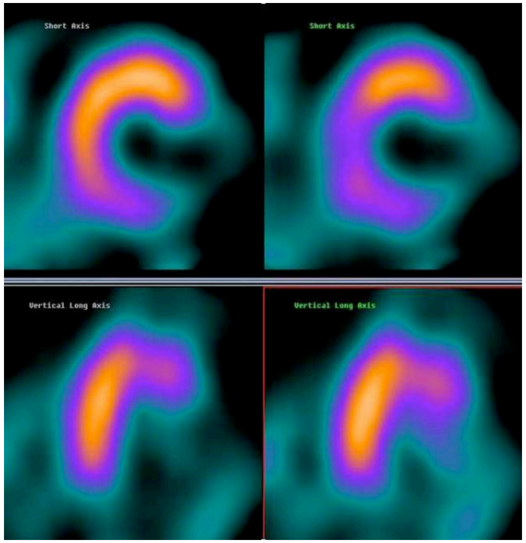


Preprint: http://tiny.cc/thoab02

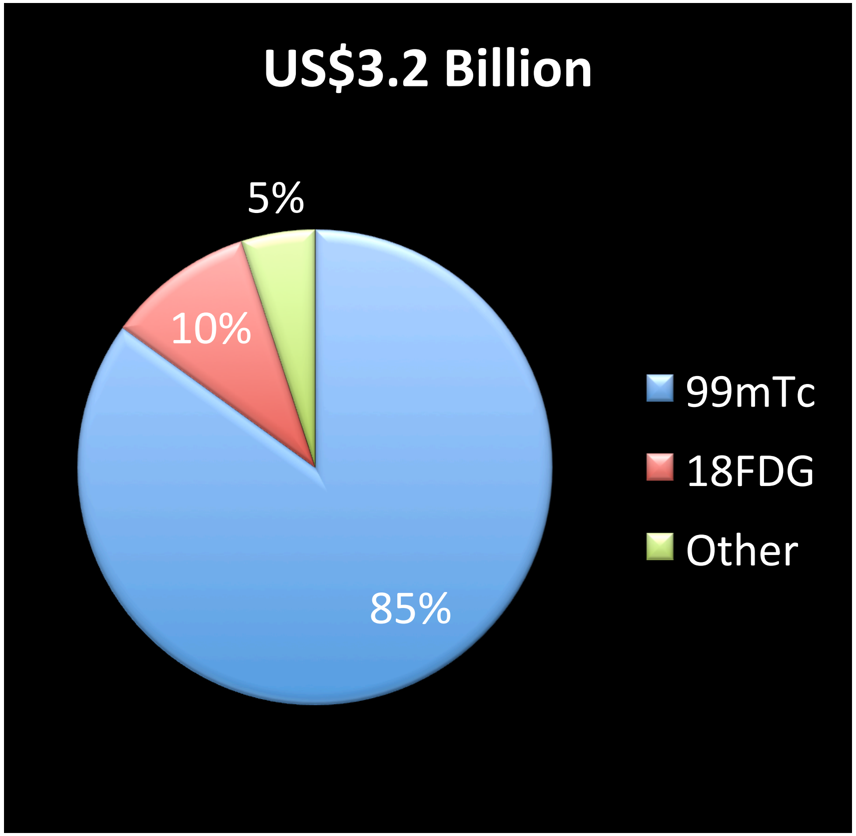
Options for UK 99mTc Production Using Accelerators

Hywel Owen
on behalf of UK Isotope Working Group

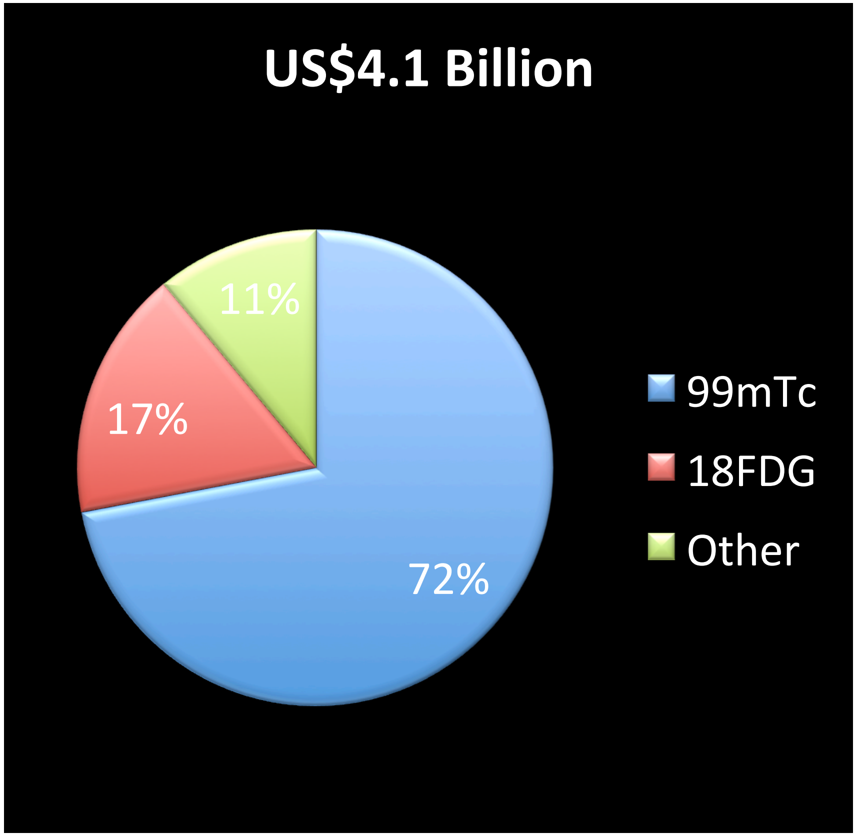
Public Health England
BNMS BRITISH NUCLEAR MEDICINE SOCIETY
King's College London
NHS
The Society of Radiographers
Science & Technology Facilities Council
The Cockcroft Institute of Accelerator Science and Technology
Manchester 1824

Global Radiopharmaceutical Diagnostic Market

2010



2017

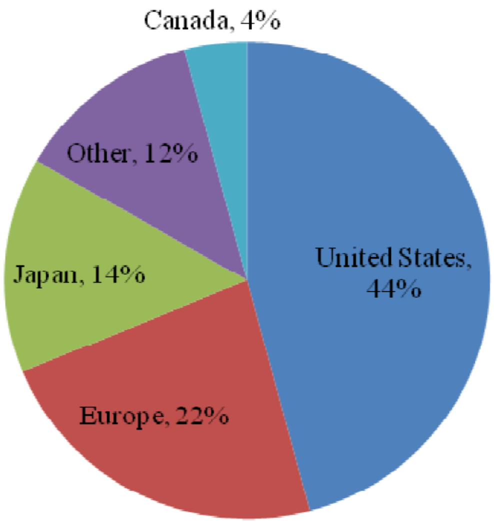


1 Global Radiopharmaceuticals Market (PET/SPECT Imaging & Therapy) – Current Trends & Forecasts (2010 – 2015); MarketsandMarkets, August 2011
2 BMI - Business Monitor International Ltd, Molybdenum-99: Privatising Nuclear Medicine, Special Report 2011
3 Interim Report on the OECD/NEA High-Level Group on Security of Supply of Medical Radioisotopes, The Supply of Medical Radioisotopes, OECD 2012

