U.K. Radiopharmacy Group

NEWSLETTER
2006 Q3

IN THIS ISSUE

There are several fairly important items in this issue which I would like to draw to your attention:

- Abstract deadline for BNMS 2007 meeting is 26 October 2006
- Awarding of European Specialisation Certificate in Radiopharmacy to "grandparents", deadline is end of 2006 (page 2)
- New regulations for transport of blood (page 3)
- New guidelines for calibration of radionuclide calibrators (page 3)

^{51}Cr-EDTA INJECTION

For several years there have been discussions between the UKRG and the MHRA over the issue of multidose use of ^{51}Cr-EDTA injection for GFR determination. Last year many of you took part in a survey of EDTA dispensing patterns around the country. A summary of the results of that survey is presented as an appendix to this Newsletter.

There have been no further developments on this issue in recent months, so we thought it useful to summarise the situation as it stands:

- Multidose use of ^{51}Cr-EDTA, even though it is preserved with benzyl alcohol, has been questioned by the MHRA during inspections of licensed units.
- ^{51}Cr-EDTA came on the market more than 30 years ago and is licensed for multidose use.
- EU guidelines state that multidose vials should not normally be used more than 28 days after first puncture even if the formulation contains a preservative. The reference document is CPMP/QWP/159/96 corr, which is available at www.eudra.org/emea.html.
- A variety of protocols are used around the country to provide doses of ^{51}Cr-EDTA and the UKRG does not recommend a particular method.
- Each unit must be able to demonstrate to an MHRA inspector and/or EL97/52 auditor that their practice maintains the sterility of the product throughout its assigned shelf-life.
- If the unit chooses to prepare a dilution containing benzyl alcohol, they should be aware of the potential toxicity of benzyl alcohol in neonates (Rabiu O, Forsey P, Patel S. Preservatives can produce harmful effects in paediatric drug preparations. *Pharmacy in Practice* 2004; 14:101-10).
- The UKRG feels it is *not* justified to limit the use of ^{51}Cr-EDTA to 24 hours from first puncture of the vial:
  - There is no evidence that this is necessary;
  - It would not be economically viable;
  - The manufacturer would not be able to produce enough material to meet the demand if all vials were discarded after 24 hours.
- The manufacturer is unlikely to reintroduce the product in a unit dose format and if challenged would likely remove the product from the market.

UKRG EVENTS

Bournville Workshop 2007

Plans are progressing for the workshop to be held on Friday 12th January 2007. The format will be similar to recent years, with topics in the morning covering equipment and process validation and practice update, followed by round table discussion groups (knights required) in the afternoon. Several vendors plan to offer demonstrations of equipment or software. More details will be circulated shortly.

BNMS Annual Meeting 2007

The Manchester meeting will be held 19-21 March 2007. The ***abstract deadline is 26 October 2006***. Participation in the radiopharmacy session is encouraged. These don't have to be major research projects. Practice-related topics are equally welcome, and seem to have been absent in the last few years.

UKRG INITIATIVES

Reporting of unusual biodistributions, adverse reactions, and product defects

Technical problems with reporting via the BNMS website have been resolved and the system is back in operation. Neil Hartman will be circulating tabulations of reports regularly. Of the reports which have come in over the last 18 months, the most frequently cited agents were medronate, mertiatide, and tetrofosmin.

Postgraduate Course in Radiopharmacy

The annual postgraduate course in radiopharmacy, sometimes known as the Easter course, is tentatively scheduled for 12-15 March 2007 at King's College London. Further information will be circulated with the Newsletter, posted on the UKRG website, or from jim.ballinger@kcl.ac.uk.

Radiopharmacy Audit

Revision of the UKRG Radiopharmacy Audit document is almost complete and the new version should be available on the website shortly.

Radiopharmacy Handbook

Revision of the UKRG Radiopharmacy Handbook is also underway. The work has been divided up among UKRG members, with some making more progress than others. Malcolm Frier will be compiling and editing the final version. It is hoped that the revised Handbook will appear on the website in the next few months.

