SNMMI Value Initiative NEWSLETTER
SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING SEPTEMBER 2019

Congressional staff and members of the public gather to learn about diagnostic radiopharmaceuticals.

SNMMI Members Talk Nuclear Medicine at Congressional Policy Briefing on Capitol Hill

On July 17, 2019, SNMMI co-hosted a briefing on Capitol Hill with clinicians, patients, and industry representatives to discuss the importance of nuclear medicine, diagnostic radiopharmaceuticals, and specifically, H.R. 3772, also known as the Medicare Diagnostic Radiopharmaceutical Payment Equity Act of 2019. The bill calls for all diagnostic radiopharmaceuticals that reach a cost of more than $500 per day to be paid separately in the Hospital Outpatient Perspective Payment System.

The change in reimbursement would correct the current flawed payment policy, under which many hospitals can't afford to offer these procedures. Successful enactment of the bill would be enormously significant for patients, helping ensure they get the best and most appropriate care possible.

Speakers for the briefing included SNMMI President Vasken Dilsizian, professor of Radiology and Medicine at the University of Maryland Medical Center, and Josh Mailman, chairman of the SNMMI Patient Advocacy Advisory Board and president of the NorCal CarciNET Community, as well as Terri Wilson, senior director of patient access and healthcare policy at Blue Earth Diagnostics and chair of the Medical Imaging & Technology Alliance (MITA) Positron Emission Tomography Group.

"Diagnostic radiopharmaceuticals are incredibly effective in the diagnosis of a number of different diseases, including prostate cancer, Alzheimer's and Parkinson's disease, and others," noted Dilsizian. "We've really only scratched the surface of potential with these technologies, and I expect we'll see future improvements in these diagnostic tools if policy is adjusted to better reflect patient need."

As a neuroendocrine tumor (NETS) patient, Mailman, offered a patient perspective on the benefits of

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Radioligand Therapy in the Treatment of Cancer – A Bright Future Driven by Imagination, Innovation and Investigation

By Mike Rossi, General Manager, United States – Advanced Accelerator Applications S.A., A Novartis Company

An article by Advanced Accelerator Applications S.A., A Novartis Company, an SNMMI Value Initiative Industry Alliance Leadership Circle Partner

When the founder of your company is a physicist whose work at the European Organization for Nuclear Research (CERN) inspired him to pursue the research and development of radiolabeled agents to target cancer cells, you know you're off to a promising start – and a future that ideally holds a wealth of new possibilities in the management of disease.

The journey that began nearly 20 years ago eventually became Advanced Accelerator Applications (AAA), a Novartis company, an innovative radiopharmaceutical company developing new therapies for the treatment of cancer – the latest therapeutic option being Lutathera® (lutetium Lu 177 dotatate), which is the first FDA-approved Peptide Receptor Radionuclide Therapy (PRRT)[1]. PRRT is a form of RadioLigand Therapy (RLT), an approach where a ligand targeting a particular receptor expressed on a tumor cell carries a radioactive component. Lutathera® is FDA approved for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults[1].

GEP-NETs are rare tumors derived from neuroendocrine cells that can occur anywhere along the gastrointestinal tract (including the stomach, small and large intestines, colon, rectum, and appendix) or in the pancreas. GEP-NETs are classified as an orphan disease by U.S. regulatory authorities, meaning there are less than 200,000 individuals in the US diagnosed with the disease each year[2]. The estimated annual rate of newly diagnosed cases (incidence) of GEP-NETs in the United States is approximately 6.98 per 100,000 people, while the estimated prevalence in 2014[3] (based on the National Cancer Institutes Surveillance, Epidemiology, and End Results, SEER, database) was 171,321. Even though GEP-NETs are rare, their incidence has grown over 500% over the last three decades[3].

But before AAA was prepared to enter the therapeutic space, the company first needed to build capabilities for the management of the diagnostic end of the process. For AAA, this provided strong impetus for the development of a theragnostic platform, a disease management strategy that involves the integration of diagnostics and therapeutics.

