FDA Perspective on Commercial Facility Design for Cell and Gene Therapy Products

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Applicable Regulatory Requirements

- Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (statutory CGMP)
- Title 21 Code of Federal Regulations
  - Parts 210s -211s – CGMP for Finished Pharmaceuticals
  - Parts 600 - 610s – Additional biological products standards
- Guidance
  - Guidance for Industry: Sterile Drug Products Produced By Aseptic Processing - Current Good Manufacturing Practice (Sept. 2004)

Unique Considerations for These Products

In-vivo and *ex-vivo* gene therapy and cell/tissue-based therapy products

- Requirement for containment/isolation during viral vector manufacturing
- Requirement for protection of products from external environment

Cell therapy products

- Highly product-specific manufacturing processes with inherent variability
  - Allogeneic vs. autologous therapies
  - Cryopreserved vs. fresh final product
  - Centralized vs. near-patient manufacturing
- Final product consists of viable cells or cell-derived matrices and not amenable to final sterilization/filtration
- Aseptic techniques often required throughout manufacture
- Full test results may not be available before final release

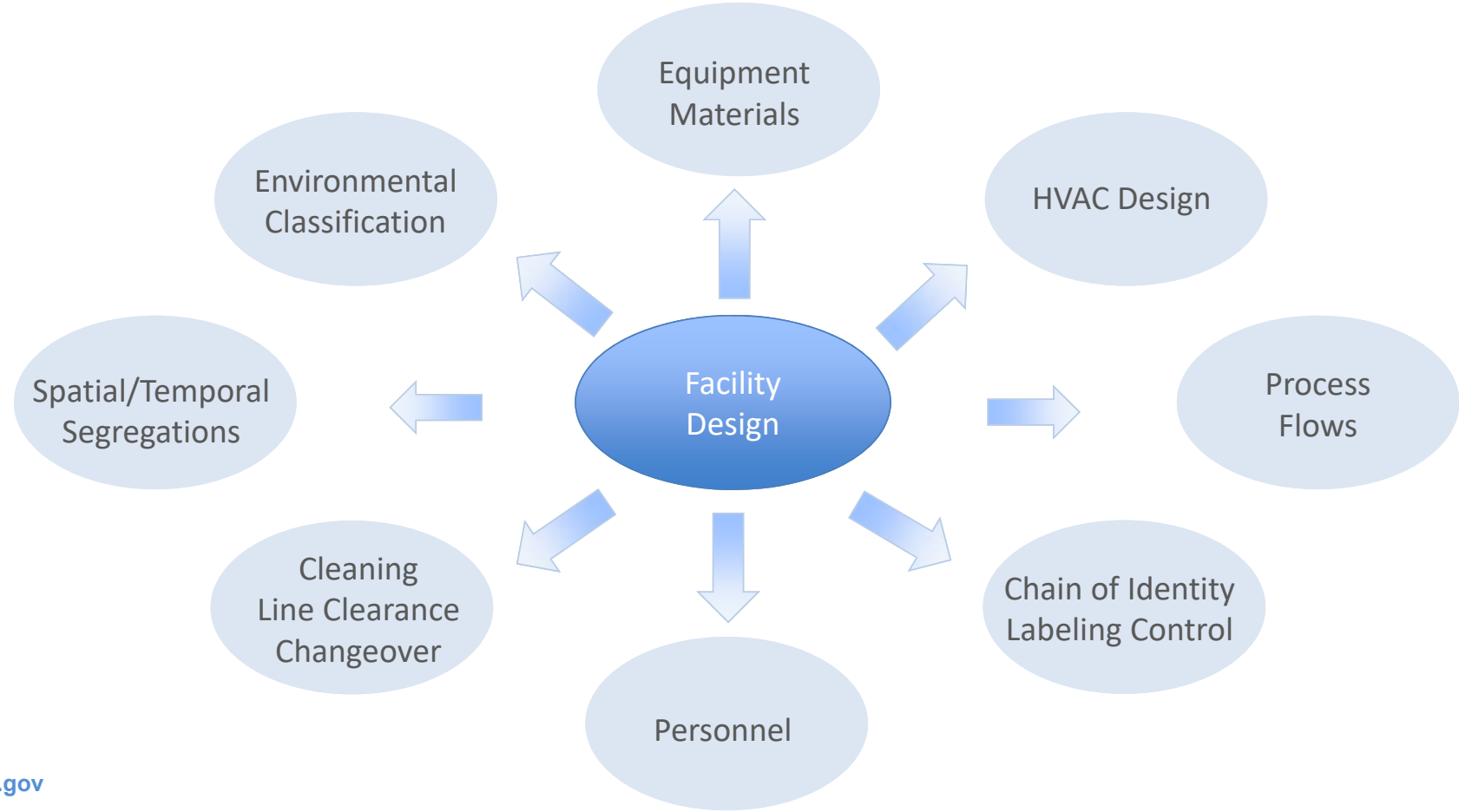
Product, Process, and Facility Design

- Facility design and layout should be appropriate for the intended operations (closed vs. open operations, aseptic processing requirements, multi-product and manufacturing capacity considerations)
    - Manufacturing suites spatially organized per process flow
    - Multi-purpose suites equipped with commonly used fixed equipment or workstations for campaign based manufacturing
    - A series of preparation suites leading to a large multipurpose “ballroom” suite where manufacturing of multiple products and/or multiple process steps take place in closed systems
    - Containment features where needed for gene therapy products
- There is no one facility design that is best - *the key is process-appropriate control and containment*

