Nuclear Regulatory Commission Public Meeting:
Training and experience requirements for beta emitter products

February 12, 2015

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Redefining Cancer Care

Executive Summary

Unintended Barrier For Cancer Patient Access to Y-90 Zevalin

- Zevalin® (Y-90 ibritumomab) is one of the Most Safe and Effective Treatments for follicular Non-Hodgkins Lymphoma (fNHL)
- Zevalin has been FDA-approved since 2002 and safely administered to over 10,000 patients
- Hematologists/Oncologists typically administer all fNHL treatment options
- There is a shortage of Authorized Users of Zevalin
- Rulemaking offers an opportunity to permit a more proportional training requirement for this low-risk beta-emitter
- This will relieve an unintended burden and increase patient access to an important therapy option

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ZEVALIN in follicular NHL

- ZEVALIN is a radiotherapeutic antibody FDA-approved to treat Follicular Lymphoma (fNHL) and other B-cell NHLs
- NHL[1]: ~70,000 new cases & ~19,000 NHL deaths projected in 2014. 85% are B-cell NHLs.
- fNHL: Not considered curable, multiple relapses, highly radiosensitive
  - Goal of Treatment = Progression-free survival
  - Available treatments: Chemotherapy, Immunotherapy, External Radiation Therapy, Radioimmunotherapy (RIT), transplantation
- **ZEVALIN Integrates Two Effective Therapeutic Approaches**

Especially important for elderly, infirm, those who prefer a chemo-free option at relapse.

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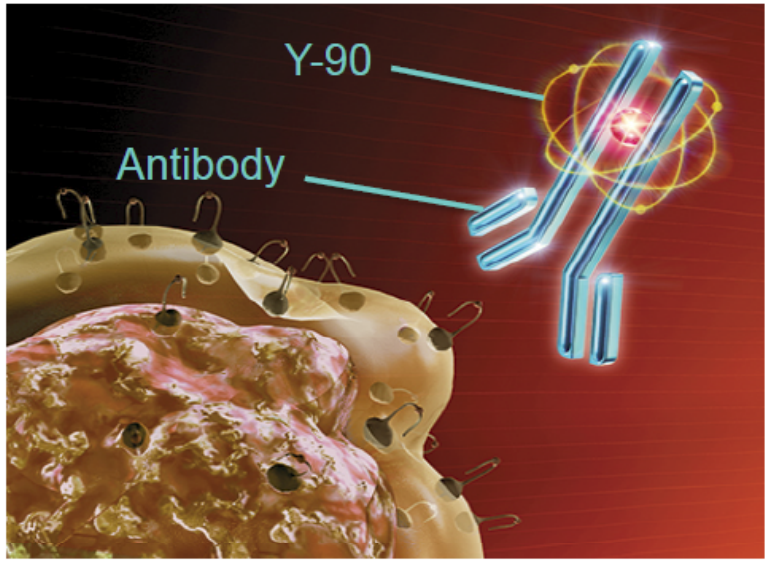
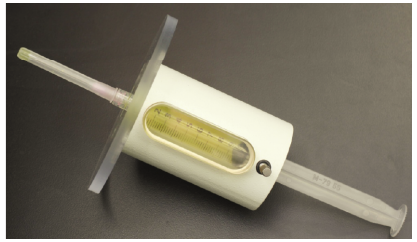
1. American Cancer Society (ACS). Cancer Facts & Figures 2014. http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014/index Accessed April 7, 2014.

Radioactive Properties of Zevalin



- Radioactive component is Ytrium-90 (Y90)
  - Pure Beta emitter, short half-life
  - Delivered pre-mixed in a syringe;
  - No additional protection needed beyond acrylic syringe shield
  - FDA-label states only standard radiation precautions are required to administer
  - No isolation during or post-treatment
- Radiolabeling, Radiochemical Purity Testing and Radiation Dosimetry (per FDA-approved label) performed at Licensed Radiopharmacy contracted by Spectrum
  - Patient-specific dose prepared per patient body weight and scheduled administration date/time
  - Maximum dose permissible is 32mCi (1184MbQ)
- In 2011, the requirement for an In-111 scan was removed by FDA



ZEVALIN

An Important Option for Patients and Physicians

"ZEVALIN is in my opinion the most effective single drug available with an acceptable hematological toxicity profile for the treatment of patients with low-grade malignant follicular non-Hodgkin's lymphoma."

