Domestic Production of Mo99

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ABSTRACT

NorthStar Medical Radioisotopes has, since 2007, been working towards developing a domestic production of Mo99. We are currently pursuing two parallel paths which will lead to an initial domestic production capability of Mo99 by mid-2012. The first short-term path uses the Missouri University Research Reactor to produce Mo99 via irradiation of natural molybdenum targets and will be in place mid-2012. This route can also be transitioned to enriched molybdenum-98 targets in the future as market needs dictate thus increasing production dramatically. The second long-term approach is to utilize electron linear accelerators to irradiate enriched molybdenum-100. This long-term approach is supported by a Cooperative Agreement from NNSA and will be operational in 2014. Our presentation will describe both approaches, the TechneGen™ system for producing HSA Tc99m from LSA Mo99, and NorthStar's approach to the market. The TechneGen FDA submission status will also be described.

Introduction

NorthStar has embarked on two separate approaches to supplying the domestic market with Mo99. The Short Term Solution ("Short Term" in that NorthStar expects to be in production in the "short term"), which will be operational in mid-2012, utilizes the Missouri University Research Reactor (MURR) and the following transmutation:

$$Mo98\ (n,\gamma)\ Mo99$$

The advantage of this approach is that NorthStar can initiate production utilizing ultra-high purity natural molybdenum (tungsten <1ppm) and transition to using enriched molybdenum-98 as market conditions warrant. With enriched molybdenum-98, NorthStar will be capable of providing up to 50% of the US need to the domestic market. NorthStar and MURR executed the production agreement in March 2011.

NorthStar's Long Term Solution ("Long Term" in that NorthStar expects to be in production in the "long term")is to use electron linear accelerators to irradiate enriched molubdenum-100 producing Mo99 via:

$$Mo100\ (\gamma,n)\ Mo99$$

This process will be operational during CY2014. Once operational, both solutions will be used to supply not only the US market but also overseas. It is important to note that both routes produce LSA Mo99 thus these two approaches require NorthStar's TechneGen™ technology in order to guarantee success.

NorthStar intends to utilize both of the Short term and Long Term Solutions in parallel once the processes have been established.

Short Term - Missouri University Research Reactor

MURR has previously produced Mo99 by the (n,γ) method and the MURR facility has an outstanding operational record as shown in Figure 1. NorthStar will begin production at MURR upon approval of its NDA for TechneGen™ by the FDA. NorthStar is in discussions with UPS Express Critical® (a 24/7/365 service) to handle shipping to client pharmacies. Spent Mo99 solutions returned ground to NorthStar for recycling of the molybdenum. MURR is capable of producing up to 50% of the US need per week. Since MURR in the past has produced Mo99 via they route, they have the unique experience needed to make the project successful and thus there are no licensing issues to overcome.

