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Pharmaceutical Cleanroom Commissioning, Certification, and Validation DQ, IQ, OQ, and PQ

Presented by
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About the Speaker – Mark Suparat Tang, Ph.D.

Professional Experience

M+W Zander (Thailand) (10/2003 – Present)

- **cGMP Quality Systems Specialist**

Alpha Therapeutic / Baxter (1/1998 – 10/2003)

- **Senior Principal Scientist and Project Manager for Alpha-1 Anti-trypsin**
  - FDA Technical Issues for Drug Approval and Licensing
  - Yield and Quality Improvement
  - Cleaning Validation and Process Validation
- **Senior Principal Scientist – Research and Development**
- **Quality Control Laboratory Manager**
- **Quality Assurance Product Release Auditor**
- **Quality Assurance Vendor Auditor**

Educational Background

Ph.D. in Biochemistry and Pharmacology (1997)

- **University of Pennsylvania School of Medicine Department of Pharmacology**

Post-doctoral Research Fellow (1/1997- 12/1997)

- **California Institute of Technology Department of Chemical Engineering**

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Topics of the Presentation

- To confirm the Purpose of the Pharmaceutical Cleanroom
- To discuss the relevant Guidelines and Regulations for Pharmaceutical Cleanroom Commissioning, Certification, and Validation
- To discuss the Cleanroom Validation Procedures

1. Design (URS, DQ, and IQ)
2. Commissioning (IQ)
3. Certification Procedures (IQ and OQ)
4. Performance and Maintenance Procedures (PQ and Cleaning Validation)

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Purpose of the Pharmaceutical Cleanroom

Thai Ministry of Public Health Food and Drug Administration:

Pharmaceutical products should be manufactured under the requirements of good manufacturing practices by licensed manufacturers with the object of ensuring that users will receive efficacious, safe and good quality products.

Good Manufacturing Practice (GMP):

The overriding principle which governs the quality of every aspect of making a medicine.

- Every action will only be undertaken by following written instructions and documentation.
- **All facilities and machinery are correct for the purpose and that they, and the environment in which they are situated, is properly cleaned and appropriately treated**
- Raw materials must be stored and handled correctly and that exactly the right materials must be used at all times.
- That people, both production workers and support staff, must dress and behave as required, be properly supervised and above all, be trained correctly.
- That Quality Control is undertaken at every stage of the storage, handling, manufacturing and packing cycle.

Cleanroom Certification and Validation Guidelines and Regulations

Guidelines

Thai FDA GMP Guidelines	**Thailand**
WHO GMP Guidelines	**International**
EEC GMP Guidelines	**EU, Partly International**
U.S. FDA GMP Guidelines	**USA, International**
ISPE Guidelines	**International**

Regulations

DIN EN ISO 14644, part 1 (2000)	**International**
ISO-DIS 14644, part 3 (2000)	**International**
DIN EN 12599 (2000)	**EU, International**
NEBB (1996)	**USA, Partly International**

Cleanroom Certification Regulations

ISO Standard 14644

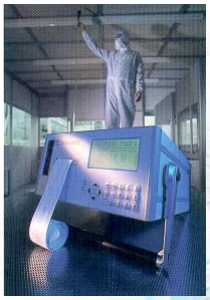
- The ISO Standard 14644 is an internationally accepted standard of Cleanroom and the associated controlled environments.
- M+W Zander has used this standard since its introduction of the First Edition in 1999.
- ISO 14644 consists of the following parts:
  - Part 1: Classification of air cleanliness
  - Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1
  - Part 3: Metrology and test methods
  - Part 4: Design, construction and start-up
  - Part 5: Operations
  - Part 6: Terms and definitions
  - Part 7: Enhanced clean devices
  - Part 8: Molecular Contamination

Cleanroom Certification Regulations

ISO 14644-3: Methods of evaluation and measurements

Part 3 - Metrology and test methods

1. Airborne particle count for classification of the installation and test measurement
2. Airflow test
3. Air pressure difference test
4. Installed filter system leakage test
5. Flow visualization
6. Airflow direction test
7. Temperature test
8. Humidity test
9. Recovery test
10. Containment leak test

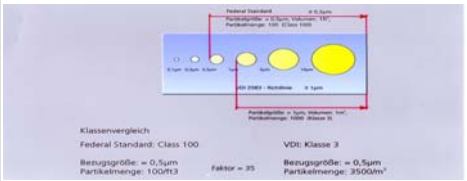


Cleanroom Certification Regulations

VDI 2083,3 (1993)

