FDA-NRC Workshop: Enhancing Development of Emerging Technologies: Radiopharmaceuticals and Radiological Devices

Product Jurisdiction: Drugs, Device, and Combination Products

October 14, 2020

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Overview / Objectives

- Definitions
- Is your product a drug, device, or combination product?
- Developmental implications

Product Jurisdiction Officer?

- Center focal point for combination product questions or issues
- Center liaisons to the Office of Combination Products (OCP)
- Provide recommendations to OCP re: classification and assignment of combination and single-entity products

- Represent their Center on combination product and jurisdiction policies
- Work with OCP to develop guidance documents and regulations that affect their Center
- Help sponsors clarify regulatory pathway for products assigned to their Center

Definitions

The Agency classifies a product based on the statutory **definitions** of drug, device, biologic and combination product

- Food, Drug, and Cosmetic (FD&C) Act
  - Drug, device, and combination product
- Public Health Service (PHS) Act
  - Biologic

Drug – FD&C Act 201(g)

The term "drug" means:

(A) articles recognized in the US Pharmacopoeia, Homeopathic Pharmacopoeia, or National Formulary;

(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals;

(C) articles (other than food) intended to affect the structure or any function of the body of man or other animals.

Device – FD&C Act 201(h)

The term “device” means:

Instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is -

(1) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Biological – PHS Act 351(a)

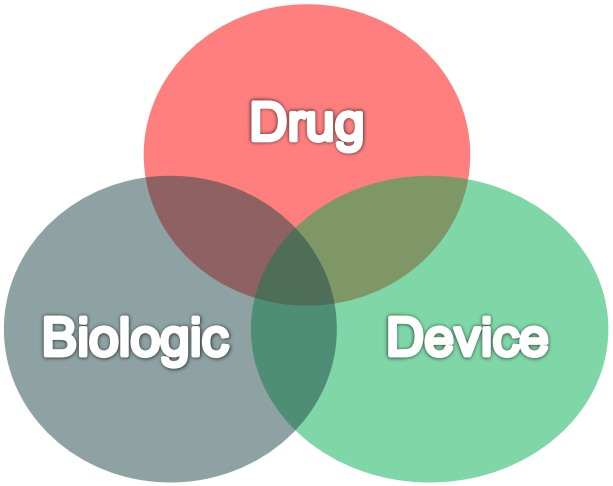
The term “biologic” means:

“a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product . . . .applicable to the prevention, treatment, or cure of a disease or condition of human beings.”

What is a combination product?

Combination product comprises 2 or more differently classified products

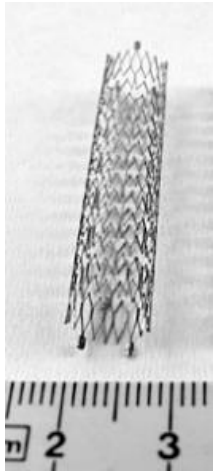
- Drug + Device
- Device + Biologic
- Drug + Biologic
- Drug + Device + Biologic



Types of Combination Products

21 CFR 3.2(e)

- Physically or chemically into a single entity
- Co-packaged / Kit
- Sold separately, but labeled for use together



Examples

- Drug-eluting stent
- Kit w/bandages and antibiotic ointment
- Photodynamic therapy

Not Combination Products

- Drug-Drug
- Device-Device
- Biologic-Biologic
- Food + Drug/Device/Biologic
- Cosmetic + Drug/Device/Biologic

Product Assignment…

- Non-combinations are assigned based on their classification:
  - Drug (FD&C Act 201(g)) - ***CDER***
  - Device (FD&C Act 201(h)) – ***CDRH***
  - Biological Product (PHS Act 351(a)) – ***CBER*** or ***CDER***

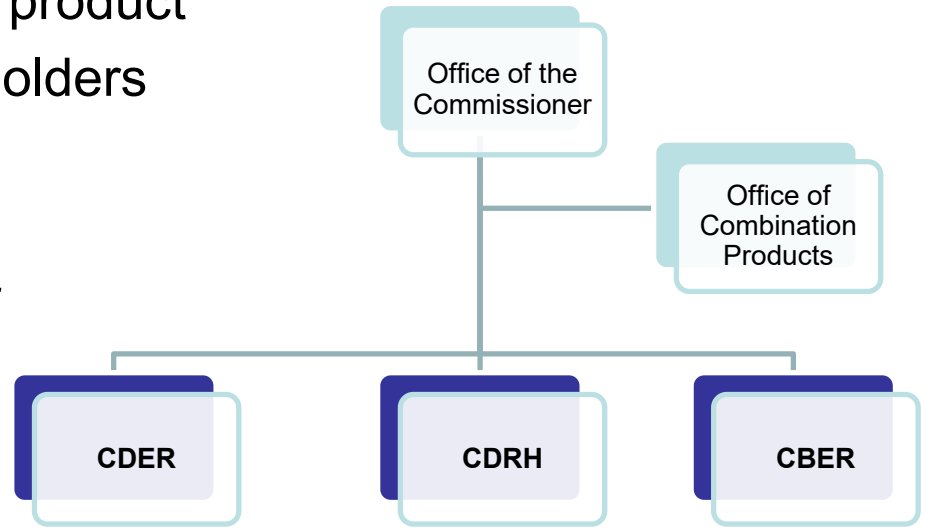
But what about a Combination Product???

