U.K. Radiopharmacy Group

NEWSLETTER

2018 Summer Edition

In this issue…

Welcome to the Summer Edition of the UKRG Newsletter!

GE PROPOSAL TO CEASE PRODUCTION OF DRYTEC GENERATORS

Customers of GE Healthcare who use their Drytec generators to obtain their Tc99m for daily production have been informed by the manufacturer that there is a proposal being considered to close the Grove Centre in Amersham and phase out the manufacturing of Drytec generators. At a meeting with the UKRG Committee in July, GE Healthcare informed the Committee that they will be entering into a supply agreement for Tc99m generators with Curium, such that customers can still purchase Tc99m generators from GE, but these will be Ultra Technekow generators manufactured by Curium.

According to this agreement with Curium, GE Healthcare will continue to independently source Mo99 from its current suppliers, but Curium will manufacture and supply the generators. GE Healthcare will sell these generators and manage ordering, logistics and delivery requirements. This keeps GE Healthcare in the generator market and therefore continues to give contingency arrangements for Molybdenum supply, as this will be sourced independently.

A specific date for the cessation of production of Drytec generators is not known at this stage, but is expected to be in the first quarter of 2019. GE are currently negotiating the logistics of reconfiguring Radiopharmacy departments to ensure the impact of switching generator types is minimised. For further information on the supply of GE Drytec generators, please contact your regional GE Healthcare representative.

BREXIT UPDATE

As you will all be very aware, the impending exit of the UK from the European Union could have significant consequences for the Nuclear Medicine industry in the UK. Given the news reported above regarding the proposed closure of the Grove Centre, all Tc99m generators will likely have to be imported once Brexit is finalised, along with other high use radiopharmaceuticals such as Cr51-EDTA. There is a large amount of information that is frequently being updated regarding Brexit and the UK's potential departure from the Euratom agreement.

Rather than provide information here that will quickly become out of date, readers are encouraged to keep up to date by following developments on the BNMS website (link: BNMS website/ Euratom articles), which updates articles relevant to this issue regularly.

Discussions are also common in the UK and EU mail-bases that we have provided links to below, so if you have not already joined one of those, we encourage you to do so.

RADIOPHARMACY UK AND RADIOPHARMACY EUROPE EMAIL DISCUSSION LIST

A good number of professionals and colleagues have joined the conversations on the Radiopharmacy UK Email Discussion List.

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.

As mentioned in the last newsletter, a European-wide discussion group has also been established where anyone in Radiopharmacy (academic or hospital) in Europe, can ask to join by sending an email to the discussion group administrator at the following address: Neil.Hartman@wales.nhs.uk

The email should include your first name, surname, email address, institution address and a brief sentence of which aspect of hospital or academic Radiopharmacy you are involved in. All communications will be strictly limited to the group and won't be able to be searched from any other source. The group email address is: europeradiopharmacy@jiscmail.ac.uk but this is only accessible once you have been added to the subscription list.

Come and join in today! We all can contribute to find answers to frequent problems in our daily routine, share best practice and keep up to date with new developments in our Radiopharmacy community.

UKRG SUPPLIER AUDITS

A summary of supplier audits and GMP requirements for 'Specials' manufacturers was published in the previous Newsletter. Following on from this, it was felt that a summary of the audits that had already been undertaken might be useful to readers who may be asked about such audits at MHRA inspections.

The UKRG have carried out the following program of supplier audits so far:

Supplier:	*Date:*
Polatom	Sept 2008
Perkin Elmer /MURR	May 2010
MAP Medical Technologies	Dec 2010
ITG	Mar 2012 & Nov 2015
AAA	Mar 2013
ABX	Jan 2014 & Mar 2018

The audit reports are available on request for NHS and University (public sector) radiopharmacy units from Istvan Boros (ib297@cam.ac.uk)

These audit reports can provide some supporting information when using a risk-based strategy approach for the evaluation and selection of raw material suppliers.

The UKRG are planning to run more supplier audits on behalf of NHS radiopharmacies depending on demand and would welcome any feedback for future audits.

NEW IRMER REGULATIONS AND ARSAC LICENCE APPLICATION FORMS

Since the new IRMER regulations came into force on 6th February 2018, many centres have completed the new Employer and Practitioner application forms for ARSAC licences. As current ARSAC certificates are still valid, these new application forms only need to be completed when there are any changes that would have required a new ARSAC certificate.

