U.K. Radiopharmacy Group

NEWSLETTER
2008 Q3

BREAKING NEWS

This Newsletter was ready to go out at the end of August, just as news was breaking of the molybdenum supply crisis. I toyed with the idea of sending it out with no mention of the elephant in the room, or rather the elephant *not* in the room.

The UKRG had begun to address the issue of what to do if one manufacturer could not supply generators, but a global shortage was beyond our grasp. An interesting report on the crisis in North America last November has been published:
http://www.csnm-scmn.ca/isotopes-e.pdf
It includes strategies for triage of patients and alternative tests which can be used.

One issue which did emerge is the lack of a process to distribute information. The BNMS website was probably the best source. EANM distributed messages to members but was very late to put anything on the website.

This second crisis in less than a year will likely tip the Americans into ensuring a domestic supply, but what about the rest of the world? Reactors are so expensive to build, run, and decommission that only governments can build them, they are not commercially viable. The available reactors are ageing, and there appears to be only informal co-ordination amongst them to ensure continuity of supply during servicing, etc.

All of this is being written on the hoof, as it were, and we hope to have more sober reflection in the next issue of the Newsletter.

UKRG EVENTS

Radiopharmacy workshop

The next radiopharmacy workshop will be held on Friday 16 January 2009 at the Beeches in Bournville, near Birmingham. One of the main topics will be blood cell labelling, in a session sponsored by GE Healthcare. Full information will be distributed in the early autumn.

Postgraduate course in radiopharmacy

The next running of the Easter course is scheduled to take place 9-12 March 2009, although the dates and location are subject to confirmation. Further information will be distributed by November. There are already 8 people on the waiting list left over from this year.

UKRG INITIATIVES

Survey of radiochemical purity testing practices

With this Newsletter you should receive a copy of the UKRG survey of radiochemical purity testing practices. In MHRA inspections it has been noted that frequency of RCP testing varies widely around the country. We want to document current practice in order to inform discussions of what is a workable minimum standard. All responses will be confidential. Contact jim.ballinger@kcl.ac.uk.

Summer school in radiopharmaceutical quality control techniques

Under the auspices of UKRG, King's College London held a 2-day summer school offering lectures and practical experience in radiopharmaceutical quality control techniques. It took place at the Waterloo campus of KCL on 17-18 July with 19 attendees. Jim Ballinger spoke about regulatory and practical aspects, Phil Blower described the techniques and their limitations, and David McGill of GE Healthcare gave the industry perspective. The attendees then went into the lab and started flinging ^{99m}Tc around. The following equipment was on loan: Miniscan with Laura software, LabLogic; MiniGita with GinaStar software from Raytest; and Cyclone phosphorimager from PerkinElmer. Cut and count was also used. In addition to thin layer chromatography, solid phase extraction columns (Sep-Pak) and size exclusion columns (PD10) were employed.

Financial support was provided by LabLogic and PerkinElmer, radiopharmaceutical kits were donated by BMS, Covidien, GE, and Qados, and Tec-Control test kits were donated by Bartec. We would also like to acknowledge the assistance of

Sheila Foolheea and Dan Asker. Initial feedback has been positive and the course was over-subscribed, so it is likely that it will be offered again next year.

Please see a somewhat related posting under Regulatory Issues.

Hetastarch

Hespan is still unavailable. The 2008 Q1 issue of the Newsletter described some alternatives, though none is completely satisfactory. Supply of methocell has been restricted by capacity issues. The UKRG is working with an NHS manufacturing unit to supply hespan from a European source. Material has been imported but further regulatory issues have arisen, so we are still some months away. Watch this space.

Targeted radiotherapy

The British Institute of Radiology has set up a working group to look at the issue of targeted radiotherapy, e.g Zevalin, somatostatin peptides, etc. Steve Mather is addressing the requirements of radiopharmaceutical preparation. Although Zevalin is a kit procedure, many of the other agents are more complicated, involving heating and/or purification, and the operator can receive a hefty radiation dose. It is not yet clear whether the types of automation used in PET will be applicable, since reaction volumes are extremely small and losses in tubing etc. would be excessive, not to mention costly.

Capacity planning in radiopharmacy

A subgroup has been working on this for some time. The final report will be published as a procedure guideline following approval by BNMS Council.