Office of Combination Products (OCP)

- Authority to assign an FDA center to have primary jurisdiction for review of both combination and single entity (i.e., non-combination) products where jurisdiction is unclear or in dispute.

- Agency focal point for combination product issues for internal / external stakeholders

- Broad oversight responsibilities covering the regulatory life cycle of combination products



www.fda.gov/combination-products

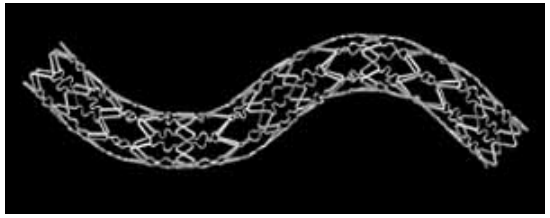
Combo Product Assignment (§ 3.4)

Combination products are assigned based on the **primary mode of action (PMOA)**.* If the Secretary determines that the primary mode of action is that of ---

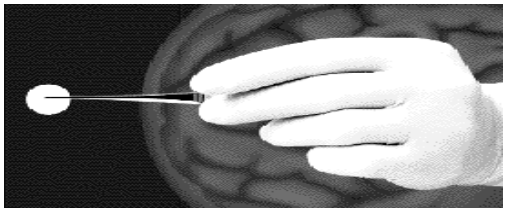
- a drug --- ***CDER***
- a device --- ***CDRH***
- a biological product --- ***CBER or CDER***

* **PMOA** – "the single mode of action of a combination product that provides the most important therapeutic action …

- Most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects…;" § 3.2(m)



Drug Eluting Stent



Drug Eluting Disk

Combo Product Assignment (§ 3.4)

If unable to determine PMOA with reasonable certainty, OCP will then consider…

- **FIRST: Consistency**
  - Assign product to Center that regulates other combination products that present similar questions of safety and effectiveness
- **SECOND: Safety and Effectiveness**
  - When FIRST does ***not*** apply, assign product to Center with most expertise related to most significant safety and effectiveness questions

Contact lens coated with glaucoma drug

Is your product a drug, device, or combination product

Device –

- 21 CFR 892 – Radiology Devices (Class I/II)
  - **Subpart B – Diagnostic Devices**
    - 67 regulations
  - **Supbart F – Therapeutic Devices**
- PMA/HDE Devices (Class III)
  - Therasphere (H980006) - Y-90 glass microspheres
    - For radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable HCC who can have placement of appropriately positioned hepatic artery catheters
  - Sirspheres (PMA P990065) - Y-90 resin microspheres
    - For the treatment of unresectable metatstatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy of FUDR

Is your product a drug, device, or combination product

Drug –

- 21 CFR 212 – Current GMP for PET Drugs
  - § 212.1 – PET Drug
  - means a radioactive drug that exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for providing dual photon positron emission tomographic diagnostic images. The definition includes any nonradioactive reagent, reagent kit, ingredient, nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program to be used in the preparation of a PET drug.

Is your product a drug, device, or combination product

BLA 125019

Drug –

- 21 CFR 310 – New Drugs
  - § 310.3(n) The term radioactive drug means any substance defined as a drug …which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any non radioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. The term " radioactive drug" includes a " radioactive biological product" as defined in 600.3(ee) of this chapter.
  - § 600.3(ee) radioactive biological product means a biological product which is labeled with a radionuclide or intended solely to be labeled with a radionuclide.

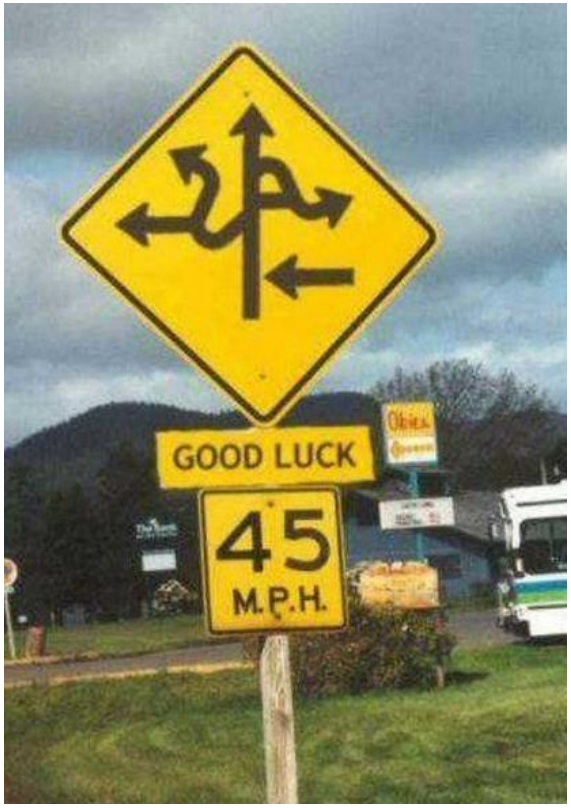
How do I get a Classification / Jurisdiction Assignment?

