U.K. Radiopharmacy Group

NEWSLETTER
2008 Q4

In This Issue

SENSIBLE ADVICE

Stannous pyrophosphate (PYP)

It has been noted that the SPC for the Covidien stannous PYP kit does not state an expiry time for its use in pretinning (as 'cold pyro'), though does state an expiry for ^{99m}Tc-PYP of 4 hours. It would be sensible to use 4 hours as the expiry time. (The expiry of GE's Stannous Agent is 6 hours post reconstitution or 2 hours after the first dose has been withdrawn.) It is difficult to validate an expiry time in house, as it would require either a stannous ion assay or an *in vitro* model which takes into account all the relevant physiological factors.

The PYP leaflet also fails to state explicitly the quantity of stannous chloride, though it can be calculated indirectly. In practice, if the kit is reconstituted with 6 mL saline, the tin concentration is similar to GE Stannous Agent and thus can be dosed at 0.03 mL/kg.

UKRG EVENTS

Radiopharmacy workshop

The annual radiopharmacy workshop will be held on Friday 16 January 2009 at the Beeches in Bournville, near Birmingham. The first session will be on computerised quality management systems. This will be followed by a regulatory update from the MHRA, primarily on clinical trials issues. The rest of the day will be devoted to clinical and technical aspects of blood cell labelling, in a session sponsored by GE Healthcare. The afternoon discussion sessions will focus on aspects of cell labelling. Registrations have poured in and the workshop is at capacity, but please contact Paul in case there are any cancellations: paul.maltby@rlbuht.nhs.uk.

Postgraduate course in radiopharmacy

The next running of the Easter course will take place 9-12 March 2009 at King's College London. You should have already received an e-mailing about this. Registrations are coming in but there is still plenty of space. Please contact: jim.ballinger@kcl.ac.uk.

UKRG INITIATIVES

Hetastarch

Following a hot tip, the UKRG identified a European source of hetastarch and arranged for an NHS pharmaceutical specials manufacturing unit to pack it down into ampoules. This has taken a number of months to work its way through the system but it is now available. Contact your regional UKRG rep for ordering information.

Survey of radiochemical purity testing practices

With the last issue of the Newsletter we distributed a survey of radiochemical purity testing practices in the UK. In MHRA inspections it had been noted that frequency of RCP testing varies widely around the country. We wanted to document current practice in order to inform discussions of what is a workable minimum standard. The response was rapid and spirited. The results are tallied in the appendix to this Newsletter. Thank you to all who participated. Many spleens were vented!

Reporting of unusual biodistributions and product defects

Reports submitted via the UKRG/BNMS system since 2006 have now been entered on the VirRad database, and all new reports will be uploaded

similarly. However, the number of reports is low and we would like to remind everyone to take part in this reporting system. Summary reports and trending are only valid if the database is complete(ish). The manufacturer should also be informed about problems found. MHRA are informed via the Analytical Information Centre, to which defect reports are now being sent, although any major or hazardous defect should be reported to DMRC directly. UKRG will attempt to raise the level of awareness of adverse reactions to radio-pharmaceuticals through an article in *Nuclear Medicine Communications* or *Hospital Pharmacist*.

Chlorhexidine wipes

Some Trusts have dictated that these should be used in pharmacy/radiopharmacy manufacturing units. However, these wipes are intended for skin cleansing only. A particular problem can arise with radiopharmaceutical kits: chlorhexidine gluconate can get into tin colloid kit, for example, and transchelate, ending up with a ^{99m}Tc gluconate complex which can give kidney uptake.

New committee member

At our last meeting we welcomed Phil Hillel from Sheffield, representing Sheffield and the East Midlands.

The committee also says goodbye to Sanjay Patel, radiopharmacist at Guy's and St Thomas' Hospital London, who is moving to Finland for the winter, then starting a new life in Australia. We wish him well and thank him for his unofficial contributions to the committee and the community.

