Validation of Biotech Facilities

Pacific Biotech Alliance

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Introduction and Background

Pacific Biotech Alliance is an established consulting firm in the Pacific Northwest that specializes in Biotech, Pharmaceutical, Medical Device and Diagnostic manufacturing, operations, facility construction & validation….

Robert J. Mackey has over 33 years of experience in the biological business with over 20 successful FDA inspections for facilities and operations….

WBBA presenter, course leader and events coordinator. Member and course coordinator for ISPE. Shoreline Community College Skills Panel Chair for Manufacturing Excellence.

Section 1

Facility Design, Construction and Validation

- **ISO 14644 and European Guidance Docs**
- **FDA Guidance**
- **Commissioning**
- **Design Qualification**
- **Risk Based Validation**
- **Equipment Procurement and Placement**
- **21 CFR Part 11 Compliance**
- **FDA Inspections & EIRs**

ISO 14644 and European Guidance Docs

- **Harmonized standard with multiple indexes**
- **HVAC Focused**
  - **Classifications from 1 to 9**
  - **Particle testing**
  - **Air Pressure Differential**
  - **Air Change Rate**
  - **Temperature and Humidity**
  - **Installed Filter Leakage**
  - **Containment Leakage**
  - **Recovery**
  - **Airflow Visualization**
- **Orange Guide:** **Rules and Guidance for Pharmaceutical Manufacturers and Distributors: The Orange Guide**

FDA Guidance

- Aseptic Processing Guidance, Section IV
- Buildings and Facilities
  - Critical Areas (Class 100 ISO Class 5)
  - Adjacent Areas (Class 10,000 ISO Class 7)
  - Support Areas (Class 100,000 ISO Class 8)
  - Clean Air Separation
  - Air Filtration
- Design
  - Optimize Material and Personnel Flow
  - Equipment Placement and Flow
  - Waste flow

Commissioning

- Critical Vs. Non-Critical
- Product Contact
- Heavy Vs. Light
- Prelude to Qualification and Validation

Design Qualification

- User Requirements
- Design Specifications
- Verification of Design Parameters
- Support to Validation
- Calibration
- Certification

Risk Based Validation

- Validation Master Plan
- Risk Assessment
- Justification Procedure
- cGMP
  - 21 CFR 210-211
  - 21 CFR 820
  - 21 CFR 600
  - Q7A
- IQ, OQ, PQ
- Requirements Traceability Matrix
- Validation Summary Plan

Equipment Procurement and Placement

- **Validation Master Plan-Systems to Validate**
- **Justification Procedure**
- **How and where to place inside facility**
- **Calibration and Certification**
- **RDS, IQ, OQ, PQ, CV**
- **Requirements Traceability Matrix**
- **Validation Summary Plan**

21 CFR Part 11 Compliance

- **Electronic Records**
  - **Building controls**
  - **Computer Controlled Process Equipment**
  - **Computer Controlled Analytical Equipment**
  - **Spreadsheets**
- **VP & RDS**
- **IQ, OQ, PQ,**
- **Requirements Traceability Matrix**
- **Validation Summary Plan**

FDA Inspections & EIRs

- **Know the inspection process**
- **Know inspector's methods (see attached MS Word File)**
- **Establishment Inspection Reports (EIRs)**
  - **Freedom of Information (Other Companies)**
  - **Resolve all 483 citations**
  - **Don't make the same mistakes**
- **Know cGxP (GMP, GLP, GCP, GEP)**
- **FDA Eases Phase I Manufacturing Requirements (See Attached MS Word File)**

Section 2
Validation of Biotech Facilities, Equipment, Utilities and Process
Introduction

- **Validation Defined**
- **When is Validation Typically Required?**
- **Master Validation Plan (MVP)**
- **Systems to be Validated**

Validation of Biotech Facilities, Equipment, Utilities and Process
Introduction Cont'd

- **Installation Qualification (IQ)**
- **Operational Qualification (OQ)**
- **Performance Qualification (PQ)**
- **Other Definitions**
- **Facility Validation Requirements**
- **Utility Validation Requirements**
- **Process Equipment Validation Requirements**

