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Training and Experience Requirements For Alpha and Beta Emitter Oncology Therapies

ACMUI Meeting

June 16, 2015

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Introduction

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Board Certified: Medical Oncology, Hematology, and Internal Medicine

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Summary

- NRC Rulemaking: The Proposed Rule specifically requests comments on whether its regulations "***discourage licensees from using certain therapy options or otherwise adversely impact clinical practice, and if so, how***."
- Certain safe and effective alpha- and beta-emitting oncology therapies are being underutilized because there is not an Authorized User (AU) known to the treating physician and convenient to the patient
- 700 hours of training and experience is disproportionate to the risks presented by these oncology treatments, which are compounded and prepared as a patient-ready dose by licensed radiopharmacies
- A new subcategory of 80 hours training & experience should be created to address such oncology therapies, delivered intravenously, and supplied as a "patient-ready dose"

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Clinical Benefit of Therapeutic Radiopharmaceuticals

- Less intensive treatment schedule
- Far less constitutional and somatic toxicities
- Potential for more durable responses when compared to conventional chemotherapy
- Benefits especially important for elderly cancer patients with mobility and access limitations

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Shortage of Authorized Users for Therapeutic Radiopharmaceuticals

- 80% of fNHL patients are treated in the community setting, managed by Medical Oncologist or Hematologist/Oncologist
- Training requirements have contributed to a shortage of AUs outside of academic institutions and large hospitals
  - Especially in the community, for elderly/infirm, people who cannot travel long distances for multiple cycles of chemotherapy
- Treatments with beta-emitter anti-cancer therapy have declined since the imposition of the 700 hour training requirement in 2002
- One RIT treatment is no longer available due to lack of use

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Clinician Role in Therapeutic Radiopharmaceutical Treatment

Diagnoses and treats patient prior to Therapeutic Radiopharmaceutical	Hematologist/ Medical Oncologist
Offers Therapeutic Radiopharmaceutical as an option to patients	Hematologist/ Medical Oncologist
Routinely administers anti-cancer drug therapy regimen	Hematologist/ Medical Oncologist
Routinely handles most common and serious side effects of Therapeutic Radiopharmaceutical	Hematologist/ Medical Oncologist
Additional training currently required to become an Authorized User to prescribe and administer Therapeutic Radiopharmaceutical	Hematologist/ Medical Oncologist require 700 hours training & experience + 3 proctored cases
Available Authorized Users to treat Therapeutic Radiopharmaceutical patients	Very few Hematologists/ Medical Oncologists

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Dr. Mace – Authorized User

- Gained Authorized User status before the current 700-hour training & experience requirement was put into place
- Completed a radiation safety and handling course that met the 80-hour requirement
  - "After my course experience, I felt fully prepared to administer Zevalin, with all of the attendant radiation safety and handling issues."
- Administering Zevalin safely for 10 years and Xofigo safely for nearly 2 years with no safety incidents
- Patients can be treated in the community oncology setting without traveling to a regional academic medical center
  - "Patients clearly appreciated the fact that it was the same physician seeing them in consultation to discuss Zevalin therapy, subsequently administering the agent, and monitoring them for the requisite 2-3 months thereafter."

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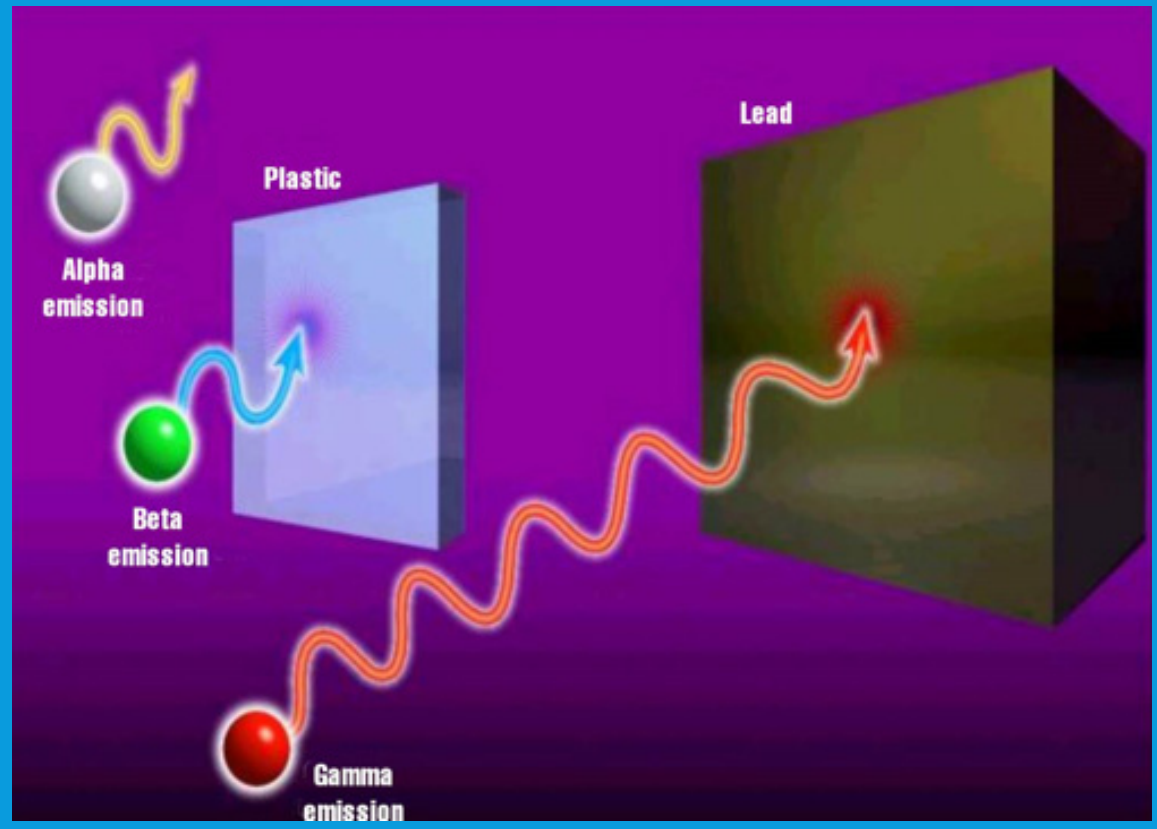
Radiation Safety of Alpha- & Beta-Emitters



