



# FDA-NRC Collaboration for Medical Radiation Safety Symposium



# Regulating the Medical Use of Radioactive Material

October 15, 2019  
Donna-Beth Howe, Ph.D.  
Senior Health Physicist  
NMSS/MSST/MSEB

---

---

# Overview of Training Topics

- What NRC Regulates
  - Diagnostic Medical Use
  - Therapeutic Medical Use
  - Related Uses
- How NRC Regulates
  - NRC (Commission, Staff, ACMUI)
  - Agreement States and Other Federal Agencies
  - Regulations, Guidance, Inspections, and Enforcement
- Part 35
- Current Issues and Activities
- Resources

---

# What the NRC Regulates

- 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

---

# What is “Medical Use”

- “[T]he intentional internal or external administration of byproduct material or the radiation therefrom 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 not
  - 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

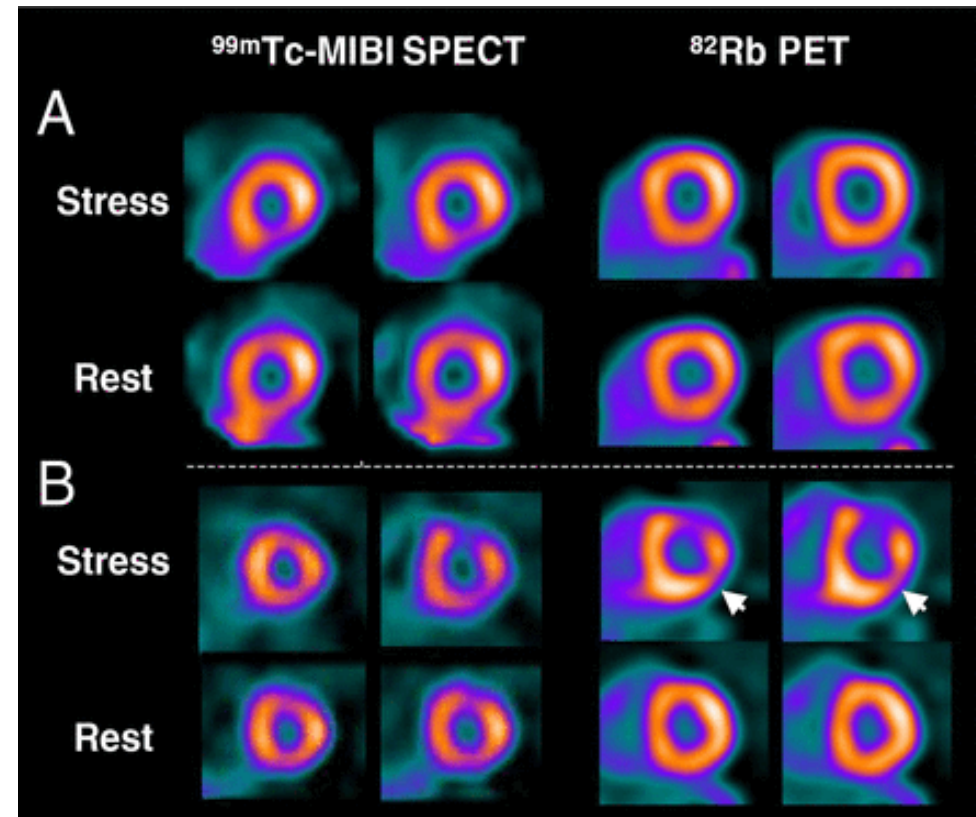
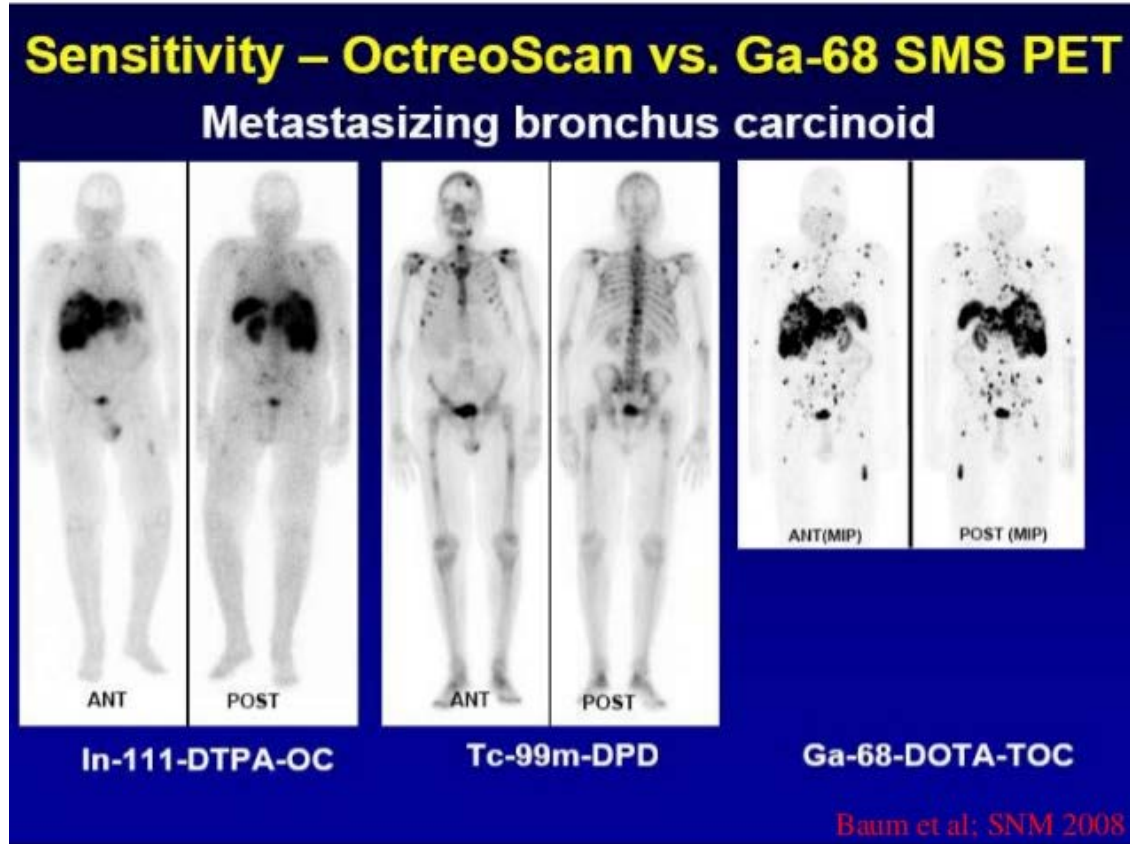
---