Validation of Biotech Facilities, Equipment, Utilities and Process
Introduction Cont'd

- **Validation of Support Processes**
- **Aseptic Filling Validations**
- **QA/QC Laboratory Validations**
- **Cleaning Validations**

Validation of Biotech Facilities, Equipment, Utilities and Process
Introduction Cont'd

- **Compliance Programs and Procedures**
- **Revalidation**
- **Clinical Phases of Validation Compliance**
- **FDA Expectations**

Validation of Biotech Facilities, Equipment, Utilities and Process
Validation Defined

Establishing documented evidence that a manufacturing process, piece of process equipment, utility system, computer system or test method routinely and reproducibly functions or performs as intended.

Validation of Biotech Facilities, Equipment, Utilities and Process

When is Validation Typically Required?

- For the start-up of new equipment, utilities, or production facilities
- For new products introduced into a production facility
- When a production process is scaled-up by a factor of 10X or more or when a formulation change is made (including changes to the container/closure system)

Validation of Biotech Facilities, Equipment, Utilities and Process

When Is Validation Typically Required?

- When other significant changes have been made to a production process, utility, equipment, or facility (including changes in location of production activities)
- After a pre-determined period of time has transpired since the last validation of the system, process, utility, or equipment (e.g., revalidation)

Validation of Biotech Facilities, Equipment, Utilities and Process

Master Validation Plan

- Overall philosophy, intentions, and approach
- Identify the items or systems that require validation
- Describe the requirements for each item or system
- Define special training requirements

Validation of Biotech Facilities, Equipment, Utilities and Process

Master Validation Plan (Cont'd)

- Assign priorities to the validation activities
- Provide a plan for integrating other activities
  - Writing Standard Operating Procedures (SOPs)
  - Calibration of equipment
  - Training of personnel
- Involve relevant groups

Validation of Biotech Facilities, Equipment, Utilities and Process
Systems to Be Validated

- **Legend:**
- CQ – Construction Qualification
- BC – Build Clean Protocol
- SS – System Specific
- DQ – Design Qualification Protocol
- IQ – Installation Qualification Protocol
- OQ – Operational Qualification Protocol

Validation of Biotech Facilities, Equipment, Utilities and Process
Systems to Be Validated

- PQ – Performance Qualification Protocol
- PV – Process Validation Protocol
- OP – Operating Procedure
- PM – Preventative Maintenance Procedure
- CL – Cleaning Procedure
- CA – Calibration Procedure

	PROTOCOLS								SOPs			
System/Equipment	CQ	BC	SS	DQ	IQ	OQ	PQ	PV	OP	PM	CL	CA
Facility	X	X									X	
HVAC			X	X	X	X	X		X	X		X
RO/DI Water			X	X	X	X	X		X	X	X	X
WFI Water			X	X	X	X	X		X	X	X	X
Clean Steam			X	X	X	X	X		X	X		X
Process Chilled Water			X	X	X	X			X	X		X
Compressed Air			X	X	X	X	X		X	X		X
CO_2 System			X	X	X	X	X		X	X		X

	PROTOCOLS								SOPs			
System/Equipment	CQ	BC	SS	DQ	IQ	OQ	PQ	PV	OP	PM	CL	CA
Nitrogen System			X	X	X	X	X		X	X		X
Oxygen System			X	X	X	X	X		X	X		X
Vacuum System			X	X	X	X	X		X	X		X
CIP Systems			X	X	X	X	X		X	X	X	X
SIP Systems			X	X	X	X	X		X	X	X	X
Biowaste Processing			X	X	X	X	X		X	X	X	X
Emergency Power			X		X	X	X		X	X		
Fermenters				X	X	X	X		X	X	X	X

