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Division of Materials Safety, Security, State
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Office of Nuclear Material Safety
and Safeguards
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001
(Andrea.Kock@nrc.gov)

**Re: Lutetium-177 Licensing Determination (STC-18-042)**

Dear Ms. Kock,

On behalf of ITM Medical Isotopes, Inc. ("ITM"), I herewith request the Nuclear Regulatory Commission ("NRC" or "Commission") to take certain actions with respect to the medical use and disposal of the radionuclide, Lutetium-177 ("$^{177}$Lu"). This radionuclide, when combined with a targeting vector, holds the potential to treat a number of different types of cancer. The actions requested herein are intended to help address regulatory confusion that is emerging within the healthcare community about the use, handling and disposal of $^{177}$Lu. That confusion stems, in part, from the NRC's June 21, 2018, licensing determination for $^{177}$Lu.[1]

Manufacturers of $^{177}$Lu currently use two distinct processes for the production of the radionuclide. One method involves the direct neutron irradiation of $^{176}$Lu targets. This process yields carrier-added Lutetium-177 (hereafter "c.a.$^{177}$Lu") and the impurity, Lutetium-177m (hereafter "$^{177m}$Lu"). A second manufacturing process involves neutron irradiation of Ytterbium-176, which yields Ytterbium-177. It decays to non-carrier-added Lutetium-177 (hereafter "n.c.a.$^{177}$Lu") without producing any contaminants (including $^{177m}$Lu). While these processes yield two different forms of $^{177}$Lu (c.a.$^{177}$Lu and n.c.a.$^{177}$Lu) with different impurity profiles, the Commission's regulations and determinations do not reflect these distinctions and that is causing confusion and unnecessary burdens within the healthcare community.

[1] *See* Memorandum to All Agreement States, Vermont, Wyoming, Licensing of Lutetium-177 (STC-18-042), June 21, 2018. https://scp.nrc.gov/asletters/tech/sp18042.pdf

To address these problems, ITM requests the NRC to revise and reissue its licensing determination for $^{177}$Lu and, if necessary, to revise its regulations so as to explicitly recognize c.a. $^{177}$Lu and n.c.a. $^{177}$Lu as separate and distinct forms of $^{177}$Lu. The NRC is fully authorized to take such actions under the Atomic Energy Act and implementing regulations, including 10 C.F.R. Part 35 (Medical Use of Byproduct Material). Beyond addressing the burdens and regulatory uncertainties surrounding storage and disposal of $^{177}$Lu, such actions would enhance efforts within the nuclear medicine community to develop a new class of highly effective and targeted oncology drug products. The bases for the actions requested in this submission follow below in detail.[2]

## I. Factual Background

### A. The Importance of $^{177}$Lu to Targeted Radionuclide Therapy

During the past two decades, radionuclide therapy has emerged as one of the most promising radiopharmaceutical treatments for a variety of different types of cancer. In targeted radionuclide therapy, a tumor-targeting molecule is conjugated with a radionuclide to create a tumor-specific radiopharmaceutical. When injected into a patient's bloodstream, the radiopharmaceutical kills tumor cells by selectively targeting receptors that are over-expressed on the tumor cells. Typically, targeted radionuclide therapy is based on a combination of targeted imaging techniques (such as PET/CT) for patient selection followed by intravenous administration of a radiopharmaceuticals that is highly selective in its ability to destroy tumor cells while limiting radiation exposure to healthy tissue. Many in the nuclear medicine community believe that radionuclide therapy presents a potentially significant advance in the treatment of certain types of cancer.

