U.K. Radiopharmacy Group

NEWSLETTER
2010 Q1

MOLYBDENUM UPDATE

International

- The Petten reactor has now shut down for 6 months of repairs, making the ^{99}Mo supply extremely precarious. However, repairs are on schedule and the reactor is due to resume operation in August.
- There has been further slippage in the repair schedule for the Chalk River reactor and it is will not be back in operation until late July. Even when the neutrons start flying it will be 10 days before the first targets are removed and a few more days before generators make their way into hospitals, so we might not see any benefit until well into August. The main benefit to the UK will be indirect: Chalk River will supply North America (half the world's demand), relaxing the strain on the reactors in Europe and South Africa.
- Covidien has negotiated supply of ^{99}Mo from the Polatom reactor, with targets being transported to Petten for processing.
- A second small reactor at Saclay will supplement production from the OSIRIS reactor.
- The EANM has endorsed the Technopolis report on projections of requirements for ^{99m}Tc radiopharmaceuticals through 2025. It is available on the EANM website.
- PETNET in the USA is offering to supply ^{18}F-fluoride for free to new customers for a limited period to help establish a market for PET bone scans.
- The European Medicines Agency (EMA, formerly EMEA) held a two day workshop on the need for radiopharmaceuticals labelled with reactor produced radionuclides. See Appendix 2 for a summary.

National

- The week of 17 May will be extremely tight for ^{99}Mo supply, with GE and Covidien not producing any generators and Qados supplying only 4 GBq generators (the French solution: see Appendix 2). There will be another period of extreme shortage in July.
- Qados/IBA is expanding their generator manufacturing facility and later this year will increase their maximum generator size to 50 GBq ^{99m}Tc (when ^{99}Mo supplies return to normal).

Medium term

- In the USA, the American Medical Isotopes Production Act was passed on 5 November. It provides US$163 million over 5 years to create a domestic supply by upgrading the Missouri reactor. The use of highly enriched ^{235}U targets is being phased out.
- A major initiative in America is the Covidien/ Babcock and Wilcox plan for aqueous homogenous reactors, though there has been little further news on this.
- The Americans are also funding development of neutron-irradiated ^{99}Mo in a project involving GE and Hitachi.
- Plans for replacement of the Dutch reactor are moving ahead, with the preferred location being the current site in Petten. Similarly, the French and Belgian reactors are being replaced.
- The Canadian research council held a special competition with rapid turnaround and awarded $6 million in funding for a total of 7 projects aimed at reducing dependence upon ^{99m}Tc. Feasibility studies of production of ^{99m}Tc by irradiation of ^{100}Mo in an existing network of medical cyclotrons have already started (see April issue of *J Nucl Med*).
- A Canadian panel of experts released its report at the end of November, recommending rapid approval and construction of a new research reactor. Limited funding is requested for speculative technologies. However, the government rejected this recommendation, but released $45 million in "guilt money" toward establishment of a national network of cyclotrons for production of ^{99m}Tc (supplementing the item above).

Sources of information

- Weekly updates on the status of repairs at the Chalk River reactor are available at: www.nrucanada.ca
- The BNMS website (www.bnms.org.uk) remains the most useful source of current information. News items and communications from manufacturers are posted in a timely fashion.

UKRG INITIATIVES

Hetastarch availability

We thought the problem had been resolved. Bulk hetastarch from a European supplier was being imported and packed down into ampoules by an NHS pharmaceutical manufacturing unit. Then the supplier changed format and no longer supplied bulk, making it not economical for the PMU.

However, individual hospitals can obtain hetastarch from Grifols UK, based in Cambridge. The UKRG has been reassured that the material is identical to what has been used for the last year, just supplied in a different sized bottle. However, this is not a licensed medicinal product, it is CE marked as a medical device. Therefore, the user must obtain a certificate of analysis from the manufacturer for each batch, as well as evidence of sterility and apyrogenicity. A TSE statement has been obtained already.

Radiopharmacy Workshop 2010

The annual workshop was held in Bournville on Friday 15th January. Once again there was a capacity crowd. A summary of the round table discussions in the afternoon session can be found in Appendix 1.

Postgraduate Course in Radiopharmacy

The Easter course was held 15-18 March in central London with a capacity attendance of 34, including 14 from the PTQA course.

REGULATORY ISSUES

ARSAC

The current focus is preparation of a report for the Department of Health advising a medium term response to the ^{99}Mo situation. The Notes for Guidance will be revised and the advice on breast-feeding will be updated.

Feedback from recent MHRA inspections

Among the topics which have featured are:

- Insufficient progress on previous actions
- Controlled documentation not controlled properly
- Labelling issues
- Stock control
- Quality Management system weakness
- Training records incomplete
- Radiopharmacy computer system not validated periodically (quarterly?) against a manual comparator
- One unit was asked about the possibility of AHU fans catching fire, and had to estimate the % of maximum speed the fans can run before constituting a fire risk.

