The University of Oklahoma
College of Pharmacy

Nuclear Medicine: Radionuclides Needed

Cambridge Lecture 30 May 2013

Wendy Galbraith, PharmD, BCNP
OUHSC Nuclear Pharmacy

THE UNIVERSITY OF OKLAHOMA • COLLEGE OF PHARMACY •

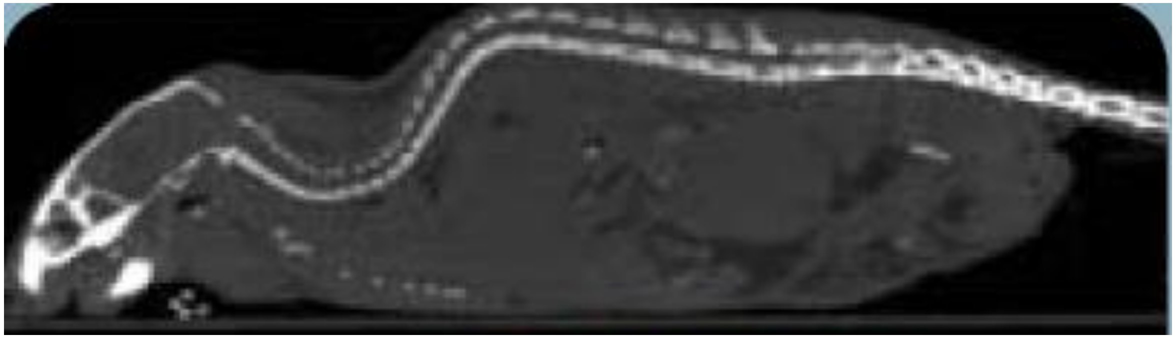
Outline

- Nuclear Medicine in the Healthcare of Patients
- Nuclear Pharmacy
- Infrastructure requirements for producing radiopharmaceuticals
- The Policy Approach to Sustainability

Radionuclides Needed

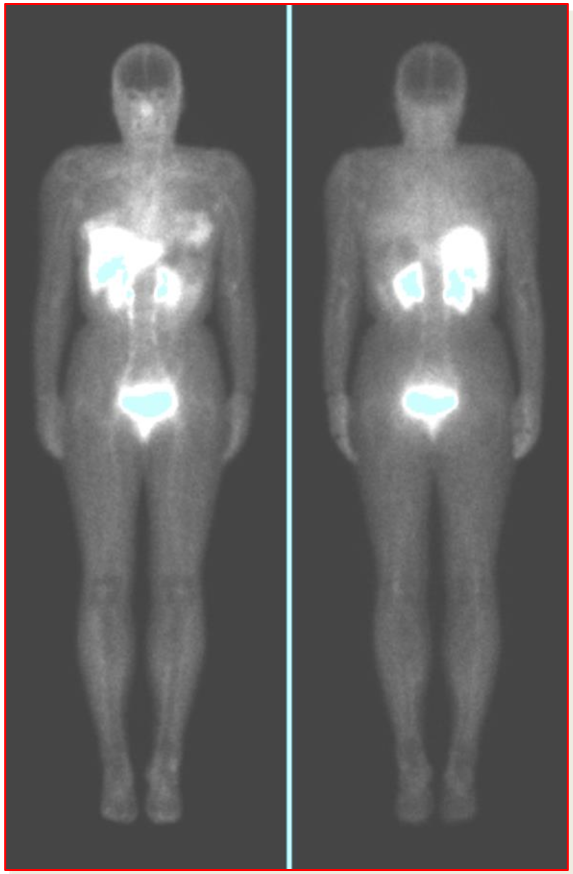
Nuclear Medicine in the Healthcare of Patients

Computed tomography vs. nuclear medicine (alive or dead)



Nuclear Medicine

- Assesses physiology and biochemistry, rather than anatomy
  - a different perspective on disease (characterization of biology)
  - earlier, more sensitive detection of disease



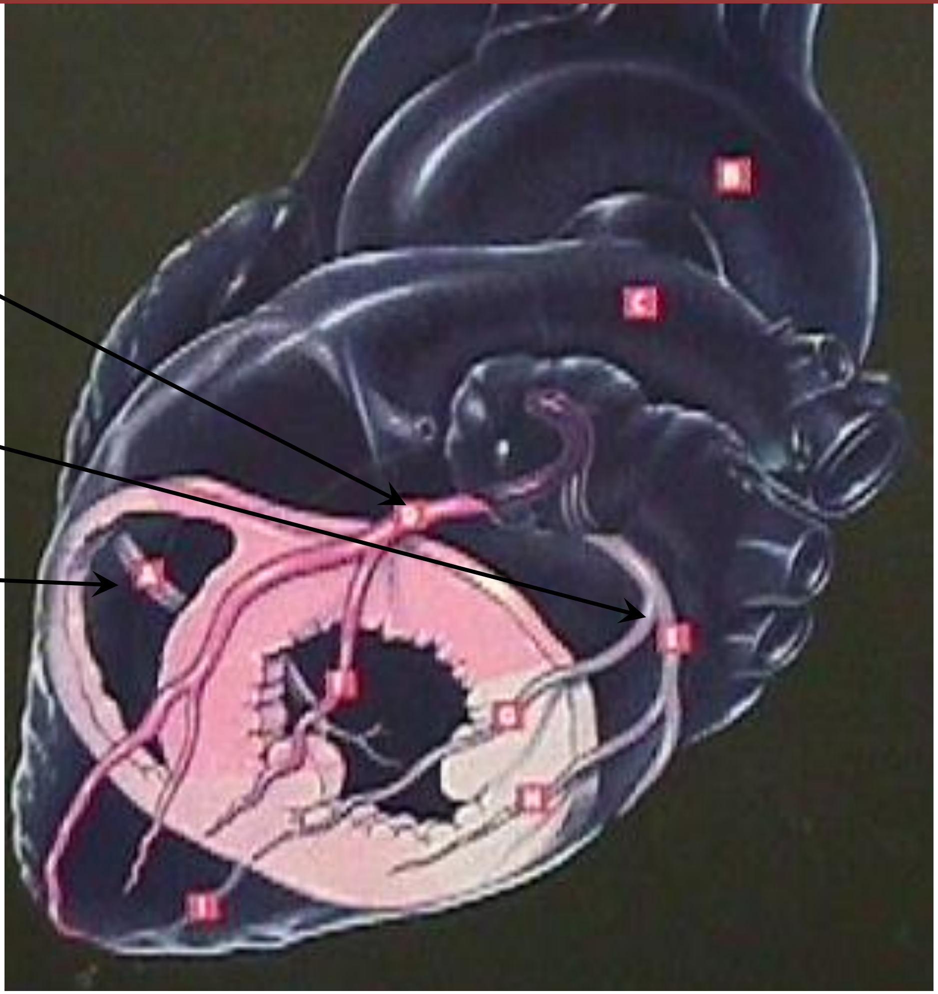
~ 35 million patients a year

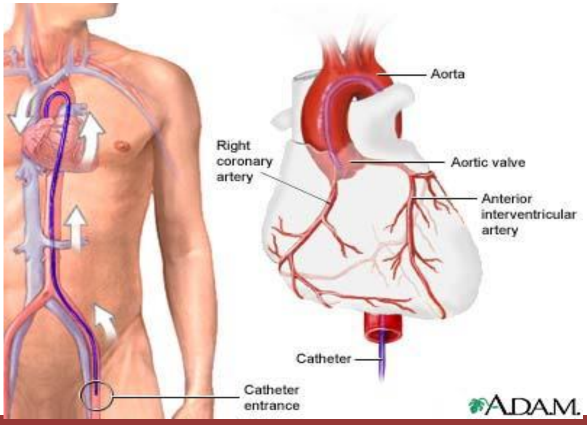
- ~ 50% North America
- ~ 40% Europe
- ~ 10% Rest of World
- Diagnostic Imaging
  - Cardiac ~ 80%
  - Oncology ~ 10%
- Therapy ~ 1%
- Global radiopharmaceutical market $3.8 billion USD in 2012 (OECD study)

Myocardial perfusion scintigraphy (MPS)

80%

- Left Coronary Artery,
  - anterior descending
- Left Coronary Artery,
  - circumflex
- Right Coronary Artery,
  - post. descending