- Informal advice:
  - Email: combination@fda.gov
  - Simple issues, uncertainty, process concerns
  - Determine whether a preRFD/RFD is needed
- Pre-RFD (pre-Request for Designation)
  - Final Guidance (Feb 2018)
  - Most common option
- RFD (Request for Designation)
  - Formal, binding determination – **60** days
  - Complex issues or dispute / uncertainty
  - Requirements in 21 CFR 3.7

Developmental Implications

- Lead center - industry contact
- Application type (e.g., NDA vs PMA vs 510(k))
- Collaborative review across center experts
- Product is still a combo once assigned, does not change classification to that of the type of products customarily in that center
- Must comply with applicable regulations / requirements of both constituent parts without being contrary or confounding

Recommendations



- Work with FDA early in your development process to establish jurisdiction / classification
- Review all applicable guidance documents
- Leverage available / existing data for constituent parts of combination product, while taking into consideration the product as a whole (e.g., synergistic effects)
- Recommend early interactions with FDA when developing your combination product

U.S.NRC
United States Nuclear Regulatory Commission
Protecting People and the Environment

NRC Jurisdiction: sealed and unsealed materials, generators for medical use

October 14, 2020

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Overview

- How NRC Regulates
  - NRC (Commission, Headquarters and Regional Staff, ACMUI)
  - Agreement States and Other Federal Agencies
  - Regulations, Guidance, Licenses, Inspections, and Enforcement
  - Policy Statement on the Medical Use of Byproduct Material

    65 FR 47654, August 3, 2000

NRC Regulated Materials

Byproduct material – defined in Section 11.e of the AEA and 10 CFR 30.4

- Reactor-produced
- Accelerator-produced (Energy Policy Act of 2005)

Other materials related to medical use

- Source material (Section 63)
  - Source material (DU) is used for shielding and counterweights, but not for “medical use”
- Special nuclear material (Section 53)
  - In plutonium-powered pacemakers, but not a “medical use”

NRC Issues Licenses Based on

- Part 30 – basic regulation of byproduct material – issue licenses, permit transfers
- Part 35 – medical use of byproduct material in private practices, clinics, hospitals and government medical facilities

  The intentional internal or external administration of byproduct material or the radiation from byproduct material to patients or human research subjects under the supervision of an authorized user (35.2)
- Part 32 – commercial nuclear pharmacies (or radiopharmacies), manufacturers, and distributors

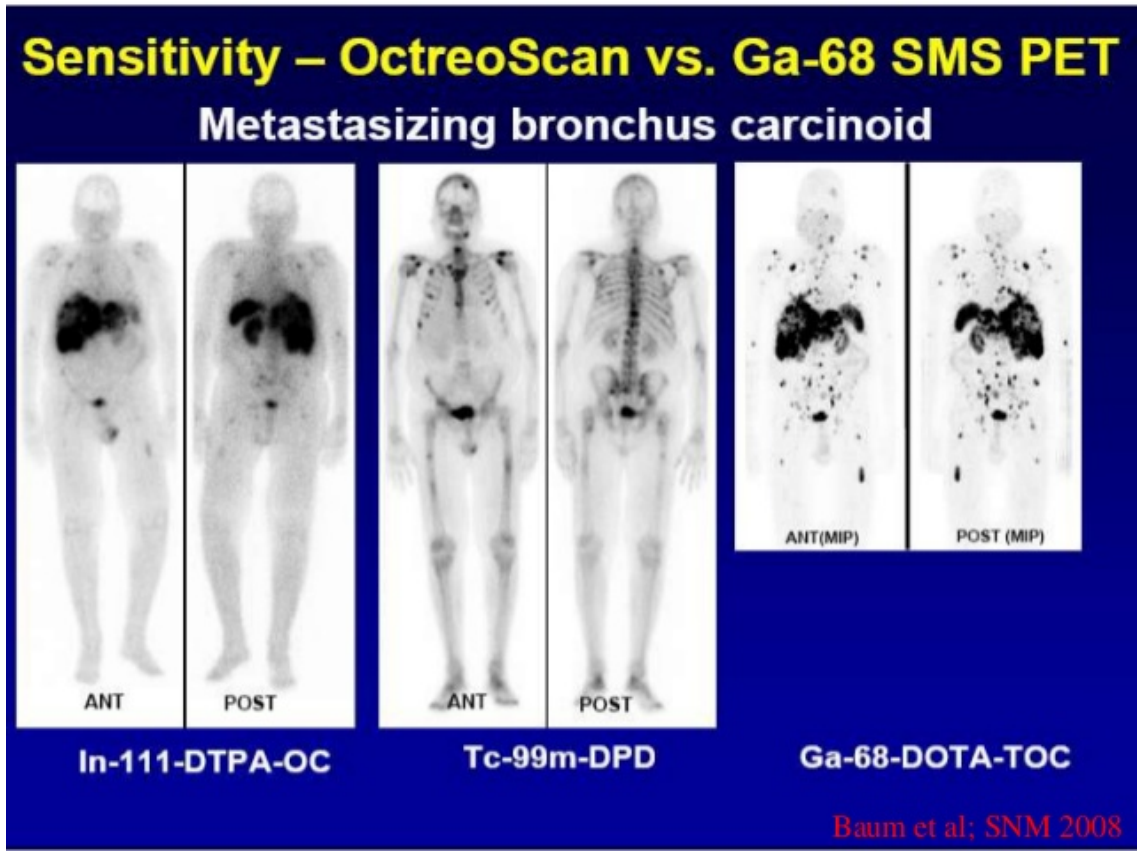
  Manufacture, distribution, or preparation of radioactive drugs, for medical use (32.72), or medical devices (32.74)
- Part 50 – medical isotope production