The Cockcroft Institute
of Accelerator Science and Technology

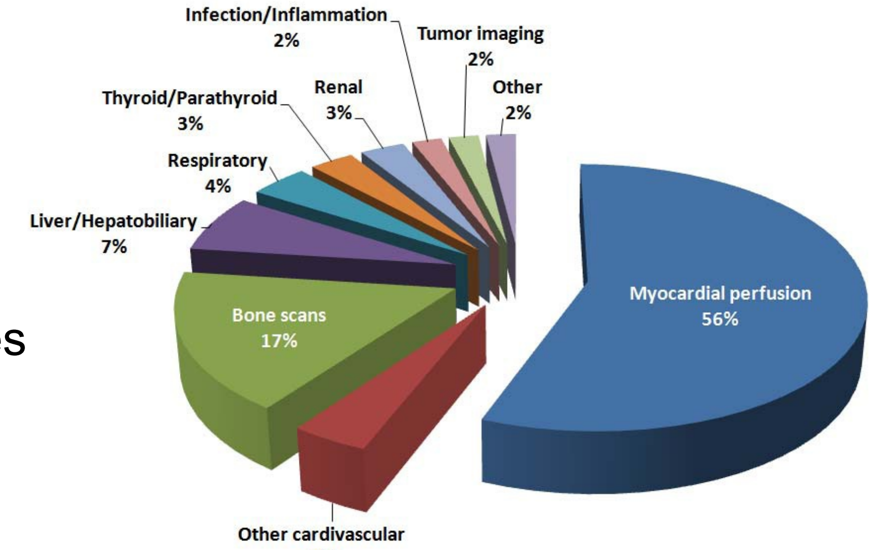
MANCHESTER
1824

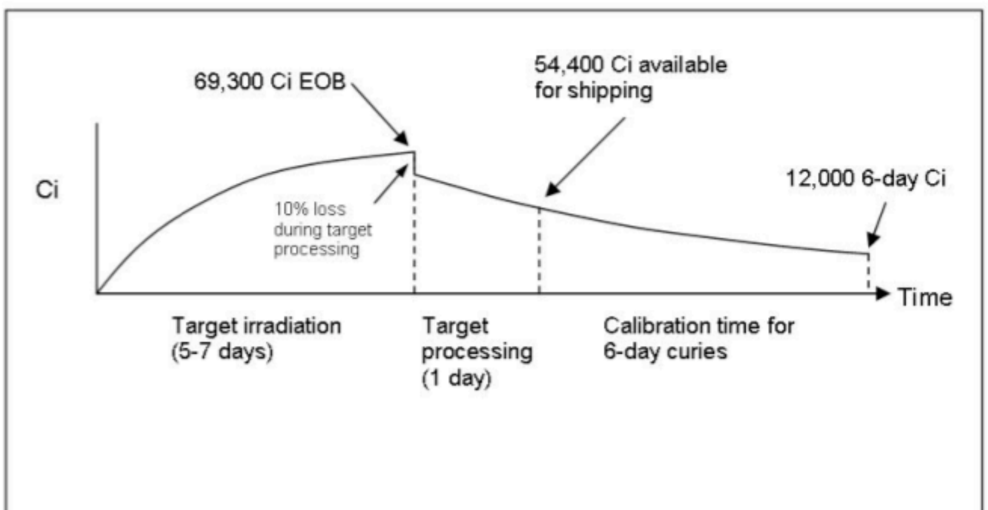
Some facts about 99mTc



>30 M procedures per year

~0.5 M in UK





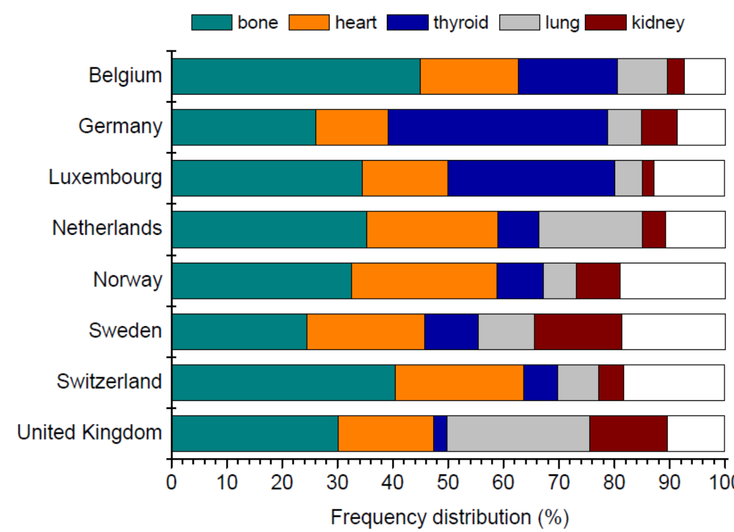
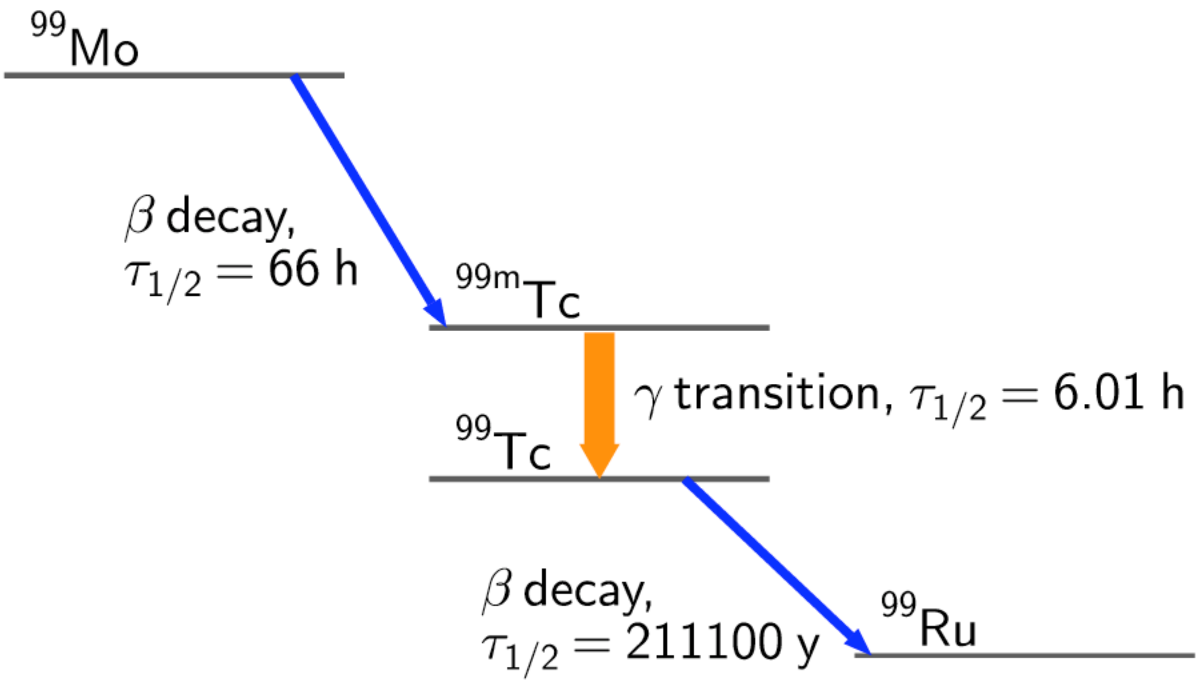


Figure 1 **Relative contribution of five groups of examinations to the total frequency of nuclear medicine examinations.**

UK HPA 2008

Mo-99/Tc-99m/Tc-99



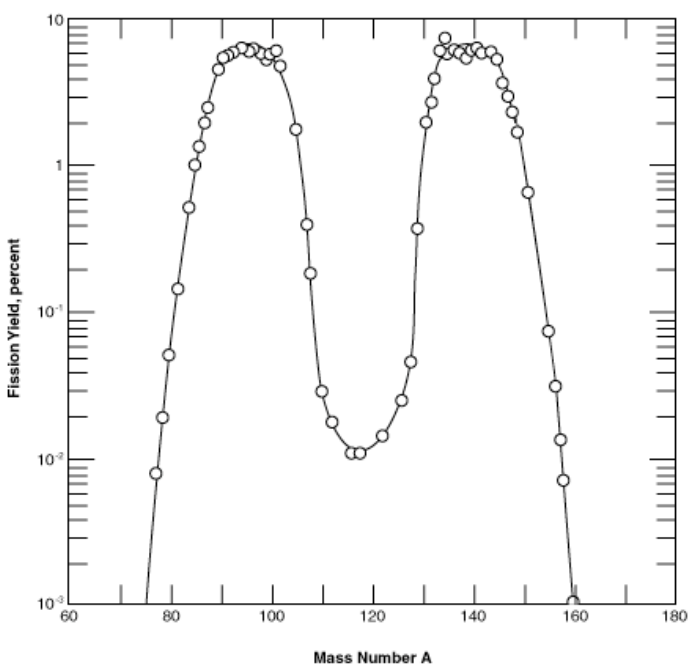
140 keV

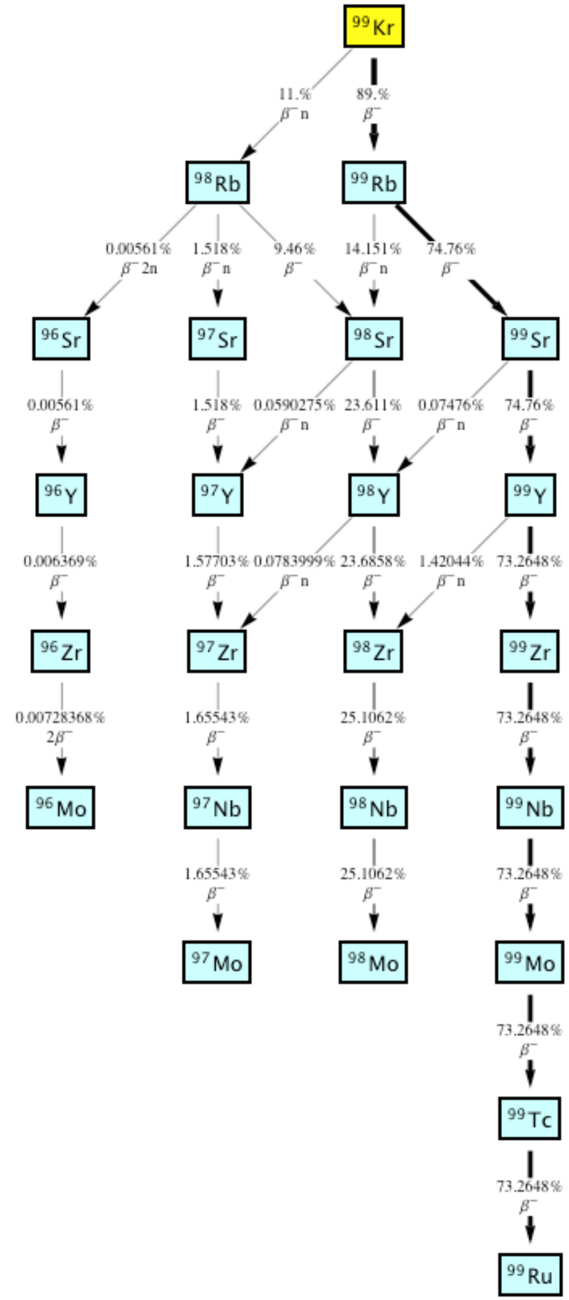
The Cockcroft Institute of Accelerator Science and Technology
MANCHESTER 1824

Mass 99 Decay Chain

Nuclide	Halflife
99Y	1.470(7) s
99Zr	2.1(1) s
99Nb	15.0(2) s
99Mo	2.7489(6) d
99Tc	2.111(12)E+5 a
99Ru	Stable

Thermal Neutron Fission of U-235





The Cockcroft Institute of Accelerator Science and Technology

MANCHESTER 1824

Current Irradiators 2013

Reactor	Targets	Normal operating days	Available weekly capacity (6-day Ci)	Potential annual production (6-day Ci)[1]	Estimated stop production date
BR-2	HEU	140	7 800	156 000	2026
HFR	HEU	280	4 680	187 200	2024
LVR-15	HEU	210	2 800	84 000	2028
MARIA	HEU	180	1 400	36 000	2030
NRU	HEU	280	4 680	187 200	2016
OPAL	LEU	290	1 000	42 900	2055
OSIRIS	HEU	182	1 200	31 200	2015
RA-3	LEU	336	400	19 200	2027
SAFARI-1	HEU[2]/LEU	305	3 000	130 700	2030

