Regulatory Aspects of Radiopharmacy Design

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Agenda / Scope

- Design and build aspects from the perspective of an EU medicines regulatory agency
- Design considerations relevant to the Healthcare setting
- Specifying the facility requirements
- Realising the design
  - Project management
  - Working with contractors
- Review of previous cases.
Radiopharmaceuticals manufactured in the Healthcare setting

• Mainly sterile dosage forms
• Imaging agents / Therapy doses
  – Varying half-life and activity
• Investigational Products
• PET agents
• (Blood labelling).
Regulatory considerations

• Licensing framework
• GMP requirements
  – Facilities and equipment
  – Contractor agreements
• Other regulatory requirements
  – HSE, Environment Agency, Counter Terrorism.
EU GMP & Radiopharmacy Design

- Chapter 3 (Premises & Equipment)
- Chapter 5 (Production)
- Annex 1 (Sterile Products)
- Annex 15 (Validation)

All in the process of revision!
‘Challenges’ of sterile radiopharmaceuticals

• Short expiry
• Prospective release
• Radiation protection measures
  – Additional equipment
  – Challenges to Grade A environment
  – Containment / cleaning of spills
• Designing facilities and systems to support a robust sterility assurance programme is important.
Specifying facility requirements

- Essential to ensure facility and equipment will be fit for intended purpose
  - User Requirement Specification*
  - Functional Design Specification
  - Design Qualification*
- Enables traceable qualification in later phases

* User’s responsibility.
Facility design considerations

• Primary regulatory focus – product & patient protection
  – Zonal environmental protection (HVAC, ΔP, interlocks)
  – Containment measures (ΔP, isolators, rooms, airflow patterns)
• Area visibility – vision panels etc
• Process flow
  – Prevention of mix-up
• Co-located preparation risks
  – Other products: blood labelling, therapy doses
  – Safety / environmental considerations (e.g. sinks, emergency showers).
Equipment selection – impact on facility design

- Clean air device selection should be considered early in the facility URS and FDS phases
- Laminar Flow Cabinet vs. Isolator differ in facility requirements
  - Classification of background environment
  - Impact on HVAC design specification (air extraction rates).
‘Future proofing’

- Crystal Ball?
- Successful strategies often focus on flexibility
- Planning to accommodate future changes, e.g.
  - Room grades capable of exceeding current requirements
  - Gassing isolators / RTP technology
  - Robotics, CCTV
  - Continuous Particle Monitoring
- Utilities planning to support these changes.
Realising the design

• Complex work, balancing different priorities
  – Radiopharmacy may be part of a bigger project
• Often working within constraints
  – Footprint size / layout
  – Immovable obstacles
• GMP-focussed project management is key from the outset
  – ‘Do it once, and do it right’.
Realising the design

• Failure to build in GMP requirements from the outset can result in:
  – Retrospective ‘fixes’
  – Sub-optimal solutions
  – Delays in project completion
  – Delays in regulatory approval
  – Increased costs.
Project management - challenges

• Few Pharma / Healthcare organisations have in-house expertise to manage a new GMP facility build from concept to implementation

• Most organisations contract-out some / all work
  – GMP / Regulatory specialist services
  – Documentation
  – Specialist work (e.g. construction / engineering / testing).
Contractor selection and collaboration

- Contractor selection and collaboration is critical to success
  - Contractor’s GMP expertise
  - Contractor willing to involve the client throughout
- There MUST be a GMP-focused contract
  - Define responsibilities
- Delegation of activity, not responsibility.
Contract considerations

- Not just a commercial document!
- Approved by all relevant parties and version controlled
- Clearly defined GMP responsibilities
  - Reference to current GMP requirements
- Reference to key documents, e.g. Functional Design Specification.
- Change control arrangements
- Permissible sub-contracting
- Auditing and oversight provisions by contract giver.
PREVIOUS CASES
Previous successful case:

- Planned refurbishment of UK facility
- Radiopharmacy staff involved throughout
  - Design and planning
  - Maintained close collaboration with their contractor throughout
- MHRA Inspectorate informed at early stage
  - Considered planning and regulatory approval of alternative facility
  - Review of 1:50 plans and project validation master plan.
Previous cases: examples of problems identified too late

- GMP focus not applied until too late in the process (e.g. hand-over from contractor)
- Underestimation of time and money costs for build management and qualification
- Qualification not documented and not sequenced in compliance with GMP
- Inappropriate room finishes (driven by cost).
Previous cases: problems identified too late

- HVAC running on the edge of failure
- Proposal to turn the HVAC off at night
- Aseptic changing room with a pillar not on the plan
- Litigation between contractor and contract giver, due to hand-over of a facility unfit for purpose
  – Mainly due to lack of detail in specification.
How can this be avoided?

- Clearly defined contracts and specifications
- GMP focus and time resources assigned from the outset.
Help the Regulator Help You!

• Early and continued communication with the Regulator is essential
  – Review of proposals
  • New facility design / interim measures
  • No ‘pre-approval’, but helps identify problems at an early stage
  – Facilitate timely assessment at key milestones in the project
  – Assist in clarifying regulatory requirements.
Thank you for listening

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