U.K. Radiopharmacy Group

NEWSLETTER
2013 Q2

UKRG INITIATIVES

UKRG Annual Report 2013 on its activities during 2012

An annual report was prepared for presentation at the BNMS Radiopharmaceutical Sciences Group meeting held as part of the BNMS annual meeting. A copy of the Report is included as Appendix 1 to this Newsletter.

Re-sheathing of needles

The Health and Safety (Sharps Instruments in Healthcare) Regulations 2013 came into effect on 11th May 2013. The EU Directive on which the UK Regulations are based is 2010/31/EU; it contains a statement that: "re-sheathing of needles is not permitted".

Following a consultation process on the implementation of this EU directive, to which the UKRG contributed, the HSE have acknowledged that there are specialist areas where it is appropriate to recap needles as long as certain conditions are met. The specialist areas include radiopharmacy and nuclear medicine. The conditions that must be met include use of appropriate risk assessments as well employment of suitable devices that adequately control the risk of injury during the recapping process. HSE has produced Health Services Information Sheet 7 - Health and Safety (Sharps Instruments in Healthcare) Regulations 2013 to provide guidance on how to comply with the Regulations.

UKRG plans to issue RP/NM-specific guidance on this topic in the next Newsletter

UKRG Radiopharmacy Handbook

The UKRG Radiopharmacy Handbook was first published (in a paperback form) in 1997. The Handbook provided a valuable reference source of information for the Radiopharmacy and Nuclear Medicine community that was not readily available via other sources. Over the years, the Handbook has been updated and could be accessed on-line on the UKRG website. The publication of Sampson's Textbook of Radiopharmacy (fourth edition, edited by Tony Theobald) in 2010 provided much of the updated information that was previously available in the Handbook.

The UKRG committee have recently reviewed the contents of Handbook and it was decided that the Handbook would not be revised as most of the information is now readily available in other sources. However there is a need to provide some sources of useful information that may not be readily available and these documents can be downloaded from the Information Resources section of the UKRG Website at this URL: http://www.bnms.org.uk/ukrg/radiopharmacy-information-resources/ .

The documents on the website will be reviewed every two years; the current list includes the following items:

- Stannous agents;
- Radiochemical Purity Testing;
- Diluent directory; and
- Non-radioactive reagents and diluents

Update on the use of Somatostatin Receptor binding peptides for diagnosis and therapy.

Jim Ballinger (Guy's) has provided the following update.

After developing slowly over the course of 15 years, significant changes have taken place in the use of Somatostatin Receptor binding peptides in the last 6 months, specifically involving enforcement of the patent for use of radiolabelled DOTATATE for diagnosis or therapy.

DIAGNOSTIC USE

Readers might recall that in 2010 the patent on DOTATOC was enforced and the peptide became unavailable for labelling with ^{68}Ga. As a result many users switched to DOTATATE with the assurance that its patent would not be enforced. Early in 2013 Covidien and/or Mallinckrodt began enforcing its patent on DOTATATE and would not allow the two manufacturers of GMP-grade

DOTATATE powder to supply it. The situation has eased somewhat and the material can now be obtained for labelling with ^{68}Ga for use in registered clinical trials (see below).

Supply of the DOTATATE kit produced by Polatom was also blocked, meaning that ^{111}In-DOTATATE could not be prepared for diagnostic scans in patients being treated with ^{90}Y or ^{177}Lu-DOTATATE. Mallinckrodt counters that ^{111}In-Pentetreotide (Octreoscan®) is available for this indication. Many clinicians would dispute this claim of equivalence. Phillip Webster from the Department of Health has been very proactive on this and is still negotiating with Mallinckrodt to allow release of DOTATATE kits for labelling with ^{111}In.

Another high affinity peptide, DOTANOC, is available in GMP form and can be labelled with ^{68}Ga (see below).

THERAPEUTIC USE

The patent enforcement arose when Advanced Accelerator Applications (AAA) obtained the rights and began supply of ^{177}Lu-DOTATATE (Lutathera) for a Phase III clinical trial. AAA claims it has the capacity to supply all the doses of ^{177}Lu-DOTATATE required in Europe from its two production sites in Italy. Patients not eligible for the clinical trial are treated on a named patient basis. There are two productions per week, on Mon for Tue-Wed and on Wed for Thu-Fri. Order deadline is 15 days in advance. Only one strength is produced, 7400 MBq. An interim price has been agreed which is covered by the National Cancer Drugs Fund.

Paul Maltby and Jilly Croasdale audited one of the production sites and AAA has an action plan in place to address the minor deficiencies noted. However, there is still a requirement for the end user to perform radiochemical purity testing prior to use as there is insufficient evidence of stability during transport. Centres which have been doing this have not found any problems.