As interest in the use of targeted radionuclide therapy to treat cancer and other diseases has surged, so too have efforts to identify and evaluate the most effective radioisotopes to combine with a tumor-targeting molecule. Indeed, to meet the requirements for ongoing and future expansion of targeted radionuclide therapy, it is critically important to establish a reliable and steady supply of therapeutic radionuclides that are suitable for patients. This has historically been a challenge for the industry, and has been compounded by the need to identify therapeutic radionuclides that also have large scale production capability. While various isotopes, including Yttrium-90 ($^{90}$Y), Iodine-131 ($^{131}$I), ($^{32}$P) Phosphorous-32, and ($^{90}$Sr) Strontium-90, have been evaluated against these criteria, $^{177}$Lu is quickly emerging as the radioisotope of choice for targeted radionuclide therapy both because of its availability and its ideal parameters for the treatment of patients.

[2] Nothing herein should be construed as a request to delay or preclude the review and approval by the U.S. Food and Drug Administration ("FDA") of products containing either form of $^{177}$Lu.

Specifically, $^{177}$Lu has a half-life of 6.64 days. It is characterized by very high activity levels and can be produced in a large number of research reactors available worldwide. $^{177}$Lu is a medium-energy $\beta^-$ -emitter with a maximum energy of 0.5 MeV and a maximal tissue penetration of 2 mm. It emits low-energy γ-rays at 208 keV and 113 keV with 10% and 6% abundance, respectively. These characteristics make $^{177}$Lu, when combined with a targeting vector, a potentially very effective treatment for a number of different types of cancer. To date, the FDA has approved one drug product containing $^{177}$Lu, Lutathera®, for the treatment of certain neuroendocrine tumors in adults.[3]

At the same time, the radionuclide is currently being investigated by other parties and for other indications. ITM is currently conducting pivotal Phase III studies of Solucin® (Lutetium-177 radiolabeled somatostatin analogue) to evaluate its safety and efficacy for the treatment of certain cancers.[4] Endocyte is also running a pivotal Phase-III clinical trial with a Lutetium-177-based PSMA inhibitor in patients with metastatic castrate-resistant prostate cancer.[5] Further, there are several ongoing clinical programs in Phase-I/II trials, which investigate the safety and efficacy of Lutetium-177 radiolabeled compounds in patients with serious oncological diseases.

B. There are Two Distinct Forms of $^{177}$Lu: c.a. $^{177}$Lu and n.c.a $^{177}$Lu

There are currently two different methods to manufacture $^{177}$Lu. The first generation method for manufacturing $^{177}$Lu involves irradiation of enriched $^{176}$Lu with neutrons. Through this process, nuclei in the target material are converted into $^{177}$Lu either directly or indirectly. Only a quarter of the atoms of the target material, however, are actually converted into $^{177}$Lu and the target material is not separated from $^{177}$Lu. As a result, this process produces c.a. $^{177}$Lu, which is characterized as containing both "hot" (radioactive) $^{177}$Lu and "cold" (non-radioactive) $^{177}$Lu from the target material. Due to the decay of radioactive $^{177}$Lu, the specific activity of c.a. $^{177}$Lu is lower and quickly diminishes.

In light of the known shortcomings of c.a. $^{177}$Lu and potentially critical problems resulting from its low specific activity, a second generation process for the production of n.c.a. $^{177}$Lu has been developed. This manufacturing process involves neutron irradiation and pharmaceutical quality separation of $^{177}$Lu from enriched Ytterbium-176 ($^{176}$Yb). Significantly, in contrast to c.a. $^{177}$Lu, n.c.a. $^{177}$Lu does not contain other carrier isotopes. As a result, the specific activity for n.c.a.

[3] *See* FDA Approves New Treatment for Certain Digestive Tract Cancers (January 26, 2018), https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-certain-digestive-tract-cancers

[4] *See* Efficacy and Safety of $^{177}$Lu-edotreotide PRRT in GEP-NET Patients (COMPETE), https://clinicaltrials.gov/ct2/show/NCT03049189

[5] *See* Study of $^{177}$LU-PSMA-617 in Metastatic Castrate-Resistant Prostrate Cancer (Vision), https://clinicaltrials.gov/ct2/show/study/NCT03511664?term=NCT03511664&rank=1

$^{177}$Lu is significantly higher than c.a. $^{177}$Lu, and it remains significantly higher over time as compared to c.a. $^{177}$Lu.