Multi-Product Facilities

- Appropriate cleaning and changeover procedures are critical
- Introduction of new products follows the change control procedure with new risk assessments
- Points of segregation may be based on product types, materials of animal origin, Biological Safety Levels, upstream vs. downstream viral vector processing
- Campaign based fumigation of manufacturing suites may be required if product is infectious
- Single-use consumables and equipment, product dedicated equipment, automated closed systems
- Implement additional segregation and containment controls if manufacturing viral vectors
    - Physical segregation within the manufacturing area, single pass filtered air, and HEPA filtration of exhaust air
    - Validated cleaning of the manufacturing area and equipment, which includes demonstration of removal of active viruses and any by-products
- *Avoid over-reliance on procedural controls!*

Contamination, Cross-contamination, Mix-up Prevention and Control



Environmental Classifications

- Environmental classifications (under dynamic conditions) are dependent on the process
    - Open process performed in a biological safety cabinet (BSC) or isolator – more stringent
    - Closed-system process based on automation, single-use technology, and aseptic connections – less stringent
- Any aseptic process, open or closed, should be validated. (i.e. media challenge)
- Specific gowning requirements are generally associated with each air classification

Open and Closed System Processing

Open processing

- Typically performed in an ISO 5 BSC in an ISO 7 surrounding
- Environmental monitoring (EM)
  - Near open manipulation inside BSC for viable and/or non-viable particulates, settling plates
  - Personnel and surface monitoring at the end of an operation/upon exiting the suite as needed
- Line clearance and changeover procedures between operations, batches, and/or campaigns

Closed system processing

- Typically performed in a functionally closed system where all material transfer is through sterile tubes connected by a tube welder or sterile aseptic connection devices (*Note: This does not include additions made through a sterilizing filter*)
- If demonstrated as closed by media challenge, this process step could be performed in controlled not classified area
- Safeguards in place if system is breached
- Critical to establish baseline EM and monitoring frequency

HVAC Design

- In general dedicated air handling units (AHU) are used for different processing areas
  - Viral vector preparation areas have a dedicated AHU that supplies single-pass air
  - Aseptic processing areas have a dedicated AHU that may supply recirculated air
  - Corridors have a dedicated AHU that supplies recirculated air
- One AHU supplying *single pass air* to multiple processing areas may also be acceptable
- Use of recirculated air for containment space may be acceptable if use is restricted to the space
- HEPA in/HEPA out HVAC systems for GMP suites to prevent contamination/cross-contamination
- Air intakes have sufficient separation from air exhausts
- Plans for containment in case of AHU failure (e.g., redundant AHUs, fail-safe isolation valves at critical duct branching points, uninterruptable power supply)
- Proper suite/airlock differential pressure (DP) design for viral vector containment, product and personnel protection, and cross-contamination prevention

Airlocks and Passthroughs

- Implementation of an airlock (AL) to interface step change in air classification is recommended
- Functional airlocks may also be used as transition spaces for the purpose of containment (i.e., to maintain DP) without a change in air classification
- Isolation of each manufacturing suite with dedicated entry/exit airlocks is recommended
  - Allows unidirectional flows and implementation of clean vs. dirty corridors
  - Allows different sanitization/decontamination procedures for personnel vs. material/equipment
  - Separates clean/dirty activities (e.g., gowning vs. degowning) and equipment, as well as waste
- Use of *HEPA filtered active* passthroughs for material transfer into or between critical areas
- Appropriate DP design for intended segregation strategy

Process Flows

- In general unidirectional flow of all process elements such as personnel, raw materials, intermediates, products, equipment, and waste is recommended
  - Parallel processing suites with entry/exit airlocks and clean vs. dirty corridors
  - If non-unidirectional, comprehensive procedural controls should be in place to mitigate cross-contamination risks
  - Appropriate restrictions in place against movement between various manufacturing suites and re-entry to the classified area
- Some form of segregation is recommended between process critical flows and waste flow
  - Spatial and temporally segregated transfer flows
  - Designated personnel for waste collection and transfer
  - Dedicated secondary containers for material/product/waste transport through shared space
  - Facility design should include a dedicated waste disposal area based on waste type and hazard

Line Clearance/Changeover

- Prevents mix-up and cross-contamination between batches/campaigns
- Clearance verified in workstation and manufacturing suite after manufacturing operation of a process step/batch/product and before initiation of a new process step/batch/product
    - Clearing of the area of previous lot (e.g., materials, equipment, labels, documents, waste)
    - Cleaning/decontamination of the equipment and area should be supported by risk assessment and supportive studies (i.e., validated cleaning, disinfecting agents/methods based on facility and cleanroom specific microbial flora profiles)
- Performed by trained manufacturing operators and independently verified
- Documented and reviewed by QA