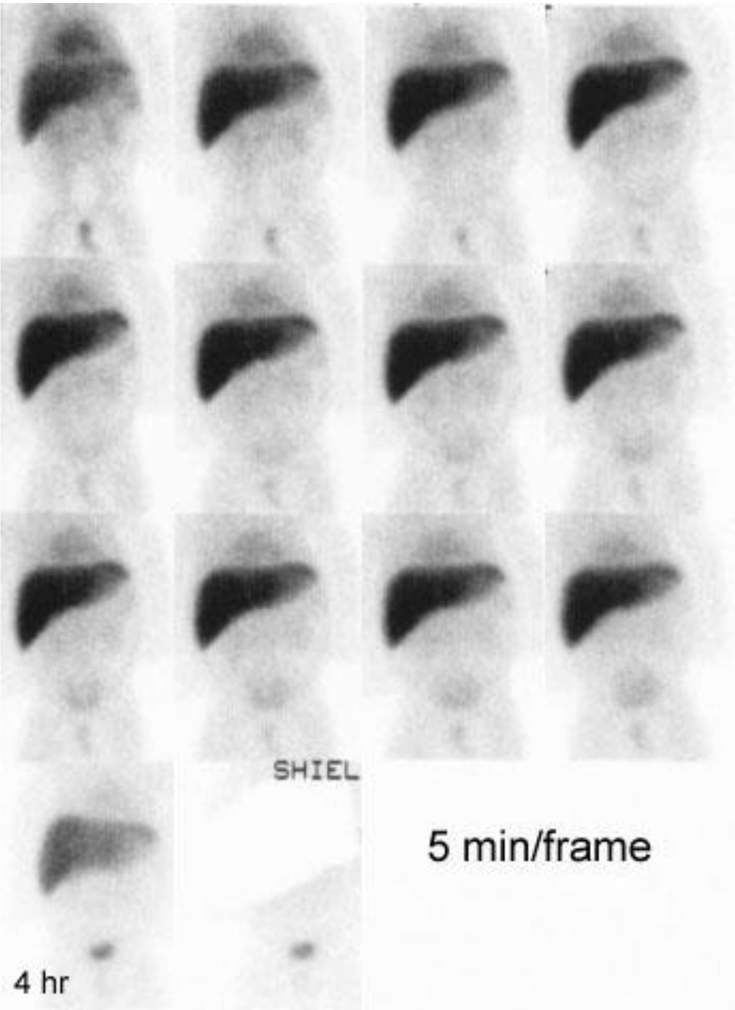




Courtesy of Dupont Pharmaceutical

Hepatobiliary Disease 3%

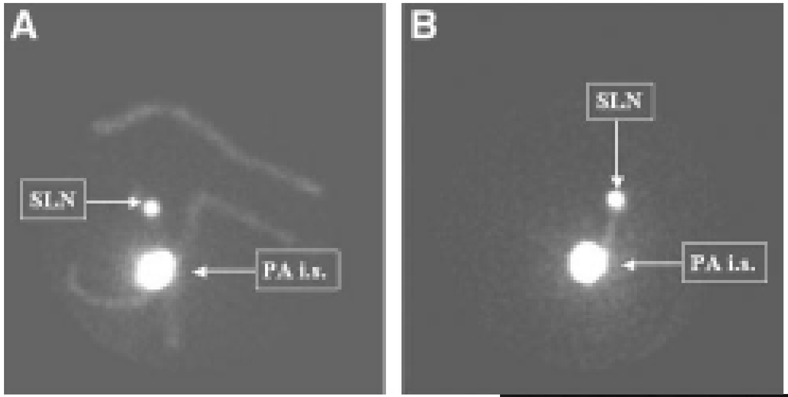
Example: Biliary Atresia

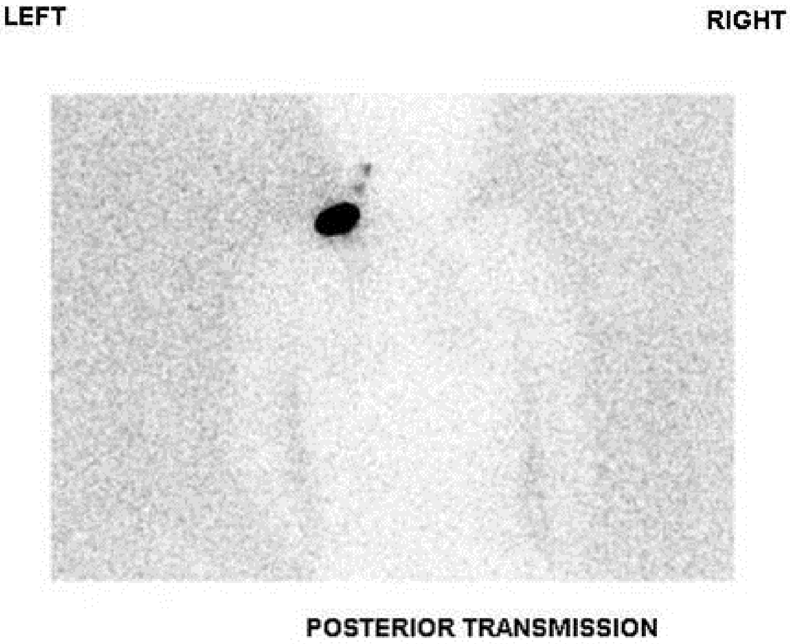


Lymphoscintigraphy (lymph mapping)

2.4%

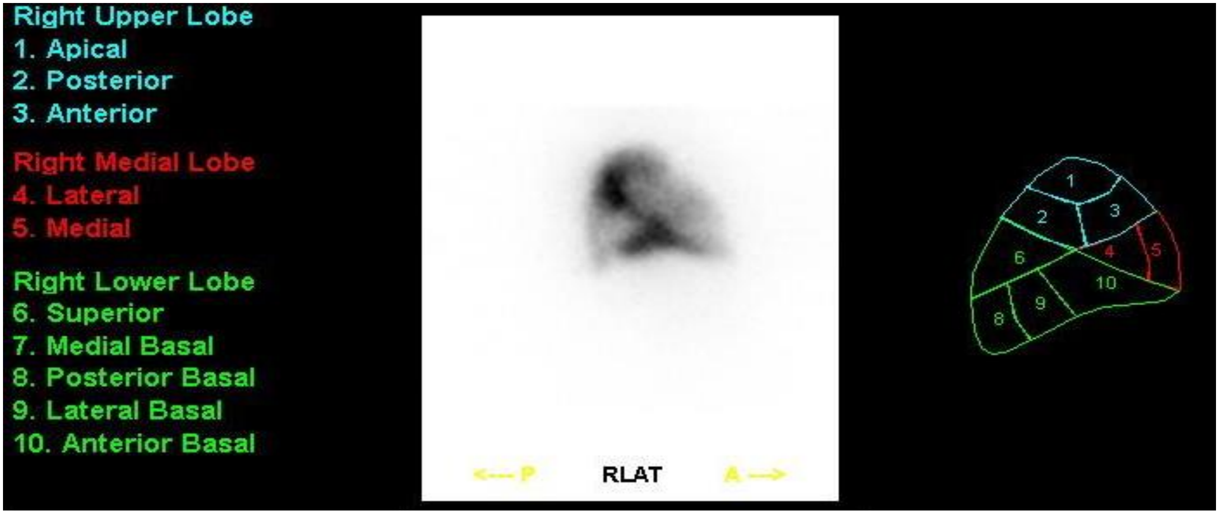
Breast





Melanoma

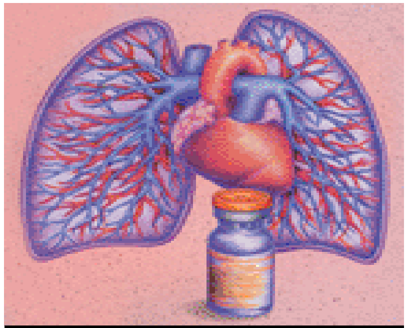
Lung and Renal Disease



Right Upper Lobe
1. Apical
2. Posterior
3. Anterior

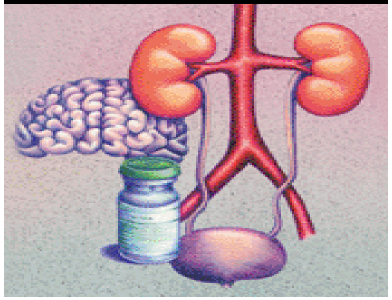
Right Medial Lobe
4. Lateral
5. Medial

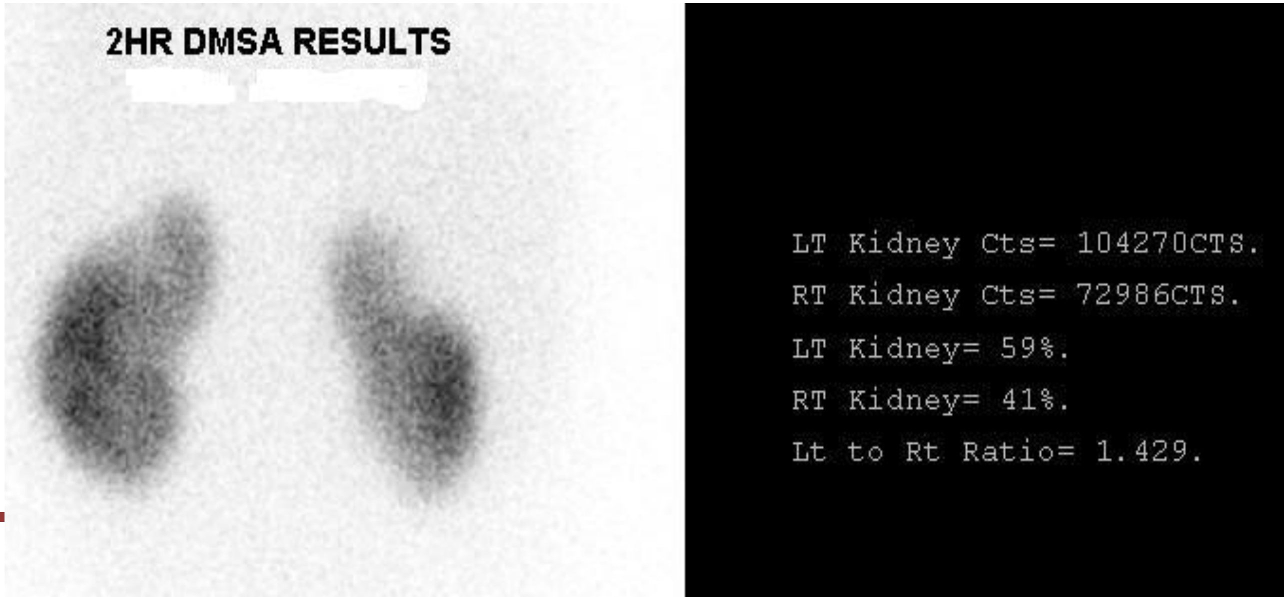
Right Lower Lobe
6. Superior
7. Medial Basal
8. Posterior Basal
9. Lateral Basal
10. Anterior Basal



