Aseptic Fill / Finish Facility Design for Compliance

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Agenda

• Review Compliance Drivers and Problems
• Review Operational Realities and Process
• Focus on architectural
• Focus on HVAC
• Building a robust facility / checklist
• Exploring alternative designs and buildings
Application

- “Brownfield” expansion
- Expansion
- Retrofit
- Replacement and required up-fit
- Aseptic conversion to multi-product
- OSD conversion to aseptic
- Introducing potent compounds (anywhere)
General Compliance

- Annex 1 – EU in the lead
- Sterile Drug Products Produced by Aseptic Processing - CGMP September 2004
- Key design liaison and relationships for new facilities
- Recurring themes:
  - Applicability (built for purpose)
  - Safety
  - Environmental
  - Containment (BSL - ?)
  - Bioburden / Contamination
  - Cross Contamination
Dealing with other Compliances

- OSHA/NIOSH/NIH/CDC
- Containment Types
- Safety of handling (in, during, and out)
- Personnel exposure
- Pressurization and HVAC
- Waste Handling
- Decontamination practices if needed
General Philosophy

- Process Location and Contain It
- Grey Space / White Space
- Architectural Layout
- Architectural Finishes
- HVAC classifications
- HVAC design
Process Core Considerations I

• The actual area where the operators interact with the process should be kept to an absolute minimum
• Operations use vs. Design Intentions (MAL / PAL)
• Restrict operator use by design!
• Only connections / sample ports and filter housing should be in operating area (white space/classified)
• Vessels need to be grey space (unclassified)
• Risk assessment on contamination should be made to decide how much of the process should be co-located
• Major process steps must be are separated to minimize risk / BSL levels, multi-products
• Self contained full process / product suites (“all in”)
Schematic Section GMP Spaces

- Piping Distribution
- HVAC Distribution
- Tech/Mechanical Spaces
- Mixing Areas, Bioreactors, etc.
- Unclassified Corridor
- Plant Uniform
- Full Gown Class 100 for operator duties and connections.
- GMP Gown Class 100,000
- Many Air Locks 100,000 to 100
- Corridor 100,000
- Process Room 100
- Process Equipment
PC II

• Bag technology for solutions eliminates the cleaning validation and minimizes vessels
• Less cleaning means less water, disposal, footprint
• Disposables are the new key to processes and can replace most fixed vessels
• Pre-sterilized hoses, ports, and connections can reduce classified space and operator interaction and potential contamination
• Transfer ports, formulation isolators, and disposable isolators for manipulation blend and sample.
• Flexible bags / peristaltic pumps / disposable filler systems (nozzles/heads/etc.)
PC Summary

• Define the process, vessels, and flow pattern
• What is the work pattern of the operators (in, work, sample, change filters, take a break, record data, out)?
• Get the paper out – use DCS/PLC/MES/EBRS – wall mounted screens – no desktop PCs – ever!
• Consolidate the number of steps and operator actions
• Consolidate the equipment footprint, and the footprint within the classified space (focus on a singular space)
• Use grey space liberally
• Keep any wash areas away from process and people traffic
• Cyto toxic materials and toxins should be restricted into a single room that is self contained (HEPA in/out, BIBO)!
Architecture / Layout
Architecture

- Unidirectional Flow:
- People
- Equipment (should anything be mobile and if so how do we move it) - design to constrain it in a pattern
- Raw material / Intermediates
- Product
- Waste (yes it flows, design needs to control it!)