Capacity planning

Issues around capacity planning have been discussed at length and a working party has been established to prepare an article on radiopharmacy capacity planning for publication in *Hospital Pharmacist*.

Error reporting

A form 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). A copy of the radiopharmacy error reporting form should be circulated with this newsletter. If it is not, you can obtain a copy from paul.maltby@rlbuht.nhs.uk. Completed forms are to be to returned to Paul. They will be treated confidentially and reported to the national scheme anonymously. The forms can be modified to take into account local practice but if the headings deviate significantly then they lose their value.

Textbook of Radiopharmacy

The most recent edition of the "Textbook of Radiopharmacy", originally edited by Charles Sampson, is becoming outdated and is also out of print. Since it is an essential reference for a number of courses, including PTQA, the UKRG proposes to issue a new edition and Tony Theobald has agreed to edit it. In particular, PET will be addressed in much greater depth and this will likely become the textbook for the MSc in Radiopharmaceutics and PET Radiochemistry course at King's College London.

Tony is about to retire for the second time. A year ago we congratulated him on his retirement from KCL (post Chelsea, etc.) After the obligatory month of gardening leave, he returned part-time to co-ordinate the first year's offering of the new MSc at KCL. In addition to editing the new edition of Sampson, he also plans to write a book on the history of radiopharmacy. Happy retirement, Tony!

WORKFORCE ISSUES

Training staff for PET/CT

Bev Ellis is a member of the UK PET/CT Advisory Board, which is chaired by Andrew Hilson and Isky Gordon. The Department of Health has allocated the SHAs £20M for PET/CT over the next two years, although the money is not ring-fenced and it does not dictate how the money is to be spent (e.g. fixed site vs mobile service). The BNMS document on training requirements of different professional groups for PET/CT will be published shortly in *Nuclear Medicine Communcations*.

Workforce survey

The UK Workforce Review Team has released for consultation its report "Professional workplace recommendations 2007/8 June 2006" (see: www.healthcareworkforce.nhs.uk/C9/2006/default.aspx). Radiopharmacy is mentioned in terms of shortages in relation to cancer services but not in any other context. The UKRG is very dissatisfied with this report and will be responding to the consultation document.

Registration of clinical technologists

The UKRG is continuing in dialogue with the IPEM Nuclear Medicine SIG regarding a separate training strand for radiopharmacy staff as part of the Clinical Technology degree.

European Postgraduate Specialisation Certificate in Radiopharmacy

The EANM certificate is normally awarded following a defined programme of education and a 2-year period of practical experience in the field. As the certificate is gaining importance in the pursuit of a professional career in radiopharmaceutical chemistry and radiopharmacy, the EANM

Radiopharmacy Committee has decided to offer a one-off opportunity to people who have been working in the field for a long time to obtain the certificate on the basis of their professional history and present-day activities ("grandfather clause"). The conditions that must be met to qualify are:

- 8 years of experience in the field before 1999, the year in which the postgraduate courses started.
- Sufficiently broad experience in the field.

This option for awarding of the certificate will be open ***during the year 2006***. A formal application containing the information on the checklist, which may be downloaded from the EANM Radiopharmacy Committee website (but without the need to have supervisors sign for the items), should be sent to the chairman of the board, Dr. G. Westera, Nuclear Medicine, Radiopharmacy, University Hospital Zürich, Rämistrasse 100, 8091 Zurich, Switzerland. The applications will be considered by the entire board.

The correct page on the website can be somewhat difficult to find. Go to www.eanm.org, select About EANM > Committees > Radiopharmacy > Committee site > Specialisation > Appendix III.

