U.K. Radiopharmacy Group

NEWSLETTER

2017 Summer Edition

THE IMPACT ON NUCLEAR MEDICINE OF THE UK LEAVING EUROTOM

The impact on Nuclear Medicine caused by the UK potentially leaving the European Atomic Energy Committee (Euratom) as part of the Brexit process, is being hotly debated between government leaders and the Nuclear Medicine community. In July, the British Nuclear Medicine Society, the Royal College of Radiologists (RCR) and Royal College of Physicians released statements on the impact leaving Euratom could have in the supply of medical isotopes. The press statement began by summarising the history and the role of the Euratom treaty:

"Since 1957 the Euratom framework has enshrined the regulation and safeguards for the transportation and use of radioactive materials and governs UK international nuclear cooperation agreements with European and third party countries, including Canada, Japan and the USA. Withdrawing from Euratom will affect the arrangements for the supply and use of radioactive isotopes to industry, power generation, academia and medicine.

The statement highlighted the UK's dependence on medical isotopes, such as Tc99m, explaining that none of the UK's reactors produced the parent radionuclide Mo99, as well as other longer half-life radioisotopes, which are all imported into the UK for Nuclear Medicine procedures for over 1 million patients per year. The statement explained that the impact on PET scanning would be less severe, as it is produced locally in cyclotrons, but SPECT scans using Tc99m, which "*is used for over 80% of the diagnostic nuclear medicine scans carried out including bone, cardiac, lung and kidney scans and for sentinel node surgical procedures in patients with breast and other cancers such as melanoma would be affected."*

The statement highlighted the impact on therapeutic radiopharmaceuticals used for molecular radiotherapy, stating that there are *"a number of other medical radioisotopes that the UK imports including I-131, which is used for the treatment of thyroid cancer, Ra-223 used in the treatment of bone tumours and Lu-177 that is used for the treatment of neuroendocrine tumours. Some radioisotopes used in radiotherapy implants will also be affected. There may also be implications for patients crossing the border between Northern Ireland and the Republic of Ireland if they have received radioisotopes for diagnosis or therapy on the other side of the border from their homes.*

The statement included acknowledgement of the UKs Tc99m generator manufacturing plant, which supplies Mo-99/Tc-99m generators throughout the world and warned that *"If appropriate agreements and cross border transport arrangements are not put into place post BREXIT this would have impact on the management of patients both in the UK and in many other countries who depend on the supply of these essential medical supplies."*

The BNMS and the RCR share the view that leaving Euratom "*will impact on the supply and cost of medical radioisotopes and would like to see greater clarity regarding the future arrangements."* Both organisations are keen that this matter is resolved as soon as possible, by "*clarifying any confusion regarding the regulatory aspects related to safe provision and transport of radioactive medicinal products between Great Britain and Europe."*

The BNMS stated they intended to *"organise a meeting with all relevant stakeholders including government, industry, professional medical societies and medical royal colleges"* to ensure there was appropriate representation for the Nuclear Medicine industry during this negotiation.

The full statement from BNMS is available on the following link:

http://www.bnms.org.uk/news/press-release-british-nuclear-medicine-society-statement-on-leaving-euratom.html

Clearly, this issue affects all of us in the Nuclear Medicine community, so follow the progress of this issue by looking for further updates at www.bnms.org.uk.

BNMS AUTUMN MEETING 2017

Given the front page topic, it might be a good time to mention the upcoming BNMS Autumn Meeting for 2017. The programme is entitled: "*British Nuclear Medicine: the way forward in the era of Brexit*", but it is not a political conference at all, with sessions on PSMA, amyloid brain imaging, cardiac imaging, updates on thyroid cancer guidelines and much more.

The BNMS Autumn Meeting will be held on Friday 15th September 2017 at the ACC, Liverpool.

For further information and to book your place, follow the link below:
http://www.bnms.org.uk/future-meetings/bnms-autumn-meeting-2017/

UKRG CAPACITY PLANNING WORKSHOP

On behalf of the UK Radiopharmacy Group, and organised by Neil Hartmann, we are excited to inform you about an upcoming workshop on Capacity Planning. The workshop will be held at St Bartholomews Hospital London, EC1A 7BE (this post code looks strange, but it is correct) on the 6th of October 2017. The workshop will focus on the development of procedures, capacity planning tool kits and managing resources. All are welcome, and registration is free.

