Options for UK 99mTc Production Using Accelerators

Hywel Owen
on behalf of UK Isotope Working Group
Global Radiopharmaceutical Diagnostic Market

2010

US$3.2 Billion

- 99mTc: 85%
- 18FDG: 10%
- Other: 5%

2017

US$4.1 Billion

- 99mTc: 72%
- 18FDG: 17%
- Other: 11%

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
Some facts about 99mTc

- >30 M procedures per year
- ~0.5 M in UK

![Pie chart showing distribution of 99mTc usage globally](image)

![Graph showing time and activity of 99mTc](image)

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

United States, 44%

Canada, 4%

Japan, 14%

Europe, 22%

Other, 12%

Myocardial perfusion 56%

Infection/Inflammation 2%

Tumor Imaging 2%

Thyroid/Parathyroid 3%

Renal 3%

Respiratory 4%

Liver/Hepatobiliary 7%

Bone scans 17%

Other cardiovascular

Source:
- Belgium
- Germany
- Luxembourg
- Netherlands
- Norway
- Sweden
- Switzerland
- United Kingdom

UK HPA 2008
Mo-99/Tc-99m/Tc-99

\[ ^{99}\text{Mo} \rightarrow ^{99}\text{Tc} \rightarrow ^{99m}\text{Tc} \rightarrow ^{99}\text{Tc} \rightarrow ^{99}\text{Ru} \]

- \( \beta \) decay, \( \tau_{1/2} = 66 \text{ h} \)
- \( \gamma \) transition, \( \tau_{1/2} = 6.01 \text{ h} \)
- \( \beta \) decay, \( \tau_{1/2} = 211100 \text{ y} \)

140 keV
Mass 99 Decay Chain

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>99Y</td>
<td>1.470(7) s</td>
</tr>
<tr>
<td>99Zr</td>
<td>2.1(1) s</td>
</tr>
<tr>
<td>99Nb</td>
<td>15.0(2) s</td>
</tr>
<tr>
<td>99Mo</td>
<td>2.7489(6) d</td>
</tr>
<tr>
<td>99Tc</td>
<td>2.111(12)E+5 a</td>
</tr>
<tr>
<td>99Ru</td>
<td>Stable</td>
</tr>
</tbody>
</table>

Thermal Neutron Fission of U-235
## Current Irradiators 2013

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

---

OECD January 2014 HLG-MR Report
## Current Processors

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

OECD January 2014 HLG-MR Report
Irradiation capacity and projected future demand, Global, 2015-2020

OECD January 2014 HLG-MR Report

6-day curies EOP

Current irradiator capacity
Demand with no ORC
Demand + 33% ORC

'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

Hywel Owen IPAC14 | THOAB02 | 19 June 2014 | 8
Technetium Generators

Eluent

Needle
Metal closure
Glass column
Lead shielding
Eluate
Sterile filter

<table>
<thead>
<tr>
<th>Supplier</th>
<th>Produce and ship</th>
<th>Deliver</th>
<th>Reference</th>
<th>Sizes</th>
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<tbody>
<tr>
<td>Covidien</td>
<td>Weekdays R-7</td>
<td>Next day R-6</td>
<td>Weekdays R-0</td>
<td>2.15-43 GBq</td>
</tr>
<tr>
<td></td>
<td>Weekdays R-6</td>
<td></td>
<td></td>
<td>_99m^Mo 12 sizes</td>
</tr>
<tr>
<td>GE</td>
<td>Tue R-6</td>
<td>Wed R-5</td>
<td>Mon R-0</td>
<td>2.5-100 GBq</td>
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<tr>
<td></td>
<td>Thu R-7</td>
<td>Fri R-6</td>
<td>Thu R-0</td>
<td>_99m^Mo 18 sizes</td>
</tr>
<tr>
<td>IBA/Qados</td>
<td>Tue R-8</td>
<td>Wed R-7</td>
<td>Wed R-0</td>
<td>2-20 GBq</td>
</tr>
<tr>
<td></td>
<td>Fri R-8</td>
<td>Sat R-7</td>
<td>Sat R-0</td>
<td>_99m^Tc 8 sizes</td>
</tr>
</tbody>
</table>
Problems with the reactor method

- Reactors are all very old, with disrupted replacement plans:
  - MAPLE-1/2 cancelled
  - 1997-2007: 4 disruptions
  - 2007-2009: 5 disruptions
  - May 2009 & October 2009 are shortage months when 3 reactors are down