WORKFORCE ISSUES

Modernising scientific careers

There is currently a proposal to have three levels of healthcare science personnel:

- Healthcare science assistants, levels 1-4 (equivalent to bands 1-4???); NVQ or apprenticeships
- Healthcare science practitioners, levels 5-7; degree level entry with practitioner training programme
- Healthcare/clinical scientists, levels 7-9; BSc/ MSc entry plus 3 year training programme with 2 years generic training and 3rd year focussed within specialist area, leading to registration as a healthcare scientist. It will be possible from here to proceed to consultant level through further training.

The question of where radiopharmacy would fit in was raised with Sue Hill. One possibility would be to set up equivalence with pharmaceutical qualifications, which may help other areas in pharmacy with the same problem.

INDUSTRY NEWS

Molybdenum shortages

The moly crisis which emerged just as the last issue of the Newsletter went to press has continued and, if this week's news is to believed, will not end in February as had been hoped. The companies have varied in how well they have responded to the shortages. GE has obtained ^{99}Mo from Chalk River and has been accused of protecting the UK market, but we have been warned that generator prices will virtually double when contracts expire. The European producers have shown some ingenuity in processing targets at alternative sites. However, supplies have been variable and subject to change at short notice. The weekly reporting to the Department of Health has been taking place but we have yet to see much of it.

Clearly there are two things needed: international coordination of reactor shutdowns in the short term and new reactors in the medium to long term. The EANM and European industry association have managed to catch the eye of European governments (though I have complained about sloppiness in their press releases, such as referring to ^{99}Tc rather than ^{99m}Tc).

As we go to press it has been announced that the University of Missouri is to proceed with construction of a reactor which could supply half the US demand for ^{99}Mo, taking some pressure off other suppliers. They say it will cost only US$40 million and will be completed in 4 years.

There is also talk of novel routes to produce ^{90}Mo but these are untested, years away, and still involve significant construction costs.

Generic sestamibi

Covidien was first to the post with approval of their generic sestamibi but others are soon to follow. Its formulation and preparation parameters are identical to Cardiolite but it is packaged in a more convenient 10 mL vial. The original Cardiolite, in the cute little vial which we have grown to love/hate, is still available from IBA.

Stannous agent shortage

In a letter which arrived Christmas Eve, GE announced that their stannous agent will likely be out of stock for a considerable time due to the same problem which has taken Hepatate off the market for an indefinite period. There is no GMP qualified producer of stannous fluoride, the active ingredient

in both kits. GE is negotiating with the MHRA but this will take some months to resolve. However, there are licensed alternatives.

GE discontinues another product

This has almost become a standing item in the Newsletter. This time it is ^{57}Co cyanocobalamin capsules which are being discontinued in the spring. There is no known alternative for this test.

TLC/HPLC system assists imaging chemistry research group

A compact and versatile system from ***LabLogic*** is meeting the radiochromatography detection needs of the Imaging Chemistry research group at King's College London. The group's laboratory at St Thomas' Hospital has a Mini-Scan radioTLC scanner and Flow-Count radioHPLC flow-through monitor.

"We explore new biological targets for molecular imaging and develop a wide variety of new radiopharmaceutical chemistry for PET and gamma imaging in cancer, heart disease and radionuclide therapy of cancer, so radiochromatography is central to most of our activities," says Professor of Imaging Chemistry Phil Blower. "The research laboratory has two LabLogic systems combining radioTLC scanning and radioHPLC. We chose them because they share can the same detector and data analysis platform, saving space and reducing cost, and because of the joint support and compatibility of HPLC and radiation measurement by Agilent and LabLogic."

The Mini-Scan can detect on narrow strips and plates all of the commonly used isotopes in nuclear medicine, radiopharmacy and PET. It can accept up to six different detectors for a wide range of radionuclides from ^{32}P up to ^{99m}Tc, ^{18}F and others. Flow-Count eliminates the need for fraction collecting and scintillation counting, offering a wide range of count rate, shielding and detection configurations in a single system. It can operate remotely up to 12 feet away from the base unit. Laura, the industry's leading radiochromatography package for data collection and analysis, is under constant development to ensure its connectivity. Currently, it can control more than 100 HPLC and liquid handling modules.

