# New Theranostics – New Challenges Lu-177 Dotatate (Lutathera®) Medical Event

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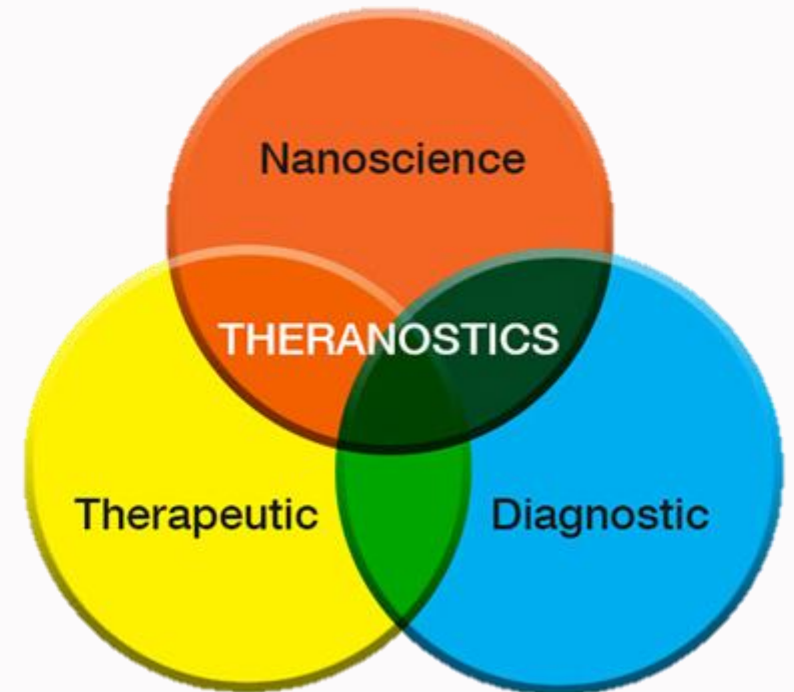
# Agenda

- **What is Theranostics?**
- **Overview of administration procedures**
- **Current Challenges**
  - Real-world examples: Lu-177 dotatate (Lutathera®) Medical Event



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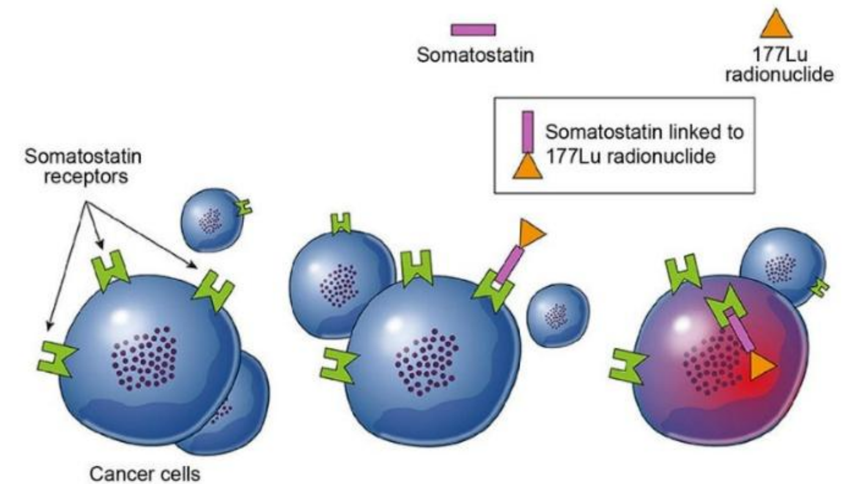
# Theranostic Definition

Theranostics combines the use of a molecular agent bound to an isotope suitable for diagnostic imaging and the same or very similar agent bound to an isotope that is appropriate for therapy. Both agents are designed to target the **same** cell biomarker or receptor.




Credit: Adapted from Frontiers in Oncology. January 2019. doi: 10.3389/fonc.201800663.

