Qualification of LEU Produced Mo-99 TechneLite® Generators for National Health Regulatory Approval

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1st Mo-99 Topical Meeting
December 5, 2011
Santa Fe, New Mexico

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Lantheus Medical Imaging

Lantheus Medical Imaging

Headquarters:	Billerica, Massachusetts
Offices:	Puerto Rico, Canada, Australia
Marketed Products:	9
Products in Development:	3

Global Presence:	• Approximately 600 employees
	  • R&D, Clinical and Medical affairs
	  • Sales & Marketing
	  • Manufacturing and Distribution
	• 25% revenue international sales

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Lantheus Product Portfolio

ABLAVAR™
gadofosveset trisodium

Cardiolite®
Kit for the Preparation of
Technetium Tc99m Sestamibi for Injection

DEFINITY®
VIAL FOR (Perflutren Lipid Microsphere)
INJECTABLE SUSPENSION

NEUROLITE®
Kit for the Preparation of
Technetium Tc99m Bicisate for Injection

TechneLite®
Technetium Tc 99m Generator

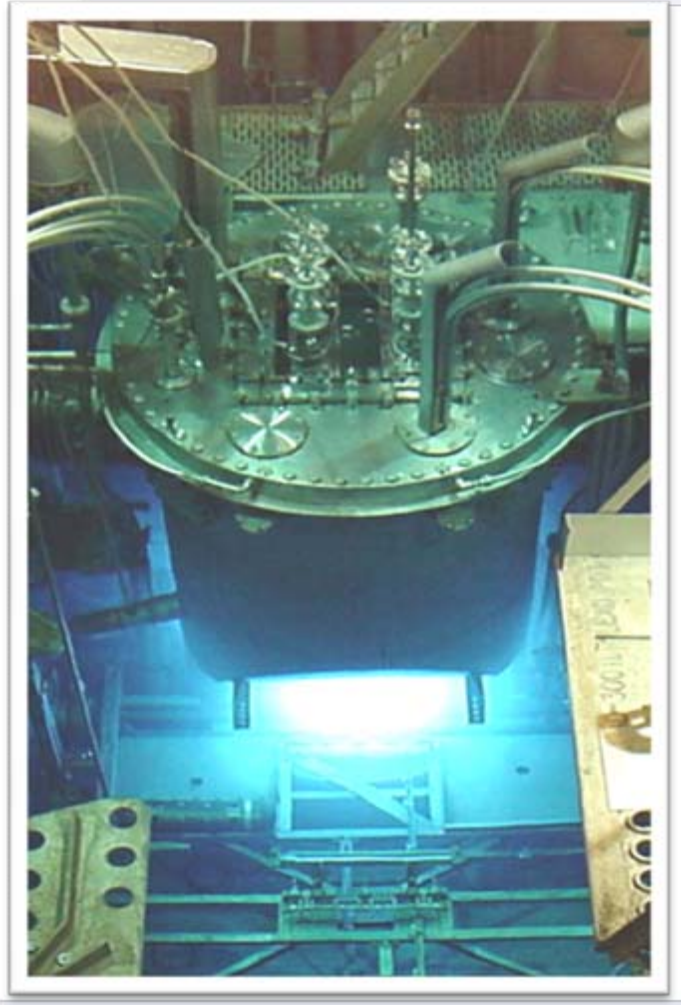
Xenon Xe
133 Gas

Gallium
Gallium Citrate
Ga 67 Injection

Thallium
Thallous Chloride
Tl 201 Injection

Lantheus