TLC scanner checks beta-emitting radionuclide purity

The Queen Elisabeth Hospital in Birmingham, UK, is using a TLC scanner and software from ***LabLogic*** Systems to check the purity of ^{90}Y Zevalin, the cancer therapy for non-Hodgkin's lymphoma. Zevalin is prepared from a radiopharmaceutical kit on the day of administration, and the manufacturer specifies that before the dose is administered thin-layer chromatography (TLC) must be used to confirm its radiochemical purity as 95% or more.

Although the Queen Elisabeth's radiopharmacy already had TLC facilities, they were designed – like those of many hospitals – for measuring the more commonly used gamma-emitting radio-nuclides rather than the pure beta-emitting ^{90}Y in Zevalin. The hospital found the beta detection capability it needed in the Mini-Scan TLC scanner and Laura radio-chromatography data collection and analysis software, both from LabLogic Systems.

Lindsey Halliburton, the hospital's specialist radiopharmacist, reports that the system began to show a return on investment immediately. "We went live with the Mini-Scan when we were preparing the dose for our first Zevalin patient," she says. "We knew it met the purity standard as soon as the chromatogram was being scanned, and then Laura confirmed it. Without the LabLogic system we would have had to do more complex dilutions to get accurate counts that would then have to be interpreted via a spreadsheet, adding time to the process while the patient was waiting for the preparation. The Mini-Scan had already won our confidence during our initial trials, because it gave us accurate results that we felt were much more trustworthy than the conventional cut and count method."

Determining purity is especially critical in the case of Zevalin which, at around US$24,000 on average, is believed to be the world's most expensive single-dose drug currently.

Ship more doses and shuffle less paper with new PET LIMS

PETra, the new LIMS from ***LabLogic*** Systems, is custom-built to save time and reduce error in the production of ^{18}FDG and other PET radio-pharmaceuticals. It supersedes laborious and potentially inaccurate manual recording of essential information for all aspects of the process, from production set up and material preparation through each stage of synthesis to final release of the product.

LabLogic's strong links with vendors of PET-related instrumentation and its on-going dialogue with clients already active in the field ensure that PETra can interface with all the equipment essential to the process - cyclotron, synthesis instruments, dose calibrator, balances, pH meter, radio HPLC/TLC/GC and others. For maximum flexibility, PETra uses the familiar Windows Explorer interface for rapid training and deployment. It can also be used alongside Windows Mobile PDAs to make pre-production checks more efficient.

UPCOMING MEETINGS

UKRG Workshop 16 January, Bournville

Radionuclide therapy and dosimetry: Where are we? Where are we going? 6 February, British Institute of Radiology, London. www.bir.org.uk

Molecular imaging in drug discovery 23-24 April, Groningen, The Netherlands. www.ngmb.umcg.nl

British Nuclear Medicine Society annual meeting 27-29 April, Manchester. Abstract deadline: 15 January. www.bnms.org.uk

Society of Nuclear Medicine annual meeting 13-17 June, Toronto. Abstract deadline: 13 January. www.snm.org

18th International Symposium of Radiopharmaceutical Sciences 12-17 July, Edmonton, Canada. Abstract deadline: 17 February. www.srsweb.org

World Molecular Imaging Congress 23-26 September, Montreal. Abstract deadline: 11 May. www.wmicmeeting.org

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

European Nuclear Medicine Congress 10-14 October, Barcelona. Abstract deadline: 12 April. www.eanm.org

From the Editor

Greetings of the season to all, and best wishes for the new year.

Jim

www.ukrg.org.uk	*Editor:* Jim Ballinger Department of Nuclear Medicine Guy's and St Thomas' NHS Foundation Trust Great Maze Pond, London, UK, SE1 9RT Phone: 020 7188 5521; Fax: 020 7188 4094 E-mail: jim.ballinger@kcl.ac.uk
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APPENDIX 1: SURVEY OF RADIOCHEMICAL PURITY TESTING IN UK RADIOPHARMACIES

A survey was distributed this autumn by the UK Radiopharmacy Group through its committee members and Newsletter in order to get an indication of the frequency of radiochemical purity testing, the methods and equipment used, and whether products other than ^{99m}Tc were tested.

