U.K. Radiopharmacy Group

NEWSLETTER
2009 Q2

IN THIS ISSUE

The molybdenum crisis
This issue consists largely of an update on the molybdenum crisis, which, I was reminded recently by an avid Newsletter reader, I once referred to as the elephant NOT in the room.

Further guidance from the UKRG will be issued in the next 1-2 months.

UKRG INITIATIVES

Survey
UKRG is undertaking a survey of ^{99}Mo/^{99m}Tc generator availability on behalf of BNMS and ARSAC. It is being distributed to every known radiopharmacy in the UK, though individual contact details are not available for all. Please keep an eye out for it in your department, as it may be directed to the licence holder or chief pharmacist. About one quarter of the units have responded already.

Bursary offered
The UKRG is offering a bursary in the form of registration for the 15th European Symposium on Radiopharmacy and Radiopharmaceuticals to be held in Edinburgh in April. The bursary will be awarded to the author of a poster accepted for presentation at the symposium. To be eligible, the author must be making his/her first presentation at an international conference, must be a junior member of staff (band 7 or lower) at a UK institution, and the topic must be within the realm of radiopharmaceutical science and/or practice. Deadline 1st December. Further details in the next Newsletter.

Error reporting
As announced previously, a form which is available from Paul Maltby (paul.maltby@rlbuht.nhs.uk) for reporting errors or near misses in radiopharmacy has been devised based on a system developed by the national CIVAS group (www.civas.co.uk). Completed forms are treated confidentially and reported to the national scheme anonymously. Submission of reports has fallen off recently, so all who have participated are encouraged to resume reporting and those not yet participating are encouraged join in.

Adverse event reporting
This came up on VirRad recently. Just to re-iterate, reports of adverse events or product defects can be made through either the UKRG or BNMS websites. All reports received in this way are entered onto the VirRad database which is searchable though has limited details.

The most recent compilation of reports should be circulated with this Newsletter.

INDUSTRY NEWS

Nanocoll
Nanocoll will be temporarily unavailable due to a re-licensing issue rather than production problems. The current batch expires at the end of August and it is believed that there is sufficient stock to meet UK requirements to that point. UKRG and BNMS are working with GE and the MHRA to find an interim solution once that material expires. Information will be distributed via the usual channels as soon as it is available.

A comparison of the properties of alternative ^{99m}Tc colloids which have been used for sentinel node detection in Europe is appended to this Newsletter. It must be emphasized that these agents are not licensed in the UK and there is little or no UK experience with them.

In the more distant future, it should be noted that extremely promising results have been reported with Lymphoseek and its clinical development is now in Phase III. It is not known if there will be any UK trials. The rights are owned by the instrument company Neoprobe and information is available on their website. Lymphoseek is not a colloid, instead it targets the mannose binding protein on the surface of macrophages. It would be the first agent specifically licensed for sentinel node detection.

Radiation monitors have free source calibration certificates

LabLogic Systems is making a money-saving offer on its Rad Monitor™ radiation contamination monitors: free source calibration certificates for customers buying three or more before the end of September. Worth at least £165, the multi-buy offer coincides with a convenient improvement in specification; the exterior casing of every monitor now has a smoother plastic coating that is easier to clean in the event of contamination.

The Rad Monitor™ range offers three Geiger Muller-based models for detection of ^{14}C, ^{32}P, ^{33}P and ^{35}S and a scintillation probe for detection of gamma emitters such as ^{125}I and ^{99m}Tc. The GM1 is a general-purpose monitor with a 28mm tube detector, a 1.5-2.0 mg/cm^2 window thickness and a unique thin screen that protects the end window. GM2 has a larger end window (45mm); GM2-P has a pancake probe and a large diameter GM tube for monitoring surfaces; and the SD10 for gamma emitters is sodium iodide crystal-based for greater sensitivity.

Addenbrooke's chooses LabLogic for PET metabolite support

The Department of Medical Physics and Clinical Engineering at Addenbrooke's Hospital in Cambridge has chosen LabLogic Systems to supply all the equipment needed to support its new metabolite analysis system for early-phase PET studies. Included are a Posi RAM radio-HPLC detector, Agilent 1200SL HPLC system and Triathler well counter, all sourced by LabLogic and controlled by the company's Laura 4 radio chromatography software.

"LabLogic's capability stood out among the other potential suppliers because they were able to offer a comprehensive service bringing together all the key components we needed," said Professor Peter Jarritt, the hospital's clinical director of medical physics and clinical engineering. "As well as the hardware and software, they provided the expertise in qualification and validation for a GLP environment and coordinated all aspects of the project - installation, training and follow-up."

