U.K. Radiopharmacy Group

NEWSLETTER
2012 Q1

UKRG INITIATIVES

UKRG Radiopharmacy Workshop 2012

A report on this meeting appears later in the Newsletter.

UKRG Website

The new UKRG website has now been launched, hosted via the BNMS. Readers are encouraged to take a look; feedback is welcome. The URL is: http://www.bnms.org.uk/general/ukrg-homepage.html which is worth bookmarking as the site contains easily accessible valuable information such as the updated Feb 2012 edition of the QA Document (see below) and links to the adverse reactions and product defect reporting system.

Stop Press !!! - Quality Assurance of Radiopharmaceuticals (2012 ed)

The long-awaited revision of the QA document has now been published and can be downloaded as a PDF from the UKRG website. This has been produced by a joint working party of the UKRG (including representation from the MHRA) and the NHS Pharmaceutical Quality Control Committee and defines recommended minimum standards for RP Quality Assurance, rather than best practice, as was the case with the previous version. This is therefore essential reading for both Specials Licensed and "Section 10" units.

Guidance on End-user Dispensing (Safe drawing up of radiopharmaceuticals)

This is undergoing its final revision stages and is expected to be published soon, hopefully in time for the BNMS 2012 Spring meeting.

Guidance on sharing Tc99m eluate and/or Mo99/Tc99m generators between hospitals

This new UKRG guidance document is also available on the website. In summary: eluate can be transferred by a Section 10 Unit or a Specials Licensed Unit; generators can only be transferred by Section 10 Units, or by a Specials Licensed Unit in co-operation with the local Pharmacy as a virtual Section 10 provision.

January 2012 UKRG meeting.

The Terms of Reference (ToR) and Objectives were reviewed and updated. Full details are on the website but the Objectives are as follows:

Short Term Objectives (1 year)

- Compilation of local network lists. Data will be supplemented by the forthcoming BNMS department survey and Dr Palmer's survey of radiopharmacies in 2009.
- Establishment of the UKRG bursary.
- Ensure that radiopharmaceutical staff are included in the career development programme for the Modernising Scientific and Pharmacy Careers initiatives.

Long Term Objectives (3 years or on-going)

- Lead on the issue of QP training of pharmaceutical NHS staff
- Interpretation of information and the provision and dissemination of "sensible" advice.
- Respond as a Group to calls for consultation, and interpret outcomes of subsequent guidance issued.
- Collate "The Problems Associated with Radiopharmaceuticals Database" in conjunction with the medical assessor of the BNMS. To publish these reports on a quarterly basis; advising the MHRA and/or Industry where appropriate
- To further develop local networks and establish funding for appropriate activities eg audit

SNOMED Clinical Terms (CT) and the coding of Radiopharmaceuticals

UKRG has been asked by Connecting for Health (CfH) to assist with a project to codify radiopharmaceutical usage in healthcare. This is a complex project which aims to produce a set of standard codes for radiopharmaceuticals similar to those used to describe diagnostic imaging procedures as used by the NHS PACS Group. Once defined it is intended that the codes will support: prescription and ordering; preparation and dispensing; recording of administration; peer-to-peer communications; audit and clinical governance; and adverse event reporting. The initial work has been delegated to a UKRG working group who have a steep learning curve to climb!

MOLYBDENUM

Molybdenum supplies

A recent letter from Covidien announced the Dutch Government's formal approval for the new PALLAS reactor to be built in Petten, Netherlands; this will replace the High-Flux Reactor (HFR), also located at Petten, and is expected to be operational by 2022 ensuring a continued robust supply of Mo99. Meanwhile, there will be some disruption to Mo99 supplies during April 2012 when there will be short overlap between maintenance shut-downs of the HFR reactor (Feb – April) and the Canadian NRU reactor (April – May). Covidien are confident they will be able to meet all regular demand for Mo99/Tc99m generators having increased Mo99 production order with their partners, including with the Maria reactor in Poland.

IBA and GE have advised that they have no Mo99 supply issues at present.

REGULATORY ISSUES

Signatures on ARSAC applications

Part C of an ARSAC application asks for the details, experience, and signature of "the scientist(s) responsible for the provision of radioactive medicinal products … to indicate that he/she is satisfied with the arrangements for which he/she is responsible." It is important that this section is completed correctly as there are a number of new members of ARSAC who may be scrutinising this section more carefully and questioning the experience of the signatory. It is most important that the scientist with local responsibility for the handling of radio-pharmaceutical products signs the form. If radio-pharmaceuticals are obtained from an external supplier, the person responsible for that service may also sign but this is not essential except for clinical trials of novel agents.