The UK guidelines[1] recommend the following: "Radiochemical purity (RCP) testing of products prepared from licensed labelling kits should preferably be undertaken on every new batch. Increased frequency will be determined locally. Unlicensed radiopharmaceuticals, whether purchased as finished products, prepared from unlicensed kits or prepared to in-house formulae, should be tested on each occasion." One region has suggested a minimum of every 20th vial or about once per month.

A total of 26 replies were received, similar to the recent survey of sterility testing (28). It was clear from the free text comments that there are strong feelings on both sides of the argument. The results are tabulated below:

Question 1. How frequently do you perform RCP testing on ^{99m}Tc products?

Daily every product	4	15%
New batch + 1 per week	3	12%
New batch + 1 per month (every 20th vial)	7	27%
New batch	2	8%
Beginning and end of each batch	1	4%
Occasionally	4	15%
Never	5	19%

Comment: Daily on problem products (2)

Question 2. Do you test products other than ^{99m}Tc kits? If so, which ones?

Some	13	50%
Occasionally	3	12%
Never	10	38%

Products: Octreoscan (9), Zevalin (6), ^{125}I-HSA (5), ^{51}Cr-EDTA (3), ^{14}C-urea/glycocholate (3), peptides (3), ^{131}I-MIBG (2), ^{123}I-MIBG (1), antibodies (2), ^{51}Cr-chromate (1), ^{67}Ga-citrate (1), blood

Question 3. Do you always test unlicensed products?

Yes	20	83%
No	4	17%
Not applicable (do not use unlicensed products)	2	

Question 4. What equipment do you have available? e.g. radiochromatogram scanner, phosphor imager, HPLC, gamma counter, gamma camera, other (please specify)

Gamma counter	15	58%
Scanner	7	27%
Gamma camera (listed only if used for QC; I presume that most nuclear medicine departments have a gamma camera!)	7	27%
HPLC	4	15%
Phosphor imager	3	12%
Film (for ^{14}C)	1	4%

Question 5. If you do *not* have the necessary equipment, have you requested it in budget planning recently?

Yes	5	19%
No	9	35%
Not applicable (have sufficient equipment)	12	46%

Question 6. What are the typical dimensions of the chromatography strips which you use? e.g. 1x8 cm, 2x20 cm

Mini (<10 cm)	12	55%
Midi (11-19 cm)	3	14%
Maxi (20 cm)	7	32%
Not applicable	4	

Question 7. If you perform cut and count, do you generally use a dose calibrator or a gamma counter?

Gamma counter	11	52%
Dose calibrator	8	38%
Gamma camera	1	5%
Mini monitor	1	5%
Not applicable	5	

Question 8. Do you aim to acquire a certain minimum number of counts for precision?

Yes	13	59%
No	9	41%
Not applicable	4	

Question 9. Who performs the RCP testing?

Radiopharmacist/clinical scientist	4	18%
Any trained radiopharmacy staff	12	55%
Technicians/technologists	4	18%
Independent technician	1	5%
QA staff	1	5%
Not applicable	4	

Question 10. What method do you generally use? e.g. manufacturer's recommendation, pharmacopoeia method, other resources e.g. textbooks, papers, UKRG handbook

A combination of various sources	15	68%
Usually manufacturer	7	32%
Not applicable	4	

Question 11. Do you use solid phase extraction cartridge (e.g. Sep-Pak) methods? If so, for which products do you use these methods?

Yes	9	41%
No	13	59%
Not applicable	4	

Products: MAG3 (9), sestamibi (6), tetrofosmin (3), ^{131}I-MIBG (2), ^{123}I-MIBG (1), ^{90}Y-peptides (1)

Question 12. Are you satisfied with your current practices or are there factors which restrict the amount of RCP testing which you do? e.g. staff time, availability of equipment, cost of consumables, low priority

Satisfied with current practices	14	54%
Not enough time	6	23%
Not enough space	3	12%
Low priority of management	3	12%

Question 13. How frequently do you encounter a *technical* problem with RCP testing which requires the test to be repeated? Are there particular products which are more troublesome?

