U.K. Radiopharmacy Group

NEWSLETTER
2009 Q1

SENSIBLE ADVICE

Generator contingency planning

On the last morning of the BNMS annual meeting there was a session on the molybdenum crisis. There will be further discussion in the next Newsletter but I wanted to bring two issues to your attention (particularly ff you are tendering for supply or buying new equipment in the near future) in light of further shortages anticipated over the next few years. :

- If you use more than one generator per week, it might be advisable to purchase them from different suppliers in order to minimise the impact of future shortages.
- If you are buying a new isolator, it is advisable to allow capacity for extra generators in case each one needs to be kept in use for a longer period.

BNMS annual meeting

This year the radiopharmacy sessions were co-sponsored by the Radiochemistry Group of the Royal Society of Chemistry. This allowed us to invite three international speakers. John Valliant from McMaster University spoke on new approaches to development of radiopharm-aceuticals. Roger Schibli from Zurich talked about click chemistry for labelling radiopharmaceuticals. And Len Wiebe from the University of Alberta spoke on nuclides, nucleosides, and nucleotides.

There were nine proffered papers from five labs on topics ranging from new labelling methods for PET and SPECT to validation of new labelling methods for ReadyBrek. There was also a session on the molybdenum crisis, leading to the sensible advice which appears at the top of this Newsletter and which will be presented in greater depth in the next Newsletter.

UKRG EVENTS

Radiopharmacy workshop

The annual radiopharmacy workshop was held on Friday 16 January 2009 at the Beeches in Bournville, near Birmingham. We drew a capacity crowd Topics included computerised quality management systems, a regulatory update from the MHRA, primarily on clinical trials issues, and clinical and technical aspects of blood cell labelling, in a session sponsored by GE Healthcare. A summary of the afternoon discussion sessions on aspects of cell labelling will be found in Appendix 1.

Postgraduate course in radiopharmacy

The Easter course ran 9-12 March 2009 at King's College London with a record attendance of 42. The same issues which delayed this Newsletter have also delayed the follow-up to the course (eg I haven't paid the speakers yet!) but certificates are going out this week.

UKRG INITIATIVES

New guidance documents published

Four guidance documents have recently been published by the UKRG:

Guidelines for the safe preparation of radio-labelled blood cells discusses issues such as risks, training, and facilities.

A capacity planning toolkit for radiopharmacy services in the UK does what it says on the tin, looking at various levels of service and providing guidance on the time and staffing level required to provide that service. This can be useful in helping justify new positions.

Advice for nuclear medicine departments following discontinuation of licensed radiopharmaceuticals and kits from the home market outlines the procedures to be followed in order to obtain alternative products from abroad.

Responsibilities of Chief Pharmacists for the purchase and supply of radiopharmaceuticals also does what it says on the tin and no further comment is required!

These documents can be downloaded from our website (www.ukrg.org.uk) in a new section called (wait for it) Guidance Notes. This will be the new route for dissemination of such information since *Nuclear Medicine Communications* will no longer publish BNMS documents.

Error reporting

As announced previously, a form (which should accompany this Newsletter but is also available from 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.

New committee member

At our last meeting we welcomed Jackie Wilkinson from Wrexham, who will alternate with John Jones in representing Wales.

The committee also says goodbye to Prof David Williams, who has represented IPEM and the North East. We wish him well in his retirement and thank him for his always well-reasoned contributions to the committee.

WORKFORCE ISSUES

Modernising scientific careers

There has been further movement in the attempt to have radiopharmacy recognised within this initiative. At the moment there is a proposal to create supernumerary posts in pharmaceutical sciences which would include 6 month rotations through radiopharmacy, aseptics, production, and quality assurance. Radiopharmacy would also become a compulsory module in the PTQA course. This situation is still in flux and further updates will be presented in upcoming Newsletters.

On a similar note, discussions are continuing at Son of Pharm Soc concerning the possibility of forming a Faculty of Pharmaceutical Sciences which would embrace pharmacists and non-pharmacists alike. Though by no means certain, this concept is gaining support.