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Alpha-Emitters: Xofigo

- Example: Ra233 dichloride (Xofigo®)
- Ra 223 is a by-product material. Although it is primarily an alpha-emitter, beta and gamma particles are also emitted during decay, allowing for measurement of radioactivity with standard instruments such as a dose calibrator and standard gamma detector probes.

SUMMARY OF PROPERTIES OF XOFIGO[1-3]			
Half-life	11.4 days	**Alpha particles**	95.3%
Total decay energy	~28 MeV	**Beta particles**	3.6%
Particle range in tissue	<100 µm	**Gamma or X-rays**	1.1%

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Beta-Emitters: Zevalin

- Example Y-90 (Zevalin®)
- 90Y is a virtually pure β-emitter, with a high β-energy and an effective pathlength of 5.3 mm

Nuclide	Radiopharmaceutical	Half -life	max. ß energy	mean ß energy	Radius of a unit density sphere inside of which 90% of the energy is emitted	Photon yield (E>20 keV)
Y-90	Ibritumomab tiuxetan	2.67 days	2.281 MeV	0.933 MeV	5.3 mm	$<10^{-7}$

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Demonstrated Safety Record

- More than 30 published studies of radiation safety with Y-90 Zevalin
- All conclude risks are minimal to negligible to administering physician and patient
- Of over 10,000 administrations, only 3 reports to the NRC of radiation safety issues
- FDA removed requirement for Indium 111 biodistribution scan based on Zevalin's excellent safety profile
- NRC acknowledges minimal exposure. Regulatory Guide 8.39 on Patient Release Instructions states Y-90 has "minimal exposures to members of the public."
- Despite low risks of Zevalin, there is a disproportionate burden to prescribe

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Impact on Development of New Therapeutic Radiopharmaceuticals

- The training and experience requirements discourage clinicians from recommending Zevalin and other therapeutic radiopharmaceuticals
- There is a lack of exposure to therapeutic radiopharmaceuticals during hematology/medical oncology fellowships due to poor access to these agents
- Regulatory barriers have already contributed to the removal of one therapeutic radiopharmaceuticals product from the market
- More therapeutic radiopharmaceuticals, specifically alpha- and beta-emitters, are in the development and approval stages, but innovation is in danger of being stifled

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Dr. Cultrera : Regulatory Barriers to Administering Therapeutic Radiopharmaceuticals

- Experienced with Therapeutic Radiopharmaceuticals in the academic setting but cannot realistically undertake 700 hours of additional training and experience
- In current community setting, need to find an AU who can provide the treatment, adversely impacting continuity of care
- Physicians discouraged from recommending treatment due to the burden regulations place on patient access

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Path to Become an Authorized User

- Two Pathways:
  1. Certification Pathway- for physician Board Certified in Radiology or Nuclear Medicine.
  2. "Alternate Pathway" – requires an additional 700 hours of Training & Experience
- Limitations of Certification Pathway
  - Most AUs are in large, academic medical centers, presenting a geographical challenge for many cancer patients
  - Still requires 3 proctored cases and attestation from a current AU
  - Not all "potential" AUs are willing and/or able to take the time to become authorized for a specific isotope they do not routinely use in their practice
  - Not all AUs are familiar/experienced with the side effects of oncology treatments, which can require significant patient management
- Limitations of "Alternate Pathway"
  - 700 hours is too much for a practicing physician to dedicate for a limited number of applicable treatments (Same T&E as required for American Board of Radiology certification)
  - Certain physicians only desire limited use of certain oncology therapies – not all radiopharmaceuticals

