



NorthStar Progress in Establishing a Domestic Mo-99 Source

Mo99 Topical Meeting

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NorthStar's Short Term and Long Term Solution



Short Term and Long Term Solutions

▶ Short Term Solution

- Missouri University Research Reactor -
 - Contract in place effective March 2011
 - It is expected that this solution will eventually be able to produce 50% of the US requirement

▶ Long Term Solution

- NorthStar's LINAC methodology for the production of Molybdenum-99
- ▶ Once up and running both solutions will be used to supply not only the US market but also overseas.
- ▶ These two approaches require NorthStar's TechneGen™ technology in order to guarantee success



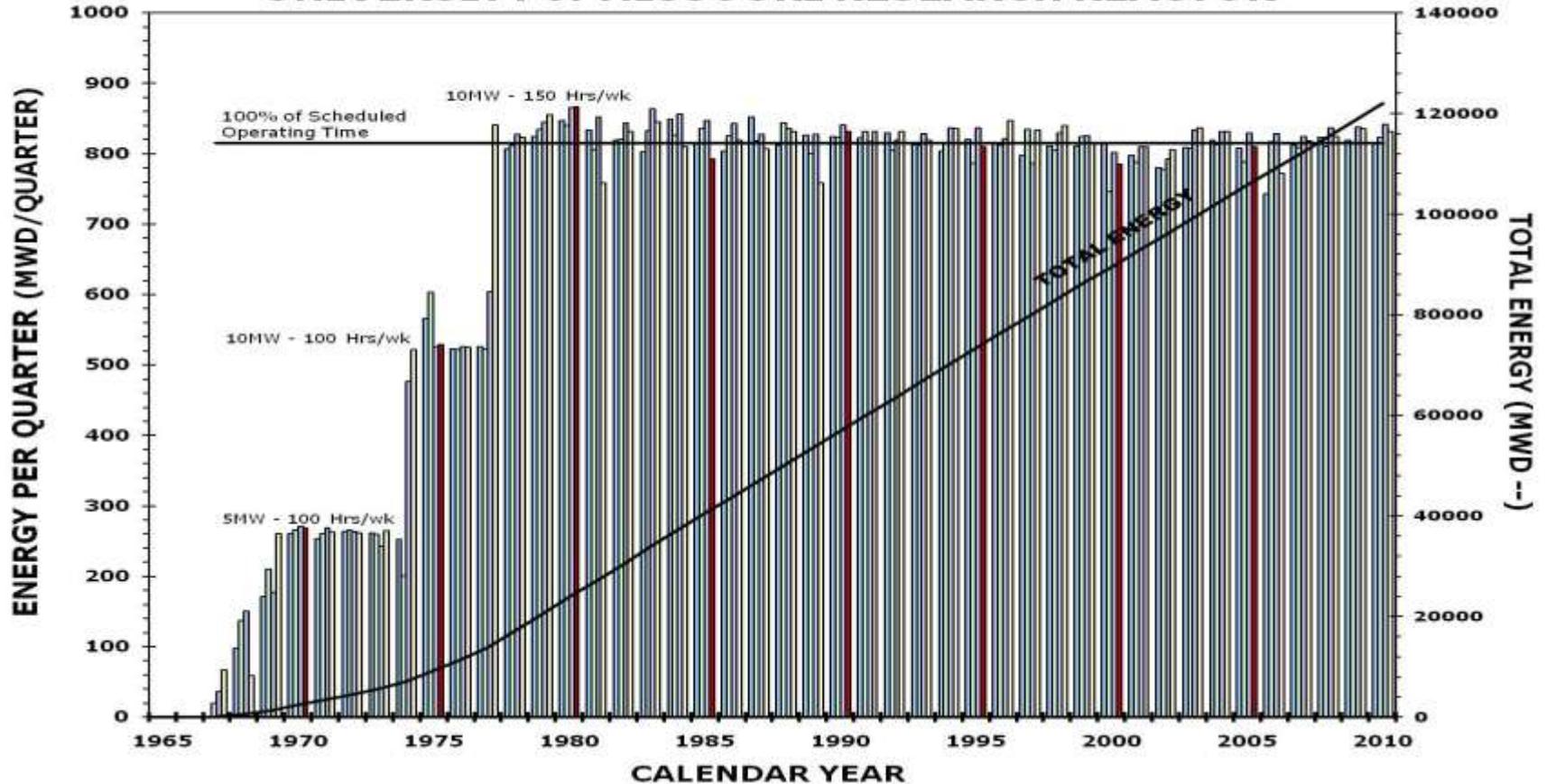
Missouri University Research Reactor (n, γ)