# Medical Use

## Two categories of medical use (Part 35)

- Diagnostic (except greater than 30 microcuries of NaI-131)
  - Nuclear medicine
  - Imaging organs, systems, and functions
- Therapeutic
  - Nuclear medicine
  - Teletherapy, brachytherapy, gamma stereotactic surgery

# Medical Use: Diagnostics



---

# Medical Use: Therapy

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



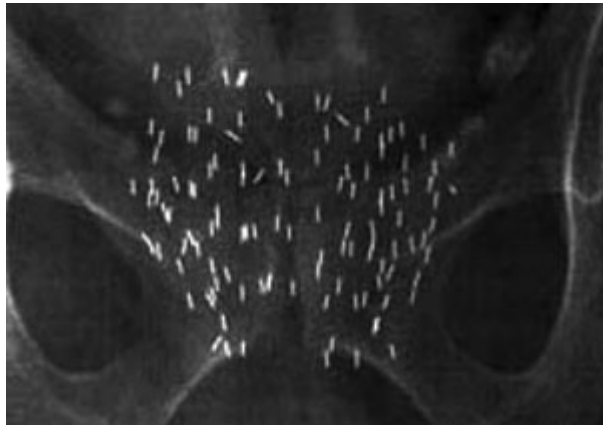
- Xofigo<sup>®</sup> (Ra-223 dichloride)



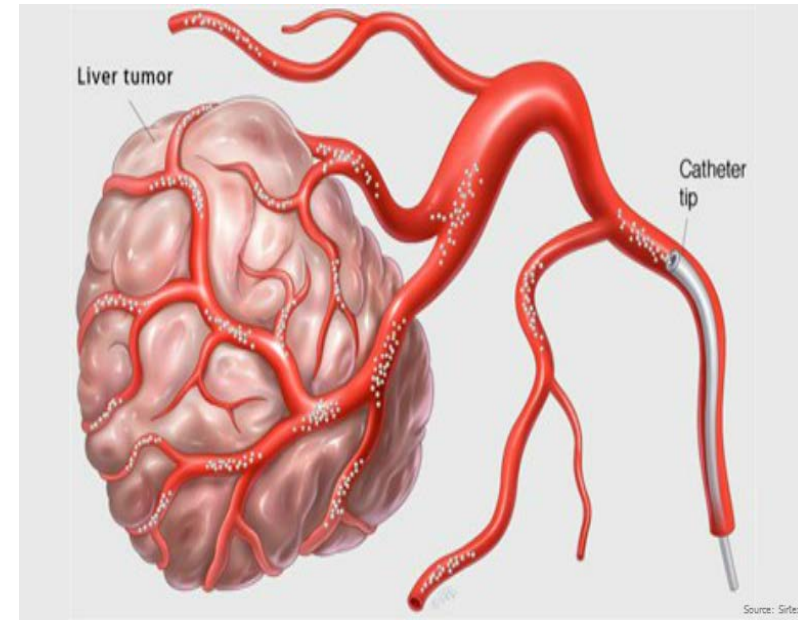


# Medical Use: Therapy

- Permanent Brachytherapy – Prostate Implant



- Y-90 Microspheres



# Medical Use: Therapy

Stereotactic Radiosurgery (Gamma

- High Dose Rate Afterloader



Specialized Applicators and Afterloader  
Matched to Treatment Needs



---

# Regulated Materials

## Byproduct material

- Reactor-produced
- Accelerator-produced (Energy Policy Act of 2005)
- See the definition of byproduct material (Section 11.e of the AEA and § 30.4)

## 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”

---

# How NRC Regulates

## Regulations

- Medical use (Part 30; Part 35)
- Manufacture and distribution (including radiopharmacies) of radiopharmaceuticals and sealed sources and devices (Part 30; 32.72, 32.74, 32.210; Part 35)

## Policy Statement on the Medical Use of Byproduct Material

- 65 FR 47654, August 3, 2000

---

# How NRC Regulates

## Guidance

- NUREG-1556, Vols. 9 (medical use), 11 (broad scope licenses), 12, Appendix R (Medical Distribution), 13 (radiopharmacies), and 21 (production using an accelerator)
- Regulatory Guides
  - Division 6 (Products)
  - Division 8 (Occupational Health)
    - 8.13 (prenatal radiation exposure)
    - 8.36 (dose to embryo/fetus)
    - 8.39 (patient release)
- 35.1000 guidance (see medical toolkit on the NRC public website)

## Licensing and Inspection

- Regions license medical use and radiopharmacies and inspect facilities
- HQ (NRR, NMSS) licenses medical isotope production

---

# How NRC Regulates

## Unique Licensees

- 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)

---

# How NRC Regulates

## Advisory Committee on the Medical Uses of Isotopes (ACMUI)

- Established by the Commission, not by statute
- Effectively dates back to the Manhattan Project; officially named ACMUI in 1959
- Members are nuclear and health care professionals, a patient advocate, an Agreement State representative, and an FDA representative
- Provides recommendations to NMSS/MSST and meets with the Commission annually
- Subject to the Federal Advisory Committee Act

---

# Part 35 Overview

- 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) – new and emerging technology
- Subpart L – Records
- Subpart M – Reports
- Subpart N - Enforcement



---

# Part 35 Highlights – Training and Experience

- For each medical modality codified, specific training and experience requirements for the Authorized User physician are provided.
- Also codifies specific training for Authorized Nuclear Pharmacist

---

# Part 35 Highlights – Written Directives

- An authorized user's (physician's) written order for the administration of material to a specific patient.
- Required for administration of greater than 1.11 MBq of I-131 and for any therapeutic administration
- Provides the specifics of administration (patient name, treatment site, dosage, route of administration, etc.) and licensees must maintain procedures to ensure that they're followed properly
- See §§ 35.40 and 35.41

---

# Part 35 Highlights – Patient Release

- Licensees may release patients if dose to member of the public from exposure to that patient is not likely to exceed 5 mSv
- Licensees must provide instructions to released patient (or guardian) if dose is likely to exceed 1 mSv
- If dose to nursing infant or child could exceed 1 mSv, the regulation requires certain instructions to the patient (or guardian)
- See § 35.75 for requirements and Regulatory Guide 8.39, Rev. 0 (soon to be revised) for guidance

---

# Part 35 Highlights - Event Reporting

## Medical Events

- Previously referred to as “misadministrations”
- Definition has been the subject of debate and rulemaking many times over the years
- See § 35.3045 for requirements