Anton Hagenbeek, M.D., Ph.D., Professor of Hematology, Academic Medical Center, Amsterdam. Journal of Clinical Oncology, April 2009

ZEVALIN
An Important Option for Patients and Physicians

For Patients:

- Single Dose Therapy completed within 9 days
- Delivered by 10 minute IV infusion
- Outpatient
- No isolation post Treatment
- A chemo-free option for relapsed patients

For Physicians:

- Excellent efficacy data, including head-to-head vs. antibody alone
- **Category 1** in National Comprehensive Cancer Network (NCCN) treatment guideline and compendia

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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
- Despite low risks of Zevalin, there is a disproportionate burden to prescribe

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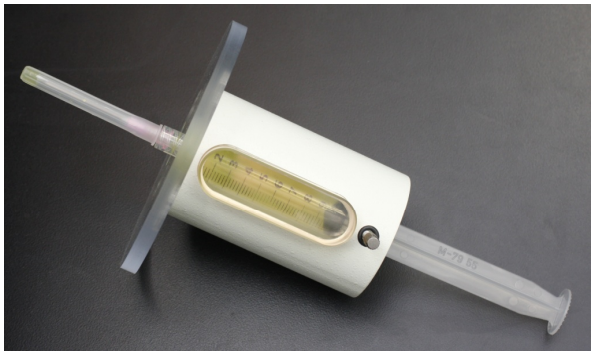
Limited Physician Preparation and Handling

ZEVALIN is Delivered to the Authorized User (A.U.) as a Patient-Ready Dose requiring only an acrylic shield and standard radiation precautions



- Administration side effects, if any, are not related to radiation exposure.

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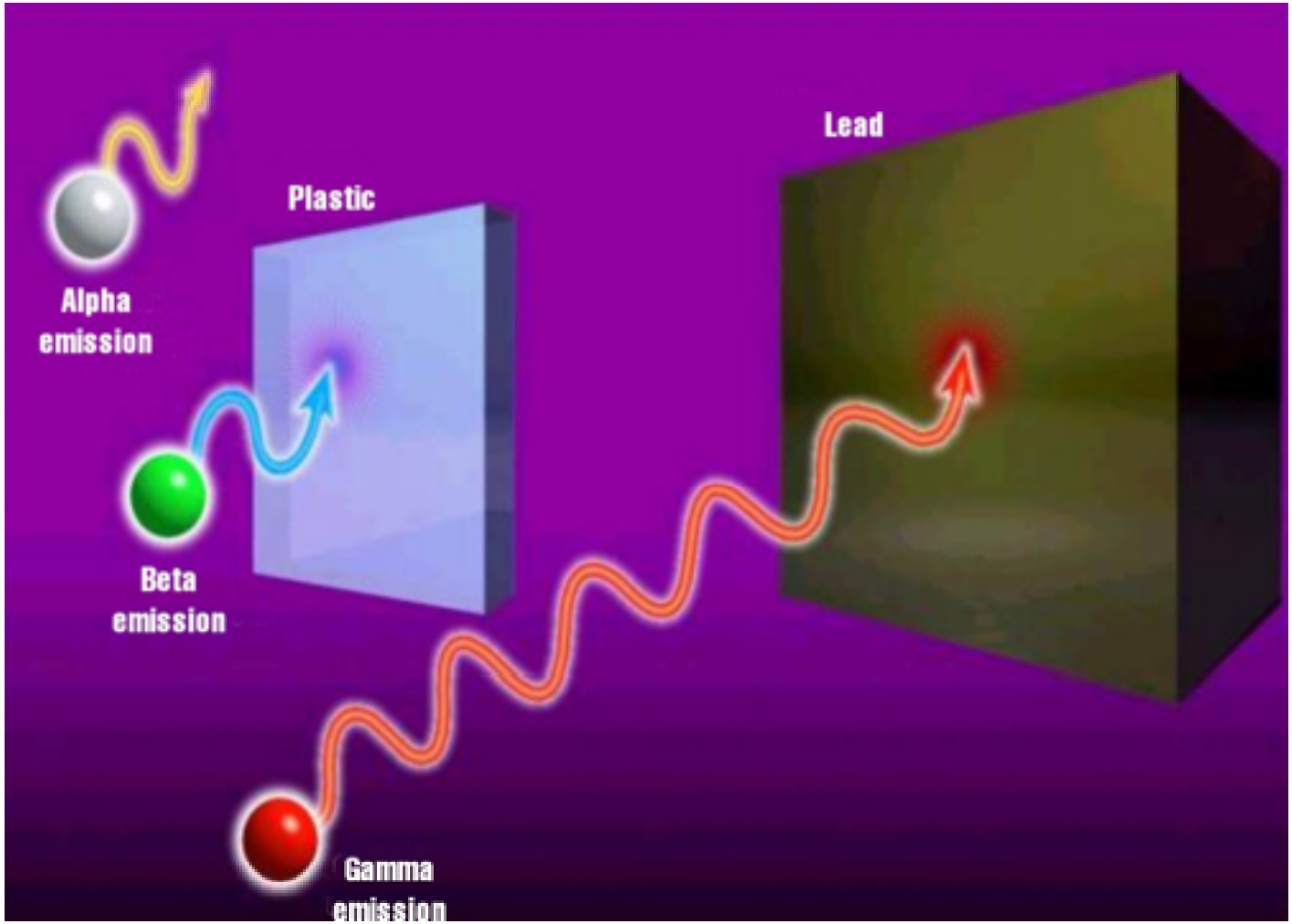
Safety Considerations of Y-90, a pure Beta-emitter