Contamination Control Measuring techniques for Cleanrooms

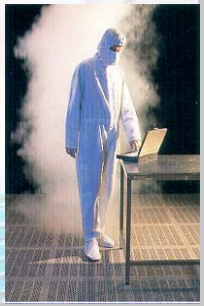
- Air pressure difference test
- Air velocity test
- Installed filter system leakage test
- Recovery
- Airborne particle count
- Airflow direction test (parallelism)



VDI 2080 (1996)

Measuring methods and Measuring instruments for air conditioning systems

- Pressure test
- Temperature and humidity
- Room air velocity
- Airflow
- Air purity and particles
- Leakage airflow



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Cleanroom Commissioning Procedures

Cleanroom (HVAC System) Commissioning

- Hydronic Balance Testing
- Sound Measurement Testing
- Vibration Testing
- Alarms and Interlocks Testing
- Air Flow rate testing in ductwork
- Air Volume Stpply and Return, Testing and Balancing
- Fan RPM and Amperage Confirmation
- Temperature, Humidity (Coil Duties) and Static Pressure Testing (Duct Leak)
- Differential Pressure Testing and Balancing
- Loop Checks
- HEPA Filter Integrity Testing
- Component (Air coil, AHU, FCU, Filters) Operation Testing (Test sequences, Shut-down, and Start-up Procedures)

Cleanroom (HVAC System) Commissioning

- Process and Instrumentation Diagram (P&ID) confirmation = As-Built P&ID
- Utilities Check
- Instrumentation Calibration
- Electrical Power Tests
- Motor Run Tests
- Lubrication Checks
- Isometric Drawing Checks
- Safety Checks

Cleanroom (Finishing) Commissioning

- Floor, Wall, Ceiling
- Doors and Airlocks and Interlocks
- Lighting and other Fixtures

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Cleanroom Certification Measurements

Standard Measurements

1. Air velocity / Air velocity distribution
2. Filter Airflow rate
3. AHU Airflow rate
4. Filter leakage test
5. Room pressurisation
6. Cleanliness classification
7. Temperature and Humidity

Optional Measurements

1. Containment leak test / Enclosure integrity test
2. Parallelism - Airflow direction test Airflow visualisation
3. Recovery time
4. Microbiological count (Air, surfaces)
5. 3rd Party Certification

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Cleanroom Certification: Air Velocity Measurement

Purpose

To check the air velocity distribution !

Not required in cleanrooms with turbulent airflow (Recovery test)

Requirements

- Cleanroom installation completed (Ceiling, filter, raised floor, walls, doors etc.)
- Velocity adjustment performances in the order of the maintenance group

Standards

- **VDI 2083, sheet 3 (Draft 1993)** or (not and)
- **IES-RP-CC006.2 (1994)** or (not and)
- **ISO (DIS) 14644-3 (Draft 2000)** or (not and)
- **NEBB (1996)**

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Cleanroom Certification: Airflow Volume Measurement

Purpose

To check the airflow volume to calculation of the air change rate !

Not required in cleanrooms with unidirectional (laminar) airflow

Requirements

- Cleanroom installation completed (Ceiling, filter, raised floor, walls, doors etc.)
  except for installation of diffuser panels below FFU
- Air volume adjustment performances in the order of the maintenance group

Standards

- **VDI 2083, sheet 3 (Draft 1993)** or (not and)
- **IES-RP-CC006.2 (1994)** or (not and)
- **ISO (DIS) 14644-3 (Draft 2000)** or (not and)
- **NEBB (1996)**

Cleanroom Certification: Filter Leakage Test Measurement

Purpose

To check the filter system for leakages

⇨ **Not an efficiency test !!!**

Requirements

- Filter installation completed
- Diffuser panels should be not installed
- Air velocity or airflow volume adjusted to a nominal value ± 20 %
- Ceiling must be completed totally
- Filter installation finished

Standards

- **VDI 2083, sheet 3 (Draft 1993)** or (not and)
- **IES-RP-CC006.2 (1994)** or (not and)
- **ISO (DIS) 14644-3 (Draft 2000)** or (not and)
- **NEBB (1996)**

Cleanroom Certification: Room Pressurization Measurement

Purpose

To check the specified room pressurisation to avoid cross contamination from cleanroom with lower cleanliness class into areas with better cleanliness class

Requirements

- Filter installation completed
- Wall installation completed
- Ceiling must be completed totally
- Air velocity adjustment, Airflow volume adjustment completed in the order of the maintenance group (make up air adjusted)
- Air velocity test, Airflow volume test, Filter leakage test completed

Standards

- **VDI 2083, sheet 3 (Draft 1993)** or (not and)
- **IES-RP-CC006.2 (1994)** or (not and)
- **ISO (DIS) 14644-3 (Draft 2000)** or (not and)
- **NEBB (1996)**