In addition to these differences in specific activity, c.a. $^{177}$Lu and n.c.a. $^{177}$Lu differ in another significant way. The first generation method for the manufacture of $^{177}$Lu yields an important impurity – $^{177m}$Lu. This atom is a natural by-product of the manufacturing process and it cannot be separated from therapeutically effective c.a. $^{177}$Lu in the ground state. $^{177m}$Lu is metastable and has a half-life of 161 days; the minimum decay time is more than four years. As a result of this impurity, all end products (including the urine of patients) associated with administration of radiopharmaceuticals utilizing c.a. $^{177}$Lu must be stored for extended periods of time under controlled conditions suitable for the prolonged decay periods of $^{177m}$Lu. On the other hand, n.c.a. $^{177}$Lu does not contain $^{177m}$Lu as an impurity and, accordingly, use of n.c.a. $^{177}$Lu avoids the significant storage and waste problems associated with c.a. $^{177}$Lu.

These different routes for the production of $^{177}$Lu, and the differences in radionuclidic purity and specific activity of $^{177}$Lu resulting from the distinct manufacturing processes, are depicted in the figures attached at the end of this submission.[6]

## II. The Legal Framework

### A. Federal Regulation of Radionuclides Used for Medical Purposes

The NRC and FDA share federal responsibility for the regulation of medical devices, drugs and biological products that utilize radionuclides. In August 1993, the two agencies established a Memorandum of Understanding ("MOU") outlining the respective responsibilities of each agency and identifying ways in which FDA and NRC should coordinate their regulatory actions involving such products.[7] Under the MOU, FDA maintains full responsibility for review and approval of radiopharmaceuticals under the Federal Food, Drug and Cosmetic Act ("FDCA"), 21 U.S.C. § 355 (drugs), and Public Health Service Act ("PHSA"), 42 U.S.C. § 262 (biologics) Pursuant to its authority under the Atomic Energy Act, the NRC regulates the medical use of nuclear materials to protect public health and safety and the environment.

In addition to the MOU, the NRC has issued a Medical Use Policy Statement. It provides that the NRC will: (1) continue to regulate the uses of radionuclides in medicine as necessary to provide for the radiation safety of workers and the general public; (2) not intrude into medical

[6] For nuclear structure and decay data relating to $^{177}$Lu, see NuDat 2.7 at https://www.nndc.bnl.gov/nudat2/

[7] *See* Memorandum of Understanding Between the U.S. Nuclear Regulatory Commission and the U.S. Department of Health and Human Services, Food and Drug Administration, August 26, 1993. 58 Fed. Reg. 47300, Sept. 8, 1993. This MOU was renewed with minor changes by both agencies on December 4, 2002. 67 Fed. Reg. 78262, Dec. 23, 2002. http://www.nrc.gov/docs/ML0235/ML023520399.pdf

judgments affecting patients, except as necessary to provide for the radiation safety of workers and the general public; (3) when justified by the risk to patients, regulate the radiation safety of patients primarily to assure the use of the radionuclides is in accordance with the physician's directions; and (4) in developing a specific regulatory approach, consider industry and professional standards that define acceptable approaches for achieving radiation safety.

Consistent with the MOU and to implement its Medical Use Policy, the Commission has established policies and regulations to govern the use, handling and disposal of byproduct materials for medical purposes. Specifically, under 10 C.F.R. Part 35, the Commission regulates the medical use of byproduct material through licensing, inspection and investigation of medical, industrial, academic and commercial facilities and authorization of physician users. These regulations are meant to provide for the radiation safety of workers, the general public, patients, and human research subjects without interfering with treatment protocols established by the physician. To that end, the rules set out procedures and standards to govern the issuance of licenses to facilities seeking to use byproduct material for medical purposes. Medical use licenses are issued by an Agreement State or, in Non-Agreement States, the NRC.