There have been some queries on the Employer Application form (section 30) on compliance with the UKRG/BNMS Guidance Note on the Safe drawing up of radiopharmaceuticals in nuclear medicine departments. If the drawing up in clinical areas is not in line with this Guidance Note, then there should be a formal risk assessment carried out on the process. The risk assessment should be signed off by the Trust Chief Pharmacist who is responsible for the safe use and custody of medicines within the organisation.

UKRG GUIDANCE DOCUMENTS

The revised Guidance Note on 'Capacity Planning Toolkit for Radiopharmacy Services in the UK' will be issued soon. The updated document will include examples of capacity monitoring templates. It is a requirement that compliance with the capacity plan is assessed monthly (usually at quality management review meetings).

It is an expectation that the adherence to the monthly capacity plan (including both the frequency and extent of excursions from the plan) is reported routinely to senior management as a core Radiopharmacy Key Performance Indicator (KPI).

The 'Responsibilities of Chief Pharmacists for the Purchase, Receipt, Storage, Supply, Receipt and Disposal of Radiopharmaceuticals' Guidance Document and 'Radiopharmacy Audit' are due to be reviewed. We will keep you updated on the progress of these.

ADVERSE REACTIONS 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 March 2017:

Product Defects

There have been 33 product defects reported since March 2017.

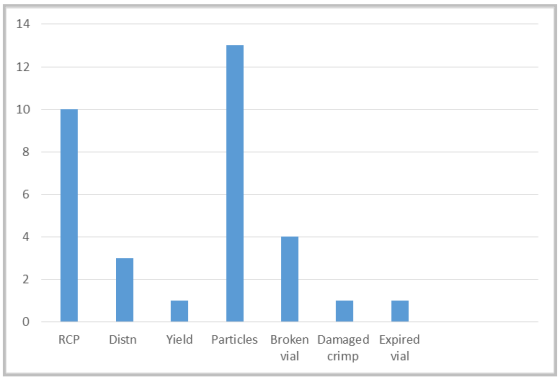
- The majority of reports are related to particulate contamination derived from the rubber septum of the vial in vials of Tc-99m-tetrofosmin after processing.

  GE Healthcare has issued the following statement regarding the above issue:

  GE Healthcare Ltd is aware of several complaints related to the product Myoview, with stopper material (coring) being found in the reconstituted Myoview product. After thorough investigation by the GE Healthcare Quality Assurance team, we are confident that the current stopper used on the Myoview 10ml vial product meets the required EU Pharmacopeia specifications.
  However, as Myoview is a flagship product for GE Healthcare, we are focused on finding a solution for our customers with regards to the stopper. GE Healthcare also sells a comparable product in the USA & Canadian markets, Myoview 30 ml. This product uses an alternative stopper to that used in the Myoview 10 ml vial. This has been in use since 2009 with no coring issues. GE Healthcare is now undertaking a feasibility study with the grey stopper to assess the impact on the product parameters for Myoview 10 ml. As this is will be a primary packaging change, the timelines for the technical and regulatory assessment are approximately 22 months.
  GE Healthcare is committed to working with our UK customers during this period and we will provide regular updates as the project progresses via the UKRG.

- Three incidences were reported for damaged vials after defrosting ^{131}I-MIBG therapy on separate occasions
- A number of radiochemical purity test failures were reported for Tc99m-nanocolloid, Tc-99m-MAG3 and Tc99-DMSA but no root cause was found.
- One radiochemical purity failure of Tc-99m-DMSA was reported after it was observed that the concentration appeared incorrect as the calculated volume for an injection had insufficient activity. Initially the vial had passed the radiochemical purity test, however it was found that the activity was stuck to the glass vial. Further testing showed a high amount of Tc-99m reduced-hydrolysed colloid which was the likely cause for the residue on the glassware.
- One product defect was not related to a radiopharmaceutical defect but to an IMS spray where the filter had fallen from its housing on three separate occasions but reported as a single incident compromising the sterility.