0.08%

1.4%





2HR DMSA RESULTS

[redacted]

```
LT Kidney Cts= 104270CTS.
RT Kidney Cts= 72986CTS.
LT Kidney= 59%.
RT Kidney= 41%.
Lt to Rt Ratio= 1.429.
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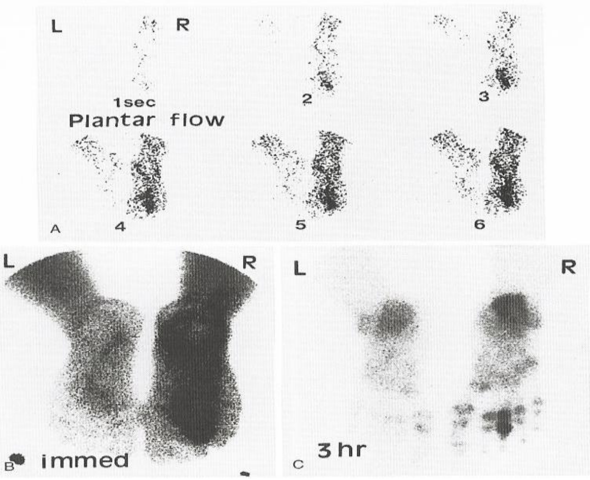
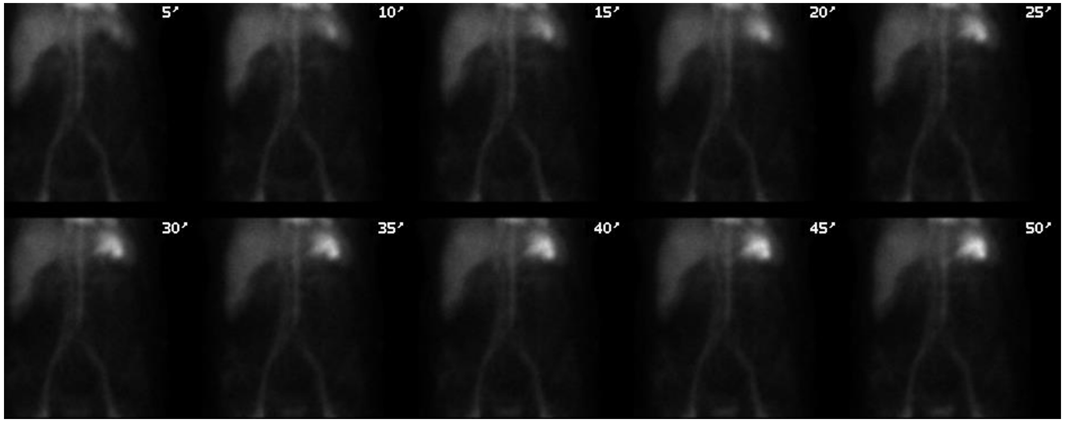
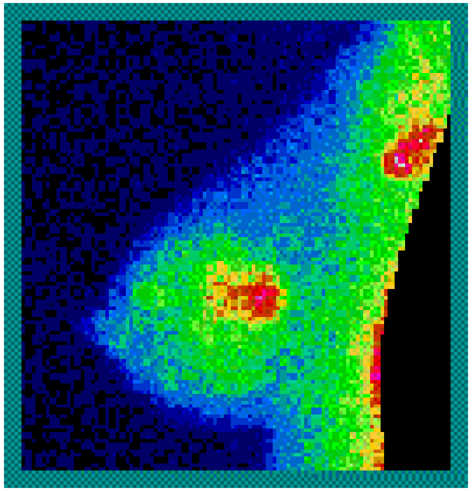
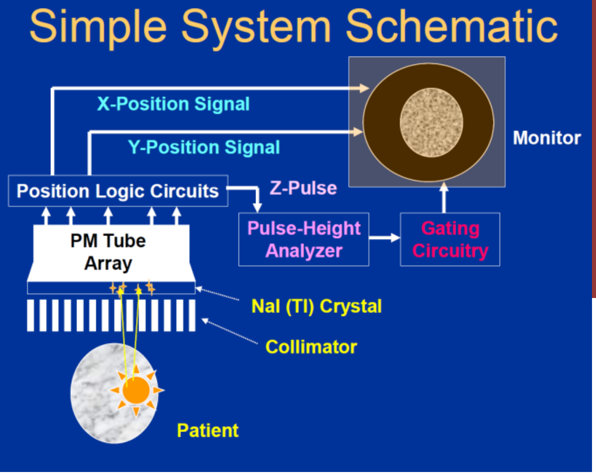
Other diagnostic radionuclide procedures 1.5%

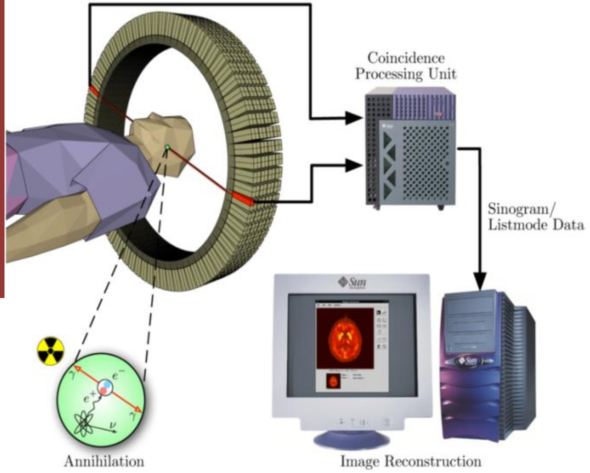






SPECT vs. PET





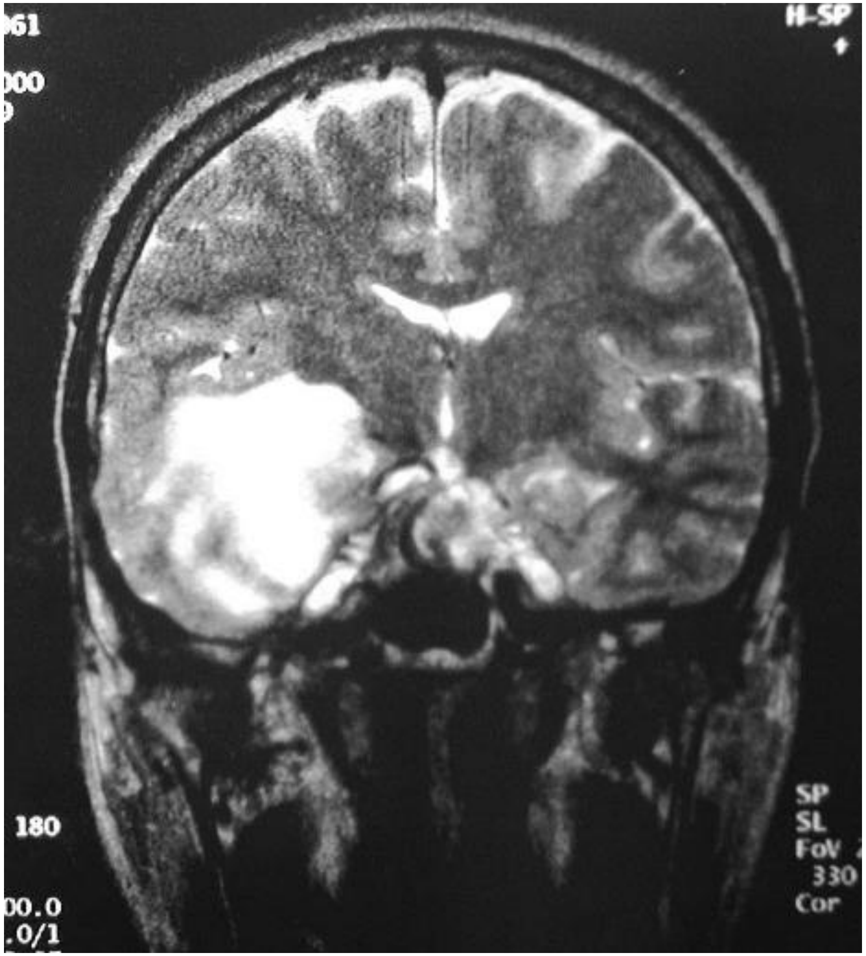
- Single Photon Emission Computed Tomography
- 50 to 400 KeV gamma
- Collimation needed for detection
- Crystal detectors: NaI(Tl)

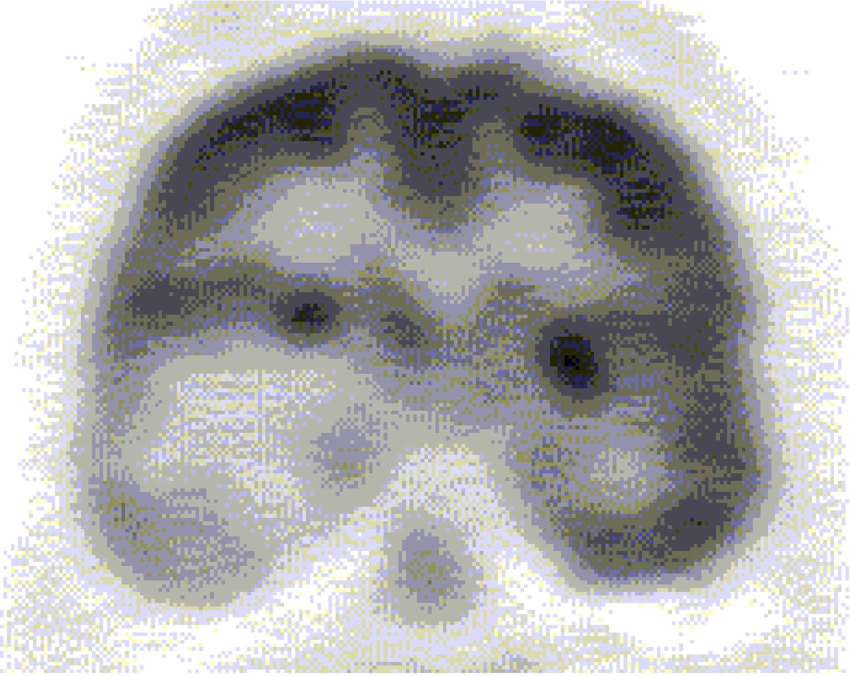
- Positron Emission Tomography
- 511 KeV gamma from annihilation with electron
- Coincidence detection
- Crystal detectors: LSO, BGO, BaF_2

Integrated PET/CT imaging in staging NSCLC NEJM 2003;348:2500

	PET/CT	MRI
T stage		
	34/46 (80%)*	24/46 (52%)
N stage		
	91/98 (93%)*	77/98 (79%)
M stage		
	92/98 (94%)	91/98(93%)

Recurrent malignancy or radiation necrosis





Case number: pb007 [Copyright by Wash U MO]

Systemic Radiation Therapy

Radiopharmaceutical	**Treatment**
I-131	Thyroid
I-131 MIBG	Neuroendocrine
Lu-177 dota-tate	Somatostatin
Sr-89 chloride	Met. Bone pain
Sm-153 lexidronam	Met. Bone pain
Ra-223 dichloride	Met. Bone pain +
P-32 Chromic (CMPD)	Pleural Effusion & Synovectomy
Y-90 micro-spheres	Liver or Met. Colorectal
Y-90 MAB; I-131 MAB	NHL

Radiation benchmarks (effective dose)

- X-Ray of the chest: 0.04 mSv (4 mrem)
- CT of the chest: 7.8 mSv (780 mrem)
- Barium enema including fluoroscopy: 8.7 mSv (870 mrem)
- Bone scintigraphy: 3.5 mSv (350 mrem)
- Thyroid Therapy: 100 Gy

<u>OU External Radiation Therapy Limits</u>

- Skin dose limit: 25 Gy
- Spinal cord: 10 Gy

Radionuclides Needed

Nuclear Pharmacy

Nuclear Pharmacy in the U.S.

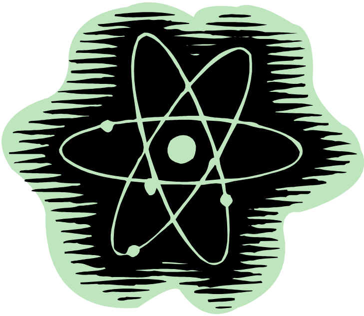
- 1981: 25 nuclear pharmacies NRC license
- 2013: > 400 nuclear pharmacies
  - 17.5 million NM Procedures
  - About 30 million unit dose preparations
- About $2.4 Billion USD market

Unit dose radiopharmaceuticals

- OUHSC Pharmacy operation since 1977
- Sterile preparation of radiopharmaceuticals
- Unit dose verified for stability and purity