OECD January 2014 HLG-MR Report

Current Processors

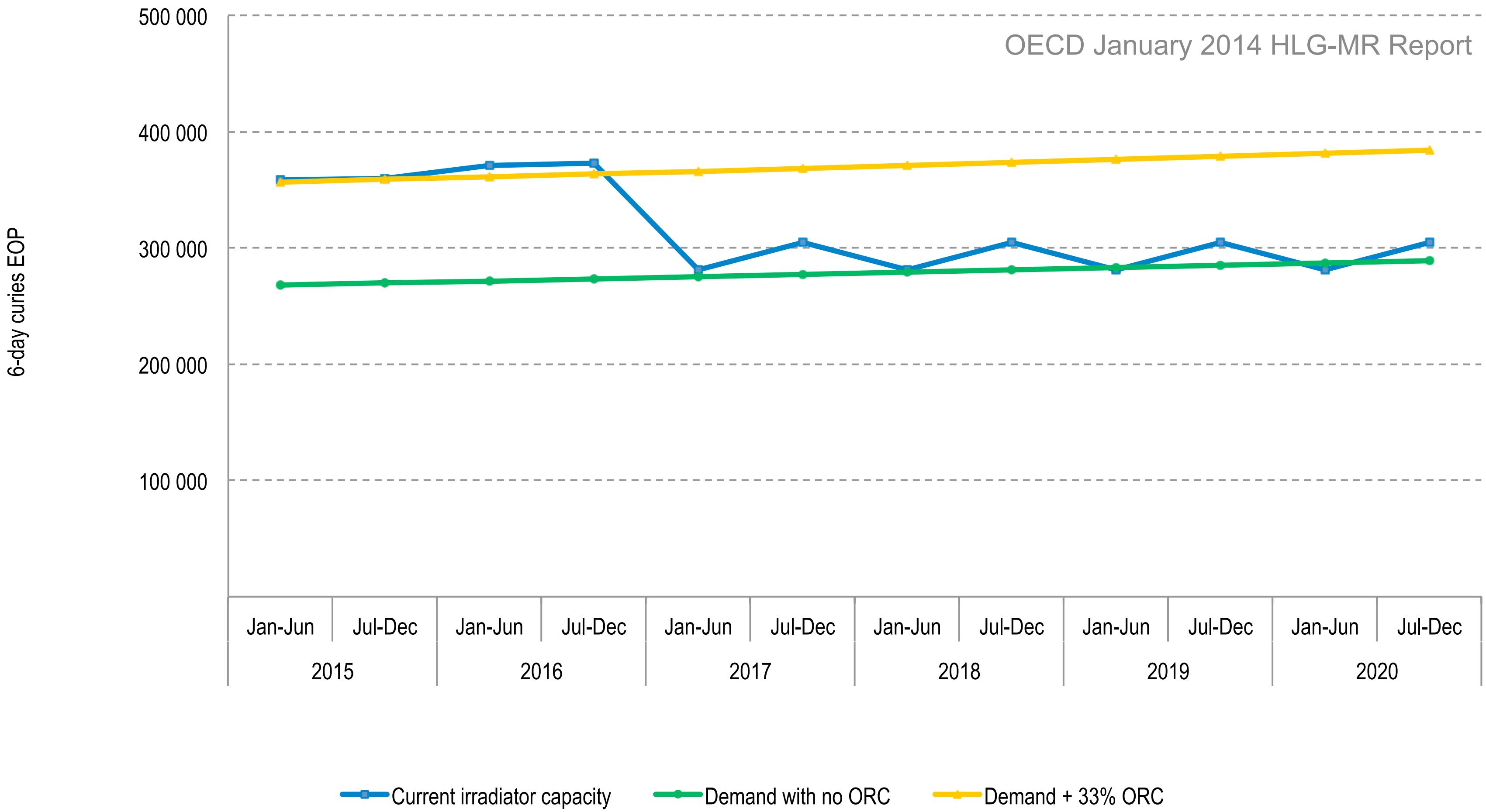
Processor	Targets	Capacity per week (6-d Ci)	Available annual capacity (6-d Ci)[1]	Expected date of conversion to LEU targets
AECL/NORDION	HEU	7 200	374 400	Not expected
ANSTO HEALTH	LEU	1 000	52 000	Started as LEU
CNEA	LEU	900	46 800	Converted
MALLINCKRODT	HEU	3 500	182 000	2016
IRE	HEU	2 500	130 000	2016
NTP	HEU[3]/LEU	3 500	182 000	2014[4]

OECD January 2014 HLG-MR Report

The Cockcroft Institute of Accelerator Science and Technology

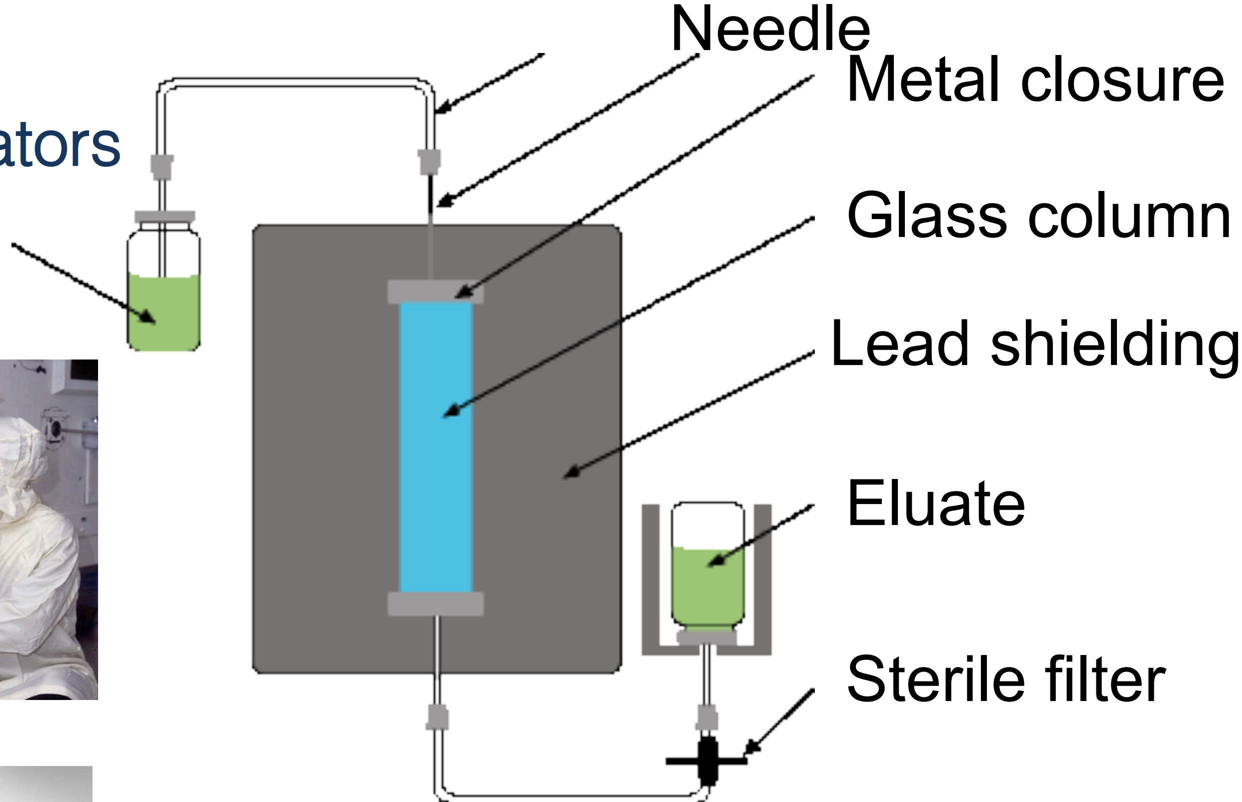
MANCHESTER 1824

Irradiation capacity and projected future demand, Global, 2015-2020



'A Review of the Supply of Molybdenum-99, the Impact of Recent Shortages and the Implications for Nuclear Medicine Services in the UK', Administration of Radioactive Substances Advisory Committee

Technetium Generators

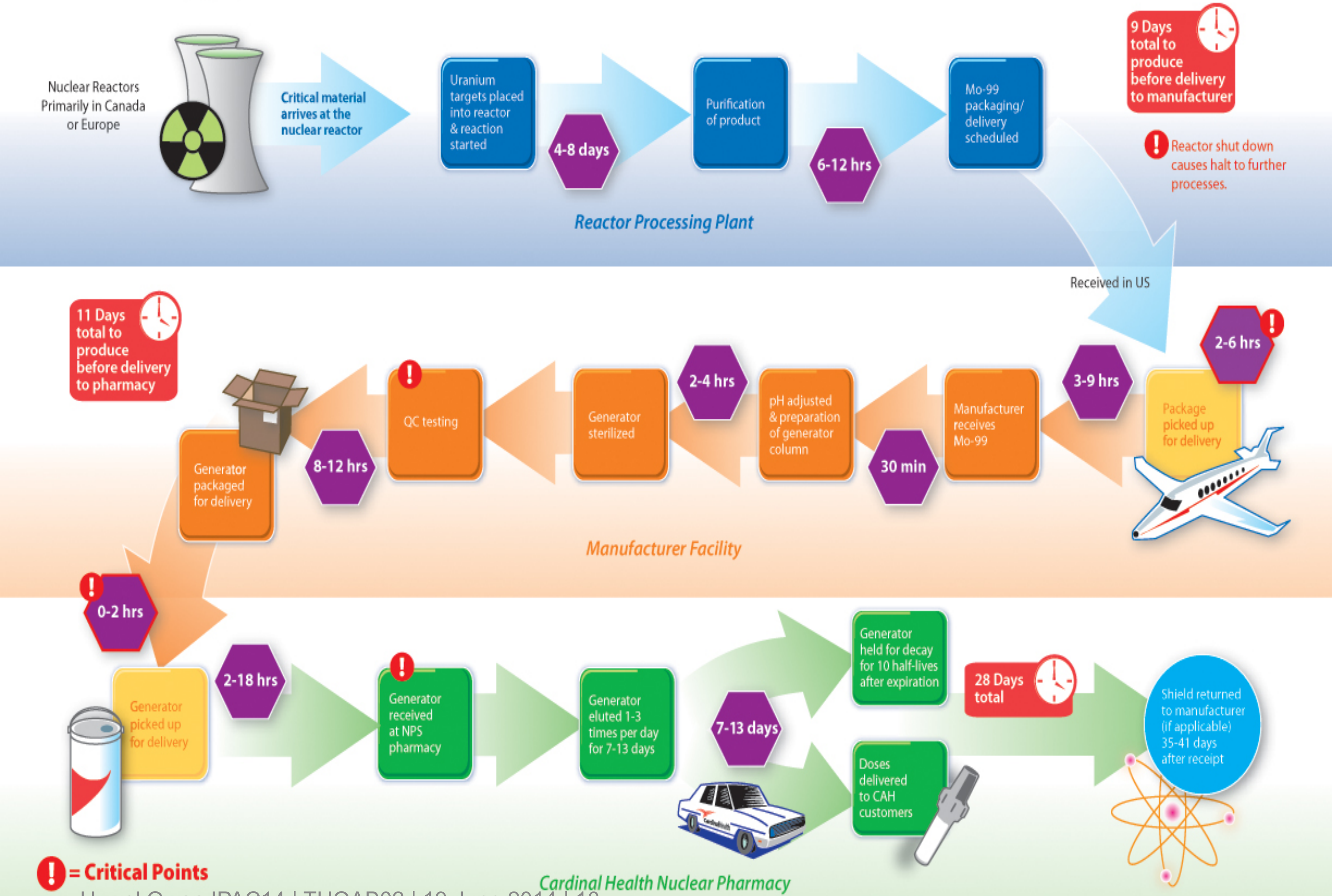


Supplier	***Produce and ship***	***Deliver***	***Reference***	***Sizes***
Covidien	Weekdays R-7	Next day R-6	Weekdays R-0	2.15-43 GBq ^{99}Mo 12 sizes
GE	Tue R-6	Wed R-5	Mon R-0	2.5-100 GBq ^{99m}Mo 18 sizes
	Thu R-7	Fri R-6	Thu R-0	
IBA/Qados	Tue R-8	Wed R-7	Wed R-0	2-20 GBq ^{99m}Tc 8 sizes
	Fri R-8	Sat R-7	Sat R-0	

