Environmental Monitoring & Aseptic Processing - Technology & Microbiology

PDA
Parenteral Drug Association

CONNECTING PEOPLE SCIENCE AND REGULATION®

Why We Monitor

- Contamination will affect product quality and possibly effectiveness
- Manufacturing Failures: Human error, use of incorrect ingredients, inadequate cleaning procedure and undetected contaminants
- Particulate matter (Inert or Nonviable and Viable) can range in size from sub-microns to several hundreds of microns, and shape and density may vary widely.
- Clean rooms can be exposed to particulate matter shed by gowns, gloves, skin flakes (personnel), sample preparation equipment, glassware, metal, metal oxides, building materials, ceramics, dust, process air, air filtration systems, and machines.
- Humans are the largest source of microbial contamination

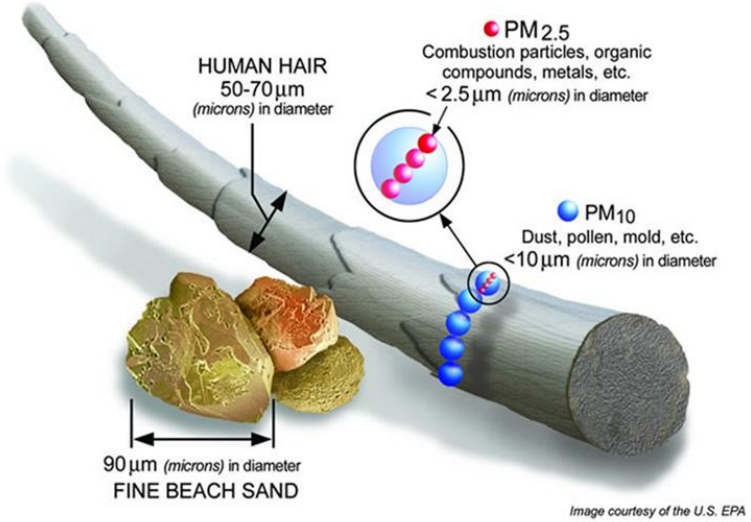
Typical Monitoring

- Typical systems consist of:
  - Particle Monitors
  - Microbial Samplers
    - Portable
    - Fixed location
  - Temperature
  - Humidity
  - Pressure
  - Other parameters that affect cleanroom operations

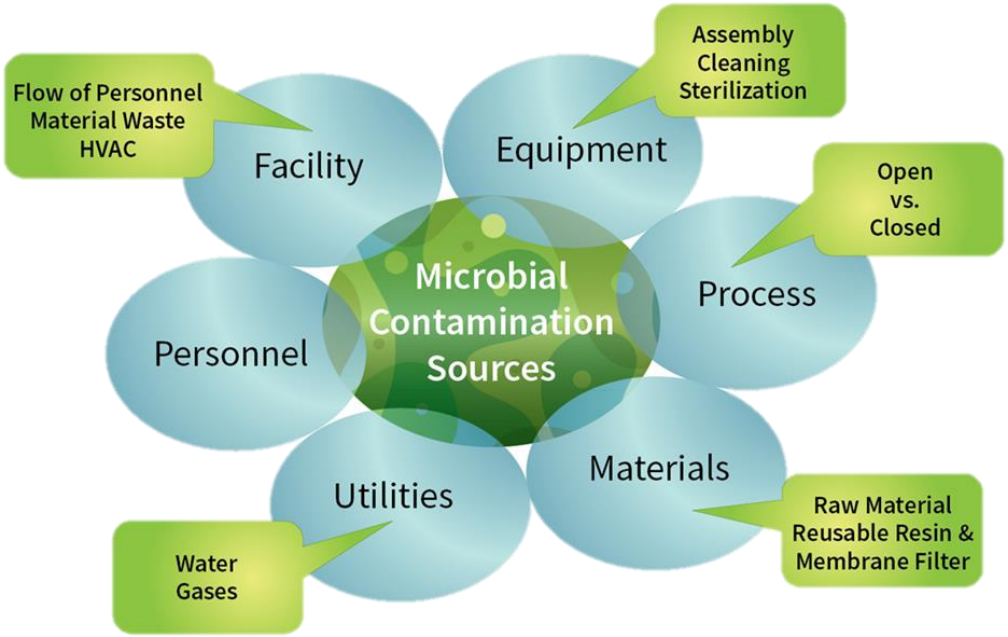
- Reasons for an Environmental Monitoring System (EMS)
- Automation - Done the same way everytime
- Eliminate routine tasks influenced by humans
- Assure conditions are under control
- Data Integrity
- 21 CFR Part II
- Notification of out of control conditions
- System integration
- Automated Reports
- Access to the data across the company

