Preparing for commercial GMP manufacture; areas for consideration

Daria Popova, Lead Technical Scientist
Gina Basman, Validation Manager
Doli Patel, Head of Quality Control
Preparing for GMP manufacture

Daria Popova, Lead Technical Scientist
The centre provides access to the expertise, skills, facilities and equipment as the stepping stone needed for organisations to develop new technologies and systems for large scale manufacturing.

**Quality control**

**Qualified persons**

**Operating policies**

**Warehouse management**

**Development assistance**

.managed warehouse with delivery to your manufacturing space**

**Flexible quality control options**
Collaborating companies

“CGT Catapult’s unique operational model allows us to grow our manufacturing capacity, while accessing a range of services provided by the centre.” **Jim Faulkner, SVP and Head of Product Delivery**

“We are looking forward to an important collaboration with CGT Catapult scaling-up GMP manufacturing strategies for commercial production.” **Gregg Sando, CEO**

“We are delighted to establish this collaboration for our next generation AAV gene therapy platform for chronic systemic disease.” **Jan Thirkettle, Chief Development Officer**

“With our own vector manufacturing capability at the Catapult facility, we will extend vector supply capacity beyond 2020.” **James Noble, CEO**

“The agreement with CGT Catapult enables us to meet our immediate clinical trials needs and have the flexibility of both our own dedicated manufacturing space” **Garry Menzel, Ph.D., President and CEO**
Preparing for GMP manufacture

Cleanroom Design & Set up Considerations

Path to GMP Readiness: Operational Perspective

Scheduling & Planning Challenge

Waste Management Challenge

Summary
Design considerations

- Consumables
- Reagents
- Patient/Starting Material
- Equipment

- Waste Consumables
- Waste Liquids
- Product
- Rejected Product/Starting Materials
Process mapping and mass/volume balance

Buffer A (8 L)
Product (1 L)
Buffer B (1 L)
Consumable Set

Drug Substance (1L)
Waste Liquid (9L)
Waste Consumable

Unit Operation (Equipment)

Visual Tool

Excel/Calculation Tools
Equipment placement

- HVAC type & supply
- Utility provision
  - Power supply
    (UPS/generator/non-essential)
  - Gas supply
  - Chilling capacity
- Environmental monitoring
  - Connection
  - Cabling route
- Identify clear zones
  - air outlets
  - equipment access routes
  - Material, product & people movement routes

Operational Considerations
- Segregation of unit operations
- Space & movement of auxiliary materials
  e.g., buffers/medium/welding stations/mobile equipment

Operational quality
  Process efficiency
  Process robustness
  Operator safety
  Cross-containment

Contamination risk
  Cross-contamination risk
  Operator error
  Unnecessary movement
Material, product and people flow

Maximise
Cleanroom Area
43% increase in production area

Maximise
Throughput

Autologous: up to 25% throughput increase
Material, product and people flow

Maximise Throughput

Viral Vector: up to 6 fold throughput increase

Segregated Small Production Area with dedicated access

Enables use of area as a QC lab, segregated seed train or additional segregated production
Material, product and people flow

Materials Clean Down

Maximise Throughput

Optimise Flows

Materials Clean Down

Segregated Material, Sample and Product Transfer
Increased efficiency in controlled transfer from CNC through to return corridor

Direct Material Transfer via CNC Corridor
Reduces need for staging of materials in shared areas. Enables delivery directly to module.
Material, product and people flow

- Materials
- Clean Down
- Maximise Throughput
- Optimise Flows
- Decrease Labour

Fumigation Chamber for Material Transfer

Improved cross-containment measure
Up to £150k annual efficiency saving in labour cost
Path to GMP readiness: Operational perspective

1. Equipment
2. Facility Adjustment/Modifications
3. Supply Chain & Logistics
4. Validation
5. Quality Assurance
6. Quality Control
7. EHS
8. Operations
Path to GMP readiness: Operational perspective

1. Equipment
2. Facility
3. Supply
4. Validation
5. Quality

<table>
<thead>
<tr>
<th>Facilitie</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Do you have an approved validation master plan compliant with section Annex 15 – Qualification and Validation?</td>
</tr>
<tr>
<td>3.2</td>
<td>Have you performed an assessment of qualification requirements of your production and QC equipment?</td>
</tr>
<tr>
<td>3.3</td>
<td>Have you qualified your production and QC equipment, as appropriate for your activities? Where qualification is not complete, do you have list of qualifications that need to be completed and the appropriate protocols in place for completion of the qualification activities?</td>
</tr>
<tr>
<td>3.4</td>
<td>For computerised systems that generate critical data, does the validation include an assessment of compliance with data integrity principles?</td>
</tr>
<tr>
<td>3.5</td>
<td>Do you have a mechanism for setting and managing equipment calibration frequencies?</td>
</tr>
<tr>
<td>3.6</td>
<td>Has all your equipment been calibrated in line with your PQS requirements, and are all calibration certificates available on request?</td>
</tr>
</tbody>
</table>
Path to GMP readiness: Operational perspective