## Dose to Embryo/Fetus or Nursing Child

- See § 35.3047 for requirements and Regulatory Guide 8.36 for guidance

## Leaking Sealed Sources

- See § 35.3067 for requirements

## Breakthrough for Mo-99/Tc-99m and Rb-82/Sr-82 generators

- See § 35.3204 for notification and reporting requirements

## Abnormal Occurrences

- “[A]n unscheduled incident or event which the Commission determines is significant from the standpoint of public health and safety.”
- Reported to Congress annually (see MD 8.1 and NUREG-0090)
- Most are medical events or doses to an embryo/fetus
- See Section 208 of the Energy Reorganization Act of 1974 for requirements

---

# Report to Congress - Event Reporting

## Abnormal Occurrences

- “[A]n unscheduled incident or event which the Commission determines is significant from the standpoint of public health and safety.”
- Reported to Congress annually (see MD 8.1 and NUREG-0090)
- Most are medical events or doses to an embryo/fetus
- See Section 208 of the Energy Reorganization Act of 1974 for requirements

---

# Current Issues and Activities

- Training and Experience for all uses, particularly 35.300 (therapeutic radiopharmaceuticals)
- Patient Release Guidance and Best Practices
- Organization of Agreement States' petition for rulemaking on decommissioning financial assurance requirements for certain radioisotopes (PRM 30-66)
- Th-227 radiopharmaceuticals licensing
- Domestic production of medical isotopes

---

# 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)





# Radioactive Materials Licensing: Diagnostic and Therapeutic Uses

October 15, 2019  
Donna-Beth Howe, Ph.D.  
Senior Health Physicist  
NMSS/MSST/MSEB

---

---

# NRC Regulation

- **10 CFR 35.7 FDA, other Federal, and State requirements.**

Nothing in this part relieves the licensee from complying with applicable FDA, other Federal, and State requirements governing radioactive drugs or devices.

---

# NRC Licensing

- Through the **licensing** process, the U.S. **Nuclear Regulatory Commission (NRC)** authorizes an applicant to conduct any or all of the following activities: ... Possess, use, process, export and import nuclear materials and waste, and handle certain aspects of their transportation.
- All nuclear materials used for medical diagnosis and therapy are subject to specific licensing.
  - carbon-14 urea for “in vivo” diagnostic use - not medical use

---

# 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

---

# Medical Research of Byproduct Material

- Subparts D-H permit human research, provided:
- A licensee may conduct research using the byproduct materials for the uses authorized on its license.
- Research is conducted, funded, supported, or regulated by another Federal agency that has implemented the Federal Policy for the Protection of Human Subjects (Federal Policy)
- If the research will not be conducted, funded, supported, or regulated by another Federal agency that has implemented the Federal Policy, the licensee must amend its NRC medical use license, have informed consent, and institutional review board approval

---

# Source of Radioactive Drugs for 35.100, 35.200, 35.300 Uses

- A licensee may use unsealed byproduct material prepared for medical use if:
  - Obtained from a drug manufacturer (32.72), radiopharmacy (32.72), non commercial PET radioactive drug producer (30.34), or equivalent Agreement State requirements, *or*
  - Prepared by an ANP, or an AU who meets §35.290 or §35.390 with generator elution experience, or an individual under the supervision of an ANP or the AU, *or*
  - Obtained from & prepared by an NRC or AS licensee for use in research in accordance with a Radioactive Drug Research Committee-approved protocol or Investigational New Drug (IND) protocol accepted by FDA, *or*
  - Prepared by the licensee for use in research in accordance with a Radioactive Drug Research Committee-approved protocol or an IND protocol accepted by FDA

---

# Importation of Radioactive Drugs

- Foreign radioactive drugs must be imported into the United States under NRC's general license in Title 10 Code of Federal Regulations (CFR) 110.27, "General license for imports." In order for a U.S. medical use licensee to import radioactive materials under the general license, all the criteria for the general license must be met. One of these criteria is that the U.S. licensee (the consignee) must be authorized to *receive* and *possess* the radioactive material.

---

# Importation of Radioactive Drugs cont.

- Therefore, medical use licensees, authorized to possess and use radioactive drugs, can **receive** and **possess** the radioactive drugs that are produced outside the US.
- However, medical licensees may only **use** radioactive drugs from a NRC or AS licensed drug manufacturer or radiopharmacy (32.72 licensee).



---

# Questions on the Importation of Radioactive Drugs

- Q: Does 10 CFR 32.72 only apply to US domestic licensees or does it also apply to foreign entities?
  - A: 10 CFR part 32, “Specific Domestic Licenses to Manufacture or Transfer Certain Items Containing Byproduct Material,” as the title indicated applies only to domestic licensees.

---

# Questions on the Importation of Radioactive Drugs

- Q: Are radiopharmaceuticals exempt from the 10 CFR 110.27 rule for General License to import radioactive materials.
  - A: There is no exemption from the 10 CFR 110.27 general license. The medical use licenses authorized for use of radioactive drugs that do not require and require a written directive (therapeutic) can receive and possess the radioactive drug. It is the provisions of 10 CFR 35,100, 35.200, and 35.300 that prevent the use of the radioactive drug shipped directly from Canada to the U. S. medical use licensee.

---

# Questions on the Importation of Radioactive Drugs

- Q: Is there is an exemption for direct shipping of radioactive drugs from Canada to the U.S. medical use licensee due to the short shelf-life of the radioactive drug?
  - A: There is no available exemption in the regulation. The short shelf-life radioactive drugs still must be imported into the U.S. by the commercial nuclear pharmacy or drug manufacturer under the provisions of 10 CFR 110.27 who is also authorized under a 10 CFR 32.72 Medical Distribution license to redistributed the radioactive drug to the medical use licensees.

---

# Questions on the Importation of Radioactive Drugs

- Q: What if the Canadian facility is licensed by FDA as a manufacturing plant?
  - A: The FDA has a different regulatory authority that permits it to register foreign entities. NRC regulations are for domestic entities only. NRC does not have any provisions that permits the direct shipment of a radioactive drug to the medical facility from a non-domestic manufacturer even if the manufacturer is registered with FDA.

