Introduction to Radiological Medical Device Regulation

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Outline

- Overview of Radiological Device Regulation
- Intended Use and Indications for Use
- Pre-market Regulation of Radiological Medical Devices

How are Radiological Medical Devices Regulated by FDA?

- ***FDA*** regulates manufacturers of the equipment and the equipment itself
- ***Other State and Federal Agencies*** regulate the use of radiation emitting devices through recommendations and requirements for:
  - Personnel qualifications
  - Institutional quality assurance programs
  - Facility accreditation

Safety and Effectiveness

Medical Device Amendments of 1976: Requires devices to be safe and effective

- **Safety**: Reasonable assurance, based on valid scientific evidence, that the *probable benefits to health from use of the device* for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, *outweigh any probable risks.*
- **Effectiveness**: Reasonable assurance, based on valid scientific evidence, that in a significant portion of the target population, the *use of the device for its intended use and conditions of use*, when accompanied by adequate directions for use and warnings against unsafe use, *will provide clinically significant results*.

Device Class and Premarket Requirements

Device Class	Controls	FDA Premarket review process
Class III (Highest Risk)	General controls + Premarket Approval	Premarket Approval [PMA]
Class II	General Controls + Special Controls	Premarket Notification [510(k)]
Class I (Lowest Risk)	General Controls	Most are exempt

General and Special Controls

	Device Type	Examples
General Controls	• All medical devices unless exempted by regulation • Identified in the classification regulation	• Establishment Registration and Device Listing • Adverse Event Reporting • Quality Systems/GMP
Special Controls	• Class II devices • Usually device specific • Identified in the classification regulation	• Special labeling requirements • Premarket data requirements • Performance Standards • Post-market surveillance

https://www.fda.gov/medical-devices/overview-device-regulation/regulatory-controls

Intended Use

Intended use – the general purpose of the device or its function and encompasses the indications for use

Indications for use – describes the disease or conditions the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended [21 CFR 814.20(b)(3)(i)]

- The indications for use and intended use may be the same for devices with general indication for use that do not specify a disease, condition or population

510(k) Premarket Notification

Marketing clearance application for introduction into interstate commerce for commercial distribution of a Class II and some Class I devices.

- Device is **substantially equivalent** to a legally marketed predicate device

  predicate = device already legally marketed in the US

Manufacturers must submit a 510(k) when:

- Introducing the device into commercial distribution for the first time
- Making a change to a currently marketed device
  i. That could **significantly affect** the safety or effectiveness of the device
  ii. A major change or modification in the **indications for use** of the device

Reference: FD&C Act Section 510(k) and 21 CFR 807 Subpart E

510(k) Premarket Notifications: How is Substantial Equivalence Determined?

Submission from the manufacturer

- Compares new device to **predicate device(s)**
- Demonstrates that the new device is **as safe and effective as predicate**
- Established special controls applicable to the predicate need to be addressed by the new device

FDA Guidance Document: The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]

510(k) Premarket Notifications: How is Substantial Equivalence Determined?

Substantially equivalent (SE)

- Same intended use *AND* same technological characteristics

OR

- Same intended use *AND* different technological characteristics (e.g., change in material, design, energy source, software) *AND* these differences do not raise different questions of safety and effectiveness

https://www.fda.gov/medical-devices/premarket-submissions/premarket-notification-510k

510(k) Premarket Notifications: How is Substantial Equivalence Determined?