Cleanroom Certification: Parallelism / Airflow Direction Test

Purpose

To verify the airflow direction in unidirectional (“laminar”) cleanrooms

Standards

- **VDI 2083, sheet 3 (Draft 1993)**
  or (not and)
- **IES-RP-CC006.2 (1994)**
  or (not and)
- **ISO (DIS) 14644-3 (Draft 2000)**
  or (not and)
- **NEBB (1996)**

Requirements

- Filter installation completed
- Wall installation completed
- Ceiling must be completed totally
- Air velocity adjustment, Airflow volume adjustment, room pressurization adjustment completed in the order of the maintenance group
- Air velocity test, Airflow volume test, Filter leakage test, Room pressurization test completed

Cleanroom Certification: Recovery Time Measurement

Purpose

To test the installations ability to eliminate airborne particles

Only performed in cleanrooms with turbulent airflow

Standards

- **VDI 2083, sheet 3 (Draft 1993)**
  or (not and)
- **IES-RP-CC006.2 (1994)**
  or (not and)
- **ISO (DIS) 14644-3 (Draft 2000)**
  or (not and)
- **NEBB (1996)**

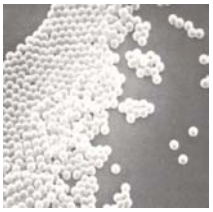
Requirements

- Cleanroom installation completed
- Air velocity adjustment, Airflow volume adjustment and room pressurization adjustment in the order of the maintenance group
- Air velocity test, Airflow volume test, Filter leakage test and room pressurization test completed

Cleanroom Certification: Cleanliness Class Measurement

Purpose

To determine the airborne particulate concentration (cleanliness class)

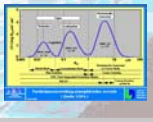


Standards

- **VDI 2083, sheet 3 (Draft 1993)**
  or (not and)
- **IES-RP-CC006.2 (1994)**
  or (not and)
- **ISO (DIS) 14644-3 (Draft 2000)**
  or (not and)
- **NEBB (1996)**

Requirements

- Cleanroom installation totally completed
- Cleanroom cleaned
- Air velocity adjustment, Airflow volume adjustment and Room pressurization adjustment completed in the order of the maintenance group
- Air velocity test, Airflow volume test, Filter leakage test, Room pressurization test and Parallelism test completed



Cleanroom Certification: Temperature and Relative Humidity

Purpose

To verify of the capability
of the Cleanroom air handling system
to maintain the specified air temperature and relative humidity

Standards

- **VDI 2083, sheet 3 (1993)**
  or (not and)
- **IES-RP-CC006.2 (1994)**
  or (not and)
- **ISO (DIS) 14644-3**
  or (not and)
- **NEBB (1996)**

Requirements

- Cleanroom installation totally completed
- Air velocity adjustment, Airflow volume adjustment and Room pressurization adjustment completed in the order of the maintenance group
- Make up air system installed and adjusted
- Temperature control system installed and adjusted
- Air velocity test, Airflow volume test, Filter leakage test, Room pressurization test and Parallelism test completed

Cleanroom Certification: Microbiological Count

Purpose

To monitoring the controlled environments effectiveness for cleaning and sanitizing practices by and of personnel that could have an impact on the bio-burden of Control area

Standards

- **United States Pharmacopeia: Microbiological Evaluation of Cleanroom and other Controlled Environments of**

Requirements

- Cleanroom installation totally completed
- Disinfection & Cleanroom cleaning following SOP of Disinfection procedure
- Air velocity adjustment, Airflow volume adjustment and Room pressurization adjustment completed in the order of the maintenance group
- Location of contract plates with sketch or drawing

Cleanroom Certification: Test Report

Minimum Test Report Information

1. Name and address of the certifying person
2. Date of the certification
3. Location of the certified cleanroom, including reference to adjacent zones, if required, as well as co-ordinates of sampling points
4. Acceptance criteria for the cleanroom or clean zone including the ISO classification, the occupancy state and the considered design criteria
5. Details of the used measuring method (Reference standard and deviations)
6. Name of the measuring device as well as the valid calibration certificate
7. Measuring results for all sampling points

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Cleanroom Validation Procedures

Preliminary Considerations

- Purpose of Cleanroom: GMP Requirement

  All facilities and machinery are correct for the purpose and that they, and the environment in which they are situated, is properly cleaned and appropriately treated.

- User Requirement Specification (URS) for the Cleanroom
  1. User-defined requirements for the Manufacturing Environment to comply with the User-defined Regulatory Requirements.
  2. Sufficiently detailed to enable design specifications to be developed.

- Room Data Sheet
  1. Defines the Cleanroom Specifications.
  2. All Cleanroom Specifications are reviewed during GMP review.
  3. Basis for the Final Acceptance Tests and Specifications for the Cleanroom.