The only thing stopping you, ironically, is whether you have the capacity to attend!

See the back page glossy advertisement for further further details.

RADIOPHARMACY UK EMAIL DISCUSSION LIST LAUNCH

After launching the Radiopharmacy UK Email Discussion List a good number of professionals and colleagues have joined the conversations.

If you belong to the UK Radiopharmacy community in the NHS or the academic sector you can still join the discussion list by following the link www.jiscmail.ac.uk/radiopharmacyuk.

Come and join in today! We all can contribute to find answers to frequent problems in our daily routine, share best practice or anything else you may think is useful for our Radiopharmacy community. Speaking of finding answers to frequent problems, it's time for a bit of this…

"Is it just me?"

You may remember from the last newsletter that we had a question relating to free pertechnetate in macrosalb scans…

"Is it just me, or has anyone had reports of lung perfusion scans using macroaggregated albumin (MAA) with the appearance of unexplained high free pertechnetate?"

The reader had experience of scans showing evidence of significantly higher free pertechnetate, than the quantity measured using radiochemical purity tests, even when the same vial was tested.
The answers we had back from the community shared similar events with differing causes attributed or suspected. A couple of interesting points from the responses were:

- The metabolism of albumin by the body differs between individuals, creating a degree of natural variation, caused by differing amounts of enzymes that metabolise albumin in-vivo
- The time between injection and scanning will have an effect, with more free pertechnetate visible, the longer that time is. This can be an issue when Tc99m-macrosalb is used in assessing hepatic embolisation, prior to the administration of Y90 SIR Spheres.
- Check the count rate of the Anterior/ Posterior view of the injection site. Is it normal? If not, this could be due to partial tissue-ing of the dose, which has an increased likelihood of faster breakdown of the albumin.

This month, we had a question about reporting failures in Radiochemical Purity Testing to regulatory authorities:

"Is it just me, or should we be reporting every radiochemical purity test failure to the MHRA?"

Now, this wasn't strictly an "Is it just me?" question, some answers have already been given by community members, which shows the benefit of the UK email discussion list. So remember to join this (see the link on the left)…

The responses we had to this are as follows:

1. Has the failure been detected before the product left the building? If not it is a QC fail which you should document, you do not need to tell the MHRA

about. It should be noted in the MHRA's recent blog on reporting failures, they stated:

What not to report:

- *Non-conformances for batches not yet released (unless the root cause also implicates released stock) – these should be managed through your Pharmaceutical Quality System (PQS)… But remember you do need to report defects for released batches, even if stock hasn't yet been distributed to market*

The full blog is available at:
https://mhrainspectorate.blog.gov.uk/2016/08/10/dmrc-reporting-dos-and-donts/

2. If it has left the building and gone to another site, then you may have to recall it. This may depend on whether you can confirm it is a real product failure, rather than operator error when performing the test, for example. The MHRA would always want to know when you've done that, so you should report this via the DMRC (dmrc@mhra.gsi.gov.uk). You may have to inform them retrospectively i.e. tell your customers quick before they use it and then tell the MHRA afterwards.

Some sites have procedures which involve transport of the product prior to QC release. In this case, it is still a QC failure, as it has not been "released."

3. If you are an unlicensed unit, you should informing your regional QA specialist as soon as practical after the event.

If you have any further advice on this topic, or you would like to ask another "Is it just me?" question, email me at clint.waight@nhs.net, with the title "Is it just me?" and I'll anonymously ask the question here for you.

SUMMARY OF ADVERSE EVENTS AND PRODUCT DEFECTS

Each year, the UKRG Newsletter will report on the product defects and adverse events experienced by Radiopharmacies and radiopharmaceutical users. Below is a summary of such events since January 2017:

Product defects

There have been 6 product defects reported since January affecting Tc99m-exametazime, ^{99}Mo/^{99m}Tc generators, Tc99m-mertiatide (2) and Tc99m-tetrofosmin (2):

