International Society
ISCT
Cell & Gene Therapy®

Manufacturing Cellular Products Using Viral Vectors

Background (I)

- FDA guidances on cell and gene therapy products mention facilities but lack specific details on environment and workflow
- USP <1047> Gene Therapy Products
  - The facility and equipment should be carefully designed, built, and validated to support the manufacturing process and to maintain the required product/facility segregation
  - Facility requirements for performing on-site preparative steps or administration of gene therapy products depend on the nature of the products, their applications, and the manipulations required. The most important determinant of facility features is the level of risk for microbial contamination associated with each step…
- Food and Drug Administration. Center for Biologics Evaluation and Research, Guidance for Industry: Chemistry, Manufacturing, and Controls (CM) Information for Human Gene Therapy Investigational New Drug Applications (INDs) January 2020.

Background (II)

- Significant variability in facility design
- Well known, reputable institutions that hold many INDs with FDA process in rooms with both positive and negative pressure
- Movement towards closed systems but many programs still use flasks, plates, open Grex devices, etc.

Background (III)

- We aim to expand manufacturing capacity while still maintaining high product quality and regulatory compliance
- We are seeking FDA clarification on facility requirements for manufacturing cellular products with non-replicating viral vectors when using open or closed systems (e.g. Prodigy, Cocoon)
- Established regulatory requirements for small molecule manufacture have greatly helped industry
  - ISO 9001, 45001, 14001, 15378
  - 21 CFR 201, 211

Significance

- Current facility designs are largely driven by regulations intended for manufacture of traditional bulk-produced drugs
- Lack of specifications, especially for early phase facilities has created confusion
- Current manufacturing paradigms add significant cost to excessive product costs
- Confusion, education, and experience has hindered widespread adoption of cell and gene therapies

Approach

- We will explore 3 example scenarios for phase 1 or 2 HCT/P manufacturing using viral vectors and plasmids
- All questions assume proper operational controls and monitoring
- Our questions for each for the Agency:
  1. Can viral vectors be used in positive air pressure rooms ?
  2. Is bidirectional traffic an option for facilities supporting early phase CGT trials
  3. Can closed systems be used in unclassified or ISO-8 spaces?
  4. Can multiple products be manufactured in one room with workstation segregation (i.e. zones)?
  5. Does the use of different viral vectors affect facility requirements?
  6. How do plasmids/RNA electroporation influence requirements?

Scenario 1: ISO-7 Laboratory with operational zones

- Large ISO-7 positive pressure lab with multiple workstations set to manufacturing multiple patient products in same room, one product per workstation
- Bidirectional people and product flow
- Each workstation has equipment for a single product, no shared equipment.
- Sterile docking for vector/media introduction; non-sterile processes in BSC level-2.

Scenario 1: ISO-7 Laboratory with operational zones

ISO 7 Pos

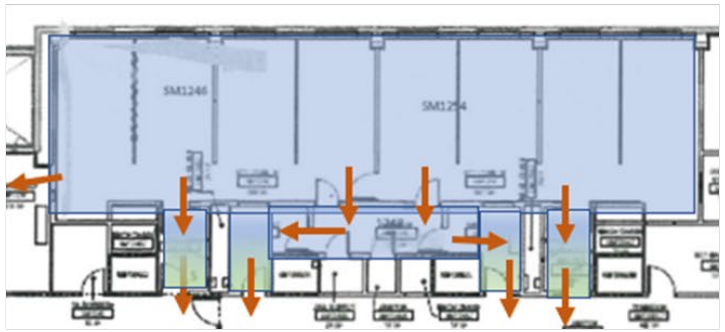
ISO 7 Neg

ISO7 +/-

ISO 7 /8-

ISO 7

Positive Air Pressure Flow Direction



Air pressurization

People Flow Bi-Directional

Bidirectional

Unidirectional

Scenario 1: ISO-7 Laboratory with operational zones

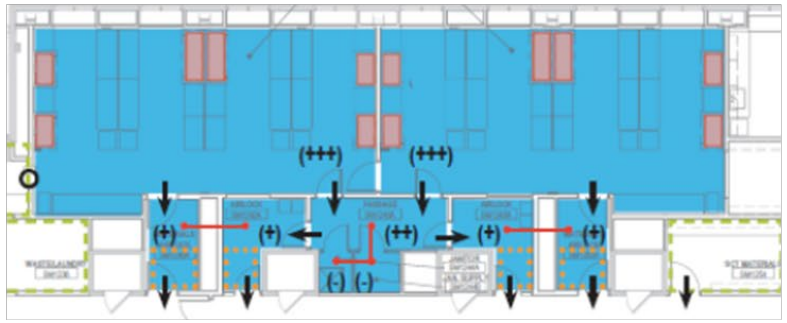
- Key Questions:
- Can multiple products be made if segregation is maintained?
- Can different viral vectors be used for separate products in the same room?
- Is there specific testing that FDA would require to demonstrate no cross-contamination or mix up?

Scenario 2: Controlled Non-Classified Laboratory

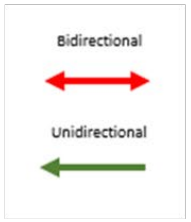
- Positive pressured but non-classified lab with multiple workstations set to manufacturing multiple patient products in same room, one product per workstation
- Each workstation is self-contained for a single product.
- Sterile docking for vector/media; no shared equipment.