B. The NRC's Determinations Governing the Use of $^{177}$Lu for Medical Purposes

On June 21, 2018, the NRC issued a Licensing Determination to all Agreement States (and Vermont and Wyoming) stating that the medical use of $^{177}$Lu is subject to the applicable licensing provisions codified at 10 CFR Part 35, Subpart E ("Unsealed Byproduct Material – Written Directive Required) (hereafter "NRC Memorandum").[8] This determination followed approval of Lutathera® by FDA on January 26, 2018. Specifically, the NRC concluded that medical use of $^{177}$Lu is similar to use of beta- and photon-emitting therapeutic radiopharmaceuticals. Thus, pursuant to 10 CFR §§ 35.390 and 35.396, the NRC indicated that physicians approved for the use of any beta emitter or any photon-emitting radionuclide with a photon energy of less than 150 keV, and physicians trained for the parenteral administration of unsealed byproduct material, may also be authorized for the medical use of $^{177}$Lu.

In this context, the NRC also evaluated waste storage issues arising from handling and disposal of $^{177}$Lu. Under the NRC's regulations governing the storage and disposal of low level radioactive waste, medical licensees may dispose of radioactive waste through "decay in storage." 10 CFR § 35.92 This typically occurs for by-product material with a physical half-life of less than 120 days if the licensee determines that radioactivity cannot be distinguished from background radiation levels and the licensee removes or obliterates all radiation labels. 10 CFR § 35.92 On the other hand, waste containing longer-lived radioactive material must be stored or

[8] *See* Memorandum to All Agreement States, Vermont, Wyoming, Licensing of Lutetium-177 (STC-18-042), June 21, 2018. https://scp.nrc.gov/asletters/tech/sp18042.pdf

sent to a low-level radioactive waste disposal facility pursuant to NRC's regulations at 10 CFR Part 20 Subpart K ("Waste Disposal").

Applying these provisions to $^{177}$Lu, the NRC determined that the radionuclide may generally be decayed in storage with one notable and important exception. The NRC staff emphasized that small quantities of $^{177m}$Lu may be present as a "contaminant generated from the production of $^{177}$Lu," and that $^{177m}$Lu emits low-energy photons and beta emissions that, even in low quantities, are detectable using standard scintillator detectors and Geiger counters. The NRC staff indicated that non-administered $^{177}$Lu may pose a particular threat since it could lead to a buildup of $^{177m}$Lu. Accordingly, the NRC determined that if $^{177m}$Lu is detected by appropriate survey methods, then licensees must dispose of the waste material as low-level radioactive waste since the half-life of $^{177m}$Lu is greater than 120 days. In addition, the NRC indicated that licensees would need to develop safe handling and disposal procedures for detectable quantities of $^{177m}$Lu.[9]

## III. Request for Administrative Action and Rulemaking

Based on the foregoing, it is clear that a major obligation of licensees under the NRC Memorandum for $^{177}$Lu turns on whether $^{177m}$Lu is present and must be stored and disposed as a low-level radioactive waste. The uncertainty surrounding that question, and the burden of making that determination, could be easily addressed if the NRC were to draw a regulatory distinction between the two different forms of $^{177}$Lu -- c.a. $^{177}$Lu and n.c.a. $^{177}$Lu. Indeed, if licensees were aware that the radiopharmaceutical product to be administered to patients only contains n.c.a. $^{177}$Lu, then they would have no need to be concerned about $^{177m}$Lu since it is not produced as a contaminant of n.c.a. $^{177}$Lu.