Differentiating Y-90 and I-131

	^{90}Y	^{131}I
Decay Type	β	β, γ
Physical Half-life	2.7 days (64 hours)	8.0 days (193 hours)
Particle Energy (MeV)	2.293	0.606
Primary Gamma Energy (MeV)	None	0.364
Mean β-Energy (keV)	939	192
Mean Range in Tissue [£]	2.76	0.40
Non-Tumor Uptake	Bone	Thyroid
Particle wavelength (mm)	5	0.8
Shielding required	Plastic/glass	Lead

[Ω] See Meredith and Knox: *Curr Pharm Biotechnol*, 2:327-339, 2001
[£] Distance in which 60% of decay energy is deposited from principal β-emissions
[#] See Wiseman et al.: *J Nucl Med*, 44:465-474, 2003
See Wiseman et al.: *Eur J Nucl Med*, 27:766-777, 2000; *Crit Rev Onc Hem*, 39:181-194, 201
Adapted from Hernandez and Knox: *Int J Radiation Oncology Biol Phys*, 59(5):1274-1287, 2004

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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(see table below)
  - 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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NRC acknowledges minimal exposure

- Regulatory Guide 8.39

Table 1. Activities and Dose Rates for Authorizing Patient Release†

Radionuclide	COLUMN 1 Activity at or Below Which Patients May Be Released		COLUMN 2 Dose Rate at 1 Meter, at or Below Which Patients May Be Released*	
	(GBq)	(mCi)	(mSv/hr)	(mrem/hr)
I-131	1.2	33	0.07	7
In-111	2.4	64	0.2	20
Y-90	**	**	**	**
Yb-169	0.37	10	0.02	2

† The activity values were computed based on 5 millisieverts (0.5 rem) total effective dose equivalent.

* If the release is based on the dose rate at 1 meter in Column 2, the licensee must maintain a record as required by 10 CFR 35.75(c) because the measurement includes shielding by tissue. See Regulatory Position 3.1, "Records of Release," for information on records.

** Activity and dose rate limits are not applicable in this case because of the minimal exposures to members of the public resulting from activities normally administered for diagnostic or therapeutic purposes.

U.S. Nuclear Regulatory Commission

REGULATORY GUIDE

Office of Nuclear Regulatory Research

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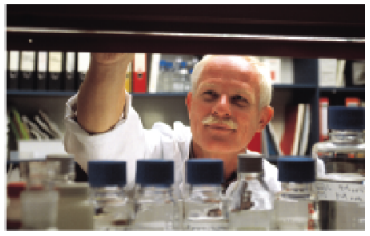
Patient Access to Y-90 Zevalin



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Shortage of ZEVALIN Authorized Users