Toward the goal, AAA developed NETSPOT™ (kit for the preparation of gallium Ga 68 dotatate injection) which was approved by the FDA in June 2016.[4] NETSPOT™, after radiolabeling with Ga 68, is FDA-approved for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients[4] Since its approval, NETSPOT™ is being used in PET procedures at more than 600 hospitals and clinics across the U.S.

The discovery and development of Lutathera® spanned more than 25 years and is a great example of collaboration between academic institutions and industry researchers. Following initial discovery and several years of compassionate use with a compounded version of the treatment at Erasmus Medical Center (the Netherlands) and a few other European academic centers, AAA acquired the rights to the drug (in 2010) with the goal of developing it into a commercial product and making it widely available to patients in many countries.

The subsequent development and commercialization of Lutathera® became the focus of AAA research

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A New Chapter For Nuclear Medicine

USP <825> ADDRESSES THE UNIQUE CHALLENGES OF RADIOPHARMACEUTICALS IN A DEDICATED CHAPTER FOR THE FIRST TIME

By Cardinal Health

An article by Cardinal Health, an SNMMI Value Initiative Industry Alliance Leadership Circle Partner

The New Standard For Success

For more than 15 years, nuclear medicine professionals have been required to reference the standards included in USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations.

The challenge has been that radiopharmaceuticals have unique preparation needs not adequately addressed by USP <797>. One example is the radioactivity itself, which requires radiation shielding, radiation detectors and radiation monitors.[1]

The lack of specific standards left USP <797> open to interpretation and created confusion across the nuclear pharmacy and nuclear medicine industries.

The disconnect was no more apparent than during the 2016 revision of USP <797>, when USP received over 1,500 comments. The organization responded by developing a new chapter: *USP<825> Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging*. Created to address the specific needs of handling, storing and transporting both sterile and non-sterile radiopharmaceuticals, the new chapter will officially go into effect December 1, 2019[2].

An idea whose time has come, USP <825> is the first set of standards unique to radiopharmaceuticals. Its development is widely supported in the nuclear medicine and nuclear pharmacy communities. [3,4]

How Was USP <825> Developed?

USP created the Expert Panel on Radiopharmaceuticals to develop the standards that would become USP <825>. Panel applicants were a diverse group, including experts from hospital practice, centralized radiopharmacies and academia. Those selected to serve on the panel included centralized radiopharmacists, hospital nuclear pharmacists, a nuclear medicine technologist, USP (including those who had written USP <797>), Health Canada and US FDA.

The overarching goal was to balance radiation safety with traditional aseptic handling practices. The panel started with USP <797> and modified it where needed for radiation safety. As a result, USP <825> has become the most comprehensive resource for how to safely handle both sterile and non-sterile radiopharmaceuticals. [1]

Richard L. Green
BS Pharm, RPh, BCNP, FAPhA
Director of Radiopharmacy Practice
Nuclear & Precision Health Solutions
Cardinal Health

"The 38-page chapter afforded only six small paragraphs to radiopharmaceuticals. We needed a separate chapter for radiopharmaceuticals, so we—along with many others—advocated for it."

Take These 3 Steps to Help You Become Compliant

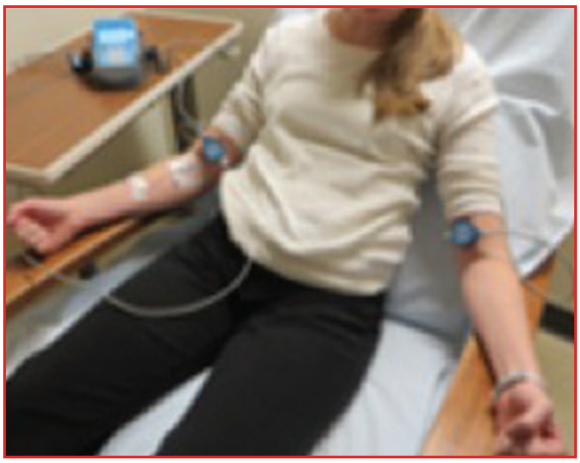
› **1. Become familiar with the final chapter, published in June 2019.**

› **2. Perform a gap analysis to determine how compliant you are with USP <825> today** and what steps are needed to become fully compliant before December 1, 2019. What are you required to do, what are you doing currently and where are the gaps?

