

CURRENT REGULATORY ISSUES IN FACILITY DESIGN

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Don Hill

Don Hill & Associates, Inc.

301-260-2200

www.donhillassociates.com/

MULTI-USE FACILITIES

- **IN TODAY'S WORLD, THE USE OF ONE FACILITY FOR ONE PRODUCT IS BECOMING A RARE CONCEPT**
- **PRODUCTION OF MULTIPLE PRODUCTS AT SIMILAR STAGES OF MANUFACTURE IN A COMMON AREA**
- **MANUFACTURE OF SINGLE PRODUCT (MULTIPLE LOTS) AT VARIOUS STAGES OF PRODUCTION WITHIN A COMMON AREA**
- **USE OF FACILITY FOR DIFFERENT PRODUCTS ON A CAMPAIGN BASIS**

CONCERNS FOR MULTI-USE FACILITIES

- **CONTAMINANTS INTRODUCED THAT ARE DIFFICULT TO DETECT**
- **CROSS-CONTAMINATION BETWEEN PRODUCTS**
- **WORKERS ALTERNATING BETWEEN TWO OR MORE PROCESSES**
- **PREPARATION OF “UNKNOWN” MATERIALS WITHIN A PRODUCTION FACILITY**
 - ... **RESEARCH MATERIALS**
 - ... **CONTRACT OPERATIONS**
 - ... **INVESTIGATIONAL BATCHES (early stage)**

CHARACTERISTICS OF BIOLOGICAL PRODUCTS

- **Derived from living organisms or components of living organisms.**
- **Complex, large molecules, often heterogeneous.**
- **Historically, biologics have been difficult to assay and quantitate.**
- **Heat sensitive; subject to shear stress.**
- **Subject to contamination from many sources.**

MULTIPRODUCT FACILITIES

- **Must have a good facility design that allows for: adequate separation of manufacturing activities, the proper flow of materials and product, the appropriate level of containment, and movement of personnel within the facility.**
- **Must have good plant systems, especially those systems that could affect directly the purity or integrity of the manufactured product (i.e., HVAC, Water, Sterilization and Biowaste).**
- **Must have a good program established for the validation of equipment, systems, manufacturing processes, and especially the validation of the effectiveness of the procedures for cleaning non-dedicated equipment and supplies during product changeover.**

MULTIPRODUCT FACILITIES

- **Must have good calibration and preventive maintenance programs in place.**
- **Must have a good environment monitoring program in place to routinely monitor the quality of air and water, especially during product manufacturing activities.**
- **Must have a good personnel training program so that operators are fully trained in cGMPs and in the necessary skills and techniques to perform their assigned functions. Awareness of the unique properties of biological products and their potential impact on a manufacturing process should be stressed in any training program.**

MUST HAVE A GOOD FACILITY DESIGN

- **Adequate Separation of Manufacturing Activities**
- **Proper Flow of Materials and Product**
- **Appropriate Level of Containment**
- **Proper Flow of Personnel**

Facilities for the Manufacture of Clinical Materials for Human Use

- **Should be in compliance with the “concepts” of cGMPs**
 - **with the manufacture of materials for Phase I studies**
- **“Full” compliance by Phase III/market**
- **General Considerations for Facilities and Compliance with cGMPs**
 - **Nature of product and production process**
 - **Specially design or regulatory requirements?**
 - **constraints, safety features**
 - **Scale-future capacity, transition parameters?**
 - **Clinical Pilot Facility Only? Or Future Licensed Facility??**
 - **Multi-Use Facility?**

SUITABLE BUILDING MATERIALS

- **Smooth, cleanable surfaces**
- **Impervious to sanitizing agents**
- **Resistant to deterioration**
- **Sealed joints**
- **Coved corners**
- **No exposed piping**

FACILITY DESIGN CONSIDERATIONS

- **Open manipulations with one cell line per area at a time**
- **Open steps performed in a biosafety cabinet (Class 100 conditions)**
- **HEPA-filtered air/Class 100,000 or 10,000 room conditions**
- **Hoods cleaned between cell line manipulations**
- **Personnel appropriately attired for room classification**
 - **Lab coat/tyvek gown/hair cover**
 - **Sterile gloves/mask with open steps**

LOGISTICS

- **Sufficient space for equipment and processes**
- **Separate or well defined areas for manufacturing processes**
 - **Time (procedural)**
 - **Space (separate, dedicated areas)**
 - **Air system control (containment areas)**
- **Flow patterns**
 - **Two corridor system**
 - **Single corridor system**
- **Adequate storage available for clean and dirty equipment and in-process materials**