WORKFORCE ISSUES

Scientist/technologist registration

Back to the ongoing issue of the lack of a single recognised specialty of radiopharmacy. At its July meeting the UKRG had representation from the Department of Health Modernising Scientific Careers programme. There are currently 51 separate disciplines in Healthcare Science (HCS) with at least 45 routes of entry. Radiopharmacy is now included with the Physical Sciences and Engineering HCS disciplines. The UKRG has prepared a position paper outlining a proposed training scheme analogous to that run by IPEM for Medical Physics.

REGULATORY ISSUES

Is your leaflet current?

A rather leading question perhaps. One of the hot topics of concern at the MHRA currently is whether units are using the most up to date product leaflet or SPC.

Manufacturers are not required to inform users of minor changes to the SPC. Obviously, if it is to their advantage they will do so, such as an increase in activity limit or expiry time. Many changes are minor, such as corporate entity or address.

It is essential to check that the most up to date leaflet is being used. Changes to leaflets can be of immediate effect or phased in changes. The item code or version number on the leaflet should be noted on the checking procedure when kits are received. A copy of the most recent leaflet should be available, and leaflets in new boxes can then be checked for changes. If the MHRA have deemed a change to be critical, all boxes of a batch will contain the same leaflet, so only one leaflet per batch needs to be checked. The manufacturer should be informing customers of critical changes, so if a new version is detected, the company should be contacted for details of the change.

To that end, the UKRG will lobby the radiopharmaceutical manufacturers to inform customers of all changes automatically.

Feedback from MHRA inspections

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

- Types of errors from the patient's point of view: quality management, training issues.
- Training of domestic staff. This can be difficult if services are contracted out. Many aseptic units have stopped using contract cleaners and use their own ATOs.
- The batch numbers of subdispensed vials must be recorded on the production record.

QP-IMP

Thanks to lobbying by the UKRG, the problem of a lack of QPs for IMPs within the NHS and the stifling effect this will have on clinical trials, which we have been banging on about for several years, has finally made it onto the radar of relevant bodies. On 31 July an initial meeting was held among the Pharm Soc, MHRA, and representatives from the Royal College of Physicians, Royal College of Radiologists, PET CT Board, and UKRG. To document the extent of the problem, a survey is underway of all IMP sites, so if you have not been contacted locally please get in touch with paul.maltby@rlbuht.nhs.uk. In addition, the MHRA

will come to the January workshop in Bournville to explain the latest requirements for application to become a QP IMP. Further meetings between the parties are planned for later in the year.

A new professional body

The transmogrification of the Pharmaceutical Society continues. The Transitional Committee has been established, chaired by Nigel Clarke of the eponymous report. There is a Working Group on improved, advanced, and specialist practice, chaired by Ian Simpson of the College of Pharmacy Practice and a member of the Waterloo Group, of which UKRG was also a part. Its remit is "to welcome and support improved, advanced and specialist practice across the whole of pharmacy, to provide support for existing specialist groups and organisations seeking to join the new professional body, and to provide for appropriate accreditation processes to establish independent verification of particular advanced qualifications". Sounds like UKRG would fit.

The workings of the Transcom are intended to be transparent and all documents are available on the website www.transitionalcommittee.com.

Proficiency testing studies

Proficiency Testing Studies (PTS) are conducted in order to evaluate the participants' performance for specific tests or measurements by means of interlaboratory comparisons. These studies are carried out in the framework of the application of the ISO/IEC 17025 standard which is the standard chosen by the Official Medicines Control Laboratories (OMCLs). This standard requires testing and control laboratories which apply it to regularly control their performance and to submit their results and evaluation when being audited.

The European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM/DBO) organises and designs various PTS programmes in accordance with the ISO/IEC Guide 43 (Part 1) on Proficiency Testing by inter-laboratory comparisons. During the coming months, the EDQM will propose the first PTS on radiopharmaceuticals, which will consist of a determination of the radiochemical purity by liquid chromatography as described in a monograph of the European Pharmacopoeia.

For these to be really successful it requires ~30 laboratories to participate. UK radiopharmacies would be most welcome to take part. One UK commercial lab and at least one UK hospital radiopharmacy took part in a pilot Proficiency Testing Study involving 13 European laboratories. The pilot was a success and the participating laboratories all received valuable feedback on the combined results and their individual performance.