Monitoring Air

- Total Particulates (Inert or Nonviables [plus Viables])
  - Particle Counting (0.5 µm in diameter and/or larger)
- Viables (typically bacterial and fungal spores)
  - Settle or Settling Plates (Passive Air Sampling)
  - Air Samplers (Active Air Sampling)



Microbial Contamination



Relevant Standards

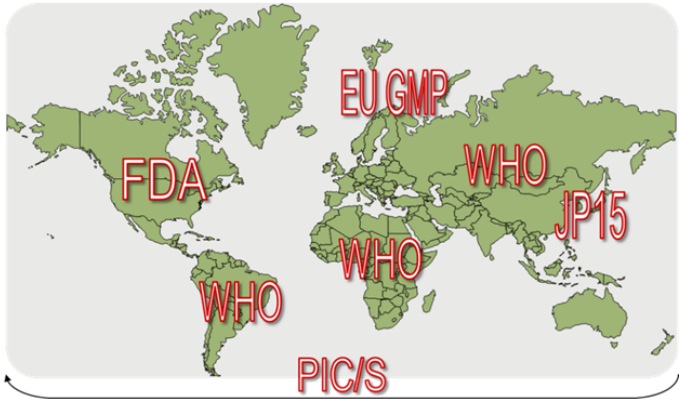
EU GMP
requirements for EU production and export/import

FDA
requirements for USA production and export/import

JP 15
requirements for Japanese production and export/import

WHO
requirements for Global production to WHO

PIC/S
requirements for Global production and export/import



Monitoring of a Cleanroom

- Particle and microbial monitoring is required
- Decisions for monitoring frequency are
  - Risk-based design applies to particle and Microbial
  - Commonly, particle and microbial points are next to each other
- Batch records must include both sets of data (V and NV), alarms, and data on Temp, humidity, and differential pressure

- EU Annex 1
- “Monitoring locations based on a formal risk analysis study and the results obtained during classification”

Sample Point Placement – PIC/S

8. Clean rooms and clean air devices should be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices.

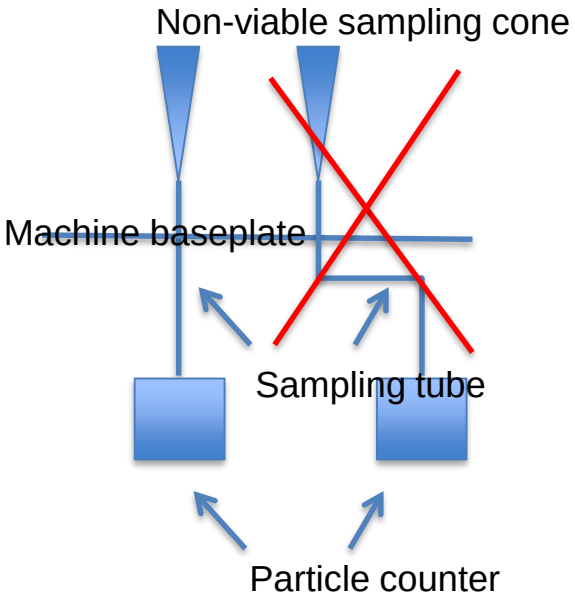
- Formal Risk Analysis & results from Classification
  - Identification of Risk is paramount
  - Room classification ‘should’ demonstrate no anomalous regions in room and cleanroom uniformity
  - Certification and Monitoring should be clearly differentiated