- Process Understanding
- Equipment Purchase
- Facility Adjustment
- Workplace & IT
- EHS
- QC
- QA
- Supply-Chain & Logistics
- Validation
- Team Training
- Tech Transfer Planning
- TT Runs
- Engineering Runs
- Process Documentation
- PQ 1
- PQ 2
- PQ 3

Year 1

Year 2
Scheduling and planning challenge

Manufacturing Operations

Module 1
Stock Management
Cleaning Regimen
Documentation
Facility Management
Cleaning Team
Quality Control
Quality Assurance

Module 2
Engineering

Module 3
Warehouse

Module 4

Material/product movement
Waste movement
Module modifications
Product process

EM

## Scheduling tool

<table>
<thead>
<tr>
<th>Module X</th>
<th>7:00 AM</th>
<th>9:00 AM</th>
<th>11:00 AM</th>
<th>1:00 PM</th>
<th>3:00 PM</th>
<th>5:00 PM</th>
<th>7:00 PM</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Waste Movement</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Waste Movement</td>
<td></td>
</tr>
<tr>
<td>Biological material movement</td>
<td></td>
<td>Process</td>
<td>EM</td>
<td></td>
<td></td>
<td>Product movement</td>
<td></td>
</tr>
<tr>
<td>Waste Movement</td>
<td></td>
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<tr>
<td>Process</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Process</td>
<td></td>
</tr>
<tr>
<td>Material movement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Material movement</td>
<td></td>
</tr>
<tr>
<td>EM</td>
<td>Process</td>
<td>Weekly Clean</td>
<td>Process</td>
<td>Eng's on site</td>
<td>Process</td>
<td>Process</td>
<td></td>
</tr>
</tbody>
</table>

- Modules and MC common areas
- Maps Activities
- Rules
- Accessible to all facility teams
Scheduling tool: Process specific

Detailed process schedule automated tool example

- Automated calendars for each piece of equipment
- In-built process step length
- Defined process step sequence to allow for automated schedule generation
- Visual and numerical outputs

- Allow to determine rules for maximum capacity schedule
- Reduce operational risk
- Assist scheduling and decision making in detailed and high level planning
Waste management challenge

1. Brainstorm
2. Options Analysis
3. Risk Assessment
Waste management challenge
Inactivation of biological process waste streams

Assess:
- Volumes
- Composition
- Conditions

Inactivation
Agent Candidate
Panel

Representative
Matrices

Design
Experiment

Consider Agent
Inhibitory Factors:
- Temperature conditions
- pH
- Salt concentration
- Buffering capacity
- Protein content

Consider:
- Waste Removal Route
- Waste Contractor
- Suitability for Drain
- Handleability
- Efficacy (available data)
- Need for pre-treatment prior to disposal
- Acceptance criteria

Consider:
- Contaminated stream (bacterial & fungal)
- Range of inhibitory materials
- Range of operating conditions
- Worst case vs DoE approach
- Matrix stability

Consider:
- Contracting out vs inhouse
- Type of study - validation vs informative package
- One vs multiple studies
- Order of experiments
- Timeline

Work to component level of detail

Develop appropriate rationale for acceptance criteria: e.g., EN 14476
# Inactivation agent selection

<table>
<thead>
<tr>
<th>Inactivation Agent</th>
<th>Concentration</th>
<th>Inactivation Time (h)</th>
<th>Pass/Fail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virkon</td>
<td>3%</td>
<td>6 hours</td>
<td>Pass</td>
</tr>
<tr>
<td>NaOH</td>
<td>0.1M</td>
<td>6 hours</td>
<td>Pass</td>
</tr>
<tr>
<td>Peracetic Acid</td>
<td>1% v/v</td>
<td>6 hours</td>
<td>Pass</td>
</tr>
</tbody>
</table>

- Additional considerations include:
  - Practical handling of reagents
  - Storage, use and disposal
  - Cost and supply reliability
  - Compatibility with trade effluent consent limits
Process mapping and varying complexity of design tools are available to aid cleanroom design and fit out.

Quality, operations and project management collaborative approach is key to timely delivery of GMP readiness.

Activity scheduling can be a challenge during operational set up, the solution needs to be appropriate for the level of planning required.

Inactivation studies take time and effort. Not all waste can go down the drain.
Acknowledgements

Marcia Mata
Majahar Sayed
Moira Francois
Iris Valero
Alexia Toufexi
Ryan McCoy
Vicky Adams

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Stephen Shapka
Kay Bussey
Ken Murfitt
Jingjing Li
Zulekha Saiyad

Kasia Averall
Julie Kerby
Kwok Pang
Jon Halling
James Biggins
Validation considerations

Establishing a cell and gene therapy manufacturing centre

Gina Basman, Validation Manager
Validation Considerations
**Validation Considerations**

**Regulatory expectation:** “The manufacturer, or— as appropriate— the sponsor or marketing authorisation holder should define the specifications for the premises and equipment.”

