Medicines and Healthcare Products Regulatory Agency

Regulatory Aspects of Radiopharmacy Design

David Churchward, Expert GMDP Inspector, MHRA

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

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.

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

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).

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

Regulatory considerations

- Licensing framework
- GMP requirements
  - Facilities and equipment
  - Contractor agreements
- Other regulatory requirements
  - HSE, Environment Agency, Counter Terrorism.

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

EU GMP & Radiopharmacy Design

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

All in the process of revision!.

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

‘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.

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

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.

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

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).

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

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).

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

‘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.

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

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’.

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

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.

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

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).

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

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.**

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

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.

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

PREVIOUS CASES

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

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.

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

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).

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

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.

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

How can this be avoided?

- Clearly defined contracts and specifications
- GMP focus and time resources assigned from the outset.

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

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.

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

Thank you for listening

david.churchward@mhra.gsi.gov.uk

CPRD NIBSC MHRA

Medicines and Healthcare Products Regulatory Agency

© Crown copyright 2013

CPRD NIBSC MHRA