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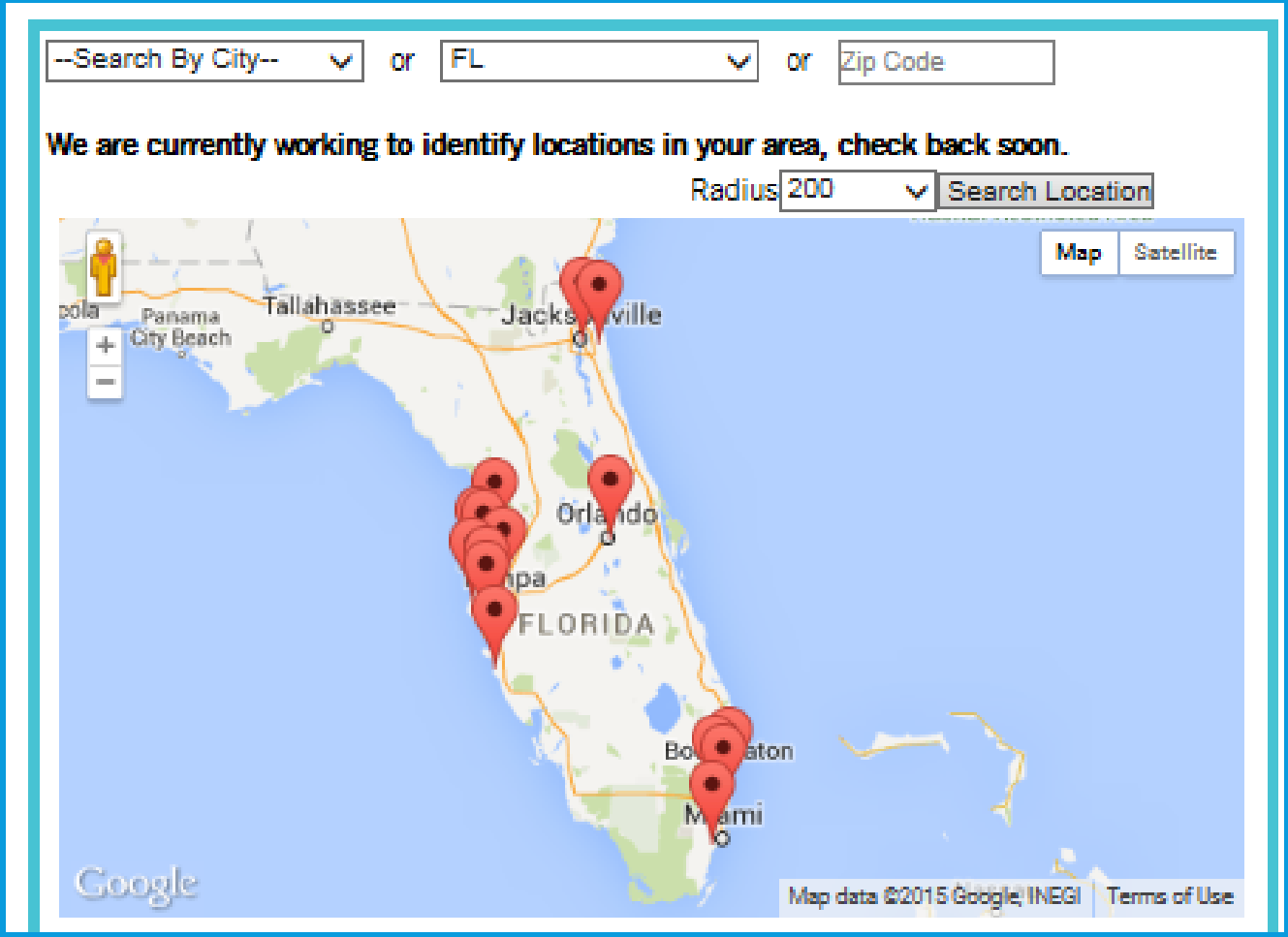
Shortage of Authorized Users Case Study: Zevalin in non-Hodgkin's lymphoma



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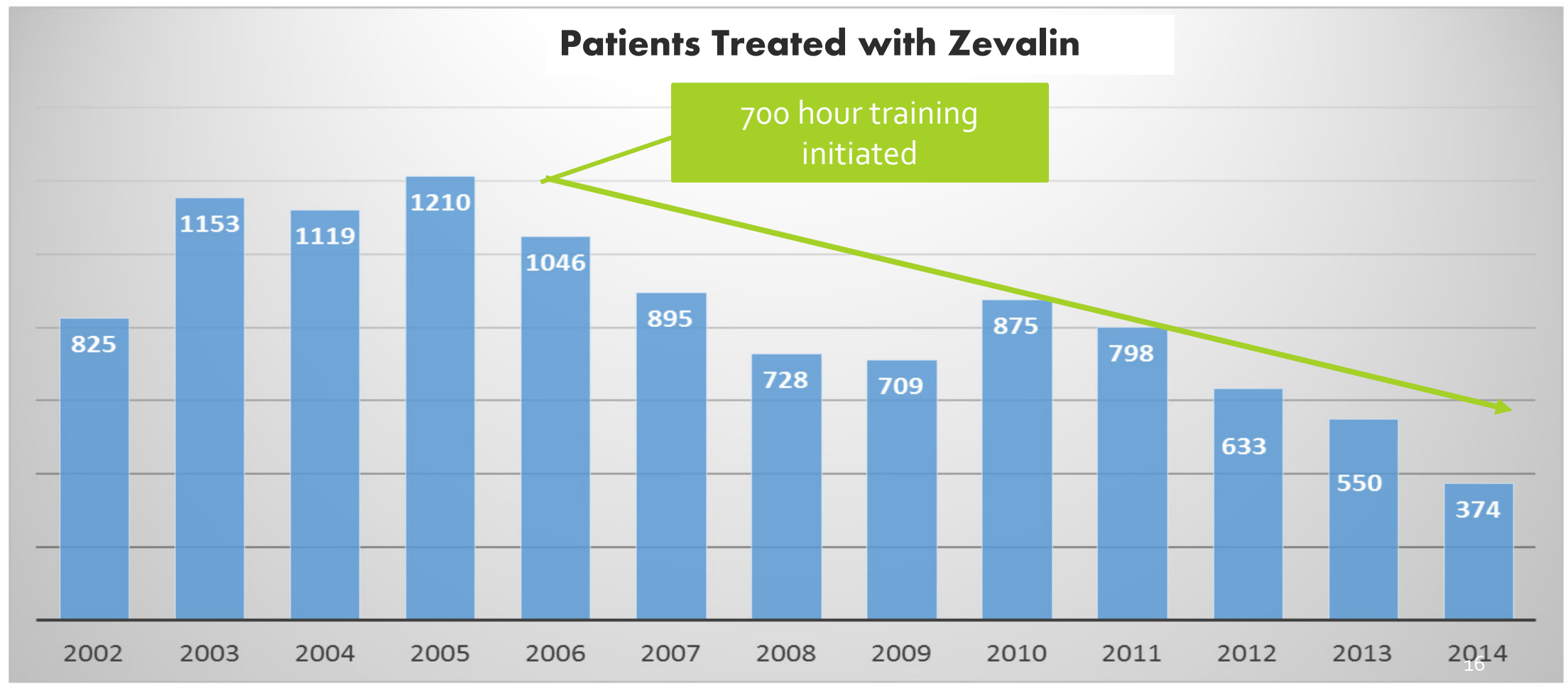
AU Restrictions Limits Patient Access to Zevalin