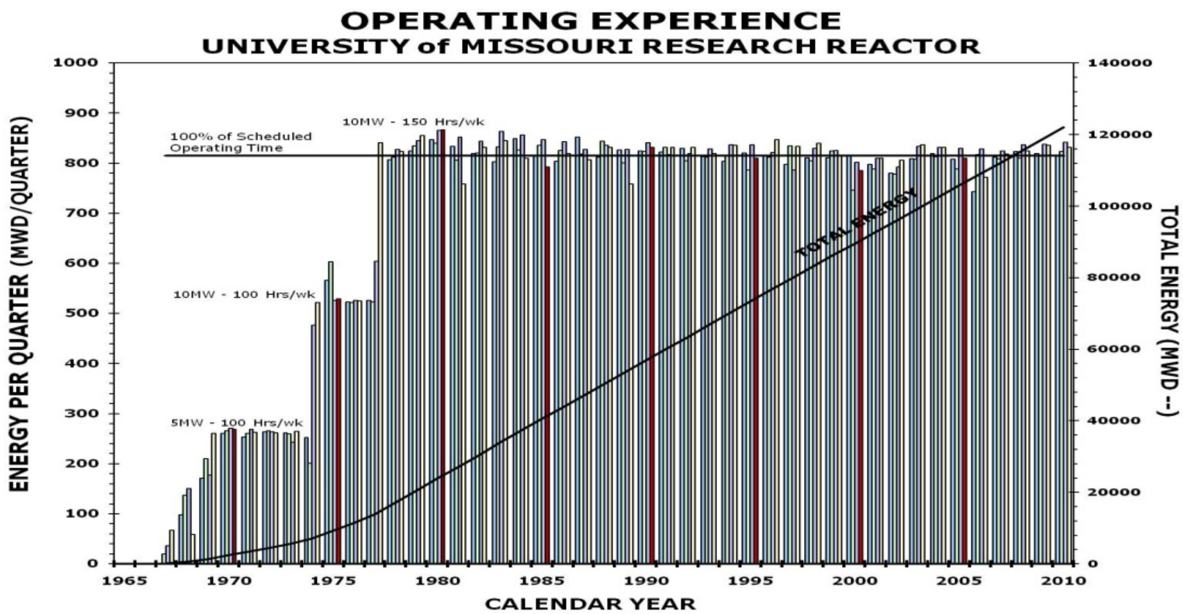

Figure 1: MURR Operating Experience

Long Term - LINAC Moly (γ, n)

NorthStar has been active in production of Mo99 via electron linear accelerators since November 2007, the previous NRU shutdown period. While working on a CRADA at INL, NorthStar became aware of a paper study conducted in this area and, with the understanding that IP licensed by NorthStar from the PG Research Foundation could solve the LSA Mo99 challenge, began in-depth this effort. NorthStar funded an effort at Rensselaer Polytechnic Institute in early 2008 to validate the 1999 INL publication. At that time, the effort produced small quantities of Mo99 and validated calculated estimates and experimental results were comparable. Over the ensuing three years, we, with NNSA support, have developed an approach to deliver greater than 3,000 6 D Ci from the facility in design to the market starting in 2014.

The NorthStar facility will house up to 16 LINAC machines where one target set per day is capable of producing more than 2,000 Ci of Mo99 per day. Of this 16, 12 are needed at a minimum to meet production goals leaving up to 4 as spares to fill in for surge needs or to take over in the event an accelerator is down for maintenance. The clear advantage of the LINAC approach with 16 accelerators available is redundancy in production – a serious issue that has proven to plague the current production efforts in the past. The model provides steady, redundant production on a daily basis. Again, UPS Express Critical® to handle shipping to client pharmacies and the return of spent Mo99 solutions returned for recycle of the enriched Mo100. The facility location was announced this past summer and will be located in Beloit, WI. The Beloit location has the advantage of being adjacent to two interstate systems providing easy access to Milwaukee, Rockford, Madison, or Chicago and their respective airports. Further, the site is located immediately adjacent to a new power substation being built with NorthStar requirements incorporated in the design by Alliant Energy. The new station will have redundant power from two separate sources with automatic switching gear to ensure the NorthStar facility is rarely without power. The provider has shown NorthStar that this arrangement is expected to result in no more than one power outage of greater than one hour every 4 years without the redundant sources feeding the station and with two separate sources, outages, other than momentary auto switching, expected to be non-existent.

Process Byproducts and Waste

Last year's OECD Report clearly noted that costs of handling and disposal of waste will be added to the cost of Mo99 going forward. Further, the FOA for the NNSA Mo99 program clearly stated applicant could not assume DOE would take back the waste associated with LEU production. For both n,γ and γ,n Mo99 production processes by NorthStar we use stable molybdenum isotopes as target material thus the cost of disposal to NorthStar byproducts & waste is a small fraction of the total costs. NorthStar expects to need to deal only with Class A waste. As no fission process is used and no uranium is in the target material, the NorthStar process yields no uranium, plutonium, or fission products (including off gases such as xenon isotopes) into the process stream or resulting process waste**.** The bulk of NorthStar's process waste will be handled allowing for Mo99 and Tc99m to decay away before recycling the enriched Mo100. NorthStar does need to be mindful that long-lived Tc99g is strictly controlled to 300mCi per cubic meter and thus will need to be monitored carefully. Figure 2 visually depicts this advantage for non-LEU based approaches to Mo99 production.

