Quality assurance of radiopharmaceuticals
An update on the new guidance for all staff preparing radiopharmaceuticals

Jilly Croasdale
Sandwell and West Birmingham Hospitals NHS Trust
On behalf of the UK Radiopharmacy Group
www.ukrg.org.uk

Outline
• Why were the guidelines updated?
• How were the guidelines updated?
• What is different about Radiopharmacy?
• Main changes (general)
• Specific areas
  – Release of products
  – Sterility assurance
  – Radiochemical purity testing
• Concluding thoughts

The starting point....

Why were the guidelines updated?
• Last issued in 2001
• Comments from auditors about difficulty in using a ‘best practice’ document
• There have been some changes in regulations and significant changes in enforcement
• Needed more detailed guidance on requirements
• The extent of radiochemical purity testing varies widely between units

How were the guidelines updated?
• Working party of UK Radiopharmacy Group met on several occasions
• Draft circulated among NHS Pharmaceutical Quality Assurance committee members
• Draft circulated among MHRA GMP inspectors
• Suggestions incorporated and next drafts circulated
• Face to face meeting with NHS QA Committee
• Final version agreed, published on BNMS website

The outcome.....
What is different about Radiopharmacy?

- Product is radioactive
  - Handling must be limited
  - BUT can easily check how much active ingredient is in product
  - Limitations to some tests – e.g. sterility
- Product is used immediately
  - Can’t wait for all test data to be available
  - Heavy reliance on Quality Assurance
  - BUT no time for large bioburden to accumulate

What is different about Radiopharmacy?

- Release has to be done before all data available (e.g. sterility testing)
- Personnel involved not always pharmacy staff
- Small numbers of staff meant Production and release has overlapped
- Confusion exists about who can release
  - ‘Retrospective release’ was born!

What is different about Radiopharmacy?

- Chemical quantities trace BUT making a new chemical entity
- Pharmacological effects rare
- Mainly used for diagnostic purposes
- Often see impurities on scan
- Implications of impurities not well defined
- All the above leads to….
  - …Having the idea Radiochemical Purity isn’t important
    - Patient isn’t a suitable vehicle for product testing!

Main changes (general)

- Previous guidelines set best practice
  - These guidelines set minimum standards
  - A decision not to adhere to these minimum standards must be assessed, documented, and approved
- Previous guidelines were primarily for $^{99m}$Tc kit preparations
  - Expanded somewhat to be applicable to PET and therapy but not comprehensive
- Clearer instructions on frequency of testing, etc

Table of contents

1. Radiopharmaceuticals and the Medicines Act 1968
2. Purchase and testing of starting materials
3. Facilities and equipment
4. Documentation
5. Pharmaceutical environmental monitoring
6. Finished product testing and quality assurance
7. Sterility assurance
8. Validation
9. Training
10. Release of products
11. Inspection and audit
Table of contents

1. Radiopharmaceuticals and the Medicines Act 1968
2. Purchase and testing of starting materials
3. Facilities and equipment
4. Documentation
5. Pharmaceutical environmental monitoring
6. Finished product testing and quality assurance
7. Sterility assurance
8. Validation
9. Training
10. Release of products
11. Inspection and audit

Release of products

- Problems:
  - Time constraints
  - Staff working in radiopharmacy wouldn't normally release pharmaceuticals
- Improper or improperly used terminology
  - Parametric release: only refers to licensed products which are terminally sterilised
  - Retrospective release: no such thing exists
- There has been a lot of confusion and a sometimes inconsistent approach by MHRA

Release of products: Section 10

- Can only be released by either:
  - Accountable Pharmacist (formerly called Responsible Pharmacist)
  - Authorised Pharmacist: person designated by Accountable Pharmacist to supervise production and to release products
- Supervisor should be present during production and available to intervene as any stage

Release of products: Specials licence

- Person named as quality controller on licence has ultimate responsibility
- The act may be delegated to a named, suitably trained and experienced person
- Independence of release from production; exception in emergencies but this should not be routine
- There might be retrospective review (e.g. by QA/QC personnel) when final results of testing (e.g. sterility) are available

Sterility assurance: Sterility testing

- Previously this entailed allowing radioactivity to decay before sending samples to microbiology lab
- Concerns about the validity of this approach
  - Are organisms viable in kit contents?
- Alternatives:
  - Direct innoculation of broth, either equal volume of double strength broth or max 10% volume of normal strength broth
  - End of session broth fill mimics radiopharmaceutical preparation but can be incubated immediately

Sterility assurance: Frequency of testing

- Generator eluate
  - Final unmanipulated eluate
  - First eluate no longer minimum requirement
- Kit residue
  - One per week
  - To build up body of evidence
- End of session broth fill
  - One per workstation per week
  - Test of product, process, and operator
Radiochemical purity (RCP) testing

- This has been a controversial area for many years

- **Absolute requirement:**
  - Deviation from manufacturer’s instructions: e.g. higher activity, altered volume, extended expiry
  - Unlicensed products, e.g. pentavalent DMSA, Nanocis, \(^{177}\)Lu-DOTATATE
  - Investigational medicinal products (IMPs)

- **Useful for:**
  - Investigation of altered biodistributions
  - Validation of integrity of kits, cold chain in transport

---

RCP testing: Methods and equipment

- Manufacturer is required to provide method; also pharmacopoeia, textbooks, Radiopharmacy Handbook

- You are not required to use the recommended method but whatever method is used must be valid

- Can be done by cut and count using dose calibrator or gamma counter, but more reliable results obtained with radiochromatogram scanner, phosphor imager, or gamma camera

---

RCP testing: Frequency of testing

- Maintain proficiency of staff and integrity of test procedures

- First vial of new batch of kits: batch to batch variation, cold chain in transport

- As part of change control: new member of staff, change in generator manufacturer, source of saline, cleaning materials, storage conditions, etc

- Based on previous experience, some products should be tested more frequently

---

Concluding thoughts

- The goal of quality assurance is to ensure that the patient receives a high quality product on every occasion

- It also ensures the smooth running of the radiopharmacy for a regulatory viewpoint

- Minimum standards with clearer recommendations on frequencies should help radiopharmacies comply

- Will be used by BNMS auditors, EL(97)52 auditors and MHRA inspectors