Medical Imaging

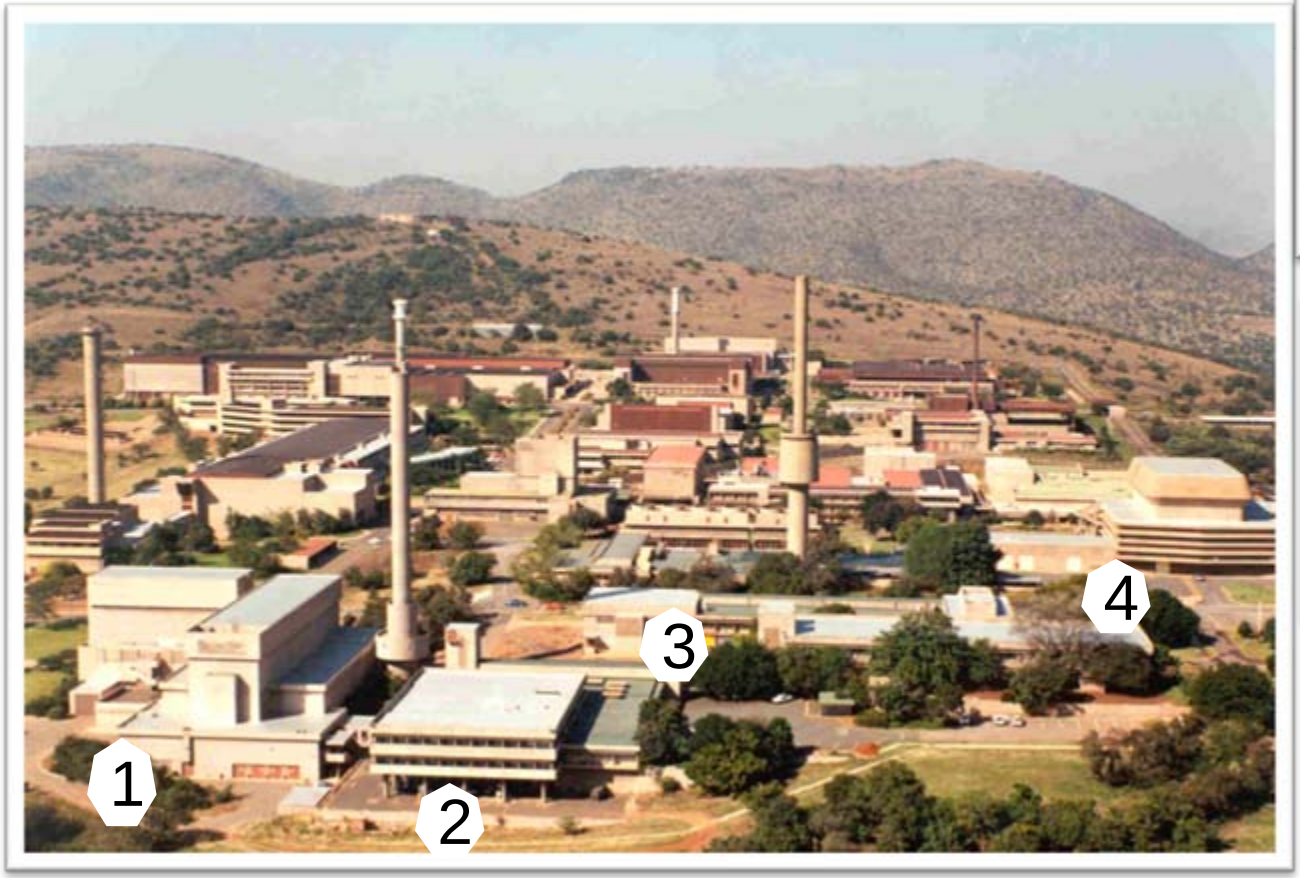
NTP Radioisotopes (Pty) Ltd.



- 20 MW SAFARI Research Reactor with exceptional availability
- 10 Hot Cells dedicated to Mo-99 manufacturing
- Proven leading supplier of Mo-99
- Full LEU conversion from HEU (Fuel and Target plates)
- Supplier to 60 Countries

NTP
Actively enhancing life

NTP
Actively enhancing life



1 – Radiochemical Production Plant
2 – Commercial Office
3 – Radiopharmaceutical Plant
4 – SAFARI-1

ANSTO Health

manufacture and advance the use of radiopharmaceuticals to improve the health of Australians

- Lucas Heights, Australia; 110 employees
- OPAL research reactor (commissioned 2007)
  - 300 days at high power /year
- Good Manufacturing Practice (GMP)
  - radiochemical and radiopharmaceutical facilities
- International Mo-99 producer
  - 100% LEU /LEU
- Supply >85% of Au Diagnostic nuclear medicine
  - 220+ nuclear medicine centers
- Gentech® generators:
  - Australia, New Zealand, SE Asia

ANSTO Health Product Portfolio

Iodine-131
Sodium Iodide [^{131}I]
Therapy Capsules

Iodine-131
Sodium Iodide [^{131}I]
Solution BP for Therapy

Iodine-131
Sodium Iodide [^{131}I] Injection B.P.

