Regulatory aspects: Radiopharmacy (GMP)

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International Course on
THERANOSTICS AND MOLECULAR RADIOTHERAPY
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Radiopharmaceuticals

for molecular imaging (diagnosis)

Radionuclide:
Emits upon decay detectable gamma rays

Vector molecule:
Specific molecular interaction (receptor, transporter, enzyme,…)
Image contrast
Radiopharmaceuticals

for therapy

Radionuclide:
Emits upon decay particulate radiation ($\beta$, $\alpha$) for destruction of target cells

Vectormolecule:
Specific molecular interaction (receptor, transporter, enzyme, …)
Radiation dose selectivity
Good manufacturing practices (GMP)

GMP = **quality** management system for pharmaceutical products ensuring consistent (for every batch)

- Production
- Control (QC)

appropriate to their intended use in agreement with product specification.

- clinical trial authorization (IMPD)
- marketing authorization

**cGMP** = **current** good manufacturing practice (dynamic continuously evolving)

Good manufacturing practices (GMP)

Why GMP?
Reduce health hazard for patients
• toxicity/side effects
• lack of therapeutic/diagnostic effect
• supply gaps

Preventive actions (validation, documentation, training, …)

Curative actions (change control, root cause investigations, …)

radiopharmaceuticals

- pharmaceuticals
- generally administered via intravenous route
- Conditionally released before all QC results are available
- Produced just-in-time (no supply redundancy)
- Diagnostics: no (side) effects anticipated (small mass amounts)
- Therapeutics: potential side effects

GMP also applies to radiopharmaceuticals!
EU Legislation: Eudralex

EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines

- Part I: Medicinal Products
- Part II: Active Pharmaceutical Ingredients
- Part III: GMP related documentation
  - Annex 1: Sterile Medicinal Products
  - Annex 3: Radiopharmaceuticals
  - Annex 13: Manufacture of investigational medicinal products
  - Annex 15: Validation and Qualification

**Quality management**

**Pharmaceutical quality system**
- all organised arrangements with the objective of ensuring that medicinal products are of required quality
- designing, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes
- Support and commitment from senior management
Personnel

- Production of (radio)pharmaceuticals depends on people!
- Sufficient number and qualification of people
- Clear roles and responsibilities (resp. QC should be different from resp. production)
- Training
  Repeated training and validation for critical tasks (e.g. aseptic handling)
  Documented in records (training matrix)
  Handling of radioactive material and radiation safety procedures
Premisses and equipment

Production

• Protect product against environment (chemical and microbiological contamination)

Radioprotection: protect environment against product!

• Qualification: IQ, OQ, PQ

• Calibration (all measuring devices against primary standards)
Premises and equipment
Sterile solutions for IV injection

Dispensing cell
(sterile filtration and dispensing)

Prechamber
Grade B

Hot cell
(synthesis module)
Grade C

Air lock
Grade D

Air quality (particles) as a function of criticality of operation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Maximum concentration limits (particles/m³) for particles ≥ sizes shown</th>
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**EU CGMP classifications**

<table>
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<tr>
<th>Grade</th>
<th>Recommended limits for microbial contamination (a)</th>
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<tr>
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Premisses and equipment
Sterile solutions for IV injection

Air quality (particles) as a function of criticality of operation

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<tr>
<th>Clean Area Classification (0.5 μm particles/ft³)</th>
<th>ISO Designation</th>
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<th>Microbiological Active Air Action Levels (cfu/m³)</th>
<th>Microbiological Settling Plates Action Levels (diam. 90mm: cfu/4 hours)</th>
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**Prechamber**
Grade B

**Dispensing cell**
(sterile filtration and dispensing)

**Hot cell**

**Air lock**
Grade D

**FDA cGMP**

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Premisses and equipment
Sterile solutions for IV injection

- Particle counter
- Continuous monitoring
  in Grade A
- Settle plate
- Active air sampling
- Contact plate
Premisses and equipment
Pressure cascades

Dispensing cell (+50 Pa)

Hot cell (-100 Pa)

**GMP**: highest pressure in production zone to protect product against environment

**Radioprotection**: lowest pressure in production zone to prevent spreading of airborne contamination

Solution: pressure “hill” in intermediary zone
equipment

• Qualification: IQ (installation qualification) OQ (operational qualification) PQ (performance qualification)
• Calibration (all measuring devices against primary standards) (thermometers, pressure gauges, chronometers, scales, dose calibrator,
Documentation

If it is not documented, it didn’t happen

GMP=give me paper!
Clinical trials - Regulation EU No 536/2014 (applicable Oct 2018)

Art. 61 manufacturing subject to (GMP) authorisation
Art. 68 labeling requirements
Do not apply to radiopharmaceuticals used as diagnostic investigational medicinal Products. Do apply to radiopharmaceuticals for therapeutic use.