- Dose is packaged and shipped to end-user

Radiopharmaceuticals

- Radioactive component
  + drug component



+

Typical pharmacy will handle 1184 GBq (32 Ci) of technetium 99m

Radionuclides in Nuclear Medicine

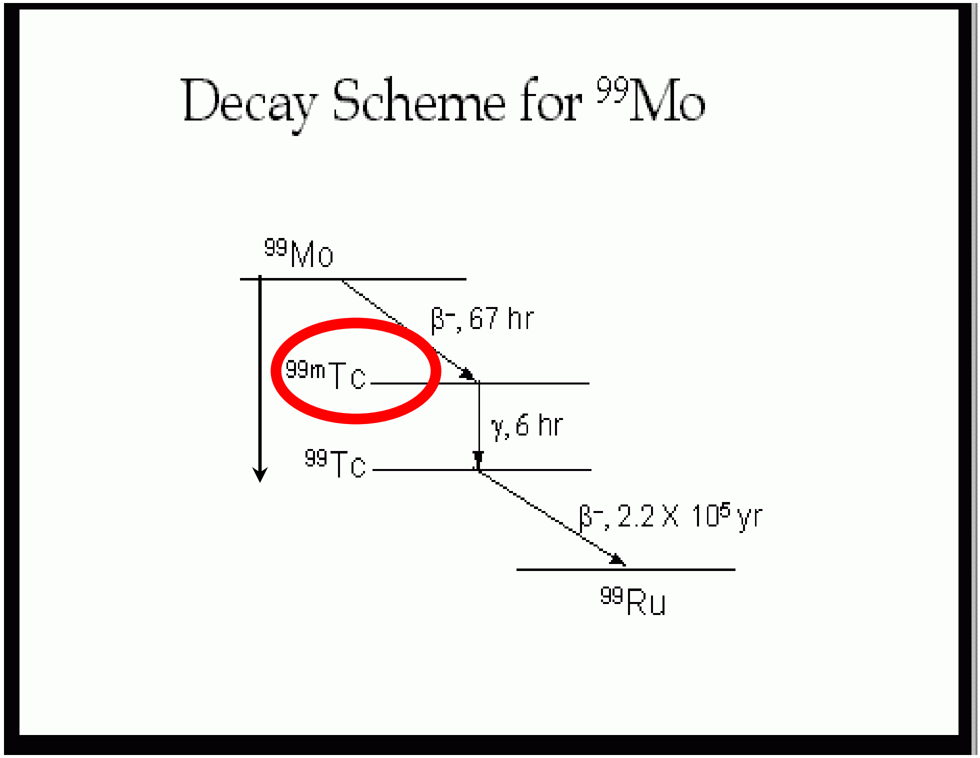
- **Reactor Fission U-235**
  - Molybdenum-99 (f)
    - Technetium-99m
  - Iodine-131 (f)
  - Xe-133 (f)
  - Sr-90 (f) -> Y-90
  - Strontium-89 (f)
- **Reactor neutron activation**
  - Phosphorus-32
  - Yttrium-90
  - Samarium-153
  - Iodine-125

- **Linear Accelerator or High Energy Cyclotron (25-100 MeV)**
  - Thallium-201
  - Indium-111
  - Iodine-123
  - Gallium-67
  - Sr-82 -> Rubidium-82
  - Co-57

- **Low Energy Cyclotron**
- **(<14 MeV)**
  - Fluorine-18
  - Carbon-11
  - Nitrogen-13
  - Oxygen-15

Tc-99m
$^{92}U_{235}$ (n, fission) $^{42}Mo_{99}$ (6%)

- Physical characteristics make this agent the ideal isotope - short half-life, *readily available*, low radiation exposure to patient, good imaging characteristics


Decay Scheme for ^{99}Mo

Mo99/Tc99m Generator

High verses Low SA of 98Mo (n,γ) 99Mo

Molybdenum-99

- Physical half-life = 66 hours
- γ emissions (740 & 780 keV)
- 86.05% to Tc-99m (86%)

Technetium-99m

- Physical half-life = 6 hours
- γ emission (140 keV)
- $Na^{99m}Tc0_4$

Patient Safety

Customs and Border Protection:
Homeland Security

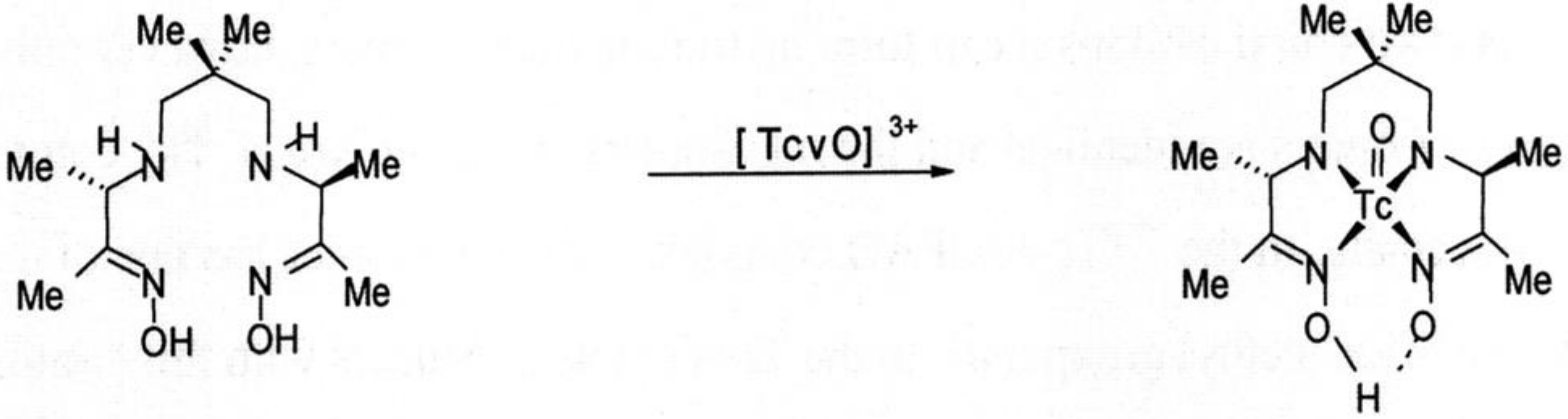
- On June 3rd 2011, an individual was stopped at the US/Canada border due to gamma ray emission sensors detecting radiation in the individual.

- Miami airport due to detection of radiation in the body.

PET MPI with Rb82, in Nevada, in late February 2011.

Contaminant: Sr-82 (25 d) & Sr-85 (65 d)

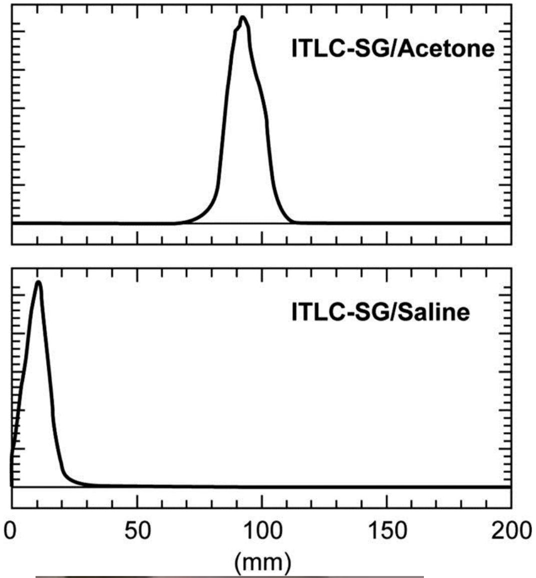
Kit Preparation



D,L-HMPAO

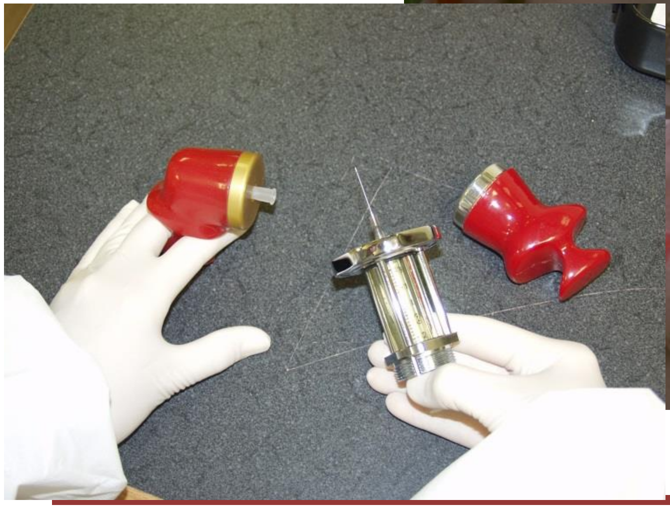
^{99m}Tc-D,L - HMPAO

Radiochemical Stability



Dispensing

Typical Extremity:
0.005 Sv/month



Handling RAM

- Delivery personnel package and deliver final product to nuclear medicine departments

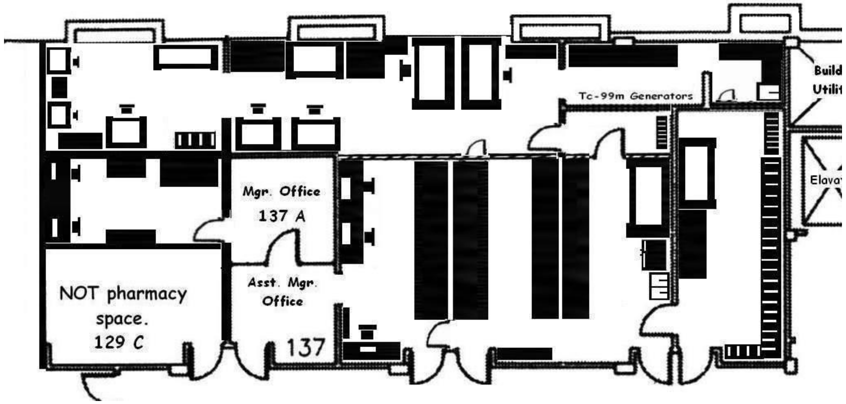
- Radioactive waste is picked up and returned to pharmacy for disposal

Nuclear Pharmacy Design

- Each pharmacy must establish it’s own quality control guidelines for parameters not established in the manufactures package insert directions
