⁹⁹Mo supply—the times they are a-changing

Dewi M. Lewis

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Introduction

Recently there has been a phenomenal growth in clinical PET using ¹⁸F-DG as well as a resurgence of interest in imaging with ¹²³I. However, ^{99m}Tc still remains the most popular radionuclide; approximately 80% of all the world's nuclear medicine procedures are carried out using ^{99m}Tc. The supply of its parent radionuclide (⁹⁹Mo) relies on access to nuclear research reactors and nuclear fission radiochemical processing. During the last 18 months, there have been supply problems with both the reactors and radiochemistry operations; therefore, it is timely to re-visit this issue and examine the options that exist for ⁹⁹Mo supply in Europe.

In a 1995 editorial in this journal on the availability of suitable reactors [1], I wrote that “the situation in North America was dire” and “whereas Europe was blessed with several good isotope-producing reactors, the situation in Europe was far from secure”. It is with regret that I can only report that the situation has deteriorated considerably since that time.

The radionuclide

^{99m}Tc is the most suitable radionuclide for SPECT imaging with a single 140 keV gamma-ray emission and a convenient half-life of 6 h. Interestingly, we have chosen a radionuclide from one of the few elements that has no naturally occurring isotope species. Delivery to the clinics

is via ⁹⁹Mo/^{99m}Tc generators and the present-day economics of industrial generator supply offer a cost effective and versatile radionuclide. The arrival of SPECT/CT scanners seems to have improved the demand for imaging with ^{99m}Tc.

The supply chain

In general the production of ¹²³I and ¹⁸F rests in the hands of the manufacturers of radiopharmaceuticals who use their own cyclotrons but the production of ⁹⁹Mo is embedded within the infrastructure of the nuclear power industry. There are three categories of organisations that participate in the ⁹⁹Mo supply chain:

1. Operators of nuclear research reactors
2. Suppliers of (radiopharmaceutical grade) ⁹⁹Mo
3. Manufacturers of ^{99m}Tc generators

Uranium is the raw material used for both reactor fuel and ⁹⁹Mo targets; it is mined only in certain countries and its extraction and conversion into gaseous UF₆ requires considerable industrial effort. Enrichment of ²³⁵U is needed for reactor fuel and this technically challenging task is expensive and subject to the constraints of the Nuclear Proliferation Treaty (NPT). Isotope targets for ⁹⁹Mo usually require further enrichment of uranium to make highly enriched (weapons grade) uranium (HEU). Both handling and storage of sub-critical amounts of uranium have to be carefully controlled.

The production of ⁹⁹Mo from the HEU targets has to be carried out by neutron irradiation and nuclear fission in special research reactors, which are usually located at government laboratories and operate around the clock in order to produce this 3-day half-life radionuclide. Radio-

D. M. Lewis (✉)
General Electric Healthcare, The Grove Centre,
White Lion Road,
Amersham, Bucks HP7 9LL, UK
e-mail: dewi.lewis@ge.com

chemical extraction of ^{99}Mo has to be performed in heavily shielded hot cells and the HEU target processing creates its own stream of highly radioactive waste. Thereafter, the high specific-activity ^{99}Mo radionuclide is transferred quickly from the facilities of the supplier companies to the production plants of the generator manufacturers.

This is a very complex supply chain and the nuclear medicine community is fortunate that this essential component for nuclear medicine imaging (i.e. ^{99}Mo) can still be made available so regularly and reliably, and in a relatively cost effective way.

Reactor irradiations

The ^{99}Mo radionuclide is generated by target irradiations in research reactors and not in electricity power generating stations because of the need for higher neutron levels and better access to the irradiation positions in the reactor cores. According to the IAEA, there used to be almost 400 research reactors operating in the world but by 2009 only around 240 are still working. In reality many of those remaining are either too small or just unsuitable for routine isotope production: the vast majority are very old and close to being shutdown. Suppliers of ^{99}Mo do require access to large radiochemical processing plants and secure disposal routes for the radioactive waste; these may be located some distance away from the actual research reactor locations.