- The bottom broke off an exametazime vial when it was being prepared.
- There was a low yield from a ^{99}Mo/^{99m}Tc generator on the 3rd elution. This is thought to be due to the ingress of alcohol into the generator. It should be noted, this topic was also discussed in the "*Is it just me?*" section in the January newsletter)
- There were two reports of low radiochemical purity for Tc99m-mertiatide with >10% hydrophilic impurities. In one case, it is known that the kit was left for about 25 minutes before heating. The Manufacturer suggests that this could be one reason for the low radiochemical purity observed.
- Particulate contamination, derived from the rubber septum of the vial was found in a vial of Tc99m-tetrofosmin, which was noticed when a dose was drawn up into the syringe.
- There was a report of low radiochemical purity for a Tc99m-tetrofosmin kit, but the problem may have been caused by the ^{99}Mo/^{99m}Tc generator used as the ^{99}Mo breakthrough was high (0.093MBq/GBq).

Adverse Events

There have been 7 adverse events reported since January 2017 affecting tetrofosmin (2), SeHCAT, Nanocolloid, ^{123}I mIBG, ^{111}In pentotreotide and Tc99m-succimer:

- Tc99m-tetrofosmin: For one patient a rash in both wrists and for the other, nausea experienced after the first part of the test.
- ^{75}Se SeHCAT: One patient experienced itching after taking the capsule.
- Nanocolloid: One patient complained of feeling out of sorts, followed by itching. The patient fainted after standing and developed welts on the abdomen and arms.
- ^{123}I mIBG: One patient experienced vomiting, reflux, sea sickness and fatigue one hour after injection. Apart from reflux all the other symptoms disappeared 24 hours after.
- ^{111}In pentotreotide: a patient experienced a reaction to the injection. The patient had known allergies. The report included a swollen tongue as the main symptom.

Even though radiopharmaceuticals are considered safe products, it is crucial any adverse effect is reported accordingly. For reporting any adverse event or product defect, please click on the link below:

http://www.bnms.org.uk/adverse-event/defect-reporting/

ADVICE FOR THE SAFE DRAWING UP AND ADMINISTRATION OF ^{223}Ra RADIUM CHLORIDE

Due to the special characteristics of alpha emitters a new addendum is now available for the safe use of ^{223}Ra Radium Chloride (Xofigo®).
The guidance note offers advice on the following areas:

- Drawing up
- Administration
- Monitoring
- Decontamination

This document has been produced by UK Radiopharmacy Group in conjunction with the IPEM Nuclear Medicine Special Interest Group and BNMS. The document can be found at this URL:

http://www.bnms.org.uk/images/Addendum_to_Safe_Drawing_up_document_for_223Ra_Radium_APR_17.pdf

THE RESPONSIBILITIES OF CHIEF PHARMACISTS FOR THE PURCHASE, RECEIPT, STORAGE, SUPPLY AND DISPOSAL OF RADIOPHARMACEUTICALS

UK Radiopharmacy Group and NHS Pharmaceutical Quality Assurance Committee have updated the Responsibilities of Chief Pharmacists for the Purchase, Receipt, Storage, Supply and Disposal of Radiopharmaceuticals.

Although the responsibility for purchasing, storing and the safe use of medicines lies with the Chief Pharmacist, due to the special nature and characteristics of radiopharmaceuticals, these activities are often discharged out with the Pharmacy Department, and therefore potentially outside the Chief Pharmacist's area of managerial control.

In order to keep responsibilities clear within the organisation, it is recommended that a technical agreement is in place describing with enough detail the arrangements for the activities involving radiopharmaceuticals.

Fortunately, the document includes a very useful template for a Technical Quality Agreement between both parties.

The new guidance note can be downloaded on the link below:

http://www.bnms.org.uk/images/Responsibilities_of_Chief_Pharmacists_June_2017.pdf

SCIENTIST TRAINING PROGRAMME (STP) IN CLINICAL PHARMACEUTICAL SCIENCE

Recruiting to highly-specialised posts, such as those in a Radiopharmacy can be challenging. Finding applicants with knowledge and experience in a combination of pharmaceutical quality systems and the intricacies of working with radiation can be almost impossible. However, the NHS' Scientific Training Programme, aims to produce professionals with exactly that skill set.

Graduates of the Clinical Pharmaceutical Sciences course of the STP programme, have an MSc qualification and are eligible for registration on the Academy of Healthcare Sciences accredited register.