Expiry dates of opened sterile alcohol sprays

This topic arose after a recent GMP inspection at a License Unit although the concerns seem to be a "storm in a tea cup". The MHRA have indicated that it is a non-issue provided the sprays are validated products used within the stated shelf life.

Re-sheathing of needles

A reminder that the EU Directive on preventing sharps injuries in healthcare has to be implemented from 11th May 2013. The European Biosafety Network has published its first Implementation Update and also some implementation guidance. Details are available at this URL: http://www.nelm.nhs.uk/en/NeLM-Area/News/2012---March/16/Implementation-guidance-for-the-EU-Prevention-of-sharps-injuries-in-the-hospital-and-healthcare-sector/ The guidance talks of the need for a risk assessment, and if there is a risk of sharps injury this must be controlled by, amongst other things, the use of safe practices which included the banning of needle re-capping, with no get-out for using a re-sheathing aid. What is clear is that two-handed re-capping is *verboten*; what is not clear is if the use of single-handed re-capping with a resheathing aid will result in a zero risk of injury and therefore a satisfactory risk assessment outcome. There is no news yet on any UK legislation to implement the EU Directive although the HSE website indicates that it is cosindering "whether we need to introduce new regulations or to amend or add to existing legislation"

Early phase clinical trials in PET

Since the introduction of the European clinical trials directive, with the requirement for preparation of radiopharmaceuticals as Investigational Medicinal Products (IMPs), the regulatory burden has been seen as an impediment to clinical research in the UK. In an attempt to address this, for several years regular meetings have been held among the Medical Research Council, UKRG, Cancer Research UK, the NCRI PET Research Network, the PET radiopharmaceutical industry, and the Medicines and Healthcare Products Regulatory Agency (MHRA). Several reports have been prepared and are available on the NCRI PRN website: www.ncri-pet.org.uk.

Last year a joint MHRA-PET Expert Panel was set up and has been meeting at six month intervals. The panel is meant to be a two way street, educating the regulators and the community, finding solutions, sharing expertise and experience. It's only a first step but it is beginning to yield results. For more information about the panel, see: www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/MHRA-PET/index.htm

Recent MHRA inspections

Issues which have come up in recent inspections have included:

Alarms – what do they mean, and what should we do in response to them.

Licence Updates – it is important to keep these under control, including keeping the MHRA informed changes in nominated personnel (eg Quality Controllers and Production Managers and Supervisors.

Change Control – this is often poorly used; it is important to think about what you are going to do as a consequence of a change in process before it happens (eg what SOPs and records need to be updated in preparation for the change).

Staffing – Units have often not given due consideration to coping with staff shortages.

PFI schemes – there is often poor co-operation with the PFI provider, eg hard facilities support for HVAC plant and cleanroom isolators; and soft facilities support for radiopharmacy suite cleaning;

MEETING REPORTS

UKRG Radiopharmacy Workshop 2012
The annual workshop was held at Bournville on Friday 13th January. Tom Murray (Glasgow) has kindly provided the following review.

The title of this year's Workshop was "***Maintaining Services in a Challenging Environment***", the challenges being posed by new legislation. Later in the day we were provided with an additional challenge in the shape of a noisy group in the adjacent room, having too much fun by far on their Team Building away day [*Editor's note: allegedly they were paying with a Nintendo Wii !!*],. As always chairman and main organiser of the day, Paul Maltby introduced each speaker.

We were pleased that Maggie Cooper's pregnancy did not prevent her from delivering her presentation posing the question "is it possible to comply with the legislation for the manufacture of PET IMPs". Maggie gave a brief history of her pre- Clinical Trial Directive days when she was active in preparing radiolabelled antibodies and peptides for clinical research. Although quality has always been paramount, the new legislation provided additional challenges not least of which was the delineation of staff roles and the requirement to have sufficient trained staff to separate production, quality control and QP release. We wish Maggie well with her impending "delivery-proper" .

The inimitable Jilly Croasdale was up next, providing details of a spreadsheet devised by her colleague Bill Thomson looking at the optimisation of activities and costs of Moly generators. This tool, which is available from Bill on request, is a welcome addition to the strategies at our disposal in tackling scarcities.