---

Licensing 35.100 and 35.200 Uses  
Unsealed Material, No Written Directive  
Required

---

# Medical Use of Byproduct Material

10 CFR Part 35 – “Medical Use of Byproduct Material” defines categories of medical use in Subparts D-H.

- Subpart D: “Unsealed Byproduct Material – Written Directive Not Required”
  - **35.100**: Uptake, Dilution, and Excretion Studies. 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  $\mu$ Ci) to assess thyroid function.*

---

# Medical Use of Byproduct Material

- Subpart D, continued
  - **35.200**: Imaging and Localization Studies. Administration of (usually) millicurie quantities of byproduct material, often by intravenous injection, but sometimes by other routes (such as orally for gastric emptying studies) 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 millicureis of Rubidium-82 for each resting and stress cardiac image.*

---

# Questions on the Importation of Radioactive Drugs

- Q: What generators are currently considered radioactive drugs?
  - A: Both the fission and non-fission technetium-99m/molybdenum (Tc-99m/Mo-99) generators as well as the rubidium-82/strontium-82 generators are considered radioactive drugs. Other generators may be added to this list as they become available in the U.S.
- Q: Is there is an exemption for direct shipping of radioactive drugs from Canada to the U.S. medical use licensee due to the short shelf-life of the radioactive drug?
  - A: There is no available exemption in the regulation. The short shelf-life radioactive drugs still must be imported into the U.S. by the commercial nuclear pharmacy or drug manufacturer under the provisions of 10 CFR 110.27 who is also authorized under a 10 CFR 32.72 Medical Distribution license to redistributed the radioactive drug to the medical use licensees.



---

# Medical Use of Byproduct Material

- Generators: Permissible concentration (breakthrough regulatory limits)
  - Mo/Tc generator
    - **0.15  $\mu\text{Ci}$  of Mo-99 per mCi of Tc-99m**
  - Sr/Rb generator
    - 0.02  $\mu\text{Ci}$  of Sr-82 per mCi of Rb-82 chloride
    - 0.2  $\mu\text{Ci}$  of Sr-85 per mCi of Rb-82 chloride
  - Ge/Ga generator
    - the manufacturer's limits in accordance with the licensee's commitment under 10 CFR 35.1000 guidance.

---

Licensing 35.300 Uses  
Unsealed Material, Written Directive Required

---

# Medical Use of Byproduct Material

- Subpart E: “Unsealed Byproduct Material - Written Directive Required”
  - When is a written directive required?
  - 35.40(a) states that a written directive is needed for sodium iodide I-131 greater than 30  $\mu\text{Ci}$ , any therapeutic dosage of unsealed byproduct material, or any therapeutic dose of radiation from byproduct material [i.e, from sealed sources].

---

# Medical Use of Byproduct Material

- Subpart E, continued

**35.300** is defined under Subpart E, and now includes 3 subcategories:

- a. Oral administration of sodium iodide [NaI] I-131 requiring a written directive in quantities  $\leq 33$  mCi [i.e.,  $>30$   $\mu$ Ci and  $\leq 33$  mCi].

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

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

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

---

# Medical Use of Byproduct Material

- Subpart E, continued
  - c. 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.*

---

# Source of Radioactive Sources and Devices under 35.400, 35.500, 35.600

- A licensee may use sealed sources and devices for medical use if:
- Obtained from a source or device manufacturer under 32.74 and approved in the Sealed Source & Device Registry; *or*
- Non commercially transferred from another medical use licensee
- Teletherapy sources manufactured and distributed by a part 30 licensee

---

# Exemption for Broad scope medical use licensees for imported sources and devices

- Broad scope licensees are exempt from the requirement to use sealed sources and devices (SSD) from a licensed distributor provided, the SSD is under an active IDE application accepted by FDA.

---

# Importation of Sealed Sources and Device

- The distributor of sealed sources and devices (SSD) must be located in the US.
- If the SSD manufacturer is located in a foreign country, then they must either:
  - (1) go through a US distributor, or
  - (2) establish their own US distribution point, including getting any necessary licenses.
- Required to establish an address to which necessary correspondence and paperwork can be served (US does not have jurisdiction outside US territories).



---

## Use of Source of Radioactive Sources and Devices under 35.400, 35.500, 35.600

- A licensee may use sealed sources and devices for medical use if:
- Approved in the Sealed Source and Device Registry specifically for 35.400, 35.500, or 35.600 medical use, respectively; *and*
- Used for the appropriate 35.400, 35.500, or 35.600 medical uses even when the use is not explicitly listed in the Sealed Source and Device Registry, but must be used in accordance with the radiation safety conditions and limitations described in the Sealed Source and Device Registry; *or*
- In research in accordance with an active Investigational Device Exemption (IDE) application accepted by FDA

---

# Licensing 35.400 Uses Manual Brachytherapy

---

# Medical Use of Byproduct Material

- Subpart F: “Manual Brachytherapy”
  - **35.400** is defined under Subpart F, and includes 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.*

---

# Licensing 35.500 Uses Sealed Sources for Diagnosis

---

# Medical Use of Byproduct Material

- Subpart G: “Sealed Sources for Diagnosis”
  - **35.500** is defined under Subpart G, and currently includes sources used external to the patient to aid in diagnosis. Current examples are Gd-153 or Cs-137 attenuation correction sources used in SPECT or PET nuclear medicine imaging systems.

*Note: use of I-125 seeds for tumor localization/ excision, while diagnostic, is not considered under 35.500*

---

Licensing 35.600 Uses  
Photon Emitting Remote Afterloader Units,  
Teletherapy Units, and Gamma Stereotactic  
Radiosurgery Units

---

# Medical Use of Byproduct Material

- Subpart H: “Photon Emitting Remote Afterloader Units, Teletherapy Units, and Gamma Stereotactic Radiosurgery Units”
  - **35.600** is defined under Subpart H and includes sealed source treatment devices. Most common examples are high dose-rate remote afterloaders (HDR) and Co-60 gamma knife. Less common examples are low dose-rate remote afterloaders (LDR) and Co-60 teletherapy.

---

# 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)*
- Subpart K—Other Medical Uses of Byproduct Material or Radiation From Byproduct Material

10 CFR 35.1000 Other medical uses of byproduct material or radiation from byproduct material.

- A licensee may use byproduct material or a radiation source approved for medical use which is not specifically addressed in subparts D through H of this part if—
- (a) The applicant or licensee has submitted the information required by § 35.12(b) through (d); and
- (b) 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 Part 35--Licensing

10 CFR 35.15 Exemptions regarding Type A specific licenses of broad scope.

- A licensee possessing a Type A specific license of broad scope for medical use, issued under Part 33 of this chapter, is exempt from—
- (a) The provisions of § 35.12(d) regarding the need to file an amendment to the license for medical use of byproduct material, as described in § 35.1000;

---

# 10 CFR Part 35--Licensing

## Examples of Devices and Drugs NRC licenses under 10 CFR 35.1000

- Drug: NorthStar Medical Radioisotopes, LLC RadioGenix™ Molybdenum-99/Techneium-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™; 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



# Radioactive Materials Licensing: Emerging Medical Technologies

October 15, 2019  
Lisa Dimmick  
Team Leader  
NMSS/MSST/MSEB

---

---

# Outline

- Introduction
- Radiopharmaceuticals
- Brachytherapy
- Gamma Stereotactic Radiosurgery
- Other Uses

---

# Introduction

---

# Emerging Medical Technologies

- If the emerging medical technology **is not** specifically addressed in 10 CFR Part 35 Subparts D through H, the NRC will develop licensing guidance describing an acceptable approach for meeting NRC regulations.
- If the emerging medical technology **is** specifically addressed in 10 CFR Part 35 Subparts D through H, the staff may provide additional information to assist in licensing and inspection based on the specific risks associated with the technology.