REGULATORY ISSUES

Transport of blood

It has recently become clear that, under the Transport of Infectious Substances document revised 1 February 2006, non-radioactive blood transported for radiolabelling would be classified as UN3373 and subject to these regulations as the blood is highly likely to include pathogenic material. This will require primary, secondary, and outer packaging, drop testing of packaging, appropriate labelling including a diamond with the UN3373 classification, written instructions for packing, consignment documents, and emergency response procedures. The UKRG will be discussing this next month and will then issue "sensible" (though perhaps not definitive) advice on how to comply with the regulations in the most practical manner.

ARSAC Notes for Guidance

The newest edition of the ARSAC Notes for Guidance was issued in March. In addition to the typos in some of the tables reported in the previous issue of the Newsletter, it has been noted that there is an error in the route of administration of nanocolloid for lymph studies. This error will be corrected in the electronic version which is accessible at www.arsac.org.uk.

Annex 1

The revised Annex 1 to the Orange Guide is still not available in final form. With respect to the requirement for continuous particle monitoring, there are indications that the MHRA recognises the differences between hospitals and industry (e.g. manual *vs* automated processes, reliance on alcohol sprays which render results meaningless). A risk assessment and justification for not monitoring should be performed, though it may be advisable to install sampling ports in new units but not the entire monitoring system.

There is a draft Pharmaceutical Inspection Convention Scheme (PICS) document on hospital pharmacy which the MHRA will use as a guide for inspections throughout the EU. This identifies the different standards applied when inspecting hospitals as opposed to industry. It is expected to go out for consultation shortly.

Hand washing facilities

The MHRA have confirmed by letter to one specials licensed unit that sinks are acceptable in radiopharmacy support areas because of health and safety issues. The NHS QA Committee will take this into consideration when reviewing the Pharmacy Clean Room Capital Schemes advisory document.

Transport of radioactive material

New legislation ADR 2005 takes effect in January 2007 and stipulates a 1-week training course for drivers. However, it has been confirmed that this *does not* apply to drivers who handle consignments of up to 10 packages with a total TI of no more than 3 (i.e. the current small user derogation remains in effect).

Radionuclide calibrators

The National Physical Laboratory (NPL) has recently issued a new document, "Protocol for establishing and maintaining the calibration of medical radionuclide calibrators and their quality control (A national measurement good practice guide – no 93)". The content for the most part reflects current practice. However, one aspect could prove problematic and/or expensive. There is a recommendation for annual accuracy checks against two traceable reference sources and that the choice of radionuclides be varied from year to year. The document can be downloaded from: www.npl.co.uk.

Radiopharmacy design requirements

Health Building Note 29 is due out imminently from the Department of Health. Chapter 8 covers design of radiopharmacies and should be used as a blueprint for new builds.

PRODUCT/INDUSTRY NEWS

Manufactured specials

A national advisory board has been set up to co-ordinate manufacturing of specials within the NHS. Paul Maltby represents the UKRG on this board. In addition to ensuring the continued availability of the specials required for radiopharmacy, concerns include the lack of freeze-drying facilities within the NHS and developments in the National Programme for Information Technology which create problems for coding of radiopharmaceuticals in the electronic patient record.

Tetrofosmin and salicylate allergy

An eagle-eyed person in Medicines Information (is there any other kind?) at one hospital has noted that the tetrofosmin formulation contains a salicylate and thus is contraindicated in patients who are allergic to aspirin. At that hospital, patients with allergies are scanned with sestamibi rather than tetrofosmin.

Given that the kit contains only 0.32 mg of disodium sulphosalicylate, which would be distributed amongst a number of patients, compared to 10 mg salicylate in a cup of tea, it seems highly unlikely that this is anything other than a theoretical risk. However, we will seek to obtain an authoritative answer for the next Newsletter.

Amersham Pharmacy Services

The Amersham central radiopharmacy has ceased operations at the Hammersmith Hospital. Their lease was not renewed due to the hospital needing the space for other uses. Supply to the former Amersham customers has been taken over temporarily by other radiopharmacies and it is believed that GE is constructing a new facility to house its central radiopharmacy operations.