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# Examples of Theranostic Pairs

| Diagnostic Agent | Therapeutic Agent | Indication | Therapeutic Administration |
| --- | --- | --- | --- |
| I-123 MIBG | I-131 MIBG (metaiodobenzylguanidine) | Neuroendocrine tumors | Infusion |
| Ga-68 PSMA-11 | Lu-177 vipivotide tetraxetan (Pluvicto®) | Metastatic prostate cancer | IV/Infusion |
| Ga-68 dotatate | Lu-177 dotatate (Lutathera®) | Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) positive for hormone receptor somatostatin | Infusion |
| Pb-203 VMT01 | Pb-212 VMT01 | Clinical trials for metastatic melanoma | Per trial protocol IV/Infusion |

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# Precision Therapy with Implementation Challenges

- **Multidisciplinary Team**
  - Train and coordinate members from Nuclear Medicine, Oncology, Nursing, and Radiation Safety
  - Ensure communication and role clarity
- **Infrastructure Requirements**
  - Infusion suite with a private restroom
  - New equipment such as infusion pumps, syringe shields and shielded waste containers compatible with the radiopharmaceutical and administration procedure
- **Operational Considerations**
  - Develop new administration methods
    - Contamination control, including protecting patients' skin from leaks (example I-131 MIBG medical event)
    - Extravasation mitigation
  - Stay current with emerging theranostic pairs
  - Determine dose calibrator settings for new isotopes and geometry (syringe/vial)
    - Also applies to radiopharmacies

# Lutathera® Dosage

- Administer 200 mCi of Lutathera® every eight weeks for a total of four doses.
- The recommended dose is reduced to 100 mCi when modification is required due to adverse reactions.
- Administer 30 mg of long-acting octreotide intramuscularly 4 to 24 hours after each Lutathera® dose.

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# Lutathera® Dosage

- Administer short-acting octreotide for symptomatic management.
- Administer 30 mg of long-acting octreotide intramuscularly every 4 weeks after completing Lutathera® until disease progression or for 18 months followings treatment initiation.

See Lutathera® package insert for full prescribing information

Advanced Accelerator Applications USA, Inc. (2024). Lutathera: Highlights of prescribing information. East Hanover, NJ: Author.

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# Day of Treatment Workflow

- Administer antiemetics before amino acid solution.
- Start intravenous administration of amino acid solution 30 minutes before, during, and for a minimum of three hours post the Lutathera® infusion completion.
- Flush catheter to be used for Lutathera® with 0.9% Sodium Chloride Injection, US Pharmacopeia (USP) to ensure patency.
- Infuse Lutathera® over 30 to 40 minutes using gravity method, peristaltic pump method, or syringe pump method.
- Confirm activity of Lutathera® in dose vial or syringe (depending on administration method) in a dose calibrator prior to and after each administration.

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# Lutathera® Administrative Methods

## Gravity Method

· Infuse directly from original Lutathera® vial.

· Ensure 2.5 cm, 20-gauge needle used for 0.9% Sodium Chloride Injection, USP does not touch Lutathera® solution and is not connected directly to the patient.

· Ensure 9 cm, 18-gauge needle used for Lutathera® touches the bottom of the vial.

## Peristaltic Pump Method

· Infuse directly from original Lutathera® vial.

· Ensure filtered 2.5 cm, 20-gauge needle used for venting does not touch Lutathera® solution and is not connected directly to the patient.

· Ensure 9 cm, 18-gauge needle used for Lutathera® touches the bottom of the vial.