Hani El-Sabbahy from the HSE provided details of the proposed changes in the revised EU Basic Safety Standard (BSS) for the radiation dose limit for the lens of the eye which represents a seven fold reduction on the current dose limit. The aim of HSE during the consultation period will be to work with stakeholders to identify groups of workers that may be affected and identify changes in work practices that may be required to avoid Classification under IRR99. Initial indications indicate that Radiopharmacy and Nuclear Medicine communities will be able to comply with the new standard without too many changes to work practice.

Anna Bliss, HSE, discussed the new EC Sharps Directive which requires to be implemented by 11 May 2013. Most of this is covered by existing UK health and safety law where there are already safe procedures for use and disposal of sharps. Where there is a risk a ban on re-capping is proposed and this is clearly at odds with some Radiopharmacy practices where minimisation of radioactive contamination and maintenance of sterility is paramount. Therefore much discussion centred on the use of re-capping devices which are commonly used in many radiopharmacies as a way of minimising needle stick injury and lowering risk.

Chris Rodman, Head of QC, PETNET Solutions, Mt Vernon Hospital, discussed the less controversial subject of "Commercial Production and Distribution of FDG". Chris was comprehensive in his delivery describing the workings of the cyclotron, and subsequent delivery of the bombarded target material to the FDG synthesiser in the hot cell assembly. Upon manufacture the QC challenges of meeting EP specification for F18-FDG were discussed as was the wider QA issues dealing with asepsis and validation including filter integrity testing.

Finally before lunch it was the turn of Derek Pearson, Nottingham University Trust, to update us on Modernising Scientific / Pharmacy Careers. Together with UKRG members some progress has been made in devising suitable syllabi as a means of integrating pharmacy and science graduates on a common training path. At this point the challenge of the acronym count and the rising din from the adjacent room provided sufficient incentive to break for lunch.

The afternoon syndicate sessions split into five as follows:

Re-sheathing of needles (team leader Jilly Croasdale)
Equipment calibration and counting limitations (Phil Hillel)
Expiry of Tc99m generator eluates (Jim Ballinger)
Growth promotion studies on microbial media (Alison Beaney)
Factors affecting the quality of Tc99m radiopharmaceuticals (Paul Maltby)

The outcome of these sessions will be reported in the next issue of the Newsletter.

We are grateful to Paul Maltby and the UKRG for organising yet another thought provoking and enjoyable day on all matters Radiopharmaceutical.

INDUSTRY NEWS

Covidien recall of cold kits

In late March Covidien recalled two Batches of Technescan MAG3^{TM} due to glass particles being discovered in unreleased product. The problem originated in a batch of glass vials from their supplier and also had an effect on other unreleased kits (DMSA, DTPA , HDP and PYP) causing short-term supply problems. The various kits are expected to return to normal supply in stages during April and early May. During this time some radiopharmacies have been using the unlicensed "no-boil" MAG3 from ROTOP.

Loss of Draximage MDP to the European market

Jubilant and Guerbet have jointly decided to end their collaboration to distribute Draximage products in Europe although some existing standing order customers may be lucky enough to receive stocks until the end of the financial year. This affects MDP as there is no licensed alternative in the UK. Another distributor is being sought by Jubilant but nothing has been confirmed yet. The Department of Health, MHRA and BNMS are aware of the situation and questions have been asked of Jubilant as to what they are going to do to ensure supplies are maintained.

Update on ^{82}Rb generator situation

In Newsletter 2011Q3 we reported that the ^{82}Rb generator has been withdrawn from the market worldwide due to three detected cases of ^{82}Sr breakthrough. ^{82}Rb (t½ 75 sec) is a positron emitting agent for myocardial perfusion imaging which is infused directly from a generator loaded with ^{82}Sr (t½ 25 days). The generator is replaced once a month. The technology has been in use for 20 years and has an excellent safety record.

In June, three patients who had undergone ^{82}Rb PET several months earlier set off sensitive radiation detectors at border crossings in America. It was determined that they contained traces of ^{82}Sr (the parent) and ^{85}Sr (a contaminant, t½ 65 days). The patients' radiation burden was estimated to be ~20 mSv (the effective dose from a ^{82}Rb study is 2.8 mSv). Since then, voluntary screening of some 375 patients revealed 54 in whom ^{82}Sr and ^{85}Sr were detected. All affected patients came from two clinics. None of the generators returned to the manufacturer showed any defects.