- Extensions of shelf-life (BUD)
- Maximum activities added to kits
- Addition of stabilizing agents

Pharmacy Layout

- Compartmentalized areas
  - Dose drawing stations (ISO 5)
  - Shipping prep area
  - Waste storage/disposal



Ancillary Equipment

- Stationary area monitors
  - Set on audible alarm
- Survey meters at exit points
- MCA for contamination identification
- Solvents and supplies for QC

General Purpose Survey Meter with GM Probe

Cyclotron for Positron Emission Drugs

Radioactive Biohazardous Drugs


12/25/2003

Manufacturing and infrastructure requirements for producing radioisotopes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Common medical Radionuclides by use category and production method

Purpose	**Reactor produced**	**Accelerator Produced**
Diagnostic Radionuclides	^{99m}Tc(f), ^{131}I (f & n), ^{133}Xe(f), ^{125}I, ^{3}H, ^{14}C	^{201}Tl, ^{111}In, ^{123}I, ^{67}Ga, ^{82}Rb, ^{57}Co, ^{18}F, ^{11}C, ^{13}N, ^{15}O, ^{67}Ga, ^{81m}Kr
Therapeutic Radionuclides	^{131}I (f & n), ^{89}Sr(f), ^{90}Y, ^{90}Sr(f)->^{90}Y, ^{32}P, ^{153}Sm, ^{125}I, ^{137}Cs, ^{177}Lu, ^{60}Co, ^{166}Ho, ^{223}Ra(f)	^{64}Cu, ^{103}Pd, ^{111}In

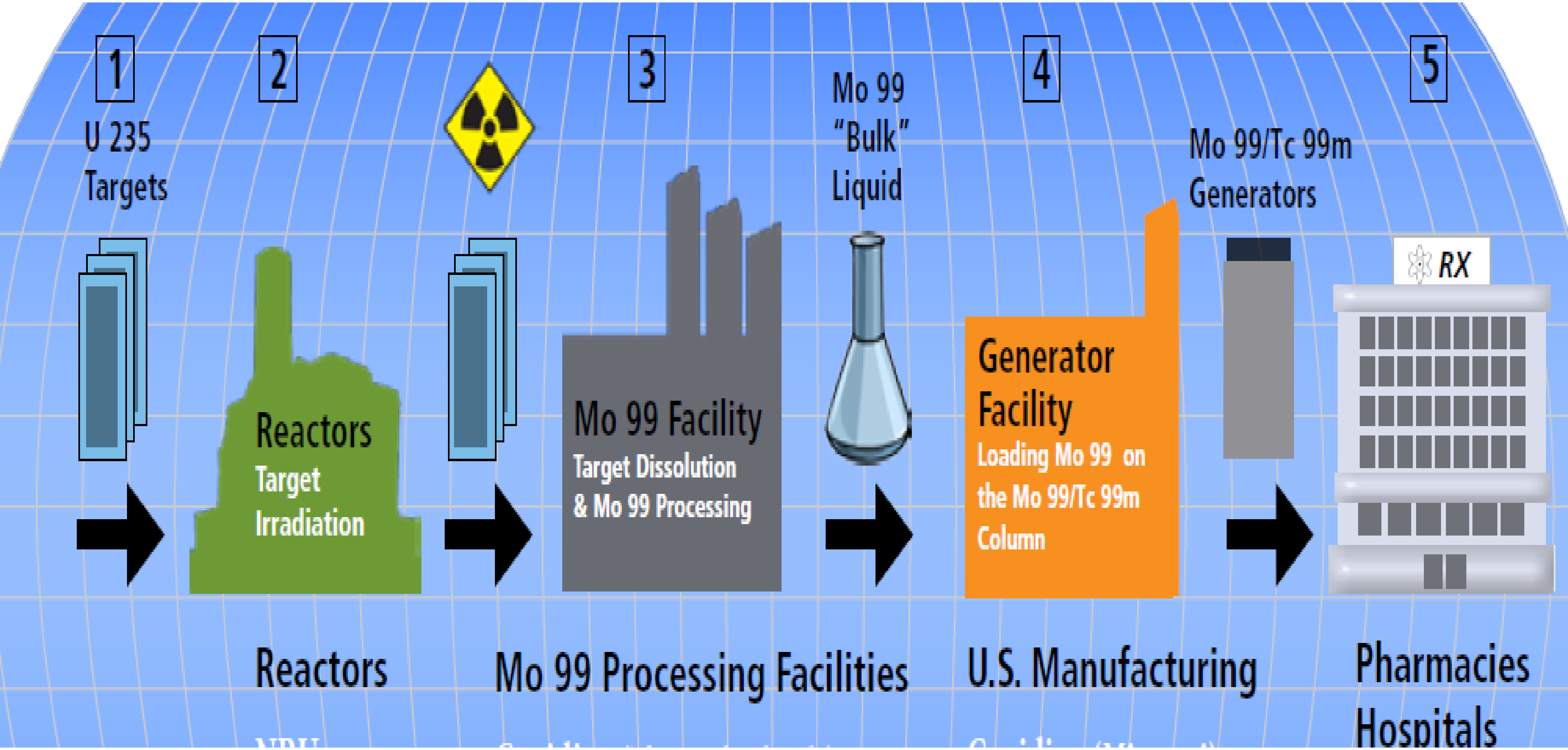
Produced on smaller scale

- 88Sr (n,γ) 89Sr σ = 0.058 b
- 152Sm (n,γ) 153Sm σ = 206
- 191Ir (n,γ) 192Ir σ = 954 b
- 124Xe(n,γ)125Xe (18hr)→125I σ = 165 ± 20 b
- 89Y (n,γ) 90Y σ = 1.28 b
- 235U (n,γ) 90Sr (29yr)→90Y
- 176Lu (n,γ) 177Lu σ = high (1770) b

Before 2010 Mo-99 Supply Matrix

Country	Name	MW (% global supply)	Start up	Fuel/Target
Chalk River, Canada	NRU	135 (38%)	1957	LEU/HEU
Petten, Netherlands	HFR	45 (26%)	1962	LEU/HEU
Mol, Belgium	BR2	100 (16%)	1961	HEU/HEU
S. Africa	SAFARI-1	20 (16%)	1965	LEU/HEU
Saclay, France	OSIRIS	70 (4%)	1967	LEU/HEU

Reactor to Patient



1
U 235
Targets

2
Reactors
Target
Irradiation

3
Mo 99 Facility
Target Dissolution
& Mo 99 Processing

Mo 99
"Bulk"
Liquid

4
Generator Facility
Loading Mo 99 on the Mo 99/Tc 99m Column

Mo 99/Tc 99m
Generators

5
RX

Reactors

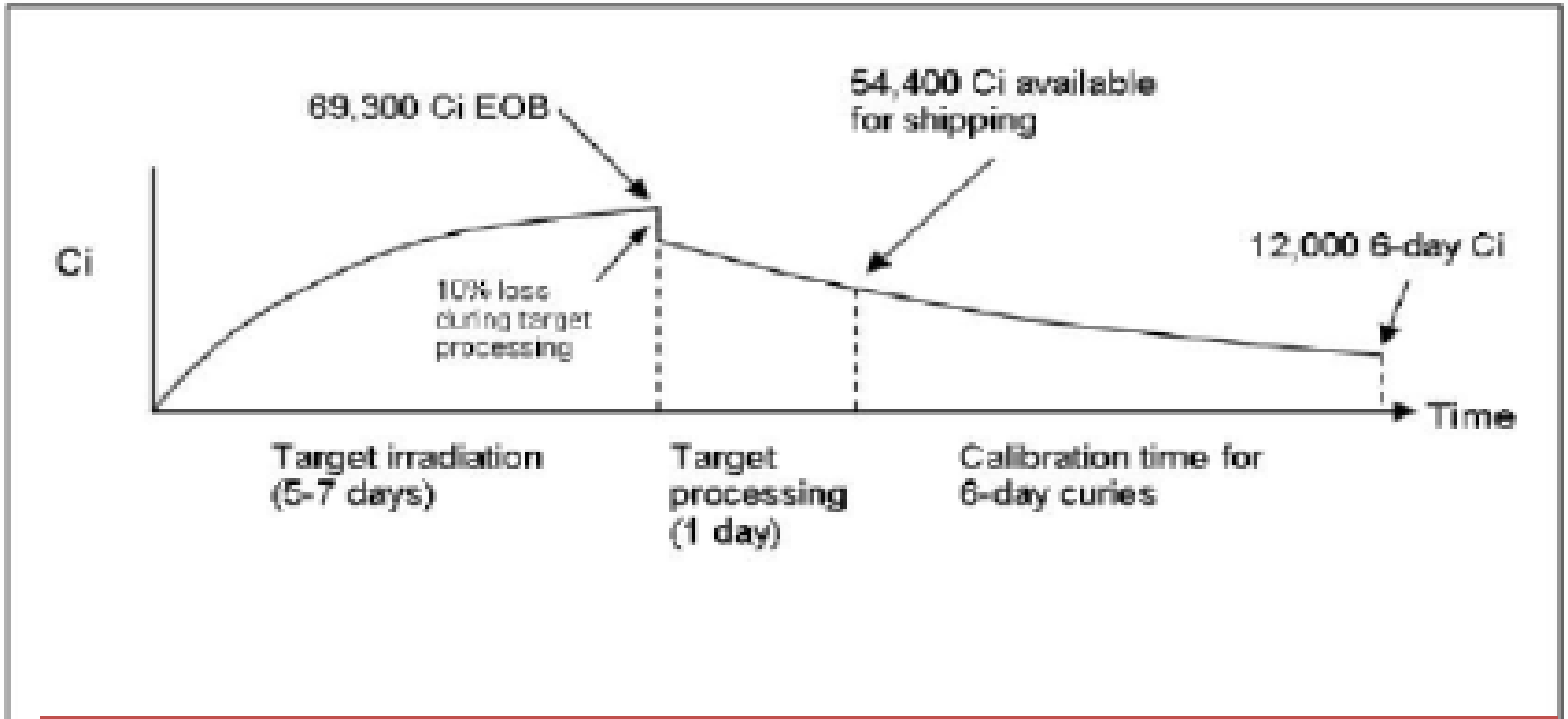
Mo 99 Processing Facilities

U.S. Manufacturing

Pharmacies
Hospitals

COVIDIEN
positive results for life™

