U.K. Radiopharmacy Group

NEWSLETTER
2005 Q1

The January 2005 meeting of the UK Radiopharmacy Group was held at the Beeches Management Centre, Bournville, in advance of the annual workshop. Items of general interest are summarised below, followed by notes on the workshop.

^{51}Cr-EDTA SURVEY

As mentioned in recent issues of the Newsletter, the UKRG is discussing with the MHRA issues around the dispensing of ^{51}Cr-EDTA for GFR determination. In particular, the MHRA has expressed concern about maintenance of sterility in multidose usage. In order to better inform this discussion, a confidential survey of dispensing practices is being carried out for the UKRG by Joti Chattha, a fourth year MPharm student at King's College London. Some of you have already participated in this when it was distributed in Bournville and during the postgrad radiopharmacy course at KCL, and for this we are grateful. For those of you who have a copy of the survey but have not returned it, let this be a gently reminder. Anyone else willing to take part in the survey can download it from the UKRG web site using the following link: SURVEY

If there are any questions or concerns, please contact james.ballinger@gstt.nhs.uk. Thanks.

WORKFORCE ISSUES

Workforce initiative

The news has finally filtered up to someone at an appropriate level: nuclear medicine is facing a serious staffing shortfall in all specialties, largely due to retirements and an insufficient number of trainees. The need in radiopharmacy is possibly the greatest. A meeting is being held in early March at which the requirements in all craft groups will be discussed. This could lead to central funding of training posts. We will keep you informed of progress.

Registration / recognition of radio-pharmaceutical scientists

Discussion is continuing on the best way to gain recognition of radiopharmaceutical science as a distinct specialty. The issue of registration is being pursued with the Health Professions Council, but accreditation from an appropriate body will be required, possibly IPEM.

National occupational standards / Career pathway

The NOS process is continuing. The latest objective is to map the individual tasks in the NOS standards to the nine stage career pathway in healthcare science. There is another meeting in early February to discuss this. A small subgroup from the committee is/are risking their remaining neurons to keep this detailed and time consuming process going. They deserve our gratitude and prayers.

Capacity planning

The expansion of myocardial perfusion imaging in response to NICE guidelines may raise capacity issues for radiopharmacy. Provision of the MPI tests may involve extended hours and/or Saturday service. While the shelf-lives of the imaging agents are not a problem, efficient use of technetium may require re-elution and reconstitution of kits late in the day. In addition, private initiatives for provision of MPI testing may rely on NHS sources of radiopharmaceuticals.

In a related development, there is a government task force looking at issues in provision of diagnostic tests, and BNMS is in the loop on this.

REGULATORY ISSUES

Out of hours deliveries

The long awaited guidelines from the BNMS, with the endorsement of the Health and Safety Executive and Environment Agency, were published in the December 2004 issue of *Nuclear Medicine Communications*, together with an editorial by Alex Elliott. To quote from the editorial:

"The article highlights the five basic principles of responsibility, training, accounting, timeliness, and security, and details some scenarios which satisfy these requirements."

Clinical trials / Investigative medicinal product (IMP) licences

There continues to be an enormous degree of confusion over this issue. There was some help in the question and answer session in Bournville (see below) but many uncertainties remain.

The Department of Health and Medical Research Council have established a Clinical Trials Tool Kit web site www.ct-toolkit.ac.uk which presents a lot of helpful information. There is a link to an algorithm released by the MHRA which takes one through a series of questions in order to establish "Is it a clinical trial?"

Pharmacy QC NorthWest have assembled a list of definitions of clinical trials activities. Individuals may look at their website www.qcnw.nhs.uk and register where necessary to enable them to view the pages relating to whether or not an IMP licence is required for the preparation/ manufacture of a range of items commonly undertaken in the past by pharmacy.

Radiopharmacy computer systems

At the business meeting in Bournville, Bob Nixon from PaxSys demonstrated the latest version of his radiopharmacy software which will soon be out for beta testing. The Veenstra product through Bright Technologies will also be beta tested soon.

The MHRA reminds us that any software must be validated under GAMP (Good Automated Manufacturing Practices). That being said, accessing information about GAMP is not straightforward. The International Society for Pharmaceutical Engineering has some links to documentation from its web site: www.ispe.org/gamp. The US Food and Drugs Administration offers the following document: www.fda.gov/cdrh/comp/guidance/938.html. (In the process of looking for this information, I came across another standard: Good Electronic Records Management or GERM!)