The Cockcroft Institute of Accelerator Science and Technology

MANCHESTER 1824

Mo-99 supply chain

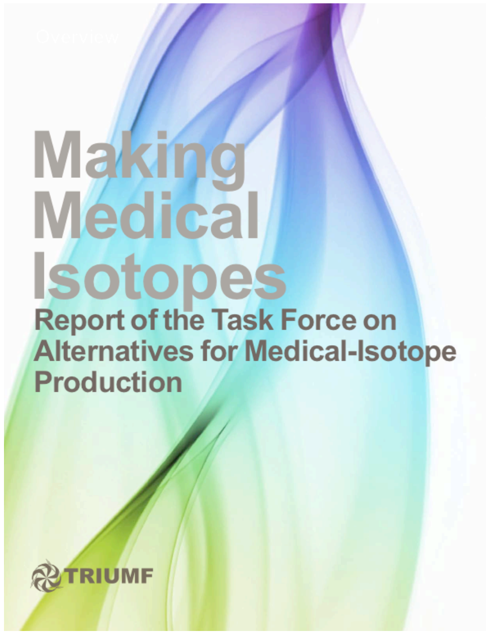


Potential New Irradiators 2013

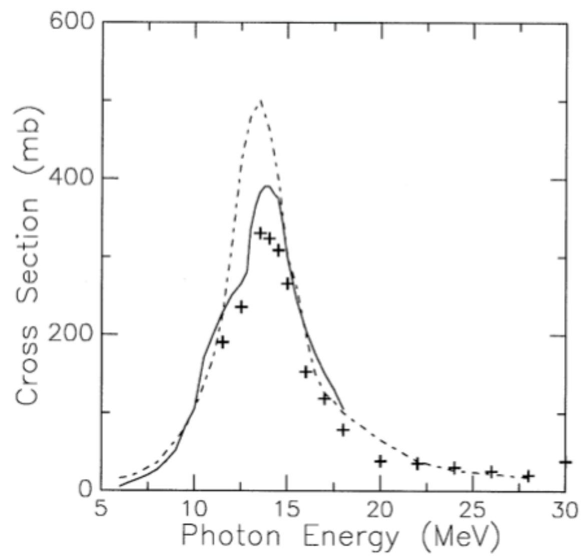
Reactor	Targets	Operating days (Number)	Available weekly capacity (6-day Ci)	Potential annual production (6-day Ci)[1]	Estimated stop production date	Status
RIAR (Russia)	HEU in CRR	350	1200	60000	2015	Started
Karpov Institute	HEU in CRR	345	300	14800	2015	Started
NORTHSTAR/ MURR (USA)	Non-fissile in CRR	365	2750/ 3000	39100/ 156400	2015/17	Phase 1
FRM-II (Germany)	LEU in CRR	240	1 600	54300	2017	Infrastructure in place
MORGRIDGE/ SHINE (US)	LEU solution with DTA	300	3000	144000	2017	NYS
OPAL	LEU in CRR	300	2600	111400	2017	NYS
KOREA	LEU in CRR	300	2000	85700	2018	Concept
NORTHSTAR (USA)	Non-fissile from LINAC	336	3000	144000	2018	NYS
CHINA Advanced RR	LEU in CRR	350	1000	50000	2019	Modification
Brazil MR	LEU in CRR	290	1000	41400	2019	Preliminary
RA-10 (Argentina)	LEU in CRR	336	2500	120000	2019	Preliminary
Jules HOROWITZ RR (France)	LEU in CRR	220	3200	100600	2020	Under Construction

OECD January 2014 HLG-MR Report

Photofission

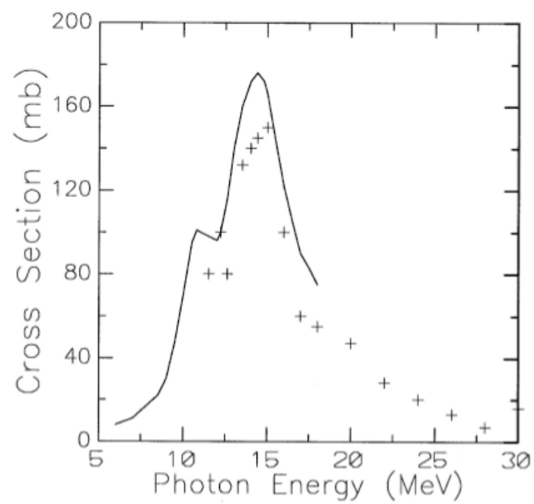


Haxby et al., Phys. Rev. 58(1), 92 (1940)

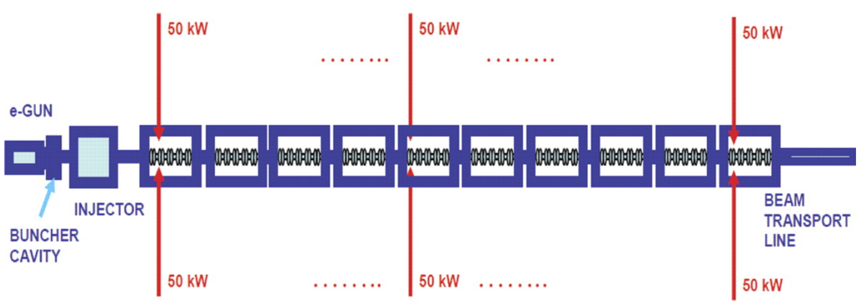


235U

(also benefits from neutron reflection and fission cascade)



238U



W. Diamond, NIM A 432, 471 (1999)
RG Bennett et al., Nucl. Tech. 126(1), 102 (1999)

Neutron Capture

65 MeV Protons into Be target (7 hour exposure)

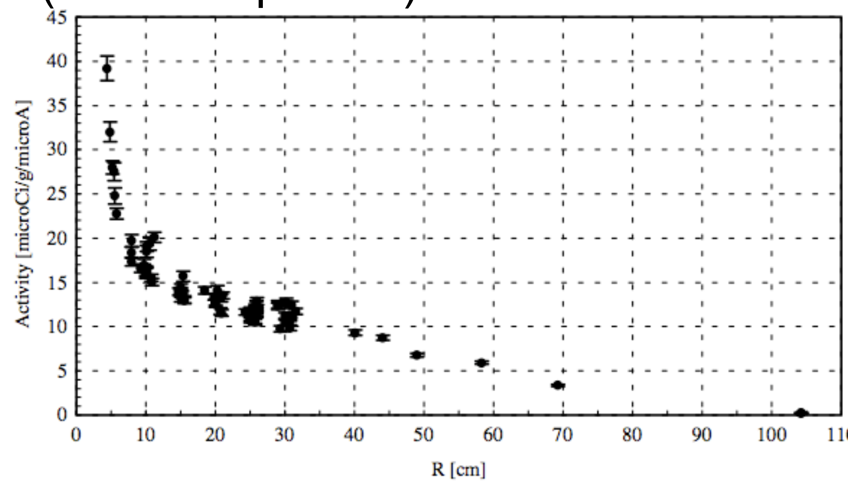
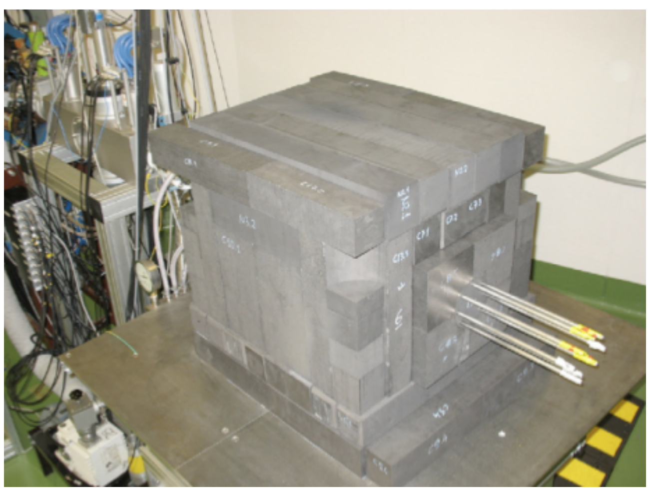


Fig. 3. ^{99}Mo activity generated by irradiation of metallic Mo foils with neutrons produced by bombarding the Be target with a 65 MeV proton beam. The results are presented as a function of the distance (R) between the sample and the Be target.



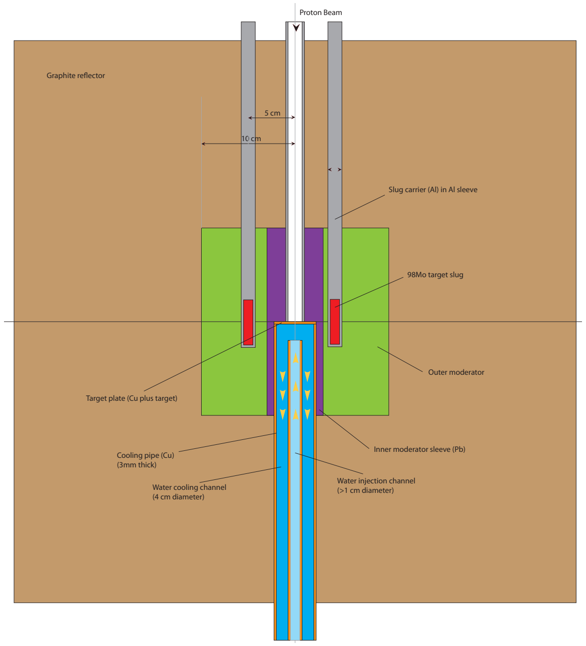
Froment et al., NIM A 493, 165 (2002)
Abbas et al. 601, 223 (2009)

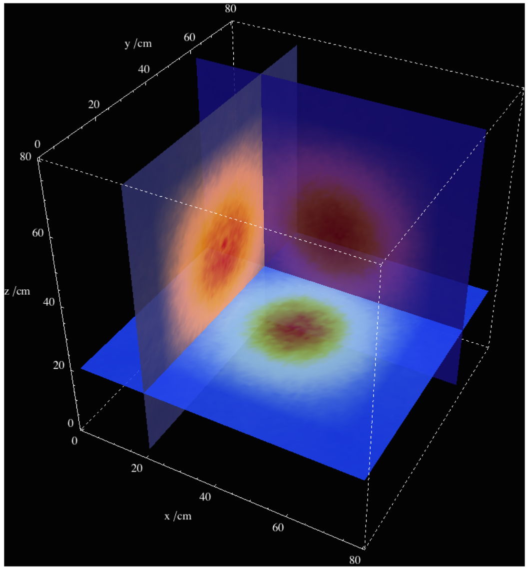
Options for neutron production:

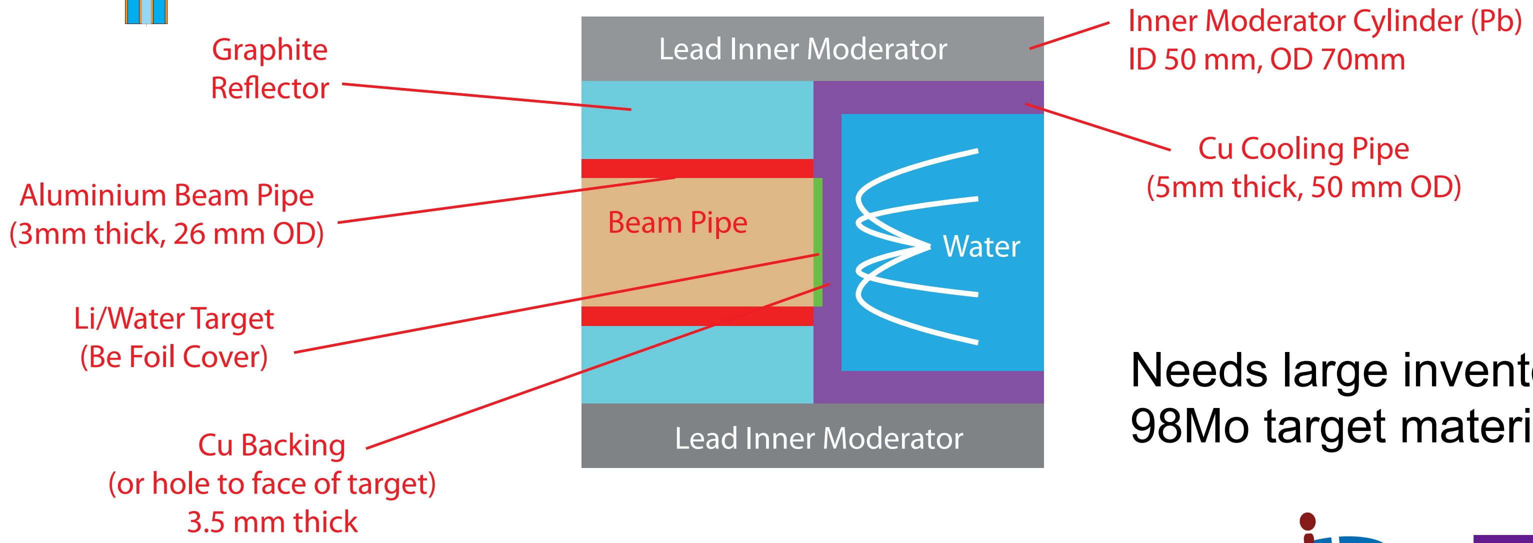
- Li, Be targets at low energy (p, 3 to 30 MeV)
- Pb spallation at high energy (p, c. 1 GeV)
- Photoneutron production (e-, 30-50 MeV)
- D-T reaction

The Cockcroft Institute of Accelerator Science and Technology
MANCHESTER 1824

Moderated Neutron Capture for 99Mo Production



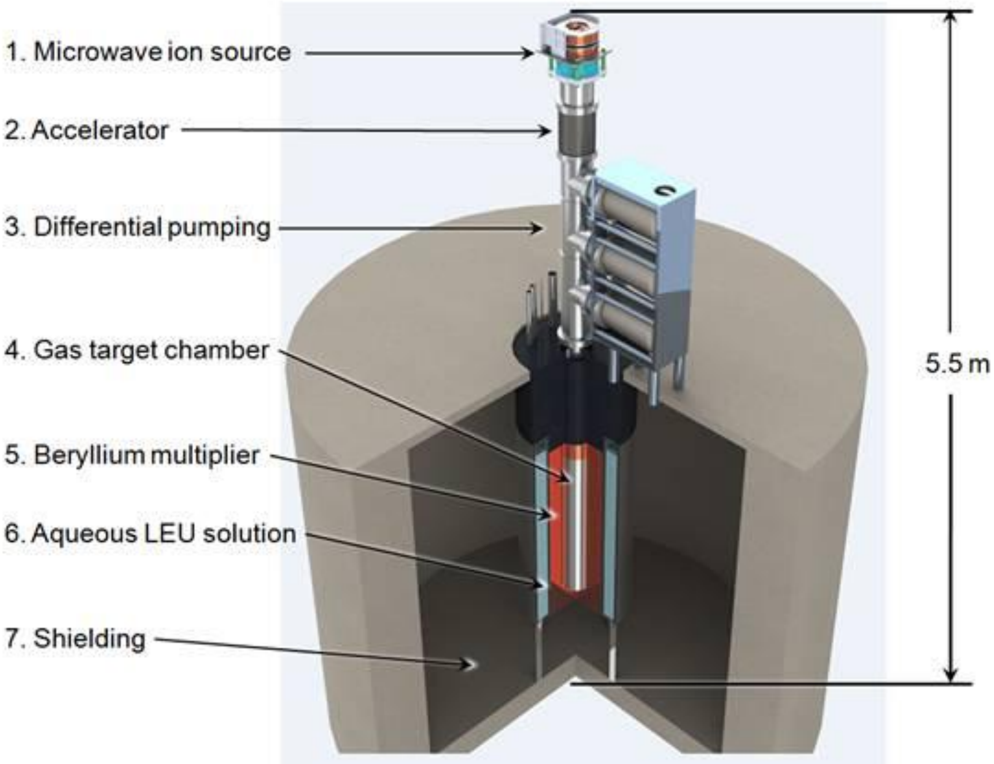




Needs large inventory of 98Mo target material

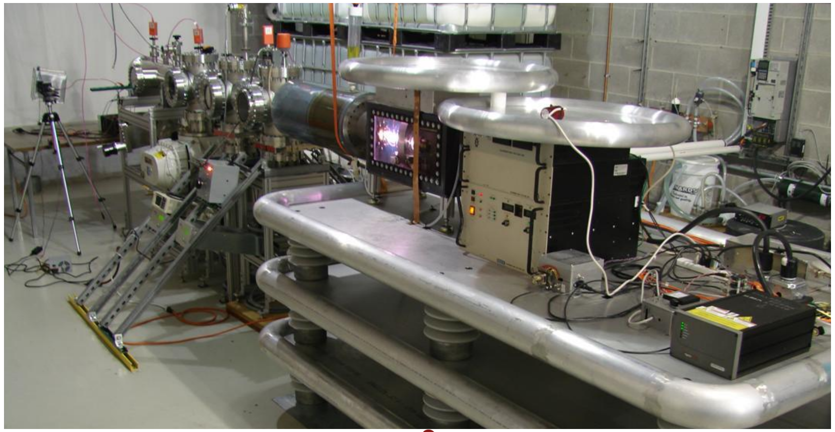
The Cockcroft Institute of Accelerator Science and Technology

Subcritical Neutron Fission



SHINE/Morgridge

- D-T source in center
- Be multiplier
- Annular Geometry
- LEU Solution
- Externally moderated
- No active control elements
- Fission power:
  ~ 75 kW per device
- ^{99}Mo production rate:
  500 6-day Ci / wk



6

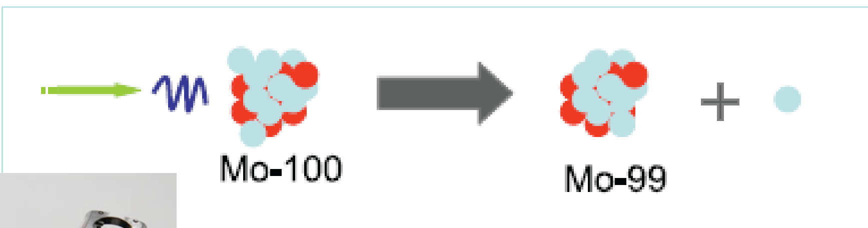
100 mA, 30 kW, 10^14 ns/s @ 14 MeV
125 Ci tritium consumption per year
Multiple isotopes cf. reactor targets

The Cockcroft Institute of Accelerator Science and Technology
MANCHESTER 1824

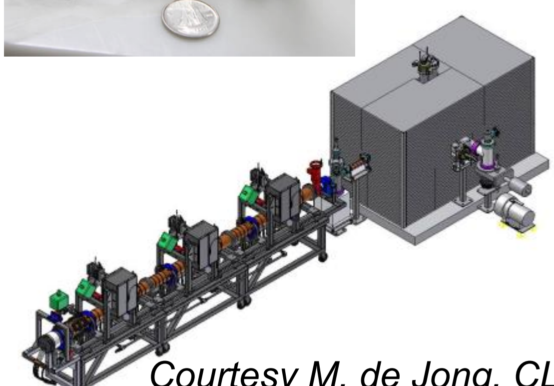
Photonuclear

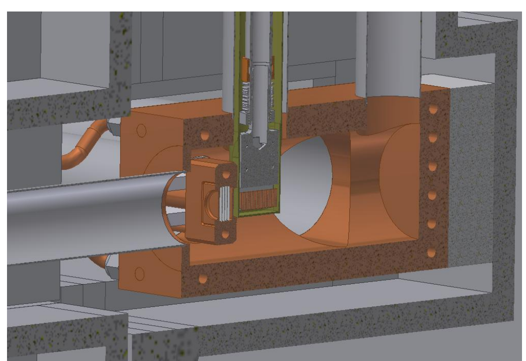
- Photo-nuclear reaction on ^{100}Mo:
  - $^{100}Mo(\gamma, n)\,^{99}Mo$

- Natural Mo about 10 % ^{100}Mo
- Available at enrichments of > 95 %
- Known for more than 40 years
- Photons produced via Bremsstrahlung using high-energy electrons from linear accelerator ⇨ high-energy X-rays



100Mo target (CLS)





