FROST & SULLIVAN

BEST PRACTICES AWARDS

NorthStar®
MEDICAL RADIOISOTOPES, LLC

2020 NORTH AMERICAN NUCLEAR MEDICINE IMAGING ENABLING TECHNOLOGY VISIONARY INNOVATION LEADERSHIP AWARD

Contents

Background and Company Performance

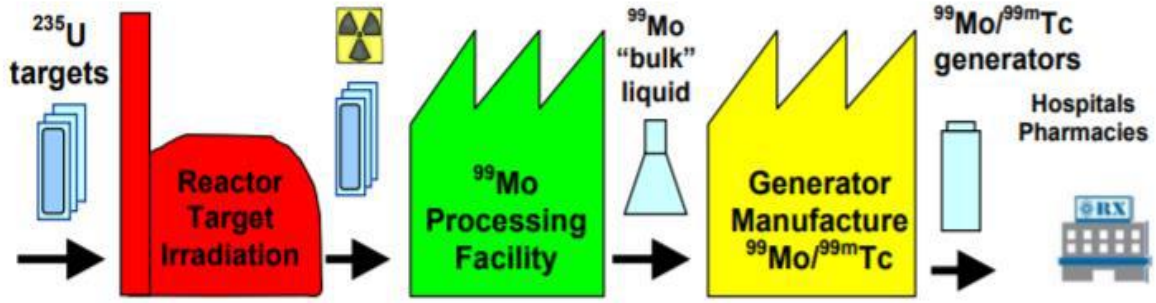
Industry Challenges

Nuclear medicine has been the backbone of diagnostic cardiology and oncology for several decades now, providing valuable insights into physiological processes at the molecular levels to identify diseases at an early stage. In spite of several emerging technologies, Frost & Sullivan monitors how nuclear medicine still maintains its position in the diagnostic imaging industry, thus playing an essential role in value-based care—quicker diagnosis, more accurate disease staging, and targeted treatment selection. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are two well-established nuclear medicine imaging modalities.

The World Health Organization defines radiopharmaceuticals as "unique medicinal formulations containing radioisotopes which are used in major clinical areas for diagnosis and/or therapy." Typically, nuclear medicine imaging, or molecular imaging (MI), involves administering radiopharmaceuticals into the bloodstream to digitally visualize, characterize, and measure the emitted radiation, i.e., "endoradiology." According to the American Nuclear Society, 90% of the world's radioisotopes are for diagnostic imaging purposes, and 10% for therapeutic procedures.[1]

Technetium-99 (Tc-99m), molybdenum-99's (Mo-99 or moly) daughter isotope, is MI's workhorse radioisotope, accounting for 80% of all nuclear medicine procedures worldwide, approximately 30 to 40 million SPECT annual scans.[2] The United States (US) is the world's top Tc-99m consumer—about 50% of the global market, performing around 40,000 to 50,000 SPECT procedures daily.[3]

Mo-99/Tc-99m Supply Network



Source: https://inis.iaea.org/collection/NCLCollectionStore/_Public/41/064/41064193.pdf?r=1&r=1

Frost & Sullivan notes that Mo-99/Tc-99m production is an intricate process involving a few participants and spans various continents, making the US supply network uniquely fragile and unreliable.

[1] *https://www.world-nuclear.org/information-library/non-power-nuclear-applications/radioisotopes-research/radioisotopes-in-medicine.aspx*
[2] *https://www.oecd-nea.org/med-radio/docs/sen-hlgmr2017-2.pdf*
[3] *https://www.ncbi.nlm.nih.gov/books/NBK487238/*

Key stakeholders include:

Uranium-235 (U-235) Providers, 1—The US is the primary supplier for weapons-grade highly enriched uranium (HEU) and low enriched uranium (LEU) globally, shipping U-235 to research reactors in Europe, Australia, and South Africa.

Irradiation Services, 6—Irradiated HEU now produces about 25% of the Mo-99 for medical use, irradiated LEU targets produce the remaining 75%.[4,5] The international community has almost completed efforts to phase-out HEU from civilian use as part of the global nuclear threat reduction initiative and to mitigate illicit nuclear trafficking for nuclear terrorism. The Department of Energy's (DOE) National Nuclear Security Administration (NNSA) implements this policy in the US.