Finger doses

The January 2005 issue of *Nuclear Medicine Communications* contains an interesting paper on the effects of dispensing methods on finger doses in UK radiopharmacies. The single most important factor in determining finger dose was, not surprisingly, the use of syringe shields.

ADVERSE REACTIONS

Reporting of adverse reactions

The UKRG has been operating an adverse reactions reporting system for radiopharmaceuticals for the BNMS for a number of years, originally co-ordinated by Stuart Hesslewood and now by Neil Hartman. This is accessed from either the UKRG or BNMS web sites. Reports are forwarded for medical assessment as well as being logged. The system is international and an annual summary appears in the blue pages of the *European Journal of Nuclear Medicine* after a suitable incubation time. Unfortunately, the database is not searchable electronically. This will be remedied to some extent by the database being collected on VirRAD. Events reported to UKRG are entered on VirRAD; however, less information is captured by VirRAD and it only captures reactions, not defects.

Summary reports, in addition to being eventually published in *EJNM*, are also available via the EANM web site, though the route is somewhat circuitous:
Go to www.eanm.org
Click on *The EANM* (on left hand side of page)
Then click on *Committees*
Scroll down to *Radiopharmacy*
Click on the word *Radiopharmacy*, then *Reporting schemes*.

Reporting of product defects

In the last Newsletter I rather glibly stated: "All are reminded that product defects should be reported to the Defective Medicines Reporting Centre at Market Towers." I was immediately taken to task by an eagle eyed reader from the northeast: "So - is there a website for submission of data to the "Defective Medicines Reporting Centre" at Market Towers?; is there a form available anywhere for defective product reports?; what is the full address for the Defective Medicines Reporting Centre at Market Towers?"

I shall attempt to remedy the scandalous insufficiency of information in the previous Newsletter. The form that pops up on the UKRG web site is the adverse reactions form, but at the left hand side of it is a link to the product defects form. The product defects form does have the question: Has the MCA defective medicines centre been informed? However, this is out of date as the agency name has changed and London phone numbers have changed!

The web address is:
http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/defmedsrepcen/dmrc.htm

or from www.mhra.gov.uk go to the alphabetical listing and select defective medicines. The form is available in Word and pdf formats. Mailing address: Defective Medicines Reporting Centre, 18-159, Market Towers, 1 Nine Elms Lane, London SW8 5NQ, telephone 020-7084 2574, fax 020-7084 2676 or e-mail info@mhra.gsi.gov.uk.

PRODUCT NEWS

Mebrofenin (Cholecis)

News of the imminent demise of Cholecis (the only hepatobiliary agent licenced in the UK), announced in the last Newsletter, was premature. Schering have found an alternative manufacturer who will continue to supply the product under licence. The final batch manufactured at Schering was extra large and should last through 2005 while the replacement plans are put into place.

Sincalide

With an ongoing supply of hepatobiliary agent ensured, what about gall bladder stress testing? Sincalide, the pharmacological agent to induce gall bladder contraction, has been on and off the market for some time. However, a recent paper suggests that a corn oil emulsion (recipe given) can be used as a suitable alternative. The paper from Bartel *et al.* in Iowa, including radiopharmacist Jim Ponto, appears in the January 2005 issue of the *Journal of Nuclear Medicine*. In addition to being effective, the emulsion was well tolerated, cheaper, and more physiological than sincalide.

UPCOMING MEETINGS

Radiotracers for *in vivo* assessment of biological function – New directions

22-23 April, Warsaw, Poland. Sponsored by COST Action B12 in co-operation with the Council of the European Union. Conference information available on the Polatom home page www.polatom.pl. Abstract deadline: 28 February.

Radionuclide therapy

The British Institute of Radiology will be holding a symposium entitled "Nuclear medicine in oncology: new perspectives and innovations in treatment" on 28 April in London. www.bir.org.uk

MEETING REPORT

Bournville 2005

The UKRG held another successful and well attended radiopharmacy workshop at Bournville on Friday 7th January 2005 with a diverse range of topics.

