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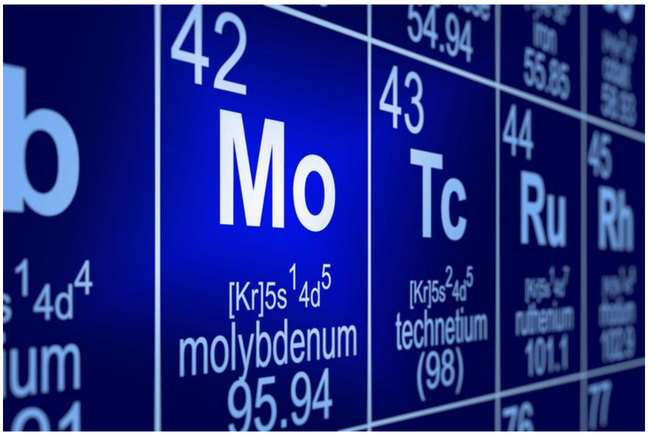
Supply of Medical Radioisotopes



Radioisotopes are essential tools used in medicine. They are made outside the UK in ageing research reactors subject to outages and shutdowns, increasing the risk of shortages. This POSTnote outlines the challenges of supplying medical radioisotopes and analyses the various options for ensuring the continuity of their supply in the UK.

Overview

- Radioactive isotopes are essential tools in medicine for both diagnosis and treatment, but rapid radioactive decay means that they cannot be stockpiled.
- Following previous shortages, the NHS has reduced the amount of radioisotopes used through efficiency savings.
- Long-term security of supply may rely on investment and agreements with international producers, or investing in new technology to produce them in the UK.
- The Government has stated that withdrawal from the European Atomic Energy Community (EURATOM) will not affect the UK's ability to import medical radioisotopes.
- Therapeutic use of radioisotopes is a small field, but expected to grow rapidly in the next decade, as new drugs are developed.

Background

Radioisotopes are unstable chemical elements that undergo radioactive decay. During decay they change form and emit excess energy as radiation. They are essential tools used in nuclear medicine, where they are typically combined with a drug that guides the radioisotope to a particular part of the body. Depending on the radioisotope and the procedure, the radiation is either detected by a scanner to produce an image (diagnosis), or damages target cells in the body (therapy). In the UK, around 700,000[1] nuclear medicine procedures using radioisotopes are carried out each year, such as diagnosing coronary disease,[2] detecting the spread of cancer to bones,[3] and treating thyroid cancer[4] (Box 1). Radioisotopes are also important biomedical research tools.

Many medically useful radioisotopes decay within hours or days, making them vulnerable to short-term disruptions to supply. The most commonly used radioisotope is technetium-99m (^{99m}Tc), which accounts for over 80% of diagnostic nuclear medicine procedures and is the focus of this note. A key part of ^{99m}Tc production is carried out in a small number of nuclear research reactors, none of which are in the UK (Box 2). Research reactors are used for materials testing, research and isotope production, and not for generating electricity.[5] In 2009, the temporary shutdown of two reactors caused a global shortage of ^{99m}Tc, leading to delayed and cancelled medical procedures in the UK, as well as disrupting research. In 2015 and 2016, two of the largest reactors producing medical radioisotopes were closed, prompting concerns over future shortages. This POSTnote explains how ^{99m}Tc is produced and describes issues with the supply chain. It summarises risks of future shortages, and explores how the UK can increase the security of supply.

Producing technetium

^{99m}Tc is produced by the radioactive decay of molybdenum-99 (^{99}Mo). ^{99}Mo is currently made in nuclear research reactors through the fission (splitting) of enriched uranium. Neither isotope can be stockpiled because they decay rapidly: the amount of useful radiation emitted by ^{99m}Tc halves every 6 hours, and the yield of ^{99m}Tc obtained from ^{99}Mo halves every 66 hours.[6] ^{99}Mo is loaded into dispensers called generators, which are shipped to the end-users, radiopharmacies (Box 1). Radiopharmacies extract ^{99m}Tc from the generators by flushing them with saline (saltwater). A generator typically lasts 1-2 weeks.