The Posi-RAM radio-HPLC detector has been developed specifically for the low-level Beta+-counting necessary for studying the metabolism of novel PET radiopharmaceuticals. It identifies PET metabolites in the fastest possible time and with inherently low backgrounds; only coincidences are recorded.

UPCOMING MEETINGS

British Nuclear Medicine Society autumn meeting 17-18 September, Guildford. www.bnms.org.uk

World Molecular Imaging Congress 23-26 September, Montreal. www.wmicmeeting.org

European Nuclear Medicine Congress 10-14 October, Barcelona. www.eanm.org

15th European Symposium on Radiopharmacy and Radiopharmaceuticals 8-11 April 2010, Edinburgh. www.eanm.org

British Nuclear Medicine Society spring meeting 26-28 April 2010, Harrogate. www.bnms.org.uk

World Federation of Nuclear Medicine and Biology Congress 18-23 September 2010, Cape Town, South Africa. www.wfnmb.org

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APPENDIX 1: UPDATE ON THE MOLYBDENUM CRISIS

What is the international situation regarding ^{99}Mo production?

- The basic problem is that most of the world's supply of ^{99}Mo comes from only 5 research reactors, none of which has medical isotope production as its primary purpose and all of which are nearing the end of their useful lifetimes. These are:

Reactor	*Location*	*Age (years)*	*Power (MW)*	*Operational days per year*
NRU	Chalk River, Canada	52	135	270
HFR	Petten, the Netherlands	47	45	270
BR2	Mol, Belgium	47	100	120
OSIRIS	Saclay, France	42	70	180
SAFARI	Pelindaba, South Africa	43	20	310

- Much hope had been placed on the construction of two Maple-X reactors at Chalk River which were intended solely for medical isotope production and which would have operated in tandem, with staggered downtimes providing a continuous supply (research reactors shut regularly for maintenance, refuelling, and to tweak the experiments). However, after years of delays and cost overrun, the project was cancelled in 2008 and there are still questions as to whether the novel technology would ever work.
- In the past there appeared to have been little co-operation among these reactors in terms of scheduling their shutdowns for preventative maintenance. This has improved in the last year, but the whole situation can be thrown off the rails when there is an emergency shutdown.

What is the situation in the UK?

- There are three suppliers of ^{99}Mo/^{99m}Tc generators in the UK. Their primary sources of ^{99}Mo and market shares are:

Supplier	*Primary ^{99}Mo source*	*Approx UK market share*
GE Healthcare	SAFARI, South Africa	50%
Covidien	HFR, Petten	35%
CISbio/IBA/Qados	OSIRIS, France	15%

- It will be immediately apparent that none of these suppliers use Chalk River as their primary source, so what happens at Chalk River should not affect supply in the UK. This was the case in 2007 but the situation is different now. Let's go back a step.

What happened in recent crises?

- In ***November 2007*** the Chalk River reactor which supplies the bulk of the ^{99}Mo for North America was shut down for routine maintenance when the Canadian Nuclear Safety Commission (CNSC) noted that actions required from a previous safety inspection had not been completed and refused to allow the reactor to start up again. Over the course of two weeks, nuclear medicine in North America virtually ground to a halt. The nuclear medicine community was so successful in raising public awareness that there was an emergency debate in parliament leading to passage within one day of legislation to allow the reactor to restart. When the chair of the CNSC refused to comply she was fired. This shutdown had very little impact in Europe.
- In **August 2008** the Petten reactor was shut down due to corroded pipes in the cooling system. In what was termed a "perfect storm", all other reactors were down for unrelated reasons at the same time – most for maintenance but one because of a massive release of ^{131}I (unintentional). After 6 months Petten resumed operation in February 2009 but will have to close for several months next year for a proper fix. This incident, too, raised interest at a political level. There was an international OECD summit meeting in Paris in January and ongoing meetings between BNMS, government, and industry in the UK. Indeed, political pressure ensured that the Dutch government allowed the restart in February. Covidien was hardest hit by this shutdown, though GE had to purchase backup supply from Chalk River.
- In **May 2009** it was Chalk River's turn again, this time a leak which continued at 4 litres per hour until very recently. It will take a minimum of 6 months to repair, and some are saying it will never return to operation. In response, Petten and South Africa have increased production and the Australian reactor is coming on line. Even though Chalk River was not the primary source for any of the UK suppliers, we have been hit hard as a result of the new era of co-operation among the providers – share the misery.