Six government-owned nuclear reactors provide about 95% of the world's moly-99:[6] HFR, Netherlands, 52 years old reactor—40%; BR2, Belgium, 52 years—20%; Safari-1, South Africa, 48 years—15%; OPAL, Australia, 12 years—15%; Maria, Poland, 39 years—5%; and LVR-15, Czech Republic, 24 years—5%.[7].

Mo-99 Suppliers, 4—Four companies with specialized processing facilities nearby research reactors extract and purify Mo-99 for global distribution: ANSTO, Australia; IRE, Belgium; HRF Petten, Netherlands; and NTP, South Africa. All but IRE have now converted to processing LEU targets.

Technetium Generator Suppliers, 2—Curium and Lantheus Medical Imaging dominate the US market. They manufacture Mo-99/Tc-99m generators, i.e., systems extracting Tc-99m from decaying Mo-99, for commercial sale to Tc-99m suppliers.

Tc-99m Providers—Approximately 350 nuclear pharmacies located across the US supply the daughter isotope to all the clinics and hospitals.[8] Nuclear pharmacy operators prepare the radioactive tracers—organ-specific unit doses per patient—and ship them to hospitals for use in diagnostic and therapeutic procedures. Mo-99 and Tc-99m have a half-life of 66 and 6 hours, respectively, requiring continuous production, rapid processing, and speedy delivery to timely match provider demands.

In 2009 to 2010, extended research reactor shutdowns led to severe Mo-99 shortages, negatively impacting medical patient care on a global scale. The inability to stockpile Mo-99 and medical-grade Tc-99m created production and supply uncertainty, often delaying diagnosis and treatment of potentially serious medical conditions. Alternatively, some healthcare providers used less effective, more expensive, and riskier interventional procedures.

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[4] *http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=23563*
[5] *https://www.nap.edu/read/23563/chapter/6#84*
[6] *http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=23563*
[7] *https://www.world-nuclear.org/information-library/non-power-nuclear-applications/radioisotopes-research/radioisotopes-in-medicine.aspx*
[8] *https://www.nrc.gov/docs/ML1903/ML19030B712.pdf*

The supply network continues to struggle. For the last 18 months, two sites are not pulling their weight—Australia offline and South Africa 40% capacity—potentially resulting in shortage situations impacting patient care around the globe.

In addition, Frost & Sullivan's own research confirms that isotope production unpredictability contributes to fluctuating market prices. Notably, the National Research Universal reactor at Chalk River Laboratories' (in Ontario, Canada) permanent shut down in March 2018 increased radioisotope prices by 1,000%.[9]

Presently, moly production generally meets current US needs, but there have been several weeks in the last 18 months when supply has been very limited. However, the international source-dependent domestic nuclear imaging industry faces concerns over future Mo-99/Tc-99m supply. The few production reactors and processing facilities combined with the inherent risk of operating aging reactors, i.e., most built during the Cold War era, exacerbate the unease surrounding the delicate Mo-99 production-demand balance.

Focus on the Future and Best Practices Implementation

Founded in 2006, Wisconsin-based NorthStar® Medical Radioisotopes (NorthStar) is a privately-held nuclear medicine technology company committed to providing the US with reliable and environmentally friendly radioisotopes.

NorthStar's intellectual property includes patented non-uranium based molybdenum-99 domestic production methods, separation chemistry and sterilization systems, and an expandable technology platform with solutions in both diagnostics and therapeutics. The company's radioisotope pipeline includes alpha therapies, e.g., actinium-225/bismuth-213, and beta therapies, e.g., rhenium-188, and diagnostic imaging agents such as gallium-68.[10]

NorthStar Medical: Dedicated to Transformational Change

> *"The old ways of using uranium byproducts from nuclear weapons or power generation programs for medical radioisotopes are becoming less sustainable and tenable. We [NorthStar] needed to find a new way of making medical radioisotopes domestically to support patient needs*.
>
> *—Steve Merrick, President and Chief Executive Officer, NorthStar Medical*

The DOE backed programs pursuing domestic Mo-99/Tc-99m production using non-HEU sources under the 2012 American Medical Isotope Production Act.[11] The NNSA funded commercial partnerships to establish Mo-99 US-based production. While many firms signed up for the challenge, NorthStar is the only company in the market today.