Different technological characteristics

- FDA reviews the scientific methods used to evaluate the difference in technological characteristics and performance data.
- Performance Testing may include bench, animal, or clinical test data
- Necessary performance tests depend on the complexity of the device and its intended use and indications

https://www.fda.gov/medical-devices/premarket-submissions/premarket-notification-510k

Part 892 Radiological Devices
Subpart B- Diagnostic Devices

- ~ 68 Regulations
- 18 Regulations that may involve isotopes

892.1200 Emission Computed Tomography – Class II

Device intended to detect location and distribution of gamma ray and positron emission in the body and produce cross sectional images

KPS: Emission Computed Tomography (PET, SPECT, PET/CT, SPECT/CT)

OUO: Tomographic Imager Combined with Magnetic Resonance Imaging

Part 892 Radiological Devices- Subpart F- Therapeutic Devices

- ~ 15 Regulations, 5 may involve isotopes

Regulation	Device	Class
892.5050	Medical charged-particle, radiation therapy system	II
892.5700	Remote controlled radionuclide applicator system	II
892.5730	Radionuclide brachytherapy source	II
892.5740	Radionuclide teletherapy source	I exempt
892.5750	Radionuclide radiation therapy system	II
892.5900	X-ray radiation therapy system	II

510(k) Clearance Example:

892.5700 - Remote controlled radionuclide applicator system (Class II, JAQ)

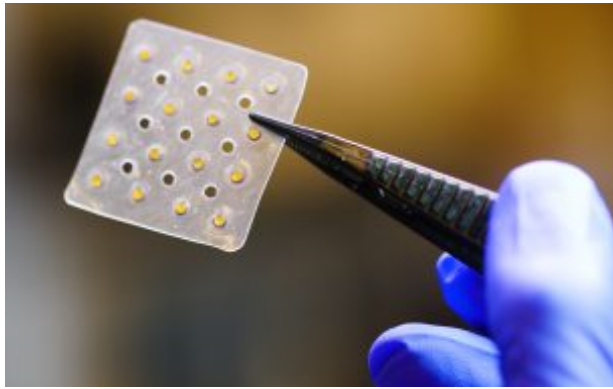
- K191580 Varian Bravos Afterloader System
  - Components: Afterloader, Transfer Guide tubes, Length assessment Device
  - High Activity Ir-192 encapsulated in steel capsule fused to steel cable.
  - For use in the treatment of both benign and malignant diseases or other conditions, for both curative and palliative intent in the delivery of remote-controlled HDR brachytherapy

Predicate Device: K181903 Bravos Afterloader

510(k) Clearance Example:

892.5730 – Radionuclide Brachytherapy Source (Class II)

- K140490 CivaTech CivaSheet
  - Product code KXK
  - Customizable, Bioabsorbable background matrix, gold encapsulated, Pd-103
  - Indicated for: Permanent interstitial brachytherapy source for treatment of selected localized tumors. Either for primary treatment or for residual disease after excision, can be given concurrently or sequentially with other treatment modalities.



Predicate Device: K082159 CivaString

What is a Class III Device?

- **Highest risk category**
- Subject to **PMA requirements**
- **Support or sustain** human life, substantial importance in **preventing impairment** of human health, potential for **unreasonable risk** of illness or injury
- **Unable to solely rely on general and special controls** to assure safety and effectiveness or when there is insufficient information to make such a determination

Reference: 513(a)(1)(C) of the FD&C Act or 21 US 360c(a)(1)(C)

PMA

Stand-alone premarket submission

- **No predicate device**
  - A PMA is not substantially equivalent to anything
- Application must contain sufficient scientific evidence to **provide a reasonable assurance** that the device is **safe and effective**
  - With respect to the persons for whose use the device is represented or intended,
  - With respect to the conditions of use prescribed, recommended, or suggested in the labeling of the device, and
  - Weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use

Reference: 513(a)(2) of the FD&C Act or 21 USC 360c(a)(2)

Benefit/Risk analysis in PMA review

Benefit	Risk	Additional Factors
Type	Severity, types, number and rates of harmful events • Device Related • Procedure Related	Uncertainty
Magnitude	Probability	Patient tolerance of risk & perspective of benefit
Probability	Duration	Alternative Treatments
Duration		Reliability
		Risk mitigation
		Post-market Data

Guidance Document: https://www.fda.gov/media/99769/download

PMA Submissions

- Includes valid scientific evidence to support the reasonable assurance of safety and effectiveness of the device for its intended use
- Submission includes data and information and/or information incorporated by reference