REGULATORY ISSUES

Feedback from MHRA inspections

Among the topics which featured in recent inspections of licensed units are deficiencies in:

- quality management system, including lack of timely closeout of quality exceptions, lack of root cause analysis, lack of change control
- microbiological monitoring, including lack of root cause analysis, improper handling and/or transfer of settle plates, lack of procedure to follow when a broth test fails
- resources, succession planning, capacity planning
- facilities.

PFI construction

Those of you involved in PFI builds should be made aware that some PFI companies are approaching the MHRA directly for comments on designs, completely sidelining NHS involvement. This further emphasises the importance of having a user specification which requires sign-off by both parties prior to commencement of the build and specifies consultation with the MHRA.

Continuous particle monitoring

As you are aware, continuous particle monitoring is not practical in NHS aseptic units (including radiopharmacy) where frequent use of alcohol spray and opening of syringe packaging mystifies the particle counting devices. However, each licensed unit must prepare its own statement justifying why CPM is not performed. The statement might include:

- comments that only closed procedures are being used
- identification of sources of particles
- steps undertaken to minimise production of particles
- recognition that unavoidable generation of particles makes monitoring impractical
- documentation that Grade A is achieved at rest
- schedule for periodic (quarterly) revalidation

INDUSTRY NEWS

ITLC-SA chromatography paper

Since the withdrawal of ITLC-SG from the market by Pall-Gelman we are all scrambling for alternatives. Varian still supplies ITLC-SA (note: silicic acid is not equivalent to silica gel). Contact: James Stratta, Sales Professional, Consumable Products, Varian Inc., 10 Mead Road, Oxford Industrial Park, Yarnton, Oxford, OX5 1QU, fax:

01865 841 945, tel: 01865 291 500. The website is: www.varianinc.com and the UK office is uk.consumablesales@varianinc.com

ITLC-SA QC method for tetrofosmin

GE Healthcare has circulated a modified method for QC of tetrofosmin (Myoview) using ITLC-SA in place of ITLC-SG but with a different solvent ratio. This method is not yet official so it would have to be validated by individual users.

University can depend on "good-value" radiation monitor

Anyone with hands-on responsibility for radiation protection cannot function without a radiation monitor, so they need to be certain that it will perform reliably, day after day. Trevor Moseley, the University of Sheffield's Radiation Protection Advisor, has been using Rad Monitors™ since they were introduced onto the UK market by LabLogic Systems six years ago.

"They're easy to use and recalibrate, robustly constructed and straightforward to repair," he says. "Better still, they cost less to buy but are just as reliable as other makes. Nonetheless, you will always have to replace the occasional broken tube, so after-sales service is an important consideration. Fortunately, LabLogic carries a good stock of spares and give excellent customer service, so you will never be without a Rad Monitor™ for long."

Complementing this fast turnaround service is the company's rigorous instrument testing programme, which is carried out by a full-time specialist. All monitors are thoroughly checked before first delivery and again after repair, and an annual testing service is also available.

The Rad Monitor™ range offers three Geiger Muller-based models for ^{14}C, ^{32}P, ^{33}P and ^{35}S. The GM1 is a general-purpose monitor, with a 28.5mm (1.125 inches) tube detector, a 1.5-2.0 mg/cm^{2}window thickness and a unique thin screen that protects the end window; the GM2 has a larger end window (45mm / 1.75 inches) ideal for detecting soft beta emitters on hands, clothing, and benchtops; and the GM2-P has a pancake probe and a large diameter GM tube for monitoring surfaces. Also available is the sodium iodide crystal-based SD10, which has a high sensitivity scintillation probe for detecting Gamma emitters such as ^{125}I and ^{99m}Tc.

User groups make the transatlantic crossing

Metabolism scientists and radiochemists will be comparing experiences of LabLogic and IN/US products on two different continents in 2009. The North American User Group will convene at the Holiday Inn in Somerset, NJ on 10 June, followed by the European meeting on 15 September at Sheffield's Kenwood Hall Hotel.