Alternative technologies for producing ^{99m}Tc have been investigated since the 2009 shortage (Box 3). None of these are in routine use, but some are likely to enter the market within the next few years, and are discussed later.

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Box 1. Nuclear medicine

Nuclear medicine procedures typically involve administering a radiopharmaceutical, created by combining a radioisotope with a drug that guides it to a particular part of the body. These are prepared in radiopharmacies. The UK is served by a network of more than 100 radiopharmacies, many of which are part of hospitals' nuclear medicine departments.[7] More than 95% of procedures carried out are diagnostic,[1] but therapeutic applications are increasing.

Diagnostic use

Diagnostic nuclear medicine uses two imaging systems:

- **Gamma cameras** are the most commonly used system in nuclear medicine. They are most often used for investigations of the brain, heart and bones. The majority of these scans use ^{99m}Tc, but some make use of other radioisotopes, including iodine-123 and indium-111.
- **PET scans** are predominantly used in oncology.[8] The radioisotopes required are different to those used for gamma camera scans; the most common is fluorine-18. They are produced in low power cyclotrons (particle accelerators) around the UK; their supply is relatively secure.

Therapeutic use

- The most common therapeutic radioisotopes are iodine-131 (produced in the same process that makes ^{99}Mo), used to treat thyroid disorders, and radium-223 for treatment of bone metastases arising from prostate cancer. Therapeutic isotopes are further discussed on page 4.

Box 2. Sources of technetium-99m

^{99m}Tc is made from the decay of ^{99}Mo, which is produced in nuclear research reactors.

Existing reactors

The table below lists the reactors that produce more than 90% of the world's ^{99}Mo supply and cites their maximum production capacity.[18]

Reactor	Location	Capacity as a proportion of global demand*	Estimated end of operation
HFR	Netherlands	38%	2024
BR-2	Belgium	26%	2026
Safari-1	South Africa	21%	2030
MARIA	Poland	15%	2030
OPAL	Australia	15%	2057
LVR-15	Czech Republic	14%	2028
NRU	Canada	Previously 30%, now none.	Closed Oct 2016**

*Global demand as estimated by the OECD-NEA and includes a 35% buffer for outage reserve capacity.[18,19] Total production capacity adds up to more than 100% of global demand because reactors mostly operate at below their maximum capacity.

**NRU is on standby and can restart production if needed until March 2018, when it will close permanently.

Future reactors

New reactors are scheduled to start producing ^{99}Mo by 2022:[18]

Reactor	Location	Capacity as a proportion of global demand*	Estimated start of operation
RA-10**	Argentina	19%	2021
JHR	France	18%	2022
FRM-II	Germany	11%	2020
KJRR**	Korea	3%	2020

*based on current global demand. **intended for domestic supply only.

Issues in the supply chain

Production in nuclear research reactors

Most research reactors that produce ^{99}Mo (Box 2) were built in the 1950s and 1960s[9] and are approaching the end of their lifespans, increasing the length of shutdowns for routine maintenance and the likelihood of unplanned outages. Investment in new facilities has been limited.[10,11]

Transport of radioactive materials

Another vulnerability is the transport of radioactive materials into the UK. Transport delays reduce the amount of useful radioactive product left. In 2008 the closure of the channel tunnel after a fire led to a short-term shortage of ^{99}Mo,[12] and industrial action in Calais in 2015 also delayed deliveries.[13] Extending transport routes (for example, importing from Australia) also reduces the amount of ^{99}Mo left as it decays.