UPCOMING COURSES

As noted in previous Newsletters, two EC-funded networks of excellence, EMIL (European Molecular Imaging Laboratories) and DiMI (Diagnostic Molecular Imaging), offer a variety of short courses on radiopharmaceutical topics. Upcoming courses include: Iodine-123 and fluorine-18 labeled radiopharmaceuticals, FLT radiosynthesis, Imaging probe preparation, and PET imaging with oligonucleotides and peptides. Details and listings are available on VirRad or from:
Emil-dimi.training@cea.fr
www.dimi-net.org

UPCOMING MEETINGS

British Nuclear Medicine Society 4-5 Sep, Cambridge. www.bnms.org

7th International Symposium on Technetium in Chemistry and Nuclear Medicine 6-9 Sep, Bressanone. http://tecnum.dsfarm.unipd.it

European Association of Nuclear Medicine 30 Sep-4 Oct, Athens. www.eanm.org

9th World Congress of Nuclear Medicine and Biology 22-27 Oct, Seoul. www.wfnmb.org (finally with the correct spelling)

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UK SURVEY OF METHODS FOR DISPENSING OF ^{51}Cr-EDTA INJECTION FOR DETERMINATION OF GLOMERULAR FILTRATION RATE

Survey conducted by: Paramjot (Joti) Chattha, MPharm, King's College London
Supervisors: Dr A E Theobald, King's College London; Dr J R Ballinger, Guy's and St Thomas' NHS Trust

METHODS

A survey was distributed in hard copy at the UKRG workshop in Bournville (~50 attendees) and during the Postgraduate Course in Radiopharmacy at King's College London (~25 students) in January 2005. The survey was distributed electronically following announcements on the VirRAD and RADPHARMUK e-mail lists.

RESULTS

A total of 32 replies were received, 17 in hard copy and 15 electronically. Of these, 20 were from teaching hospitals, 7 from district general hospitals, 3 from specialist cancer hospitals, and 2 from acute trusts. In 30 of the centres the radiopharmacies operated under a manufacturing specials licence while the other two were run by pharmacy under the Section 10 Medicines Act exemption.

The number of GFR studies per month varied widely among institutions as shown in Table 1.

Table 1. Number of GFR studies per month (n = 32)

Number of GFR studies per month	Number (%) of centres
1 – 10	7 (22)
11 – 20	5 (16)
21 – 40	6 (19)
41 – 70	4 (13)
71 – 100	1 (3)
101 – 200	2 (6)
200+	1 (3)
Not stated	6 (19)

The method of purchase of ^{51}Cr-EDTA is shown in Table 2. About one third of centres have a standing order while the rest order as required.

Table 2. How is ^{51}Cr-EDTA purchased (n = 32)?

Response	Number (%) of centres
Standing order, 1-2 vials/month	6 (20)
Standing order, 3-5 vials/month	4 (12)
Standing order, >5 vials/month	2 (6)
As required	20 (62)

The frequency of use of the various dispensing methods is presented in Table 3. In about one half of centres, individual doses are drawn directly from the stock vial. The next most frequently used method was dilution into a secondary stock vial which occurs in about one quarter of centres.

Table 3. Frequency of use of various dispensing methods (n = 32)

Dispensing method	Number (%) of centres
Individual dose drawn from stock vial	17 (53)
Subdispensing of aliquots from stock vial into secondary vials without dilution	2 (6)
Dilution into secondary stock vial	9 (28)
Dilution and subdispensing into unit dose vial	3 (9)
Dilution and subdispensing into unit dose syringe	1 (3)

Table 4 presents the methods of subdispensing and dilution for the 13 centres represented in the bottom 3 lines of Table 3. About half the centres prepare unit dose vials and half multidose. The type of diluent is also an equal split between saline and saline containing benzyl alcohol, and this split is the same for unit dose and multidose. All centres used standard vials available in radiopharmacy, either nitrogen filled or evacuated.