^{90}Y-DOTATATE is not covered by the patent and DOTATATE kits from Polatom can be obtained on the condition that they are used solely for labelling with ^{90}Y chloride.

^{90}Y and ^{177}Lu-DOTATOC are not covered by the patent and other companies are offering to supply these.

DOTANOC is not suitable for therapy due to the excessive retention in normal tissues.

^{68}Ga GENERATORS AND PEPTIDES

An update has been issued recently and is available on the BNMS website.

The IGG101 GMP-grade generator from Eckert and Ziegler (imported by Imaging Equipment Ltd) can only be purchased for use in registered clinical trials, as can the GMP grade DOTATATE for use with it.

The generators from ITG (imported by Diagnostic Imaging Ltd) and iThemba/IDB (imported by Link Medical) require full end user validation but have been used clinically.

The availability of pharmaceutical grade reagents is improving but depends on which generator and automated synthesizer are used as all have different requirements.

Mo99 ASSAY ERRORS

Readers will be well aware of the importance of undertaking a Mo99 assay on Tc99m generator eluate, to detect any significant Mo99 breakthrough which would lead to an increased patient dose. UKRG has recently become aware of some problems with the Mo99 assay procedure on some Capintec calibrators when using the Capintec canister method. It seems that on some Capintec models with a particular EPROM software version (we are aware that the CRC-15R can have this problem) the Mo99 assay gives an invalid result if the background is measured as part of the procedure; if the background measurement is omitted then a valid Mo99 breakthrough result is obtained.

UKRG has asked Southern Scientific Ltd, the UK agents, to investigate this with Capintec in the US. We hope to report the outcome of the investigation in the next Newsletter

REVISION TO EU GMP

Readers are reminded that the revised EU GMP Chapter 1 came into effect on 31st January 2013. This covers Pharmaceutical Quality Systems (*Editor's note: or perhaps for UKRG readers Radiopharmaceutical Quality Systems !!*) and is essential reading for RP operations. The updated Chapter 1 covers the following PQS topics:

- Definition of a PQS;
- GMP for medicinal products;
- Quality Control;

- Product Quality Review; and
- Quality Risk Management

As mentioned in the last edition of the Newsletter the European Commission has launched the public consultation of the following revised guidelines on good manufacturing practices (GMP):

- Chapter 3 Premises and Equipment
- Chapter 5 Production, specifically the control of starting materials
    - Includes 'pedigree' / supply chain traceability
    - New testing requirements
    - Incorporates the requirements of the Falsified Medicines Directive (FMD)
- Chapter 6 Quality Control
    - Updated to reflect current practice in analytical method transfer; and
    - Guidance on out-of-specification and out-of-trend results
- Chapter 8 Complaints, Quality Defects and Product Recall
    - Incorporates QRM principles on complaints and recalls; and
    - Defines responsibilities in the case of products shortages due to manufacturing problems

Comments and suggestions are invited by 18 July 2013. For details please see the MHRA website at this URL:

http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodManufacturingPractice/News/CON228757

To keep up-to-date with changes in EU GMP readers are advised to bookmark this URL: http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

REGULATORY ISSUES

Recent MHRA inspections

During 2013-Q1 nine radiopharmacies had received a GMP Inspection of which two were PET facilities. During the various inspections the following points of non-compliance with EU GMP were observed.

- Investigations not carried out in a timely manner and not being done particularly well.
- Lack of communication of outcomes of investigations to staff.
- Root cause of issues not being identified.
- Lack of urgency of investigation of bacillus in the Grade A work zone
- Lack of Trend Analysis. Good investigation and trend analysis is very important. Recurrence of a problem suggests that the root cause has not been identified).
- Quality Systems. Key points such as capacity planning, validation and change control were missing from the Quality system in some inspections. Risk management including capacity planning is an essential part of the Quality System particularly when new products are being introduced.
- Lack of regular reviews of staff training.
- Isolators. Results of leak testing were recorded but failures ignored. Some isolators were in poor condition and there was a lack of Service Level Agreements with service providers. Servicing test results should be checked to make sure they are within specification, and recommendations acted upon.
- Some unlicensed products were being used without TSE approval.
- Deficiencies due to fabric of building in older facilities, eg poor changing facilities, no mirrors or hand gel, and inaccurate SOPs.

New Radiopharmacy Inspectors

At the April UKRG Committee meeting Malcolm Olver announced his retirement from front-line Radiopharmacy GMP Inspections. UKRG thanked Malcolm for his support at meetings over a number of years.

