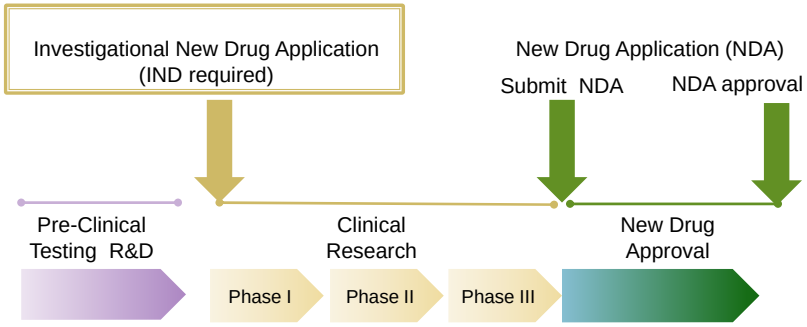
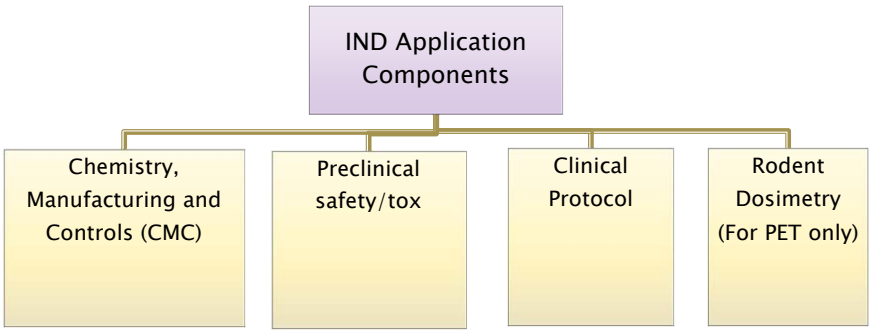
C.FDA Drug approval process



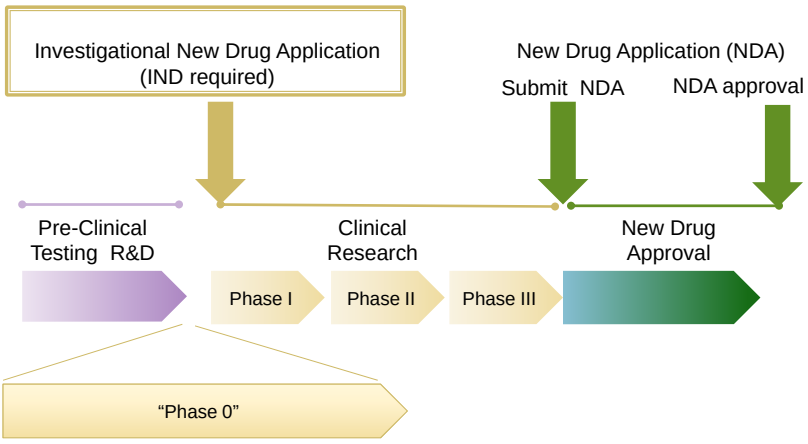
Investigational New Drug application requirements



Steps for successful IND submission

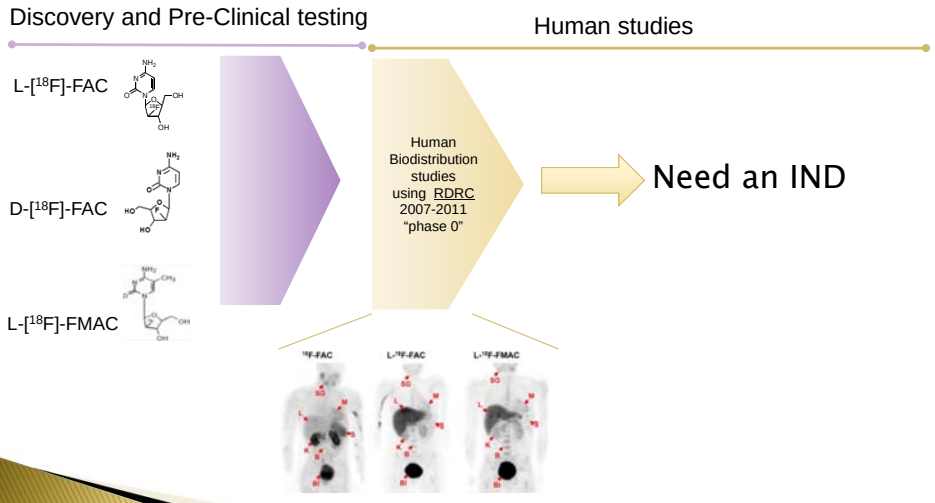
1. Arrange a pre-IND meeting with the FDA to determine the types of pre-clinical data, manufacturing requirements, clinical indication etc. needed for the IND application.
2. Obtain all data required for the IND application.
3. Assemble and submit IND.
4. IND assigned to a project manager at FDA.
5. FDA will have 30days to review and provide feedback regarding the IND.