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Recommendation for Rulemaking

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Rationale for Reduced Training & Experience Requirement

- **Need**: Patient access severely limited and declining outside of academic medical center setting
- **Safety**: Straightforward application procedures present few risks and low exposure levels
- **Low-Risk Alpha- and Beta-Emitters**: 80 hours T&E and relevant work experience is appropriate for hematologists and oncologists seeking to administer low risk beta- and alpha-emitting radiopharmaceuticals
- **Precedent**: 80 hours T&E is the same as was required of clinicians prior to 2005, and the same as that available to clinicians seeking to administer oral I-131

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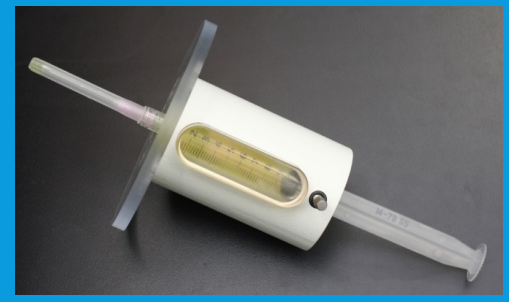
Low-Risk Alpha- and Beta-Emitter Therapies

- Compounded at a licensed radiopharmacy
- Delivered to administration site as a Patient-Ready Dose
- Low level of radiation (Zevalin max dose 32mCi, Xofigo in µCi range)
- Some states require dose verification
- Delivered intravenously
- Only Universal Radiation Precautions required
  - Site still required to have a Radioactive Materials License and Radiation Safety Officer
- Administration side effects are not related to radiation exposure.
- No patient release restrictions, due to minimal exposures*



*See NRC Regulatory Guide 8.39 "Activities and Dose Rates for Authorizing Patient Release"

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Precedent for 80-hours of T&E: Pre-2002 Rulemaking

- Prior to 2005, hematologists and oncologist could become AUs to administer beta-emitting radiopharmaceuticals such as Zevalin with 80 hours of classroom and laboratory training
- Rulemaking created an alternative pathway of 700 hours of training & experience for a broad authorization to elute generators, prepare radioactive drugs, and administer a wide variety of radionuclides requiring written directives.
- *The proposed limited authorization would be solely for the administration of limited class of low-risk alpha- and beta-emitter (no generators or elutions involved)*

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Precedent for 80-hours of T&E: Oral Administration of I-131

- In 2002 rulemaking, NRC retained an alternate pathway of 80 hours of training & experience for a limited authorization for the oral administration of I-131.
- The limited scope license does not authorize preparation of radioactive drugs using generators and reagent kits.
- NRC did not increase the training and experience requirements from 80 hours, noting impeccable safety record of the product, the low risk of therapeutic misadministration, and the burden placed on patients who might have to travel far distances to unfamiliar settings if their primary treating physician were unable to administer the treatment.
- *The proposed limited authorization would be solely for the administration of a class of products with similarly excellent safety records, low risks of misadministration, and high burdens to patient access*

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Precedent for 80-hours of T&E: Sufficient and Appropriate for Y-90 and I-131

Post-administration Considerations

- Yttrium 90 (Y-90 Zevalin) patient release instructions:
  - no need for hospital stay after receiving Zevalin
  - No need to avoid contact with others after treatment since the radiation's effects stay within your body and bodily fluids
  - For the first 3 days, clean up spilled urine and dispose of materials that are contaminated by bodily fluids, so that others will not handle it (flush down toilet or place in plastic bag in household trash)
  - Wash hands thoroughly after using toilet
  - For 1 week after treatment, use condoms for sexual relations