Following six months of investigation the FDA have concluded that the overexposures were due to user error and inadequate quality assurance on eluates, notably the recommended daily breakthrough test on a purge elution. With strengthened warnings to users, the product is being allowed back on the market. Yet again we see that it doesn't pay to take short cuts.

Lymphoseek

The first agent specifically developed for sentinel node imaging is closer to becoming a reality. Last discussed in Newsletter 2011Q3, Lymphoseek is a soluble molecule, ^{99m}Tc-mannosyl-dextran, which targets mannose receptors on the surface of macrophages in lymph nodes. Being soluble, it migrates from the injection depot more rapidly and extensively, producing higher nodal counts. The rights were bought by the sentinel node probe company Neoprobe, who have since sold off their probe business to concentrate on targeted radiopharmaceuticals for intra-operative detection. Neoprobe has rebranded itself as Navidea Biopharmaceuticals (www.navidea.com) and in addition to Lymphoseek they are developing another radiopharmaceutical for interoperative guidance of surgery. Bizarrely, they have also bought the rights to the dopamine transporter agent altropane and another beta amyloid agent in what is quickly becoming a crowded market. FDA approval of Lymphoseek is expected this year and Navidea have recently announced that they will be filing for pan-European approval.

What's in a name (part 1)?

The players don't stay the same for very long. There are more changes coming in the radiopharmaceutical industry. Covidien is splitting off its pharmaceutical and radiopharmaceutical division which will be reborn as (*wait for it!*) Mallinckrodt. Everything old is new again. IBA (Ion Beam Applications SA) is also splitting off its molecular imaging division, which includes its radiopharmaceutical unit, as a joint venture with US private investment firm SK Capital Partners to be called (*wait for it again!*) IBA Molecular Imaging. This is expected to complete in 2012Q2. You can't tell the players without a programme.

Equipment update from LabLogic

LabLogic detectors and software aid PET /SPECT collaboration

Two healthcare organisations in Grenoble, France, are using LabLogic's "Laura" radio-chromatography system and instrumentation sourced from the same

company to enhance their ability to work closely together.

The nuclear medicine service at Grenoble Hospital has a Flow-RAM radio HPLC detector for PET and SPECT applications, while the nuclear biophysics laboratory of INSERM (France's national institute of health and medical research) at the city's medical college has a Gamma-RAM radio-HPLC detector for soft and intermediate gamma emitters. The laboratory also undertakes PET and SPECT work using the dual-purpose Scan-RAM radio TLC / HPLC scanner.

"Laura" controls all the instruments at both locations and also gathers data ready for analysis – a single-source arrangement that all concerned find very practical.

The hospital's main concern is with quality control of labelled PET molecules after HPLC separation, one of the two methods sanctioned by the European standards. In the long term it hopes to develop techniques that allow molecules to carry larger amounts of radioactivity. At the medical college the laboratory is primarily a research centre carrying out traditional labelling with nuclear medicine isotopes such as Technetium-99m, various forms of iodine, and molecules used in PET such as Gallium and Indium (*sic*). In addition, LabLogic's detectors are used to validate the radiochemical labels themselves and to check the radio-chemical control of them, both in continuous flow and on TLC strips.

More acclaim for Scan-RAM from Czech PET facility

The PET Centre in Brno has added to the growing positive feedback about LabLogic's Scan-RAM radio TLC scanner for PET and SPECT.

Part of the Czech Republic's Nuclear Research Institute Rez, the Centre purchased the Scan-RAM from LabLogic representative ENVINET as a replacement for a TLC scanner supplied ten years ago by a rival manufacturer.

"We need to determine the critical quality parameters of the radiopharmaceuticals we manufacture, and we were not satisfied with the scanner we had because of its unreliability and frequent breakdowns," said Alena Novotná, quality controller of radiopharmaceuticals.

"With the Scan-RAM, on the other hand, we can be confident of the radiochemical purity of the 18F-labelled radiopharmaceuticals we routinely produced, and in exercising quality control over products we develop in the future.

"Since we validated control methods for the Scan-RAM and put it into full operation, we have been really pleased with its reliability. LabLogic's "Laura" software is user-friendly, and we appreciate the wide range of settings the Scan-RAM offers us - speed of scanning, measurement time, configuration of measuring methods, precise adjustment of the detector over a thin layer and the audit trail function."