- Only marginal cost appears in Tc99m cost
  - NEA recommend full cost recovery now

Uranium enrichment

- 5% for power, e.g. PWR
- 20% for research
- 95% for Mo-99 (or bombs)
- LEU < 20%
- HEU >20%

- 95% of global HEU use is for Mo-99 production
- USA does not like HEU being shipped around in boxes
  - RERTR programme is changing all HEU fuel for LEU
<table>
<thead>
<tr>
<th>Reactor</th>
<th>Targets</th>
<th>Operating days (Number)</th>
<th>Available weekly capacity (6-day Ci)</th>
<th>Potential annual production (6-day Ci)</th>
<th>Estimated stop production date</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>RIAR (Russia)</td>
<td>HEU in CRR</td>
<td>350</td>
<td>1200</td>
<td>60000</td>
<td>2015</td>
<td>Started</td>
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<tr>
<td>Karpov Institute</td>
<td>HEU in CRR</td>
<td>345</td>
<td>300</td>
<td>14800</td>
<td>2015</td>
<td>Started</td>
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<tr>
<td>NORTHSTAR/MURR (USA)</td>
<td>Non-fissile in CRR</td>
<td>365</td>
<td>2750/3000</td>
<td>39100/156400</td>
<td>2015/17</td>
<td>Phase 1</td>
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<tr>
<td>FRM-II (Germany)</td>
<td>LEU in CRR</td>
<td>240</td>
<td>1600</td>
<td>54300</td>
<td>2017</td>
<td>Infrastructure in place</td>
</tr>
<tr>
<td>MORGRIDGE/SHINE (US)</td>
<td>LEU solution with DTA</td>
<td>300</td>
<td>3000</td>
<td>144000</td>
<td>2017</td>
<td>NYS</td>
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<td>OPAL</td>
<td>LEU in CRR</td>
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<td>2600</td>
<td>111400</td>
<td>2017</td>
<td>NYS</td>
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<td>KOREA</td>
<td>LEU in CRR</td>
<td>300</td>
<td>2000</td>
<td>85700</td>
<td>2018</td>
<td>Concept</td>
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<tr>
<td>NORTHSTAR (USA)</td>
<td>Non-fissile from LINAC</td>
<td>336</td>
<td>3000</td>
<td>144000</td>
<td>2018</td>
<td>NYS</td>
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<tr>
<td>CHINA Advanced RR</td>
<td>LEU in CRR</td>
<td>350</td>
<td>1000</td>
<td>50000</td>
<td>2019</td>
<td>Modification</td>
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<td>Brazil MR</td>
<td>LEU in CRR</td>
<td>290</td>
<td>1000</td>
<td>41400</td>
<td>2019</td>
<td>Preliminary</td>
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<tr>
<td>RA-10 (Argentina)</td>
<td>LEU in CRR</td>
<td>336</td>
<td>2500</td>
<td>120000</td>
<td>2019</td>
<td>Preliminary</td>
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<tr>
<td>Jules HOROWITZ RR (France)</td>
<td>LEU in CRR</td>
<td>220</td>
<td>3200</td>
<td>100600</td>
<td>2020</td>
<td>Under Construction</td>
</tr>
</tbody>
</table>
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)

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
Moderated Neutron Capture for 99Mo Production

Graphite Reflector
Aluminium Beam Pipe (3mm thick, 26 mm OD)
Li/Water Target (Be Foil Cover)
Cu Backing (or hole to face of target) 3.5 mm thick

Lead Inner Moderator
Inner Moderator Cylinder (Pb)
ID 50 mm, OD 70mm
Cu Cooling Pipe (5mm thick, 50 mm OD)

Needs large inventory of 98Mo target material
Subcritical Neutron Fission

- 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

SHINE/Morgridge

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

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

• Natural Mo about 10% $^{100}\text{Mo}$
• 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)

Cyclotron Production of Tc-99m

Theoretical modeling of yields for proton-induced reactions on natural and enriched molybdenum targets

Figure 2. Excitation functions corresponding to the $^{100}\text{Mo} + p$ reaction products with the highest cross sections in the investigated energy range. Stable isotopes are marked by an asterisk.