Unfortunately, that transparency does not currently exist under the NRC's regulatory framework and, specifically, the NRC Memorandum for medical use of $^{177}$Lu. While the NRC staff expressly recognized that there are two different manufacturing processes for $^{177}$Lu, the NRC Memorandum does not draw any distinction at all between the two different forms of $^{177}$Lu and their respective impurity profiles. In fact, the NRC staff concluded that the information contained in their memorandum is applicable to all $^{177}$Lu labelled products (not just

[9] In an attachment to the NRC Staff Memorandum entitled "Radiation Safety Considerations for Lutetium-177 (Lu-177)," the NRC staff also recommended that licensees should establish precautions for managing patients that are hospitalized and they should provide patient instructions for those that are released. The staff noted that such measures will be important since there is the potential for $^{177}$Lu contamination from the excretion of 60-80 percent of the administered dose within a few hours after administration of the radiopharmaceutical product.

Lutathera®).[10] As a result, the NRC's appropriate concerns about the need to ensure proper disposal of $^{177m}$Lu have unnecessarily been imposed on licensees using radiopharmaceuticals containing n.c.a. $^{177}$Lu.

Specifically, this burden arises in the context of regulatory measures that licensees must take to handle disposal of waste containing $^{177m}$Lu, which has a half-life of more than 120 days. As the NRC regulations at 10 CFR Part 20 Subpart K make clear, and as the NRC recently emphasized in licensing guidance concerning $Ga^{68}$ radiopharmaceuticals and an impurity ($Ge^{68}$),[11] more stringent regulations govern the disposal of radioactive waste with a half-life of greater than 120 days. Those regulations provide that licenses may dispose of such waste in accordance with 10 CFR 20.2003 or transfer the waste to an authorized recipient. Yet while these requirements will apply to radiopharmaceutical products containing c.a. $^{177}$Lu, they will not apply products containing n.c.a. $^{177}$Lu.

Accordingly, ITM requests the NRC to revise and reissue its Licensing Determination for $^{177}$Lu so as to clarify this important distinction. The reissued Licensing Determination should state that there are two distinct forms of the radionuclide which trigger different waste disposal requirements. In particular, in a new penultimate paragraph in the NRC Memorandum, the NRC should state that "licensees need not develop and utilize survey methods and safe handling and disposal procedures for $^{177m}$Lu, including procedures to comply with 10 CFR Part 20 Subpart K, when using a radiopharmaceutical that contains n.c.a. $^{177}$Lu."[12] This action would allow licensees to understand the particular NRC regulatory requirements that apply to both c.a. $^{177}$Lu and n.c.a. $^{177}$Lu, and that would facilitate administration, handling and disposal of all drug products containing $^{177}$Lu.

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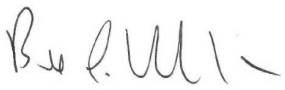
[10] *See* "Radiation Safety Considerations for Lutetium-177 (Lu-177)," attached to NRC Staff Memorandum Regarding Licensing of Lutetium-177 to James M. Trapp, Director, Division of Materials Safety (Region 1), John B. Giessner, Director, Division of Nuclear Materials Safety, Region III, and Troy W. Pruett, Director of Nuclear Materials Safety, Region IV, from Theresa V. Clark, Acting Director, Division of Materials Safety, Security, State and Tribal Programs, June 1, 2018. https://www.nj.gov/dep/rpp/rms/agreedown/lic_of_lu-177.pdf

[11] *See* "Germanium-68/Gallium-68 Pharmaceutical Grade Generators Licensing Guidance," July 2019. https://www.nrc.gov/docs/ML1910/ML19106A367.pdf

[12] The NRC has previously taken regulatory actions to distinguish different forms of the same radionuclide. These include Europium-150 (12.62 h) and Europium-150 (34.2y); Indium-110 (4.9 h) and Indium-110 (69.1 min); Neptunium–236 (1.15E + 5y) and Neptium-236 (22.5); Rhenium-182 (12.7h) and Rhenium-182 (64.0 h); and Terbium-156m (5.0 h) and Terbium-156m (24.4 h).

Thank you for your attention and your consideration of the request in this submission.