Whilst echoing those opinions, two other LabLogic customers - the University of Illinois Biomedical Imaging Center and a US drug discovery company – have highlighted the Scan-RAM's dual TLC / HPLC facility, which they say has saved them both money and bench space and improved workflow.

Personal radiation dosimeter improves staff safety

The Tracerco T404 personal electronic dosimeter, which is now available in the UK from LabLogic Systems, is proving to be greatly effective in improving the safety of personnel working with radiation in both nuclear medicine and research environments.

Mount Vernon Hospital in Northwood Hertfordshire, for example, is using the T404 to record exposure to all kinds of radiation sources, from iodine patients to PET scanners. The data collected is then displayed as a graph, which makes it possible to identify the areas and procedures where staff are most vulnerable.

The hospital's radiation protection adviser Janis Brown said: "With its minute by minute breakdown of the wearer's dose, the Tracerco T404 does what a modern PED should do; you can just put it on and forget about it. Afterwards it's very easy to retrieve the data in the right format. In fact the whole business of using it is so intuitive that you hardly need to read the manual."

Similar benefits have been experienced in research applications. One UK university tracked radiation exposure during a cell labelling procedure, pin-pointing instances of high exposure and measuring the degree to which the member of staff was complying with good laboratory practice.

These experiences – graphs from which can be seen on the LabLogic website http://lablogic.com/NewsDisplay.asp?Name=NewTracercoPEDmeetsourcustomersexpectations substantiate the Tracerco T404 PED's status as the easiest to read and operate on the market – despite a selling price half that of others.

Lightweight, weatherproof and drop-resistant, it offers a choice of three measurement modes and four alarm settings, and has one of the largest

memories available. It is also intrinsically safe, so there is no need for a 'hot work' permit if it is used in a potentially explosive environment.

What's in a name (part 2)

With effect from 1st April 2012, subject to normal parliamentary approval) Barts and The London Hospital, Whipps Cross University Hospital, and Newnham University Hospital will merge to become one entity, to be operated by the new Barts Health NHS Trust, the biggest Trust in the NHS.

UPCOMING MEETINGS - 2012

Positron Emission Tomography (PET): Technology and Application
25-27 April, King's College London
www.sthpetcentre.org.uk/petcourse

Clinical Trials course
23-25 April, Leeds University. Leeds
www.healthcare.leeds.ac.uk/study/CPD/PTQA

16th European Symposium on Radiopharmacy and Radiopharmaceuticals
26-29 April, Nantes, France, http://esrr12.eanm.org

British Nuclear Medicine Society (BNMS) 40th Annual Meeting
29 April–2 May, Harrogate Conference Centre, Harrogate, www.bnms.org.uk

PETRAD 2012: Positron Emission Tomography in Research and Diagnostics
16-19 May, Warsaw Scientific Campus, Poland,
www.petrad2012.pl

PET Chemistry UK 2012
24 May, King's College London
sheila.foolheea@kcl.ac.uk

Society of Nuclear Medicine (SNM) 59th Annual Meeting
9–13 June, Miami Beach, Florida, USA
www.snm.org/am12

WMIC 2012: World Molecular Imaging Congress
5-9 September, Dublin, Ireland
www.wmicmeeting.org

11th International Isotope Symposium on the Synthesis and Applications of Isotopes and Isotopically Labelled Compounds
9-13 September, Rupprecht-Karls-Universität, Heidelberg, Germany, www.iis2012.unitt.de/iis2012/

Medical Physics & Engineering Conference (MPEC) 2012
10–12 September, University of Oxford
www.ipem.ac.uk

British Nuclear Medicine Society (BNMS) 2012 Autumn Meeting
13-14 September, University of Oxford
www.bnms.org.uk

European Association of Nuclear Medicine (EANM) Annual Congress
27–31 October, Milan, Italy
www.eanm.org

From the Editor

At this point in the proceedings it gives me great pleasure to acknowledge the great contribution that Jim Ballinger has made as Newsletter Editor over the past 11 years. The UKRG and the wider radiopharmacy community owe him a debt of gratitude for keeping us so well informed over that time. I just hope that the "new boy" can come even part way up to Jim's standard. This is the first time that a non-pharmacist has taken on the role of Newsletter Editor so I hope the Committee's faith in me is justified. The appointment is for a three-year term to the end on 2014; colleagues keep telling me not to stick my head above the parapet!

If anything you have read stirs you I should be pleased to receive your correspondence in some form or another.

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