Production of Mo99 via Reactor at MURR

- MURR has produced Mo99 previously in large quantities by the (n, γ) method,
- MURR has outstanding operational record,
- MURR/NorthStar production agreement announced March 1st, 2011
- Production upon FDA approval,
- Spent Mo99 solutions returned for recycle,
- MURR capable of producing up to 3,000 6-day Ci per week, and
- No licensing issues.

Production of Mo99 via Reactor at MURR

OPERATING EXPERIENCE UNIVERSITY of MISSOURI RESEARCH REACTOR



BEST SHORT TERM SOLUTION TO ESTABLISH SIGNIFICANT DOMESTIC MARKET SUPPLY



LINAC Moly (γ , n)



Production of Mo99 via LINAC

- NorthStar has been active in this field since Nov 2007
 - NorthStar funded effort at RPI in early 2008 to validate the 1999 INL publication
 - Produced small quantities of Mo99 in that study and validated calculated estimates and experimental results were comparable
- NorthStar facility will house LINAC machines capable of producing >3,000 6D Ci per week
 - SA of Mo99 ~10Ci/g
 - one target set ~2,500Ci Mo99
 - steady, redundant production on a daily basis matched to meet market demand
 - NNSA supported via Cooperative Agreement
- Facility location - Beloit, WI
 - Located immediately adjacent to a new power substation - will have redundant power from two separate sources with automatic switching gear



Licensing and Permitting Progress

- No licensing or permitting issues associated with the MURR operation
- NorthStar's NEPA EA for the LINAC facility was completed and signed off with a FONSI on August 24, 2012
- NorthStar submitted its initial Rad License applications to the State of WI on December 31, 2012
 - "Machines" license covering the LINACs
 - Initial "machines" license received on January 15, 2013 for up to 16 LINACs
 - "Materials" license covering the radioactive materials generated on site under review



TechneGen™

Technegen



- Single Control System for up to (4) Mo99 Isotope Sources (scalable & shielded),
- Chemistry for Tc99m production is unaffected by Mo99 production route: Natural Mo material, enriched Mo, neutron activated, photon activated, or fission (uranium)
- Single administrative computer capable of multiple Technegen control
- Microprocessor controlled instrument which runs independently from the PC when processing begins,
- Local shielding for Mo99 sources,
- Complete database history logged for each Tc99m elution,
- Automated operation after prerequisites, and
- Separable PC to a laboratory area – dedicated TCP/IP network link.

TechneGen Instrument



- Localized shielding for Tc99m elution,
- Chemistry “kits” developed to control use of the instrument,
- User Interface optimized to reduce bioburden,
- Certified Protocols allow authorization for Tc99m elution
- Local display on instrument for progress review,
- Tc99m produced after passing thru a virgin Alumina Column, and redundant (2) sterility filters,
- Spent isotope source materials completely recyclable, and
- Ease of install, training and daily use – nuclear pharmacist assisted in design

NorthStar & the FDA

- ▶ FDA Interaction started August, 2009 and has continued with Type C, Type B and NDA Orientation meetings to discuss the NDA process

- ▶ FDA filings to date:
 - DMF for MURR produced Mo99 submitted on September 12, 2012
 - DMF for TechneGen submitted on October 22, 2012
 - NDA for TechneGen submitted on January 4, 2013.
 - 7 Amendments submitted
 - NDA Orientation Meeting on February 6, 2013
 - NorthStar received notice on March 18, 2013 the NDA had passed administrative review permitting “substantive” review
 - NorthStar received a PDUFA goal date of November 4, 2013.