3. Results

3.1. Results of the cross-section calculations

When taking into account all creation/decay possibilities (and the selection criteria listed in section 2.4), $^{99m}\text{Tc}$ can be produced by two dominant reaction channels, namely $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ and $^{100}\text{Mo}(p,pn)^{99}\text{Mo} \rightarrow ^{99m}\text{Tc}$. However, as mentioned, other reactions on $^{100}\text{Mo}$ and other molybdenum isotopes will lead to the creation of a number of different (i.e. $\neq^{99m}\text{Tc}$) technetium isotopes. Radioactive technetium isotopes other than $^{99m}\text{Tc}$ must be considered as contaminants as they will contribute to the radiation dose to the patient, while production of stable technetium isotopes (please remember $T_{1/2} > 10^3$ years are considered stable) will decrease the specific activity of the sample.

Table 2 summarizes the cross sections for the proton-induced production of all technetium isotopes. For each isotope its half-life and decay products are listed, together with the corresponding branching ratios. The asterisk next to the isotope symbol signifies a stable product (i.e. $T_{1/2} > 10^3$ years). Table 3 presents the same data for the production of radioactive isotopes other than technetium. The data presented in both tables follow the criteria listed in section 2.4.

Figure 2 shows the excitation functions for the four reaction channels which have the highest cross sections for the $^{100}\text{Mo} + p$ reaction. Fortunately $^{99}\text{Mo}$, whose yield increases at higher energies, decays to $^{99m}\text{Tc}$ (with branching ratio of 87.6% (Alfassi et al. 2005, Brown and Tuli 2011)); therefore, contribution from this (p,pn) reaction will only increase the $^{99m}\text{Tc}$ production yield.

Additionally, figure 3 compares the excitation functions for the $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ production to the six radioactive (isomeric and ground states) technetium isotopes produced through the (p,n) reaction channels. Figure 4 presents similar data for the (p,2n) reaction.

3.2. Reaction yield results

In order to identify the optimal conditions for the cyclotron production of $^{99m}\text{Tc}$ the 99.54% enriched molybdenum thick target yields were calculated for irradiation times of 3, 6, 9 and 12 h. Proton beam energies of 16–10 MeV, 19–10 MeV and 24–10 MeV and 200 $\mu$A were used. This energy range was selected based on the analysis of the results of cross-section calculations. The excitation functions presented in figures 3 and 4 indicate that in the 6–10 MeV energy range the contributions from the (p,n) reactions dominate, while the $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ production begins only at about 9 MeV. Therefore, in our opinion, in order to

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

6 Hour Irradiation

Approx. Daily UK Requirement

Curries (Ci) vs. Current (uA)

- 24 MeV
- 18 MeV
- 14 MeV

AJB McEwan, U Alberta
Target Issues

- 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%)

**TABLE 3**

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


Yield is Not Everything...

<table>
<thead>
<tr>
<th>Isotopes</th>
<th>Option A</th>
<th>Option B</th>
<th>Option C</th>
<th>Natural</th>
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</thead>
<tbody>
<tr>
<td>$^{92}$Mo</td>
<td>0.005</td>
<td>0.0060</td>
<td>0.09</td>
<td>14.85</td>
</tr>
<tr>
<td>$^{94}$Mo</td>
<td>0.005</td>
<td>0.0051</td>
<td>0.06</td>
<td>9.25</td>
</tr>
<tr>
<td>$^{95}$Mo</td>
<td>0.005</td>
<td>0.0076</td>
<td>0.10</td>
<td>15.92</td>
</tr>
<tr>
<td>$^{96}$Mo</td>
<td>0.005</td>
<td>0.0012</td>
<td>0.11</td>
<td>16.68</td>
</tr>
<tr>
<td>$^{97}$Mo</td>
<td>0.01</td>
<td>0.0016</td>
<td>0.08</td>
<td>9.55</td>
</tr>
<tr>
<td>$^{98}$Mo</td>
<td>2.58</td>
<td>0.41</td>
<td>0.55</td>
<td>24.13</td>
</tr>
<tr>
<td>$^{100}$Mo</td>
<td>0.005</td>
<td>0.0012</td>
<td>0.09</td>
<td>9.63</td>
</tr>
</tbody>
</table>

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

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

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
Sources of protons

Siemens Oniac, IPAC14/TUPME039

Conventional and/or compact cyclotrons

Ionetix ‘Isotron’ SC cyclotron (6T, 12.5MeV)
RAL FETS, IPAC2013/THPWO086
6 mA!

PIP FFAG, IPAC2013/THPWA037

All too low energy; laser-based sources too low current
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.
Fission Mo99 moving to Full Cost Recovery
Accelerators have to achieve c.£10 per dose (~27 mCi)
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...*
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