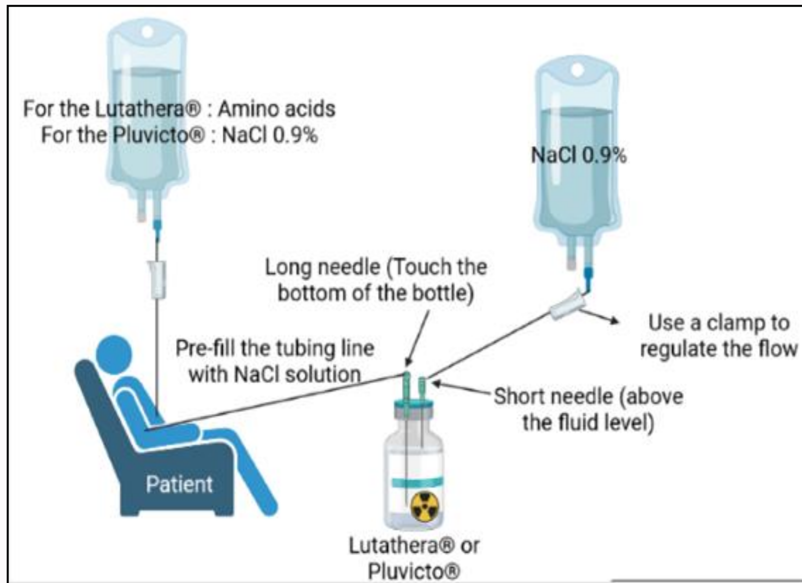
## Syringe Pump Method

· Ensure correct volume of Lutathera® is drawn into a disposable syringe fitted with a 9 cm, 18-gauge needle.

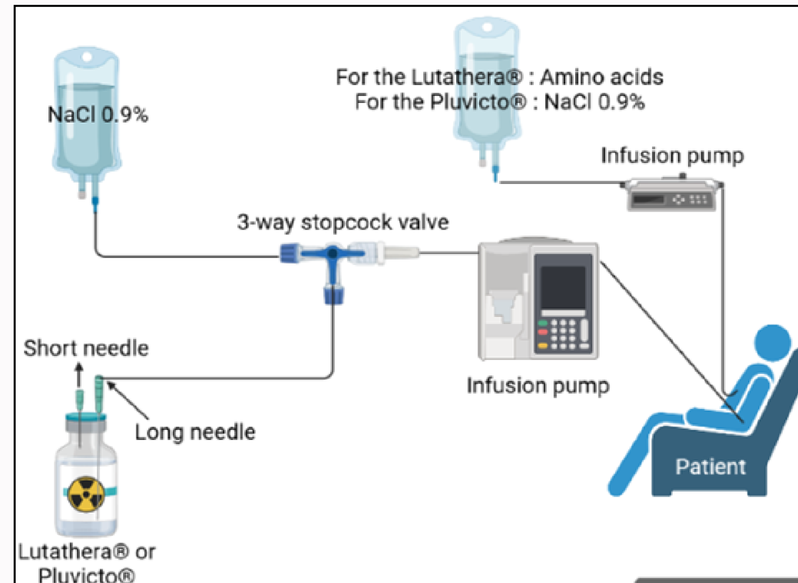
Note: Lutathera® package insert recommends peristaltic pump or syringe pump methods for reduced dose administration. If the gravity method is used, the activity in the Lutathera® vial must be adjusted prior to administration.