Chain of Identity and Labeling Control

- Tracking of materials (raw, starting, intermediates, QC samples, etc.), final product, product/batch dedicated components and equipment, primary/secondary containers, pre-decontaminated waste, etc.
    - Paper-based or validated electronic traceability systems
    - Robust tracking of patient materials from receipt through the manufacturing process, storage, and shipment
    - Comprehensive tracking system for multi-product facilities to support segregation and identification
- Documented in the batch records
- All printed labels should be reconciled as part of line clearance/changeover
- In-process and release identity testing

Full-Capacity Analysis

- Perform capacity analysis to determine the limits of scalability and robustness (e.g., number of lots and products that can be manufactured concurrently on site, in the same production areas, and/or same production suites)
- Capacity bottleneck points may include:
  - Facility and equipment
  - Trained operators
  - QC testing
  - Logistics
- Understand overall capacity and implement phased expansion with re-assessment performed at each phase
- Built-in design possibility and flexibility for incremental additions of capacity is recommended
- Can be leveraged to support concurrent manufacturing schemes

Case Study #1

Multi-Viral Vector Manufacturing Facility

- Products:
  - Viral vectors for *In vivo* and *ex vivo* gene therapies
- Process:
  - Aseptic upstream cell expansion and transfection occur in cell culture suites; aseptic downstream purification occur in purification suites; aseptic viral vector fill/finish in filling suites (no sterile filtration of the bulk prior to fill)
  - Open manipulations are performed inside a ISO 5 BSC in a ISO 7 suite
- Facility layout:
  - Central viral vector filling suites flanked by purification and cell culture suites
  - Unidirectional flows

Case Study #1

Multi-Viral Vector Manufacturing Facility

- HVAC:
  - Dedicated AHUs for each manufacturing suite supplying 80% recirculated air that is restricted to each suite. Isolation dampers are installed on supply and exhaust air ducts to seal/segregate in case of emergency or failure.
  - For each manufacturing suite, entry personnel airlock/material airlock (PAL/MAL) "bubble" positively while exit PAL/MAL "sink" negatively with respect to the common corridor and suite
  - ALs between the ISO 7 suites and CNC corridor are comprised of a double-airlock system to interface multi-step change in air classification and provide robust isolation
- Labeling control:
  - QA prepares pre-printed labels prior to operation and reconciles all labels during line clearance
  - Labeling required for equipment, single-use tube sets, QC samples, intermediates, primary and secondary containers, transfer carts, etc.
  - Secondary verification and documentation in batch records

Case Study #1

Multi-Viral Vector Manufacturing Facility

- Manufacturing schedule:
  - Campaign based manufacturing of different viral vector products in the same suite with appropriate line clearance/changeover procedures between campaigns
  - Concurrent manufacturing of multiple products in separate suites
  - Concurrent manufacturing of multiple batches of the same vector product in the same suite with appropriate line clearance between operations
  - Only one batch can be openly processed at a time in an ISO 5 BSC

Case Study #2

Multiple Ex-vivo Gene Therapy Product Facility

- Products:
  - Autologous *ex-vivo* gene therapy products
- Process:
  - Aseptic processing of autologous patient cells, including cell selection, activation, transduction, expansion in bioreactors, harvest, formulation, and fill/finish
  - Open manipulations are performed inside a ISO 5 BSC in ISO 7 suites
- Facility layout:
  - Parallel autologous patient cell processing suites with common corridors
  - Each suite is equipped with multiple workstations (a workstation consists of a BSC, bead separator, incubators, centrifuge, tube welder, etc.)
  - Unidirectional flows

Case Study #2

Multiple Ex-vivo Gene Therapy Product Facility

- HVAC:
  - Dedicated AHUs for each manufacturing suite supplying 80% recirculated air
  - For each manufacturing suite, entry/exit PAL/MAL cascade positively relative to the corridor
- Labeling control:
  - A validated electronic traceability program based on barcoding is in place
  - Each label contains multiple unique identifiers (e.g., patient ID, lot #, process #)
- Manufacturing schedule:
  - The use of a suite is product campaign based (i.e., same viral vector)
  - Multiple patient batches can be concurrently manufactured at the different workstations in the same suite
  - Only one patient batch can be openly processed at a time in an ISO 5 BSC of a workstation with proper line clearance/changeover after each processing step, but concurrent open processing of different batches may occur in different workstations in the same suite by dedicated operators

Facility Meetings with DMPQ

- Facility and equipment layout
- Product (commercial or clinical) and process mapping with regards to suites
- Appropriate risk evaluations and capacity analysis
- Concurrent manufacturing schemes
- Segregation, containment, and cross-contamination/mix-up prevention strategies including engineering, temporal, procedural controls
  - Flows (personnel, material, product, equipment, waste, etc.)
  - HVAC diagrams (AHU zoning, room classifications, room pressurization with illustrative directional arrows)
  - Cleaning/line clearance/changeover procedures
  - Labeling and tracking procedures
- Agency references:
  - *FDA SOPP 8101.1 "Regulatory Meetings with Sponsors and Applications for Drugs and Biological Products"*
  - *2018 Draft Guidance "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry"*

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