- Iodine 131 (I-131)
  - Needs to be at least 6 feet away from other people
  - Avoid crowds and public places; Avoid traveling on long trips
  - Avoid handling any of your body fluids without wearing latex rubber gloves. If another person is handling your fluids (vomit, stool or urine), they should wear gloves, eye protection and a mask to cover the nose and mouth
  - When cleaning any spills of bodily fluid, use only disposable cleaning cloths that can be flushed down a toilet
  - Do not share a bed or bathroom with another person
  - Sit on the toilet while urinating and flush 3 times with the lid down after use; Always wash your hands after using the bathroom.
  - Do not share a towel, wash cloth or toothbrush with another person
  - Do not share drinking glasses, plates or silverware
  - Wait at least 1 week before washing any of the clothing and bed or bath linens used during the week after your treatment. Keep them separate from the laundry of other people in your home
  - Wash your clothing and other items separately from other laundry in your home

Training Requirements: **700 hours** **80 hours**

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Recommendation:

- Finalize an appropriate training and experience requirement for a limited authorization to administer alpha- and beta-emitters that are delivered intravenously in a patient-ready dose prepared at a licensed specialty pharmacy.
- Training and experience requirement should include 80 hours for classroom and laboratory training plus relevant work experience and case administrations.

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

Sub-Committee Report on Radioactive Seed Localization for Non-Palpable Breast Lesions Guidance June 16, 2015

Dr. Ronald Ennis (Chair)
Dr. Philip Alderson
Mr. Frank Costello
Dr. Pat Zanzonico

Background

- **Radioactive seed localization (RSL) for non-papable breast tumors began in early 2000s**
- **First NRC Guidance issued in 2006**
- **This review stimulated by request from users**

Background

- Use of RSL has increased
- Use has been applied to other parts of body – e.g. the axilla
- Usually I-125 seeds of ~0.2 mCi activity are used - Same seeds as used in brachytherapy
- Dose to surrounding tissue is very low if seeds removed in timely manner but can be significant if permanently left in place

3

Authorized User (AU)

- No change in requirements are recommended
- Work experience for AU should not include removing RSL seeds
- Radiation safety training for surgeon should not include preparing sources for placement

4

Written Directive (WD) Recommendations

- **A WD must be dated and signed by an AU before the administration of I-125 or Pd-103 for seed localization. The WD must contain the patient or human research subject's name and the following information:**
  - **(i) *Before* implantation: implantation site, the radionuclide, and activity per source; and**
  - **(ii) *After* implantation, but before completion of the procedure: the radionuclide, implantation site, number of sources, and total activity implanted and exposure time/time planned before surgery.**

5

Medical Event Recommendations

(a) A licensee shall report any event, except for an event that results from patient intervention, in which the administration of byproduct material or radiation from byproduct material results in

- **(i) An administration of radioactive byproduct material to the wrong individual or human research subject;**
- **(ii) An administration of the wrong radioactive byproduct material;**
- **(iii) An administration of the radioactive byproduct material to the wrong site (part of body);**
- **(iv) Administration of radioactive byproduct material for more than 20% longer than planned;**
- **(v) An administration of the radioactive byproduct material activity of more than 20% of the intended activity;**
- **(vi) A leaking sealed source.**

(b) 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.

6

Safety

- No change due to concern for ruptured seeds
- Independent seed activity verification is important
- NaI or GM meters are both acceptable (Annual calibration of meter is not needed)
- Patient should be advised not to breast feed with the breast into which a seed has been implanted until the seed has been surgically removed

7

Safety cont

- Written polices also needed for:
  - loss of a seed
  - implant of a seed in the wrong location or wrong patient
  - inability to locate an implanted seed during surgery or pathological processing, and
  - if a patient implanted with a radioactive seed does not present for scheduled surgery

8

Other recommended changes to guidance

- To reflect that this is not a therapy
- To remove any consideration of dose as a criterion for a medical event
- To clarify that returning seeds to supplier is acceptable

9

Other recommended changes to guidance cont

- To clarify that training of staff for patients who cannot be discharged is unnecessary
- To reflect possible use outside of breast
- To clarify that since sources have now been approved by FDA for this use, the section "Change in Physical Conditions of Use" should be modified to reflect this

10

Nuclear Regulatory Commission (NRC)
Advisory Committee on the Medical Use of Isotopes (ACMUI)

Sub-Committee on
Radioactive Seed Localization for Non-Palpable Breast Lesions

Sub-Committee Members:
Dr. Ronald Ennis (Chair)
Dr. Philip Alderson
Mr. Frank Costello
Dr. Pat Zanzonico

Draft Report Submitted on May 29, 2015

Introduction

Radioactive seed localization (RSL) is a relatively new medical procedure, the first such procedures being performed in the early 2000s. The first Guidance regarding RSL was issued by the NRC in 2006. This Sub-committee was formed in response to a request for possible modifications to the regulatory Guidance for RSL. The Sub-committee also felt enough time had elapsed since the initial issuance of the Guidance to warrant a review of the Guidance.