Nuclear non-proliferation

Reactors produce ^{99}Mo from highly-enriched uranium (HEU) or low-enriched uranium (LEU). Production using LEU is less efficient and more expensive[14] but HEU is a proliferation risk[15] and all major producers of medical radioisotopes have agreed to convert to using LEU. Five of the six operational reactors shown in Box 2 use at least some HEU, although they are in the process of converting to LEU.[16] The US plans to end the export of HEU for ^{99}Mo production by 2020.[17] Some reactors also use HEU as fuel; the US may still export HEU for fuel after 2020.[17]

Future demand and supply

Global ^{99}Mo demand is estimated by the Organisation for Economic Co-operation and Development's Nuclear Energy Agency (OECD-NEA).[18] It forecasts growth in demand to be 0.5% per year in developed countries, which account for 84% of global demand, and 5% in developing markets leading to an overall growth of 1.2% per year.[18,20] Other sources predict growth rates as high as 10% in some developing markets,[21] leading to an overall growth rate of 7%.[22] To ensure sufficient worldwide supply of ^{99}Mo, the NEA estimates that supply capacity needs to equal market demand plus an outage reserve capacity (ORC) of 35% of market demand.[18] Current supply is greater than 135% of demand.[18]

Short term supply

The short-term (1-2 years) security of supply has been affected by the closure of the reactor in Canada (Box 2). However the risk is mitigated by capacity expansions of existing reactors[18] and the Canadian reactor remaining on standby in case of shortage until March 2018. The Association of Imaging Producers and Equipment Suppliers (AIPES), a European Economic Interest Grouping, has worked to coordinate planned reactor closures, increasing supply reliability. A 2016 report judged that there is a greater than 50% likelihood of severe supply shortages until planned capacity expansions are complete.[9] However, the NEA, AIPES and several companies consider supply will be reliable in the short term.[18,23,24,25,26]

Box 3. New technologies for producing technetium-99m
Since the 2009 shortage there has been interest in new ways to produce ^{99m}Tc.

Cyclotron production
One mature alternative uses cyclotrons: particle accelerators used in medicine, industry and scientific research.[27] Cyclotron-produced ^{99m}Tc is currently undergoing clinical trials to assess if it can replace reactor derived material.[28] Some cyclotrons can directly produce ^{99m}Tc (rather than its precursor ^{99}Mo) by bombarding ^{100}Mo with protons (positively charged particles).[29] Advantages of this process are that it does not depend on uranium as a source material and that it produces less radioactive waste. Work to develop this process is being led by Canadian teams at the national laboratory for particle physics (TRIUMF) and the University of Alberta.

New processes using reactors or accelerators
Other processes that make use of reactors and accelerators are also in development. The US Department of Energy National Nuclear Security Administration (DOE NNSA) has funded five companies to develop domestic ^{99}Mo production, alongside several private initiatives.[9] It is not certain that all of the technologies used by these companies will work on a commercial scale, or produce ^{99}Mo at a competitive price. The most mature projects are the four remaining DOE NNSA initiatives:[9]

- NorthStar plans to produce ^{99}Mo with two different projects: one uses a research reactor but replaces the uranium source material with ^{98}Mo, and plans to begin production in 2018. The other uses a particle accelerator to bombard a ^{100}Mo target with photons, and plans to start production in 2020. It estimates that both projects could supply 49% of global demand by 2022.
- SHINE plans to produce ^{99}Mo by bombarding uranium salts with neutrons from an accelerator. It aims to begin production in 2020 and hope to meet 32% of global demand by 2022.
- General Atomic and Nordion plan to produce ^{99}Mo in a research reactor with new extraction technology. It plans to begin in 2019 and expect to produce 26% of global demand by 2022.

Note that production estimates are supplied by the companies and that they have not been independently verified.

Medium term supply
In the medium-term (until 2022) the NEA predicts that existing reactors can meet forecast demand.[18] Organisations involved in establishing new reactors (Box 2) and technologies (Box 3) expect to bolster supply, though some of the new methods may not succeed. Estimated production start-dates have already been delayed; for example, the company SHINE first predicted that it could begin production by 2017,[30] now revised to 2020.[18]

Long term supply
A number of factors make it difficult to predict security of supply in the long-term (beyond 2021):

- Significant differences in estimates of market growth.
- If several new technologies do succeed before 2026, there could be an excess of ^{99}Mo capacity. Market pressures could then make some of these companies unviable, forcing them to close.
- Two of the current largest reactors may close by 2026 (Box 2). Failure to replace their supply by new technologies/reactors could lead to further shortages.