WORKFORCE ISSUES

National Occupational Standards (NOS)

You may recall that a few years ago much time and effort was spent on this process, culminating with a set of 15 radiopharmacy NOSs promulgated via the Skills for Health website. In the autumn we were informed that the radiopharmacy NOSs had been mapped onto generic pharmacy and radiation protection NOSs. A hastily convened UKRG subcommittee examined the proposed mapping and substantial gaps became evident. This was fed back to Skills for Health with the recommendation that the original NOSs be reinstated. Accordingly the original NOSs have been amended slightly and converted to the format *du jour*.

New professional body

Discussions are continuing in the new pharmaceutical professional body as to whether non-pharmacists will be allowed to join. There are huge numbers of such people in radiopharmacy, quality assurance, and the pharmaceutical industry.

RESEARCH NEWS

Alpharadin

Phase III studies are commencing with ^{223}Ra, an alpha emitting bone seeker which is showing great promise for palliative treatment of bone metastases which may also affect the course of disease. Bayer Schering has bought the rights to this product.

Lymphoseek

Phase III studies of the sentinel node detection agent ^{99m}Tc-mannosyl dextran (Lymphoseek) have been completed in the USA and Neoprobe is taking the product forward for licensing. No news on what's happening with this agent in Europe.

INDUSTRY NEWS

Tin colloid

Tin colloid (Hepatate II) has been unavailable for some time. GE has transferred the product to Mediam who will be marketing it shortly. It is hoped that Mediam will also market Choledíam directly to the UK. For further information please contact Franck Rouiax, contact@mediam-pharma.com

UPCOMING MEETINGS

5th European Molecular Imaging Meeting, European Society for Molecular Imaging. 26-29 May, Warsaw.
http://esmi2010.pacifico-meetings.es/

Society of Nuclear Medicine annual meeting 5-9 June, Salt Lake City. www.snm.org

Terachem-2010: International Symposium on Technetium and Other Radiometals in Chemistry and Medicine 9-11 September, Bressanone, Italy. www.terachem2010.com

World Molecular Imaging Congress 8-11 September, Kyoto, Japan. www.wmicmeeting.org

BNMS autumn meeting 13-14 September, Nottingham. Abstract deadline: 30 June. www.bnms.org.uk

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

European Association of Nuclear Medicine annual congress 9-13 October, Vienna. Abstract deadline: 11 April. www.eanm.org

UKRG Radiopharmacy Workshop 14 January 2011, Bournville

From the Editor

I started off 2010 with the best intentions in the world and began work on this Newsletter in February. Then along came March and April, and my diary went into meltdown, exacerbated by a certain volcano. So I'm still calling this the Q1 issue and intend to get the next one out by the end of June. There will be plenty to report on, with the hugely successful European Symposium on Radiopharmacy and Radiopharmaceuticals held in Edinburgh (congratulations to Alistair and his team) and the more modest BNMS in Harrogate.

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Issue 2010 Q1 Published 12 May 2010	This and previous issues of the Newsletter are available from the UKRG web site and are posted in the library section at www.VirRad.org

APPENDIX 1: FEEDBACK FROM ROUND TABLE DISCUSSION GROUPS AT UKRG WORKSHOP, BOURNVILLE, JANUARY 2010

As has been the pattern for several years now, the afternoon session consisted of round table discussions (actually, some of the tables were rectangular and one particularly adventuresome group did not have a table at all, but what's in a name?) where participants rotated amongst three rooms where one hapless soul tried to elicit discussion (some groups were much more loquacious than others) of topics which have importance for radiopharmaceutical quality assurance. The ubiquitous Paul Maltby has prepared the following summary from the feedback session, with additional details on the RCP topic by Alistair Millar.

Sterility Testing

The great majority of delegates perform this on 1st and last elutions of the generator and one from a range of many different kits throughout the week as specified in the QA document from 2001.

Some choose to let the kit decay first then send to QC for testing, some choose to sample an aliquot directly into broth. Is this valid?

Many questions or statements were made: Will the kits support growth? Positive controls don't always work; QA/micro staff may be sceptical; failures are very rare and may lead to a false sense of security? Is this evidence based medicine?

RCP testing

A wide range of views expressed:

- Do not perform testing on products made using licensed generators and kits - already licensed.
- Test 1 in 20 regardless of batch. Perform some testing every day.
- Test all products. (comment made in 2 groups)
- Time-consuming to do testing on all products - more manpower needed.
- Testing done before release. (comment made in 2 groups)
- Is it worth investing in something that is unnecessary?
- If not doing testing regularly then can get out of practice.
- What is the frequency of failures? If low, then no need for every product to be tested.
- Don't have facilities to perform testing. (comment made in 2 groups)
- If problems arose maybe tests would be performed more frequently - at what limit would this happen i.e. action be taken?
- Changes of sundries important - there is literature showing effects
- Do all radiopharmacies use manufacturers' methods for RCP testing?
- Test when there is a significant change to practice.