Gentech®
Molybdenum [^{99}Mo] Technetium [^{99m}Tc]
Sterile Generator

Chromium-51 Chromium [^{51}Cr]
Edetate Injection BP

QUADRAMET
Samarium (^{153}Sm) Lexidronam Pentasodium Injection

LeukoScan®
(sulesomab)

Iodine-123
MIBGen® Iobenguane [^{123}I]
Injection Diagnostic

Lyophilised Kits
MDP Skeleton Agent

Pentastan DTPA Reagent
Single and Multi Dose Vials

ansto

Regulatory Requirements

- **NTP, ANSTO submitted Drug Master File (DMF) to FDA/HC**
  - Lantheus given access to applicable portion(s) of DMF via Letter of Authorization following Lantheus access request
- **FDA/HC reviews the DMF when a submission is made referencing it**
  - **Demonstrate chemical equivalence in side-by-side comparison of radiolabeled kits (anionic, cationic and neutral)**
- **Provide data to demonstrate that Tc-99m produced from the LEU Mo-99 generator meets USP monograph**
  - Does not contain radionuclidic impurities greater than that specified
- **Information formally submitted to FDA in Prior Approval Supplement (21 CFR § 314.70)**
  - Notifiable Change to HC
- **Lantheus maintained regular contact with FDA and HC prior to and during the regulatory review process**

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Qualification Runs

- Evaluation runs performed prior to executing qualification runs
- FDA/HC requires 3 independent qualification runs (no mixing)
  - Mo-99 produced only from LEU targets
- Performed on Lantheus TechneLite® commercial line
- Scheduled between commercial HEU-based production during the period of Mo-99 shortage
- Lantheus conducted extra tests to ensure that production line is clean before performing TechneLite® commercial runs

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Qualification Testing

Testing	Comments
In-Process Formulation and Filling testing	pH, Mo-99 batch activity concentration Mo-99 breakthrough and generator column assay on 100% of all units manufactured
QC Release testing (Date of Manufacture)	Functional, eluate description, pH, chemical purity, radiochemical and radionuclidic purity, radionucludic ID, Mo-99 breakthrough, sterility, endotoxin)
Stability testing	QC release testing repeated at Date of Expiry (14 days post DOM), plus beta testing at DOM and DOE
Customer Use elution simulation testing	Performed at three timepoints Elution function, Mo-99 Breakthrough, Tc-99m Yield, pH and Aluminum ion
Kit Compatibility testing	Performed on anionic, cationic and neutral kits at T0 and at expiry
Microbiological testing	Bacteriostasis and Fungistasis

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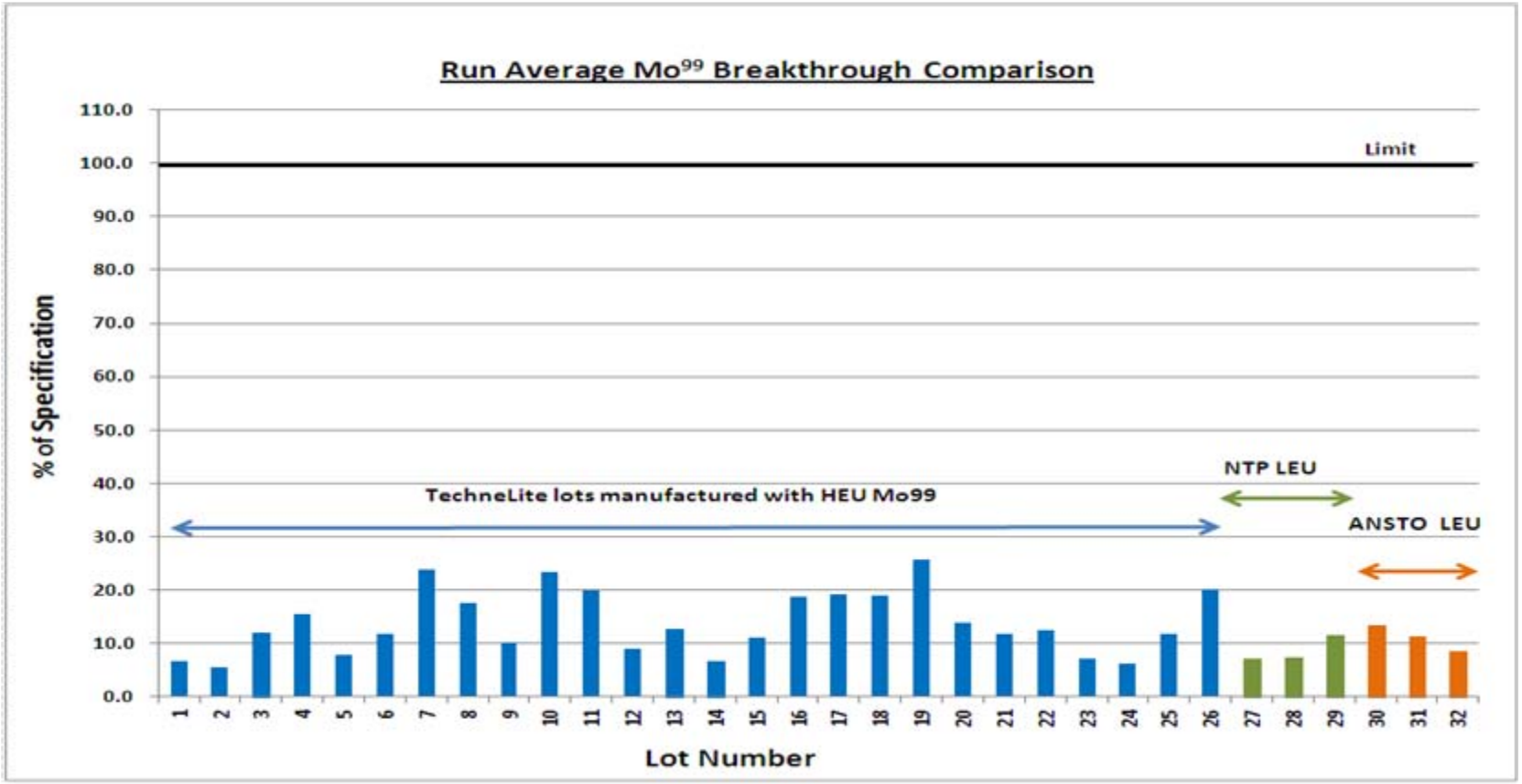
NTP Qualification Timeline