---

# Examples of Past Reviews

- Germanium-68/Gallium-68 (Ge-68/Ga-68) Pharmaceutical Grade Generators, *July 2019*
- Leksell Gamma Knife® Perfexion™ and Leksell Gamma Knife® Icon™ (Rev 1), *January 2019*
- NorthStar Medical Radioisotopes, LLC RadioGenix™ Molybdenum-99/ Technetium-99m Generator, *February 2018*
- Low Activity Radioactive Seeds Used for Localization of Non-Palpable Lesions and Lymph Nodes, *October 2016*
- Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres®, *February 2016*



---

# Examples of Past Reviews **not 35.1000**

- **GammaTile** – determined to be licensed under 10 CFR 35.400 in April 2019
- **Lutetium-177 dotatate** – determined to be licensed under 10 CFR 35.300 in June 2018
- **SalutarisMD<sup>®</sup> Manual Radionuclide Eye Applicator** – determined to be licensed under 10 CFR 35.400 in October 2017
- **Radium-223 Dichloride** – determined to be licensed under 10 CFR 35.300 in January 2013

---

# Examples of In-Process Reviews

- MASEP Infini™ cobalt-60 stereotactic radiosurgery for treating brain tumors and lesions
- GammaPod™ cobalt-60 stereotactic radiotherapy for treating breast cancer
- Yttrium-90 Microsphere Brachytherapy Sources and Devices  
TheraSphere® and SIR-Spheres® – updating existing licensing guidance (Rev 10)

---

# Radiopharmaceuticals

---

# FDA approved Therapy Radiopharmaceuticals

- Iodine I 131 iobenguane (Azedra)
- Iodine I 131 sodium iodide
- Lutetium Lu 177 dotatate (Lutathera<sup>®</sup>)
- Radium Ra 223 dichloride (Zofigo<sup>®</sup>)
- Samarium Sm 153 lexidronam
- Strontium Sr 89 chloride
- Yttrium Y 90 ibritumomab tiuxetan (Zevalin<sup>®</sup>)

---

# Therapy Radiopharmaceuticals in Clinical Trials

- Actinium Ac 225 Lintuzumab
- Iodine I 131 Apamistamab
- Lutetium Lu 177 PSMA
- Thorium Th 227

---

# Therapy Radiopharmaceuticals: 35.300 versus 35.1000

- Radiation Characteristics
- Authorized User Physician
- Complex Patient Specific Dosimetry
- Patient Release
- Waste
- Other aspects applicable to radiation safety not addressed in the regulations

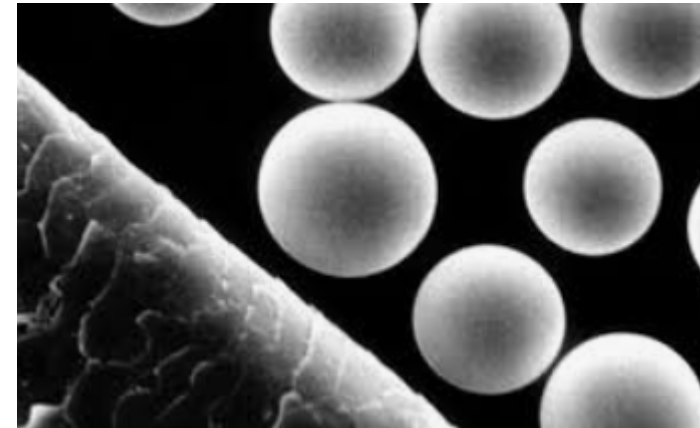
---

# Brachytherapy

---

# Yttrium-90 Microspheres

- Permanent Implant Brachytherapy with Y-90 microspheres for treatment of liver tumor
- Original 10 CFR 35.1000 licensing guidance issued in 2002
- Licensed under 10 CFR 35.1000 because of -
  - Unique delivery system
  - Size and large number of spheres





---

# Yttrium-90 Microspheres

- Training and Experience
  - Combination of radiopharmaceutical and manual brachytherapy training
  - Training allowed after authorization
  - Manufacturer representatives allowed to give training
- Medical Event Criteria
  - Excludes reporting of known medical risks such as underexposures due to stasis or wrong treatment site delivery due to shunting when pre-treatment assessment is done in accordance with the manufacturer procedures
- Inventory and Waste Concerns
- Leak Testing

---

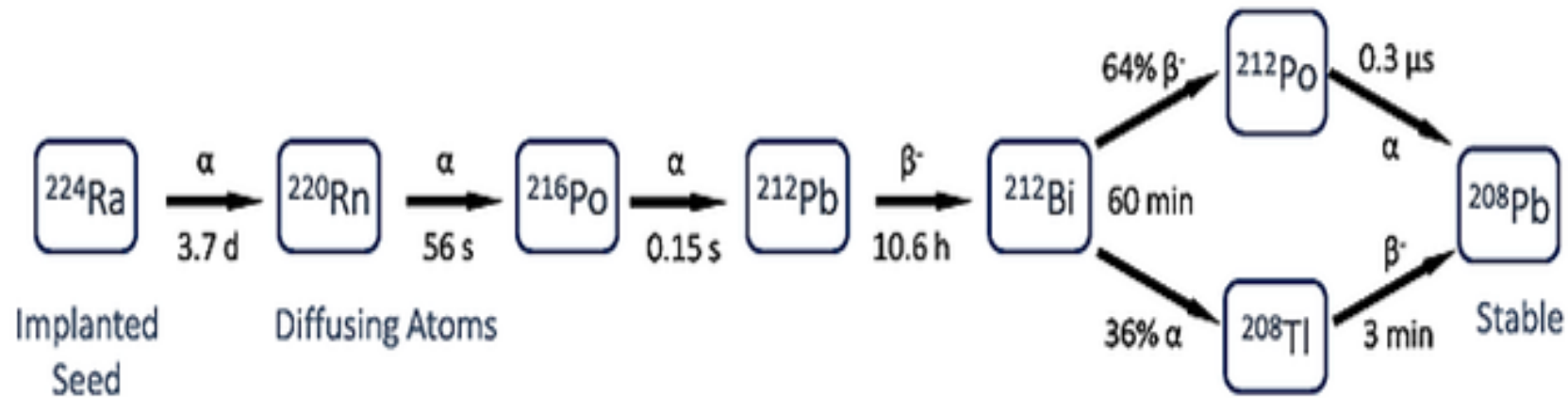
# Oncosil

- Permanent Implant Brachytherapy with Phosphorous-32 particles implanted using endoscopic ultrasound guidance for treatment of pancreatic cancer
- Will likely be licensed under 10 CFR 35.1000 similar to Y-90 microspheres, starting NRC's evaluation
- Licensed under 10 CFR 35.1000 because of -
  - Unsealed material, but used like permanent implant brachytherapy
  - No SSD