Table 4. Methods of subdispensing and dilution (n = 13)

Vial type	Number (%) of centres	Diluent	
		Saline	Saline + benzyl alcohol
Unit dose	7 (54)	3	4
Multidose	6 (46)	3	3

The standard diluent containing preservative is 0.9% saline plus 1% benzyl alcohol; no other preservatives were reported. One centre added 1% disodium EDTA (i.e. to maintain the same EDTA concentration as in the stock vial) and another centre used 0.75% sodium chloride.

However, Table 5 shows that the vast majority of subdispensing is intended for immediate use.

Table 5. Purpose of preparation of each vial (n = 24)

Purpose	Number (%) of centres
For each session of GFR studies	8 (33)
For each individual patient	10 (42)
Other: stock	1 (4)
Other: single dose aliquots dispensed from stock and given 14 day expiry	1 (4)
Not applicable: dispense unit dose syringes	2 (8)
Not stated	2 (8)

There was great variation in the shelf life given to multidose vials among the six centres which produced them as seen in Table 6. While half were used for only a single session and given an expiry of 24 hours, the other half were used as late as the expiry of the original stock vial.

Table 6. Shelf life given to multidose vials following first puncture (n = 6)

Shelf life	Number (%) of centres
24 hours or less (single session)	3 (50)
4 weeks	1 (17)
Until expiry (up to 3 months)	2 (33)

Storage conditions also varied between centres as seen in Table 7. Half of the centres stored the product in the refrigerator. Of those stored at room temperature, some were behind lead shielding while others were in a laminar flow hood. The manufacturer recommends storage below 25^{o}C but not frozen.

Table 7. How are dispensed vials stored (n = 32)?

Mode of storage	Number (%) of centres
Pharmacy refrigerator	17 (53)
Room temperature with lead shielding	10 (31)
Room temperature in laminar flow hood	3 (10)
Not applicable (not dispensing into vials)	2 (6)

Moving on to preparation of the patient doses in Table 8, almost half use small volume measurements.

Table 8. How is appropriate dose obtained (n = 32)?

Method	Number (%) of centres
Small volume measurement	13 (41)
Dilution with saline	10 (31)
Dilution with unlicensed diluent	2 (6)
Other method	7 (22)

It can be seen in Table 9 that 59% of centres responding measure their doses by weighing the syringe while the remainder are split equally between volume alone or an activity measurement.

Table 9. How are doses measured (n = 32)?

Method	Number (%) of centres
By weight pre and post drawing up	5 (16)
By weight pre and post injection	14 (43)
By volume	6 (19)
By activity	7 (22)

Table 10 shows that slightly more than one half of centres have performed some sort of validation of their dispensing method.

Table 10. Validation of formulation (n = 32)

Method	Number (%) of centres
Microbiological testing	6 (19)
Process validation	7 (22)
Stability testing	0 (0)
Other	4 (13)
None/unknown	15 (46)

The MHRA has commented during inspections on the procedures used in about one third of the centres (Table 11).

Table 11. Has MHRA commented on your method (n = 32)?

Response	Number (%) of centres
Yes	9 (28)
No	19 (60)
Don't know	2 (6)
Not applicable (Section 10 exemption)	2 (6)

In only a small number of centres has a risk assessment definitely been performed (Table 12).

Table 12. Has department conducted risk assessment (n = 32)?

Response	Number (%) of centres
Yes	4 (12)
No	14 (44)
Don't know	14 (44)

An alternative to ^{51}Cr-EDTA is the use of ^{99m}Tc-DTPA which can provide equivalent results without the concern about maintenance of sterility over prolonged periods, as each batch is only used for one day. About one third of centres have used this method.

Table 13. Utilisation of DTPA (n = 32)

Response	Number (%) of centres
Currently use ^{99m}Tc-DTPA	3 (9)
Previously used ^{99m}Tc-DTPA	7 (21)
Never used ^{99m}Tc-DTPA	22 (70)

Thank you to everyone who participated in the survey!