- Define scope, and
- deliverables for quality,
- engineering, IT and
- business compliance
**Validation Considerations**

**Regulatory expectation:** “The key elements of the site qualification and validation programme should be clearly defined and documented in a validation master plan (VMP).”

- Validation Scope and Strategy
- Deliverables
- Roles and Responsibilities
- System Criticality Assessment
Validation Considerations

Regulatory expectation: “Compliance with user requirements should be demonstrated.”

- Design Specifications
- Design Review
- Design Freeze
- Change Management
- Design Qualification Protocol

<table>
<thead>
<tr>
<th>Project Title: Design Qualification Protocol for the Facility &amp; Utilities at the CST-UC (Completed)</th>
<th>Cell and Gene Therapy, Catapult, Sweeney生物技术, Harwell, UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Document Reference Number: HC-58889-DQ-BD (version 1.3)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The building will be built to meet the operational requirements of Sections 4.1, 4.2, 6.1, 7, 8.1, and 9.1 of the Design Qualification Protocol.</td>
<td>The building will be designed, fabricated and erected in accordance with the Design Qualification Protocol.</td>
<td>Section 4 (Design Qualification)</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>The building will be designed to facilitate and be capable of being used for the storage, handling, processing, and disposal of hazardous materials.</td>
<td>The building will be designed and equipped to facilitate the safe and efficient storage and handling of hazardous materials.</td>
<td>Section 6 (Design Qualification)</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table: Compliance with User Requirements

- Design Specifications
- Design Review
- Design Freeze
- Change Management
- Design Qualification Protocol
Validation Considerations

**Regulatory expectation:** “Equipment, especially if incorporating novel or complex technology, may be evaluated, if applicable, at the vendor prior to delivery.”

- Good Engineering Practices
- Agree inspection test plans
- Commissioning Master Plan
- Leveraging Matrix
- Documented Inspections
- Acceptance of pre-qualification activities
- FAT, SAT, Commissioning
- Handover
Validation Considerations

Regulatory expectation: “The manufacturer or - as appropriate - the sponsor or marketing authorisation holder should verify that the premises/equipment comply with the user specifications and are in line with GMP requirements.”

- Validation Protocols
- Verification of Installation and Functionality
- Leveraged Tests as per Plan
- Establishing Procedures

Installation Qualification → Operational Qualification → Performance Qualification → Validation Sign Off

Installation Qualification Protocol for the Cleanroom Module 01 and its Dedicated Heating Ventilation Air Conditioning (HVAC) at Cell and Gene Therapy Catapult Manufacturing Centre (CGT-MC)

### Table

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Pass/Fail</th>
<th>Comments</th>
<th>Non-Conformance</th>
<th>Initial/Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.1</td>
<td>Installation has been carried out as per the as built drawings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.2</td>
<td>Commissioning activities for HVAC system has been completed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.3</td>
<td>The Cleanroom Module 01 is installed as per the design specification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Validation Considerations**

**Regulatory expectation:** “The suitability of the premises and equipment to operate consistently in accordance with the requirements of the intended manufacturing process (assuming worst case conditions) should be tested. A test with surrogate materials or simulated product is acceptable.”

- Verification of Performance
- Training
- Cleaning Qualification (where applicable)

### 12.0 TEST SUMMARY

The following tests will be executed under the authority of this protocol.

<table>
<thead>
<tr>
<th>Test Section</th>
<th>Test Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Verification of Air Cleanliness by Particle Concentration (Run 1)</td>
</tr>
<tr>
<td>14</td>
<td>Verification of Air Cleanliness by Particle Concentration (Run 2)</td>
</tr>
<tr>
<td>15</td>
<td>Verification of Air Cleanliness by Particle Concentration (Run 3)</td>
</tr>
<tr>
<td>16</td>
<td>Verification of Viable Concentration (Run 1)</td>
</tr>
<tr>
<td>17</td>
<td>Verification of Viable Concentration (Run 2)</td>
</tr>
<tr>
<td>18</td>
<td>Verification of Viable Concentration (Run 3)</td>
</tr>
<tr>
<td>19</td>
<td>Review of the Environmental Conditions Within the Cleanroom Module</td>
</tr>
</tbody>
</table>
**Validation Considerations**

**Regulatory expectation:** “A formal release for the next stage in the qualification and validation process should be authorised by the relevant responsible personnel either as part of the validation report approval or as a separate summary document.”