Future shortages
Both of the UK ^{99}Mo generator suppliers have a stated policy of treating clients equally in shortages.[31,32] In previous shortages radiopharmacies were concerned by inequitable supply, with larger radiopharmacies prioritised.[33]

Increasing security of supply
Increased security of supply could be achieved through reducing ^{99m}Tc use, relying on accelerator production, investing in new reactors overseas, supporting the market and mitigating the potential effects of Brexit.

Designing clinical services to reduce ^{99m}Tc use
Since 2009, radiopharmacies have reduced the amount of ^{99m}Tc they need through efficiency savings. Many radiopharmacies have achieved this by optimising generator management, delivery and extraction schedules, sometimes assisted by specialised software.[34,35,36] Some nuclear medicine departments have gamma cameras that use special software which can produce comparable quality diagnostic images using a lower (as much as 50%) dose of the radioisotope.[33] In the absence of any systematic review of radiopharmacies' actions to reduce ^{99m}Tc use, it is not known if these efficiency savings have been widely adopted across the NHS.

The Administration of Radioactive Services Advisory Committee (ARSAC) notes that weekend working could enable more efficient use of generators.[33] Nuclear medicine departments do not routinely operate over weekends but some did during shortages. The British Nuclear Medicine Society (BNMS) argues that 7-day working would put pressure on an already stretched workforce and would need to be fully funded to be effective.[1] The Department of Health's (DH) National Imaging Clinical Advisory Group has released guidelines for 7-day working in imaging departments,[37] but nuclear medicine services were excluded because of complex issues around staffing.[38]

The 2014 BNMS report concludes that "patients will be poorly served by not having a cheap, plentiful supply of ^{99m}Tc".[1] Alternative investigations not using ^{99m}Tc are sometimes possible, such as PET or MRI, but a large scale switchover to these would require significant investment. Some procedures can use alternative radioisotopes, but they are typically either more expensive or expose the patient to a higher dose of radioactivity.[1]

Making technetium in accelerators
^{99m}Tc can be produced directly in a cyclotron (see Box 3). The short half-life of ^{99m}Tc means that it has to be distributed daily to end users and is thus suitable only for domestic supply.[39] In contrast, a single ^{99}Mo generator lasts 1-2 weeks. Existing UK cyclotrons are not powerful enough to produce significant quantities of ^{99m}Tc.[40] The private company Alliance Medical is building two sufficiently powerful cyclotrons.[41] Cyclotron-produced ^{99m}Tc would need to be licensed by the UK regulatory authority (MHRA) and meet the purity standards[42] recently laid out in EU guidelines.[43] It is not known how the cost of cyclotron-produced ^{99m}Tc would compare with that obtained from ^{99}Mo generators, though some estimate it would be more

expensive.[44] Pharmaceuticals made with cyclotron-produced ^{99m}Tc may be most efficiently prepared centrally by a small number of larger radiopharmacies; a model used in the US.[45] However, ARSAC and the BNMS suggest that this approach may leave supply vulnerable to equipment failure and increased dependence upon timely transport.[33] The BNMS recommends that any independent sector-led production of ^{99m}Tc should be preceded by an impact assessment on radiopharmacies and nuclear medicine.[1] DH discussed undertaking this review with the BNMS in 2012[38] but nothing has been published.

Building new research reactors

The Nuclear Innovation and Research Advisory Board estimates that building a new research reactor in the UK capable of producing medical isotopes would take ten years and cost £250-400m.[46] Existing reactors have been government funded, but future reactors are likely to depend on private funding, at least in part.[10] Two long-term projects in Europe aim to address the potential isotope shortfall after the planned closures of reactors in Belgium (2026) and the Netherlands (2024). MYRRHA would be built in Belgium, and PALLAS in the Netherlands. The PALLAS business team is seeking investment for the reactor through an international consortium (potentially including the UK), perhaps in exchange for guaranteed access to isotopes.[47]