ASEPTIC PROCESSING

- **ASEPTIC PROCESSING: Product, container and closure are subjected to sterilization processes separately and are then brought together**
- **Because there is no further processing to sterilize the product in its final container, it is critical to produce biological products by aseptic processing from early stages of manufacturing.**
 - **0.22u-filtration steps?**
 - **Endotoxin removal steps?**
 - **Environmental control?**
- **There are more variables and potential failures for aseptic processing than for terminal sterilization.**

MATERIAL FLOW

- **Questions to ask:**
- **Suitable areas for quarantine/release?**
 - **Raw materials and components**
 - **In-process intermediates**
 - **Bulk material (API)**
 - **Final product**
- **Logical flow through facility?**
- **Hard piped versus vessel transport?**

REGULATORY CONSTRAINTS

BUILDING RESTRICTIONS ON MANUFACTURING

- **Infectious agents (plasma fractionation)**
- **Penicillin/Cephalosporins**
- **Live vaccines**

REQUIRES

- **Suitable design of facilities/air systems**
- **Restricted work areas or separate building**

PERSONNEL FLOW

Questions to ask:

- **Restricted access?**
- **Adequate gowning areas/levels?**
- **Segregation of different functions?**
 - **animal handling, glassware washing, production, filling operations**

EQUIPMENT CONSIDERATIONS

- **Class/Type: Disposable, Dedicated, Shared**
- **Dedicated:**
 - Properly identified/labeled/stored
 - Adequate maintenance and calibration
 - Documented use (logs)
- **Shared:**
 - Appropriately design for >1 product/host
 - Easily cleaned and sterilized
 - Properly identified as to use and status
 - Rigorous maintenance and calibration program
 - Documented use (logs) and changeover procedures

EQUIPMENT FLOW

Questions to ask:

- **Adequate segregation of clean/dirty equipment?**
- **Appropriate areas for decontamination and cleaning?**
- **Adequate areas for storage of equipment when not in use?**

Must Have Good Plant System

- **HVAC**
- **Water**
- **Sterilization**
- **Waste Treatment**

AIR HANDLING SYSTEMS

- **HEPA filtration**
 - **In-line**
 - **Terminal**
- **Single pass air**
- **Recirculated air**

H.V.A.C. SYSTEM

- **Classification of Air Quality (ISO Class Standards) ex., Class 10,000 (ISO 7) –dynamic conditions**
- **Maintaining Proper Airflow from Areas of Higher Air Cleanliness to less Clean Areas.**
 - **Pressure Differentials, Airlocks**
- **Number of Air Changes**
- **Temperature Control**
- **Humidity Control**

TEMPERATURE AND HUMIDITY CONTROL

- **High humidity and temperature increases perspiration and personnel shedding**
- **Rusting of equipment and parts can occur at humidity above 60%**
- **Low humidity (35-50%) enhances electrostatic entrapment capabilities of filters**
- **Low humidity (35-50%) helps prevent growth of molds**

WATER SYSTEMS

- **Potable Water**
- **Purified Water**
- **Water for Injection**

Water Use

Cell Propagation and fermentation/recovery for Bacterial systems

Purification for Bacterial Systems

Cell propagation and fermentation of bacterial products using poorly defined medium:

Cell Culture Fermentation/ Recovery and Purification

Required Water Quality

Purified Water USP quality

Water for Injection USP

**Potable Water
Purified Water**

Water for Injection USP

Water Use

Parenteral operations

In-vitro diagnostics

Required Water Quality Cont'd

**Water for Injection
USP**

**Purified Water USP
Quality**

STERILIZATION SYSTEMS

Facility should be provided with adequate sterilization systems for the containment and aseptic processing areas

- **Autoclaves for Moist Heat Sterilization**
- **Dry-heat Ovens for Depyrogenation**
- **Use of Double Doors for Appropriate Materials Flow**
- **Separate Systems for Decontamination Recommended**
- **Sterilized Materials should “Cool-Down” Under Controlled Air**
- **Validation Studies Should Include:**
 - **Empty Chamber Studies**
 - **Representative Loads**
 - **Challenge Studies, as appropriate**

WASTE TREATMENT

LIQUID WASTE

- **Is the capacity of waste reservoirs adequate for full-scale production? Safeguards for preventing backflow?**
- **Are decontamination procedures validated using appropriate challenge(s)?**

SOLID WASTE

- **Are there separate autoclaves for clean use vs. decontamination?**
- **Frequency of Removal from Manufacturing Areas.**
- **Adequate Dedicated Space for Storage Before Decontamination?**