# Lutathera® Administrative Methods

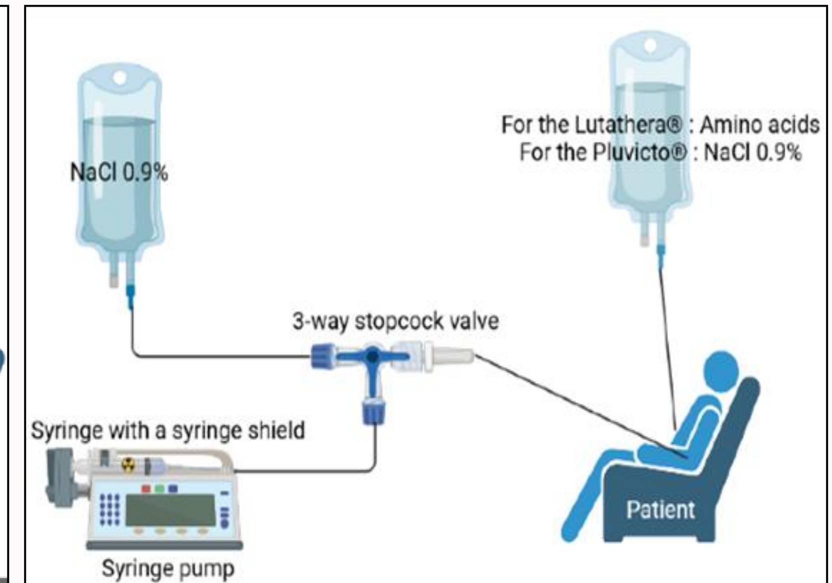
## Gravity Method




## Peristaltic Pump Method




## Syringe Pump Method




Credit: Adapted from Safety and Therapeutic Optimization of Lutetium-177 Based Radiopharmaceuticals. April 2023. doi: 10.3390/pharmaceutics15041240.

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# Lu-177 Dotatate (Lutathera®) Medical Event

**Background**

· Patient was prescribed 200 mCi (7.4 GBq) of Lutathera® for their second of four treatments, but only 88.4 mCi (3.27 GBq) was administered.

· This is a reportable event as per Title 10 CFR 35.3045 (a)(1)(i)(B) as less than 80% (44.2 %) of the prescribed dose was administered.

# Medical Event Description

- The Staff Nuclear Medicine Technologist (NMT) drew up and calibrated the Lutathera® dose, placed it in a shielded container, then assembled and primed the intravenous (IV) tubing and extension connection with 0.9% Sodium Chloride Injection, USP.
- The shielded container and supplies were placed on a cart that was walked by the Staff NMT, Lead NMT, and Radiation Safety staff to the Oncology Center treatment room.
- The Staff NMT realized that the extension was incorrectly connected to the IV tubing instead of to the Smiths Medical Medex 3-Way Stopcock, Model MX5311L during the administration set-up. The NMT went back to the Nuclear Medicine Department for another extension tubing.

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# Medical Event Description

- After the syringe pump had been on for approximately half of the expected infusion time, the Radiation Safety Officer (RSO) questioned how the infusion was going.
- The NMT checked and advised the Lead NMT that something was wrong with the infusion rate.
- The Lead NMT found that the syringe pump flow rate was set to 25 ml/hour instead of the correct rate of 50 ml/hour and corrected flow rate.
- The IV Nurse questioned the remaining infusion time to determine if more amino acid solution would be needed.

# Medical Event Description

- The Lead NMT suspected something was wrong with the pump, removed the dose syringe from the syringe pump, and slowly depressed the syringe plunger by hand.
- The Lead NMT noted and advised the other administration team members that there was 11.4 ml left in the syringe when the manual administration was started.
- What appeared to be minor leaking from the 3-way stopcock side port covered with a cap was noted.

# Medical Event Description

- The Lead NMT noticed that the 3-way stopcock was incorrectly set as “closed to the patient”, corrected the position, completed the administration, and flushed the dose syringe with 0.9% Sodium Chloride Injection, USP.
- The NMTs transported the syringe in the shielded carrier box and supplies back to the Nuclear Medicine Department where the syringe was measured in the dose calibrator to obtain the residual activity (1.9 mCi).