Important Components [21 CFR 814.20]	
Indications for use	Summary of clinical results
Device description	Methods of manufacture
Marketing history	Reference to performance standards
Proposed labeling	Summary of non-clinical results
Principles of operation	Bibliography of published reports

PMA Safety and Effectiveness - Examples of Valid Scientific Evidence

Valid Scientific Evidence	Not Valid Scientific Evidence
Well controlled investigations	Isolated case studies
Partially controlled studies	Random Experience
Studies and objective trials without matched controls	Reports lacking sufficient details to permit scientific evaluation
Well-documented case histories conducted by qualified experts	Unsubstantiated opinions
Reports of significant human experience with a marketed device	

Reference 21 CFR 860.7(c)(2)

PMA Post-approval Controls

Class III devices are subject to PMA controls after approval

- Post-approval studies (PAS) and reports
  - May be required *at the time of approval, as a condition of approval*
- Amendments
- Supplements
- 30-day Notices
- Post-approval periodic reporting (annual reports)

Microsphere PMA Approval Example:

SirTeX SIR-Spheres (P990065, Class III, NAW)

- Resin-based microspheres labeled with Yttrium-90 20-40 µm
- Permanent implant, single use only
- Microspheres lodge preferentially in the microvasculature
- Indicated for: Treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy of FUDR (Floxuridine)

Tips for Successful Submissions

- Use the **pre-submission program** to interact early with the review Division.
  - Help identify performance testing needs based on intended use of device before starting testing
- Provide a clear description of your device
- Be consistent throughout the submission
- "**Tell the story**"
  - Focus on "why" in addition to "what"
  - Provide rationale for adequacy of data provided

Guidance Document: Requests for Feedback and Meetings for Medical Device Submissions: The Q-submission Program:

Conclusion

- FDA regulates manufacturers of the devices and the device itself
- FDA takes a risk-based approach to device regulation
  - Classification of the device, regulatory controls, and type of premarket submission depend on risk
- Multiple types of premarket device regulations
  - PMA directly reviews safety and effectiveness of unproven technology
  - 510(k) reviews for substantial equivalence to a predicate device
- FDA recommends sponsors use the pre-submission process to interact with review divisions during device development

Industry Education Resources

CDRH Learn – Multi-Media Industry Education

- videos, audio recordings, power point presentations, software-based "how to" modules
  http://www.fda.gov/Training/CDRHLearn

Device Advice – Text-Based Education

- comprehensive regulatory information on premarket and postmarket topics
  www.fda.gov/MedicalDevices/DeviceRegulationandGuidance

Division of Industry and Consumer Education (DICE)

- Email: DICE@fda.hhs.gov
- Phone: 1(800) 638-2014 or (301) 796-7100

Thank you!

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

Sealed Source and Device Reviews

October 14, 2020
Tomas Herrera
Team Leader
NMSS/MSST/MSTB

Purpose of The Review

- Ensure that sealed sources and devices will maintain their integrity during normal use and likely accident conditions.

- Allows for the registration of a product and provides a means for having a single safety evaluation of the product performed. (10 CFR 32.210)

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
  - Industrial, Medical, and Consumer Products
  - Maintained by the NRC

Major Areas of a Review

- NRC Guidance – NUREG-1556, Vol. 3, Rev. 2
- Design
- Prototype testing
- Operation/Instructions to Users
- External radiation levels
- Quality assurance/quality control

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

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 maximum activity
- Tests of moving parts
- Test conditions should exceed normal conditions of use and adverse environments
- May refer to substantially similar source/device design and use conditions

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 maximum 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

Medical Products

- 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).