If you are interested in receiving additional information on this PTS and on any other studies of this type which EDQM might organise in the future, please send your contact details to the programme coordinator, Dr Silvia Muñoz Botella (Silvia.Munoz-Botella@edqm.eu).

INDUSTRY NEWS

Demise of BMS Medical Imaging

It was with sadness we received the news that the new owners of BMS Medical Imaging, Lantheus, had decided to discontinue operations in Europe. In the short term, the sole UK product, Cardiolite, will be available from "Big BMS" but there has been an announcement that an agreement has been signed with IBA to be the European distributor. *(See also the editorial on page 5).*

GE discontinues more products

GE has announced they will discontinue gallium and thallium after this month. They feel there are sufficient generic equivalents available. Perhaps they will delay the thallium decision until the ^{99}Mo crisis is resolved.

Progress on amyloid agents

Alzheimer's disease (AD) is seen as an untapped market for PET and a lot of effort is going into the development of β-amyloid binding agents for detection of AD. In recent weeks there have been announcements on progress with two agents. GE purchased the rights to ^{11}C-PIB (Pittsburgh compound B), developed by Chet Mathis in, where else, Pittsburgh. There have been numerous reports, most recently a comparison with brain biopsy specimens during life (I don't think I'd volunteer for that study) in *Archives of Neurology*. But ^{11}C will never be commercially viable so they have been looking for an ^{18}F analogue, known variously as Son-of-PIB or FIB. The search has been long but now we know it is GE-057 and Phase I results are promising. Whole body distribution was studied in 6 volunteers for dosimetry, then 8 controls and 8 patients with probable AD underwent brain scans.

Avid Radiopharmaceuticals based in Philadelphia also announced promising results recently with its amyloid agent, ^{18}F-AV-45. This agent is now in a multicentre Phase II trial in America.

The third agent in the running is ^{18}F-FDDNP, developed at UCLA and sponsored by Siemens.

Progress on apoptosis agents

The amyloid imaging tracers were developed from the dyes used for staining tissue slices in histology. A similar approach is happening with apoptosis, where a small molecule marker previously used for *in vitro* tests has been labelled with ^{18}F and shown in Phase I and IIa studies to be promising for detecting apoptosis resulting from radiation therapy. It has recently been announced that IBA will prepare GMP grade Aposense ^{18}F-ML-10 for clinical trials in America.

Previous attempts to image apoptosis have concentrated on labelled annexin V, a 35-kD protein. Though results have been promising, several agents in clinical development have been dropped and it is difficult to obtain GMP grade material for clinical research.

Radiopharmacy study determines TLC scanning best practice

Radiopharmacy staff at Edinburgh Royal Infirmary have investigated the optimal conditions for measuring RCP of ^{99m}Tc radiopharmaceuticals using the Mini-Scan TLC scanner and Laura chromatogram acquisition software from LabLogic Systems. The study explored the effect of dead-time at different count rates and determined the optimum method for background correction. Reproducibility of the scanning technique was found to be excellent, with no coefficient of variation greater than 0.3%. The full text of the study, which includes a table giving ideal dwell times and scan speeds for ^{99m}Tc radioactive concentrations from 10 to 1000 MBq/ml, can be downloaded from the LabLogic website:
http://www.lablogic.com/Moreinfo/AppNotes/MiniScan/MiniscanPoster.pdf

PET labs can rely on AR2000 imaging scanner

Laboratories manufacturing PET radio-tracers who need to check the purity of their product without investing in a full HPLC system are turning in increasing numbers to the AR2000 imaging scanner from LabLogic Systems. Its direct imaging capability (which is incorporated into the USP standard method for purity analysis of ^{18}F-FDG) gives the fastest possible analysis for all isotopes - less then one minute in the case of moderate activity samples.

St Thomas' Hospital London, one of the UK's longest established PET facilities, has had the AR2000 and LabLogic's Laura software for more than eight years. "We have an annual throughput of up to 520 scans and the AR2000 has always proven to be reliable," says laboratory manager Ms Kam Kahlon. "It is simple and easy to use, such that on the rare occasions when a problem has occurred our staff were able to resolve the issues very quickly. Because we work with very short lived isotopes, reliability and support is key when you have patients waiting for FDG scans."