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Cleanroom Validation Procedures

Steps of Validation

1. User Requirement Specification (URS) by User
2. Cleanroom and Facility Design by Cleanroom Engineer
3. Design Qualification (DQ) = Commissioning – Procurement
4. Installation Qualification (IQ) = Commissioning – Installation and Testing
5. Operation Qualification (OQ) = Commissioning – Certification
6. Performance Qualification (PQ) = Compliance to Room Data Sheet
7. Cleaning Validation

** DQ can be covered in normal design reviews

Thai FDA Cleanroom Presentation 08.03.05
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Cleanroom Validation Procedures: Design Qualification

Design Qualification (DQ)

The documented evidence that the Cleanroom Design Objectives concerning GMP and compliance of the project have been properly described in Cleanroom design documentation, and that the Design if 'Fit for Purpose'

Objective:

To Confirm that the Designs fit the User Required Specification

- Specifications
- Purchase Orders
- Vendor Proposal Documents
- Layouts
- P&ID/Flowsheets
- Contractor Strategy / Interfaces

Executed in Parallel with During Commissioning – Procurement

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Cleanroom Validation Procedures: Installation Qualification

Installation Qualification (IQ)

The documented verification that all aspects of the Cleanroom that can affect final quality of the Cleanroom environment adhere to approved specifications and are correctly installed.

Objective:

To demonstrate that the item as installed, conforms to the Design Specification (Referring to the Design Specification and User Required Specification)

- HVAC and other Critical Instruments are still in Calibration
- Equipment specifications, drawings, operation and maintenance manuals
- Installation check of Critical Components
- Critical Component P&ID and Loop Check
- Testing and Balancing Report
- HEPA filter Integrity Testing Data Review

Executed in Parallel with During Commissioning – Installation

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Cleanroom Validation Procedures: Operation Qualification

Operation Qualification (OQ)

The documented verification that all aspects of the Cleanroom that can affect the final Cleanroom quality can operate as intended throughout all anticipated ranges.

Objective:

To demonstrate that the Cleanroom can be operated in conformance to the Design Specification (Referring to the Design Specification and User Required Specification)

- HVAC and other Critical Instruments are still in Calibration
- Testing of Critical Alarms and Interlocks
- List of Critical Operating Parameters encompassed by Room Data Sheet
- Testing for the Specifications detailed in the Room Data Sheet
- Standard Operation Protocol for HVAC System Controls
- Cleanroom Operation Protocols for Cleanroom Operations

Executed in Parallel with During Commissioning – Testing, Balancing, Certification

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Cleanroom Validation Procedures: Performance Qualification

Operation Qualification (PQ)

A documented program to demonstrate that the Cleanroom, when operating within the defined parameters, can consistently perform and maintain the Cleanroom conditions.

Objective:

To demonstrate that the Cleanroom can reliably perform in conformance to the Design Specification (Referring to the User Required Specification and Room Data Sheet)

- Monitoring and Testing for Particulate Levels (Surface and Airborne)
  - Static (non-viable) Particulate Monitoring (As-built / At rest)
  - Static (viable) Particulate Monitoring (Microbial Monitoring) (As-built / At rest)
    - Dynamic (non-viable) Particulate Monitoring (Sterile Areas) (In Operation)
    - Dynamic (Viable) Particulate Monitoring (Sterile Areas) (In Operation)
- Room Data Sheet is the Cleanroom User Required Specification

Executed after Commissioning – Certification

Cleanroom Validation Procedures: Additional Considerations

Worst Case Scenarios

- Identify critical operating parameters
- Set operational ranges for each critical parameter
- Design worst case scenarios to test extremes of ranges
  - min/max temperatures and humidity
  - process equipment operational contamination
  - personnel operational contamination
  - Equipment maintenance schedule

Operational Considerations

- Recovery Time
- Cleaning Procedures
- Cleaning Validation
- Re-testing, Re-Certification, and Re-Validation Schedule

About M+W Zander (Thai) Co.

M+W Zander (Thai) is a Consultant Firm Specializing in

- Designing Cleanroom Facility, Utility, Building, and Process Equipment and
- Executing Turnkey Projects for the Pharmaceutical and Microelectronic Industries

M+W Zander (Thai) has developed its own standard operation procedures.

- that are in accordance to above listed international standards and
- that can be adjusted to the client's specific requirements.
- With Recommendation and Consultancy on scope of the measurements!

M+W Zander (Thai) provides Measurement and Certification services for Cleanroom and HVAC systems.

- Following (DIN EN) ISO 14644-1, VDI 2083, IES-RP-CC006.2 or NEBB
- Following Pharmaceutical and Biological Product GMP Requirements
- Following the specific process, facility, and client requirements.