Never (yet)	3	14%
Rarely	7	32%
Occasionally	9	41%
Frequently	3	14%
Not applicable	4	

Products: MAG3 (8), HDP (4), tetrofosmin (4), nanocolloid (2), mebrofenin (2), HMPAO (1), DMSA (1), pentavalent DMSA (1)

Frequency: 1-2/week, 1/month, 2/month (2), every 20th test, every 50th test

Comments:

- Sep-Pak methods are most troublesome
- MAG3 ITLC-SG method using ethyl acetate:MEK is most troublesome
- Free pertechnetate in mebrofenin is most troublesome
- Training issue: worst with new operators or infrequent users
- Always run in duplicate; sometimes need 3rd strip to confirm
- Cut-and-count with the recommended tetrofosmin method is very dodgy
- ITLC-SG is going off the market? I'm inconsolable!

Question 14. How frequently does RCP testing detect real product failures? What products fail most frequently?

Never (yet)	4	18%
Rarely	15	68%
Occasionally	3	14%
Not applicable	4	

Products: MAG3 (7), tetrofosmin (2), sestamibi (1), HMPAO (1), MAA (1), ^{123}I-products (1)
Frequency: 1/month to 1/quarter; 1/quarter
Comment: Can be useful for sorting out radiopharmaceutical mix-ups (i.e. identification)

Question 15. If a clinician reports an unusual appearance on a scan, do you generally perform RCP testing on the product? Does this usually confirm the problem (e.g. free pertechnetate)?

Yes, unless too late in day	16	73%
No	2	9%
No (already test every vial prior to release)	2	9%
Not yet needed to (touch wood)	2	9%
Not applicable	4	

Comments:

- Usually confirms problem, especially if it is free pertechnetate (4)
- Usually confirms that product is NOT the problem (3)
- Usually inconclusive
- Not done if problem occurs with single patient from multidose vial where all other scans were normal

Question 16. Any other comments? [reported verbatim]
There were three full pages of comments, a selection of which are presented here. The attitudes fell into three groups:
Group 1: Every product should be tested

- We test all manufactured kits – whether licensed or not, and all licensed unit dose radiopharmaceuticals supplied by external manufacturers. On average, we find that all RCP testing takes about 45 minutes per day. We do not release products for clinical use until RCP testing has been completed and deemed to be acceptable. Testing is normally started at between 7.30 and 8.00 am, so is complete by between 8.30 and 8.45 am. Although we have a reasonable array of equipment, most RCP testing is done using ITLC or SPE. The volume of solvent used is sufficiently small that our COSHH and risk assessments allow this to be done in an ordinary room without the necessity to have fume extraction facilities. Our personal experience is that arguments about not testing because of lack of equipment, facilities, staff or time just don't hold water.
- In addition to the measurement made soon after preparation, our testing routine includes a measurement at the expiry time for the product to a) demonstrate that the product is stable and b) provide validation data for the expiry that we give to the product. In reality, the second test is usually at approx 6 hours as this fits comfortably into a day's work.
- We have found prospective QC testing very useful to capture failures before release. One sample from each batch (i.e. same kit batch number and eluate batch number) should be tested each day.

Group 2: Some testing should be performed

- Although it is rare to have real product failures, performing RCP regularly maintains the necessary expertise for testing a kit should a clinician report an unusual scan. It also helps with validation of use of a product outside of the manufacturer's instructions.
- RCP fails are more common than sterility fails
- I feel it provides staff with the necessary skill and knowledge in undertaking RCP and being aware of the potential problems for when we do need to test a product due to unusual scans and when undertaking less often for therapy products as well as for validation work.
- We used to do it but not any more. I feel that we are offering a less than ideal service because we can't and don't do any RCP but the Trust priorities are different from ours.
- Not routinely. In the early days of ^{111}In-Octreoscan and ^{123}I-MIBG TLC confirmed product integrity. It provided historic data on which to base future use.
- RCP tests are often too specific to answer questions. The loss of ITLC-SA prevents us investigating reduced hydrolysed species, for example.
- Restricting factors are primarily staff time. Some years ago we had a policy of performing RCP on every type of kit once a month, but this was not achieved in practice. At an MHRA inspection the failure to adhere to our policy was criticised and in response the policy was changed to state that we perform RCP only as an investigative tool if something is suspected to be a problem (i.e. abnormal biodistribution). I