FDA Drug approval process– PET "drugs"



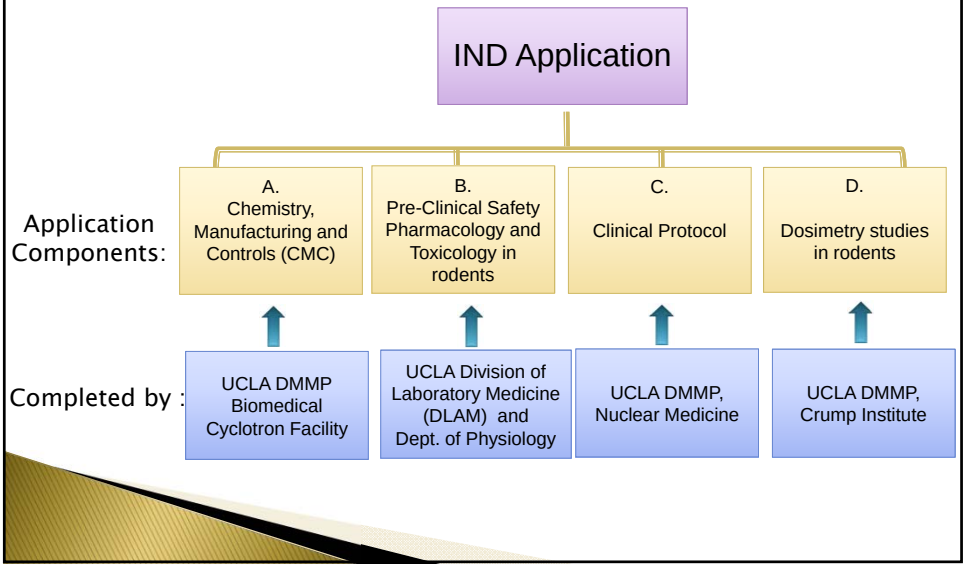
- RDRC: Radioactive Drug Research Committee approval

Example of IND process at UCLA– FAC probes



Schwarzenberg et.al., Eur J Nucl Med Mol Imaging. 2011 Apr;38(4):711-21

IND supporting data for FAC



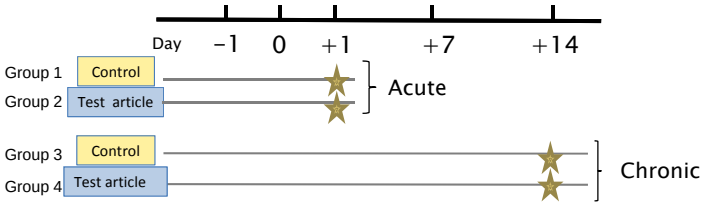
A. Chemistry, Manufacturing and controls (CMC)

- Involves data on the manufacturing process and ensuring product safety and quality.
- Requires compliance with cGMP requirements
  - For research PET compounds (INDs and RDRC) compliance with USP 823 or CFR 212 is required.
  - For manufacturing approved PET drugs (NDAs and ANDAs), compliance with CFR 212 is required.

cGMP Guidance PET Drugs — Current Good Manufacturing Practice (CGMP) (Small Entity Compliance Guide)

- Personnel Resources
- Quality Assurance
- Facilities and Equipment
- Control of Components, Containers, and Closures
- Production and Process Controls
- Laboratory Controls
- Stability testing
- Finished Drug Product Controls and Acceptance Criteria
- Labeling and Packaging
- Distribution
- Complaint handling
- Records

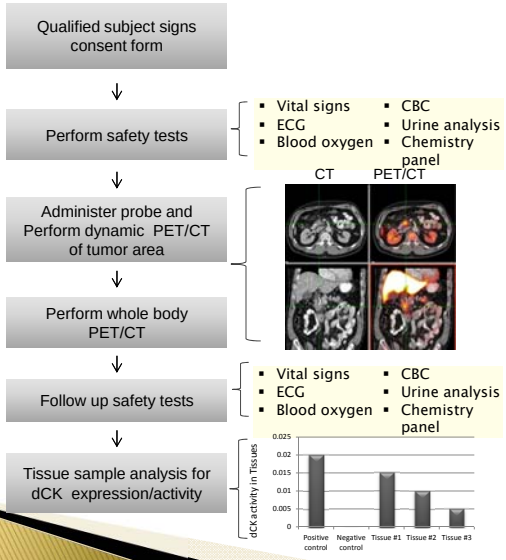
B. Pre-Clinical Safety Pharmacology and Toxicology