Respectfully submitted,



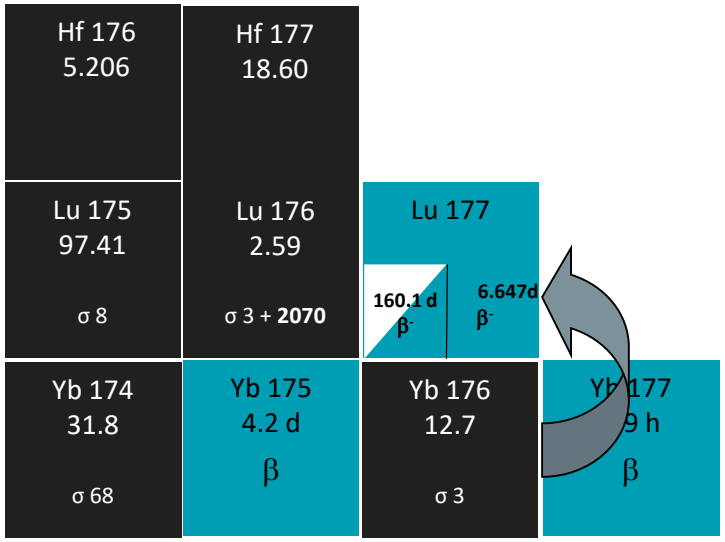
Bruce S. Manheim

cc: Dr. Said Daibes Figueroa, NRC (Said.DaibesFigueroa@nrc.gov)

# THE PRODUCTION ROUTES FOR $^{177}$LU

**Indirect Production Route of highly pure n.c.a. $^{177}$Lu**

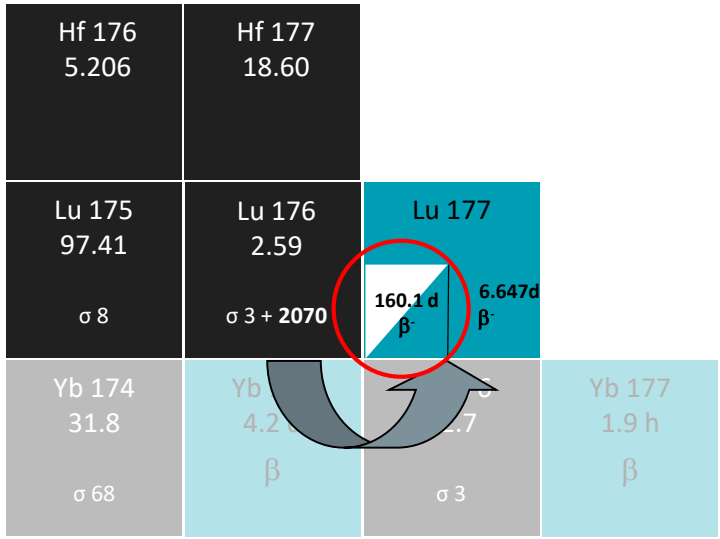
$^{176}Yb(n,\gamma)^{177}Yb \rightarrow {}^{177}Lu$