Two experienced GMP Inspectors have now been accredited by the MHRA to undertake Radiopharmacy inspections. They are Rachel Carmichael and Kevin Page

INDUSTRY NEWS

UKRG Disclaimer: Information in this section is proffered by UKRG Industry colleagues. Inclusion in the Newsletter does not imply endorsement of any particular product by the UKRG.

GE Healthcare Customer Portal

GE Healthcare is working towards a paper-free communications process and has a launched a "Customer Portal" giving GE customers access to a wide range of important information. Customers can register to use the Portal by completing an online form at the following URL: http://supportcentral.ge.com/esurvey/takesurvey.asp?p=17778&d=3771689 (registration instructions will be sent once the form is submitted). Information currently on the Portal includes, *inter alia*: customer letters; current SPCs; current PILs (a limited range at present); Technologist Guides (currently just for DaTSCAN® and SeHCAT); a DaTSCAN® reporting

guide; and a form for reporting adverse events to GE Healthcare.

The most recent customer letter notifies a temporary removal of the "Drytec®" logo from the case of the "Drytec®" generator whilst GE Healthcare expands into new markets and where time is required for the registration of the brand name; there are no changes to labels on the generators, or to the leaflets.

Imaging Equipment Ltd (IEL) markets Kits for Ga-68 DOTA-conjugated peptides

Imaging Equipment Limited are now able to supply customers (*Editors note: from June 2013*) with GMP kits for labelling Ga-68 DOTA-conjugated peptides, including processing of Ga-68 generator eluate. The GMP quality kits, which are manufactured by ABX, can be used for the following two methods of preparing Ga-68 DOTA-conjugated peptides on the Eckert & Ziegler synthesis systems.

a) Purification of ^{68}Ga on cation-exchange column using a HCl/acetone mixture as eluent (known as the Rosch method)
b) Purification of ^{68}Ga on cation-exchange columns using a HCl/NaCl mixture as eluent

Each kit will be available either excluding or including the peptide.
For more details contact Jeevan Virk on jeevan@imagingequipment.co.uk or call 01761-417-402

IEL publicises the "NETTER-1" trial

"NETTER-1": ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Pivotal Phase III study, a new investigational therapy for midgut carcinoid tumour.

Carcinoid tumours are part of the so called GEPNET (Gastro-Entero-Pancreatic Neuro-endocrine Tumours), which can develop anywhere there are neuroendocrine cells, most commonly in the lungs, appendix, small intestine, rectum and pancreas.

Advanced Accelerator Applications (*Editor's note: company details at* www.adacap.com) is currently conducting an international Phase III clinical trial involving more than 50 nuclear medicine centres in Europe and USA. The study, known as NETTER-1, is a multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing the investigational treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to the established treatment with Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumour. In the NETTER-1 study, only patients with midgut origin GEPNETs can be enrolled.

In the United Kingdom, eight clinical sites are involved in the study, in London, Oxford, Glasgow, Manchester, Liverpool and Birmingham.

If you wish to obtain more information on the study please contact netter-1@adacap.com , or Jessica Johnson at: jessica@imagingequipment.co.uk

New Products / Withdrawal of Products / Supply Issues

IBA Molecular launches TEKCIS® Mo99/Tc99m Generator

IBA has now launched in new 4th generation Mo99/Tc99m generator in the UK (*Editor's Note: by the time readers receive this Newsletter most IBA customers will have already been migrated from the old Elumatic-III generator to the new TEKCIS generator*). This new product has a smoother, sleeker design and is available with higher nominal Mo99 loading than the Elumatic-III, and contains a larger Saline (0.9% NaCl) bag. Full details are available from IBA Molecular (contact Mike Ward, at mike.ward@ibamolecular.com)

Draximage Medronate (MDP)

The UK distribution arrangements for Draximage MDP are still to be confirmed. Readers may be concerned that this item is beginning to sound like a broken record. To mix the metaphors, there is perhaps some light at the end of the tunnel and UKRG hopes to publicise the details in the next Newsletter.

Hameln Potassium Iodate

Potassium Iodide tablets 65mg (the iodine content is equivalent to potassium iodate 85mg) will soon be available from Hameln as a pre-pack of 4 tablets complete with a PIL that has information relating to a Nuclear Medicine test rather than just a Nuclear Incident/Emergency).

This pack size will mean that pre-packing in the pharmacy dispensary is no longer required and the pack will conform to future MHRA requirements for anti-counterfeiting measures. One pack will be sufficient for I-123-Ioflupane (DaTSCAN®) and two packs for I-123-Iobenguane
For further details contact: Stephen Watkin at Hameln Pharmaceuticals Ltd,
e-mail:s.watkin@hameln.co.uk , www.hameln.co.uk

SPC Updates

UKRG is not aware of any recent revisions to radiopharmaceutical SPCs.