Positioning the Sample Inlet

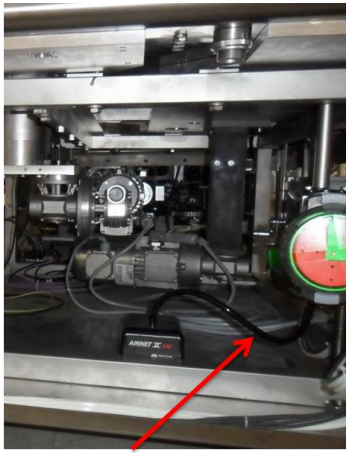
- Measure to one side, close to the critical location
  - FDA guidance…within 1 foot (0.3m)
- Just above the critical point
  - Verifies the quality of the air shroud
  - Not too close to the filters
  - Not to close to the process
- Not directly over the critical point
  - Creates turbulence
  - Starves the process of air
- Locations Must be Risk Based

Physical Installations

Ideally only straight connections between sample ISP's and particle counters

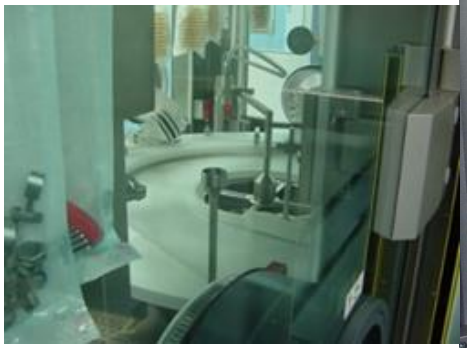


Ideal installation:
Straight connection



Non-ideal installation:
NON Straight connection

Filling Lines



- Typically 3 monitoring locations
  - Entry / accumulator
  - Point of Fill (filling needles)
  - Stopper activities
- Capping point
  - Grade A quality air
- Lyophilization areas
  - Monitor the transfer from filler to the freeze drier

- Monitoring for critical areas should be continuous and the zone immediately surrounding the product whenever the product or open container is exposed to the environment.
- The monitoring locations should be as close as possible to the exposed product or semi-stoppered vials.
- End of filling line, semi-stoppering, and loading of the lyophilizer, the product should be maintained within an ISO Class 5 environment and monitored throughout this distance

Grade B (ISO 6/7) areas

- Multiple choices for sensor mounting:

Direct mount to wall
or machine

Flush mount
(inside wall enclosure)

Other side of wall
(bring tubing through)