Supporting the market for radioisotopes

The OECD-NEA has published principles[48] on the security of radioisotope supply that countries (including the UK) have committed to.[49] One is full cost recovery, meaning the full cost of producing ^{99}Mo, including the repair and replacement of reactors, should be included in the price of the isotope and passed along the full supply chain. It is estimated that these price increases will lead to small additional costs per procedure (for example a bone scan).[10] However competition between generator manufacturers has made it difficult to pass increased costs on to radiopharmacies.[50] The OECD-NEA has suggested that unbundling the cost of the radioisotope from the cost of the rest of a procedure may assist full cost recovery.[51] It is difficult to tell whether higher prices charged by operators have led to reactor improvements resulting in increased reliability of supply.[50] Another principle outlined by the OECD-NEA is that there should be reserve capacity to produce ^{99}Mo in case of outages, paid for by the supply chain. Progress has been made towards securing this capacity, but it has not been universally implemented by reactor operators.[50]

Supply of radioisotopes after Brexit

The European Atomic Energy Community (Euratom) regulates civilian nuclear activity[52] and supports the "secure and safe supply and use of medical radioisotopes".[53] The Government confirmed the UK's withdrawal from Euratom in an explanatory note to the EU (Notification of Withdrawal) Bill.[54,55] It considers that the Euratom and EU Treaties are legally joined (the legal basis of this is debated[56]), such that triggering Article 50 gave notice of leaving Euratom. This is also the European Commission's position: a recent statement said that the Euratom Treaty will cease to apply to the UK on 30 March 2019.[63] The Government will establish new agreements to replace Euratom before March 2019. [64,65] Concerns have been raised by stakeholders across academia and industry as to how realistic this is, and its potential negative impacts on the UK's nuclear sector including nuclear research, power and medicine.[66,67,68,69,70,71] Although there has been speculation that the UK will be unable to import radioactive materials, including ^{99}Mo [72,73] the Government has recently stated in a parliamentary question that Euratom does not apply to the import and export of medical radioisotopes, as they are not fissile materials.[64]

Box 4. New radiotherapeutic drugs

Alpha emitters are radioisotopes that emit helium nuclei and have shown promise in treating cancers. The National Institute for Health and Care Excellence (NICE) approved the first of these drugs, a treatment for bone metastases arising from prostate cancer called Xofigo, owned by Bayer, in 2016.[57] Several new therapies using beta-emitters (isotopes that emit electrons) are also in the pipeline,[58,59] a number of which are based on lutetium-177 (^{177}Lu). Some ^{177}Lu based therapies for intestinal, prostate and lung cancers are in clinical trials[60] or being reviewed by NICE.[61,62]

Using radioisotopes as therapeutics

Isotopes with therapeutic uses, such as iodine-131, can also be made in research reactors and their supply is of potential concern. Radiotherapeutics is a small field, accounting for fewer than 5,000 procedures in the UK in 2015.[74] They are most commonly used to treat thyroid cancer and bone metastases.[74] Given the comparatively small market, both international and national organisations working on security of supply have paid less attention to therapeutic isotopes. Recently the field has been growing,[74] driven by an interest in radioisotopes known as alpha and beta emitters (Box 4). Speculative market analysis predicts that the market for radiotherapeutics might grow by 27% annually until 2030, and that five new radiotherapeutics each with annual sales potential of $1 billion may reach the market before 2025.[22]

Shortage of radiotherapeutics can delay or interrupt therapy, which can be more harmful to a patient than the shortage of isotopes used in diagnostic techniques, such as ^{99m}Tc. The short half-life of radiotherapeutics means they also cannot be stockpiled (for example, Xofigo (Box 4) has a half-life of 11 days). One issue with supply is that production of radio-therapeutics has traditionally been the domain of small specialist firms, with small manufacturing operations.[1,58] In October 2014, there was a shortage of Xofigo due to contamination in the drug production process, which was based at a single site in Norway.[1] Furthermore many of the radioisotopes used in therapeutics are produced in research reactors, so reliability issues with the production of ^{99}Mo could apply to these, too. However, the sector is already attracting larger pharmaceutical companies[58] and if it becomes as valuable as forecast, there will be market incentives for ensuring continuity of supply. However the UK will remain dependent on imports.

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