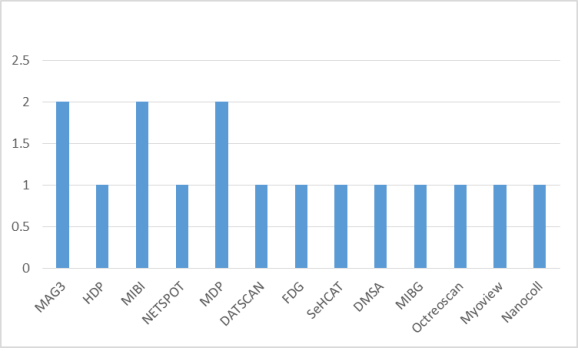
Figure 1: Summary of Product Defects



Adverse Events

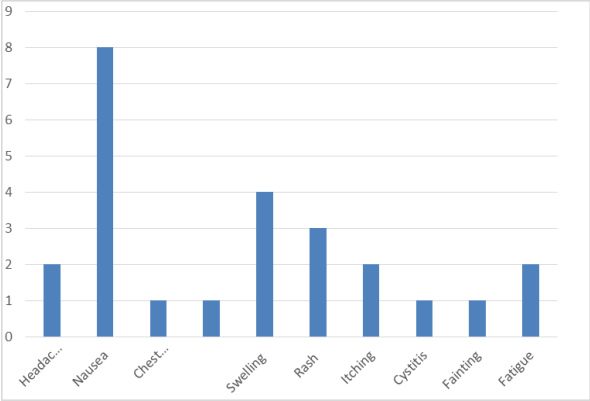
There have been 17 adverse events since March 2017. These events are spread across a variety of radiopharmaceuticals but a higher incidence observed with Tc-99m-medronate, Tc99m-sestamibi and Tc-99m-mertiatide, which may be due to these agents being the most commonly used in Nuclear Medicine.

Figure 2: Adverse events reported for different radiopharmaceuticals



The most common reactions were nausea/vomiting and skin complaints exhibited as swelling, itching and rashes. It should be noted that a number of patients who experienced skin complaints were known to have allergies prior to administration.

Figure 3: Adverse events reported in 2017/18

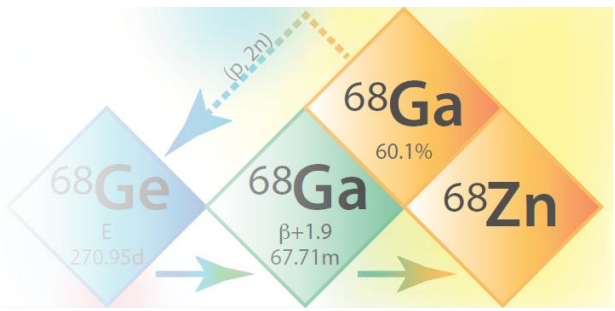


- Most events were classified as mild or moderate and reported retrospectively by the patient and were mostly resolved within 24 hours
- Patients who suffered anaphylactic reactions and chest pains were referred to Accident and Emergency.
- A patient who fainted also suffered from claustrophobia which was considered a contributing factor.

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

UKRG GALLIUM-68 WORKSHOP

A one-day workshop on how to start a GMP compliant gallium-68 manufacturing service is being held on Friday 21st September 2018 at St Bartholomew's Hospital, London. This one day workshop is ideal for departments looking to establish a new gallium-68 radiopharmaceutical service from their department, with presentations by current UK radiopharmacists detailing their experience and offering advice for colleagues about to embark on this new venture. Further information and booking details can be found at https://ukrg.meeting.org.uk and a full description of the programme for the day is provided at the end of this newsletter.



"Is it just me?"

Is it just me, or is anyone else having difficulty complying with recommendations to manufacture kits that require boiling within the Grade A zone?

The manufacture of sterile injections according to GMP requires all processes to be handled within the sterile (Grade A) work zone. This is easily achievable for almost all products manufactured in radiopharmacies, however the long history of radiopharmaceuticals requiring boiling during manufacture presents a challenging issue. Products such as sestamibi, some brands of mertiatide and most recently Tektrotyd and SomaKIT require boiling to enable radiolabelling of the radionuclide to the ligand. As seen with Tektrotyd, there are still new products being manufactured that require this step, so it is not an issue that is going to go away any time soon.

Boiling can be conducted in a water bath or heating block. If it is contained within the Grade A zone, water can cause complications and the interaction between the heat of the block and the laminar or turbulent air flow can affect both airflow patterns and the temperatures reached by heating blocks. In addition to this, the vials are not shielded while being heated, meaning that operators in the production area are receiving radiation doses that are not as low as reasonable practicable (ALARP).

So what can we do?

1. Site the boiling apparatus in the highest grade environment that it is safe to do so in.
This might be a separate shielded compartment of an isolator or safety cabinet. This is not available in most existing cabinets, but cabinet manufacturer's are now aware that this is becoming an issue for regulators and users, so innovative designs are beginning to appear. If you cannot site the apparatus within the Grade A zone, then it should be in the adjacent Grade B or C zone.