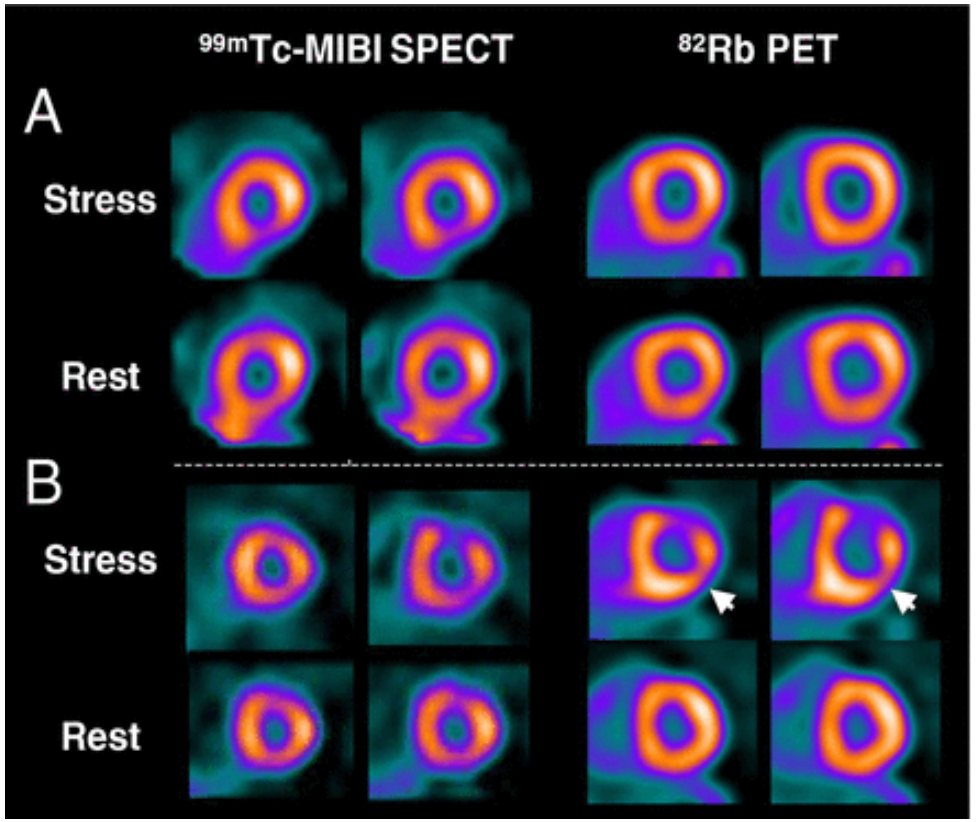
  Construction permits and licenses for production and utilization facilities used to produce medical isotopes (Mo-99) (Shine) and therapy use of reactors

Radiochemicals vs Radiopharmaceuticals

- Part 30 – byproduct radiochemicals like Mo-99, Ge-68 , Ge-68/Ga-68 generators - license, posses, use, transfer,
- Part 35 – Use byproduct radiopharmaceuticals for medical use like Tc-99m, Rb-82, Ga-68, Mo-99/Tc-99m generator, and Sr-82/Rb-82 generator
- Part 32 – commercial nuclear pharmacies and manufacturers - make and prepare radiopharmaceuticals from radiochemicals
- Part 50 – medical isotope production

Medical Use: Diagnostic Radiopharmaceuticals





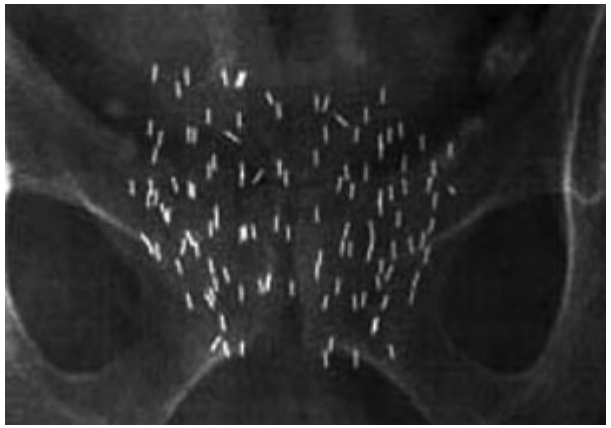
Medical Use: Therapy Radiopharmaceuticals