The seven-year NNSA-NorthStar collaborative work led to the first FDA-approved non-uranium based Mo-99/Tc-99m production process in the US since 1989. The RadioGenix® System, its flagship product, received initial FDA approval in February 2018 for sterile sodium pertechnetate Tc-99m injection production, meeting US Pharmacopeia (USP) standards for Mo-99. Subsequent approvals for its cGMP Beloit manufacturing facility, along with issued

[9] *Technologies Enabling Nuclear Medicine Imaging (Frost & Sullivan, May 2018)*
[10] *https://www.northstarnm.com/development/radioisotope-pipeline/*
[11] *https://www.ncbi.nlm.nih.gov/books/NBK396175/*

guidance by the Nuclear Regulatory Commission (NRC), sanctioned the product's commercial deployment late in 2018.

"Today US nuclear pharmacies have an FDA-approved, domestic, non-uranium based Mo-99 source and a generating system for Tc-99m for the first time in approximately 30 years."

—James T. Harvey, Ph.D., Senior Vice President and Chief Science Officer

RadioGenix® System

Courtesy of NorthStar

The RadioGenix® System: Domestic, Reliable, Clean

First-of-its-kind, the RadioGenix® System is a flexible, high-tech separation platform for processing non-uranium/non-HEU based Mo-99. The technology leverages two production routes using naturally occurring Molybdenum (nMo)—a mixture of seven isotopes—as starting material.

Neutron capture—First developed in the 1970s, NorthStar upgraded the chemistry and processing for 21st-century technology design. The company uses the University of Missouri Research Reactor, MURR®, to add a neutron to the Mo-98 isotope—about 24% of nMo—for Mo-99. In the near future, NorthStar will irradiate a concentrated form of Molybdenum (>95% Mo-98) to improve production yields for Neutron Capture by a factor of four.

Neutron 'knock-out'—A longer-term strategy that complements Neutron Capture. NorthStar worked with an electron accelerator manufacturer to bring this cutting-edge approach to the market. It relies on high-power electron accelerators to knock-out a neutron from the Mo-100 isotope to produce Mo-99. Since there is only 9.6% abundance of Mo-100 in naturally occurring Molybdenum, NorthStar will also irradiate a concentrated form of Molybdenum (>95% Mo-100).

Source Vessel

Courtesy of NorthStar

NorthStar envisages using both Neutron Capture Mo-99 produced in Missouri and Neutron Knock-out Mo-99 produced in Wisconsin to

ensure highly reliable domestic supply throughout the week, every week of the year.

The company puts the liquid moly into Source Vessels shielded with tungsten and ships these containers to radiopharmacies across the US. With the automated isotope separation platform installed on-site, the nuclear pharmacy operator puts the Source Vessel in the device, like placing a battery. The RadioGenix® System extracts the Tc-99 from the moly and delivers the critical medical radioisotope in a vial ready for patient use.

Frost & Sullivan points out that other competing suppliers mostly use uranium-based moly produced overseas. Also, unlike HEU and LEU-sourced Mo-99, by using nMo, NorthStar's system is environmentally friendly—U-235 generates a vast amount of long half-life radioactive waste.