The students complete modules in Aseptic Services, Radiopharmacy, Quality Assurance, Quality Control and many others that have direct application to working in a Radiopharmacy.

To help plan the workforce in your radiopharmacy unit, it is always useful to bear in mind that a new STP cohort of qualified trainees graduates every summer, which is a great time of the year to advertise posts that could suit these highly qualified scientists. Six direct entry training posts and one in-service post have been approved by Health Education England for 2017.

REGULATORY ISSUES

Recent Inspection Issues
Below are listed a number of non-compliances found during recent MHRA inspections:

1. *Quality Management System (QMS)*
   There are ongoing issues with QMSs. What is often still found is a lack of detail in investigations, change controls, handling of CAPAs etc. There will be a workshop at the 2018 UKRG Bournville meeting on this topic.

   An important aspect of the QMS is dealing with deviations and showing enough evidence that a thorough Root Cause

Analysis (RCA) has been carried out. A number of tools can be used for this purpose (i.e. Ishikawa diagrams, 5 whys, Is/Is Not Analysis). Once the cause has been found, enough risk reduction measures should be implemented, then these formally assessed after a certain period of time.

The MHRA also have produced a YouTube clip going over what they are looking for during inspections, which can be found following the link below (*it probably won't work from your office PC!*):

https://m.youtube.com/watch?v=hl7KvJrHXlQ

2. *Dealing with Suppliers:*
   Inspectors have noticed a lack of procedures covering the monitoring of suppliers. This should cover details for how the products are transported to a department and should be risk based - i.e. more effort put into high risk products such as unlicensed materials.

3. *Capacity Plans*
   Where these are in place they are often not referred to and are not a 'living' document. There needs to be a system to generate CAPAs where capacity issues are highlighted. This may improve when the UKRG publish their updated capacity plan toolkit that looks to address this issue.

4. *Data Integrity*
   Data Integrity has become a very important part of a GMP inspection. A new issue was being seen at some sites where Microsoft Word was being used as a paperless document system (i.e. critical data being entered into a word document). Doing this results in a lack of audit trail and does not conform to good data integrity principles. They recommended that users look at the MHRA blogs on data integrity.

5. *Technical agreement/ Service Level Agreements (SLAs)*
   For those units supplying radiopharmaceuticals to external Nuclear Medicine departments (and for any other outsourced service) a SLA or technical agreement should be in place covering all the arrangements and outlining the responsibilities of each party involved.

6. *Action Plan after MHRA inspection.*
   Time scales in action plans should be realistic but it is also an expectation that the deficiencies found during a MHRA inspection are addressed in a timely manner.

UKRG SUPPLIER AUDIT SCHEME

The UKRG is looking to establish a central point for all units to access audits conducted by UKRG members and colleagues from Quality Assurance. The audits may be for sites manufacturing unlicensed active pharmaceutical ingredients (APIs) or other essential components and materials used in GMP production.

Once established, a list will be published at least annually in the UKRG Newsletter, detailing which audits have been performed by which individuals, with contact details for the auditors, with their consent.

Supplier audits are a GMP requirement, but it is not practical for small units to conduct them individually. As a representative group, the UKRG can conduct these audits and make them available on the UKRG website for all of us to access. Further information on this scheme will come in the December edition of the UKRG Newsletter.

MHRA ANNUAL REVIEW OF DEFICIENCIES - 2016

As every year the MHRA publishes their GMP inspection deficiency data trend. The document for 2016 was published the 21st April 2017 and it could be very useful for identifying most common deficiencies in our daily practice. These deficiencies can be used by aseptic units to perform their own assessments as part of the self-inspection programme and continuous improvement.

Definitely, it is worth looking to ensure we take on board in our units this feedback from the MHRA. The full document can be found on this link: www.gov.uk/government/uploads/system/uploads/attachment_data/file/609030/MHRA_GMP_Inspection_Deficiency_Data_Trend_2016.pdf

EMA REVIEW OF NEW MEDICINAL PRODUCTS

The EMA publishes a monthly list of applications for centralised marketing authorisations for human medicines [including radiopharmaceuticals] that are under evaluation by the European Medicines Agency's Committee for Medicinal Products for

Human Use **(**CHMP**).** The list can be found at this URL:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/document_listing/document_listing_000349.jsp&mid=WC0b01ac05805083eb

INDUSTRY NEWS

UKRG Disclaimer: Much of the 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. In addition, UKRG is not responsible for any claims made by individual companies.