- I-131 capsules for treatment of hyperthyroidism and thyroid cancer

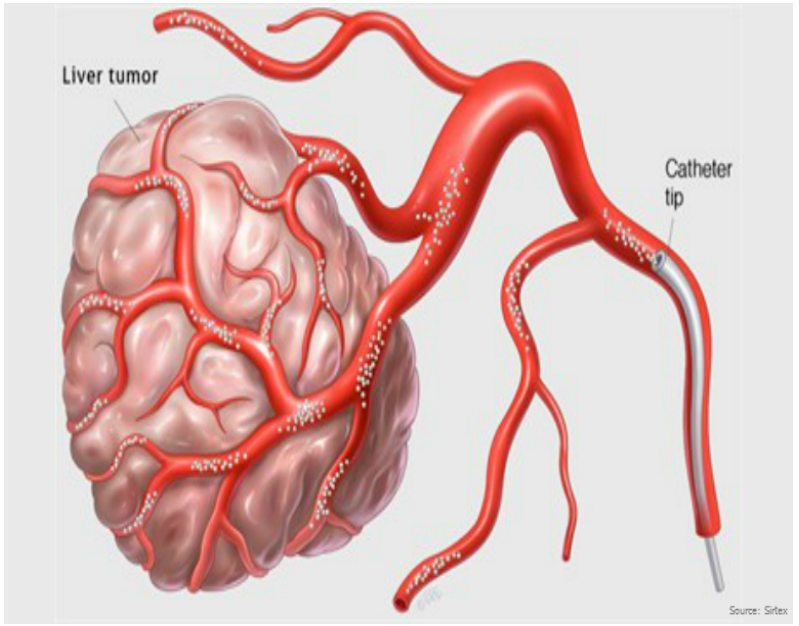
- Xofigo® (Ra-223 dichloride)

Medical Use: Sealed Sources in Therapy

- Permanent Brachytherapy – Prostate Implant



- Y-90 Microspheres



Medical Use: Sealed Sources in Therapy Devices

Stereotactic Radiosurgery (Gamma

- High Dose Rate Afterloader

What is “Medical Use”

- “[T]he intentional internal or external administration of byproduct material or the radiation from byproduct material to patients or human research subjects under the supervision of an authorized user as defined in 10 CFR Part 35.” (§ 30.4)
- Medical use related to, but is <u>not</u>
  - Use of DU in shielding
  - Use of Pu to power pacemakers
  - Production of medical isotopes
  - Manufacture and distribution of radiopharmaceuticals
  - Manufacture and distribution of medical sealed sources and devices
  - Administration of nuclear material to animals for diagnostic, therapeutic, or research purposes
  - Use of blood irradiators
  - Performance of in vitro tests or research

NRC Issues Possession and Use Licenses

- Limited specific licensees medical use licenses
- Master Materials Licensees
  - –Department of Veterans Affairs, Navy, and Air Force (and perhaps soon Defense Health Agency)
  - –Authorized to issue permits to entities within their agency, e.g., issuance of a permit by DVA to an individual DVA hospital or clinic
  - –Permittees are equivalent to NRC licensee and must meet NRC requirements
- Medical Type A Broad Scope Licensees
  - –Usually large teaching and research hospitals with large, established programs
  - –Appoint a radiation safety committee
  - –Exempt from certain requirements (e.g., certain notification requirements) (§ 35.15)

Additional Resources

NRC Webpage

- Medical Uses Licensee Toolkit, https://www.nrc.gov/materials/miau/med-use-toolkit.html
- Medical Product Distribution Toolkit, https://www.nrc.gov/materials/miau/product-manufac/med-toolkit.html
- ACMUI Webpage, https://www.nrc.gov/about-nrc/regulatory/advisory/acmui.html

Guidance

- NUREG-1556, Vol. 9 (Medical Use), 11 (Broad Scope), 12, Appendix R (Medical Distribution), 13 (Radiopharmacies), and 21 (Production using an Accelerator)
- Regulatory Guide 8.39 (Patient Release)

Clinical Development of Radiopharmaceutical Products: Regulatory Considerations for FDA Approval