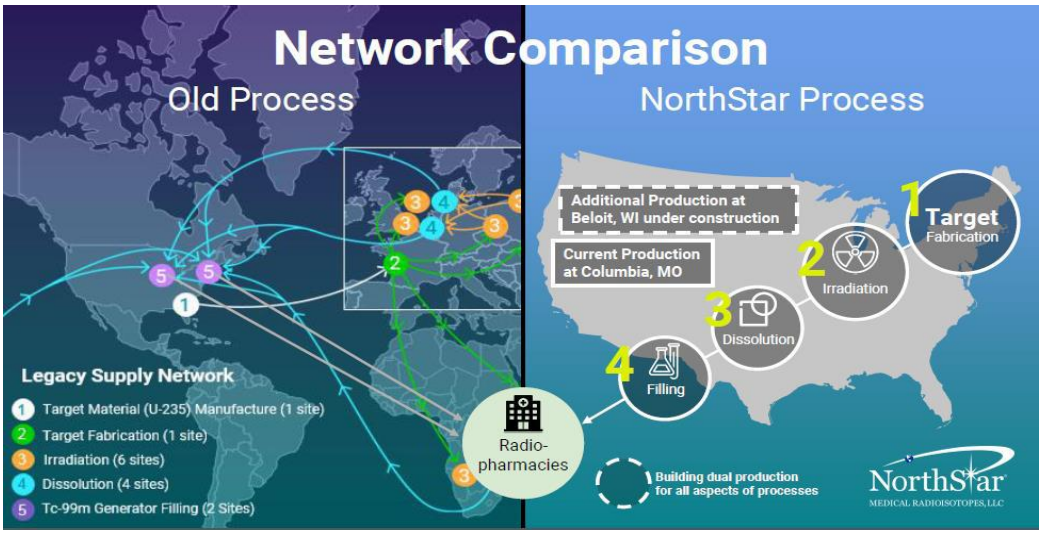
"We started with Mo-99/Tc-99m because it is widely used, cost-effective, and very good at diagnosing CAD and some forms of cancer. The link to nuclear proliferation and environmental problems around Moly-99 was fortuitous. We address the supply, proliferation, and environmental issues by using molybdenum instead of uranium."

—Steve Merrick

Supply Chain Paradigm Shift

Before the RadioGenix technology, the US supply chain depended solely on foreign Mo-99 sources, with frequent, sometimes severe, interruptions. Frost & Sullivan believes that NorthStar's end-to-end solution, both Mo-99 supplier and Tc generator manufacturer, truly revolutionizes the US medical radioisotope industry. As the first domestic supplier and the only vertically integrated company, it streamlines the supply chain, mitigates risks along the process, and minimizes care disruptions; at the same time, Mo-99 supply reliability stabilizes the market prices, enabling more predictable costs for healthcare providers.

Unprecedented Supply Chain Vertical Integration



Courtesy of NorthStar

One year after its first device installation, NorthStar boasts over 52 weeks of uninterrupted domestic Mo-99 supply for US healthcare providers. The company is placing a system a week on average and anticipates having about 30 operational sites by the end of the first quarter in 2020.

"It is very exciting what is happening at NorthStar. Last week you came to our rescue with extra source vessels during both generator suppliers' shortages. I really thought in the beginning that the RadioGenix system would just be extra material, but we have fully worked it into our profile and our production runs. It has become part of our family."

—Nuclear Pharmacy Owner

Paving the Road towards Market Leadership

Meeting stringent regulatory standards constitutes a substantial hurdle across the healthcare industry. It takes millions of dollars and about five to seven years to build, equip, and validate isotope processing and manufacturing facilities—both by the FDA and Federal / State Nuclear Regulators—creating a formidable barrier to entry.

NorthStar is growing steadily, establishing a strong foothold with US radiopharmacy customers while scaling up capacity. It has a contract for 8 electron accelerators; the first pair will be ready next year for installation in the Beloit, Wisconsin isotope processing and manufacturing facility. The company is also adding processing capacity in Columbia, Missouri, to increase Mo-99 production. NorthStar anticipates having up to 60 installed systems by the end of 2020, and around 300 by the end of 2023, ensuring consistent US moly supply.

NorthStar is in preliminary discussions with European and Japanese potential partners and is confident its production technology is applicable to both Asia and Europe. With an established regional supply, the company commits to providing a reliable supply and predictable pricing to international customers, while eliminating harmful, radioactive waste. Still early in discussions, NorthStar envisions a successful roll-out on those markets.

"We are very optimistic that, as we execute our expansion plans over the next few years, we will make Mo-99 supply issues a thing of the past."