Courtesy M. de Jong, CLS

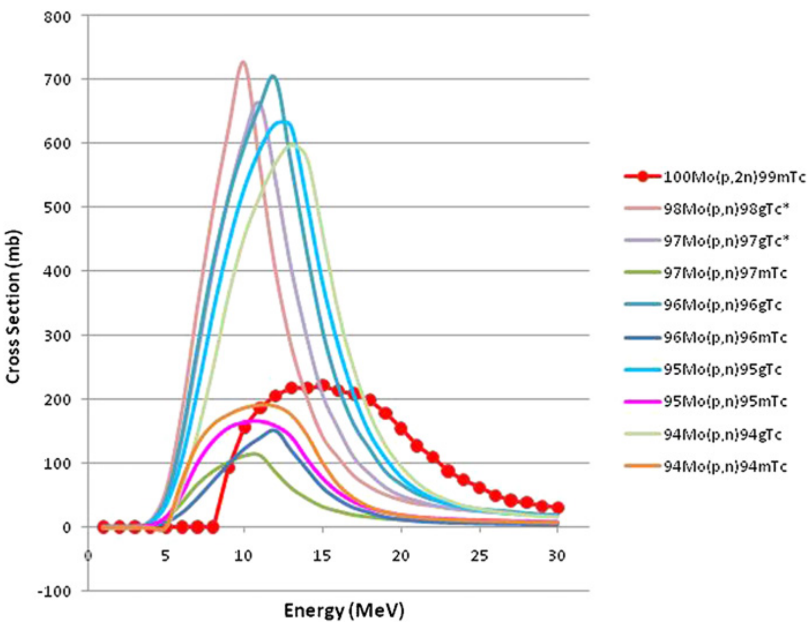
NRC INMS Proof-of-concept

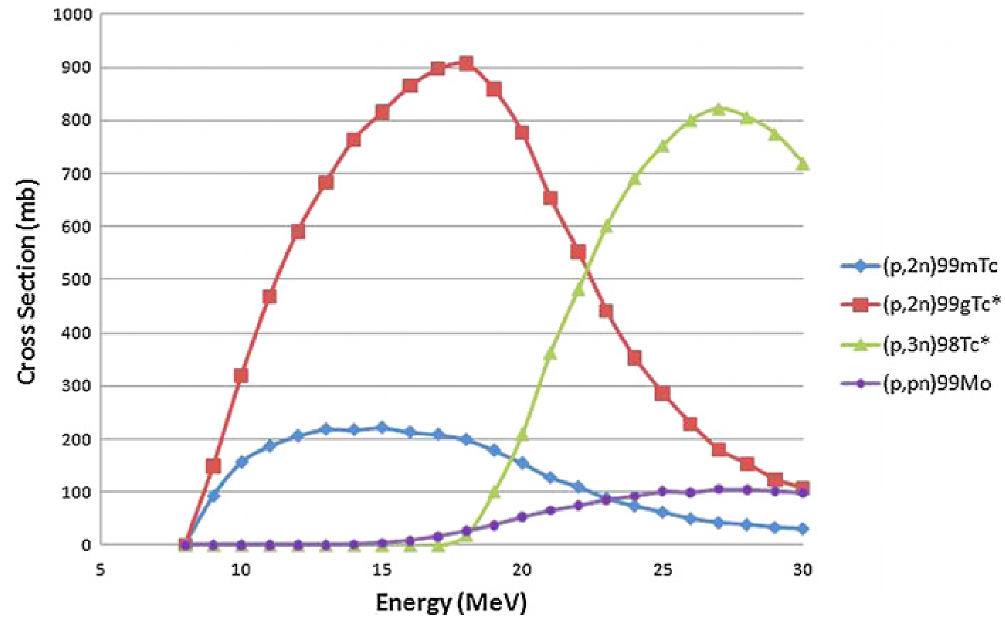
GE Dale et al., AIP Conf.Proc.1525, 355(2013)
JA Osso Jr, Curr. Radiopharm. 5, 178 (2012)

The Cockcroft Institute of Accelerator Science and Technology
MANCHESTER 1824

Cyclotron Production of Tc-99m

$^{98}Mo(p,\gamma)^{99m}Tc$
$^{100}Mo(p,2n)^{99m}Tc$
$^{100}Mo(p,pn)^{99}Mo \rightarrow {}^{99m}Tc$





Celler et al., PMB 56, 5469 (2011)

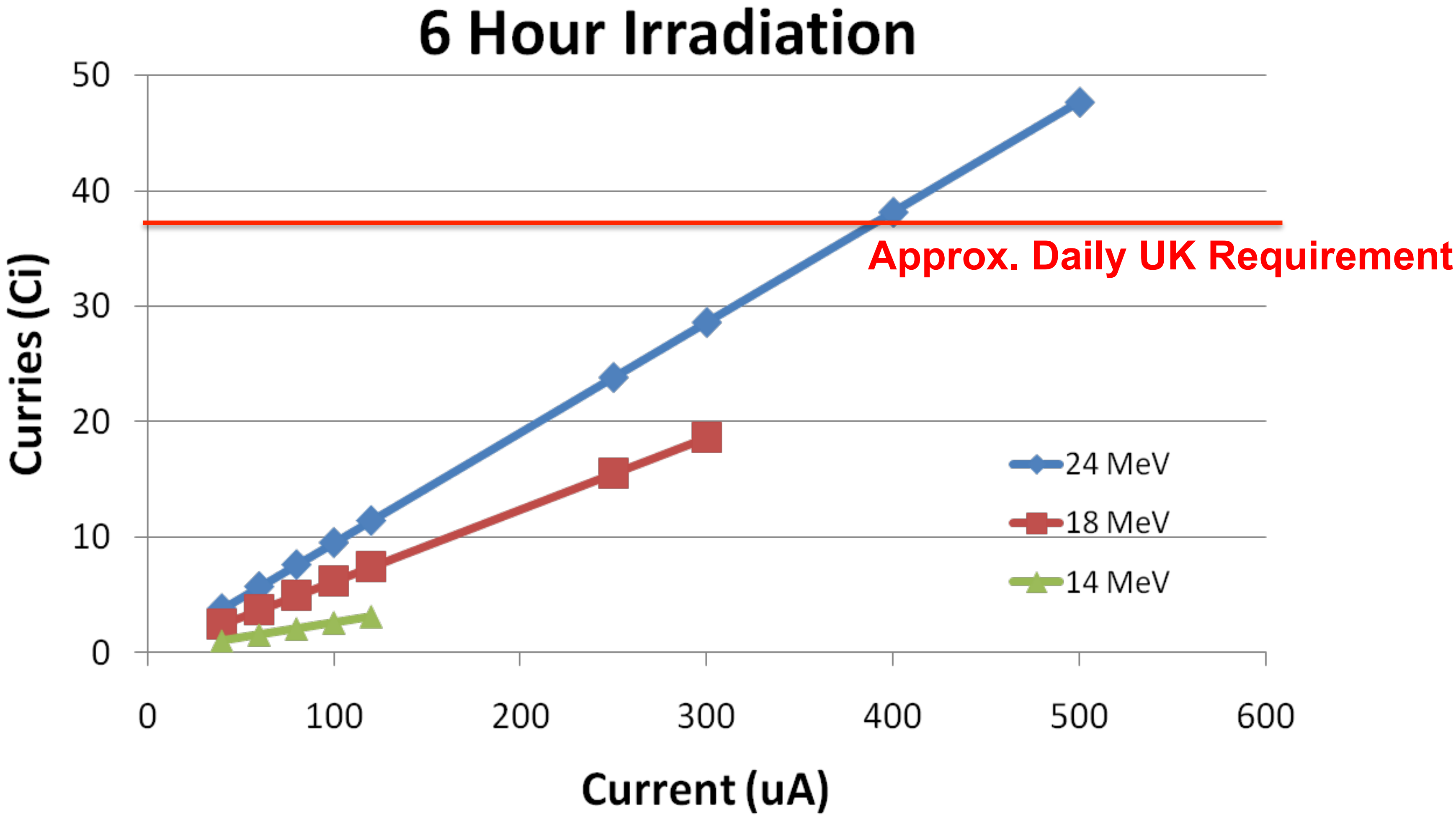
The Cockcroft Institute of Accelerator Science and Technology

MANCHESTER 1824

Steps in Accelerator (Cyclotron) Production of 99mTc

- Enriched ^{100}Mo target
- Irradiate in proton cyclotron, 4-6 h at around 19MeV/500 uA
- Extract ^{99m}Tc from target
- (Recover and recycle ^{100}Mo)
- Purify ^{99m}Tc to pharmaceutical standards
- Prepare ^{99m}Tc products on site or ship ^{99m}Tc pertechnetate to satellite radiopharmacies
- Do the same thing again later...

Yield vs. Current



AJB McEwan, U Alberta

The Cockcroft Institute of Accelerator Science and Technology

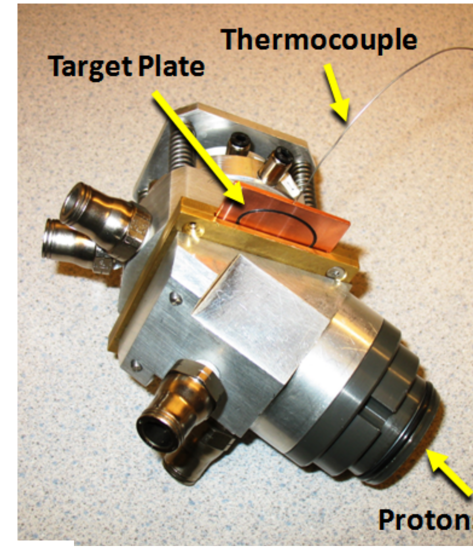
MANCHESTER 1824

Target Issues

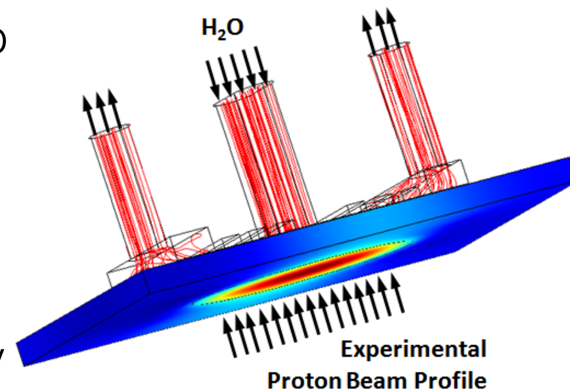
Benard F et al., 'Implementation of Multi-Curie Production of 99mTc by Conventional Medical Cyclotrons', J Nucl. Med. 2014;55(6):1017-1022.
Gagnon et al., 'Cyclotron production of 99mTc: recycling of enriched 100Mo metal targets', Appl. Radiat. Isot. 2012; 70:1685-90

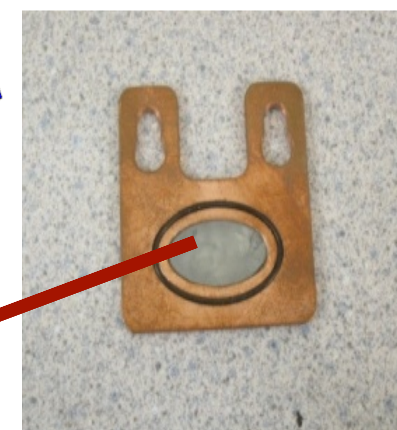
TABLE 3
Large Target Production Runs

Parameter	Run 1	Run 2	Run 3	Run 4
Target enrichment (%)	99.01	99.01	97.39	97.39
Energy (MeV)	18–11	18–12	18–12	18–12
Irradiation time (h)	1.5	1.32	6.43	6.9
Average current (μA)	85	159	188	223
Charge (μA·min)	7,775	13,555	74,895	83,223
^{99m}Tc activity (GBq)	55.5*	96.2*	333	348
Saturated yield (GBq/μA)	4.05*	4.0*	3.3	3.03



