U.K. Radiopharmacy Group

NEWSLETTER
2012 Q4

UKRG INITIATIVES

The UKRG Terms of Reference and Business plan has been updated. In the short and long term the Committee will concentrate on the following:

Short Term Objectives (1 year)

1. Compilation and updating local network lists. Data will be supplemented by the most recent BNMS department survey.
2. Influence national policy on implementation of EU directive 2010/32/EU on the prevention of sharps injuries
3. Ensure that radiopharmaceutical staff are included in the career development programme for the Modernising Scientific and Pharmacy Careers initiatives.
4. Implementation of guidance documents: QA of radiopharmaceuticals, safe drawing up of radiopharmaceuticals and Audit tool
5. Undertake manufacturer audits as required
6. Update the sections of the UKRG Handbook and publish on the UKRG website

Long Term Objectives (3 years or on-going)

1. Lead on the issue of QP training of pharmaceutical NHS staff
2. Introduction of Ga68 based radiopharmaceuticals into clinical practice
3. Populate SNOMED CT with radiopharmaceutical data set.
4. Facilitating appropriate implementation of the ARSAC strategic report
5. 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
6. To further develop local networks and establish funding for appropriate activities eg audit
7. Reviewing the implications of withdrawal of products from the market.

Success (or failure) of the UKRG to achieve targets or objectives will be recorded on an annual basis by means of an Annual Report of the Activities of the Group, which will be published on the website and in the Newsletter.

ARSAC Strategic Report on Mo99 supply

One recommendation of the report was to consider centralisation of radiopharmacy facilities. UKRG was represented at a meeting of Stakeholders chaired by Prof Alan Perkins, one action from which was to circulate a questionnaire to the whole radiopharmacy community to seek view on this issue. Many readers will have contributed to the survey. It is hoped that a draft report of the responses will be submitted to the DH National Imaging Clinical Advisory Group (NICAG) early in the New Year.

CR-UK / ECMC / UKRG WORKSHOP: RADIOPHARMACEUTICAL IMPs IN EARLY PHASE CLINICAL TRIALS

Rob Smith (Cambridge) has provided the following summary of this one-day workshop, held on 23rd October 2012.

Background

The purpose of the workshop was to identify and begin to develop opportunities for improving delivery early phase clinical trials using radiopharmaceutical (RP) IMPs in the UK.

Executive Summary

Introduction: The goals of the workshop and the DDO experience of setting up trials using RP IMPs was given by Nigel Westwood. Jonathon Bull introduced the ECMC Networking Initiative, its scope, what support it could provide for any identified initiatives and the need for a business case.

Regulatory Requirements and an Update from CTRad: An overview of the latest regulations and activities from the key stakeholders that regulate human trials using radiopharmaceuticals was given by speakers from ARSAC, MHRA and CTRad followed by a 30 minute Q&A session.

Key highlights:
ARSAC: Key issue with current ARSAC licensing system is that the lead applicant is contacted to

resolve any queries rather than the study sponsor often leading to delays in approvals. A new system is being introduced which will be integrated with IRAS and will have the sponsor as primary contact point. A meeting between ARSAC and IRAS is scheduled for Dec-12 with the new application system being introduced in 2013. It was suggested that an option to indicate whether a manufacturing certificate is already in place at site should be included on the IRAS form.

CTRad: There is huge variability in so-called standard practice when using established radiotherapies in the UK; treatment of thyroid cancer, bone metastasis and refractory neuroendocrine tumours were used as examples to highlight this. Due to this there are inherent difficulties in standardising multi-centre studies. The need for more dosimetry was also discussed due to the fact that administration of fixed doses of radioactivity does not mean that the tumour will be exposed to the same intensity level. The report "Molecular Radiotherapy in the UK: Current Status & Recommendations for Further Investigation, 2011" by The British Institute of Radiology (BIR) provides a nice summary of current status.

MHRA: An introduction and overview was given of the relevant clinical trial regulations. It was stressed that applicants for MHRA approval of CTAs should not feel constrained by the structure of the IMPD and build one to suit the product. There is often lack of justification as to why certain tests or specifications are or are not used and needs to be given a large amount of consideration in the IMPD. The MHRA are happy to work with the RP community to pull together an IMPD template that is specific to RPs and to take a look at examples of "mechanistic" trials to provide guidance as to whether they fall under the clinical trial regulations.