IBA Molecular Acquisition of Mallinckrodt Nuclear Imaging
The merger between IBA and Mallinckrodt has resulted in a new company name and brand for Mallinckrodt, which are now known as Curium. Curium is specifically the Nuclear Medicine branch of IBA, and do not deal with other aspects of IBA's portfolio. Curium Pharma is not to be confused with the alpha-emitting radioisotope curium (^{242}Cm), although it not something we're likely to see in Nuclear Medicine!

UKRG ANNUAL WORKSHOP AT BOURNVILLE

(it's back on a Friday again)

The UKRG Annual Workshop at Bournville is the only meeting in the UK devoted specifically to Radiopharmacy. The details are:

When: **Friday 12th January, 2018**
Where: The Beeches Hotel, Bournville

The full programme will be published in the next newsletter, which will be out in December, but may be sent out earlier on the jiscmail mailbase. So keep an eye out for registration details.

UPCOMING MEETINGS

British Nuclear Medicine Society Autumn Autumn Meeting
15th September 2017, ACC, Liverpool
Website: http://www.bnms.org.uk/meetings-and-events/future-meetings/

Capacity Planning for Radiopharmacies
A workshop supported by the UKRG.
6th October 2017
The Great Hall, North Wing
St Bartholomew's Hospital, London EC1A 7BE

30th Annual Congress of the European Association of Nuclear Medicine Congress
21st-25th October 2017, Vienna
Website: http://www.eanm.org/

UKRG Annual Workshop 2018
Friday 12th January 2018, Bournville, UK
Website: www.ukrg.org.uk

12th Congress of the World Federation of Nuclear Medicine and Biology
20-24 April 2018, Melbourne, Australia
Website: http://wfnmb2018.com/

GOOD BYE TO RETIRING MEMBERS

The UKRG would like to acknowledge the retirements of two of its committee members, Alison Beaney, and Kishor Solanki.

Though not a Radiopharmacist, Alison made an enormous contribution to the practice of Radiopharmacy, through her expertise in Quality Assurance. While Alison has retired from NHS duties, she may still appear at educational events and on courses, where she continues to provide a significant input to the teaching of QA, and is still involved in the publication of the Quality Assurance of Aseptic Preparation Services, now in its 5th Edition, which provides the standards for all NHS Aseptic units and Radiopharmacies operating under the Section 10 exemption. Alison has been a member of our committee for a long time, and has our special thanks for all she has done to support us.

A Special Farewell to a Former Editor of the UKRG Newsletter
It is with a little sadness and a lot of pride that we say farewell to Jim Ballinger who has now fully retired and has moved to Canada. The UKRG wished to formally pass on their gratitude for his substantial contribution to the group and to Radiopharmacy as a discipline, over many years - in particular for the years he spent editing the UKRG newsletter. He set the bar very high with his combination of knowledge and humour, and has been a very hard act to follow!

Jim made an enormous contribution to education in Radiopharmacy, running the King's Radiopharmacy course which has contributed to the training of many people working in radiopharmacy in the UK. Indeed, many people reading will have attended that course, or some other educational event run by or taught by Jim Ballinger, so his legacy will remain in the UK for many years to come.

Congratulations to Alison, Kishor and Jim on your careers, and thank you the inspiration you have given to those that follow on from you.

From the Editor

The newsletters are all published on the UKRG website, so if you're interested, please go to www.bnms.org.uk/ukrg/general/newsletters.html where you can read the entire back-catalogue if you wish!

From this month onwards, the UKRG Newsletter will also go out to the jiscmail mailing list – yet another reason to join!

The next meeting of the UKRG Committee will be on the 5th of October 2017, followed by the Strategic Meeting and Committee Meetings at Bournville on the 10th and 11th of January 2018. If readers have any issues they of wish to be discussed please raise them with your regional rep on the Committee (full details at this URL): http://www.bnms.org.uk/ukrg/general/ukrg-committee-list-2011.html

Alternatively, comments on the Newsletter content or on any radiopharmacy issue can be sent direct to the Editor at the address below.

www.ukrg.org.uk

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