WASTE FLOW

Questions to ask:

- **Separation from product/personnel flows?**
- **Decontamination of materials from contained areas?**
- **Sterilization process separate from decontamination process (particularly for product contact equipment)?**

EQUIPMENT CALIBRATION AND MAINTENANCE

- **Frequency of Calibration (including laboratory instruments)**
- **Records of Calibration**
- **Preventive Maintenance Program**
 - **Facilities**
 - **Systems**
 - **Major Equipment**
 - **Frequency**
 - **Documentation**
 - **Contracted Services**

Must Have a Good Validation Program

- **Equipment**
- **Systems**
- **Process**
- **Cleaning**
- **Assay**
- **Computer**

FACILITY VALIDATION MASTER PLAN

The plan should define the company's approach/philosophy and management's commitment to the validation program.

The following parameters should be included:

- Pre-validation engineering design**
- Construction validation**
- Facility qualification**
- Utility systems qualification and validation**
- Equipment qualification and validation**
- Documentation**
- Calibration/Maintenance**
- Revalidation**

FACILITY QUALIFICATION

- **Equipment-System IQ, OQ and PQ**
- **Critical vs. Less Critical**
- **Critical Systems**
 - **Air**
 - **Water**
 - **Clean Steam**
 - **Process Gases**
 - **Biowaste Kill**

FACILITY QUALIFICATION CONT'D.

- **Critical Equipment**
 - Autoclaves, Ovens
 - Bioreactors, Lyophilizers
 - Product Storage (Refrigerators, Freezers)
 - Cell Bank Storage (Nitrogen Freezers)
- **FDA Expectations for Manufacturing**
 - Phase I Clinical Materials
 - Phase II Clinical Materials
 - Phase III Clinical Materials

CLEANING VALIDATION

- **Product Lots Should be Tested for Residuals of Previous Manufactured Lots**
 - Especially when equipment is shared with other products.
 - “Spiking” experiments to show detection of “old” product residuals in “new” products.
 - Validated assays should be used for determining levels of detection.
 - Residual cleaning agents (detergents) tested.
- **Intended Patient Population of Product**
 - a. Should be considered when examining levels of residuals from previous product campaigns
- **FDA Expectations**
 - Phase I, II, III Clinical Materials
 - Licensed products

“TAKING OWNERSHIP”

Be Responsible for the

- **Operations Performed**
- **Equipment and Work Areas**
- **Adhering to SOPs and Documentation**
- **Supervisory Role – Personnel Training**

CHANGEOVER PROCEDURES FOR MULTIPRODUCT FACILITIES

- **Removal of all product, process materials and disposable equipment from the processing area**
- **Equipment that is dedicated to a single product is adequately identified, cleaned and removed from processing area to a controlled storage area.**
- **All non-dedicated equipment that remain in the processing area are cleaned using validated cleaning agents. Protective covering during non-use.**
- **A close out inventory (checklist) is conducted to assure that all materials, documents, equipment and SOPs have been properly attended to and completed. Processing areas approved for the next product campaign by Quality.**

FDA INSPECTION OF SYSTEMS

- **Quality Systems**
- **Facilities and Equipment System**
- **Materials System**
- **Production System**
- **Packaging and Labeling System**
- **Laboratory Control System**

THE FDA “SYSTEM” APPROACH

- **Inspection coverage of 2 or more systems with mandatory coverage of the Quality System**
- **A shift from product orientation inspection to focus on acceptability/non-acceptability of systems put in place by manufacturers to resolve and prevent deviations/problems**
- **Intended by FDA to enhance efficiency and consistency of inspections and to optimize the use of FDA inspection resources**

FACILITIES AND EQUIPMENT SYSTEM

- **Facilities**
 - **Facility Layout and Air Handling Systems**
 - **Sanitation and Maintenance of the Building**
 - **Documented Procedures for Implementing Changes to the Facilities, Utilities, Equipment**
 - **Plant Shutdown and Start-Up Procedures**
 - **Water for Production Use, Equipment Cleaning**

KEY CONCERNS OF FDA

- 1. Cross-contamination**
 - **Generation of aerosols (spills, equipment leakage)**
 - **Campaigning within the same area**
 - **Concurrent production**
- 2. Potential for mix-ups and microbial contamination**
 - **Inadequate segregation - restricted access**
 - **Open processing – air quality/monitoring**
- 3. Lack of Facility Controls**
 - **Area clearance/cleaning/inactivation**
 - **Personnel training/qualification**
 - **Good documentation practices**