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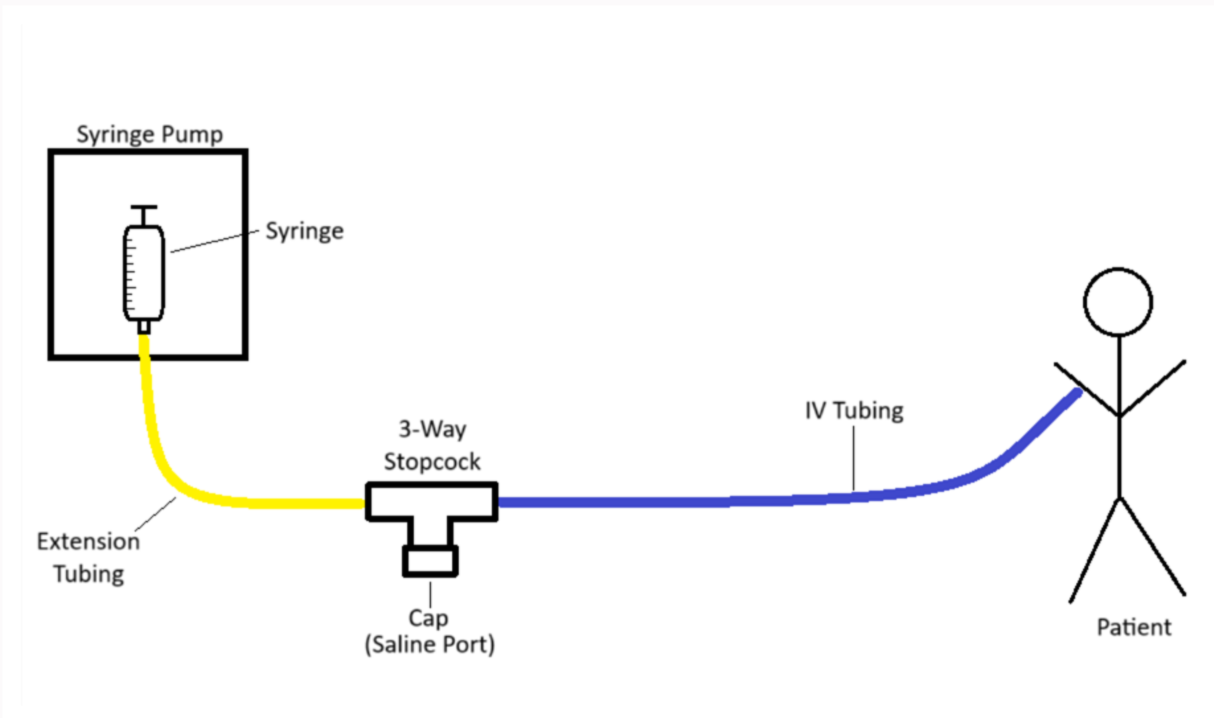
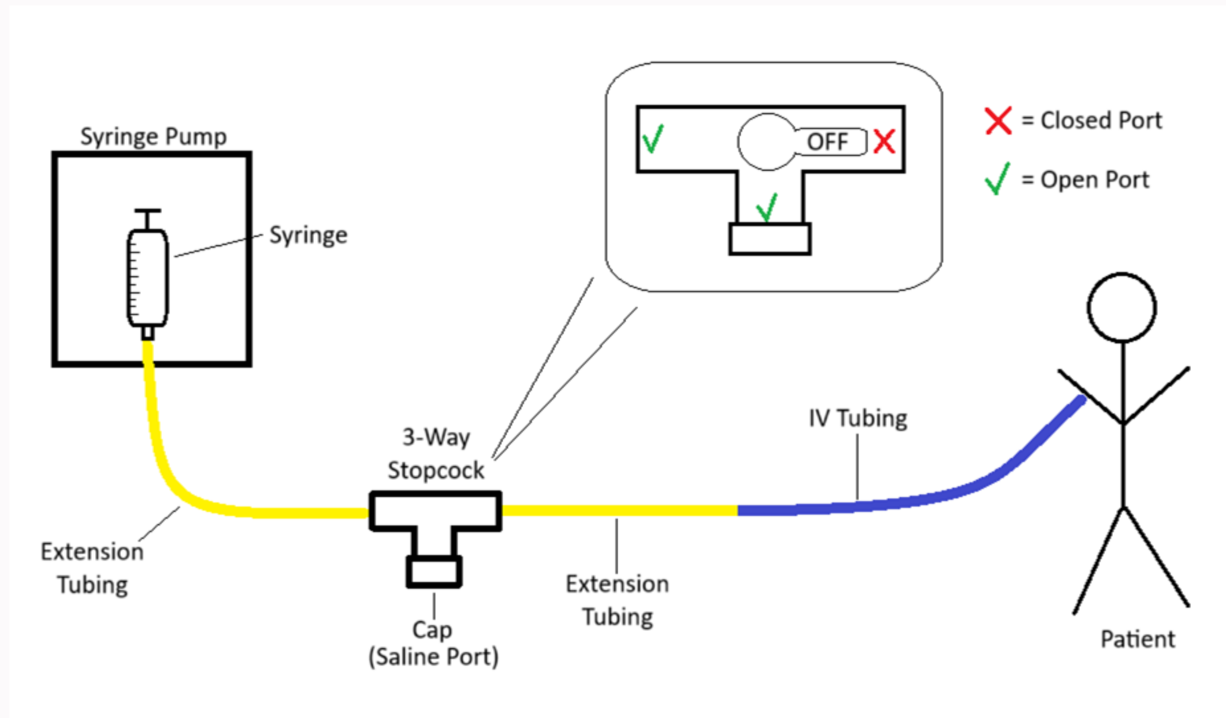
# Medical Event Description