Keeping tabs on radioisotopes - and more

Users of STacy, the sample management and radioisotope inventory system from LabLogic Systems, are still finding new applications for the software. In radiosynthesis laboratories it is tracking radioactivity against licensed safety limits for the usage and disposal of the large amounts of radioactivity that have to be handled. For ADME drug metabolism studies it is often interfaced with LabLogic's Debra LIMS to track samples and radioactivity from the initial test compound through dosing and sample collection to long-term freezer storage and final disposal. And others are taking advantage of its flexibility to manage a variety of records, from the location and type of radioactive sealed sources to user training schedules, re-ordering bulk chemicals, and maintaining instrument service histories.

Fully compliant with GLP and 21 CFR Part 11, STacy is totally configurable, allowing the user to define location trees, sample and transaction types. Security is similarly flexible, so that access can be assigned on a user-by-user basis to the permitted access level. Once created, samples or collections of samples can be selected and moved around the location tree by a simple 'drag and drop' mechanism. They can be defined with complete control over the entry fields and type of identifying data required, and details can be entered via spreadsheet, file import or bar-code reader. The bar-coding facility can create, print and read labels in many industry-standard formats.

UPCOMING MEETINGS

World Molecular Imaging Congress 10-13 Sept, Nice, France. www.wmicmeeting.org

Small Scale Biotherapeutics – Clinical Trials, Cell & Gene Therapies 18 Sept, Bristol. www.bioapproaches.co.uk

British Nuclear Medicine Society autumn meeting 25-26 September, Liverpool. www.bnms.org.uk

National Cancer Research Institute 5-8 October, Birmingham. www.ncri.org.uk

European Nuclear Medicine Congress 11-15 October, Munich. www.eanm.org

7Th International Meeting on the Effects of Low Doses of Radiation in Biological Systems: New Perspectives on Human Exposure 27-29 Nov, Lisbon http://www.lowrad2008.itn.pt/

18th International Symposium of Radiopharmaceutical Sciences 12-17 July, Edmonton, Canada. Abstract deadline: 15 January. www.srsweb.org

From the Editor

An old friend? Perhaps not, but it is still sad to see the closure of BMS European operations. What we knew most recently as BMS Medical Imaging started life as New England Nuclear, located in the Boston area, one of the original radiopharm companies. Indeed, its address of Treble Cove Road is as famous as Amersham's White Lion Road (the name of the pub on the corner). In the mid 1980's NEN was taken over by DuPont and thrived with the introduction of Cardiolite. A few years ago it was bought by Bristol Myers Squibb. Earlier this year came the news that BMS had sold off its radiopharm division to a venture capital company which then set it up as Lantheus Imaging. Now comes the news that Lantheus is closing its operations in Europe in order to concentrate on the American market. [As an aside, this is actually the *second* time that naughty BMS has sold off its radiopharm division: Squibb, like NEN, was one of the original radiopharm companies, merged into BMS in the mid 80's and was divested in the mid 90's to Bracco, from whence little more has been heard.]

BMS had a much wider line of cyclotron and reactor products until about 5 years ago when their contract with Nordion in Belgium was cancelled, leaving them with only Cardiolite in the UK as well as Neurolite in Europe. What some may not realise is that in North America BMS is one of the biggest radiopharm companies, with a full line of kits, generators, and cyclotron products. Indeed, they supply 80% of the generators used in Canada and probably the majority in America.

Lantheus does have a PET myocardial perfusion agent which shows promise (*J Nucl Med* 2008;49: 630-6), but the driving force must be the imminent expiry of the patent on sestamibi and the entry of generic equivalents into the market. It is a textbook case of how *not* to manage the life cycle of a product. Cardiolite was the most commercially successful radiopharmaceutical ever. In the wake of the introduction of Cardiolite, DuPont (as it was at the time) was very active in radiopharm research. But over the years they cut back on research, and seem to have depended on MIBI as a cash cow.