	HEU produced Mo99	**LEU produced Mo99**	**Mo99 Production Processes (2)**
Uranium including U238, U235, U234	**Yes**	**Yes**	**No**
Plutonium-239	**Yes**	**Yes**	**No**
Fission Products	**Yes**	**Yes**	**No**
Alpha emitting waste	**Yes**	**Yes**	**No**
Long-lived radioisotopes (1)	**Yes**	**Yes**	**Yes**

Figure 2: Visual Comparison of LEU vs. non-uranium production of Mo99

1. Includes long-lived technetium-99g
2. The cost to dispose of NorthStar's waste is <1¢ per mCi of Technetium-99m.

TechneGen™

The precursor to TechneGen was developed by the PG Research Foundation beginning in the late 1990's. NorthStar licensed all the IP associated with the development in 2005 and has pursued the development of the technology through two additional generations over the ensuing six years.

Figure 3 provides a visual of the TechneGen system. The TechneGen system is designed to facilitate ease of installation, training and use. It is virtually a hands-off operation once started and the protocols can be easily followed on the associated computer is desired.

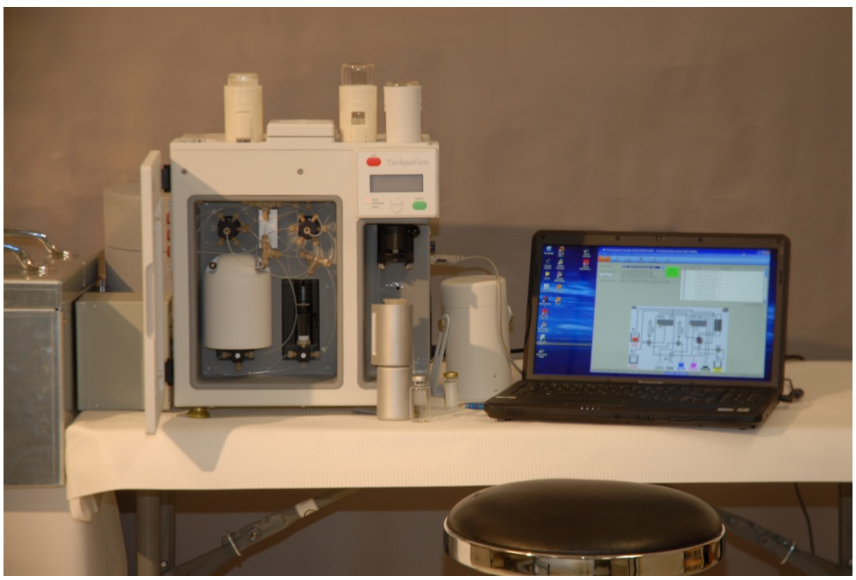

Figure 3: TechneGen Tc99m Generating System

Specific attributes of TechneGen are:

- Single Control System for up to (4) Mo99 Isotope Sources (scalable & shielded) allowing nuclear pharmacist here-to-fore unavailable options in generating management and combinations each day - pooling of generators, including those nearly spent, in such a manner increases Tc99m output and productivity,
- Tc99m production is unaffected by Mo99 production route – TechneGen can use LSA Mo99 produced from natural Mo, enriched Mo, neutron activation, photon activation, and it could even use HSA Mo99 produced from LEU – TechneGen is the only generating system currently available that can make this claim and it represents the first new piece of technology introduced into the market,
- Single administrative computer capable of multiple TechneGen control with a microprocessor controlled instrument which runs independently from the PC when processing begins,
- Local shielding for Mo99 sources up to 20 Ci (USDOT Type A limit),

- Complete database history logged for each Tc99m elution – each individual step in the protocol is recorded and UTC time stamped,
- Automated, hands-off operation after prerequisites satisfied freeing the nuclear pharmacy employee to continue preparing the day's activities and minimizing worker exposure,
- Separable PC to a laboratory area – dedicated TCP/IP network link – which allows the control to be outside the "generator room".
- Additional localized shielding for Tc99m elution providing additional protection to the user,
- User Interface is optimized to reduce bioburden,
- Certified Protocols allow authorization for Tc99m elution by only those trained and authorized to operate the instrument,
- Tc99m produced after passing thru a virgin Alumina Column, and redundant (2) sterility filters,
- Spent isotope source materials completely recyclable, and
- Ease of install and daily use

NorthStar has an NDA application in process. We have received comments on our proposed Monograph and Microbiology test plans and is proceeding with FDA comments incorporated into those test plans. We expect to submit the NDA in January 2012. Examples of technical results in operating the previous generation of the instrument, the ARSII with the protocol to be run on TechneGen are:

- *Run 4 cycles, ~10 days each cycle, to mimic nuclear pharmacy operations, over a 3 month period at ANL beginning March 2010*
    - *Tc99m yields averaged >95% (industry avg. with current generators ranges from 70%-90%[1])*
    - *pH in range required by the USP (4.5-7.5)*
        - *Al breakthrough <10ppm (<10ppm required)*
        - *Mo breakthrough <0.015μCi/mCi Tc99m (<0.15μCi/mCi required)*

- *ARSII installed at NRC-Canada in October 2009*
    - *Tc99m yields averaging >90%; purity 99% (>95% required)*
    - *pH in range required by Eu. Pharm. (4-8)*
        - *Al breakthrough <10ppm (<10ppm required)*
        - *Mo breakthrough <0.015μCi/mCi Tc99m (<0.15μCi/mCi required)*
    - *Sterile product (even <u>without</u> sterile input solutions and columns)*

Of most importance in the data presented above is the fact that the TechneGen system yield higher than industry average Tc99m yields and the product is sterile even without sterile input solutions or columns. The higher yield results in lower costs for the nuclear pharmacy.

Additional data gathered by researchers at the National Research Council of Canada is depicted in Figures 4 and 5.

QC test	Criterion	^{99m}Tc tagged to tetrofosmin	^{99m}Tc tagged to MDP
Appearance	Clear, colourless	Pass	Pass
pH	5-9	6	6
Aluminum	< 10 ppm	Pass	Pass
Radiochemical purity	>95%	99%	99%
Radionuclidic purity	^{99}Mo/^{99m}Tc < 0.00015	Pass	Pass

Figure 5: QC data for Tc99m eluted

QC test	Criterion	^{99m}Tc-tetrofosmin	^{99m}Tc-MDP
Appearance	Clear, colourless	Pass	Pass
pH	7.5-9 and 6.5-7.5	6	7
Radiochemical purity	>90%	98.3%	96.5%[1]
Radionuclidic purity	^{99}Mo/^{99m}Tc < 0.00015	Pass	Pass
Bacterial enodtoxins	<0.125 EU/mL	Pass	Pass
Sterility	Sterile	Sterile	Sterile

Figure 6: QC data for Tc99m tagged compounds

The above data, while limited, demonstrates the ability of the TechneGen system to produce compliant Tc99m and tagged compounds with the Tc99m generated. Do not that again, without sterile input solutions or separation columns, the final tagged product is not only sterile but passes the endotoxin test. Further compounding studies performed for NorthStar by a separate third party yielded compounding yields >99% using sestimibi while also producing a sterile and endotoxin free product.

Supply Chain

One of the most important attributes of the NorthStar approach is how we approach the market with a product that is lower in costs than the current market model. Figure 6 depicts the current market model. In Figure 6, one can see that the current market supply chain is fractionated amongst a number of players. Each of these players has a costs and profit structure added to the product they provide. In some cases, the same player may represent more than one piece of the supply chain but multiple overheads, G&A, and profit is added into the costs as the Mo99 product proceeds to market.

On the other hand, one can note from Figure 7 that NorthStar's approach flattens the supply chain. The distinct difference here is that from raw material to shipment to the nuclear pharmacy, NorthStar has only a single cost structure – a single overhead, a single G&A and a single profit. Combined with the technological approach NorthStar is using, this costs structure we believe allows NorthStar to be the lowest cost producer in the market. Further, NorthStar is pursuing options for raw material acquisition that will allow it to further reduce its costs structure.