# Alpha DART

- Intra-tumoral brachytherapy utilizing diffusing alpha-emitting Radium-224 atoms
- SS&D issued in August 2018
- Starting NRC's evaluation



---

# Gamma Stereotactic Radiosurgery (GSR)

---

# Perfexion/Icon

- GSR Unit for treatment of the head
- Licensed under 10 CFR 35.1000 because -
  - Elimination of the helmet
  - Sources are in movable sectors to adjust collimation without changing helmets
  - Icon has frameless option
- Modified physical presence requirement
- Modified periodic spot check and full calibration conditions



---

# ViewRay

- GSR Unit for treatment of the head licensed under 10 CFR 35.1000
- Licensed under 10 CFR 35.1000 because - Rotating gantry assembly
  - Integrated Magnetic Resonance Imaging for real time image guidance
  - Multi-leaf collimation
  - Gating
  - Allow use of manufacturer procedures when there are no published protocols accepted by nationally recognized bodies.



---

# GammaPod

- GSR Unit for breast cancer treatment
- Licensed under 10 CFR 35.1000 because -
  - Rotating sources and collimator carrier
  - Table movement during treatment
  - Vacuum-assisted breast cup immobilization and stereotactic localization system



---

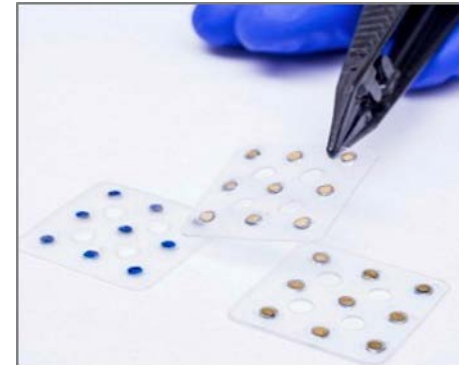
# Other Uses



---

# CivaDerm

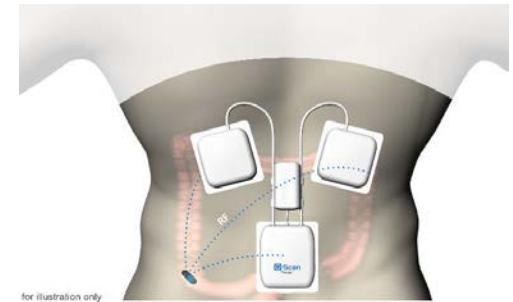
- Skin application
- 35.400 versus 35.1000
- Can this use be classified as an implant?
- Patient Release
- Written Directive
- Authorized User Physicians
- 510k, September 2019
- SSD, March 2018



# CheckCap

## Colorectal Cancer Screening

- Sealed Source for diagnosis  
35.500 versus 35.1000
- Authorized User Physicians
- Waste disposal



---

# Animal Use

- Tin 117m colloid for radiosynoviorthesis for treatment of osteoarthritis of the canine elbow
- Y-90 particles for treatment of pet sarcomas
- Release of Animals must comply with 10 CFR Part 20 public dose limits
  - 100 mrem per year
  - 2 mrem per any one hour
  - NUREG-1556, Volume 7 provides limited guidance for animal release



# Sealed Source and Device Reviews

October 15, 2019  
Tomas Herrera  
Team Leader  
NMSS/MSST/MSTB

---

---

# Radioactive Materials Program

- Radiation safety programs for the use of radioactive material as a sealed source or device are structured on the presumption that the radioactive material will not breach its containment and contaminate the environment or unnecessarily expose individuals to radiation.
- This presumption depends largely upon the adequacy of the containment properties of the sealed sources or devices in withstanding the stresses imposed by the environment in which they are possessed and used.

---

# Radioactive Materials Program

- Title 10 of the *Code of Federal Regulations* (CFR), Section 30.32(g), requires that an applicant for a specific license to use a sealed source or device identify the sealed source or device as registered with NRC, in accordance with 10 CFR 32.210 or to provide the information contained in 10 CFR 32.210.

---

# Purpose of The Review

- 10 CFR 32.210 provides for the registration of a product and provides a means for having a single safety evaluation of the product performed.
- This process allows applicants and license reviewers to reference the evaluation when licensing the product for use or distribution without having to perform a complete evaluation of the product for each licensing action.



---

# Sealed Source and Device Registry

- National registry that contains all the registration certificates issued NRC and the Agreement States
  - Registration certificates summarize the radiation safety information for the sealed sources and devices and describe the licensing and use conditions approved for the product
  - Maintained by the NRC

---

# Typical Requests

- A licensee may submit a license application to manufacture and/or distribute products to be used by specific licensees, by general licensees (or both), by an exempt or a custom user.
- A licensee may request registration of new product, amendment to a current existing certificate, or inactivation of a certificate.

---

# The Review

- The application has
  - assumptions and approximations that are reasonable;
  - adequate, complete, accurate information for a review; and;
  - is signed by a senior level manager who has the responsibility for overseeing regulatory activities.
- Note deficiencies or discrepancies, distortions, and if possible, complete the checklist as the general review proceeds.
- Guidance Document – NUREG-1556, Vol. 3 Rev. 2

---

# The Review

- Medical Products
  - If the application is for a medical product needs to notify the FDA.
  - NRC's policy is that the registration certificate will not be issued until the applicant has provided Premarket Notification [510(k)], Premarket Approval (PMA), Humanitarian Device Exemptions (HDE), or Investigational Device Exemption (IDE).