15/45 delegates said that they met the frequency of testing in the current guidance document. 2/45 exceed it.

Questions were raised over unlicensed products; raw materials and sundries and the risk of not doing it.

End of session broth fills

First conclusion was that nobody really understood the purpose of this test. Was it a test of the operator, process or the session that day? (Post meeting note: the NHS Pharmaceutical QA committee have now been asked for guidance.)

Assuming we know the answer, then 20 - 70% of delegates were undertaking this at a frequency of daily and each operator to once per quarter (in line with the universal operator test). The technique ranged from simply filling a few extra syringes with broth to effectively a full process validation utilising syringe shields, vial shields (lead pots) and different operators (if that was the usual process).

If this technique were to be introduced, then would the frequency of the other tests (eg sterility, operator validation, process validation) be amended (relaxed!) to take this into account or would it just mean additional work which may have no scientific evidence that it is achieving anything.

Paul Maltby
Feb 2010

APPENDIX 2: HOW CAN NUCLEAR MEDICINE DEAL WITH SHORTAGES OF REACTOR PRODUCED RADIONUCLIDES? NOTES ON A WORKSHOP HELD BY THE EUROPEAN MEDICINES AGENCY, LONDON, 4-5 FEBRUARY 2010

This started off with good intentions but turned into a bit of a dog's dinner. At least it was an improvement on the response of the EMA (formerly EMEA) to the 2008 Petten shutdown when they issued their infamous statement which essentially said: Not our problem, guv. (There are only 7 centrally approved radiopharmaceuticals, only two of which are ^{99m}Tc kits – Neospect and Leukoscan.)

The format of this pan European meeting, held at the EMA offices in Canary Wharf, was to spend a day on diagnostics and a half day on therapeutics, with each area being addressed by a nuclear medicine clinician and by a specialist referring physician. However, there was little co-ordination between the two, and no one paid any attention to the schedule. The chair, Prof Jean-Noel Talbot, was tearing his hair out.

Diagnostics

- Brain: ^{99m}Tc-ECD for ictal SPECT in epilepsy was felt to be an essential use
- Heart: ^{99m}Tc myocardial perfusion agents will remain important even as other modalities threaten to take a portion of the workload; patient selection may change but volumes will not evaporate
- Bone: even if use of ^{18}F-fluoride/PET increases there will still be an important role for ^{99m}Tc diphosphonates
- Paediatric renal and Meckels
- Sentinel node
- Lung: V/Q scintigraphy should be available 24/7
- Parathyroid: now included in European Society of Endocrine Surgery guidelines

Also interesting was a report from the French medicines agency on their response to the 2008 Petten shutdown. The French government took the opposite approach to the UK – they forced the suppliers to report weekly availability, and also mandated equitable distribution such that each hospital must receive a generator each week (as IBA is doing now), ideally at least 30% of the usual size and in no case less than 2 GBq, to maintain essential services in 6 areas: lung scans in pregnant women, paediatric studies, sentinel node detection during surgery, preoperative localisation of parathyroid adenoma, renal studies prior to total or partial nephrectomy, and studies in patients with contraindication for contrast media (these 6 indications were estimated to comprise 20% of normal ^{99m}Tc usage).

Therapeutics

Therapy radionuclides are not under threat: the demand is so much smaller and the range of reactors which can produce them is wider.

- Thyroid: there are society guidelines now but patient selection may need to be tightened up
- Bone palliation: useful for disseminated disease but focal lesions generally treated by external beam radiotherapy; ^{223}Ra is promising
- Radiosynovectomy: not widely used due to medical alternatives
- Lymphoma: indications for ^{90}Y-Zevalin are broadening and usage may increase somewhat, but rituximab itself is being used more effectively than it was during the clinical trials of Zevalin
- Peptide therapy: promising but limited by lack of licensed product

The outcome was lukewarm and the impact uncertain. Even at the conclusion of the meeting it was unclear whether the Committee for Medicinal Products for Human Use (CHMP) would act upon anything which had been discussed. Here we are, three months on, and nothing has been sent to the participants.

[While I am generally a Europhile, let me relate one instance of Brussels gone mad. The futuristic EMA building at Canary Wharf (apparently it is the only EU institution based in the UK) operates a cashless cafeteria. Even though the participants would be claiming their lunch expenses, they had to individually load money onto their electronic badges. Four of us from the UK found this too confusing so we went to the sandwich shop next door, though it was a bit of a challenge to get out of the building – our badges would only let us in or out of the lifts and stairwells at particular floors. And you had to select the floor before getting into the lift – there were no buttons inside.]