Case Studies: a series of case studies were presented covering most aspects of the set up and execution of early phase trials with radiopharmaceuticals. This session flagged where the key challenges are and whether any lessons could be learned/applied more widely. Key challenges:

- Need involvement of hospital and radiopharmacy staff early on in projects and ideally during the conception phase.
- Lead in times for patient recruitment need to be incorporated to avoid over-optimistic timelines.
- RP preparation time is enormous and most staff have no time allocated for research, leading to after-hours working and delays to study set up.
- Radiopharmacy staff often unsure of regulatory and documentation requirements and have little experience in their set up.
- Lack of cross-site sharing leading to duplication of effort and time wastage.
- To fulfil requirements of GMP Annex 13 it takes up to six people to produce a RP IMP which is way beyond staffing levels at most radiopharmacies.
- Lack of resource is a major issue with QPs being key.
- Development of IMPD is often left too late and it is unusual for a complete package of documentation to be provided to the radiopharmacy.

Panel Discussion Forum: a panel was formed by the six workshop Chairs and an open discussion forum held with delegates in order to identify ways in which the challenges around RP IMP production could be solved. Proposed solutions and improvements to the way radiopharmacies operate and work together were:

Quick wins:

- Setting up a working group to build an ECMC Networking business case and to identify those proposals that should be supported.
- Setting up a central web-based resource site to support knowledge sharing.
- Build a "road map" for how studies involving RP IMPs should be set up; could possibly be bolted onto the clinical trials toolkit.
- Build an IMPD template, agree content with MHRA and share with wider RP community.
- Share SOPs and other process documentation amongst wider community to avoid duplication of effort.
- Share examples of "mechanistic" clinical trials with MHRA to seek guidance as to when a CTA can be avoided.
- Delegates should make sure facilities expertise are on their Trust website alongside an operational capacity statement.

Medium Term:

- Update QC standards for molecularly targeted RPs and publish to wider community → could "fall out" of the IMPD template initiative.
- Link in more closely with other groups working on the same areas.
- Produce a report on the RP research capacity similar to that of the BIR report and/or build an ECMC radiopharmacy capability map to aid understanding of what the network can already deliver and increase collaboration.

Long Term:

- A key solution supported by the workshop was to set up "National Centres of Excellence" or "hub and spoke" system to support RP research in the UK akin to the CR-UK Imaging Centres.
- It was accepted that the ECMC Networking budget could not support this but it may be able to help build a business case for this; i.e. leverage resource and funding from other sources.

- More industry-like models of operating could be introduced as well as closer collaboration with industry (ideas need further development).

Post-Workshop Actions

Primary action: ***ECMC team to provide secretariat support for setting up a post meeting task force to tackle next steps***. As soon as the task force has been set up (end of Nov 2012?) the actions will be required:

- Decision to be taken as to which initiatives can be supported; complete by end Jan-13.
- Develop ECMC networking business case for supporting the initiatives; complete by end Jan-13.
- Identify volunteers from the RP community to form working groups to put each initiative into action.
- Glenn Flux to help identify which other collaborators the task force can link up with.
- ECMC team to compile list of sites with radiopharmacy staff funded by ECMCs and compile a capabilities map.
- Presenters to be asked whether they are willing to share slides; once approval given they will be uploaded onto the CR-UK website and distributed to workshop delegates.

NICE initiatives

The National Institute for Health and Clinical Excellence (NICE) is consulting on the following.