—Steve Merrick

NorthStar prioritizes its isotope pipeline to meet evolving market demands. It is currently working on actinium-225 and copper-67 for therapeutic applications.

Frost & Sullivan classifies NorthStar at the forefront of innovation, with approximately a three- to five-year competitive advantage and considerable market potential. SPECT's expanding clinical utility offers an insight into the company's economic future.

Frost & Sullivan projects single-digit market growth for the next several years, driven by cardiology as well as growing clinical indications, e.g., neurodegenerative diseases.[12] Furthermore, an aging population will increase utilization rates exponentially. With estimates of nearly 1.6 billion people worldwide projected into the 65 years and over cohort

[12] *Analysis of the United States Molecular Imaging Equipment and Radiopharmaceuticals Market, Forecast to 2023 (Frost & Sullivan, March 2017)*

by the year 2050[13], the rising incidence and prevalence of cardiovascular diseases and cancer alone result in potentially millions of new SPECT procedures.

Frost & Sullivan analysts thus conclude that NorthStar is exceptionally well-positioned to capitalize on emerging needs and opportunities while supporting nuclear medicine's evolving role in value-based care.

Conclusion

Single-photon emission computed tomography (SPECT) using technetium-99m (Tc-99m) tracer technology accounts for 80% of all nuclear medicine procedures worldwide.[14] While making up around 50% of the global market, the United States (US) was solely dependent on international sources for Tc-99m's parent isotope, molybdenum-99 (Mo-99 or moly), until recently.[15] Additionally, with the nuclear medicine industry relying on a small number of critical stakeholders, unexpected supply chain changes cause significant disruptions affecting care delivery and patient outcomes.

Frost & Sullivan's own research identifies Wisconsin-based NorthStar Medical Radioisotope's (NorthStar) RadioGenix® System as a disruptive, innovative separation platform for processing non-uranium/non-highly enriched uranium-based Mo-99. As the first US-based company to achieve production in more than 30 years, vertically integrated NorthStar ensures reliable Mo-99/Tc-99m US supply with predictable pricing for essential diagnostic imaging procedures while eliminating harmful radioactive waste—addresses moly availability, nuclear proliferation, and environmental concerns.

Frost & Sullivan believes that NorthStar is exceptionally well-positioned to capitalize on emerging needs and opportunities while supporting nuclear medicine's evolving role in value-based care; as such, NorthStar earns the 2020 Frost & Sullivan Visionary Innovation Leadership Award.

[13] *https://www.census.gov/content/dam/Census/library/publications/2016/demo/p95-16-1.pdf*
[14] *https://www.oecd-nea.org/med-radio/docs/sen-hlgmr2017-2.pdf*
[15] *https://www.ncbi.nlm.nih.gov/books/NBK487238/*

Significance of Visionary Innovation Leadership

A Visionary Innovation Leadership position enables a market participant to deliver highly competitive products and solutions that transform the way individuals and businesses perform their daily activities. Such products and solutions set new, long-lasting trends in how technologies are deployed and consumed by businesses and end users. Most important, they deliver unique and differentiated benefits that can greatly improve business performance as well as individuals' work and personal lives. These improvements are measured by customer demand, brand strength, and competitive positioning.

Understanding Visionary Innovation Leadership

Visionary Innovation is the ability to innovate today in the light of perceived changes and opportunities that will arise from Mega Trends in the future. It is the ability to scout and detect unmet (and as yet undefined) needs and proactively address them with disruptive solutions that cater to new and unique customers, lifestyles, technologies, and markets. At the heart of visionary innovation is a deep understanding of the implications and global ramifications of Mega Trends, leading to correct identification and ultimate capture of niche and white-space market opportunities in the future.

Key Benchmarking Criteria

For the Visionary Innovation Leadership Award, Frost & Sullivan analysts independently evaluated two key factors—Focus on the Future and Best Practices Implementation—according to the criteria identified below.