What can we do to cope during the crisis?

- Maximise the use of available ^{99m}Tc
- Use alternative nuclear medicine procedures when available
- Use alternative PET procedures when available and appropriate
- Use alternative diagnostic methods (not addressed further here)

How do we maximise the use of available ^{99m}Tc?

- Book high activity studies (bones, cardiacs) when the generator is fresh, low activity studies when it is on its last legs.
- Keep the generator for an extra week. It may yield enough for low activity studies. With the 3-day half-life of ^{99}Mo, the yield is ~12% after one week and it's free.
- Share the generator – send it along to a smaller department (see caveat below).
- Share pertechnetate with a smaller department.
- Work extended days (or weekends) when ^{99m}Tc is plentiful.
- Reduce the administered activity and image longer or use resolution recovery software (see guidance on BNMS website).

However, there will be more details of all of these initiatives in the upcoming weeks – see contact information below. Each of these options opens up other problems, from waiting times to transport to licensing.

What logistical problems are there?

- Keeping generators for an extra week or purchasing from multiple suppliers creates problems for storage and elution in a class A environment (most isolators will only hold 2 generators).
- Weekends and extended days require only partial cover by technologists, physicists, and medics, but pretty much the full complement in radiopharmacy is required. Even a limited production run of a couple of products requires all the usual preparation, documentation, and clean down.
- Generator producers have been able to increase their efficiency though changing schedules, cutting process time and saving 22% ^{99}Mo per day. While it may seem wasteful that generators are delivered on Saturday, there are problems finding couriers who will deliver on Sunday and some trusts still don't have adequate provision for receiving out of hours deliveries.

What alternative nuclear medicine procedures can we use?

- Many people are rediscovering ^{201}Tl for myocardial perfusion imaging and finding it is not as bad as they remembered, partly due to improvements in camera technology. However, there are significant practical differences. Unlike the ^{99m}Tc agents, imaging must commence immediately after stress before there is significant redistribution into ischaemic regions (see guidance on BNMS website).
- Many other potential alternatives cannot be implemented rapidly (^{81m}Kr for lung ventilation), are not readily available (^{123}I-hippuran for renal function) or not simple to image and interpret (^{123}I-fatty acids for myocardial metabolism).

What PET procedures can be used?

- There is some scope for increasing the use of FDG for tumour imaging.
- Fluoride was used in the 1960s for bone scanning with rectilinear scanners. Although ^{18}F-fluoride is technically easy to make (since it is the starting material for FDG synthesis) most cyclotron units are not licensed to prepare it as a radiopharmaceutical.
- Myocardial perfusion imaging can be performed with ^{82}Rb which is available from the ^{82}Sr/^{82}Rb generator, half-life 25 days. However, at present there is only one UK centre with this generator (and its associated infusion device) and it would take other centres quite some time (and expense) to set up.
- ^{13}N-Ammonia can be used for MPI in centres with a cyclotron.

However, the interchangeability of these techniques is uncertain. If a patient is being followed with ^{18}F-fluoride and then has a ^{99m}Tc-MDP scan, if fewer lesions are seen is it response or lower sensitivity of SPECT? Furthermore, the software for processing images is not well developed for PET MPI [Fricke, *EJNMMI*, in press].

What prospects are there for improving supply in the future?

- The 20-MW OPAL reactor in Sydney, Australia is coming on line and will provide some ^{99}Mo to North America, primarily through Lantheus (formerly NEN/DuPont/BMS which is the largest supplier of generators in North America and previously almost entirely dependent upon Chalk River).
- The Missouri university reactor is making a bid for funding to boost isotope production, which would be much less expensive than construction of new reactors and could occur within a couple of years.
- France is building a 100-MW reactor to be operational by 2014.
- The Petten reactor is due to be decommissioned in 2015, however there is a commitment to build a replacement, the 80-MW PALLAS. A final decision has not been made as to whether it will be located on the Petten site or adjacent to a nuclear power reactor elsewhere in the Netherlands.
- There are reactors in Russia which could be used. MDS Nordion is in negotiation with the Karpov Institute in Moscow but nothing is expected for a year or so.
- The Maple-X project at Chalk River could be reinstated but would take a number of years to complete.

What about these novel technologies we've heard about?