- Gavin Barrett of Gravatom kicked off the day with a description of the processes involved in specification, design, and procurement of radiation protection equipment.
- Bronwyn Phillips of the MHRA fielded questions on the clinical trials directive and IMP licences.
- Professor Terry Jones gave an entertaining description of the development of the Manchester Molecular Imaging Centre, one of the largest PET research facilities in the world.
- This was followed by Bob Pringle who addressed issues of validation and qualification of the Manchester GMP PET facility.
- Dr Rosemary Allen from St George's Hospital, Tooting, gave an update on sentinel node imaging, which is now the standard of care in melanoma and breast cancer.
- The final presentation was from Professor Steve Mather who described the current status of the VirRAD project as it nears the end of its start up phase.

The syndicate groups in the afternoon session were dubbed "Controversy Corners". The attendees circulated among six locations where various hot topics were discussed. The moderator of each group has summarised the discussion:

To (air) bleed or not to bleed: that is the question (with apologies to Shakespeare)

Moderator: Adrian Hall

- All participants use an air bleed for Myoview; none use an air bleed for any other kits.
- Whilst conventional wisdom suggests that air should never be added to a vial containing a technetium radiopharmaceutical, some participants DO add air to multidose vials to ease withdrawal of individual patient doses. None of those who add air reported any adverse impact on radiochemical purity. HOWEVER, it was not clear whether these users had performed extensive testing to definitely establish any impact from oxygen/air.
- A number of participants use air-bleed needles in the eluate vial; for some of these, MHRA Inspectors have insisted that such air-bleed needles have appropriate filters fitted.

- A number of people use air-bleed needles to relieve pressure build-up in kits which have been boiled, to prevent aerosol generation; others wait the appropriate length of time given in the SPC and appear to have no problems with aerosols.

The use of LuerLok syringes in radiopharmacy Moderator: Paul Maltby

- Whilst there appeared to be a wide variety of practices using LuerLok syringes around the country, it was agreed that Luer slip syringes were generally used for reduction of radiation dose to the fingertips of operators, dispensers and staff administering the products. The additional radiation dose for Luerlok syringes was perceived to be due to the time taken to ensure the needle was fitted securely to the thread at the tip of the syringe.
- Participants agreed that this extra time was justified with products that could be considered to be additionally hazardous, especially where spillage could not be contemplated. Thus, they should be considered routinely for the administration of therapeutic radiopharm-aceuticals, for radiolabelled blood products e.g. white cells, and where the use of 0.2-µm filters was necessary.
- The use of LuerLok syringes for transferring large volumes of ^{99m}Tc generator eluate was discussed, although no clear majority felt that it should be mandated.
- Finally, their use for administering myocardial perfusion agents during the stress phase of the test was considered as this study was deemed by many to be additionally hazardous. However, no clear view was reached.

Scan or cut and count for determination of radiochemical purity? Moderator: Bev Ellis

- Scanning was felt to be the more accurate and more scientific method, but involved the capital expense of the equipment and the need for calibration
- The cut and count method can be made more accurate by cutting the strip into 1-cm portions rather than just into two parts. There can be problems with artefacts and accidental contamination producing invalid results which may be difficult to detect; for example, the cut point may be within a peak. In terms of equipment, a dose calibrator may not be accurate enough for low activity yet a gamma counter is too sensitive.
- The Sep Pak methods were felt to suffer limitations similar to cut and count; i.e. fine when they work but prone to misinterpretation.
- The frequency of RCP testing was discussed. UK guidelines (*Nucl Med Commun* 2001; 22:909-916) recommend each new batch of kits, then once per month, while recent discussion on VirRad has suggested much more frequent testing. Since the reconstitution of a kit with ^{99m}Tc results in the formation of a new chemical entity, some people argue it is difficult to justify *not* testing every preparation.

How best to dispense ^{51}Cr-EDTA? Moderator: Stuart Hesslewood

- The currently available product has a reference activity of 37 MBq in 10 mL. It is licensed for multidose use and contains benzyl alcohol as a preservative. Theoretical problems are introduction of microbiological contamination during use and possible benzyl alcohol toxicity problems that have been reported in neonates.
- **Dispensing methods:** Most common is to withdraw individual patient doses as and when required. The vast majority of participants withdrew more than one dose. Time interval between first and last withdrawals varied from 2 days to several weeks. The following techniques are also used in some departments:
  a) Split the original vial into 0.5- or 1-mL aliquots without dilution. Each aliquot is then a single dose vial.
  b) Dilute the original vial with benzyl alcohol and split into unit dose aliquots.
  c) Dilute the original vial with saline or water and split into unit dose aliquots.