- Validation Sign Off
- Quality Approval
- Regulatory Approval
Validation Considerations

**Regulatory expectation:** “Equipment used in production or control operations should be suitable for its intended purpose and it should not present any hazard to the product.”

- Process Equipment Qualification
- Data Collection, Critical Process Parameters
- Process Development / Optimisation

**Regulatory expectation:** “The validation of analytical methods is intended to ensure the suitability of the analytical methods for the intended purpose.”

- QC Equipment Qualification
- Analytical Test Method Validation
**Validation Considerations**

**Regulatory expectation:** “The aim of the process validation for ATMPs is to demonstrate that the finished product characteristics are within a given range (in compliance with the terms of the marketing authorisation).”

- Validation Protocol
- Strategy to Process Validation
- Critical Process Parameters
- Critical Quality Attributes
Regulatory expectation: “Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated.”

- Product Process Monitoring
- Environmental Monitoring
- Calibration Program
- Preventative Maintenance Program
- Change Control Management
- Non Conformance Process


Validation Considerations

- Process Pre-qualification Runs
- Process Validation
- Validated State
- Periodic Evaluation

**Regulatory Expectation:** “Equipment, facilities, utilities and systems should be evaluated at an appropriate frequency to confirm that they remain in a state of control.”

- Periodic Review Schedule (risk based)
- Periodic Qualification Tests
- Temperature Mapping
- Decommissioning

---

3.0 Reference Documentation

The following table details the last approved report for the Binder Incubators:

<table>
<thead>
<tr>
<th>Last Validation Summary Report No.</th>
<th>Approval Date</th>
<th>15 April 2019*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preceding Periodic Review Report No.</td>
<td>First review</td>
<td>Review Period</td>
</tr>
</tbody>
</table>

* The review period has been taken from the approval of the PQ report conducted on the 21 Dec 17 (ref MC-SR038-PQR-001), therefore making the review date January 2018 to March 2019.

4.0 Review of Key Documentation
Validation is a lifecycle that begins with a conceptual design of the manufacturing process or facility and ends with system retirement.

Validation activities and requirements are taken into account at the earliest stages of the design process.

Risk-based approach where supplier testing is leveraged and used to reduce repetitive validation testing.

Activities that support the manufacturing process such as analytical methods, and computer systems are adequately validated.

The need for periodic reviews, changes to the validated system and revalidation activities are adequately addressed.
# References

1. The principles of Orange Guide ‘Rules and Guidance for Pharmaceutical Manufacturers and Distributors’ (MHRA)

2. EU EudraLex Vol 4 -
   - Annex 15: Qualification & Validation
   - Annex 1: Manufacture of Sterile Medicinal Products
   - Annex 11: Computerised Systems
   - Part 4: GMP Requirements for Advanced Therapy Medicinal Products

3. International Conference on Harmonisation (ICH) Q9 Quality Risk Management and Q10 Pharmaceutical Quality Systems guides will be used to support the validation studies.

4. International standards, such as ISO 14644

5. ISPE GAMP 5: Compliant GxP Computerised Systems

6. ISPE Baseline Guide Vol 5: Commissioning and Qualification

7. The Genetically Modified Organisms (Contained Use) Regulations 201

8. FDA Guidance for Industry Process validation: General Principles and Practices
Quality control considerations

Doli Patel, Head of Quality Control
Quality Control Considerations
QC load Vs. Process Model
Approximately half of all cell therapy products under clinical development are autologous therapies

- **Product release - several complex assays**
- **manual and time consuming**
- **Each individual patient treatment is a separate batch that requires product release**

- Significant strain on its way for a QC facility - can limit the number of products that can be released

As companies strive to improve manufacturing processes to increase throughput the ability to release products will become an industry bottleneck
Quality Control – Strategy and Delivery

- Advanced Analytics
- Characterisation
- Biosafety
- Core QC
• Date integrity
• Validation cycles
• Staff Training
• Staff Availability
• Assay life cycles
• Modernization
• Capital Investment
References

1. The principles of Orange Guide ‘Rules and Guidance for Pharmaceutical Manufacturers and Distributors’ (MHRA)
2. EU EudraLex Vol 4 -
   - Annex 15: Qualification & Validation
   - Annex 1: Manufacture of Sterile Medicinal Products
   - Annex 11: Computerised Systems
   - Part 4: GMP Requirements for Advanced Therapy Medicinal Products
3. International Conference on Harmonisation (ICH)
   - Q2 Validation of Analytical Procedures
   - Q9 Quality Risk Management
   - Q10 Pharmaceutical Quality Systems guides will be used to support the validation studies.
4. The Genetically Modified Organisms (Contained Use) Regulations 2014
5. European Pharmacopoeia
Cell and Gene Therapy Catapult is committed to ensuring high standards of research integrity and research best practice in the activities we carry out. We subscribe to the principles described in the UK concordat to support research integrity.

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