- The first is not novel but very old – neutron activation of ^{98}Mo targets to produce low specific activity ^{99}Mo. Larger generator columns would be required due to low specific activity, yields are low, and still requires a reactor. Prospects: little benefit.
- Cyclotron production of ^{99m}Tc by irradiation of ^{100}Mo. Requires higher beam current than generally available at present; low capacity; requires large amounts of enriched ^{100}Mo target material; new target design and rapid processing. Prospects: not likely to be useful.
- Photonuclear fission of ^{238}U in a large cyclotron. TRIUMF cyclotron in Vancouver pursuing this with MDS Nordion. Prospects: unproven but potentially useful.
- Liquid core reactors. Babcock and Wilcox are pursuing this with Covidien. Could be smaller (the size of a Tardis) and more widely distributed, though this creates logistical problems as noted below. Low power requirements, little radioactive waste. As this is a new type of reactor it could be a regulatory minefield. Projected completion 5-6 years. Prospects: reasonably good.

What logistical problems remain?

- Even if ^{99}Mo were produced in a larger number of centres, it still needs to be processed and at the moment there are a limited number of centres with this capability. Processing generates a large amount of radioactive waste.
- Even if ^{99}Mo could be processed, generator loading is not something you could do in your garage. It requires shielding, automation, and aseptic conditions. GE loads all its generators for the world in the sleepy town of Amersham; Covidien has one plant in Petten and one in Missouri. Draximage has proposed an alternative technology where cassettes of ^{99}Mo would be distributed for insertion into reusable generators.

What solutions are NOT feasible?

- ***There are plenty of nuclear power reactors around: why can't they be used to produce isotopes?*** Unfortunately the technology is completely different and not transferable. Power reactors are closed systems to generate heat and pressure to run turbines; high flux production reactors are open. However, it might be feasible to construct new production reactors adjacent to power reactors to minimise the NIMBY factor, as is being proposed in the Netherlands.
- ***There is a positron emitting radionuclide of Tc: why can't it be used?*** Yes, ^{94m}Tc does exist but it has a half-life of 53 minutes and is difficult to produce and process, so it would not be feasible to use it clinically on a widespread basis. Its high energy positron degrades spatial resolution and other emissions such as the 871 keV cascade gamma in 94% abundance results in spurious coincidences. Few cyclotrons are set up to handle solid targets.

What about the government and regulatory agencies?

- There are indications that the government will relax waiting time targets in response to the crisis.
- The Environment Agency has reissued its statement of last autumn which states that the agency will not be strictly enforcing holdings or waste limits if they have to be exceeded in order to provide a clinical service (see BNMS website).
- The Department for Transport will be concerned with driver training, appropriate vehicles, and Type A transport containers. BNMS is assessing the availability of transport cases.
- The MHRA will no doubt put its oar in.
- ARSAC is preparing a report on medium to long term solutions.

How can I stay informed?

- The UKRG is conducting a survey of generator usage on behalf of BNMS and ARSAC. Please return this quickly when it appears in your department.
- The BNMS website (www.bnms.org.uk) is updated regularly and the link to the molybdenum crisis is front and centre!

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End of factual content. The following is purely speculation by the Editor. You have been warned.

There are a lot of competing agendas (agendae?) here.

- The weekly reports to the SHAs are a dual edge sword. Do we report the true impact and risk slapped wrists for failing to meet targets or do we paint a rosy picture? It appears that during last autumn's unpleasantness we erred on the side of the smiley faces. How do we maintain the political pressure that will be required for a medium to long term solution (more production reactors in Europe and new technologies) whilst avoiding undermining our short term viability? Should we be lobbying for a British production reactor?
- Internationally (less so in the UK), proponents of PET are using this as a foot in the door. It's even been said that PET is cheaper than SPECT because a cyclotron costs only a few million while a reactor costs a billion! But there needs to be a reality check. Yes, fluoride bone scans can be done, but at 10 times the cost and with extremely restricted availability. There is much talk of ^{68}Ga generators (an interest of mine since building one during my training year 1979-80) but despite recent interest still a long way from being ready for prime time.
- Proponents of alternative technologies have made some pretty irresponsible statements for commercial purposes. We must remember that the main reason we are in this mess is that the Maple reactors were based on unproven technology.
- As a result of the current crisis, America will likely develop a domestic supply of ^{99}Mo (most probably at Missouri), which is good in that it will take some of the pressure off other sources. However, there is also an agenda to eliminate the use of highly enriched uranium (HEU) which can be diverted for nuclear weapons. Many reactors have successfully switched to low enrichment uranium (LEU) as their fuel, but currently ^{99}Mo production still requires small amounts of HEU in aluminium alloy as targets (only Australia and Argentina use LEU targets). It would be possible for all producers to switch to LEU targets but many more targets would be required (the same total amount of ^{235}U is needed), there may not be enough high flux positions within the reactor core for these additional targets, and current ^{90}Mo processing plants may not have the capacity the handle the larger volumes.
- There is a lot of misinformation flying around (I hope I'm not compounding the problem). The companies have been struggling to obtain and distribute accurate information. There has been some improvement recently but it remains spotty.
- The resultant increase (tripling) in generator costs will change the economics of conventional radiopharmacy. While people have been saying for years that ^{99m}Tc was underpriced, rapid increases will be a challenge in the short term. While it doesn't approach the costs of PET, it may tip the balance toward other imaging modalities and we could be losers in the long term. Even temporary switches during the current shortage may be difficult to repatriate.
- The profile of nuclear medicine has certainly been raised, but that too is a dual edged sword. Sometimes it's better to be ticking along quietly in the background – the spotlight reveals our warts and can distract us from our mission. We have certainly been shaken from our complacency and may be forced to find new ways of working. Not necessarily a bad thing, but change is always stressful.