- Sintering/pressing of 100Mo onto Cu backing
- Target power is a limiting factor
- Set thickness to optimise yield/ purity
- Need efficient chemical recovery of unconverted 100Mo (>95%)





Critical component

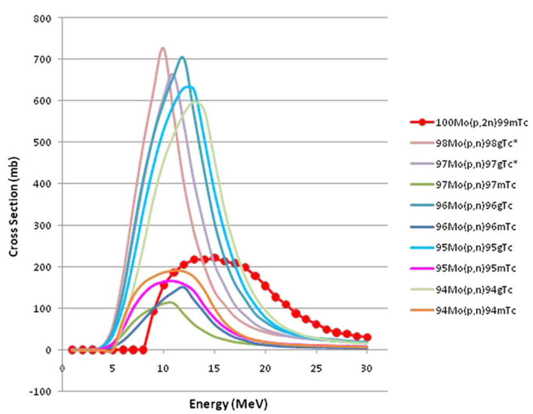
The Cockcroft Institute of Accelerator Science and Technology

MANCHESTER 1824

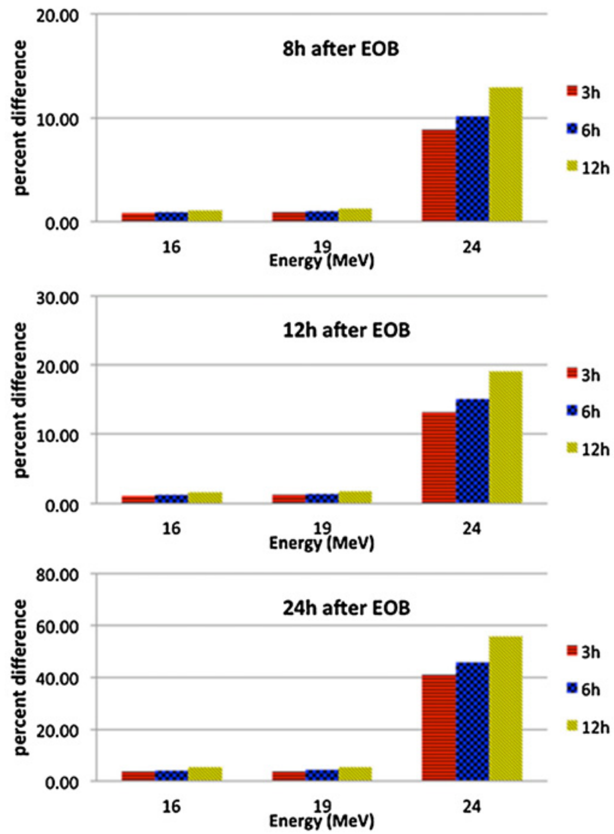
Yield is Not Everything...

Typical radiation dose: 2-4 mSv
(~0.5 J energy deposited)

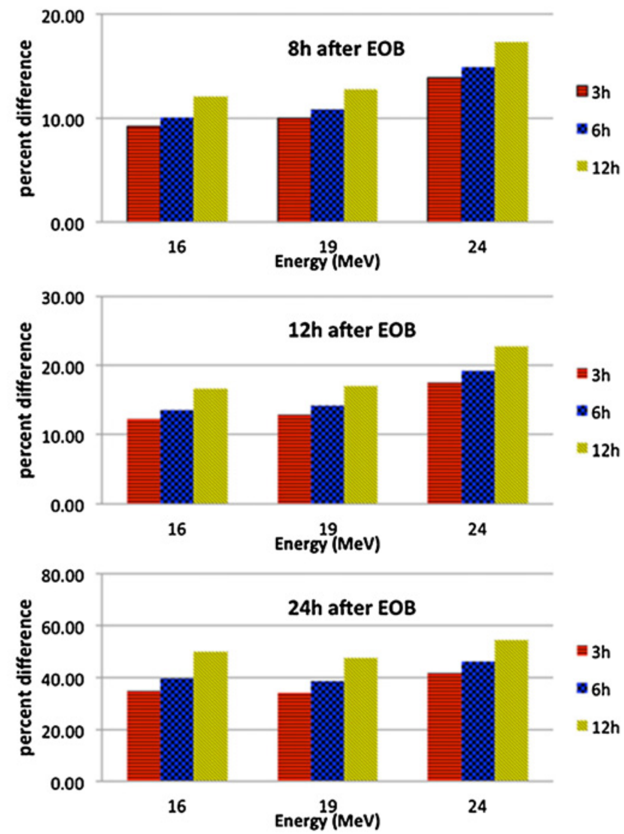
	Enriched targets			
Isotopes	Option A[a]	Option B[b]	Option C[b]	Natural
^{92}Mo	0.005	0.0060	0.09	14.85
^{94}Mo	0.005	0.0051	0.06	9.25
^{95}Mo	0.005	0.0076	0.10	15.92
^{96}Mo	0.005	0.0012	0.11	16.68
^{97}Mo	0.01	0.0016	0.08	9.55
^{98}Mo	2.58	0.41	0.55	24.13
^{100}Mo	97.39	99.54	99.01	9.63



Optimum energy: 19->10 MeV
(thin target)



Option A



Option C

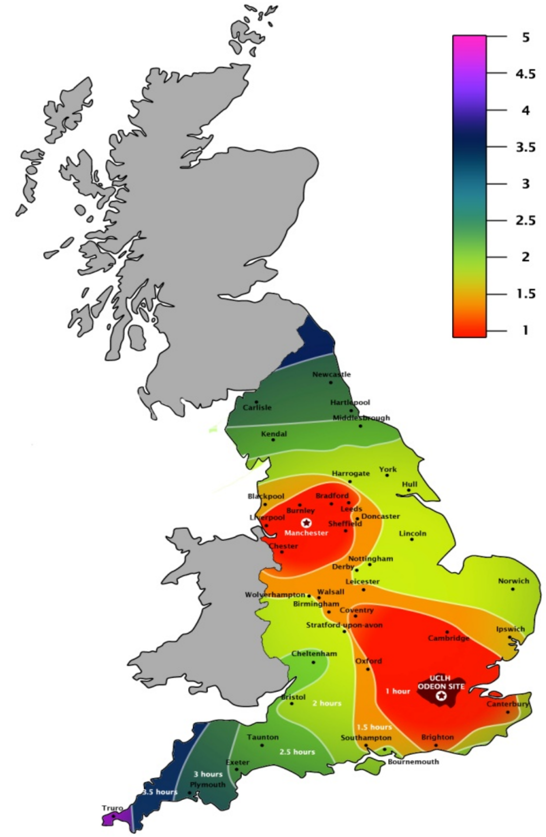
Hou X, Celler A, Grimes J, Benard F, Ruth T, 'Theoretical dosimetry estimations for radioisotopes produced by proton-induced reactions on natural and enriched molybdenum targets', Phys. Med. Biol. 2012; 57:1499-1515

The Cockcroft Institute of Accelerator Science and Technology

MANCHESTER 1824

Distributed production, shipping each day

AJB McEwan, U Alberta



99Mo (fission): 1 centre, UK/overseas
99mTc (direct): Local centres, commercial/hospital

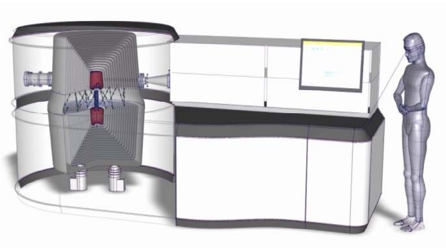
UK: 2 cyclotrons?
1 North
1 South

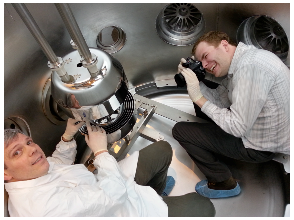
The Cockcroft Institute of Accelerator Science and Technology

MANCHESTER 1824

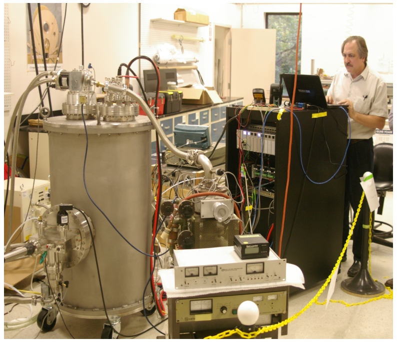
Sources of protons

Conventional and/or compact cyclotrons

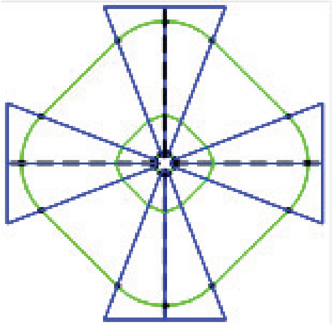




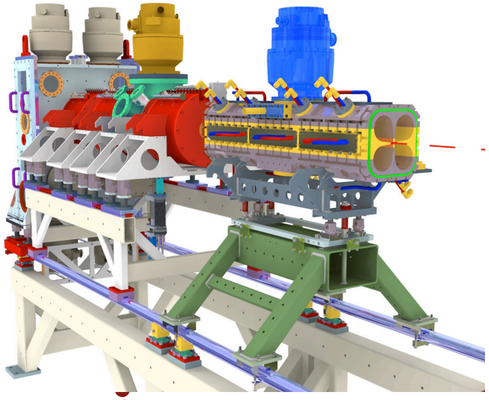
Siemens Oniac, IPAC14/TUPME039



Ionetix ‘Isotron’ SC cyclotron (6T,12.5MeV)
Rev. Acc. Sci. Tech. 5, 227 (2012)



RAL FETS, IPAC2013/THPWO086
6 mA!