---

# Major Areas of a Review

- Design
- Operation/Instructions to Users
- External radiation levels
- Quality assurance/quality control
- Prototype testing

---

# Design Review

- Dimensions/tolerances
- Materials
- Fasteners
- Manufacturing processes
- Function
- Safety features
- On/off mechanism and indicators
- Labeling – durable, visible
- Appropriateness of assumptions, approx. and calculations

---

# Operation/Instructions to Users Review

- Normal operation,
- Installation/removal/reinstallation,
- Leak and on/off testing,
- Source exchange,
- Servicing,
- Conditions and limitations of use, and
- Maintenance

---

# External Radiation Levels Review

- Dose rates reasonable for type of use, amount of radionuclide, and shielding
- Measured with maximal loading for each radionuclide, and radionuclide combination for each device
- Measured for all model series if shielding or activity levels differ in model series



---

# Quality Assurance/Quality Control Review

- Uses standard operating procedures and check lists as appropriate
- Ensure that sources and devices manufactured and/or distributed meet the approved specifications
- Verify operation of safety features
- Verify final radiation profiles
- Verify leak test

---

# Prototype Testing Review

- Testing may be done without source loading for many performance tests
- Tests of dose rates may be done with less than maximum loading and scaled provided that the test source is a meaningful percentage of maximal activity
- Tests of moving parts should exceed the maximum number of operational life cycles expected
- Test conditions should exceed normal conditions of use and adverse environments
- May refer to substantially similar source/device design and use conditions

---

# Deficiencies

- If additional information is necessary in order to address all issue, you may need to send the applicant a deficiency letter (request for additional information), then evaluate their response. Sometimes this step may need to be repeated in order to obtain all necessary information.
- It is the applicant's responsibility to provide clear and sufficient information to demonstrate that the product safe and meets all the regulatory requirements.

---

# Foreign Vendors

- The distributor must be located in the US.
- If the applicant is located in a foreign country, then they must either:
  - (1) go through a US distributor, or
  - (2) establish their own US distribution point, including getting any necessary licenses.
- Required to establish an address to which necessary correspondence and paperwork can be served (US does not have jurisdiction outside US territories).

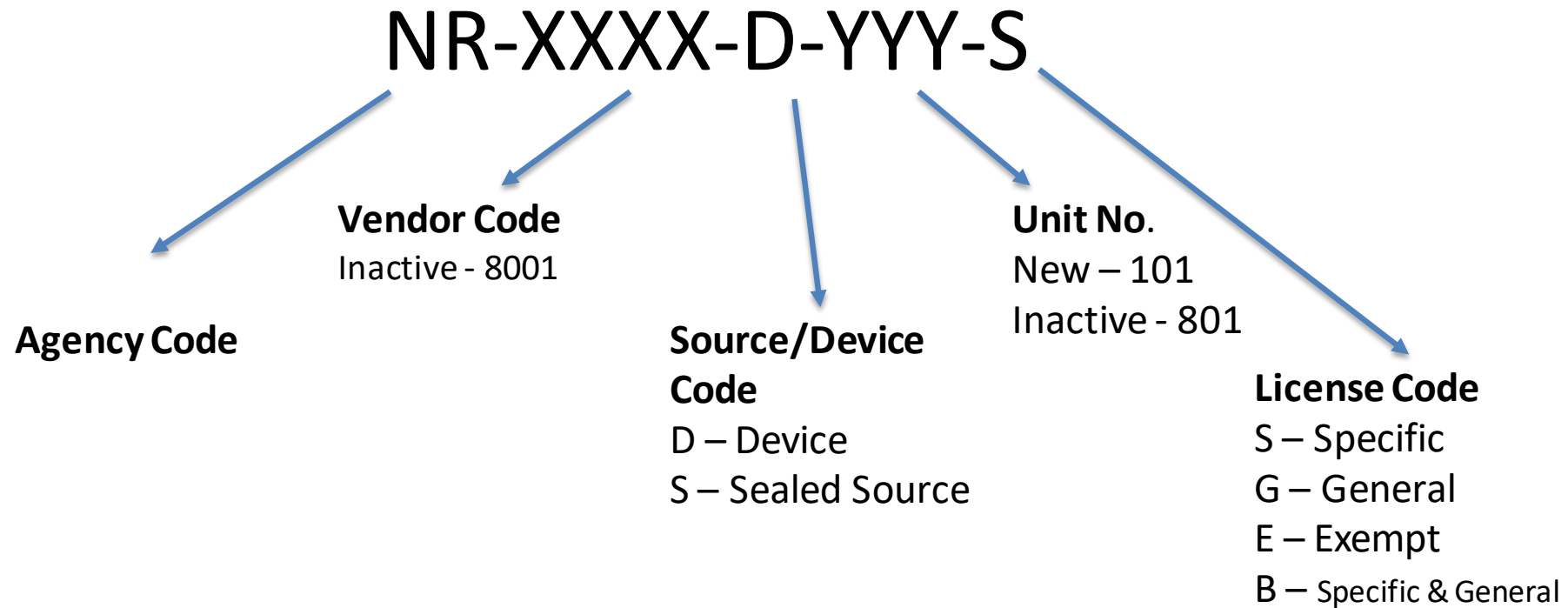
---

# Drafting the Registration Certificate

- The registration certificate is:
  - A summary of the information submitted in the application.
  - A statement that the source or device has been reviewed and approved.
- Standard format
- NUREG-1556, Vol. 3, Rev. 2, Chapter 12 and Appendix D contain templates to ensure that all necessary information is present and in the correct format.

---

# Certificate Numbering



REGISTRY OF RADIOACTIVE SEALED SOURCES AND DEVICES  
SAFETY EVALUATION OF DEVICE  
(AMENDED IN ITS ENTIRETY)

NO.: NR-\*\*\*\*-D-\*\*\*\*-X

DATE:

PAGE 1 OF 8

(For "X", the following designations should be used: "S" for specifically licensed devices, "G" for generally licensed devices, and "B" for both types.)

Important note for reviewers: Some devices are distributed as "B" (both specifically licensed and general licensed devices). For these devices, the reviewer should clearly differentiate between the specifically licensed design and the generally licensed design in the registration certificate. These differences can include, for example, description of tamper proofing, labeling, and other applicable features.

DEVICE TYPE: Provide a short description of the device type.

MODEL: ABC

MANUFACTURER/DISTRIBUTOR: NameStreetCity, State, Zip (If manufacturer and distributor are the same, keep subheading as shown. If different, delete the word "manufacturer" from the subheading.)

MANUFACTURER: NameStreetCity, State, Zip (This subheading and information is not necessary, if the manufacturer and distributor are the same.)

SEALED SOURCE MODEL DESIGNATION: ACME MODEL 123

ISOTOPE: MAXIMUM ACTIVITY: XX GBq (XX mCi)  
List Isotopes (Units should be such that the amount is in the 1 to 999 range.)