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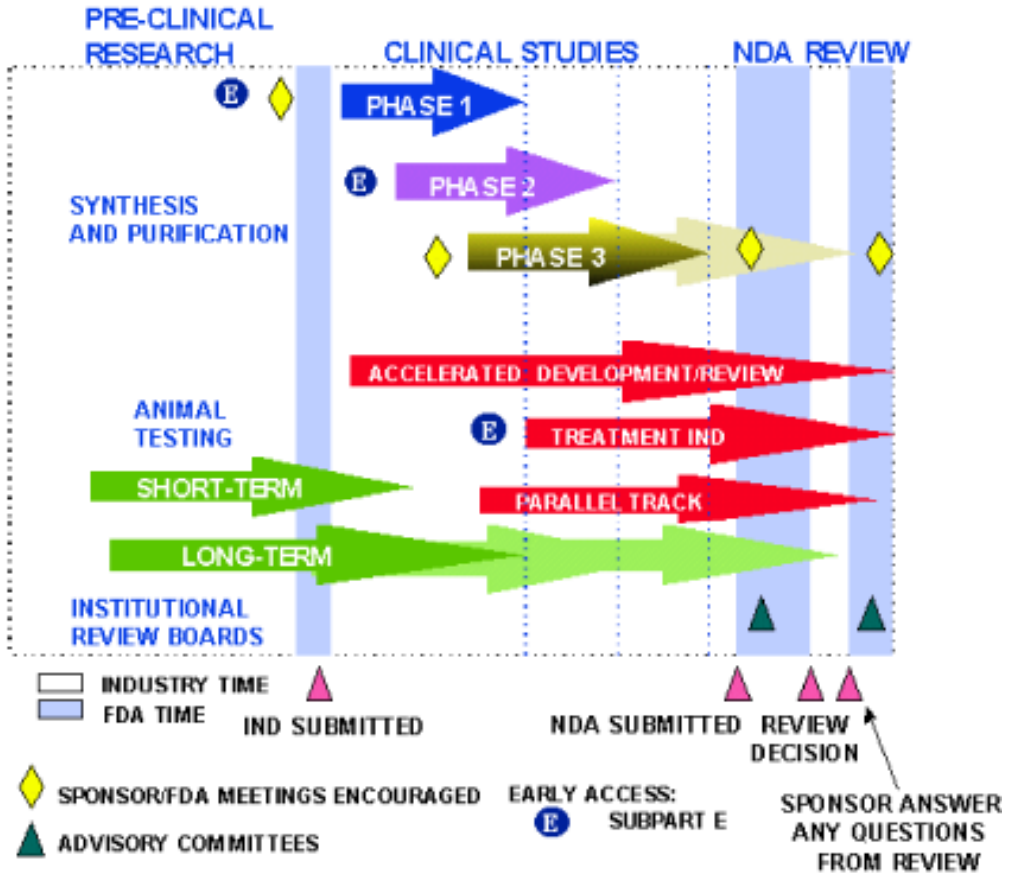
Division of Regulatory Operations—Specialty Medicine

Office of Regulatory Operations
Center for Drug Evaluation and Research

Outline

- Overview Drug Development Process
- Regulating the Use of Radioactive Drugs in Basic Research
- Pre-Clinical Phase
- Clinical Phase
- Meetings
- New Drug Application Review and Labeling

Drug Development Process



Regulating Radioactive Drugs in Basic Research

- Radioactive Drug Research Committee (RDRC) (*21 CFR 361.1*)
- For basic science research
- Not for use for immediate therapeutic, diagnostic or similar purpose
- No intent to determine safety or effectiveness for clinical use

https://www.fda.gov/drugs/science-and-research-drugs/radioactive-drug-research-committee-rdrc-program

New Drug Development Process

Pre-Clinical Research

- Synthesis and purification
  - Target affinity
  - Selectivity etc.
- Animal Testing
  - PK
  - Proof of concept
  - Toxicity
  - Translation to humans
- Meetings with FDA

https://www.fda.gov/media/109951/download

New Drug Development Process
Clinical Phase

Phase 1

Phase 1 approaches involve Investigational New Drug Application (IND) and may involve:

1. Exploratory IND
2. Traditional IND

- *INDs are governed by 21 CFR 312.21*
- *INDs are used to establish the safety or effectiveness of a drug to support the approval of a new use*

New Drug Development Process

Clinical Phase

Phase 1(Exploratory IND)

An exploratory IND study is a clinical trial that

- is conducted early in phase 1,
- involves very limited human exposure, and
- has no therapeutic or diagnostic intent.

The main purpose of this approach is to find promising drug candidates to enable the sponsor proceed efficiently with the most promising drug.

https://www.fda.gov/media/72325/download

New Drug Development Process

Clinical Phase

Phase 1(Traditional IND)

- Traditional Phase 1 trials usually involve healthy volunteers to determine the drug's most frequent and serious adverse events, and often, how the drug is metabolized and excreted by the body

- Involve a small number of participants generally in the range of 20 to 80 subjects

https://clinicaltrials.gov/ct2/about-studies/glossary
21 CFR312.21 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.21

New Drug Development Process
Clinical Phase
Phase 2

- Phase 2 clinical trial gathers more information about a drugs safety and effectiveness in the condition/disease being studied
- Larger groups of subjects/participants are enrolled
- Subjects/participants receiving the drug may be compared with others receiving placebo.
- Safety and short term adverse reactions continues to be evaluated

New Drug Development Process
Clinical Phase
Phase 3

- During Phase 3, more information is gathered about a drug's safety and effectiveness by studying different populations and different dosages and by using the drug in combination with other drugs
- Studies typically involve more participants and efficacy endpoints are assessed
- If safety and efficacy are adequately confirmed, clinical testing may end at this step and a New Drug Application(NDA) may be submitted