The infamous 6-day curie



Amount of Mo-99m needed

- Worldwide was about 12,000 Ci per week, now about 10,000 Ci per week

http://www.isotopes.gov/outreach/reports/Reactor_Isotopes.pdf

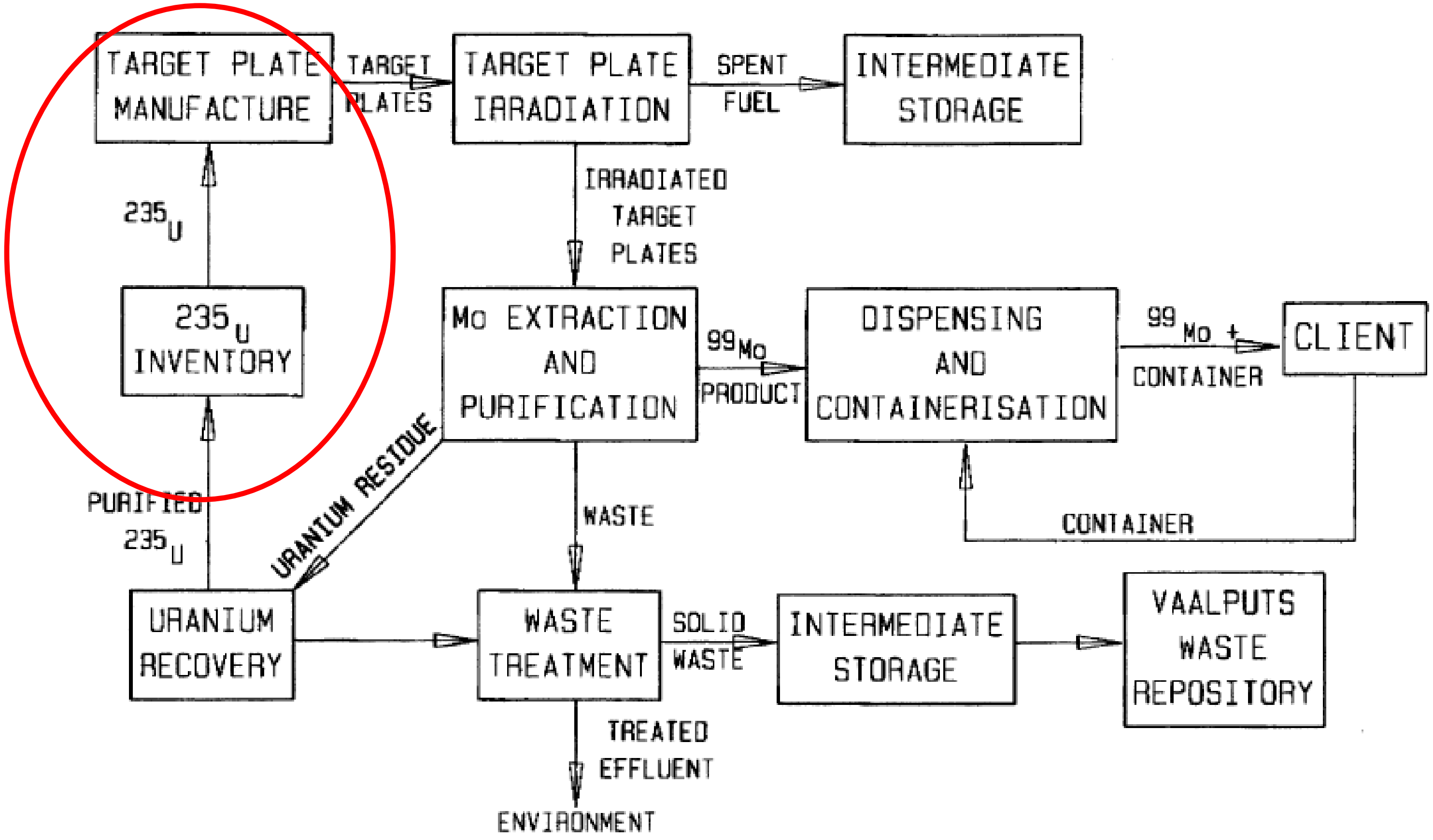


FIG. 1. Mo-99 process flow sheet.

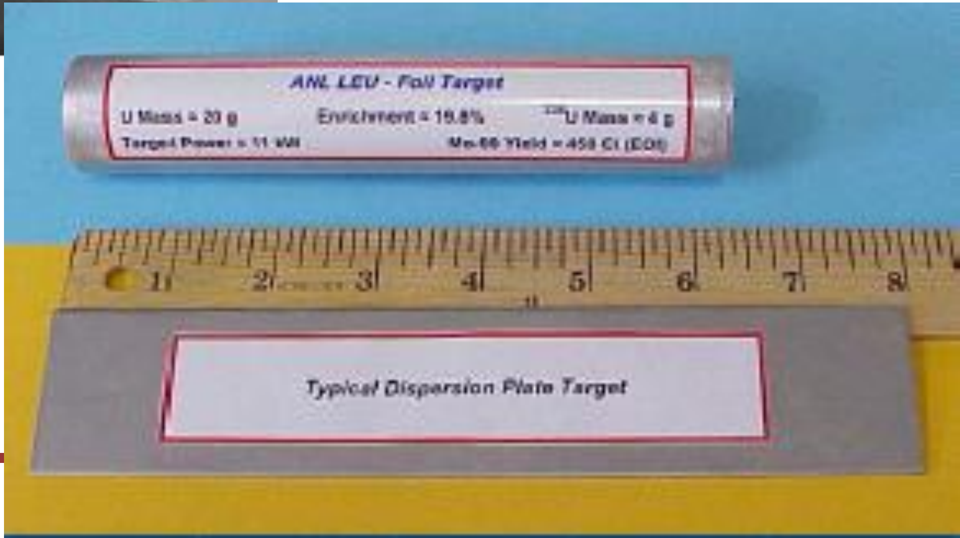
IAEA-TECDOC-1340. Manual for reactor produced radioisotopes. IAEA Jan 2003

U235 Target Design

- 235U (n,γ) 99Mo + F.P. + 2.5 n σ = 586 b

Total of 8 Dispersion Plate Targets
Irradiated / Processed as a Batch

Photos Courtesy of NRG
Mo-99 CRP Workshop
Vienna, November 2006



2009-2010 Mo-99 Supply Matrix

Country	Name	MW	Start up	% World Supply Tc-- I131	6-day Curie	Fuel/Target	Processing facility
Mol, Belgium	BR2	100	1961	16	5200	HEU/HEU	Covidien/IRE
S. Africa	SAFARI-1	20	1965	16--25	2500	LEU/HEU	NTP
Saclay, France	OSIRIS	70	1967	4--75	1200	LEU/HEU	Covidien/IRE

Current producers of Mo-99 (f)

Country	Reactor Name	MW	Start up	% World Supply Tc—I-131	Potential 6-day Curie	Fuel/Target	Processing facility
Chalk River Canada	NRU	135	1957	40 --100 (Xe-133)	4680	LEU/HEU	Nordion
Petten, Netherlands	HFR	45	1962	30	4680	LEU/HEU	Covidien in Netherlands /IRE in Belgium
Mol Belgium	BR2	100	1961	12	5200-7800	HEU/HEU	Covidien in Netherlands /IRE in Belgium
S. Africa	SAFARI-1	20	1965	15--25	2500	LEU/LEU	NTP
Saclay France	OSIRIS	70	1967	3--75	1200	LEU/HEU	Covidien in Netherlands /IRE in Belgium

Current producers of Mo-99 (f)

Country	Reactor Name	MW	Start up	% World Supply Tc	Potential 6-day Curie	Fuel/Target	Processing facility
Poland	MARIA	30	1974	15	700-1500 (2010)	HEU/HEU	Covidien in Netherlands /IRE in Belgium
Australia	OPAL	20	2006	15	1000-1500	LEU/LEU	ANSTO
Rez Czech Republic	LVR-15	10	1957	12 (Xe-133)	1200 (2800)	LEU/HEU	IRE in Belgium
Russia	RIAR	100	1967	18	1800-2000	HEU/HEU	Russia
Argentina	RA-3	5	1990	3	300	LEU/LEU	CNEA
Julich Germany	FRM-II	20	2004	20	1950 (2016)	LEU/LEU	Covidien in Netherlands /IRE in Belgium
Chengdu China	HFETR	125	1979	?	?	LEU/HEU	China

The Policy Approach to Sustainability

NNSA (National Academy Sciences) Study: “Production of Medical Isotopes with out HEU”

- Strike a balance between
  1) Availability of reasonably priced medical isotopes in the U.S.
  2) HEU proliferation prevention