Member States shall make proportionate requirements to ensure subject safety and reliability and robustness of the data generated in the clinical trial. They shall subject the processes to regular inspections

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<th></th>
<th>IMP</th>
<th>Non-IMP</th>
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<th>Therapeutic</th>
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Radiopharmaceuticals: QC

• radioactive

(Chemical purity)
Radiochemical purity (radiolysis!)
Radionuclidical purity
Molar activity (specific activity)

• Small mass amount

Identification generally based on retention time on HPLC
Radiopharmaceuticals: QC

- **Small batch (one vial)**
Vial which is used is tested (no batch heterogeneity problems)
Radiopharmaceuticals

• Short half-life, volume dose not constant

Limits for chemical impurities and endotoxins: per dose (“V”) instead of per ml

\[ \text{Limit:} \]
- the central portion of the spot due to the test solution is less intense than that of the spot due to reference solution (b) (2.2 mg/V).

\textbf{Bacterial endotoxins (2.6.14):} less than 175/V IU/mL, V being the maximum recommended dose in millilitres. The preparation may be released for use before completion of the test.
Radiopharmaceuticals

• **Short half-life**

Some QC tests take a long time (e.g., sterility test 14 days) conditional and final release
Radiopharmaceuticals

Since sterility test result not know at time of injection:
- sterile filter bubble point test
- aseptic handling
= critical

For diagnostic radiopharmaceuticals:
Risk microbial contamination > risk associated with radioactivity
Contamination catastrophe at NECC
But consumer advocates say a recent crackdown by the agency shows it most certainly can – and should. A spate of recent FDA inspections have shown that the dirty conditions that led to an outbreak of fungal meningitis that killed 51 people and sickened more than 700 are anything but rare at pharmacies that mix up what are supposed to be “sterile” injectable drugs.
Radiopharmaceuticals for therapy

- Additional radiopharmacological risk

  Polonium-210: 50 ng

  Alexander Litvinenko

- Important to check identity, radiochemical & radionuclidical purity, stability (radiolysis) \textit{in vitro} and \textit{in vivo}
Radiopharmaceuticals for therapy tox testing?

“microdosing” applicable for diagnostic radiopharmaceuticals (<100 µg)
100 fold dose 14 day study in single species (rats/mice)
Radiopharmaceuticals for therapy tox testing?

Exploit theranostic advantage:
prediction of toxicity/side effects from:

- **physicochemical properties** (radionuclide decay particle energy, half-life, affinity, microdistribution (microdosimetry) in target and non-target tissue, in-vivo stability)

- **Companion diagnostic**: individual real-time dosimetry

Modeling and treatment planning (similar to external radiotherapy) and evaluation of tumor response

Relevance of tox testing in small animals?
Single tox test for theranostics pairs?
Radiopharmaceuticals for therapy

QC?

Dose measurement
• Dose calibrator: geometry, vial configuration, calibration standard (calibration vs liquid scintillation?)

Radiochemical purity (and stability)
• Radio-thin layer chromatography TLC (simple fast, cheap): low resolution, no cold mass quantification, no quantification of volatiles
• HPLC (high performance liquid chromatography):
  High resolution, colloids not quantified, cold mass quantification

Radionuclidical purity
Long lived radionuclides (generator), radioactive daughter nuclides (recoil energy)

Li et al. Applied Radiation and Isotopes 127, 2017, p. 52-60

Two-dimensional ITLC
Conclusion

• GMP mandatory for both diagnostic and therapeutic radiopharmaceuticals

• Clinical evaluation of new theranostics
  • Non clinical evaluation RPC therapy
    o QC package, accurate dose measurement, RCP and RNP quantification, validated methods
    o in-vitro stability, in-vivo stability, similarity between diagnostic and therapeutic RPC, microdistribution and microdosimetry
    o tox testing necessary and useful?
Thanks for your attention

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A Joint Initiative of IAEA – BELNUC - JULES BORDET INSTITUTE

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