U.K. Radiopharmacy Group

NEWSLETTER

2016 Q2

MANIPULATION OF SIR-SPHERES IN AN ASEPTIC ENVIRONMENT

Hepatic radioembolization using Y-90 (resin or glass) microspheres is nowadays widely used for the treatment of un-resectable metastatic liver tumours from primary colorectal cancer.

One of the products available, considered a medical device, is SIR-Spheres® Y-90 microspheres manufactured by SIRTeX. These SIR-spheres (resin) are provided in a vial with water for injection. Each vial contains 3 GBq of Y-90 in a total of 5ml water for injection. The patient dose is worked out individually, based on different parameters such as the percentage of involvement by the tumour in the liver and the evaluation of the lung shunt.

Due to these aspects, the prescribed dose must be sub-dispensed from the original SIR-spheres shipping vial to a specific V-vial before the treatment begins. Trained members of the staff in nuclear medicine departments or radiopharmacies generally perform this process.

The UKRG has reached a consensus where their members recommend that this sub-dispensing step be considered as an aseptic procedure that should take place in an appropriately controlled Grade A environment. Setting up the administration lines and delivery box should be performed in a controlled environment rather than in an un-controlled area. If the spheres are prepared in advance of administering them, then there is a requirement for this preparation to be compliant with the principles of Good Manufacturing Practice. As always, the maximum priority should be protecting the product (and therefore the patient) from any potential microbial contamination, while being mindful of radioprotection measures designed to protect the operator when working with Y-90.

To offer some guidance on this matter the Committee will prepare a guidance document covering the procedure. The document will be available on the Guidance Note section in the UKRG website.

CHANGE TO Ra-223 CALIBRATION FACTOR

Since April 14th, 2016, the following change applies to Xofigo (Ra-223 dichloride). In 2015, The National Institute of Standards and Technology (NIST) revised the primary standardization for Ra-223. Updated NIST 2015-traceable reference material was distributed to treatment centres by Bayer in 2015 to ensure all centres' calibrators were recalibrated with the appropriate reference source.

When comparing the former NIST traceable reference material against the new one, the result is that all the numerical values of radioactivity contained in vials of Xofigo have increased by 10%. The values that have changed are the following:

1. The radioactivity concentration has changed from 1000 Bq/ml to 1100 Bq/ml at reference date.

2. The patient dose has increased from 50 kBq/kg to 55 kBq/kg.

As Bayer Pharma AG stresses in the letter attached to all the Xofigo vials suplied after the review, these changes do not affect the actual product radioactivity or the final activity given to the patient, so we can conclude that there should not be any impact on the safety and efficacy of Xofigo due to this change.

Bayer Pharma AG has informed all the users of these changes and provided a new dial setting for dose calibrators before the change took place. In addition to this, all the vials are now labelled with an orange coloured sticker "NIST 2015" on each lead container.

We should remind all users that this product is subject to additional safety monitoring as long as the ▼ symbol is displayed on the SPC, so any adverse reaction should be reported. This will help regulatory agencies to gather more information and keep monitoring on the safety of this radiopharmaceutical, which is now widely used.

For further advice on how to report suspected adverse reactions, see page 2 of this newsletter.

ADVERSE REACTIONS AND PRODUCT DEFECT REPORTING

Although in general, adverse reactions caused by radiopharmaceuticals are very rare and when they happen, they are often mild and transitory it is important that they are not ignored.

As part of a multi-disciplinary community, all of us can play a key role reporting these adverse reactions. It is essential then to maintain good levels of adherence to current pharmacovigilance systems. In order to do so, the UKRG would like to encourage everyone suspecting any adverse reaction caused by a radiopharmaceutical to report it using the following links:

BNMS:
http://www.bnms.org.uk/adversereactions

and,

MHRA Yellow card:
https://yellowcard.mhra.gov.uk/

On this subject, a number of Technescan-MAG3 radiochemical purity failures have been reported to Mallinckrodt and the MHRA. Batches affected are 346105 and 346512. Due to these failures, Mallinckrodt has opened an investigation to clarify the possible causes.

Extra vigilance is recommended when using these batches of Technescan MAG3®. If facilities and resources permit, increasing the frequency of radiochemical purity testing is recommended.