NNSA Study Results

- Mo-99m supply is fragile without refurbished or new reactors
  - AECL's decision to discontinue the MAPLE reactors is a blow to worldwide supply
- DOE-assist producers with conversion R&D (share costs/maintain LEU/HEU price)

MAPLE Project

- 1996-MDS Nordion commissioned the AECL to build two 10 MW reactors w/ capacity to meet world demand x 2.

OECD-NEA HLG-MR

- Principle 1: All ^{99m}Tc supply chain participants should implement full-cost recovery, including costs related to capital replacement.
- Principle 2: Reserve capacity should be sourced and paid for by the supply chain. A common approach should be used to determine the amount of reserve capacity required and the price of reserve capacity options.
- Principle 3: Recognizing and encouraging the role of the market, governments should: establish the proper environment for infrastructure investment; set the rules and establish the regulatory environment for safe and efficient market operation; ensure that all market-ready technologies implement full-cost recovery methodology; and refrain from direct intervention in day-to-day market operations as such intervention may hinder long-term security of supply.
- Principle 4: Governments should provide support, as appropriate, to reactors and processors to facilitate the conversion of their facilities to low enriched uranium or to transition away from the use of highly enriched uranium, wherever technically and economically feasible.
- Principle 5: International collaboration should be continued through policy
- Principle 6: There is a need for periodic review whether essential players are implementing approaches co-ordination of operating schedules

American Isotope production bill passed Jan 17 2013

- Eliminate use of HEU (deadline of 7-13 years depending on US supply)
- Encourage domestic Mo99
- $143 million to explore US production
- LEU lease and waste take-back provisions

Council of the European Union

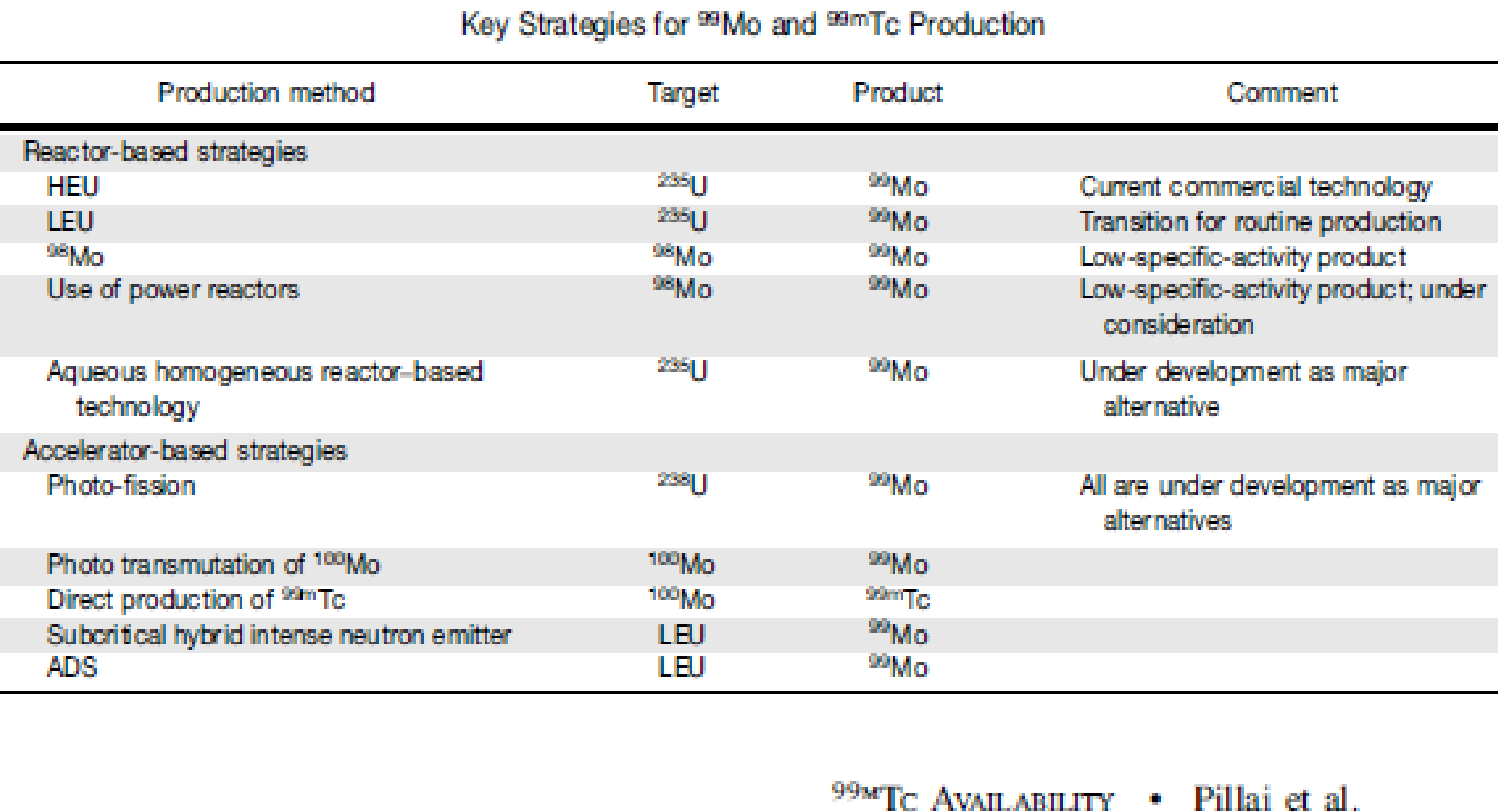
- European Observatory on the supply of medical radioisotopes established Jun 2012
- Effective coordination of reactor preventative and extended maintenance
- Support full cost recovery principle by HLG-MR