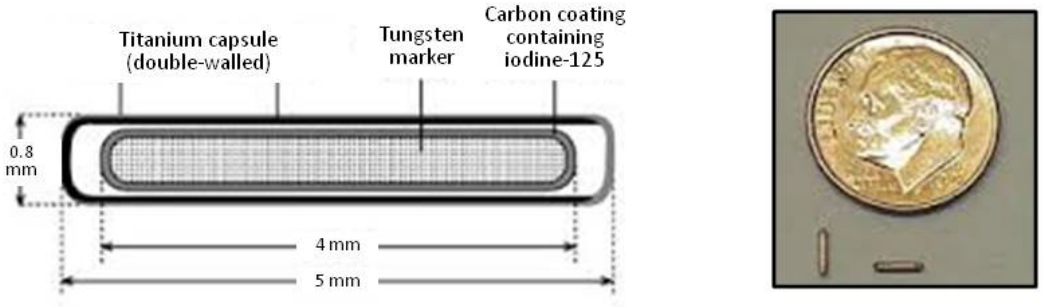
Background

The main current use of RSL is in localization of non-palpable breast lesions prior to surgical excision, although other indications are emerging. In the breast, RSL is an alternative to the traditional localization procedure to guide breast surgery, wherein a non-radioactive radio-opaque percutaneous wire is implanted into the lesion and excised with the suspicious tissue. The RSL technique offers the following main advantages over the wire-implantation technique: scheduling is more flexible, as RSL can be performed up to a week (or longer) before surgery; wires protruding from the skin, which some patients find disconcerting, are avoided; and cosmesis is potentially improved, as the surgeon can place the incision at the optimal location and is not restricted to the sites of the localization needles.

RSL uses the same radioactive seeds as those used for brachytherapy. Iodine-125 or palladium-103 seeds (typically only one but as many as four) containing 200-300 μCi each are implanted percutaneously by a radiologist under image (mammography or ultrasound) guidance into the breast lesion using a needle; iodine-125 seeds are used far more commonly than palladium-103 seeds. The surgical procedure and removal of the seeds are typically performed 2 to 7 days post-implantation, although seed implantation is sometimes performed on the same day as the surgical procedure. The radioactive seed(s) and thus the lesions can be localized with an intraoperative gamma probe identical to that use for sentinel node biopsy and surgically removed. The seed(s) may be removed from the tissue specimen in surgery or, more commonly, the tissue specimen containing the seed(s) are sent to Pathology for removal of the seed(s) and analysis. The seed or seeds are then disposed of in accordance with 10 CFR 35.92 or the equivalent Agreement-State regulations.

Physical and dosimetric properties of iodine-125 seeds

Iodine-125 seeds used for localization of non-palpable breast masses as well as for permanent-implant brachytherapy are comparable in size and shape to a grain of rice and are comprised of a double-walled titanium capsule containing an iodine-125-containing carbon-based material coating a radiographically imageable tungsten marker (See the figure below).

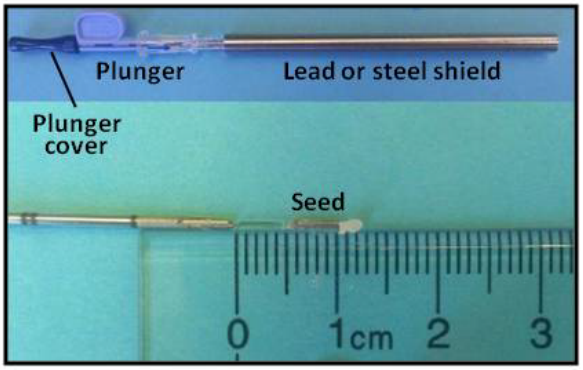


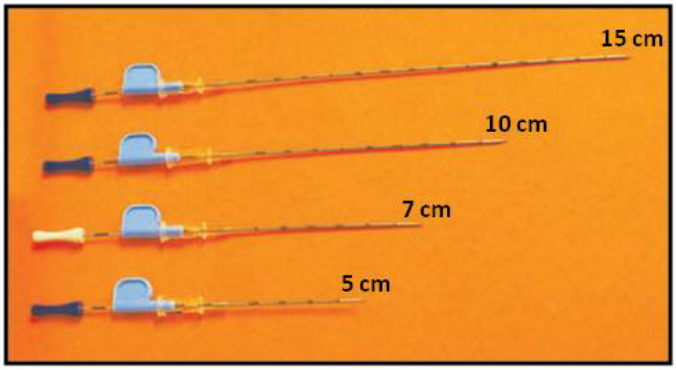
Iodine-125, with a physical half-life of 60.1 days, decays by electron capture accompanied by the emission of low-energy gamma rays and a cascade of characteristic x-rays ranging in energy from ~4 to ~45 keV; its most abundant photon emissions (3 x-rays with a collective abundance of 128%) are in the energy range 27-31 keV. Its overall half-value layer is only 0.02 mm in lead and 1.7 cm in water or soft tissue. Its gamma constant is 0.27 mR/h/mCi at 1 m, yielding an exposure rate from a 300-μCi (0.3-mCi) iodine-125 seed of ~0.081 mR/h at 1 m. Therefore, the absorbed dose at 1 m from such an iodine-125 seed would be only 58 mrad if an implanted seed were not removed (i.e., for complete decay) and only 7 mrad if the seed were removed 7 days post-implantation, assuming the seed was implanted at a depth of 1.7 cm (or 1 half-value layer) in the breast; the actual doses to individuals at 1 m from the patient would be 15 and 1.8 mrad, respectively, assuming the standard occupancy factor value of 0.25 for such individuals. The corresponding absorbed doses at 0.3 m (approximating the position of a child being held by the patient, for example) would be 640 and 78 mrad, respectively; the actual doses to a held child at 0.3 m would be 130 and 16 mrad, respectively, assuming an occupancy factor of 0.2 for such a child. Realistically, therefore, the absorbed doses from a patient implanted with an iodine-125 seed for localization of a breast lesion are extremely low, of the order of those received by passengers over the course of a trans-continental airline flight or less. Accordingly, there is no need for the patient or her family members to follow any radiation safety precautions in the time interval between seed implantation and explantation.