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.
  - Each certificate has a unique number (NR-XXXX-D-YYY-S)
- Standard format
  - NRC and Agreement States
- NUREG-1556, Vol. 3, Rev. 2, provides templates

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

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Protecting People and the Environment

Gamma Stereotactic Radiosurgery Units and Microsphere Brachytherapy

October 14, 2020
Katie Tapp, Ph.D.
Medical Physicist
NMSS/MSST/MSEB

Emerging Medical Technology

- When NRC learns of a new emerging medical technology, we evaluate it to determine if it can be licensed under the 10 CFR Subparts D through H
- If the technology is not specifically addressed in 10 CFR Part 35 Subparts D through H, the staff will develop licensing guidance describing regulations and specific conditions the Commission has evaluated and considers acceptable for the specific technology to be licensed under Subpart K, 10 CFR 35.1000

Gamma Stereotactic Radiosurgery Units

Subpart H, 10 CFR 35.600

- Provides regulations for Teletherapy, Remote Afterloaders, and Gamma Stereotactic Radiosurgery (GSR) Units
- Specific requirements include safety procedures and precautions, full calibrations, periodic spot checks, and training and experience for authorized users.
- Gammaknife model C is licensed under 10 CFR 35.600

GSR Licensing under 10 CFR 35.600

- Recent GSR units have been unable to meet many of the specific requirements for GSR units listed in 10 CFR 35.600, including
  - Calibration and periodic spot checks of the relative helmet factors, helmet microswitches, and trunnions
  - Regulations did not consider fractions, moving sources, frameless options, or dynamic treatments

Elekta Perfexion/Icon

- 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

Perfexion/Icon Licensing Conditions

- Unique Written Directive
  - Patient name, date, treatment site
  - Gamma angle and target coordinate and sector settings for each shot
  - For Icon, requires dose per fraction and number of fractions
- Commitments to verify patient fixation prior to treatment, pausing and checking location in cases of movement, and visually checking patient set up if gamma angle is changed
- Modified physical presence requirement
- Modified periodic spot check and full calibration

conditions

Perfexion/Icon Licensing Conditions (cont.)

- Allow use of manufacturer procedures when there are no published protocols accepted by nationally recognized bodies
- Training and Experience

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

ViewRay Licensing Conditions

- Written Directive
  - patient name, total dose, dose per fraction, number of fractions
  - isocenter and gantry angle positions
  - treatment site
- Procedure will include validation of geometric and dosimetric accuracy of each patient's treatment
- Modified physical presence requirement
- Modified periodic spot check and full calibration conditions
- Allow use of manufacturer procedures when there are no published protocols accepted by nationally recognized bodies.
- Training and experience

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

Gammapod Licensing Conditions

- Written Directive
  - Patient name, total dose, dose per fraction, and number of fractions
  - Treatment site including the planning target volume
  - Inner and outer cup sizes
- Modified physical presence requirement
- Modified periodic spot check and full calibration conditions to account for differences due to the
  - the breast immobilization and localization system
  - Source and collimator movement and dynamic treatments
- Allows use of manufacturer procedures when there are no published protocols accepted by nationally recognized bodies
- Training and experience

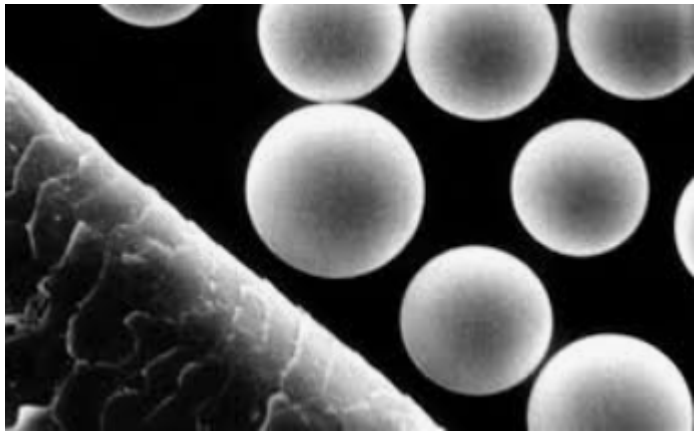
MICROSPHERE AND PARTICLE BRACHYTHERAPY

Subpart H, 10 CFR 35.400

- Provides regulations for manual brachytherapy using sources either:
  - Approved in the sealed source and device registry for manual brachytherapy, or
  - Used in research to deliver therapeutic doses for medical use in accordance with an active Investigational Device Exemption
- Specific requirements include calibration, brachytherapy source accountability, authorized user training and experience, patient surveys, safety instructions and precautions.