Molybdenum-99 Results Summary

- Mo99 produced at MURR with natural molybdenum targets
- Average Mo99 half-life from 3 independently produced lots from MURR was 66.01 hours vs. 65.94 hours (EU chapter 5.7)
- Average Radioactivity Assay (referenced to time of calibration) was 98%
- Radiochemical purity (RCP) averaged 100% with an R_f average of 0.92 vs. expected R_f of ~0.90
- Gamma analysis: ^{131}I <0.005%; ^{103}Ru <0.005%; ^{132}Te <0.005%; ^{122}Sb <0.04%; total all other γ <0.01% (no other gammas detected)

Molybdenum-99 Results Summary

- Sr89 and Sr90 tested to the lower Sr90 specification; result: $<6E-5\%$
- Total alpha results $<1E-7\%$
- Appearance of clear, pale straw passes requirement of “clear and colorless or almost colorless”
- Alkalinity pH >12

Technetium-99m Results Summary

- Mo99 produced at MURR (3 lots) with natural molybdenum targets were mounted on 3 different TechneGen instruments and run X10 each over a 14 day period
- Average Tc99m half-life from the produced Mo99 from MURR was 6.01 hours (5.95 hours – 6.06 hours) vs. 6.01 hours (NIST)
- Appearance of clear & colorless with no particulate matter and stable ≥ 12 hour period
- Radiochemical purity (RCP) averaged 100% with an R_f average of 0.93 vs. expected R_f of ~ 0.90

Technetium-99m Results Summary

- Gamma analysis:
 - Total β/γ <0.1 $\mu\text{Ci}/\text{mCi}$ Tc99m;
 - I131 <0.05 $\mu\text{Ci}/\text{mCi}$ Tc99m;
 - Ru103 <0.05 $\mu\text{Ci}/\text{mCi}$ Tc99m
 - Additionally,
 - Sb122 <0.05 $\mu\text{Ci}/\text{mCi}$ Tc99m;
 - Sb124 <0.05 $\mu\text{Ci}/\text{mCi}$ Tc99m;
 - Mo99 <0.05 $\mu\text{Ci}/\text{mCi}$ Tc99m.
 - No other gammas detected.
- pH 5.6 ± 0.2 ; within 4.5 – 7.5

Technetium-99m Results Summary

- Mo99 breakthrough $<0.01 \mu\text{Ci}/\text{mCi}$ Tc99m at $t=0$ vs. USP requirement of $<0.15 \mu\text{Ci}/\text{mCi}$ Tc99m. Supported by stable Mo concentration in product of <20 ppb.
- Aluminum result: <1.5 ppm vs. USP required <10 ppm
- Sr89 and Sr90 tested to the lower Sr90 specification and found to be $<6\text{E}-5 \mu\text{Ci}/\text{mCi}$ Tc99m
- Total alpha found to be $<1\text{E}-6 \mu\text{Ci}/\text{mCi}$ Tc99m
- Appearance of clear & colorless with no particulate matter and stable ≥ 12 hour period
- Endotoxin <0.25 EU/mL vs. required <2.5 EU/mL
- 14 day sterility: all samples Pass

Tc99m Results Summary Kit Labeling

- NorthStar labeled 3 different kits, suggested by FDA, over a 14 day period
 - Initial (day 1 or day 2) and at end of run (day 8, day 9 or day 10) with Tc99m at t=0 or t=expire (per kit instructions)
 - Sestimibi average: t=0: 98.2%; t=expire: 98.7% vs. Kit required >90%
 - MAG3 average: t=0: 99.4%; t=expire: 99.3% vs. Kit required >90%
 - Ceretec average: t=0: 88.1%; t=expire: 89.1% vs. Kit required >80%

Microbiology Testing

- ▶ Component Level (Reagents & Cartridges)
 - Sterility & Endotoxin
 - Package Integrity
 - Stability Testing
 - 2 Year Test Protocol, 1 year completed to date
 - Growth Promotion Studies of Reagents
 - No growth seen from 8 microbe inoculates

- ▶ System (TechneGen Instrument)
 - Drug Product Filtration
 - Hold Time/Bioburden
 - 0 CFUs
 - Process Simulation (Media Fill)
 - No turbidity (2X)
 - Cleaning & Sanitization
 - >3 log reduction in microbe inoculate (3x)
 - System Depyrogenation:
 - > 3 log reduction

Summary

- NorthStar has produced Mo99 from both production methods and has demonstrated that its Mo99 meets the European monograph for Mo99
- NorthStar's TechneGen™ technology has consistently produced Tc99m 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
 - With (γ,n) or (n, γ) Moly, the target material is recoverable thus reducing the cost of the Mo100 or Mo98
- Both production methods present a more reliable supply
 - 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



Discussion