RADIOPHARMACY DESIGN

A two-day symposium on Radiopharmacy design is to be held at St Bartholomew's Hospital, London, on 24th-25th October 2013. If any Newsletter reader is interested in this meeting and has not already received an invitation to attend, details can be obtained from Neil Hartman at this e-mail address neil.hartman@bartshealth.nhs.uk

UPCOMING MEETINGS

2013

6th Annual World Molecular Imaging Congress
Date: 18-21 September, Savannah, Georgia, USA
Website: www.wmicmeeting.org

15th International Symposium on Radionuclides in Nephrourology
Date: 15–17 October 2013, Varese, Italy
Website: www.iscorn2013.org

EANM'13 Annual Congress of the European Association of Nuclear Medicine
19-23 October, Lyon, France
www.eanm.org

2014

ESRR'14 European Symposium on Radiopharmacy and Radiopharmaceuticals
24-27 April, Pamplona, Spain

11th Congress World Federation of Nuclear Medicine and Biology (WFNMB)
27-31 Aug, Mexico
www.wfnmb.org

From the Editor

My thanks to all who contributed items for inclusion in this issue of the Newsletter.

The next meeting of the UKRG Committee will take place Aston University, Birmingham on 17-18th July 2013. The one after that will be in London on 8th October 2013. If readers have any issues they wish to be discussed please raise them with your regional rep on the Committee. Alternatively, comments on the Newsletter content or on any radiopharmacy issue can be sent direct to the Editor at the address below.

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Appendix 1 - BNMS Radiopharmaceutical Sciences Group Annual Report 2013

Response to ARSAC report to DoH on continued supply of Medical Isotopes: The Department of Health asked BNMS, via the National Imaging Clinical Advisory Group (NICAG) to review Radiopharmacy services in the UK. BNMS conducted a survey in October 2012 and had a response rate of around 50%. The results were collated into a preliminary report for NICAG in December 2012. Work is ongoing to further process the data on Molybdenum usage in order to make recommendations on how efficiencies can be made. The information is now available on the BNMS website.

Audit Document review: The BNMS Organisational Audit document has been reviewed, as has the specific Radiopharmacy stand-alone audit tool. A higher level Radiopharmacy audit is now an integral part of the BNMS Organisational Audit document. However, there is reference to the need for the full stand-alone audit (using the audit tool with which we are more familiar) if necessary. If a department wishes to conduct a self-audit, the stand-alone Radiopharmacy audit tool is recommended.

Radiolabelled peptides for therapy: The enforcement of a patent on radiolabelling DOTATATE means that departments wanting to use Lu-177-DOTATATE for therapy will have to buy an unlicensed ready-labelled product. The supplier (AAA) has been audited on behalf of the Department of Health, BNMS and UKRG.

Education and Training: The UKRG held its annual workshop at Beeches Management Centre in Bournville, Birmingham. The meeting focussed on Quality Management Systems in Radiopharmacy, with fruitful discussion in the afternoon on how theoretical situations should be managed and recorded.

Clinical Pharmaceutical Scientist training: The joint task force set up by Modernising Scientific Careers and Modernising Pharmacy Careers boards has now established a Clinical Pharmaceutical Scientist training scheme. This involves rotation between Radiopharmacy, Pharmaceutical Production and Quality Control. Expressions of interest were sought in September 2012, and there were over 130 applicants nationally for the scheme. Short-listing has now taken place, with interviews arranged for 21st March 2013. Trainees will commence in post in September 2013.

Needle re-sheathing: The consultation on the Council Directive for the safer use of sharps was conducted towards the end of 2012. The social partners subsequently issued a clarification statement that explained the intentions behind the Directive and that allows some degree of interpretation. HSE have now issued guidance on how it can be implemented. See Health Services Information sheet 7. (*Editor's note: available for free download at this URL* - http://www.hse.gov.uk/pubns/hsis7.htm). However, a note of caution is needed, as HSE may be challenged on the one-handed re-sheathing element. Lobbying in Europe may be necessary to allow this practice.

Reactors

The reactor at Petten is out of action at the moment and recommencement of supply has been further delayed due to the discovery of Tritium in ground-water around the site. Shortages are therefore possible from mid April – Mid May. There may also be shortages at the end of May as a result of shut-down of the Chalk River reactor. Contingencies are being looked at for long-terms security of Molybdenum supply, but all of these involve increased costs. Watch this space!