2. Effective sanitization
It is difficult to appropriately sanitize radioactive vials due to the obvious risk to operators. This is one of the main reasons the MHRA are keen to retain this process in the Grade A zone. Ensure your sanitization process for these items has been properly risk assessed, for both effectiveness in reducing bioburden, and in terms of radiation protection and product stability. It is essential that the critical area of the vial is sanitized effectively, however there is a significant risk involved with sanitizing the vial septum with a sporicidal agent during the transfer process.

3. Validation of the process
Whatever your process is, it should be validated to demonstrate it produces sterile products that meet your product specification. The routine aseptic process validation test, or end of session broth fill, should validate your highest-risk procedure, therefore it should involve removal of the product from the Grade A zone if that is what your process involves. End product sterility tests should also be performed as part of your Sterility Assurance Control Strategy, if this is possible. In addition to this, radiochemical purity tests should be performed as part of the validation of an additional sanitization step when introducing a boiled kit back into the Grade A zone, as this may affect product stability.

4. Review the process
Whether you can validate it or not, your process may not be deemed acceptable by regulators. Through continual employment of Quality Risk Management principles, compliance with GMP will be achieved, but this may involve a significant change to what you do, or what equipment you have to work with. In light of feedback from inspectors, some units have needed to switch to multi-dose vials, or prepare multiple vials for different customers to reduce the amount of manipulations following boiling

One such Quality Risk Management tool that may be suitable for this process is a failure mode effects analysis (FMEA). This will highlight the aspects of your production method for these products that are highest risk in terms of stability, sterility and radiation safety, and allow you to decide on the production method that carries the least risk for your department.

If you would like to ask another "*Is it just me?*" question, email the UKRG Newsletter editor at clint.waight@nhs.net, with the title "Is it just me?" and I'll anonymously ask the question here for you.

FEEDBACK FROM THE MHRA

Update from recent inspections
The MHRA regularly provide the UKRG with an update on common findings they have reported when performing GMP inspections of UK Radiopharmacies. This month's feedback focused mainly on two issues:

1. Lack of support from senior management of the Trust or Health Board
The MHRA have stated clearly in their Guidance for Specials Manufacturers that licensed units must have sufficient resource to maintain the Pharmaceutical Quality System. Some NHS Trusts or Health Boards may not have the staffing resource available to appropriately staff all areas and may not always prioritise GMP units ahead of clinical areas. If you think that you do not have the staffing resource you require to conduct GMP duties effectively, there are measures you can take, such as:

- Use the UKRG Capacity Planning Toolkit to objectively identify the resource gap in your department.
- Perform a risk assessment on the ability of your department to meet GMP standards with your current staff resource
- State that risk clearly on your department's, risk register, with sign off from senior management and escalation to the appropriate risk register within the hospital, Trust or Health Board.
- Record any correspondence you have with senior management on this matter

The MHRA want to see that departments are assessing their capacity, identifying any risk associated with this and escalating it to the right level of authority. If this is still declined, the MHRA can take the matter up with the senior management representatives themselves.

2. Temperature monitoring during storage and distribution

Whether your products are stored at room temperature or require refrigeration, it is your responsibility as a manufacturer to ensure they are stored and distributed at the correct temperature. The only way to be assured of this is to have data on the temperature of products during storage and transport.

Recently, there has been a lot of discussion about how Tc99m-tetrofosmin is stored and transported after reconstitution, as the product SPC stated that it must be stored at 2-8°C, [although this has now been changed by GE Healthcare to below 25°C]. Transporting radiopharmaceuticals at refrigerated temperatures, while complying with transport regulations, can be a significant challenge. If you are required to transport products, it is a good idea to have a validated transport system in place, with data demonstrating transport conditions in summer and winter to measure the possible extremes in temperature, during the shelf life of your product.

EC GMP Annex 1 Consultation - Update

The consultation on the new EU GMP Annex 1 by the European Commission has now closed. Comments (6000) have been received and collated. More information will be available when the new document is formally issued.

Annex 2
Annex 2 (Manufacture of biological active substances and Medicinal Products for Human

Use) is no longer applicable to Advanced Therapy Medicinal Products, which are now covered by EudraLex Volume IV Part IV: Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (ATMPs). A revised Annex 2 therefore came into operation on 26th June 2018, after the new guidance for ATMPs came into operation on 22nd May 2018.