	PROTOCOLS								SOPs			
System/Equipment	CQ	BC	SS	DQ	IQ	OQ	PQ	PV	OP	PM	CL	CA
Bioreactors				X	X	X	X		X	X	X	X
Purification Columns					X	X	X		X	X	X	X
Chromatography Skid					X	X			X	X	X	X
Centrifuges	[CLG1]				X	X			X	X	X	X
Prep/Hold Tanks				X	X	X	X		X	X	X	X
Harvest Tanks				X	X	X	X		X	X	X	X

	PROTOCOLS								SOPs			
System/Equipment	CQ	BC	SS	DQ	IQ	OQ	PQ	PV	OP	PM	CL	CA
Process Tanks				X	X	X	X		X	X	X	X
CO_2 Incubators					X	X			X	X	X	X
Incubators					X	X			X	X	X	X
Mixers					X	X	X		X	X	X	X
Floor Scales					X	X			X	X	X	X
Dust Extractor					X	X			X	X	X	

	PROTOCOLS								SOPs			
System/Equipment	CQ	BC	SS	DQ	IQ	OQ	PQ	PV	OP	PM	CL	CA
Warm Rooms					X	X			X	X	X	X
Cold Rooms					X	X			X	X	X	X
Refrigerators					X	X			X	X	X	X
Freezers					X	X			X	X	X	X
Liquid Nitrogen Freezers					X	X			X	X	X	X

	PROTOCOLS								SOPs			
System/Equipment	CQ	BC	SS	DQ	IQ	OQ	PQ	PV	OP	PM	CL	CA
Biological Safety Cabinets					X	X			X	X	X	X
Laminar Air Flow Hoods					X	X			X	X	X	X
Fume Hoods					X	X			X	X	X	X
Autoclave					X	X	X		X	X	X	X

PROTOCOLS									SOPs			
System/Equipment	CQ	BC	SS	DQ	IQ	OQ	PQ	PV	OP	PM	CL	CA
Depyrogenation Tunnel					X	X	X		X	X	X	X
Glassware Drying Oven					X	X			X	X	X	X
Glassware Washer					X	X	X		X	X	X	X
Vial Washer					X	X	X		X	X	X	X
Stopper Washer					X	X	X		X	X	X	X

PROTOCOLS									SOPs			
System/Equipment	CQ	BC	SS	DQ	IQ	OQ	PQ	PV	OP	PM	CL	CA
Filling/Stoppering Machine					X	X	X		X	X	X	X
Capper					X	X			X	X	X	X
Labeler					X	X			X	X	X	X
Lyophilizer					X	X	X		X	X	X	X
Aseptic Processing Media Fills								X				

Validation of Biotech Facilities, Equipment, Utilities and Process

- **Installation Qualification (IQ)**

  Documented verification that equipment, system, or subsystem has been properly built and installed and adheres to applicable codes and approved design intentions and that supplier recommendations have been suitably addressed

Validation of Biotech Facilities, Equipment, Utilities and Process

- **Operational Qualification (OQ)**

  Providing documented verification that a utility system, subsystem or piece of process equipment operates as intended throughout the manufacturer’s specified operating ranges

Validation of Biotech Facilities, Equipment, Utilities and Process

- **Performance Qualification (PQ)**

  Providing documented verification that a utility system, subsystem or piece of process equipment performs its intended function(s) reliably and reproducibly throughout specified operating ranges

Validation of Biotech Facilities, Equipment, Utilities and Process

- **Facility Validation Requirements-Construction Qualification**
  - **Build Clean Protocol and Documentation**
  - **Contractor turn-over packages/compliance verifications**
  - **Architectural layout and mechanical system blueprints**
  - **"As-Built" documentation, including verification of drain inverts and piping slopes**

Validation of Biotech Facilities, Equipment, Utilities and Process

- **Utility Validation requirements**
  - Heating, Ventilation and Air Conditioning (HVAC) Control System - Examples
    - Individual room requirements
      - Temperature control
      - Pressurization (0.05WG)
      - Air change rate (min 20 Air changes per hour)
      - Room exhaust requirements
      - Supply filters (number/type/rating)
      - Maximum allowable viable count under static conditions
      - Maximum allowable airborne particulate count (0.5 μm or larger and 5μm or larger) under static conditions