Yttrium-90 Microspheres

- Classified by FDA as a brachytherapy device
- 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

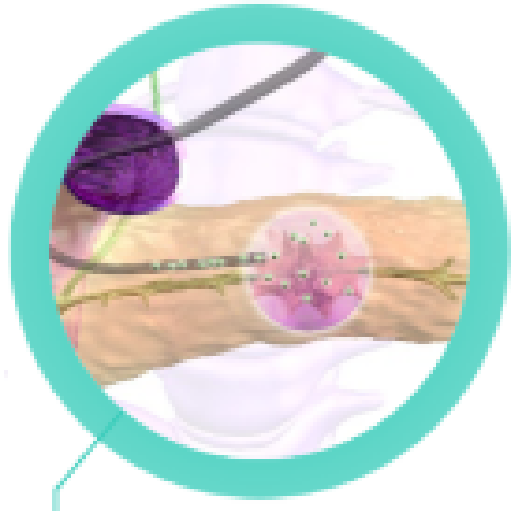


Yttrium-90 Microsphere Licensing Guidance

- Training and Experience
  - Combination of radiopharmaceutical and manual brachytherapy training
  - Training allowed after authorization
- 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

Particle Brachytherapy

- Permanent Implant Brachytherapy using with particles similar to Microtherapy, such as Phosphorous-32 used in Oncosil
- Likely to be licensed under 10 CFR 35.1000 due to
  - the small size,
  - large number of particles, and
  - depending on the applicator, might not need a sealed source and device registry



PROPOSED EMERGING TECHNOLOGY RULEMAKING

Proposed Rulemaking for Emerging Technologies

- The staff is developing a rulemaking plan that provides options for codifying requirements for emerging technologies.
  - Codifying requirements would mean that some technologies would be licensed without the need for 10 CFR 35.1000
- Potential rulemaking options include codifying requirements for GSR units and microspheres, or a broader rulemaking that would codify more approved emerging technologies and create added flexibility in 10 CFR Part 35 to possibly accommodate future emerging technologies.
- The rulemaking plan will go to the Commission in December 2020 for their determination on whether the staff should pursue a rulemaking for emerging technologies.

Industry Experience in Regulatory Process for Radiological Devices

Diana Thompson, MS, CHP, RRPT
Radiation Safety Scientific Advisor, Regulatory Affairs
Sirtex Medical Inc.
15 October 2020

SIRTeX

DISCLAIMER

The information, views and opinions expressed in this presentation and any accompanying materials are those of myself and do not necessarily reflect the views or position of Sirtex Medical, Inc.

SIRTeX

AGENDA

To share experience of the development and approval process from the industry perspective to support timely access for patients to emerging therapies especially when treatment is for unmet medical needs for serious and life-threatening conditions

SIRTeX

DEVICE DESCRIPTION

SIR-Spheres® Yttrium-90 Resin Microspheres

- SIR-Spheres consist of biocompatible (resin) microspheres containing yttrium-90 between 20 and 60 um diameter.
- The microspheres are permanently implanted into a hepatic tumor by injection through a hepatic artery using a catheter or chemotherapy catheter port.
- Yttrium-90 is shielded using acrylic and implanted using Class I accessories that connect to the catheter.
- The delivery system and accessories are considered Class I devices and are not radioactive, they facilitate implantation of the microspheres while providing beta radiation shielding.