Formal Communications: Meetings

- Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products
  - https://www.fda.gov/media/109951/download

- Meetings Types:
  - Type A
  - Type B
  - Type B (End of Phase (EOP))
  - Type C

Meeting Types

(calendar days)

Meeting Type	Response Goal	Schedule Goal or expected WRO	Receipt of Background Package	Preliminary Comments Goal
A	14 days	30 days	Time of request	1 -2 days
B	21 days	60 days	30 days before the date of the meeting or expected written response	1 – 2 days
B (EOP)	14 days	70 days	50 days before the date of the meeting or expected written response	5 days
C	21 days	75 days	47 days before the date of the meeting or expected written response	5 days

NDA Review

- Preclinical data (Pharmacology/Toxicology, Chemistry Manufacturing and Controls), and data from the clinical trials are reviewed to assist FDA in making a benefit/risk assessment
- A favorable benefit/risk assessment culminates in the review and approval of the drug labeling

New Drug Label and Labeling

Label

Any display of written, printed, or graphic matter ***on the immediate container*** of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity

21CFR1.3 (b) / FD&C Act section 201(k)

Labeling

All labels, as well as other written, printed, or graphic matter ***accompanying the product***.

21CFR1.3 (a) /FD&C Act section 201(m)

Labeling

- Carton and Container Labels
- Prescribing Information (PI) “Package Insert”
- Patient Labeling
  - Patient Instructions for Use, Patient Information, Medication Guide
- Operator Guide (User Manual)

Prescribing Information

- Physician Labeling Rule (PLR) Format was implemented in 2006

- Contents of the Prescribing Information (PI)
  - **Highlights**
  - **Table of Contents**
  - Full Prescribing Information (FPI)
    - Pregnancy and Lactation Labeling Rule (PLLR)

21 CFR 201.56 and 201.57

Physician's Labeling Rule Requirements for Prescribing Information

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

PLLR

- Label ***format change*** to reflect an integrated assessment of known risks relevant to pregnancy, lactation and infertility based on available information/data

Draft Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425398.pdf

Pregnancy and Lactation Labeling Final Rule

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

General Table of Contents in FPI

Post-Market Activity

- Supplemental applications
- INDs
- Drug Advertising
- Manufacturer Inspections
- Active Surveillance
- Safety Reports

Examples of Radiological Drugs Regulated at CDER

- Positron Emission Tomography Agents
- Scintigraphic Agents
- Magnetic Resonance Imaging Media
- Ultrasound Contrast Media
- Iodinated Contrast Media
- Non-iodinated Contrast Media

Conclusions

- The discovery and development of new drugs follow a well defined regulatory path
- From conception to the marketing application of a drug, FDA engages with sponsors to optimize drug development
- For radiopharmaceuticals and contrast agents NDA and labeling regulations refer to: 21 CFR 314, *21 CFR 201.56 and 201.57*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ADMINISTRATION

Backup Slides

New Drug Development Process Links

- https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process

Labeling for Radiopharmaceuticals

- Imaging instructions are placed in the “Dosage and Administration” sections

IMAGING INSTRUCTIONS

- Image Acquisition Guidelines
  - Timing and Duration
  - Location (head, body)
  - Patient Instructions (voiding)
  - Device Parameters (e.g. 2D or 3D PET, software reconstruction)

- Image Display
  - Orientation
  - Coloring Display

- Image Interpretation
  - “Positive” vs. “Negative”

U.S.NRC
United States Nuclear Regulatory Commission
Protecting People and the Environment

Medical Use Licensing

October 14, 2020
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NRC Licensing

- Through the **licensing** process, the U.S. **Nuclear Regulatory Commission** (**NRC**) authorizes an applicant to possess, use, process, export and import nuclear materials and waste, and handle certain aspects of their transportation.
- **10 CFR 35** contains the requirements and provisions for issuance of licenses authorizing the **medical use** of nuclear material.

NRC Medical Licensing

- NUREG-1556, Volume 9, Revision 3, “Consolidated Guidance About Materials Licenses, Program-Specific Guidance About Medical Use Licenses,” provides licensing guidance to assist applications and licensees in preparing applications for the medical use of nuclear materials.
- To apply for a license, applications should complete and file a NRC Form 313 with appropriate NRC region or Agreement State

Authorized User

- A medical licensee needs at least 1 individual authorized to use nuclear material for medical purposes
- An *Authorized User* is a physician, dentist, or podiatrist who:
  - Meets training and experience requirements listed in 10 CFR 35 for specific medical use, and
  - Is listed on an NRC or Agreement State license or permit authorized to use nuclear material for medical use
- NRC Forms 313a can be submitted with license applications to document individuals meet the training and experience requirements listed in 10 CFR 35

10 CFR Part 35 – Licensing

- Subparts A-C – general information, administrative requirements, and technical requirements
- Subparts D-H – specific requirements for specific uses (training and experience requirements, health and safety procedures)
  - D (35.100, 35.200) – unsealed material, no written directive required
  - E (35.300) – unsealed material, written directive required
  - F (35.400) – manual brachytherapy
  - G (35.500) – sealed sources for diagnosis
  - H (35.600) – afterloader, teletherapy, gamma stereotactic radiosurgery
- Subpart K (35.1000) – other medical uses of nuclear material

Specific Medical Use – Subpart D, 35.100

- Uptake, Dilution, and Excretion Studies of unsealed byproduct material for which no written directive is required.
- Administration of small (usually microcuries) quantities of byproduct material, generally by intravenous injection or oral administration.