## Intended Set Up




## Actual Set Up



# Medical Event Description

- The RSO and Health Physics Assistant surveyed the patient and found that the contact reading was only 6.1 mR/hour as compared to the 20 mR/hour that was measured during the patient's first treatment.
- They also found that the absorbent material under the 3-way stopcock measured much greater 100 mR/hour.
- The leaked material was contained in the absorbent material and was properly disposed. The treatment room, personnel, and patient surveys did not identify any other areas of contamination.

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# Medical Event Description

- From these surveys, the Radiation Safety staff presumed a significant portion of the dose was not administered to the patient.
- Dose delivered was calculated to be 88.4 mCi (3.27 GBq).
- Authorized User (AU), who was present during administration, notified the patient and referring physician of the underdose on the day of the treatment.

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# Medical Event Inspection

- Inspectors observed the licensee reenact the administration with sodium chloride during the site inspection.
- The Nuclear Medicine Supervisor and all administration team members were interviewed.
- Inspectors reviewed the records associated with dose prescribed, dose delivered, surveys, procedures, and corrective actions.
- Inspectors discussed findings with the licensee.

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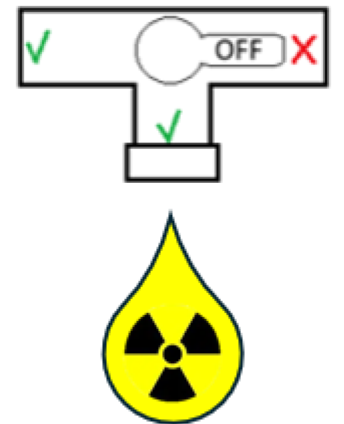
# Inspection Conclusions

- The medical event was caused by an infusion line set-up error. An extension tubing was incorrectly positioned during set-up, necessitating the addition of a second extension tubing prior to the start of the infusion.
- The 3-way stopcock was set to “closed to the patient” to prime the additional tubing and the licensee failed to set it to “open to the patient” before starting the infusion. This prevented delivery of Lutathera® to the patient and caused the Lutathera® to leak out of the 3-way stopcock side port which was covered with the cap supplied with the stopcock.