Firstly, it is consulting on the use of Selective Internal Radiation Therapy for primary cholangiocarcinoma (SIRT) using Y-90 micro-spheres. The closing date for comments was 17/12/12, but readers will wish to look out for the final Guidance document which it is hoped will be published in March 2013 – full details can be found at his URL:
http://guidance.nice.org.uk/IP/1081/DraftGuidance

Secondly, NICE has recently published its Diagnostic Guidance No 7 on the use of SeHCAT® in the investigation of chronic diarrhoea. It is available in this URL:
http://guidance.nice.org.uk/DG7

The NICE recommendation is:

1.1 SeHCAT (tauroselcholic [^{75}selenium] acid) is a potentially clinically important test for diagnosing bile acid mal-absorption, which may be currently under-diagnosed. There is insufficient evidence to determine whether SeHCAT is a cost-effective option for diagnosing bile acid mal-absorption in people with diarrhoea-predominant irritable bowel syndrome (IBS-D) and people with Crohn's disease without ileal resection. Therefore, for people with these conditions, SeHCAT is recommended for use in research to collect evidence about its clinical benefits and risks and the acceptability associated with diagnosing and treating bile acid mal-absorption.

REGULATORY ISSUES

EU Directive on Prevention of Sharps Injuries in the hospital and health sector (2010/32/EU)

Alison Beaney (Newcastle) has provided the following update.

A consultation on the incorporation of the new EU Directive on the Prevention of Sharps Injuries closed in November. A requirement of the Directive is that where risk of injury exists there should be an immediate ban on recapping of sharps. Although the draft UK legislation proposed that there is an exemption from this ban for radiopharmacy, this is not the case for wider aseptic practices in pharmacy.

A joint letter was sent to the HSE from the Royal Pharmaceutical Society on behalf of the specialist pharmacy groups, including UKRG and NHS PQA Committee, highlighting the problems with a blanket ban on manual recapping of needles in controlled environments. Additionally individual aseptic units and national committees submitted responses suggesting that a ban on recapping needles would have a detrimental impact on patient care for no benefit. We are now waiting to see how the EU Directive is actually translated into UK law. (This Directive must be implemented by May 2013.) Fingers crossed we will have got our points across.

Human Medicines Regulations 2012 and the "Orange Guide".

Following a recent visit to one UKRG Committee member the GMP Inspector, Rachel Carmichael, was asked to comment on the relationship between the HMR12 and the "Orange Guide"; this is her response.

The amending Statutory Instruments of the Medicines Act have been consolidated with the original Medicines Act and in effect (for our needs) The Medicines Act of 1968 has ceased to be - as have the old amending SIs (*Editor's note: a PDF*

listing all the out-of-date legislation is available on request from the Editor). The Medicines Act 1968 is effectively left "alive" but is probably around a 3 page document containing Section 10, Section 64 and Part IV. In practical terms for our (MHRA GMP) activities it will not apply. It has been replaced by The Human Medicines Regulations 2012, SI 2012 No. 1916, which can be found at this URL:
http://www.legislation.gov.uk/uksi/2012/1916/contents/made

Details of the relevant Regulations from the HMR2012 that relate to nuclear medicine can be found on the BNMS Website at this URL: http://www.bnms.org.uk/radiopharmacy/human-medicines-regulations-2012.html. This includes a reminder that: Crucially for NM departments - Regulation 240 now means that Radioactive Medicinal Products and medicines used as adjuncts to Nuclear Medicine studies (with the exception of Controlled Drugs) can be administered (under the direction of an ARSAC certificate holder) by ALL healthcare professionals working as an operator acting under written instructions.

The ***Orange Guide*** is really always out of date.
The reference to use is EU GMP, found at this URL:
http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

Important aspects to note - Chapters 1 and 7 have changed their names and been updated - apply from January 2013

Chapter 1 is now Pharmaceutical Quality System (Deadline for coming into operation: 31 January 2013)
Chapter 7 is now Outsourced activities (Deadline for coming into operation: 31 January 2013)
Many more Chapters / Annexes are under review so it is important to keep any eye on the web site.

Recent MHRA inspections

During 2012-Q3 four radiopharmacies had received a GMP Inspection; the following issues were raised:

- In one radiopharmacy facility: staff working with a LAFC safety cabinet in a grade B room were not wearing sterile face masks; also, there was no plan showing where sessional settle plates should be located, and no recent air-flow pattern testing to show that the position of a trolley in the cleanroom did not adversely affect the airflow.