The bottom line:

- A lot depends on whether Chalk River comes back online by January. If it doesn't, and Petten shuts down for major repairs, we will be extremely tight next year.
- Other upgrades (eg Missouri) are at least 2 years away.
- New European reactors are 5 years away.
- New technologies are at least 5, more likely 10 years away.

And if you've read this far, thank you for your patience and welcome to the new world!

APPENDIX 2: COMPARISON OF ^{99m}Tc COLLOIDS USED FOR SENTINEL NODE DETECTION IN EUROPE

Generic name	Albumin nanocolloid	Colloidal rhenium sulphide	Human serum albumin colloid	Nano-sized human serum albumin colloid
Trade name	**Nanocoll**	**Nanocis**	**Senti-Scint**	**Nano-Albumon**
Manufacturer	GE	IBA-CISbio	Medi-Radiopharma	Medi-Radiopharma
UK licence status	Yes	No	No	No
References to use in SN detection	Numerous	1,2	3,4	None
Activity range	185–5550 MBq	370–5550 MBq	up to 2220 MBq	up to 2220 MBq
Volume range	1–5 mL	2.5–3.5 mL	1–3 mL	1–3 mL
Incubation time	10–30 min RT	boil 15–30 min	20 min RT	20 min RT
Expiry	6 h	4 h	6 h	6 h
Median particle size	6–12 nm	100 nm	200 nm	not stated
Particle size range	>95% ≤80 nm	50-200 nm	>80% 100-600 nm	>80% <100 nm

For information about Nanocis:
http://www.iba-worldwide.com/molecular/radiopharmaceuticals-isotopes-eu/SPECT-products/23-nanocis.php
For information about Senti-Scint and Nano-Albumon:
http://www.mediradiopharma.com/products/second_generation/index.html

Notes on preparation of Nanocis:

- Nanocis is a multi-vial kit: Vial A contains rhenium sulphide colloid and gelatin in 1 mL water; Vial B contains stannous pyrophosphate. Vial B is reconstituted with 2 mL water for injection, then 0.5 mL of this is added to Vial A. Pertechnetate (1-2 mL) is added and the vial is boiled for 15-30 minutes.
- When prepared as directed, Nanocis frequently fails radiochemical purity testing (refs 2, 5, and anecdotal reports). Manoeuvres which have been shown to improve labelling include:
  - using minimal volume of pertechnetate (≤ 1 mL)
  - boiling for 30 minutes
  - using a heating block at 130^{o}C (ref 5)
- Radiochemical purity testing is not straightforward. The manufacturer's recommended method (Whatman No 1/butanone) can give apparently acceptable values if the spot is allowed to dry for 5-10 minutes. However, testing the same preparation with the EP method (Whatman No 1/saline) can result in a failure.

Notes on Senti-Scint/Nano-Albumon:

- Senti-Scint was designed to have what is believed to be the optimal particle size range for sentinel node detection, which is much larger than that of Nanocoll. Since it is larger it would be expected to show slower migration from the injection site and greater retention in the sentinel node with less leakage through to second echelon nodes. Thus its distribution may be quantitatively and qualitatively different from Nanocoll, which could present problems in interpretation. The kinetics may also be different.
- Nano-Albumon appears to have characteristics more similar to Nanocoll though there are no published reports of its use for sentinel node detection.

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