The radiation doses to a patient implanted with a 300-μCi iodine-125 seed may be estimated using the OLINDA/EXM computer code. If an implanted seed were not removed (i.e., for complete decay), the mean absorbed dose to the breasts would be 120 rad and the effective dose 6.1 rem; the absorbed doses to tissues other than the breasts would of the order of 1 rad or less. However, the doses to the tissue immediately adjacent to the seed(s) would be substantially higher than this. If these tissues are not subsequently excised at surgery along with the seed(s), long term consequences such as fibrosis are possible. More realistically, if the seed were removed 7 days post-implantation, the mean absorbed dose to the breasts would be 5 rad and the effective dose 0.23 rem; the absorbed doses to tissues other than the breasts would less than 0.1 rad. Importantly, the foregoing first-order dose estimates are conservative in that they assume a maximal seed activity of 300-μCi (0.3-mCi) and maximal time interval of 7 days from implantation to explantation. The actual doses would be

proportionately lower for lower activities and/or shorter time intervals. (The dose estimates based on the assumption that the implanted seed was not removed and underwent complete decay in situ represent the doses for a rare, worst-case scenario.)

Iodine-125 seeds for localization of non-palpable breast masses are packaged in a sterile pre-loaded needle assembly (See the figure below) and are thus ready-to-use. The available needle lengths are 5, 7, 10, and 15 cm and the seeds themselves are shielded by a lead or steel sleeve. Once the shield





is removed and the tip of the needle percutaneously positioned in the lesion, as guided by mammographic or ultrasound imaging, the plunger cover is removed and the plunger pushed to implant the seed within the lesion. As marketed, the seed and needle assembly have a shelf life of 90 days; this is dictated not by the physical decay of the iodine-125 but rather by the sterility of the assembly. The supplier of the iodine-125 seeds can, and should, provide the Sealed Source and Device Registry (SSDR) certificate.

Changes to Guidance Considered by the Sub-committee and its Recommendations

Title of Guidance

No change in the title of the Guidance is recommended. Although the sources are not being used for therapy, they are commonly called "brachytherapy sources." Therefore, the use of that term in the title is only meant for clarity and not to imply this is a brachytherapy procedure. In addition, although Pd-103 has not been used to date for this procedure, the Sub-committee sees no reason to exclude this isotope and therefore recommends retaining the reference to it in the title.

Purpose

The wording in the beginning of this section should be modified to address the current use of RSL, which includes possible non-breast (e.g., axilla) applications, as follows:

"The purpose of radioactive seed localization (RSL) of non-palpable lesions is to localize suspicious tissues for excision with the use of radioactive seeds. Most commonly, this is being used in the breast where RSL differs from current localization procedures…"

Footnote #1 should also be deleted.

Waste Disposal
The Guidance currently states: "The seed or seeds are then disposed of in accordance with 10 CFR 35.92 or the equivalent Agreement State regulations."

The Sub-committee agrees that seeds can be returned to the supplier following proper procedures and do not have to be retained at the facility that used them. Therefore, this sentence should be modified to state the following:

"The seed or seeds can be returned to the supplier following proper procedures or disposed of in accordance with 10 CFR 35.92 or the equivalent Agreement State regulations."

General
Radionuclides, Form, Possession Limits

Since RSL is not a treatment, the following text in the Guidance should be changed:

"Authorization 8: 1.5 millicuries maximum per procedure and 15 millicuries total,"

Authorized User
Seed placement must be performed by the Authorized User (AU) as defined in the existing Guidance. The Sub-committee considered changes to this requirement, but feels that the proper handling of the radioactive source used in this procedure require this level of expertise in radiation protection.

For clarity, in the AU section of the Guidance that begins, "Pathology personnel…", the following statement should be added "This training should be provided by the AU described above or the Radiation Safety Officer, as applicable." This would provide consistency between pathology and surgical personnel with respect to the requisite radiation safety training.

The Sub-committee agrees that the work experience required for the AU should not include "removing RSL sources safely," since this is performed by the breast surgeon. The Sub-committee also agrees that radiation safety training for surgeons working under the supervision of the AU should not include preparing and implanting brachytherapy sources, since these procedures are not performed by the surgeon.