In order to raise more awareness about product defects, there will be an annual report of product defects in the October newsletter.

"*IS IT JUST ME*?"

-From the Editor…

Following on from the article regarding radiochemical purity issues in Technescan MAG3, I thought this would be a good time to introduce a new section to the UKRG Newsletter, *called* ***"Is it just me?"***

This section will be devoted to readers who may be having a problem with a product, or a technique that they may have enquired about and wants to ask Radiopharmacy colleagues around the UK the question "*is it just me, or has anyone else noticed…*" then this is the place for you! Please send your questions via email to me, with the title *"Is it just me?"* and I will actively seek a response from our colleagues to discover if it is indeed just you, or if the issue is more widespread than you thought.

This month, I am going to kick it off with an issue in my department…

"Is it just me, or has anyone else noticed an increase in particles (floaters) appearing in their products?" **–Clint Waight, Edinburgh.**

Particulate contamination is not something I have seen much of in my experience in Radiopharmacy, however, we have detected "floaters" in several doses over the past two months. From the colour of the particles, it is likely to be fragments of the rubber septum of the elution vial, as this is a distinctly different colour to the seals of our patient dose vials and most kit vials. The issue has been seen over several batches of elution vials, two batches of needles and has been experienced by six different operators during production, with experience ranging from 1 to 30 years.

I am actively pursuing this issue with the generator and needle manufacturers, so I will report back the findings in the next newsletter. In the meantime, have a think if you have recently been wondering, "*is it just me?"* and drop me an email

clint.waight@nhs.net

(I must please ask that you keep the content relevant to radiopharmacy or nuclear medicine issues!)

-Clint Waight, Editor

UKRG SUPPLIER AUDITS

The UKRG conducts audits of suppliers to NHS radiopharmacy units, to assist licensed radiopharmacies in satisfying their GMP requirement to conduct audits of suppliers from which they receive raw materials, particularly unlicensed raw materials. These audits are conducted by UKRG Committee members, in conjunction with National Quality Assurance representatives and committees. The results of these audits can be requested by holders of NHS MHRA Manufacturing Licences who are in need of them, however they are not for public distribution, so cannot be shared on the UKRG website. If you wish to review an audit from a supplier in which you are purchasing raw materials from, please contact your local UKRG representative, who may be able to access the report for you.

MALLINCKRODT PRESENTATION TO UKRG

Lee Scott (National Sales Manager) and Roy Brown (Senior Director) from Mallinckrodt attended the April UKRG meeting in order to update the group on the current and future status of ^{99}Mo supply.

They summarised the current status of the ^{99}Mo-producing reactors worldwide and the future plans for closure of some of these. They then summarised the plans in place for new ^{99}Mo-producing reactors as well as the other newer methods for producing both ^{99}Mo and ^{99m}Tc that are at various stages of development. The other methods included the SHINE project (for ^{99}Mo production) that was presented at the recent annual BNMS conference, as well as cyclotron-produced ^{99m}Tc. An update on the developments made (and planned) for the ^{99}Mo processing plants was given, which will improve the availability and the efficiency of the manufacturing process.

As a company, Mallinckrodt remain confident that the future world requirements for ^{99}Mo can be met, even if a reactor has to stop production unexpectedly. They stated that this was the case even if none of the new methods of isotope production come to fruition. A consequence of this outage reserve capacity, along with full cost recovery and a move to using low-enriched Uranium is an increase in generator costs, which we may see incrementally over the coming few years.

BOURNVILLE WORKSHOP 2017: CHANGE OF DATE (it's on a Wednesday!)

Due to availability issues at the Beeches Hotel in Bournville, the Annual Bournville Workshop will be held on a Wednesday next year. The date for the workshop is **Wednesday 11th January**, with the UKRG Strategic Group and the UKRG Committee meetings happening on Monday the 9th and Tuesday the 10th of January respectively.

Ideas for presentations & workshops

The UKRG Committee discuss potential topics for presentations and workshops at the Bournville Workshop in April and July, with the final line-up being agreed by October. If you have any ideas on presentations you would like to see this year, or in the future, please contact your local UKRG Committee member.