  Example: I-131 uptake (oral ingestion of capsule 10 μCi) to assess thyroid function.

Specific Medical Use – Subpart D, 35.200

- Imaging and Localization Studies using unsealed byproduct material for which no written directive is required.
- Administration of (usually) millicurie quantities of byproduct material to create images.

Example is intravenous administration of 20-25 millicuries of Tc-99m HDP, then delayed imaging of distribution of uptake in bone; and up to 50 millicuries of Rubidium-82 for each resting and stress cardiac image.

Specific Medical Use – 35.200 (cont.)

- Contains specific generators breakthrough limits
  - Mo/Tc generator
    - **0.15 µCi of Mo-99 per mCi of Tc-99m**
  - Sr/Rb generator
    - 0.02 **µCi** of Sr-82 per mCi of Rb-82 chloride
    - 0.2 **µCi** of Sr-85 per mCi of Rb-82 chloride
- Other generators are evaluated on a case by case basis and limits are listed in 35.1000 at this time

Specific Medical Use – Subpart E, 35.300

- Use of unsealed byproduct material for which a written directive is required
- 3 categories
  - Oral administration of sodium iodide [NaI] I-131 requiring a written directive in quantities ≤ 33 mCi [i.e., >30 μCi and ≤ 33 mCi].

    Example: 2-5 mCi for whole body scan for thyroid carcinoma patient or 7-30 mCi for treatment of hyperthyroidism.

  - Oral administration of NaI I-131 in quantities >33 mCi.

    Example: 50-250 mCi [or higher] for treatment of thyroid carcinoma.

  - Parenteral [i.e., not oral] administration of any radioactive drug used for primarily for its electron emission, beta radiation, alpha radiation, or photon energy less than 150 keV.

    Examples: Lu-177, Ra-223 dichloride, IV I-131 MIBG for treatment of neuroblastoma.

Specific Medical Use – Subpart F, 35.400

- Manual brachytherapy, including temporary and permanent sealed source implants.

Examples: temporary intracavitary Cs-137 implants for gynecological cancers, temporary interstitial Ir-192 implants for head for neck cancers, permanent I-125 interstitial implants for prostate cancer.

Specific Medical Use – Subpart G, 35.500

- Sealed sources for diagnosis
- I-125 seeds for tumor localization/excision is not considered under 35.500, but instead licensed under 10 CFR 35.1000

Examples: Gd-153 for bone density scans

Specific Medical Use – Subpart H, 35.600

- Photon Emitting Remote Afterloader Units, Teletherapy Units, and Gamma Stereotactic Radiosurgery (GSR) Units
- Recent GSR units have been licensed under 10 CFR 35.1000 as regulations in 10 CFR 35.600 contain specific spot check and calibration requirements that they cannot meet like calibration of relative helmet factors

Examples: Gamma Knife Model C, High-Dose Rate Remote Afterloaders, Low-Dose Rate Remote Afterloaders.

Other Medical Use – Subpart K, 10 CFR 35.1000

- Subpart K—Other Medical Uses of Nuclear Material
  - A licensee may use nuclear material approved for medical use which is not specifically addressed in subparts D through H of this part if—
    - The applicant or licensee has submitted the information required by 10 CFR 35.12(b) through (d); and
    - The applicant or licensee has received written approval from the Commission in a license or license amendment and uses the material in accordance with the regulations and specific conditions the Commission considers necessary for the medical use of the material.

10 CFR 35.1000 – Licensing Guidance

- The licensing guidance contains the regulations and specific conditions for radiation protection the Commission has evaluated and considers acceptable for the specific medical use listed
- NRC works with the FDA, manufacturers, early users, and Agreement States to develop these guidance documents
- Alternative conditions are allowed, but would be reviewed by the NRC on a case-by-case basis

Examples of 10 CFR 35.1000

- Drug: NorthStar Medical Radioisotopes, LLC RadioGenix™ Molybdenum-99/Technetium-99m Generator System

- Devices: Best Vascular, Inc. Beta-Cath Intravascular Brachytherapy (IVB) System; Low Activity Radioactive Seeds Used for Localization of Non-Palpable Lesions and Lymph Nodes; Leksell Gamma Knife® Perfexion™ and Leksell Gamma Knife® Icon™; Xcision Gammapod; NeoVista, Inc's Epi-Rad90 (Sr-90) Ophthalmic System; TheraSphere and SIRSpheres Yttrium-90 Microspheres; ViewRay System for Radiation Therapy

- Other: Germanium-68/Gallium-68 Pharmaceutical Grade Generators