believe that if we were to purchase a modern device such as a scanner where the information produced is more interesting than the “yes” or “no” of cut and count then we might be able to increase the enthusiasm for performing RCP, though additional staff would be the real breakthrough.

Group 3: RCP testing is a waste of time

- The kits are supplied and prepared as recommended by the manufacturer. It should not be necessary to further validate such products.
- Unnecessary pre injection testing leads to delayed imaging schedules.
- The cost (in effort, delay, consumables) does not justify widespread use of this time consuming analysis considering the small risks of having to repeat occasional studies.
- False positive ‘failures’ are expensive in terms of delaying clinical schedules.
- The ultimate test of the product is a satisfactory biodistribution. It is extremely rare that this is not achieved with modern kits when then manufacturer’s instructions are adhered to. RCP is a complex procedure, which is not always easy to get right. The number of failures would be expected to be extremely small and so, with routine testing, there is a significant risk of rejecting a kit that is, in fact, perfectly satisfactory with the inherent waste, cost and, most importantly, potential for delaying a clinically important test. Also, due to the extreme rarity of failures, it is likely that testing a kit from each batch would not identify the one faulty vial. Therefore routine testing of a vial from each batch is likely to result in a very small number of false negative results, possibly rather more false positive results and is unlikely to produce the extremely small number of true positive results, which would potentially benefit the patient.
- Imaging failures are most commonly down to individual patients and are not batch related.
- It is known that some laboratories carry out testing on a random selection of newly prepared radiopharmaceuticals on the basis that some testing is better than none. Unless the selected kits are chosen from risk analysis data (historical likelihood of failure) then sampling presumably risks an untested kit failure being used.
- There may well be a case in validation of preparations used outside manufacturers instructions or other off-label use (e.g. we validated our method for storage and reconstitution of HMPAO aliquots for cell labelling). I would strongly resist any proposals to introduce routine RCP testing.
- Overall, I think routine use of RCP fails on a risk-benefit analysis. Its routine use mainly risks prevention of use of satisfactory products, thus degrading clinical services by delaying investigations. The potential benefits if testing were much more reliable are still minimal - preventing a few repeated scans every ten years? I would strongly oppose the requirement to routinely do RCP testing. I think it would be another bureaucratic nonsense imposed by the MHRA completely unrelated to a proper risk benefit analysis and consideration of what is in the interest of the patient.

Summary:

- Frequency of RCP testing varies widely around the country and there are strongly held feelings
- A substantial majority of centres (66%) are meeting the minimum UK guidelines, and 83% test unlicensed products
- About half of the centres scan chromatography strips (with a scanner, phosphor imager, or gamma camera) while the other half uses mainly cut and count
- 41% of respondents use Sep-Pak methods, particularly for MAG3
- Technical failures (false positives) do occur, requiring investigation and delaying injection; this is partly a training issue, but even experienced operators encounter failures
- True failures are rare
- MAG3 wins the triple Ignoble Prize for most difficult to analyse, most common false positives, and most common true failures
- Anecdotally, unusual scan appearances are most often due to patient factors rather than the radiopharmaceutical, except in the case of thyroid/salivary gland/stomach activity where re-analysis of the product generally shows free pertechnetate

Reference:

[1]Report of a joint working party: the UK Radiopharmacy Group and the NHS Pharmaceutical Quality Control Committee. Quality assurance of radiopharmaceuticals. *Nucl Med Commun* 2001; 22: 909-916