- Layout of the physical plant must follow the logic of the operational steps
- Washing / Sanitizing / Sterilizing must be in an accessible but separate suite – not near people traffic
- Weigh / Dispense should be handled in a separate suite, accessible – not in the warehouse.
Architecture II

• Unidirectional flow eliminates cross over and confines bioburden or contamination
• No cross over corridors- separate in/out of locker room
• Gowning and Degowning are separate
• Transitions from one classification require an airlock and some gowning upgrade
• Regardless of type of process, operators must work in a unidirectional mode and within each room/suite as a node (no back tracking)
• An effort must be made to fix the equipment in place not move it around the plant
• Using what we said in the process area----→
Architecture III

- Clockwise or counter clock circular motion
- Equipment and personnel do not share airlocks
- Equipment and material can share the MAL
- Operators put in material / equipment into the MAL-sanitize it and wait
- Operators already in side the suite pull the equipment/material into the suite
- Waste ejection systems must be evaluated, any and all waste movement in the facility must be minimized. An alternative is autoclaving
- Build an office environment within an aseptic area?
Filling Rooms Detail

Class 10,000

Class 100,000

Local Class 100
Architectural finishes - floors

- Hard finish polymer floor systems – poured on epoxy, epoxy terrazzo, Stonehard or NORA.
- Coving up the wall, beaded seal to wall
- Smooth application, not polished, not gritty – orange peel
- Not painted on epoxy
- Watch for multi-layer application
- No drains / traps or clean outs in most classified operating areas
- In a retro-fit, class 100,000 & CNC – all floors fittings should have SS plate with gasketed O ring seal
Architectural Finishes – walls

- Polymer wall systems only
- The epoxy painted gyp board does not last and absorbs moisture
- Mipolam, Trakion, even FRP board
- Smooth seamless and caulked seams only
- Any non-lighting fixtures should be wall mounted (sprinkler heads, speakers, fire or smoke sensors, cameras, door alarms, HVAC alarm lights, etc).
- Fit and finish is key with no potential infiltration of air
- Mold loves gyp board!
Architectural Finishes Ceilings

• Polymer ceiling system with integrated tear drop lighting/HEPA system
• Gordon gasketed ceiling
• No ceiling penetrations!
• Sealed and caulked to wall
• HEPA installation is sealed / clipped to ceiling correctly
• No ceiling penetrations!
Architectural Finishes - other

- Autoclaves – bioseals and steel wall panels
- Doors / Door Seals / Door sweeps
- Observation windows
- Drains and sloped floor in wash areas
- Drain seals

- WOOD?
- Residential Grade Gyp Board?
- Cellulosic fiber insulation?
HVAC
Key functions

- Maintaining Grade A for product exposure
- Proper background B for A operation
- Bioburden
- Separation for risk reduction
- Airlocks, air sinks, air!
## Air Change Rates and Distribution Parameters

<table>
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<tr>
<th>Class ISO 146144-1 (Federal Standard 209E)</th>
<th>Average Airflow Velocity m/s (ft/min)</th>
<th>Air Changes Per Hour</th>
<th>Ceiling Coverage</th>
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<tr>
<td>ISO 8 (Class 100,000)</td>
<td>0.005 – 0.041 (1 – 8)</td>
<td>5 – 48</td>
<td>5 – 15%</td>
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<td>ISO 7 (Class 10,000)</td>
<td>0.051 – 0.076 (10 – 15)</td>
<td>60 – 90</td>
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<td>ISO 6 (Class 1,000)</td>
<td>0.127 – 0.203 (25 – 40)</td>
<td>150 – 240</td>
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<tr>
<td>ISO 5 (Class 100)</td>
<td>0.203 – 0.406 (40 – 80)</td>
<td>240 – 480</td>
<td>35 – 70%</td>
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<tr>
<td>ISO 4 (Class 10)</td>
<td>0.254 – 0.457 (50 – 90)</td>
<td>300 – 540</td>
<td>50 – 90%</td>
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<tr>
<td>ISO 3 (Class 1)</td>
<td>0.305 – 0.457 (60 – 90)</td>
<td>360 – 540</td>
<td>60 – 100%</td>
</tr>
<tr>
<td>ISO 1 – 2</td>
<td>0.305 – 0.508 (60 – 100)</td>
<td>360 – 600</td>
<td>80 – 100%</td>
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</tbody>
</table>


ISO 5 = Grade A  
ISO 7 = Grade B  
ISO 8 = Grade C
In concert with the architectural layout the HVAC is key in all pharm/bio installations