Written Directive
The Sub-committee also considered a request to remove the requirement for a Written Directive (WD) for RSL. Pursuant to §35.40, a WD is required when a therapeutic dose of byproduct material is being delivered. Although the goal of the procedure is guidance of surgery rather than therapy, from the perspective of patient safety these sources may deliver doses considered to be in the therapeutic dose range close to the source or when left in for long periods of time. Therefore, the Sub-committee feels the WD is an integral component of the proper regulatory requirements to assure safe RSL. The Sub-committee does agree, however, with the suggestion to modify the specific elements of the WD and to eliminate dose as one of the required elements of the pre-procedure WD. In addition, the language of the requirement regarding the location into which the seed will be implanted should be modified from "treatment site" to "implant site," consistent with the non-therapeutic intent of RSL. Thus, prior to the procedure, the WD must specify the implant

site (i.e., location within patient's body), the radionuclide to be used and the activity of the source. The post-procedure part of the WD must specify the implant site, radionuclide, number of sources implanted, total activity implanted and total time planned until surgery. If a violation of the WD occurs, a report must be completed as required in §35.3045.

The Sub-committee, therefore, recommends the following language in the revised Guidance:

A written directive must be dated and signed by an authorized user before the administration of I-125 or Pd-103 for seed localization. The written directive must contain the patient or human research subject's name and the following information –
(i) Before implantation: implantation site, the radionuclide, and activity per source; and
(ii) After implantation, but before completion of the procedure: the radionuclide, implantation site, number of sources, and total activity implanted and exposure time/time planned before surgery.

Medical Event Reporting
The Sub-committee also recommends the following language in the revised Guidance:
Medical Event Reporting -
(a) A licensee shall report any event, except for an event that results from patient intervention, in which the administration of byproduct material or radiation from byproduct material results in-
(i) An administration of radioactive byproduct material to the wrong individual or human research subject;
(ii) An administration of the wrong radioactive byproduct material;
(ii) An administration of the radioactive byproduct material to the wrong site (part of body)
(iii) Administration of radioactive byproduct material for more than 20% longer than planned
(iv) An administration of the radioactive byproduct material activity of more than 20% of the intended activity
(v) A leaking sealed source.
(b) 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.

Safety Precautions
The Sub-committee feels the precautions regarding source rupture or cutting are warranted, as such incidents have been reported. In addition to written emergency procedures for such an occurrence, the Sub-Committee recommends written emergency procedures be required for other abnormal situations including: loss of a seed, implant of a seed in the wrong location or wrong patient, inability to locate an implanted seed during surgery or pathological processing, and if a patient implanted with a radioactive seed does not present for scheduled surgery. Finally, the Sub-committee recommends patients be advised not to breast feed from a breast into which a seed(s) has(ve) been implanted and not yet removed. Breast feeding is, of course, permissible once the seed(s) has(ve) been removed.

Verification of Source Activity
Independent verification (i.e., assay) of source activity by the recipient is a crucial element of quality control and should remain in place.

Training
The Sub-committee agrees that training on topics described in §35.410 should not be required. These apply to brachytherapy procedures after which the patient cannot be released from the medical facility; this does not apply to RSL.

Survey Instrumentation and Radiation Survey Requirements
Seed removal is required to be verified on the basis of a radiation survey using a sodium iodide (NaI) or Geiger-Muller (GM) meter. While imaging, such as a specimen radiograph or ultrasound, can visualize a seed as well, confusion could arise if the patient has also had the placement of items such as surgical clips prior to this procedure (e.g., at the time of biopsy). Performance of a radiation survey using a NaI or GM meter avoids any such potential confusion and should continue to be required. The Sub-committee does recommend, however, that the preference for NaI meter over a GM meter be removed from the Guidance, since both are effective for this task given that the I-125 activities used for RSL are easily detected by both types of meters. The Sub-Committee also agrees that annual calibration of the survey meter is not required for the purpose of verifying seed removal, since the meter is used in this context simply for source detection and not, for example, for a exposure-rate measurement.

Change in Physical Conditions of Use
This section should be modified as follows, given that the radioactive seeds are currently approved by FDA for localization procedures:

If the physical conditions of use exceed those reported in the Sealed Source and Device (SS&D) certificate, the limited specific medical use licensee should request an amendment for the new conditions, and a broad scope licensee should perform its own engineering and radiation safety evaluation addressing those differences.

Procedures
The Sub-committee agrees that the procedures described in §35.410 are not necessary, since patients are always released from the medical facility following RSL. These procedures should be removed from the Guidance.

The Sub-committee also feels that §35.41 should be changed to §35.41 (a), (b) (1), (2), (c), excluding §35.41 (b) (3) and (b) (4), which require dose calculations.

In addition, §35.432 should be changed to include only 35.432 (a) and (c) because (b) allows the licensee to rely on source strength measurements provided by the manufacturer. The Sub-committee believes, as stated elsewhere in the guidance , that the licensee must make their own measurement to verify source strength.

Therefore, the language in the guidance should be modified to state the following:

Because the iodine and palladium seeds are temporarily implanted, the applicant may simplify its submission by confirming that it will:

Meet the requirements for temporary implants and develop, implement, and maintain the appropriate procedures in the following regulations: 10 CFR 35.40(a), (c), (d), and as modified above in the Written Directions Section, 35.41(a), (b)(1), (b)(2) and (c), 35.67, 35.75, 35.310, 35.404, 35.406, 35.432(a) and (c), or the equivalent Agreement State regulations.

Respectfully submitted, May 29, 2015,
***Sub-Committee on* Radioactive Seed Localization for Non-Palpable Breast Lesions,**
Advisory Committee on the Medical Use of Isotopes (ACMUI),
Nuclear Regulatory Commission (NRC)