Scenario 2: Controlled Non-Classified Laboratory

Air Pressure Flow Direction



People Flow Bi-Directional



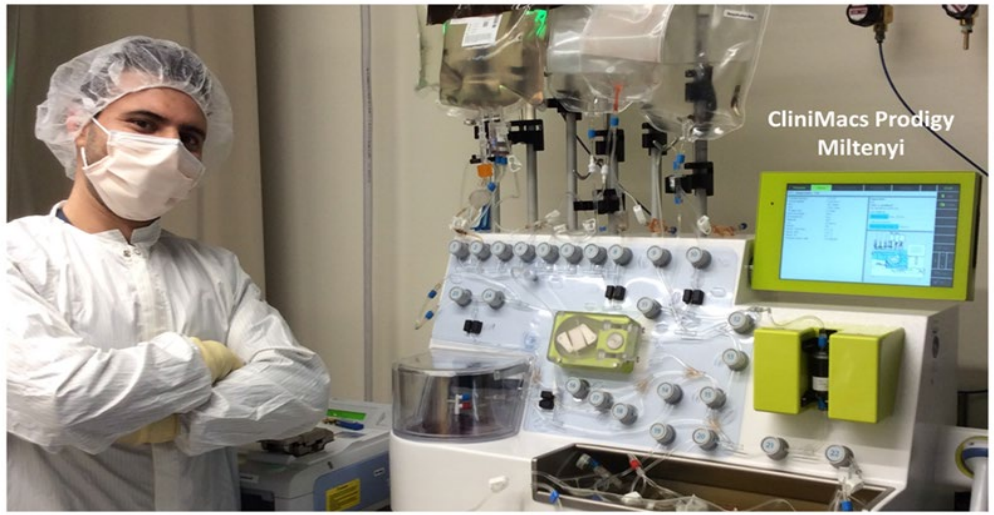
Scenario 2: Controlled Non-Classified Laboratory

- Key Questions:
- Can multiple products be manufactured simultaneously with segregation?
- Is it acceptable to use different viral vectors for products in the same space?

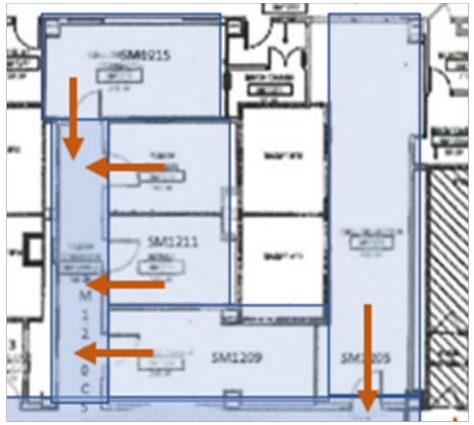
Scenario 3: Non-Classified Laboratory for Single Product

- Positive pressured, controlled space used for single-product manufacturing (pressure flow out to corridor)
- *Room* has all needed equipment.
- Sterile docking and Class-2 biosafety cabinets used for all processes.

Scenario 3: Non-Classified Laboratory for Single Product



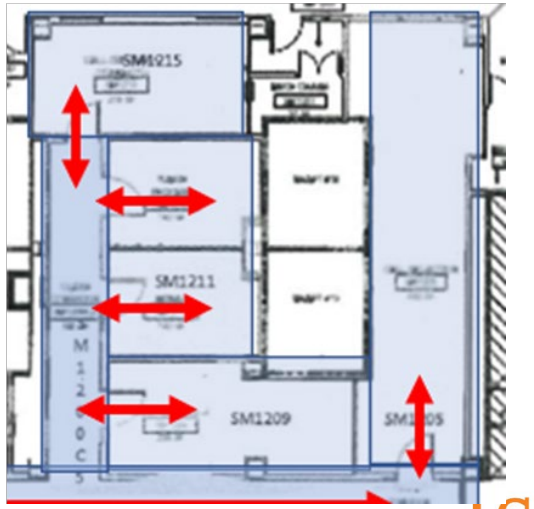
Positive Air Pressure Flow Direction



Air pressurization

Bidirectional

Unidirectional



Scenario 3: Non-Classified Laboratory for Single Product

- Key Question:
- Is positive pressure space acceptable for single-product manufacturing?

Scenario Modification: Plasmids and RNA Electroporation Impact

- Do the facility requirements differ when replacing viral vectors with plasmids or RNA electroporation?
- Are different environmental requirements applicable to closed systems in these scenarios?

Questions and Considerations

- Our questions for each for the Agency:
  - Can viral vectors be used in positive air pressure rooms ?
  - Is bidirectional traffic an option for facilities supporting early phase CGT trials
  - Can closed systems be used in unclassified or ISO-8 spaces?
  - Can multiple products be manufactured in one room with workstation segregation (i.e. zones)?
  - Does the use of different viral vectors affect facility requirements?
  - How do plasmids/RNA electroporation influence requirements?

  - Is there a way CTLM can take information from today or from informal meetings to publish a "best practices" or "how to" paper?