  These 3 techniques were used at approximately equal frequencies. All departments used more than one of the aliquots prepared.
- **Sterility testing:** Most users performed some form of sterility testing either on the remnants of the original vial or an unused aliquot. No sterility failures had been observed. One user had on one occasion failed to grow organisms when a positive control was performed. (Insufficient dilution of benzyl alcohol?) One department that withdraws doses from the original vial as required has a valuable process control. A 10-mL vial of nutrient broth "shadows" the ^{51}Cr-EDTA vial. Each time a dose is withdrawn from the latter an equivalent volume of broth is withdrawn. Syringes and vial remnants are the incubated. No growth has been observed in 153 batches over 6 years.
- **Possible toxicity of benzyl alcohol:** No problems had been observed. The product has been used in young children, but not neonates.
- **Possible reformulation issues:** It was considered that an alternative to benzyl alcohol was not necessary (and unlikely to be made available). The possibility of unit dose vials containing smaller activities would solve potential microbiological issues, but no

problems had been encountered with the exiting formulation. Unit dose vials raised the following concerns:

a) increase in overall costs
b) logistics of supply by manufacturer
c) logistics of ordering – would this increase or decrease amount of radioactive waste generated (volume and/or activity)?

Where to boil your MAG3/MIBI? Moderator: Jim Ballinger

- 65% (20) of participants boiled these products in the clean room, 28% (9) boiled them in the support room and sent them back into the clean room for splitting, and 7% (2) boiled them in the support room and did not need to take them back into the clean room.
- Everyone used (or claimed they used) a fresh bottle of sterile water each day and emptied and dried the bath after use. One person reported starting a fire when someone forgot to turn off the bath.
- Some participants are evaluating dry baths. No one is still using a microwave oven.
- Practices for cooling varied. Some people followed the manufacturer's instructions religiously while others reasoned that the product would have cooled adequately by the time it reached the clinic.
- Only one participant had been quizzed by the MHRA about practices.
- It was noted that many new ^{99m}Tc kits in development will require heating.

Supplying radiopharmaceuticals in multidose vials / single dose vials / single dose syringes Moderator: Alistair Millar

- 72% (23) of participants supplied in multidose vials, 6% (2) in single dose vials and 22% (7) in single dose syringes. The main comments made about each technique were as follows.

- **Multidose vials:** The flexibility of dose volume that can be obtained from a multidose vial was seen as the most important advantage of this container. No-one limited the number of doses per vial up to the manufacturer's specified maximum for activity and volume. The introduction of microbial contamination during successive withdrawals from the vial is a potential disadvantage, although several participants reported that routine sterility testing of residues had shown no contamination. The potential for the air that is admitted to the vial during each withdrawal affecting the radiochemical purity of the remaining doses was raised. The exposure to a high activity during the withdrawal of the first doses was noted.
- **Single dose vials (a Scottish phenomenon?):** Eliminates the consequences for other patients of microbial contamination introduced during withdrawal. Minimises the potential for overdose by restricting the activity per vial. For ^{99m}Tc radiopharmaceuticals, each dose is maintained in a nitrogen atmosphere until required. Is expensive due to the cost of empty vials.
- **Single dose syringes:** All handling is undertaken in the controlled environment of the radiopharmacy. Eliminates the consequences for other patients of microbial contamination introduced during withdrawal. Minimises the potential for overdose by restricting the activity per dose but is inflexible for large patients or patients who are not injected at the scheduled time. Is inexpensive due to the low cost of syringes. Members of the radiopharmacy staff are exposed to the radiation dose from preparing the radiopharmaceutical and drawing it up for injection.

www.ukrg.org.uk	Editor: Jim Ballinger Department of Nuclear Medicine Guy's and St Thomas' NHS Foundation Trust St Thomas Street, London, UK, SE1 9RT Phone: 020 7188 5521; Fax: 020 7188 4094 E-mail: james.ballinger@gstt.nhs.uk
Issue 2005 Q1 Published 2 February 2005	This and previous issues of the Newsletter are available from the UKRG web site and are now posted in the library section at www.VirRad.org