LEAK TEST FREQUENCY: Not Required/6 Months

PRINCIPAL USE: (...) See Appendix C

CUSTOM SOURCE: \_\_\_ Yes \_\_\_ No

---

# Certificate Sections

- Description
- Labeling
- Diagram
- Conditions of Normal Use
- Prototype Testing
- Quality Assurance and Control
- Limitations and/or Other Considerations of Use
- FDA Approval Summary (for medical)
- Safety Analysis Summary





# Medical Event Reporting

October 15, 2019  
Lisa Dimmick  
Team Leader  
NMSS/MSST/MSEB

---

---

# Medical Event Reporting

- The purpose of reporting medical events is to identify their causes in order to correct them and prevent their recurrence.
- Medical events reporting allows for identification of trends and ability to provide information that may prevent similar incidences.

---

# Written Directives (10 CFR 35.40)

- Requirements are different depending on the types of administrations as each has different safety concerns
- All require
  - AU Signature,
  - Dated, before the administration, and
  - Patient Name, and
  - Dosage for unsealed byproduct material, or
  - Total dose for sealed sources, or
  - Total source strength for permanent implant brachytherapy

---

# Written Directives (10 CFR 35.40)

- Revision to existing written directive may be made if revision is dated and signed by AU before administration, or
- Oral revision is possible if a delay in order to provide a written revision would jeopardize patients health

---

# Medical Event Reporting (10 CFR 35.3045)

- A dose that differs from the prescribed dose more than
  - 0.05 Sv (5 rem) effective dose equivalent, 0.5 Sv (50 rem) to an organ or tissue, or 0.5 Sv (50 rem) shallow dose equivalent to the skin;
  - and

---

# Medical Event Reporting (10 CFR 35.3045)

- The total dose delivered differs from the prescribed dose by 20 percent or more;
- The total dosage delivered differs from the prescribed dosage by 20 percent or more or falls outside the prescribed dosage range; **or**
- The fractionated dose delivered differs from the prescribed dose, for a single fraction, by 50 percent or more.

---

# Medical Event Reporting (10 CFR 35.3045)

- A dose that exceeds 0.05 Sv (5 rem) effective dose equivalent, 0.5 Sv (50 rem) to an organ or tissue, or 0.5 Sv (50 rem) shallow dose equivalent to the skin from any of the following-
  - (i) An administration of a wrong radioactive drug containing byproduct material;
  - (ii) An administration of a radioactive drug containing byproduct material by the wrong route of administration;



---

# Medical Event Reporting (10 CFR 35.3045)

- (iii) An administration of a dose or dosage to the wrong individual or human research subject;
- (iv) An administration of a dose or dosage delivered by the wrong mode of treatment; or
- (v) A leaking sealed source.

---

# Medical Event Reporting (10 CFR 35.3045)

- A licensee shall report any event **resulting from intervention of a patient or human research subject** in which the administration of byproduct material or radiation from byproduct material results or will result in **unintended permanent functional damage to an organ or a physiological system, as determined by a physician.**

# Medical Events: 2014—2017

Regulatory Use	Types of Use	Number of Events
10 CFR 35.200	Imaging and Localization using Unsealed Byproduct Material	21
10 CFR 35.300	Unsealed Byproduct Material With Written Directive Required	20
10 CFR 35.400	Manual Brachytherapy	27
10 CFR 35.600	Afterloader Brachytherapy	34
10 CFR 35.1000 10 CFR 35.600	Gamma Stereotactic Units	15
10 CFR 35.1000	Radiation Seed Localization	4
10 CFR 35.1000	Yttrium-90 Microsphere	91

---

# Abnormal Occurrence

- To be classified as an abnormal occurrence (AO), a medical event must meet a dose threshold and incident criteria
- The event must meet the following dose threshold
  - Equal or greater than
  - 1 Gy to bone marrow or lens of the eye
  - 2.5 Gy to the gonads, or
- Exceeds, by 10 Gy, the expected dose to any other tissue

---

# Abnormal Occurrence

- In addition, the event must involve one of the following
  - A dose that is at least 50% greater than prescribed
  - The wrong radiopharmaceutical, route of administration, or treatment mode
  - A leaking source
  - Wrong patient or research subject

---

# Abnormal Occurrence

- Since 2006, over 95% of AOs have been medically related.
- In most AOs reported, the event descriptions stated the patient experienced no significant harm.
- There were 9 medical AOs reported in FY 2018 using.

---

# Information Notices (IN)

- August 26, 2019, NRC issued two INs
  - IN-19-06, Patient Skin Contamination Events Associated with I-131 Metaiodobenzylguanidine (MIBG) During Neuroblastoma Treatments
  - IN-19-07, Methods to Prevent Medical Events
- NRC is drafting two additional INs with a planned release date of December 2019
  - IN-xx-xx, Recent Reported Medical Events Involving the Administration of Yttrium-90 Microspheres
  - IN-xx-xx, Strontium-82/Rubidium-82 Generator Breakthrough Events and Issues

---

# 1980 Policy on Extravasations

- Extravasation is the infiltration of injected fluid into the tissue surrounding a vein or artery.
- Extravasation frequently occurs in otherwise normal intravenous or intra-arterial injections.
- It is virtually impossible to avoid.
- Therefore, the NRC does not consider extravasation to be a misadministration.
- In 1980, misadministration means the administration of wrong source, wrong patient, wrong route, diagnostic dose differing by more than 50%, therapeutic dose differing by more than 10%



---

# Why Reconsider Extravasation?

- Currently 48 radiopharmaceuticals approved by the FDA, including 5 IV therapeutic drugs.
- Extravasation of the F-18 labeled PET drugs can bring about discrepancies in the standard uptake value (SUV).



# Open Forum

(Questions and Answers)



## FDA-NRC Collaboration for Medical Radiation Safety Symposium

### Session I: FDA overview of Drug Development Process

Drug Development Regulatory Processes: Phase 1 to Phase 3, & the Review process

Kyong Kang, PharmD

Dosimetry Requirements through the Drug Development Process

Christy John, Ph.D.

Devices and new agents at the CDRH review process and Labeling

Mike O'Hara, Ph.D.

PET agents at the CDRH Review process and Labeling

Xin He, Ph.D.

FDA 101: Drug Product Pharmaceutical and Microbiologic Quality, Manufacturing

Danae Christodoulou, Ph.D.

Data and Other Information Required for Labeling

Michele Fedowitz, M.D.

### Session II NRC overview of Licensing Process

Regulating the Medical Use of Byproduct Material

Donna-Beth Howe, Ph.D.

Radioactive Materials Licensing: Diagnostic and Therapeutic Uses

Donna-Beth Howe, Ph.D.

Radioactive Materials Licensing of Emerging Medical Technologies

Lisa Dimmick

Sealed Source and Device Evaluations

Tomas Herrera

Medical Event Reporting

Lisa Dimmick