Action	Quantity	Date	Remarks
Evaluation run	32 (1-20Ci)	February 1, 2010	Full scale, but reduced testing DOM only (with customer use and sestamibi); no sterility or endotoxin
Qualification run 1	38 (1-20Ci)	July 22, 2010	Full scale, non-commercial, full testing
Prior Approval Supplement		September 8, 2010	Submitted to FDA
Supplement Approval		September 28, 2010	FDA Approval Letter
Qualification run 2	35 (1-20Ci)	September 30, 2010	Full scale, non-commercial*, full-testing
Notifiable Change (HC)		November 25, 2010	Results of 3 qualification lots
Qualification run 3	291 (1-20Ci)	December 6, 2010	Full scale, full testing Commercialized within US
Notifiable Change (HC)		March 15, 2011	No Objection letter
Routine shipments		Late May 2011	Commercial

ANSTO Health Qualification Timeline

Action	Target Source/Quantity	Date	Remarks
Evaluation run 1	CERCA; 13 (1-2Ci)	April 6, 2010	Non-commercial, 1/10th concentration DOM testing, customer use and sestamibi testing. No sterility, endotoxin
Evaluation run 2	CNEA; None	January 5, 2011	1/10th concentration due to limited activity available
Qualification run 1	CNEA; 38 (1-20Ci)	January 20, 2011	Non-commercial, full testing
Qualification run 2	CNEA/CERCA; 35 (1-20Ci)	February 3, 2011	Non-commercial, full testing
Qualification run 3	CERCA; 37 (1-20Ci)	March 30, 2011	Non-commercial, full testing
Prior Approval Supplement		March 11, 2011	Submitted to FDA
Notifiable Change (HC)		March 28, 2011	Submitted to Health Canada
Supplement Approval		May 4, 2011	FDA Approval Letter
Notifiable Change (HC)		May 30, 2011	No Objection Letter
Routine Shipments		Late May 2011	Commercial

Comparison of Run Average Mo-99 Breakthrough on TechneLite® Generator Runs Manufactured using HEU vs. LEU Mo-99