Companies attending will also have the opportunity to offer 20-minute presentations drawing on their own work with instruments such as the IN/US Beta-RAM radio HPLC detector, LabLogic's Laura chromatography software and the Debra LIMS for ADME studies. Possible topics include radiochromatography in metabolite profiling; review of the FDA's MIST guidelines; software validation; optimising radiochromatography for fast LC; clinical PET applications for radiochromatography; external reporting tools; implementing LIMS across multiple sites; and sharing data between CRO and sponsor.

Delegates will also learn about the latest developments across the product range of both companies, and about innovations such as PETRA, a LIMS designed specifically for PET radiopharmaceuticals.

Places for either meeting can be booked online at www.lablogic.com.

Tracking radioactive waste from reactor decommissioning

Sample tracking software from LabLogic Systems is assisting in the decommissioning of the UK's only civilian research nuclear reactor. The 100 kW reactor at Imperial College London's Silwood Park campus in Ascot, Berkshire has been producing irradiated samples for nuclear science research and training since 1965, but operational work is likely to be discontinued within the next few years. LabLogic's Stacy tracking and stock control system ─ which was originally developed for radioisotopes used in drug metabolism studies ─ will maintain records of the large amount of radioactive waste generated by the clean-up, de-fuelling and decommissioning of the reactor.

"One of the advantages of Stacy is that it can link directly to our Gammavision software, which records the many different types of isotopes present in the waste," says environmental protection manager Vincent Malachanne. "The ability to enter data easily, track by location and also see who entered or edited data through the security/audit trail are also important considerations for the job that the system has to do."

LabLogic's systems director Huw Loaring said: "We are pleased to have Imperial College as our latest customer for Stacy. It shows the system is flexible enough to be used by universities, pharmaceutical industry drug metabolism laboratories and contract laboratories - anywhere when there is a need to track the use and disposal of radioactivity."

In order to demonstrate regulatory compliance at Silwood Park, Stacy must account for radioactive material and waste arising from three different sources - sample analysis, decommissioning and previous works and operations. It must also keep track of every radioactive waste item from the time it is generated until its disposal off-site. In addition. records must also be kept on a monthly and annual basis of disposal through each waste route, and of the authorised sites to which the waste was transferred. Waste officers with full control over radioactive waste management have full access to Stacy in order to populate the database, assess the compliance of the site and prepare reports, while waste producers have a lower level of read-only access.

UPCOMING MEETINGS

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

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

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

British Nuclear Medicine Society autumn meeting 17-18 September, Guildford. Abstract deadline: 26 June www.bnms.org.uk

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

From the Editor

Believe it or not, we are still in the first quarter of 2009. In my own mind at least. Thank you to those who have enquired about the late arrival of this Newsletter service. There was no shortage of material, only an abundance of conflicting priorities.

Jim

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APPENDIX 1: CELL LABELLING – FEEDBACK FROM ROUND TABLE DISCUSSION GROUPS AT UKRG WORKSHOP, BOURNVILLE, JANUARY 2009

Sedimentation agents/centrifugation/sickle cell patients

- Ratio of red cells to white cells at least 1000:1
- Radiopharmaceuticals used are not cell specific thus WBCs must comprise the majority of cells present
- In most cases sedimentation agents are not necessary if there were no time limits, so it is a question of availability of specials – methocell or hespan
- Have to consider to ADR profile of each (ie potential for reactions), must keep separate sample of cell-free plasma with no sedimentation agent present for final cell resuspension
- Other sedimentation agents have been used eg gelofusine, but concern about TSE status
- Sedimentation with tube held at 45 degree angle has been proposed as speeding up the process
- For sickle cell patients a slow spin at 14*g* (**not** rpm) has worked to separate cell rich supernatant
- Dilution of sickle cell patients blood with saline and/or ACD has also allowed sedimentation to occur.