Annex 13
Annex 13 (Manufacture of Investigational Medicinal Products) will remain as per the Eudralex website until the new Clinical Trial Regulations are in place. The guidance to these new regulations will then become the new Annex 13 to Eudralex Volume IV.

Annex 17
The new Annex 17 (Real Time Release Testing and Parametric Release) comes in to operation on 26th December 2018.

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.

Supply problems with GI Pharma products: Nanocoll and Choledíam

GE Healthcare and Mediam have informed customers that there is an "*internal, non-quality related supply issue*" affecting products manufactured by GI Pharma, which includes Nanocoll and Choledíam (mebrofenin) respectively. No date for a resolution to this issue has been given at the time of issuing this newsletter. UK licensed alternatives to Nanocoll exist, but Mediam is the only provider of a UK licensed Tc99m-mebrofenin product.

Supply problems with Chromium-51 (Cr51) EDTA, Cr51 sodium chromate and Metastron® (Sr89)

Due to issues with an oven that is used to bake the products prior to dispensing, there is a supply issue with Cr51-EDTA, Cr51 sodium chromate and Metastron® (Sr89). The latest update from GE is that the oven issue has been resolved and supply will recommence once validation tests are completed.

UPCOMING MEETINGS

Ga-68 for Beginners
Friday 21st September 2018, The Great Hall, St Bartholomew's Hospital, London
Website: https://ukrg.meeting.org.uk

31st Annual Congress of the European Association of Nuclear Medicine
13th – 17th October 2018, Dusseldorf
Website: www.eanm.org/congresses-events/future-congress

Joint Meeting of the British Nuclear Medicine Society and Irish Nuclear Medicine Association
19th November 2018, Dublin, Ireland
Website: https://www.bnms.org.uk/meetings-and-events/joint-meeting-with-the-irish-nuclear-medicine-association-2018/

UKRG Annual Workshop 2019
Friday 11th January 2019, Bournville, UK
Website: www.ukrg.org.uk

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!

The next meeting of the UKRG Committee will be on 28th September 2018. If readers have any issues they wish to be discussed please raise them with your regional rep on the Committee
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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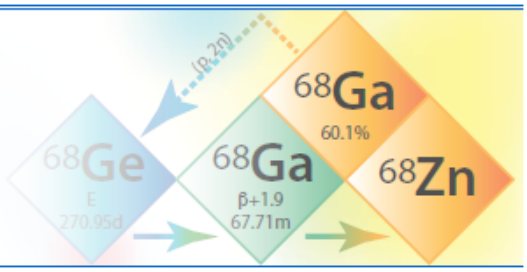
Ga-68 for Beginners

A one day workshop on how to start a GMP Ga-68 manufacturing service

Friday 21st September 2018



08:00 – 09:00	Registration Great Hall	
09:00 – 09:15	Walk to lecture hall	
09:15 – 09:30	Welcome **Dr Neil Hartman**, Swansea	
09:30 – 09:45	Ge-68/Ga-68 generators: what is on the market, and how to procure it? **Dr Maggie Cooper** KCL	
09:45 – 10:15	Radiation risk assessments **Brian Murby**, The Christie, Manchester	
10:15 – 10:45	Kits or synthesis modules? A review of both strategies **José Calero**, The Christie, Manchester	
10:45 – 11:15	What equipment to buy? **Dr Jane Sosabowski**, QMUL	
11:15 – 12:00	Coffee break in the Great Hall	
12:00 – 12:15	Ga-68 chemistry (peptides) and elution technology **Jen Young**, Manchester	
12:15 – 13:15	Manufacturing and QC of Ga-68 radiopharmaceuticals: step-by-step **José Calero** The Christie, Manchester	
13:15 – 14:45	Lunch and visiting exhibitions	
14:45 – 15:30	Quality control of Ga-68 radiopharmaceuticals **Vickie Gibson** Guy's & St Thomas', London	
15:30 – 15:45	Ge-68 breakthrough determination **David Ashworth** The Christie, Manchester	
15:45 – 16:15	Staffing needs and a suitable training programme **Pei-San Chan** Royal Free Hospital, London	
16:15 – 16:45	Validation (equipment, process, continuous) **Charly Monihan** Royal Marsden, London	
16:45 – 17:05	An overview of documentation (SOPs, worksheets, etc) **Dr Neil Hartman**, Swansea	
17:05 – 17:30	Future Ga-68 radiopharmaceuticals developments **Dr Clemens Decristoforo** Innsbruck **Dr Stefano Boschi** Bologna	

U.K. Radiopharmacy Group