Validation of Biotech Facilities, Equipment, Utilities and Process

- **Utility Validation requirements - Examples**
  - Purified Water and Clean Steam Systems
    - Applicable building codes and standards
    - System design requirements and materials of construction
    - Operating requirements
    - Points of use (number, location
    - Water quality requirements (chemical, microbial, endotoxin)
    - System labeling/tagging verifications
    - System pressure and flow rate verifications

Validation of Biotech Facilities, Equipment, Utilities and Process

- **Process Equipment Validation Requirements-Examples**
  - –Fermenters
    - Control system verifications
    - Utility verifications
    - Piping verifications
    - Labeling/tagging verifications
    - Aseptic charging, inoculation and sampling verifications (media fills)
    - Hold time studies

Validation of Biotech Facilities, Equipment, Utilities and Process

- **Process Equipment Validation Requirements-Examples**
  - – Purification Columns
    - Verify proper function of pumps, instruments and controls
    - Column packing studies
    - Viral clearance studies
    - DNA clearance studies
    - Endotoxin clearance studies
    - Column regeneration studies

Validation of Biotech Facilities, Equipment, Utilities and Process

- **Validation of Support Processes-Examples**
  - – Sterilization of Components and Equipment
    - Validated for each load configuration
  - – Storage of Sterile Components
    - maximum time sterilized vials, stoppers and glassware may be stored and maintain sterility must be determined
    - Testing is performed a minimum of three, consecutive times and a maximum storage time is established for each component

Validation of Biotech Facilities, Equipment, Utilities and Process

- **Validation of Support Processes-Examples**
  - – Depyrogenation of Components and Equipment
    - Validated for each load configuration
    - Heat penetration thermocouples and endotoxin challenge units of at least 1000 EUs
  - – Washing of Glassware, Vials and Stoppers
    - Cycle development studies
    - A minimum of three, consecutive successful cycles

Validation of Biotech Facilities, Equipment, Utilities and Process

- **Validation of Support Processes-Examples**
  - Facility Sanitization Program
    - Clean rooms and manufacturing areas
    - Controlling bioburden within specified levels
    - Floors, walls, ceilings, work surfaces
    - Focus on areas of high traffic
    - Studies are performed for each sanitization agent used in the program

Validation of Biotech Facilities, Equipment, Utilities and Process

- **Aseptic Filling Validations**
  - Validated for each type of container-closure system used in product manufacture
  - Reliably filling product with a sterility assurance level (SAL) of not less than 99.9%
  - Media fill studies are conducted according to an approved protocol using the same components, equipment, fill volumes, number of filled units, personnel, operations and procedures used for product manufacture
  - A minimum of three, consecutive, successful media fills are required for an aseptic filling process to be validated

Validation of Biotech Facilities, Equipment, Utilities and Process

- **Aseptic Filling Validations (Cont'd)**
  - Worst case challenges such as personnel breaks, equipment adjustments, slower line speeds and maximum number of personnel in the room are incorporated into each media fill
  - Environmental monitoring (viable and non-viable air particulates) is performed throughout the media fill operations
  - Personnel monitoring is performed
  - All media used in the media fill operations as well as for environmental and personnel monitoring must have previously passed USP/NF growth promotion testing

Validation of Biotech Facilities, Equipment, Utilities and Process

- **QC/QA Laboratory Validations**
  - Laboratory equipment (e.g., incubators, biosafety cabinets, laminar flow hoods, freezers, refrigerators, sterilizers, depyrogenation ovens, analytical instruments, etc.)
  - Validated using same methods used in production operations

	PROTOCOLS			SOPs			
QA/QC Equipment	IQ	OQ	PQ	OP	PM	CL	CA
HPLC	X	X	X	X	X	X	X
TOC	X	X		X	X	X	X
FTIR	X	X		X	X	X	X
Plate Reader/Washer	X	X		X	X	X	X
Milliflex	X	X	X[CLG1]	X	X	X	X
Met-One Particle Counter	X	X		X	X	X	X
Steritest	X	X	X[CLG2]	X	X	X	X
Viable Air Monitor	X	X		X	X	X	X