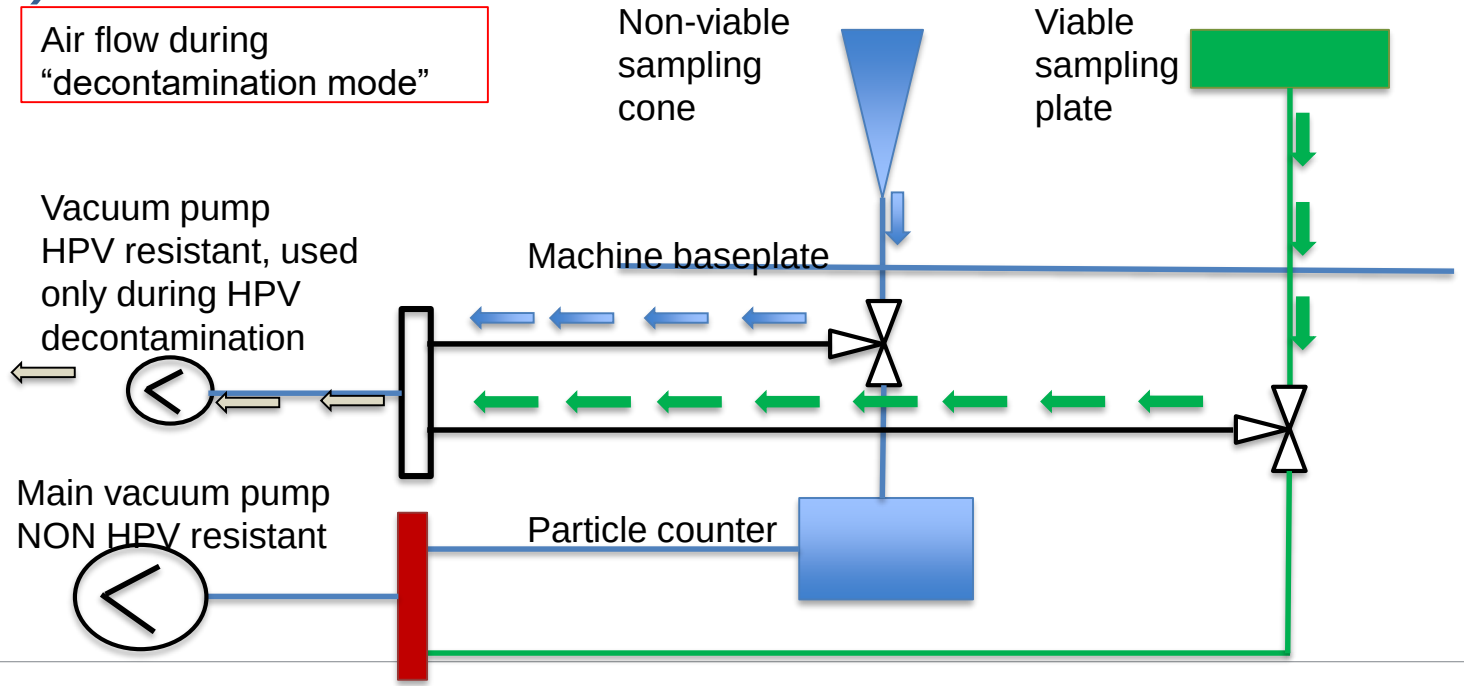
Isolators

- Tubing access
  - Install ports to plumb transport tubing inside
  - Bulkhead or tri-clamp fittings are common
- Mount sensors under or onside of isolator
  - Work in conjunction with Isolator manufacturers during build phase
- VHP resistance equipment

VHP vs Standard Processes

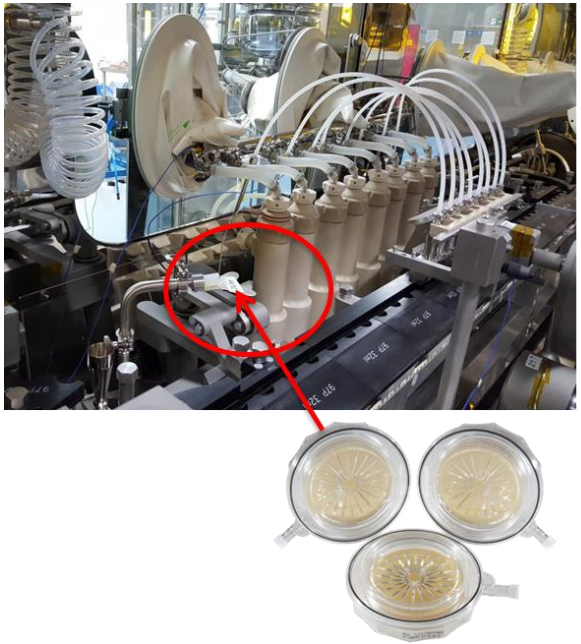
- Similar monitoring requirements to traditional filling lines
- Need VHP resistant products or single use products such as biological sampling units that are disposable or protect against VHP contamination
- Particle sensors which are resistant to VHP sterilization process OR valving that routes the air flow around the sensors to protect them.