› **3. Turn to your hospital pharmacy and DOP for help:**

- Accreditation organizations recognize hospital pharmacies as having oversight responsibility for the use of all drugs, including radiopharmaceuticals.

Continued on page 6. See **A New Chapter**



Why Quality Matters to Quantification: The Case for Monitoring Radiotracer Injections

By Lucerno Dynamics, LLC

An article by Lucerno Dynamics, LLC, an SNMMI Value Initiative Industry Alliance Principal Member Partner

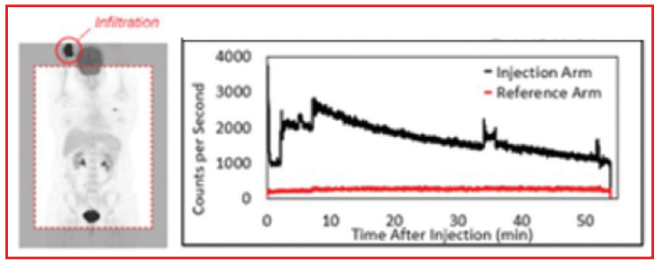
Nuclear medicine plays a critical role in healthcare. Its role is expected to grow in importance as new radiotherapies are introduced, and as functional imaging and quantification are used to address the challenges of precision medicine. To fulfill its expectations in patient care, nuclear medicine scans must be performed with the highest accuracy and reproducibility. However, radiopharmaceutical infiltrations, a nuclear medicine quality issue, compromise image accuracy and reproducibility, patient care, and waste valuable resources.

Infiltrations Are Common, Not Always Detectable, and Underreported

An infiltration is the inadvertent injection or leakage of a fluid or drug into the tissue surrounding the vein during an intravenous injection procedure. Infiltrations in PET/CT and gamma camera procedure injections are typically difficult to detect because volumes are small and are not vesicants, so neither technologists nor patients are aware of them. Additionally, reading physicians are often unaware of infiltrations as they are frequently out of the imaging field of view (FOV). Published infiltration rates report an aggregate of ~15%, but this is likely underestimated due to FOV limitations.

Why Is This Important?

Over 3 million PET/CT procedures and 15 million gamma camera radiotracer injections are administered each year in the U.S. Nuclear medicine radiotracer injection infiltrations are relevant across oncology, cardiology, neurology, and many other specialties. At current estimated infiltration rates, over two million patients may be infiltrated each year, several hundred thousand of whom may have large infiltrations. Patient management decisions often consider nuclear medicine images, and with many infiltrations unnoticed and unreported, patient care and safety may be affected.



Knowledge is Power - When Infiltrations Are Monitored, They Can Be Reduced

When infiltrations cause immediate harm to patients, they are typically monitored and reported. For example, injections of chemotherapy or CT contrast agents are closely monitored for the possibility of infiltration. As a result, infiltration rates for these procedures have been methodically reduced over decades to very low levels (<0.24%).

Retrospective static images are insufficient for monitoring due to FOV issues and lack of information from the entire uptake period. As a result, PET/CT and gamma camera imaging procedures performed in the US are not routinely or effectively monitored for infiltrations.

Infiltrations Can Matter to Patient Care

Over 90% of the PET/CT procedures done each year in the US are used to help oncologists diagnose, stage, choose therapy, plan treatments, assess tumor response, or longitudinally monitor cancer patients. Infiltrations negatively affect the sensitivity of PET/CT, and with the number of new cancer cases per year expected to rise significantly by 2030, it is critical that PET/CT scans be done with the highest accuracy and reproducibility.

Examples of implications of infiltrated PET/CT studies for the management of cancer patients:

Continued on page 6. See **Why Quality Matters**

SNMMI Members Continued from page 1.