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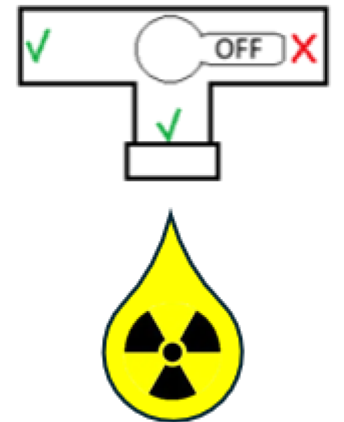
# Inspection Conclusions

- The licensee was not aware that this cap on the Smiths Medical Medex 3-Way Stopcock, Model MX5311L is designed to maintain sterility but not to seal the port. If the port had been sealed, backpressure would have caused the syringe pump to alarm, alerting the administration team of an infusion problem.
- The 3-way stopcock position error was not detected until 13.6 ml of the 25 ml Lutathera® dose leaked into the absorbent material under the stopcock.

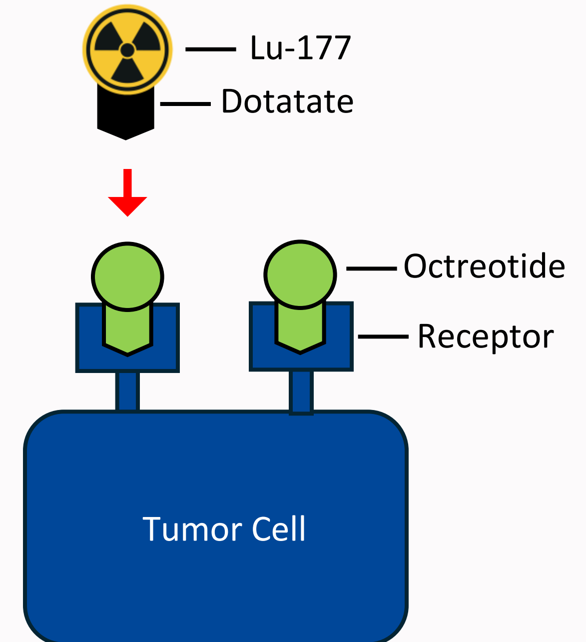


# Inspection Conclusions

- In addition to the side port cap function misunderstanding, training deficiencies were also a contributing factor. The Staff NMT indicated they were not proficient in the 3-way stopcock operation and did not have a checklist to follow.
- The administration team expected the Novartis representative to attend the first 3 cases to ensure they were proficient with this administration and to develop a final checklist. The representative attended the first treatment, but did not attend this second administration, possibly due to a miscommunication error.

# Effect on Patient and Treatment Plan

- The AU said the dose delivered was close to the reduced dosing guidelines (100 mCi) for patients requiring dose modification due to clinical factors. This adjusted dose provides a therapeutic effect.
- The treatment plan is to continue with the standard schedule of Lutathera® infusions every eight weeks for a total of four doses, along with octreotide injections.
- Administering an additional dose of Lutathera® following a post-infusion octreotide injection to compensate for the underdose would be ineffective due to receptor saturation.
- Octreotide binds to the primary Lutathera® target, thereby preventing Lutathera® binding.



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# Corrective Actions

- The licensee finalized a Lutathera® administration checklist.
- The Novartis representative provided retraining to the administration team on June 12, 2025.
- Novartis was scheduled to provide another retraining and dry run on July 31, 2025, as the licensee changed their administration set-up to remove the 3-way stopcock.
- The RSO confirmed that the representative would proctor the next Lutathera® administration on August 1, 2025.

# Corrective Actions

- Radiation safety training to review Lutathera® Quality Management Plan preventing medical events, and the new administration procedure was scheduled for July 14, 2025.
- Written counseling memos were issued to the two Nuclear Medicine Technologists involved in the event.
- DEP plans to evaluate the Lutathera® procedure during routine inspections.

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# Summary

- Theranostics offer precision therapy but can have implementation challenges.
- Regulators and licensees need to stay current with the rapid development of new theranostic procedures.
- Whenever possible, observe therapy procedures during inspections.
- Do not limit interviews and observations to Radiation Safety staff and senior team members. Interview and observe individuals who normally perform the task.
- Observing one type of theranostic procedure does not ensure the licensee has adequate procedures for all procedures.

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# Acknowledgements


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