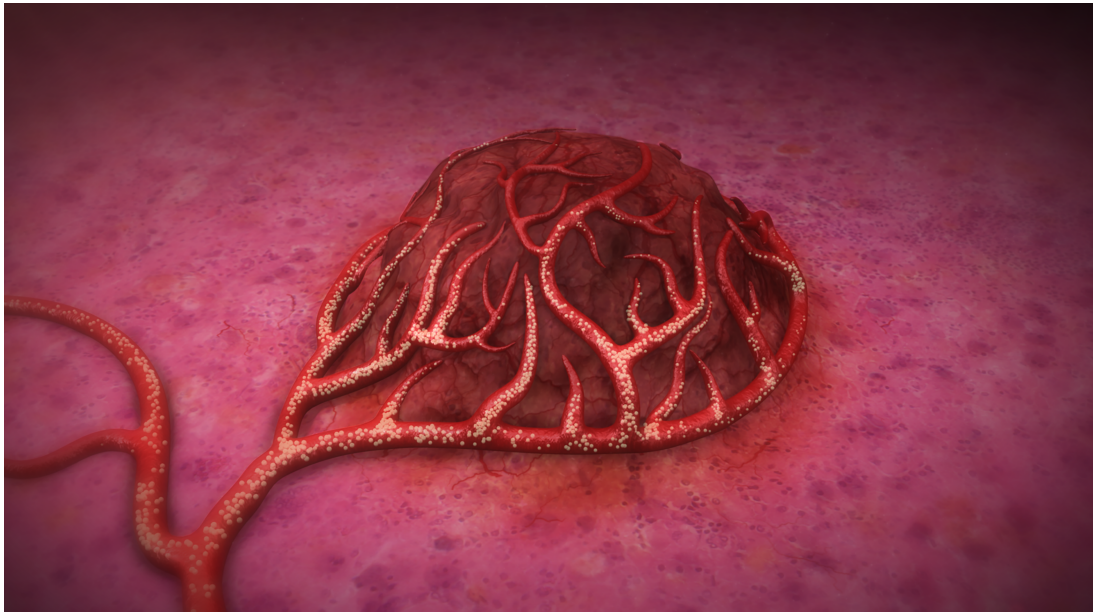
SIRTeX

DEVICE DESCRIPTION

SIR-Spheres® Yttrium-90 Resin Microspheres

SIRTeX

DEVICE DESCRIPTION



SIRTeX

SIR-Spheres

- Initial PMA # 99065 approval was issued March 2002 as an implantable medical device
  - This device is indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (Floxuridine).
  - Medical Device
    - "*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 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****."*

SIRTeX

FDA Approval

- Training Education and Certification program
  - Physician proctored cases for treating physicians
  - Restricted to Trained and licensed Physicians
    - Our device is licensed by the agency for distribution to persons licensed pursuant to 10 CFR 35.1000. Only doctors qualified and licensed under 10 CFR 35 and trained under the Sirtex TEC training program may order and implant SIR-Spheres microspheres.

FDA Approvals

Distribution

- PMA supplement P990065_S004 to manufacture in United States was approved in January 2008 for Sirtex Wilmington
  - Adding facility as FDA manufacturing site
  - Two additional state licenses required for possession and distribution of radioactive material

SIRTeX

NRC interactions

Guidance

- Sealed Source and Device type Safety Assessment informed NRC's guidance development
- Updates to Guidance

October 2002*	**August 2008**	**June 2012**
January 2004	**September 2008**	**February 2016**
September 2007**	**January 2011*****	**November 2019**
December 2007	**October 2011**	**March 2020********

SIRTeX

Massachusetts Sealed Source and Device Registration

MA-1229-D-101-S

- Originally Approved as MA-1056-D-356-S March 2002
- Package Insert updates submitted through SSDR
  - ensure consistency between approvals i.e. PMA supplement P990065_S007 updated to allow for the option to use D5W as non-ionic solution in administration

SIRTeX

Conclusion

Client Access

- Ensure consistency among approvals
  - SSDR
  - Instructions for Use
  - Client Guidance Compliance
    - Physician training requirements

SIRTeX