Non-carrier-added (n.c.a.) $^{177}$Lu

**Direct production route of c.a. $^{177}$Lu with $^{177m}$Lu impurities**

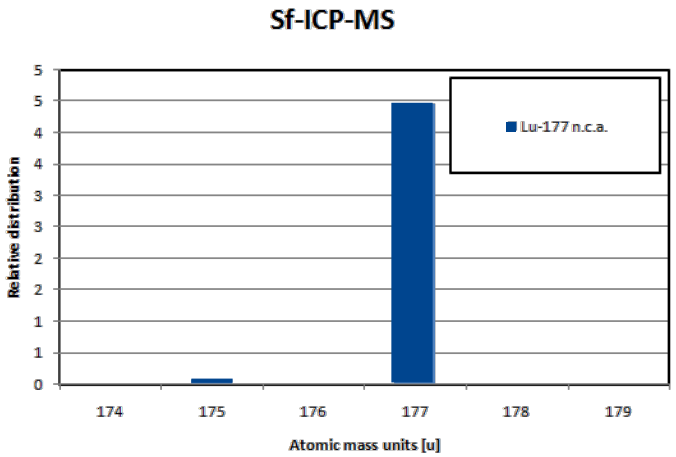
$^{176}Lu(n,\gamma)^{177}Lu$




Carrier-added (c.a.) $^{177}$Lu

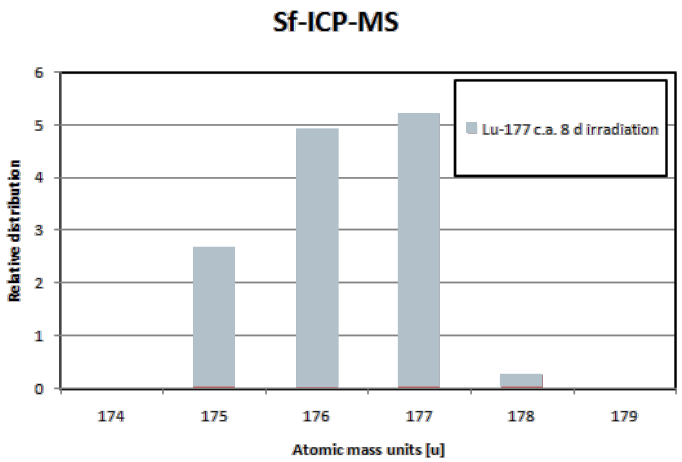
# Radionuclidic Purity of n.c.a. $^{177}$Lu and c.a. $^{177}$Lu

## n.c.a. $^{177}$Lu



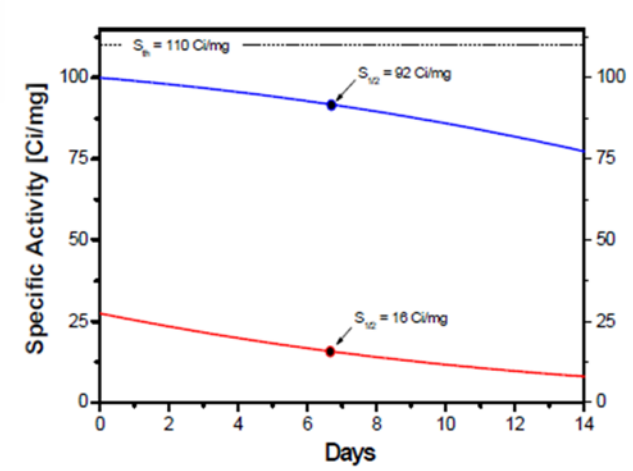

- High specific activity with over 90 % “hot” $^{177}$Lu atoms
- No contamination from $^{177m}$Lu

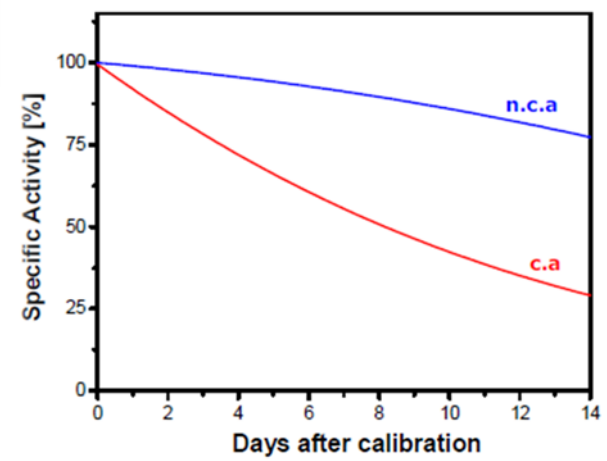
## c.a $^{177}$Lu




- Low specific activity with only 25 % “hot” $^{177}$Lu atoms
- Contamination from $^{177m}$Lu

# Specific Activity of n.c.a. $^{177}$Lu and c.a. $^{177}$Lu




$$S = \frac{A \cdot e^{-\lambda t}}{m_{st} + m_{^{177}Lu} \cdot e^{-\lambda t}}$$