- 80% of fNHL patients are treated in the Community setting, managed by Medical Oncologist or Hematologist/Oncologist
- Primary oncologist physician must refer a patient to an Authorized User to receive ZEVALIN
- Only an Authorized User can Prescribe, Administer, and be Reimbursed for ZEVALIN
- Requirements to become an AU are set by NRC:
  - Must be Board Certified in Nuclear Medicine or Radiation Oncology
  - Extensive training requirements for other specialties (Alternate pathway)
  - All require 3 proctored cases & attestation by current AU

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Shortage of Zevalin Authorized Users

- These 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
- Many hematologists and oncologists do not present Zevalin as an option for these reasons
- Zevalin treatments have declined since the imposition of the 700 hour training requirement
- **>5%** of 2nd line fNHL patients treated in centers with radiation therapy services receive Zevalin **vs. ~2%** in centers without radiation services
- One RIT treatment is no longer available due to lack of use

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Regulatory Hurdles to the Broader Use of Zevalin

- 10 CFR 35.390 – Training for use of unsealed byproduct material for which a written directive is required
  - Alternate pathway requires 700 hours of T&E, including minimum 200 hours classroom/ laboratory training.
- 10 CFR 35.396 – Training for the parenteral administration of unsealed byproduct material requiring a written directive
  - Requires 80 hours of classroom/laboratory training for parenteral administration if AU is certified by recognized medical specialty board (certification pathway)

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Physician Feedback on NRC Requirements:

- Uncertainty about NRC Authorized User requirements
- Questions on existing NRC training & experience requirements relative to specific risk associated with this product.
- Hematologists and oncologists want to treat patients with ZEVALIN but are unable to meet 700 hour training requirement.
- Even Radiation Oncologists / Nuclear Medicine Physicians have difficulty obtaining 3 proctored cases and attestation from an Authorized User.

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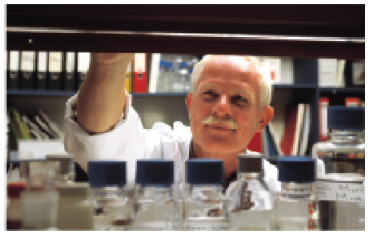
Proposed Rulemaking Recommendations



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NRC Rulemaking Process

- NRC specifically requests comments on whether its regulations "***discourage licensees from using certain therapy options or otherwise adversely impact clinical practice, and if so, how.***"
- In this rulemaking, NRC should address the shortage of authorized users available to administer Zevalin by modifying the framework to permit hematologists and oncologists, with appropriate training and work experience, to administer Zevalin to a patient population that is currently unable to access the treatment.
- Spectrum and other stakeholders submitted detailed comments documenting authorized user shortage and requesting modification of training and experience requirement.

Proposed Rule Pathway

- § 35.396 - *Training for the parenteral administration of unsealed byproduct material requiring a written directive*.
- Existing Rule allows for "alternate pathways" to Authorized User status under §§ 35.390, 35.490, and 35.690, each of which require 700 hours of training and experience.
- Proposed Rule creates an "alternate pathway" to Authorized User status for those seeking to administer beta- or alpha-emitting radiopharmaceuticals, consisting of:
  - **80** hours of **classroom and laboratory training** applicable to the parenteral administrations referenced in § 35.396(d)(1) and
  - Relevant **work experience** described in § 35.396(d)(2)

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80 Hours T&E is Sufficient

- **Classroom and Laboratory Training** must include:
  - Radiation physics and instrumentation; Radiation protection; Mathematics pertaining to the use and measurement of radioactivity; Chemistry of byproduct material for medical use; and Radiation biology;
- **Work Experience** must be supervised by AU and include:
  - Ordering, receiving, and unpacking radioactive materials safely, and performing the related radiation surveys;
  - Performing QC procedures;
  - Calculating, measuring, and safely preparing dosages;
  - Using administrative controls to prevent a medical event involving the use of unsealed byproduct material; and
  - Using procedures to safely contain any spilled byproduct material
  - Administering dosages including 3 proctored cases of any alpha or beta emitter.

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Recommendation

- The “alternate pathway” of 80 hours T&E and relevant work experience is appropriate for hematologists and oncologists seeking to administer low risk beta- and alpha-emitting radiopharmaceuticals
- The “alternate pathway” of 80 hours T&E is the same available to clinicians seeking to administer I-131
- NRC should create a new T&E requirement providing this “alternate pathway” for beta- and alpha-emitters with a high safety profile and low-risk process of administration in the final rule.

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