Validation of Biotech Facilities, Equipment, Utilities and Process

- **Cleaning Validations**
  - –Each product or process that is introduced into the manufacturing facility must have validated cleaning and analytical detection procedures
  - –Cleaning validation demonstrates that cleaning processes used in support of product manufacture are capable of consistently and reliably removing product, excipient, bioburden and/or cleaning agent residue from equipment and component surfaces
  - –In a multi-use facility, effective cleaning of non-dedicated equipment is crucial so as to preclude product cross-contamination

Validation of Biotech Facilities, Equipment, Utilities and Process

- **Compliance Programs and Procedures**
  - –Engineering Change Control Program
    - The engineering change control program ensures that proposed changes to the facility, equipment, systems, utilities, processes or software are reviewed and approved by Regulatory/QA and other appropriate departmental personnel prior to the changes being instituted
    - The review also defines any required testing, documentation or re-validation required once the change has been made to verify that the system, equipment, utility or process remains in a validated state

Validation of Biotech Facilities, Equipment, Utilities and Process

- **Compliance Programs and Procedures (Cont'd)**
  - – Calibration Program
    - The calibration program ensures that all instruments used to measure, monitor and record are calibrated to standards traceable to NIST or other approved standard
    - Calibration intervals are established for each instrument in the program based upon the criticality of the instrument, instrument capability and calibration history

Validation of Biotech Facilities, Equipment, Utilities and Process

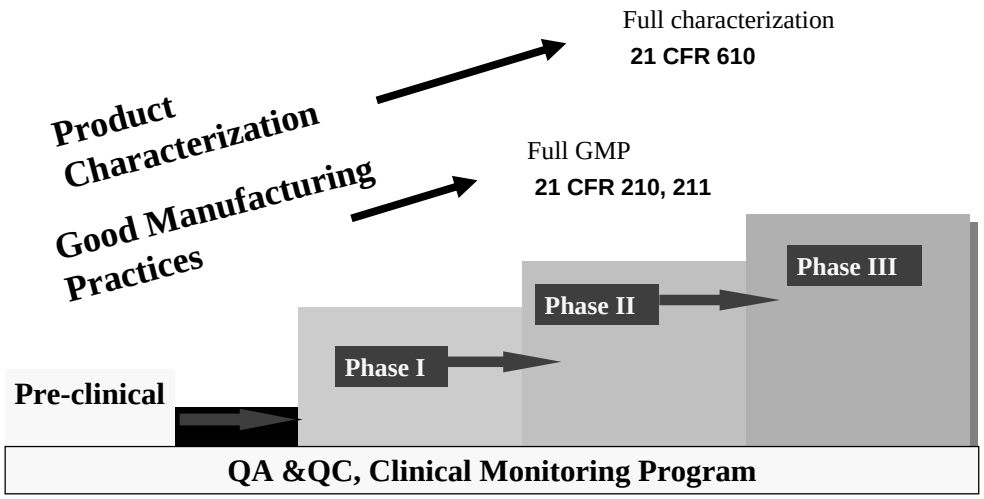
- **Compliance Programs and Procedures (Cont'd)**
  - Preventative Maintenance Program
    - The preventative maintenance program ensures that systems and equipment are maintained in proper working condition and reduces the likelihood of malfunctions
    - Equipment/System preventative maintenance procedures and frequencies of performing the work are developed
    - Preventative maintenance work is documented in logbooks and forms that are retained as pert of the equipment history files

Validation of Biotech Facilities, Equipment, Utilities and Process

- **Compliance Programs and Procedures (Cont'd)**
  - Document Control
    - The document control function is responsible for issuing, tracking and storing controlled documents such as Standard Operating Procedures, specifications, batch production records and validation protocols
    - Procedures describing the preparation, review, approval, issuance, control, revision and retention of standard operating procedures are typically the first to be developed and approved

FDA Expectations

Step-wise Approach to Application of Regulatory Requirements



Prior to Phase I : need product safety testing and basic characterization info