Key factors:
- Isolation
- Segregation
- Pressurization
- Distribution
- Computation Fluid Dynamics (CFD)
- ACR (air change rate)
Isolation

• Isolation means the unique process suite should be isolated from the other suites via air flow and pressurization

• Conceptually this will allow any contamination or bioburden within a suite to remain isolated within the suite

• This also allows singular products within a multiple product plant to be isolated within a suite avoiding cross contamination

• This is accomplished by HVAC pressurization and the use of “air sinks”
Segregation

- Segregation refers to the separation of HVAC AHU controlling the processing suites.
- The plant design needs to execute a risk assessment to determine the impact in the event of a failure of a single AHU.
- A single AHU should only impact one process train or one process suite or one product in a multi-product facility.
- In addition, segregation refers to an AHU providing service air (supply and return) for only one product maximum, and generally one process step.
- Also, this applies to one BSL level within a multi-BSL level facility (one AHU for BSL-1, one for BSL-2).
Pressurization

- Pressurization schemes provide the mechanism to control the air flow, infiltration of clean HEPA filtered air, control the direction of particulates, and enable the isolation of products.
- Pressurizations should focus on having a clean interior process suite that is “contained” by air sinks for product control.
- Pressurization must also cascade down through the facility and the pressurize the air out from the facility to prevent external contaminants from entering in the critical process area.
- Pressurization must also act to provide a net negative internal pressure for cytotoxic compounds, chemical toxins, and other potent compounds.
Modified BSL / Toxin Containing Suite Pressurization Scheme

Standard Pressurization Scheme

Note the airlocks are air sinks
Distribution

- Air distribution within any room must be designed and not left up to a field HVAC installer!!
- Air distribution must be designed after the process vessel/equipment/piping and interior fit is confirmed
- 3D CADD design to control utility interaction/clash
- HEPA air supply must be ceiling mounted with the proper diffusers to provide a laminar flowing air “blanket” (CFD calc for coverage, direction and velocity)
- The air must force particulates down consistently around all the vessels and work surfaces
- All HVAC returns should be FLOOR LEVEL returns, integrated with the flooring and termination of the walls. There is no need for register grills
- Floor level does not mean knee height nor ankle height
Remediation of HVAC

- Focus on reduction of supply register velocity
- Increase the number of supply registers
- Careful of equipment and people location
- Selection of supply diffusers (2x2, 2x4, angle, pattern)
- Increasing the number of return registers
- Return registers have only vertical (floor) intake
- Block undersides of tables and equipment with SS sheet
- Keep the floors clean
What and How to Build

- On-site “stick-built” is an option that is declining due to construction time, cost, time to market, validation and quality
- Modular systems- prefabricated walls and utilities and assembled below a “built from scratch” HVAC matrix. These are factory sections built (without floors), disassembled, shipped and reassembled on an enclosed GMP floor. Too much control over the interstitial area
- Podular systems – prebuilt facilities (all inclusive with HVAC, utility drops, fire suppression, floors, scales, floor drains, etc.) that are built, qualified and shipped entirely whole and intact. They are set on a slab within a building shell.
Past Facility Models

- Traditional Hardwall
- Offsite Built Modular
- Modular - Stick Built
- Isolator Based (e.g. CEM)

lead to
Standard POD Base Design

Mechanical Area - accessed from “grey space”

Gown In / Gown Out Area and Equipment Pass through
- Optional: adds 108 ft² when it is part of the connecting hallway
Benefit Case – Scaling

- Scaling without interruption
- Opportunity to delay time to investment
- Unidirectional flow and corridor incorporated
Conclusion

- PODs represent a Paradigm Shift in Biopharmaceutical Production Area Designs and Implementation:
  - Autonomous & Agile
  - Efficient Designs & Process Flows
  - Faster Time to Run
  - Repurposing of the Processes or Unit Operations
  - Rapid Deployment & Mobility
  - Ease of Scalability to Adjust Capacities
  - Multi-Product Flexibility

- Ultimately, this application meets the demand of the biopharmaceutical industry for cost efficient, flexible processing & facility solutions
Questions/Discussions