Focus on the Future

Criterion 1: Focus on Unmet Needs
Criterion 2: Visionary Scenarios through Mega Trends
Criterion 3: Growth Pipeline
Criterion 4: Blue Ocean Strategy
Criterion 5: Growth Performance

Best Practices Implementation

Criterion 1: Vision Alignment
Criterion 2: Process Design
Criterion 3: Operational Efficiency
Criterion 4: Technological Sophistication
Criterion 5: Company Culture

Best Practices Recognition: 10 Steps to Researching, Identifying, and Recognizing Best Practices

Frost & Sullivan Awards follow a 10-step process to evaluate Award candidates and assess their fit with select best practice criteria. The reputation and integrity of the Awards are based on close adherence to this process.

	STEP	OBJECTIVE	KEY ACTIVITIES	OUTPUT
1	**Monitor, target, and screen**	Identify Award recipient candidates from around the globe	• Conduct in-depth industry research • Identify emerging sectors • Scan multiple geographies	Pipeline of candidates who potentially meet all best-practice criteria
2	**Perform 360-degree research**	Perform comprehensive, 360-degree research on all candidates in the pipeline	• Interview thought leaders and industry practitioners • Assess candidates' fit with best-practice criteria • Rank all candidates	Matrix positioning of all candidates' performance relative to one another
3	**Invite thought leadership in best practices**	Perform in-depth examination of all candidates	• Confirm best-practice criteria • Examine eligibility of all candidates • Identify any information gaps	Detailed profiles of all ranked candidates
4	**Initiate research director review**	Conduct an unbiased evaluation of all candidate profiles	• Brainstorm ranking options • Invite multiple perspectives on candidates' performance • Update candidate profiles	Final prioritization of all eligible candidates and companion best-practice positioning paper
5	**Assemble panel of industry experts**	Present findings to an expert panel of industry thought leaders	• Share findings • Strengthen cases for candidate eligibility • Prioritize candidates	Refined list of prioritized Award candidates
6	**Conduct global industry review**	Build consensus on Award candidates' eligibility	• Hold global team meeting to review all candidates • Pressure-test fit with criteria • Confirm inclusion of all eligible candidates	Final list of eligible Award candidates, representing success stories worldwide
7	**Perform quality check**	Develop official Award consideration materials	• Perform final performance benchmarking activities • Write nominations • Perform quality review	High-quality, accurate, and creative presentation of nominees' successes
8	**Reconnect with panel of industry experts**	Finalize the selection of the best-practice Award recipient	• Review analysis with panel • Build consensus • Select recipient	Decision on which company performs best against all best-practice criteria
9	**Communicate recognition**	Inform Award recipient of Award recognition	• Present Award to the CEO • Inspire the organization for continued success • Celebrate the recipient's performance	Announcement of Award and plan for how recipient can use the Award to enhance the brand
10	**Take strategic action**	Upon licensing, company is able to share Award news with stakeholders and customers	• Coordinate media outreach • Design a marketing plan • Assess Award's role in future strategic planning	Widespread awareness of recipient's Award status among investors, media personnel, and employees

The Intersection between 360-Degree Research and Best Practices Awards

Research Methodology

Frost & Sullivan's 360-degree research methodology represents the analytical rigor of our research process. It offers a 360-degree-view of industry challenges, trends, and issues by integrating all 7 of Frost & Sullivan's research methodologies. Too often companies make important growth decisions based on a narrow understanding of their environment, leading to errors of both omission and commission. Successful growth strategies are founded on a thorough understanding of market, technical, economic, financial, customer, best practices, and demographic analyses. The integration of these research disciplines into the 360-degree research methodology provides an evaluation platform for benchmarking industry players and for identifying those performing at best-in-class levels.

360-DEGREE RESEARCH: SEEING ORDER IN THE CHAOS

About Frost & Sullivan

Frost & Sullivan, the Growth Partnership Company, enables clients to accelerate growth and achieve best-in-class positions in growth, innovation and leadership. The company's Growth Partnership Service provides the CEO and the CEO's Growth Team with disciplined research and best practice models to drive the generation, evaluation and implementation of powerful growth strategies. Frost & Sullivan leverages more than 50 years of experience in partnering with Global 1000 companies, emerging businesses, and the investment community from 45 offices on six continents. To join our Growth Partnership, please visit http://www.frost.com.