- In another radiopharmacy facility: syringes and needles were being assembled in the transfer hatch rather than in the Grade A workzone;

- In a PET facility: media fill trials did not include the filter used as part of the aseptic process, and they were being incubated at only a single temperature and not using local isolators for growth control.

- In another PET facility: there was a transfer hatch with a moving plate in it and the unit had never cleaned underneath the sliding plate.

MHRA-MRC PET Survey

The following has been received from Graham McNaughton, Pharmaceutical Assessor, MHRA Clinical Trials Unit.

Newsletter readers will wish to know that a survey on the MHRA-MRC PET expert panel has been launched at the following URL: (http://www.surveymonkey.com/s/MHRA_MRC_PET).
The purpose of the survey is to allow stakeholders from the PET community to provide information in relation to Clinical Trial Authorisation (CTA) applications and Good Manufacturing Practice (GMP) in the UK.

Members of the MHRA-MRC PET expert panel are invited to complete the survey. Other readers from the PET community are alos invited to complete the survey so that their views and opinions can be included.

The survey should take a maximum of 20 minutes to complete and should not require any preparatory work on the part of the respondent prior to completion. The survey will be available until **Friday 18th January 2013**. Results from the survey will be used to inform and determine the functions of the MHRA-MRC PET expert panel.

If you require any further details please contact me, Graham M^{c}Naughton, either by email (graham.mcnaughton@mhra.gsi.gov.uk) or by telephone (020 3080 6148).

Yours faithfully
Graham.

Withdrawal of Products / Supply Issues

Draximage Medronate (MDP)

The UK distribution arrangement for Draximage MDP are still to be confirmed. Hopefully we can publicise the details in the next Newsletter.

SPC Updates

UKRG is not aware of any SPC updates being issued recently.

INDUSTRY NEWS

Alpharadin filed for approval in EU

The following briefing appeared in **PharmaTimes** on **13/12/2012.**
Bayer/Algeta has filed alpharadin for approval in the EU for the treatment of patients with castration-resistant prostate cancer and bone metastases.

Alpharadin is the first in a new class of 'alpha-pharmaceuticals' which is based on radium-223. The submission is based on data from the phase III ALSYMPCA trial which reported a median overall survival (OS) benefit in patients with radium-223 of 3.6 months based on 14.9 months OS with the drug plus best standard of care (BSC), versus 11.3 months with placebo plus BSC.

New Raytest Rep

Andy Holley has joined Raytest UK to promote the Raytest range of instruments in the UK. These include radiation detectors for HPLC, GC , TLC as well as automated synthesis modules. More details at www.raytestuk.co.uk . Andy can be contacted at andy@raytestuk.co.uk

MEETING REPORTS

Jim Ballinger (Guy's and St Thomas') has provided the following two meeting reports.

BNMS Radionuclide Therapy Group

At the invitation of Glenn Flux from the Royal Marsden Hospital, a group of 14 interested persons, plus three separated by geography but not technology, held a preliminary meeting on 27 November to look at how radionuclide therapy could be co-ordinated and advanced in the UK.

They started by considering the various groups with an interest in radionuclide therapy, including of course UKRG. BNMS is the appropriate organisation to serve as an umbrella for these disparate (but not desperate) initiatives. Of particular interest was which groups had access to funds, particularly for introduction of new therapies.

In terms of funding of current clinical uses, it really is a post code lottery. Some regions include one or other of the newer therapies such a Zevalin or radiopeptides while others include none. It was news to me that one region has agreed a tariff for Y-90 and Lu-177 radiopeptide therapy. Some centres are able to recover costs through contracts.

The group then reviewed the status of current therapies. It was evident that practice varies greatly around the country. One of the roles of the group could be to establish good practice guidelines; however, it is recognised that it may be difficult to gain sufficient agreement.

In terms of actions, the BNMS president will write to all members, informing them of the group and inviting their participation. The group will hold an open meeting during the BNMS conference in Brighton. There is the intention to hold a one day workshop later in the year, possibly at the Royal Society of Medicine.

Finally to terminology. I have been saying radionuclide therapy but maybe I'm being old fashioned (some would say there's no maybe about it!). The new term is molecular radiotherapy (MRT).