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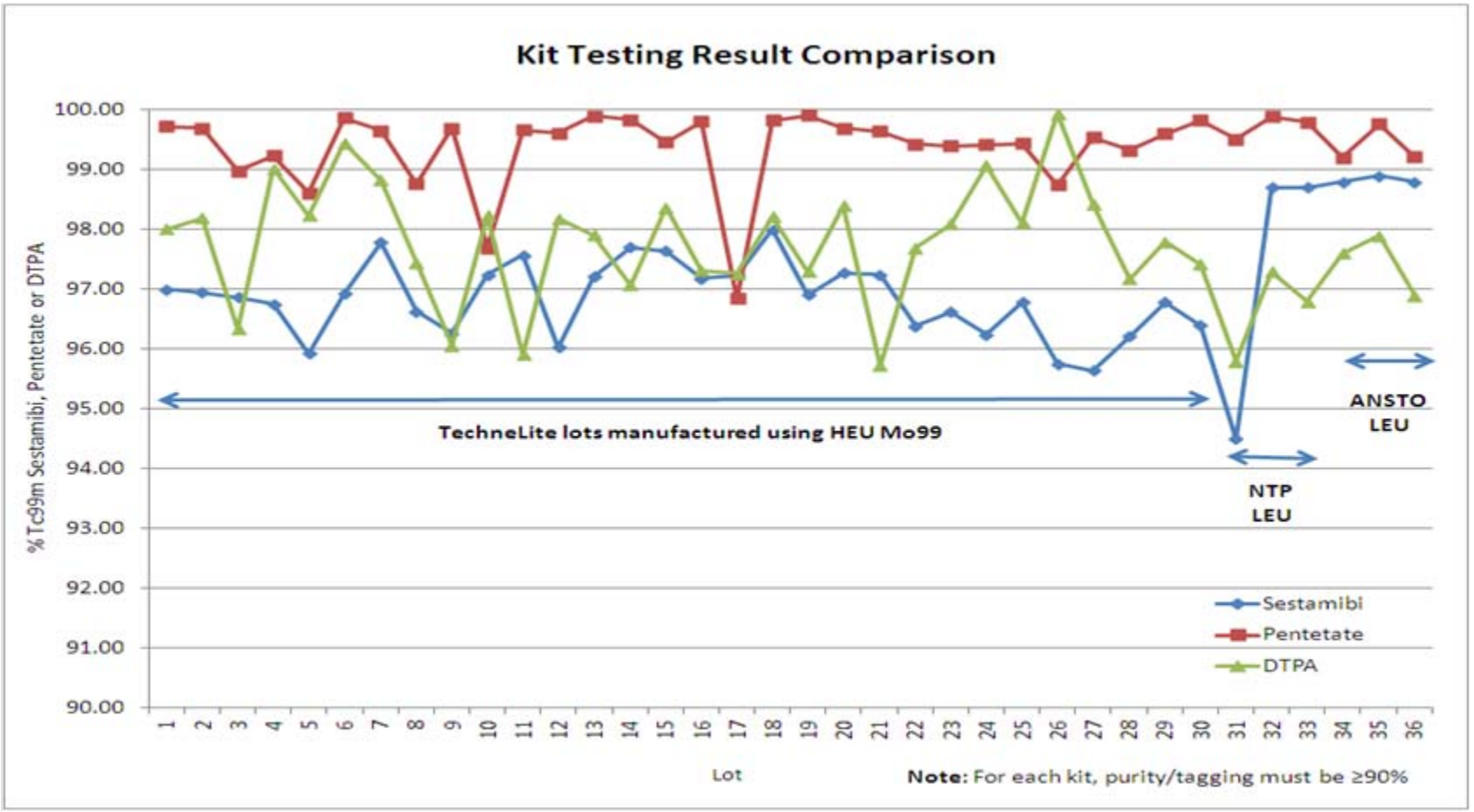
Comparison of Kit Testing results on TechneLite® Generator runs manufactured using HEU vs. LEU Mo-99



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Conclusions

- **Quality and properties of TechneLite® generators using LEU Mo-99 are equivalent to those using HEU Mo-99**
- **NTP qualification**
  - 10-11 months (FDA), 15.5-16.5 months (HC) including prep discussions
  - 8 months from 1st evaluation run to the receipt of FDA approval
- **ANSTO qualification**
  - 4 months (FDA), 5 months (HC) formal qualification process
  - 2 evaluations (1 run) in prior 9 months
- **LMI aggregate cost in range of $250,000- $500,000**
  - Mo-99 provided free of charge by NTP and ANSTO for all non-commercial validation and qualification runs; considerable expense; 100's of Ci
- **Qualification applicable only to LMI generators**

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Acknowledgements

- **Excellent cooperation and collaboration between Lantheus, NTP, and ANSTO**
- **Appreciation to FDA and HC for their efforts and cooperation in expediting review and approvals**
- **All concerned are proud that efforts resulted in first commercial approval for the use of LEU-produced Mo-99 in North America**
- **Set foundation for more secure and reliable supply of Mo-99**
  - **benefits customers, patients, and global efforts to enhance nuclear security**

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