- Periodic reviews of worldwide need and LEU conversion

Conversion status (OECD NEA)

Reactor Name	ORC	Full Cost Recovery	LEU conversion	Processing facility	ORC	Full Cost Recovery
NRU	No	No-permanent agreement with Nordion	No-planning shutdown in 2016 with "gradual market transition"	Nordion	No	Yes
HFR	Some progress	Working towards FCR Decommissioning 2023/ PALLAS reactor for FCR	Full conversion 2016	Covidien/IRE	Yes	No
BR2	Yes, Life into 2020; plans for new reactor (MYRRHA)	No/Planning for MYRRHA to be FCR	Estimated completion 2016	Covidien/IRE	Yes	No
SAFARI-1		Yes	Completion 2014	NTP	Yes	Yes

Reactor Name	ORC	Full Cost Recovery	LEU conversion	Processing facility	ORC	Full Cost Recovery
OSIRIS	No	Replacement with Jules Horowitz-JHR with FCR	License extension 2015-completion of JHR 2018	Covidien/IRE	Yes	No
MARIA	No	No		Covidien/IRE New facility 2017		
OPAL	Yes	Yes	Already LEU	ANSTO	No	New processing and waste facility
LVR-15	Yes	No				
RIAR	No response	Some	By 2018			
RA-3	No	No, 2018 planned new reactorRA-10 with capacity of 3000	Already LEU	CNEA	No	No
FRM-II	Yes, 2016	Yes	LEU (2016)	Covidien/IRE	Yes	No

Key Strategies for Tc99m production

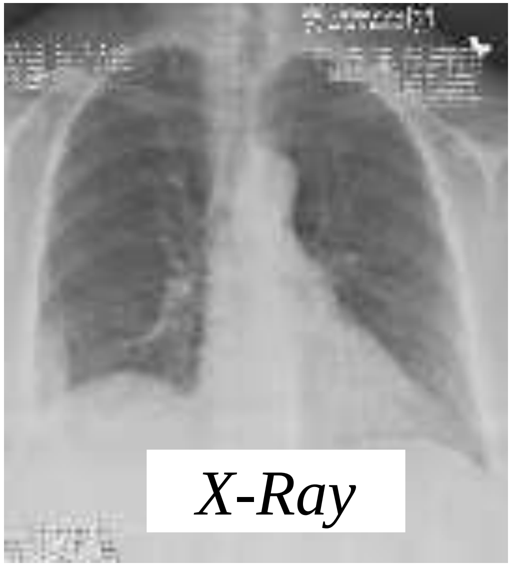


Key Strategies for ^{99}Mo and ^{99m}Tc Production

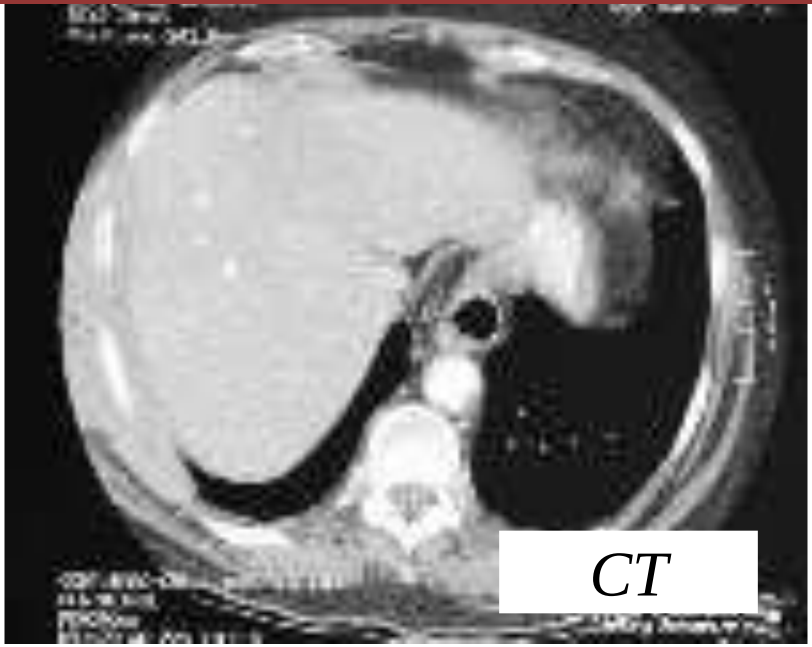
Production method	Target	Product	Comment
Reactor-based strategies			
HEU	^{235}U	^{99}Mo	Current commercial technology
LEU	^{235}U	^{99}Mo	Transition for routine production
^{98}Mo	^{98}Mo	^{99}Mo	Low-specific-activity product
Use of power reactors	^{98}Mo	^{99}Mo	Low-specific-activity product; under consideration
Aqueous homogeneous reactor–based technology	^{235}U	^{99}Mo	Under development as major alternative
Accelerator-based strategies			
Photo-fission	^{238}U	^{99}Mo	All are under development as major alternatives
Photo transmutation of ^{100}Mo	^{100}Mo	^{99}Mo	
Direct production of ^{99m}Tc	^{100}Mo	^{99m}Tc	
Subcritical hybrid intense neutron emitter	LEU	^{99}Mo	
ADS	LEU	^{99}Mo	

^{99M}TC AVAILABILITY • Pillai et al.

Nuclear medicine and molecular imaging

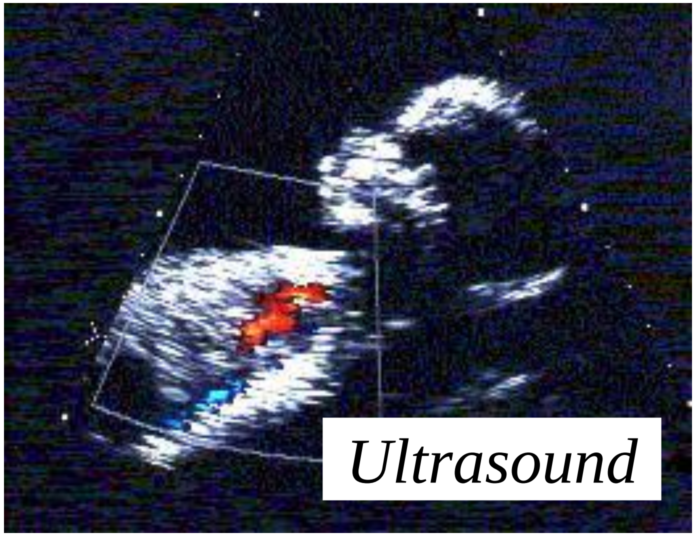


X-Ray



CT

MRI



Ultrasound

“Never, never, never give up”

Radionuclides Needed

Thank you for your attention!

wendy-galbraith@ouhsc.edu