PIP FFAG, IPAC2013/THPWA037

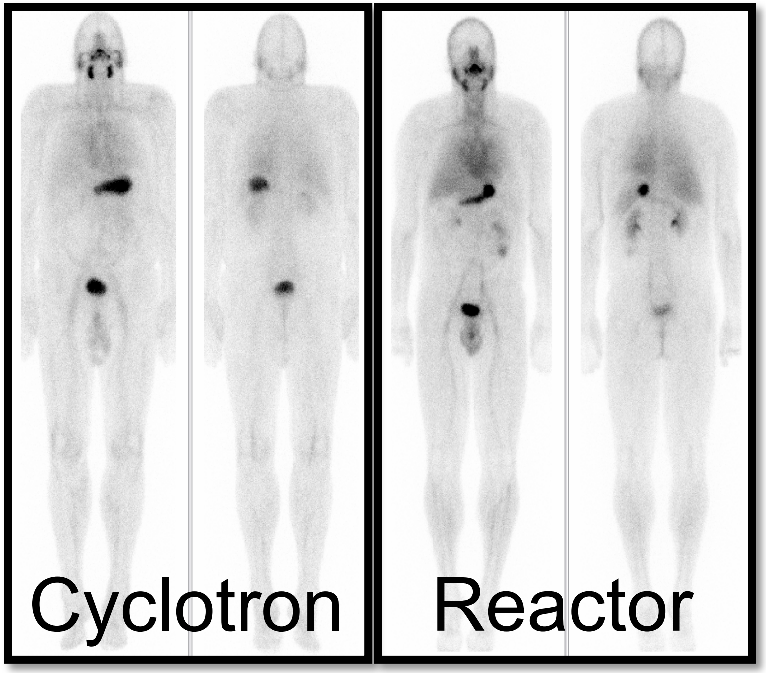
All too low energy;
laser-based sources too low current

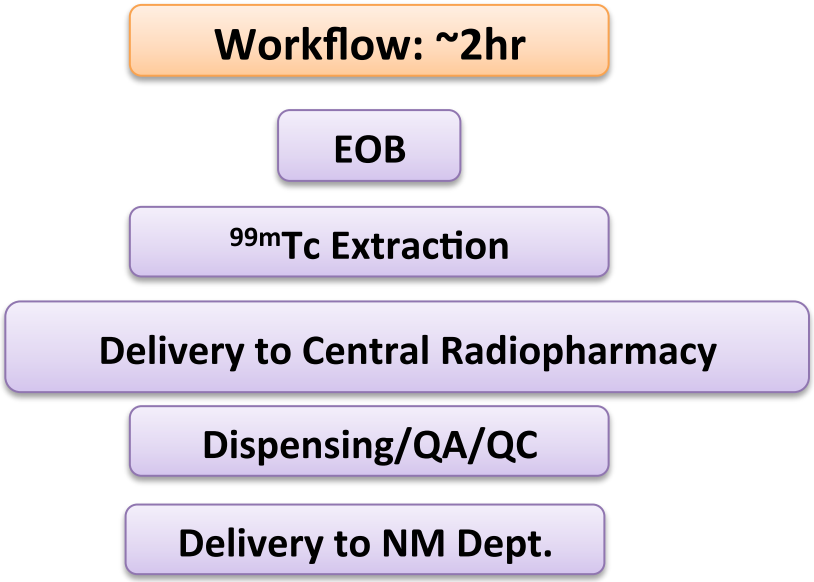
The Cockcroft Institute of Accelerator Science and Technology

MANCHESTER 1824

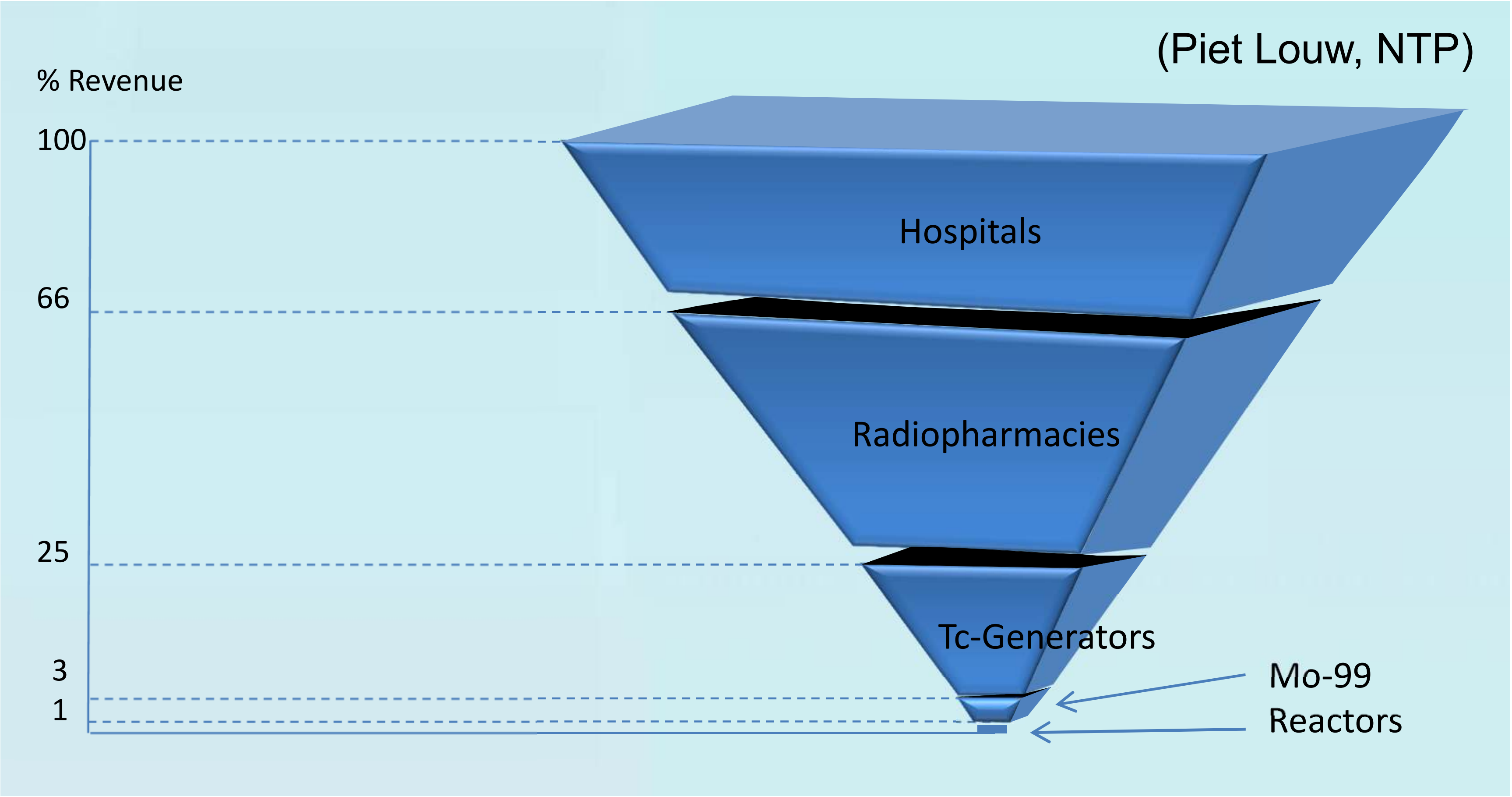
Clinical Comparison

- First two patients in cyclotron arm of trial imaged 12 Oct 2011.
  - Images were first presented at the Annual Congress of the European Association of Nuclear Medicine, Birmingham, UK, Oct 2011.
- Phase 1 trial; completed March 2012.
  - J Nucl Med, 53 (2012) S1: 1487





Share of Revenue



Fission Mo99 moving to Full Cost Recovery
Accelerators have to achieve c.£10 per dose (~27 mCi)

The Cockcroft Institute of Accelerator Science and Technology
MANCHESTER 1824

How much might a cyclotron dose cost? (v. approx.)

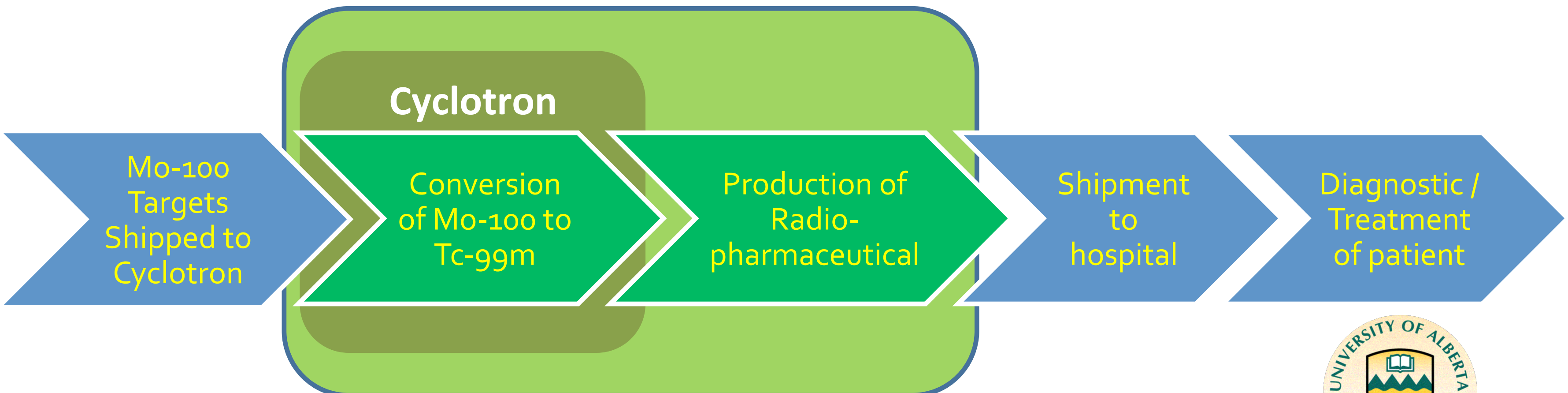
• 1 Accelerator over 20y:	$1,000,000
– Construction: $9,000,000	
– Equipment: $6,000,000	
• Annual Licensing:	$750,000
• Consumables:	$500,000
• Staff	$900,000
• Operation and Maintenance	$800,000
• Total:	$4,000,000
• Assume 200,000 doses per year:	
	$20.00/Dose

Might be profitable...

The Cockcroft Institute of Accelerator Science and Technology

MANCHESTER 1824

Possible 99mTc Cyclotron Supply Chain



- Advantages of direct (cyclotron) model:
  - No use of uranium/LEU/HEU
  - No radioactive material crossing borders
  - No time sensitive material crossing borders
  - No fissile waste
  - Production on demand/local control of supply – seen as particular advantage in UK
  - Co-production of other isotopes, e.g. PET – PET in the morning, 99mTc at night

Summary

- Direct production of 99mTc is advantageous in number of ways
  - No fission/HEU/waste
  - Local control and distribution
  - but needs different model to conventional fission supply

- Cyclotron technology is well-established
  - New technologies must compete on price

- Choice must be based on commercial considerations
  - Uncertainty about future price/availability from reactor supply
  - Growth/decline in need for 99mTc