In addition, SNMMI has launched a letter-writing campaign in support of H.R. 3772, the Medicare Diagnostic Radiopharmaceutical Payment Equity Act of 2019. Visit **www.snmmi.org/hr3772** to get involved!

Josh Mailman, MBA, shares what life is like as a neuroendocrine patient.

President Vasken Dilsizian, MD, Senator Ben Cardin, Sukhjeet Ahuja MD, MS, Ira Goldman (Lantheus), and Rosemary Cioti (FORCE) meet to discuss H.R. 3772.

radiopharmaceutical imaging. "Having advanced imaging available for neuroendocrine tumors patients is critical, as these advancements have helped clinicians determine the location and the extent of disease so they can better plan appropriate therapy for improved patient outcomes." Following the congressional briefing, SNMMI members met with more than forty congressional offices asking for support of H.R. 3772.

Radioligand Therapy Continued from page 2.

over the course of the next 15 years. The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) approvals of this treatment subsequently came in 2017 and 2018, respectively.

For AAA, these successes support additional research and development into the potential use RLT has in the treatment of other malignancies. As such, the company is currently exploring potential applications for RLT across a broad range of cancers.

For example, ^{177}Lu-PSMA-617 is an investigational therapeutic that potentially targets Prostate-Specific Membrane Antigen (PSMA). A Phase 3 study is being conducted in metastatic castration-resistant prostate cancer (mCRPC). Beyond this, AAA is working on earlier stage development programs looking at tumors over-expressing other receptors such as gastrin-releasing peptide receptor (GRPR) in Breast, Gastro-Intestinal Stromal Tumors (GIST), Glioblastoma, Neuroblastoma, Ovarian, Head & Neck and Esophageal.

Clearly, the qualities of imagination, discovery and innovation, confirmed through the rigors of scientific investigation, will greatly influence new directions for RLT in the future.

With 19 production and R&D facilities, and over 800 employees across 13 countries, AAA is clearly up to the challenge and committed to reimagining nuclear medicine in the 21st century.

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[1] For full Lutathera® prescribing information, including important safety information, visit: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208700s000lbl.pdf)

[2] FAQs About Rare Diseases https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases

[3] Dasari A, Shen C, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol. 2017 Oct 1;3(10):1335-1342 https://www.ncbi.nlm.nih.gov/pubmed/28448665

[4] For full NETSPOT™ prescribing information, including important safety information, visit: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208547s000lbl.pdf

A New Chapter Continued from page 3.

- Hospital pharmacists already have deep USP experience, working to maintain compliance with USP <795> (non-sterile pharmaceutical compounding), USP <797> (sterile pharmaceutical compounding) and USP <800> (hazardous drug compounding).
- Directors of Pharmacy are experts in compounding and responsible for all medication use in the institution. Your hospital pharmacy department will be your allies as your nuclear medicine department prepares for USP <825>. They can help with documentation, updating equipment and procedures and more.

Applying USP <825> standards may change protocols used in the past for both imaging and the hot lab—including how to prepare doses, make kits and handle functions in the hot lab. Facilities will want to assess needs for additional internal resources needed to accomplish any necessary changes.

The bottom line: review the drug handling procedures your nuclear medicine department performs now. What would you like them to be, under USP <825> standards? Your contracted provider may serve as a resource as you determine how best to meet your objectives.

As you prepare for compliance, visit cardinalhealth.com/usp825 for such tools as:

- Our comprehensive white paper on this topic, which includes more depth into the history of USP <825>, how it was developed and why.
- Current list of FDA-approved radiopharmaceuticals and their contraindications, to help ensure your hospital or health system's formulary is up-to-date and that your department is using only FDA-approved radiopharmaceuticals.
- Frequently asked questions for both a director of pharmacy (DOP) and the nuclear medicine department, to better understand how USP <825> will impact the DOP's oversight of the nuclear medicine department.

References

1. USP General Chapter <825> Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging 1. Introduction

2. https://www.usp.org/chemical-medicines/general-chapter-825

3. http://snmmi.files.cms-plus.com/SNMMI-USP-Recommendations-Final_2016.pdf

4. https://nanp.net/assets/docs/NANP-Position-Paper-on-Compounding-Radiopharmaceuticals-February-2017.pdf

Why Quality Matters Continued from page 4.