Canada

It is reported that 40–50% of the world's supply of ^{99}Mo comes from Canada via MDS Nordion, and until recently this supply has been extremely reliable. In order to participate in the market for nuclear power stations, the Atomic Energy of Canada (AECL) has built a centre of expertise at its laboratories in Chalk River in Ontario. The ^{99}Mo supplier company, MDS Nordion, which was originally privatized from AECL, has access to these nuclear operations at Chalk River. Unfortunately, however, MDS Nordion now has to rely on just one research AECL reactor for its ^{99}Mo production the National Research Universal reactor or NRU. This 51-year-old, large reactor with 135 MW of power, has been producing ^{99}Mo regularly and reliably for 17 years and without backup since its companion reactor (the NRX) was closed down. Furthermore, the Canadian project to build two dedicated medical isotope-producing reactors (the Maple-X) at Chalk River has been cancelled. The radiopharmaceutical community should not be surprised to hear from time to time that this old workhorse reactor, the NRU, may

have to be stopped for maintenance. It is hoped that the nuclear operating licence for NRU will be renewed for the period beyond 2011. Nevertheless, another stoppage of the NRU reactor in Canada would have a serious impact on ^{99}Mo supplies, particularly to North America and Japan.

Europe

^{99}Mo production in Europe is not so dependent on one single source of supply. The research reactors of BR2 in Belgium, the HFR in Holland and OSIRIS in France all provide the neutrons for ^{99}Mo production. Fission radiochemistry processing occurs at two locations in Europe:– at Fleurus in Belgium by IRE and at Petten in Holland by Covidien Inc. Over many years, the imaging companies' trade association in Europe (AIPES) has successfully arranged European operating schedules with the individual reactor managements. The isotope supply into Europe has benefited greatly from their coordinated programme of reactor irradiations. In addition the South African company NTP, using the 43-year old SAFARI reactor, have been routinely and reliably supplying ^{99}Mo into Europe for several years.

However the situation is not as secure as it used to be; several useful isotope producing European reactors have recently stopped:– R2 in Sweden (2005), SILOE in France (1997), FRJ-2 in Germany (2006). These closures have seriously compromised AIPES' ability to organize robust weekly reactor schedules. Now there are so few reactors available that there are several weeks in the annual calendar when Europe has to rely on only one operating reactor. This precarious situation was cruelly exposed recently when one of the most productive European isotope generating reactors – the 47-year-old HFR reactor at Petten in Holland developed a serious technical fault necessitating several months' shutdown. The absence of HFR for these few months created a major shortage of ^{99}Mo in Europe.

Research reactors

The strategy of relying on existing research reactors to carry out isotope irradiations is subject to several risk factors:

- Stoppages can arise from nuclear regulatory requirements.
- Reactor closures may occur due to government research budget restrictions.
- Upgrading ageing reactor systems is expensive and time-consuming.

- Accessing HEU target material for ^{99}Mo target production is becoming more difficult.
- Radioactive waste disposal remains a major concern.

In fact, a research reactor can be shut down at very short notice, whereas construction and approval of a new facility may take up to 10 years. Around the world there are only seven new research reactors currently being built: the latest reactors that have been commissioned include OPAL in Australia (2006) and FRM-II in Germany (2004). All new research reactors are planned for either nuclear material testing or nuclear physics experimentation or both. There is no major research reactor dedicated 100% to medical isotope production.

Alternative methods

Several alternative methods of producing ^{99}Mo have already been proposed:

- Returning to the traditional ‘non-fission’ reactor irradiations for producing ^{99}Mo would be one option. This would need large quantities of enriched ^{98}Mo as the raw material and considerably more reactor irradiation space. Only low-specific-activity ^{99}Mo could be produced and historically only lower activity generators have been manufactured using this method.
- Cyclotrons that are used for SPECT radionuclides could possibly be upgraded to produce very high beam currents for bombarding ^{100}Mo targets to produce $^{99\text{m}}\text{Tc}$ directly. This untried method would have low capacity and would require large amounts of enriched ^{100}Mo as the raw material. Then there would be the need to design target assemblies and rapid radiochemical extraction processes to manufacture directly the short-lived $^{99\text{m}}\text{Tc}$ radionuclide.
- Other methods have been proposed using large accelerators for spallation reactions and electron accelerators. One such proposal is to use the photonuclear fission reaction. This option deserves serious consideration since it does not rely on reactors and uses ^{238}U , not ^{235}U , as the raw material. Technical development is needed to evaluate production capacity and to assess the commercial viability of this alternative approach. MDS Nordion and TRIUMF, the Canadian accelerator laboratory, have just agreed to proceed with this development work.
- The exploitation of liquid-core reactors has been proposed, and a collaboration has already been announced between Covidien Inc. and the reactor constructor B&W to build a complete ^{99}Mo production system using this technology.

All these alternative methods will require some degree of radiopharmaceutical regulatory submissions and some will also need full nuclear regulatory approvals.

Strategic considerations

All the alternative methods pose severe technical risks and imply major infrastructure changes for ^{99}Mo production and $^{99\text{m}}\text{Tc}$ generator delivery, and these methods cannot be implemented easily in the medium term. Clearly accessing a non ^{235}U fission method would avoid many of the strategic challenges of producing ^{99}Mo and this may be the opportune time to re-evaluate yet again some of these alternative technologies. However, one is drawn to the inevitable conclusion that the pragmatic and immediate way forward would be to build new research reactors dedicated to full-time production of radionuclides for medicine. A new, dedicated research reactor, would probably be a swimming pool type, customised to service the needs of the radiopharmaceutical users and eventual customers, i.e. the patients.

In Europe, there are a very few new research reactor projects planned:

- France is planning to build a large 100-MW (Jules Horowitz) material testing reactor by around 2014.
- Preliminary discussions with a consortium have also begun in Holland, to build another large general-purpose 80-MW test reactor (PALLAS) to replace the HFR reactor by 2015.

In North America, the most likely option is:

- The University of Missouri (MURR) small 10-MW research reactor has already been operating since 1966 and has been an excellent source of isotopes over the years. In order to convert to ^{99}Mo production, MURR needs a major investment so as to construct a fission radiochemistry plant.

Constructing large material testing research reactors for isotope production has serious disadvantages:

- The reactors will be very expensive to construct and to operate.
- Priority for neutron irradiation would probably be given to the material testing programmes for the nuclear power industry ahead of the needs of isotope production.

The recent cancellation of the MAPLE-X reactor programme in Canada does not change anything today, but the absence of a future MAPLE production capacity does. It means that in the event that NRU were to shut down there would be inadequate global ^{99}Mo production

capacity and realistically there will be times when NRU will just not be available.

Recommendations

- A) In the first instance, the whole ^{99}Mo supply industry must ensure that in the event of a future serious supply problem, there should be a robust contingency plan already agreed and people already in place to ensure optimum and efficient distribution of any ^{99}Mo supplies that may be available globally.
- B) The current suppliers of ^{99}Mo need to start immediately to access additional research reactors in Europe for their irradiations.
- C) The opportunity exists and the time is now right for the radiopharmaceutical industry and the users to start planning proactively for a dedicated long-term ^{99}Mo production reactor capacity. This would underpin the future use of $^{99\text{m}}\text{Tc}$ and of SPECT imaging in general. There is a real argument for establishing a manufacturing supply chain that is independent of nuclear power programmes. There is also a clear need to build dedicated medical isotope-producing reac-

tors, with at least one in Europe and one in North America; this would also reduce the number of airline transfer shipments of ^{99}Mo . Dedicated medical isotope reactors could be much smaller than today's material testing research reactors, the reactor designs could be optimised just for isotope production and reactor operations planned to be commercially viable for supplying isotopes to the nuclear medicine community.

- D) In parallel, development programmes should be started to evaluate whether, in the longer term, some of the alternatives such as the photo fission method could provide sufficient ^{99}Mo production capacity in an economic manner.

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