Speaking of MIBI, it will be interesting to see how this pans out from a business perspective. This is the first time that a major radiopharmaceutical has come off patent and there are like to be at least 4 generic versions. On the scientific side, I expect that the generics will slavishly copy the original formulation, but put it in a 10 mL vial. (I recall being told by a DuPont chemist in 1987 that the reason they chose the dumpy little vial was to limit how many doses could be obtained, i.e. to prevent kit-bashing. At the time they had no idea that the product would be as successful as it turned out to be, nor that the market would develop as it has. In retrospect - always 20:20 - they should have repackaged it at some point along the way.) However, I would like to think that over the last 20 years someone would have found an alternative route (perhaps a stronger reducing agent) to a room temperature preparation.

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APPENDIX 1: SURVEY OF STERILITY TESTING IN UK RADIOPHARMACIES

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

The UK guidelines[1] recommend the following: "The remnants of the first vial of eluate from each technetium generator, the final unmanipulated eluate, and the residue of a kit should be tested each week. The kit should be chosen to cover the range commonly in use on a systematic basis." The guidelines further state: "The frequency of testing should be reviewed in the light of the proven performance of the unit." (The latter statement could be interpreted in either direction.)

A total of 28 replies were received, 23 electronically and 5 by fax. The results are tabulated below:

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

After decay send to external lab (NHS or commercial)	11 (39%)
After decay inoculate broth	3 (11%)
After decay add double strength broth	5(18%)
After decay perform filtration test	1(4%)
Inoculate hot samples	6 (21%)
No sterility testing of products; weekly broth validation	1 (4%)
Not applicable (PET centre)	1 (4%)

Question 2a. How frequently do you perform sterility testing on ^{99m}Tc eluates?

Every eluate	3 (11%)
First and last eluates of each generator	15 (54%)
Last eluate of each generator	6 (21%)
Two elutions per week	1 (4%)
Never	1 (4%)
Not applicable (PET centre)	1 (4%)
Not applicable (no generator on site)	1 (4%)

Question 2b. How frequently do you perform sterility testing on ^{99m}Tc products?

Two kits per day	1 (4%)
One kit per day	5 (18%)
One kit of each product per week	1 (4%)
Two kits per week	1 (4%)
One kit per week	12 (43%)
Two kits per month	1 (4%)
One kit of each product per month	2 (7%)
Unused kits (e.g. cancelled tests)	2 (7%)
Never	2 (7%)
Not applicable (PET centre)	1 (4%)

Question 3. Do you test any non-^{99m}Tc products and, if so, how?

No	15 (54%)
Occasionally	2 (7%)
Regularly	11 (39%)

Products tested include: ^{51}Cr-EDTA, ^{51}Cr-chromate, ^{90}Y antibodies, ^{111}In antibodies and peptides, ^{14}C products, ^{125}I-albumin, ^{123}I products, unlicensed products, stannous agents, saline bag post session, and PET products. Methods include: inoculation, double strength broth, and filtration.

Question 4. Who does the test? [Most interpreted this as: who inoculates the samples?]

Radiopharmacy staff	12 (46%)
External QC department (hospital or regional)	7 (25%)
External lab (commercial)	8 (29%)
Not done	1 (4%)

Question 5. Where are the test samples prepared?

Class A	16 (61%)
Class B	1 (4%)
Class D	3 (11%)
By external lab	7 (25%)
Not done	1 (4%)

Question 6. Any other comments? [reported verbatim]

- Method revalidated every two years using EP procedure
- Planning to change to put final eluate straight into broth, incubate at room temperature before sending to QC lab, but need more vial shields
- MHRA inspector discouraged us from taking aliquots from kits before use (to be mixed with broth) as this would be unnecessary breach of the septum
- Also do weekly broth validation
- Number of sterility tests was increased from first and last eluate and one kit per week to every eluate and one kit per day quite some time ago
- Positive controls not always positive (a few a year)
- MAA can yield false positives if particles are read as growth
- No fails in recent years
- Never had an eluate failure
- Non-Tc procedures are validated so don't need testing
- Pharmacy QC can now accept radioactive samples
- Switched from first and last eluate to last eluate only because never had failure
- Previously used hospital microbiology but forced to go external by MHRA due to lab not meeting EP standards
- I'm worried about the increased use of broth simulations. Isn't broth the *worst* thing you can take into an isolator?

Summary:

- Virtually all centres are doing some sterility testing
- Most centres are meeting the spirit, if not the letter, of the UK guidelines
- More than 75% of testing is done following decay of ^{99m}Tc
- A surprising number of centres are testing non-^{99m}Tc products

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