Toxicity Testing	Safety Pharmacology
▪Duration: 14 days ▪Analyze: - CBC - Clinical Chemistry - Necropsy - Histopathology	▪Duration: 14 days ▪Analyze: - EKG - Blood pressure - Heart rate - Weight - Pulse oximetry - Body temp

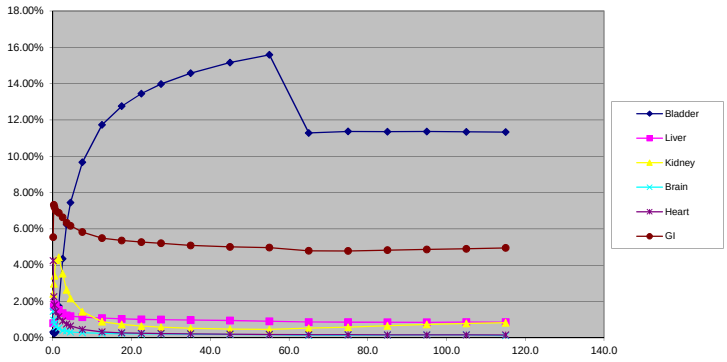
Note: the types of studies and species requirements should be determined during the pre-IND meeting with the FDA.

C. Clinical protocol– Phase 1



D. Rodent dosimetry data

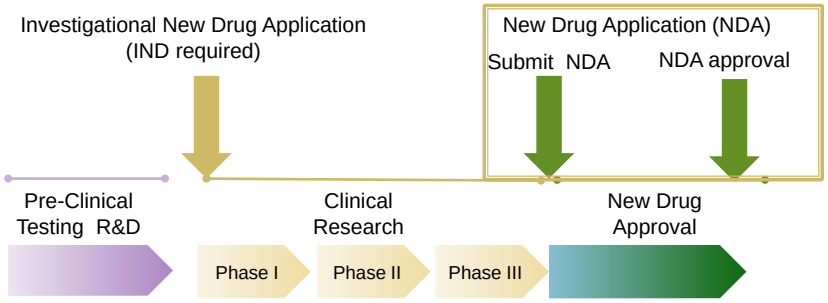
- Dynamic analysis of radioactivity within major organs
- Absorbed dose calculations



FAC INDs

- Pre-IND meeting was scheduled with the FDA
  - Waivers were granted for reduced safety/tox data
  - Waiver was provided for genotox data.
- IND supporting data was obtained from Crump and DLAM.
- 3 IND applications were submitted to the FDA and all three passed the review process.
- We currently have 3 INDs (D-FAC, L-FAC and L-FMAC) and clinical studies are in progress.
- The cost for each IND was $50K/probe.

At the end of the trial, manufacturing an approved drug requires an NDA or an ANDA



- Require submission, review and approval of an NDA or ANDA.
- Requires a pre-approval inspection.

Pre-approval inspection

- FDA will notify the site on the date of inspection.
- Require review/inspection of documents and review/inspection of manufacturing space.
- FDA will specify the scope/areas to be inspected.
- Inspection can take 3-7 days.
- FDA will issue form 483 "inspectional Observations" to address deficiencies observed.
  - The recipient should respond to the agency to avoid receiving a warning letter.
- Severe violations result in a Warning letter.

UCLA has filed ANDAs for Fludeoxyglucose and Ammonia

- ANDA: Abbreviated New Drug Application.
- Referencing another NDA for clinical and safety data, but must provide manufacturing data.
- ANDAs have been filed for FDG and Ammonia to allow UCLA to manufacture these compounds.
- ANDAs are currently under review and UCLA passed the pre-approval inspection successfully.
- Expecting ANDA approvals by summer 2013.

Learning Objectives

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- C. Understand drug/PET probe regulatory approval process.

Resources

- FDA website:
www.FDA.gov
- FDA Forms:
http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms
- CFR search:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm
- FDA guidance document search:
http://www.fda.gov/regulatoryinformation/guidances

Resources continued

- Search FDA approved drugs on **Drugs@FDA**
- Search FDA approved Devices on **Devices@FDA**

- FDA Drug Master Files are available on the FDA website.
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs

- Search database of clinical studies:
www.clinicaltrials.gov

- FDA employee list, 483s, etc:
www.FDAzilla.com

Questions?