Expiry times for radiolabelled cells – ^{111}In *versus* ^{99m}Tc

- Consensus is that re-injection should be 'as soon as possible' after radiolabelling. This time varied considerably and ranged from 15 min, 30 min 1, 2 h to 4 h plus. However no scientific evidence to support expiry time. Use of trypan blue test for investigating viability at different expiry times? This may vary depending on whether cells are resuspended in saline or plasma
- ^{111}In considered to be generally more stable on cells than ^{99m}Tc
- Resuspension of cells – ensure that cells are resuspended and no clumps or floating particles, if so then not injected; invert several times immediately prior to re-injection
- What is the acceptable minimum labelling efficiency? Should be enough activity on cells to obtain satisfactory images. Is there any correlation between poor labelling efficiencies and false negative results and/or higher blood pool?
- White cell or platelet count: what is the minimum to obtain satisfactory radiolabelling of leucocytes or platelets? Should this be known when booking the test so that staff time is not wasted if cell count is too low. Generally the white cell count is not known prior to test, however if it known to be low then more blood is taken. Use of donor cells (WBC's or platelets) if low count?

Isolator disinfection

- All blood samples handled as if infected, no differentiation in the disinfection process
- **Two main regimens**
  - 70/30 spray/wipes as routine followed by Klercide B if a spill occurs
  - Klercide B as routine followed by Sanitab or equivalent if a spill occurs
  - Both these techniques require a cleandown with 70/30 after the appropriate contact time with either the Klercide B or Sanitabs to reduce the risk of corrosion in the isolator/cabinet
  - Contact times are based on manufacturers' literature
- **Other regimens**
  - One unit on the advice of infection control wash the isolator/cabinet with sterile neutral detergent spray then wipe down with 70/30 wipes
  - Fumigation with formaldehyde is carried out in some units but not many and only once or twice a year in addition to the normal clean down. General feeling was that once or twice a year was a waste of time and if it was going to be employed it would have to be after each blood labelling. This would be expensive and also pose a risk to staff.
  - UV light is also used in some units but no real evidence to support its use.

Poor labelling – what steps can be taken to rescue a procedure

- Poor sedimentation
  - Allow to settle longer (up to 2 hours in Slovenia) [Editor's note: that's an awfully long way to send your cells!]
  - Settle at a 45 degree angle (not vertical)
  - Low speed centrifugation (14*g* – not rpm)
  - Change sedimenting agent (methylcellulose *versus* hespan) - differing opinions!
- Small cell pellet
  - Incubate with activity for longer
  - Add more activity
- Clean taking of blood by venepuncture
  - Size of needle: 19G best
  - Size of syringe: 2 x 30ml may be better than 1 x 60ml in case 1 may clot!

- Patient problem
    - Referred too late – chronic infection may not be primarily granulocytic
    - Educate medics

Clumping/clotting and anticoagulation

- Anticoagulant
    - Best to use ACD as a single unit dose (specials only)
    - In the proportion of 15% ACD to blood
    - Heparin can be used in emergency if ACD not available although lower labelling yield may be expected (but not everyone agrees this is the case)
    - Two separate patient identifiers should be clearly visible on the syringe containing the blood
- Clotting blood
    - If blood has started to clot in the syringe no matter how little it is better to obtain a second sample
    - If only small sample of blood obtained due to difficulty in taking sample then the ratio of ACD to blood is not too important as long as minimum of 15%
- Clumping
    - At the final stage of resuspension prior to re-injection, it is important to ensure no clumps are visible in the cell suspension as they may lodge in the lung for several hours. However the technique used to resuspend must be firm but gentle as too vigorous a technique can cause excess frothing and cell damage. Patience is required!

Microbial process validation

- Most people did not simulate the blood labelling process
- The discussions mainly surrounded operator, environmental and materials validation. Frequency of these tests ranged considerably
- Other validation issues included sessional plates, hand wash plates, in addition to hand wash validation. Sterility testing of containers and transfer systems were also included.
- Various discussions on the type of microbiological growth media used
- There was discussion on types of workstations and the importance of ensuring their optimum operation.
- Must ensure the broth is pre-sterilised and is fertile to support growth
- Processes should be validated whenever a change is made, ie Change control
- Differences between ^{99m}Tc, ^{111}In and ^{51}Cr labelling of blood. There should be a different process simulation for each method
- Validation of WBC viability by tryptan blue test was mentioned
- Summary: Although microbial process simulation was rarely carried out by any of the delegates it was felt to be best practice
- This would involve handling and transferring nutrient broth through all the stages that patient blood would travel during a labelling process. This should be carried by each new operator prior to going live and should be repeated at regular intervals and at any point where significant change had occurred