Cancer Care: New Accelerator Technologies for Radiotherapy and Radioisotope Production

The Science and Technology Facilities Council (STFC) and Department of Health (DH) co-sponsored a two day workshop at the School of Physics and Astronomy at the University of Manchester in early December. Attendance was limited to 70 and STFC chose the successful applicants by some mysterious criteria. Nuclear medicine was under-represented with Jim Ballinger, Chris Marshall, Peter Julyan, and Jose Calero from radiopharmacy and Alan Perkins and Glenn Flux from medical physics.

The first day concentrated on proton therapy, which was a new field to me and extremely interesting. Currently 400 patients per year, mainly children, are sent abroad for treatment in Europe or America at a cost of ~£100k each. There are plans to construct two proton therapy facilities in the UK to be operational by 2018 to treat about four times as many patients. This is big business in America where it is seen as the rich man's preferred treatment for prostate cancer, even though there is no evidence of reduced morbidity compared to standard radiotherapy. Prostate cancer would not be an indication in the UK.

The focus of the second day was the ^{99}Mo crisis, which is due to rear its ugly head again in 67 weeks' time when 40% of the world's supply become unavailable for a period. Erika Denton and Philip Webster from DH presented a bleak picture. They both emphasized how brilliantly radiopharmacy staff had managed the crisis in 2009 but that this was not sustainable for the longer term. Alan Perkins then educated the accelerator physics audience on current means of production of ^{99}Mo and potential non reactor alternatives. Breakout sessions with groups of 8 then looked at the issues but these were not terribly productive as only a small number of physicists had enough background on the issue.

However, the following three points emerged. Firstly, with a timeline of 67 weeks the only definite solution is flexible working (i.e. not letting the generator happily decay unused over the weekend); however, this obviously has workforce implications. Secondly, the UK needs to look seriously at cyclotron production of ^{99m}Tc. This is the solution which Canada has adopted and is developing a network of 8 cyclotrons to supply the country. A high level UK meeting will be convened early in 2013 to assess this. A small number of existing cyclotrons in the UK have sufficient energy to produce ^{99m}Tc but perhaps not sufficient current for useful amounts. Chris Marshall pointed out that running cyclotrons that many extra hours per day could lead to reliability issues. Thirdly, some promising very preliminary work has been carried out in the UK using a high power laser to convert ^{100}Mo to ^{99}Mo. For the longer term this could provide a new technology.

Finally, Glenn Flux raised the question: why are we fixated on ^{99m}Tc? Shouldn't we start from square one and look for the ideal radionuclide for nuclear medicine? Food for thought, but it's not going to happen overnight.

UPCOMING MEETINGS

2013

UKRG Annual Workshop
11 January, The Beeches Conference Centre Bournville, Birmingham, UK
www.ukrg.org.uk

Radiopharmacy Course
4-15 February, IEO - European Institute of Oncology, Milan, Italy
www.eanm.org

2nd European Conference on Clinical Neuroimaging
11-12 February, Lille University School of Medicine, Lille, France
Contact: franck.semah@chru-lille.fr

2nd World Congress on ^{68}Ga Molecular Imaging (PET/CT), Targeted Radionuclide Therapy and Dosimetry (SWC-2013)
28 February – 2 March 2013, Postgraduate Institute for Medical Education and Research, Chandigarh, India
www.2ndworldcongress-ga-68.de

51st Annual Congress of the German Society of Nuclear Medicine
17-20 April, Bremen, Germany
Contact: nukmed@vokativ.de

British Nuclear Medicine Society (BNMS) 41st Annual Meeting
22-24 April, Brighton, UK
www.bnms.org.uk

20th International Symposium on Radiopharmaceutical Sciences
12–17 May 2013, International Convention Centre, Jeju, Korea
Website: www.isrs2013.org

Society of Nuclear Medicine (SNM) 60th Annual Meeting
8–12 June 2013 , Vancouver, British Columbia, Canada
Website: www.snm.org

6th Annual World Molecular Imaging Congress
Date: 18-21 September, Savannah, Georgia, USA
Website: www.wmicmeeting.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 in Bournville, 9th-10th January 2013; the one after that in London, 16th April 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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