Instruments bypass during decontamination cycles (HPV)



Disposable Viable Monitoring

- Disposable Viable monitoring systems are an alternative to traditional units
- Bags containing these devices should be loaded inside an isolator before the decontamination cycle development.



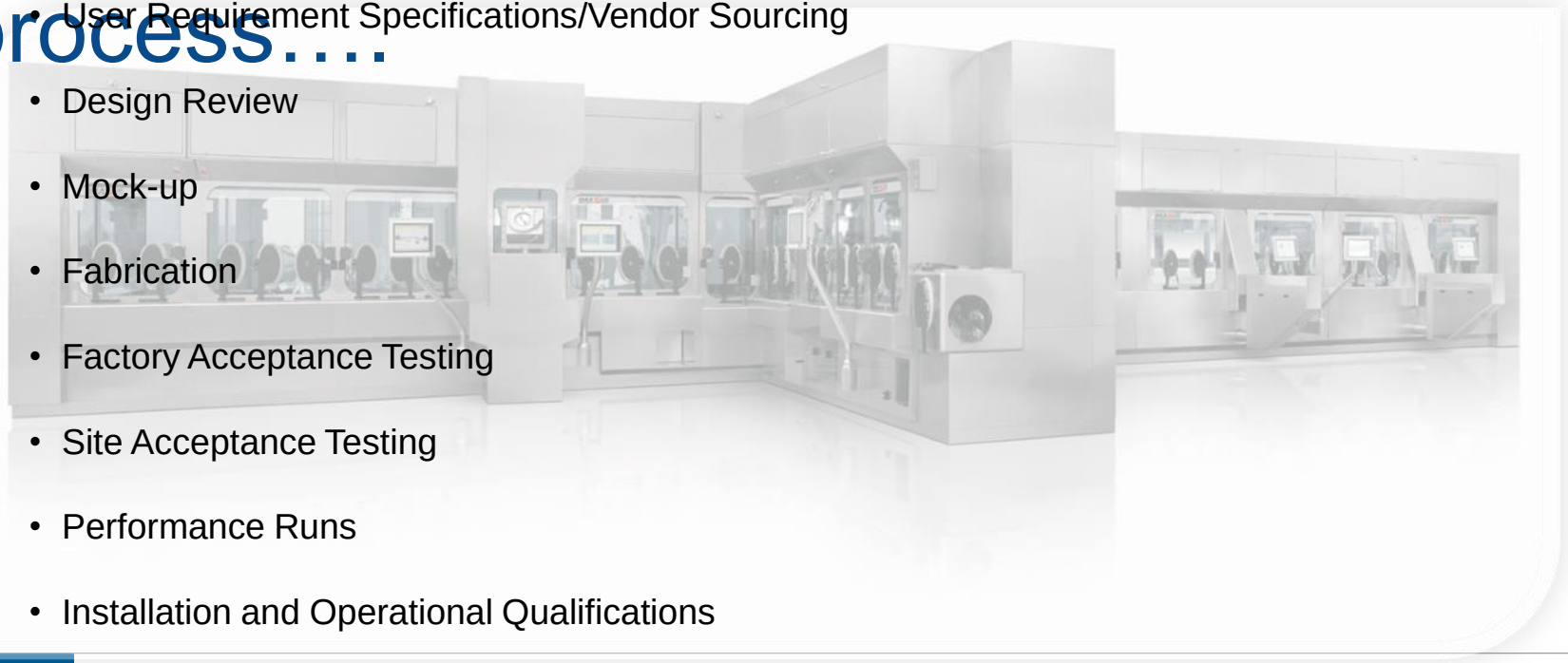
Isolators with VHP sterilization are becoming more common and monitoring equipment suited for the environment is required

Case Study:
Design and Implementation of an Isolator Based Filling Line



What step are you entering the process….