- **Under staging disease** can lead to unnecessary surgery, and cost and delay in initiation of treatment. Metastatic disease may also be missed or misinterpreted.
- **Over staging disease** can lead to inappropriate treatment for metastatic disease, and potential withholding of lifesaving regional therapy from the patient.
- **Therapeutic procedure planning errors** can result in incorrect treatment planning.
- **Therapy assessment errors** caused by underestimated quantification of a baseline or follow-up scan.
- **Ambiguous image results** may unnecessarily subject patients to invasive procedures or repeat scans, with additional radiation exposure.

Additionally, infiltrations of diagnostic and therapeutic radiopharmaceuticals can lead to unintended radiation exposure to tissue that exceeds U.S. Nuclear Regulatory Commission Subpart M reporting limits of 0.5 Sv.

What Can Be Done?

When clinicians are aware of infiltrations and their contributing factors, they can lead quality improvement efforts and significantly reduce infiltration rates and sustain these results. A prospective multi-center quality improvement project using the Lucerno Dynamics Lara® System monitored 5,541 patients in 7 PET/CT centers in the United States and demonstrated that centers monitoring injection quality as part of their routine practice were able to reduce infiltration rates and sustain improvements. The Lara System uses time-activity curves to provide quality control for each individual patient and generates infiltration contributing factors so centers can design tailored quality improvement plans specific to their needs.

With an increasing emphasis on precision medicine and quantification and the introduction of new radiotherapeutics, now is the time for nuclear medicine to address the quality issue of radiopharmaceutical infiltrations. Technologists need feedback on injections and patients and treating physicians need the highest quality images.

To learn more visit: **http://laraknows.lucernodynamics.com/**

Highlights from the SNMMI 2019 Annual Meeting

Emerging disciplines and companies were a focus at the recent 2019 Annual Meeting, June 22-25 in Anaheim, California:

Concept to Commercialization

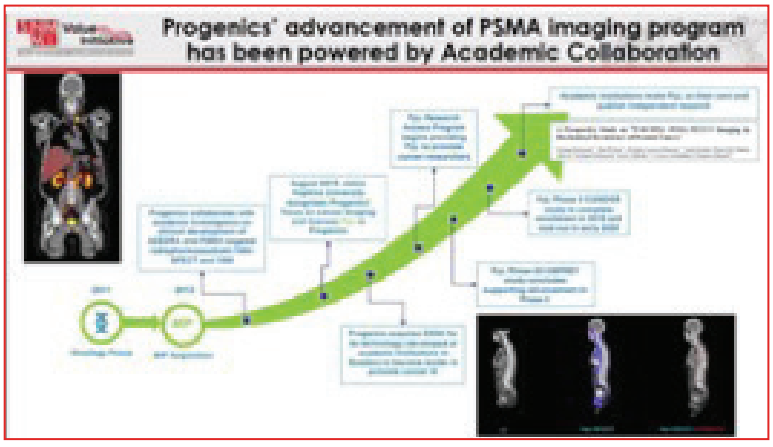
Dedicated session for small and emerging technology companies.

At the recent SNMMI Annual Meeting, experts from industry and venture capital organizations convened for a special session on facilitating a healthy molecular imaging and therapy ecosystem to grow innovative ideas into successful products that benefit patients. Core challenges specific to small and emerging technology companies, and ways to foster cross-sector partnerships were also addressed.

Theranostics: Regulatory Considerations for Product Development

Sponsored by the Clinical Trials Network, the U.S. Food and Drug Administration, and the NCI

In this highly attended categorical seminar, speakers examined clinical, nonclinical and CMC information needed for theranostics product development, including a discussion on regulatory perspectives of products combining an imaging modality with therapeutic radiopharmaceuticals. The content of the session was specific to the needs of the community based on what FDA members in medical imaging and other divisions are seeing in INDs, NDAs, aNDAs, and DMF applications filed with the agency and in other interactions with the community.



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