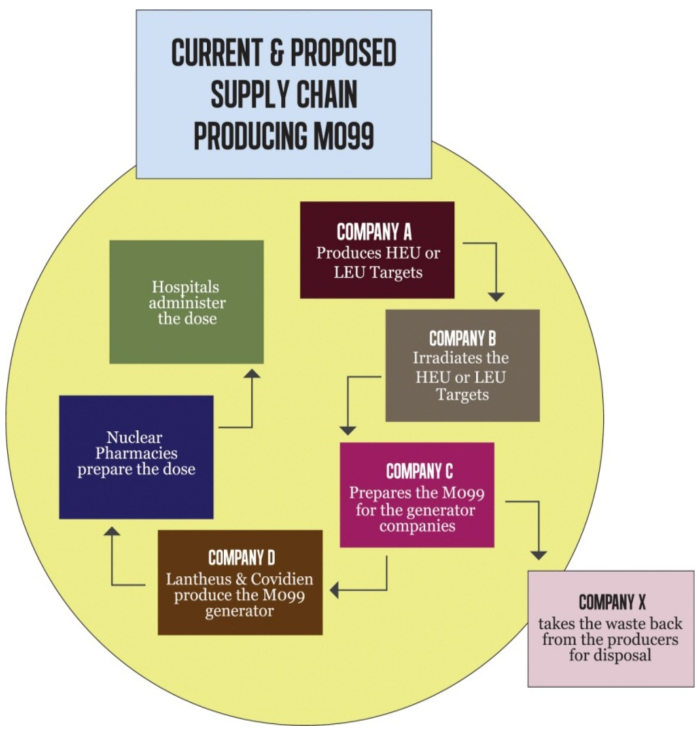

Figure 6: Representation of Current Market Supply Chain

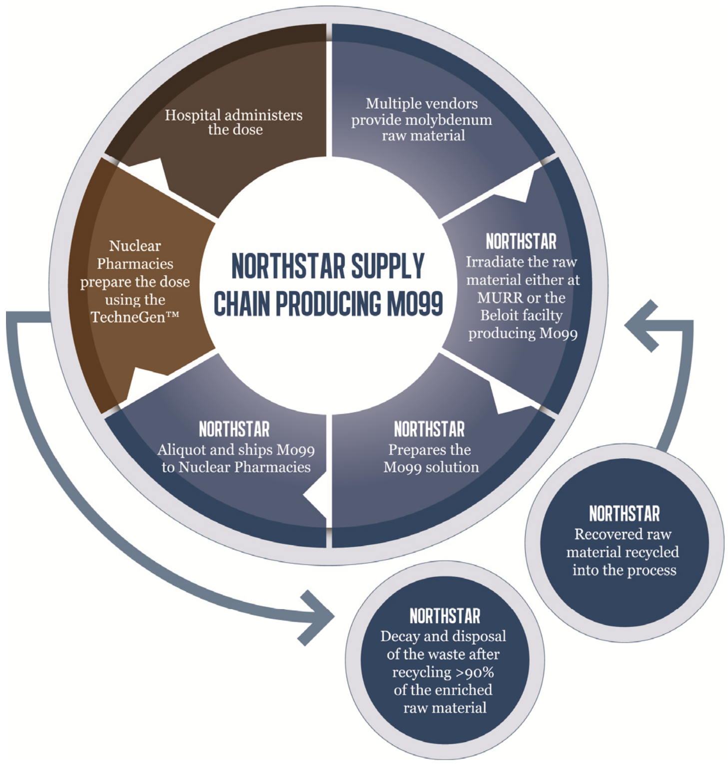

Figure 7: NorthStar Supply chain

Summary

Both approaches to producing Mo99 for the US domestic market have been well demonstrated by NorthStar. Our relationship with MURR uses a long standing production route and the LINAC approach applies reliable accelerator technology to the production of Mo99.
NorthStar has produced Mo99 from both production methods meets the European Pharmacopeia monograph for Mo99 and NorthStar's TechneGen™ system has consistently produced Tc99m with yields and purity levels drastically improved over current generators and has demonstrated that the Tc99m meets the USP monograph.

Both (n,γ) and (γ,n) Mo99 production processes by NorthStar use stable molybdenum isotopes as target material. In both cases, the enriched target material is recoverable thus reducing the cost of the Mo100 or Mo98.

Both production methods present a more reliable, cost-effective supply in that:

- MURR's reactor up time performance cannot be matched by any reactor at least in the US,
- NorthStar's (γ,n) LINAC Moly produced is completely redundant where down time will be transparent to the customer,

- NorthStar performs most steps in the supply chain – one corporate overhead, G&A and profit.

These factors along with the low cost associated with the disposing of the waste produced by both of NorthStar's processes, the increased Tc99m output and productivity attributed to the TechneGen™'s performance, increased compounding yields and the low cost of NorthStar's raw material, offer NorthStar a powerful competitive advantage.

References

[1] *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*, 2nd Edition, by Richard J. Kowalsky and Steven W. Falen, published by the American Pharmacists Association, 2004, p. 218