- User Requirement Specifications/Vendor Sourcing
- Design Review
- Mock-up
- Fabrication
- Factory Acceptance Testing
- Site Acceptance Testing
- Performance Runs
- Installation and Operational Qualifications



User Requirement Specifications/Vendor Sourcing

- Congrats!

- Environmental Monitoring Specifications
  - Based on regulatory market: US or Ex-US or both
  - Quantity, Type and Function
    - Passive Viable
    - Active Viable (continuous vs non-continuous)
    - Total Particulates
    - Isolator vs RABS
  - OEM provided or Integration
    - Functionality and data reporting capabilities
    - Is this a standalone system or will there be future expansion

Design Review

- Time to review and pontificate
  - Interaction with vendors is extremely important
    - Tour the machine floor
    - Engage vendor AND internal subject matter experts
    - Make sure vendors are speaking the same language with you and with other vendors, all processes are an integration
  - Quantity and Type ($)
    - Passive Viable
    - Active Viable (continuous vs non-continuous)
    - Total Particulates
    - Isolator or RABS (debagging and capping)

Mock-up

- Location, location, location
  - Hands on interaction with the “machine”
  - Key activities
    - Bring props – plates, forceps, tape measure
    - Bring people –operators, Microbiologist(s)
    - Glove port placement
    - Test Ergonomics
    - Set your Christmas tree
    - Visualization of equipment and aseptic processes
      - determination of monitoring locations
    - Change ($)

FABRICATION

- Wear out the welcome mat
  - One visit is not enough, plan on progress review meeting**S**
  - Visit vendors independently and set group review meetings
  - Signal exchange and sequence of operations are key topics
  - Inspection pays dividends
    - DO NOT drill holes for EM components
      wait for FAT, esp. in an isolator
    - Trust but verify
    - Continued visualization & solidification of the equipment
      and aseptic process is useful for risk analysis for EM locations
    - Change ($$)

FAT

- Where the metal meets the road
  - Set the machine up for performance: TEST
  - Key activities
    - Bring vendors and your local technician and solidify relationships
    - Consider integrated FAT
      - Test signal exchange and sequence of operations & performance runs
      - Smoke visualization studies
      - Perform final deck placement of EM components and evaluate runs
    - “Break the machine” – don’t let the OEM run the show fix it while it is on-site at the vendor
    - Change ($$$)

SAT

- Just when you thought you were done
  - Investigation phase: What's a site issue vs a machine issue
  - Key activities
    - Test components in production conditions (should be done at FAT as well)
    - Involve the entire team– production, microbiology, QA, visual inspection, engineering, facilities
    - Run EM, especially if an integrated FAT was not performed
    - Make sure to test interaction with site systems
    - Stay on top of vendor punch-lists
    - Hold daily planning and progress meetings (PM likely to be off-site)
    - Change is ($$$$)

Performance Runs

- When the wheels fall off the bus
  - Vendor has left the building and now you are on your own
  - Key concepts
    - Teamwork
    - Positive attitude
    - Vendor relationships
    - Investigation and troubleshooting skills
    - It's not what you know, it's who you know
    - The equipment parabola concept

Installation and Operational Qualification

- How to juggle
  - Isolated filling lines are an integration of multiple machines and vendors
  - Key concepts
    - Patience
    - Timeline and planning
    - Teamwork
    - Positive attitude
    - Vendor relationships
    - Leverage FAT, SAT and vendor established protocols
    - Management of upper management

Lessons Learned

- “Turnkey” does not exist
- Establish relationships with reputable vendors who are SMEs in their field
- Plan early and often but when you can’t, it’s not what you know, it’s who you know
- Trust but verify
- A positive attitude goes a long way

Questions?

- **Stacy Sutton**
  VP Quality and Regulatory Affairs
- Argonaut Manufacturing Services

- **Paul Hartigan**
  Global Product Line Manager Systems and Software