CLINICAL PHARMACEUTICAL SCIENCES: NHS SCIENTIFIST TRAINING PROGRAMME

The NHS Scientist Training Programme (STP) is a three-year training programme that includes work-based and academic learning. The Clinical Pharmaceutical Sciences STP offers students experience in four areas of practice: Aseptic; Production; Quality Control/ Assurance and Radiopharmacy. The programme results in the students graduating with a Masters Degree and eligibility to register with the Health and Care Professions Council as a Clinical Scientist, and to become a member of the Royal Pharmaceutical Society.

These trainees are ideal candidates for Production Manager, Quality Control, or other posts within licensed NHS Radiopharmacies, offering viable options for succession planning within Radiopharmacy. Other benefits to hosting a STP trainee include the development of your service, including research, validation and preparation for MHRA inspections.

For more details on the advantages of being involved in the Clinical pharmaceutical Sciences programme, follow the link below:

http://www.nshcs.hee.nhs.uk/faqs/item/178-questions-about-the-clinical-pharmaceutical-sciences-stp

REGULATORY ISSUES

Feedback from recent GMP inspections

Some delays have been reported on MHRA inspections that were due. The organization is in the process of recruiting and training more inspectors to address this issue. In the meantime, below there is a summary of the areas where MHRA inspectors have identified non-compliance with current EU GMP in recent inspections:

1. Poor completion of investigations for deviations (i.e: broth-fill failure).
2. Failures in the quality system for recalls, complaints and change controls forms.
3. Information on labels of manufactured products must be legible and cannot contain amendments.

4. Spraying items in to the clean room the day before is not acceptable.

5. Records of equipment maintenance and calibration certificates must be up to date.

6. Lack of stability studies for those radiopharmaceuticals that require storage at 2-8 ℃ and are transported without meeting these conditions.

As mentioned on the previous Newsletter data integrity is becoming a new hot topic during MHRA inspections. One of the main concerns is ensuring that original recorded data is not intentionally or accidentally modified (or erased) so enough measures must be in place to avoid this from happening. It is recommended that data integrity issues are considered as part of the self-inspection process.

Update on EU GMP

In addition to keeping up to date with MHRA guidance, it is a good idea to routinely check for updates on the EudraLex website at this URL: http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

Annex 16 on **Certification by a Qualified Person and Batch Release** has been revised. The annex officially came into practice on **the 16th of April 2016.**

Annex 17 on Parametric Release is being revised. A consultation was launched on the 15th of September 2015 on a draft revised version of Annex 17. The consultation closed on the 11th of December 2015.

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**).**

Radiopharmaceuticals appearing in this list over the past three months include: Fluciclovine (F18); Edotreotide and Lutetium (Lu177) Dotatate

The full 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.

Changes to ^{99m}Tc-Tektrotyd

^{99m}Tc Tektrotyd, a new neuro-endocrine tumour imaging agent, was initially marketed to allow two patients to be scanned per vial, however, the product SPC states that it is a "*single use vial*." The MHRA have clarified this ambiguity by stating that a single use vial is only suitable for single patient use. In light of this, Imaging Equipment Ltd is advising customers to use one pair of vials per patient, and has revised its pricing structure for ^{99m}Tc Tektrotyd accordingly. IEL will be contacting customers individually regarding this issue.

UPCOMING MEETINGS

2016

BNMS Autumn Meeting 2016
07 September, 2016, Assembly Rooms, Bath.

EANMS 29th Annual Congress 2016
15-19 October, 2016, Centre Convencions Internacional, Barcelona, Spain.Website: http://eanm16.eanm.org/

^{99m}Tc DPD Scintigraphy Workshop
4 October 2016, Royal Free Hospital, London

2017

UKRG Annual Workshop 2017
11 January, Bournville, UK
Website: www.ukrg.org.uk

12th European Molecular Imaging Meeting
5-7 April, Cologne, Germany
Website: http://www.e-smi.eu/index.php?id=2652

BNMS Annual Spring Meeting 2017
20-22 May 2017, ICC, Birmingham

From the Editor:

The next meetings of the UKRG Committee will be on September 22nd 2016 and January 9th 2017. The Strategic Group will meet on January 10th 2017. If readers have any issues they 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.

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