Risk-Based Cleanroom and Environmental Controls for Terminal Sterilization Operations

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Sterile Manufacturing - Product Quality Risks From Microbial Hazards

- *Recalls, Warning Letters*
- *Themes and Conclusions*

Terminal Sterilized Products - Product Quality Risks From Microbial Hazards

- *Cleanroom Guidance*
- *Quality System Improvements – Risk-Based Controls*

A New Tool – Quantitative Risk Assessments

- *What is Quantitative Risk Assessment*

A New Tool - Real Time Risk Assessment (RTRA)

- *Relevant 483s*
- *What is RTRA*

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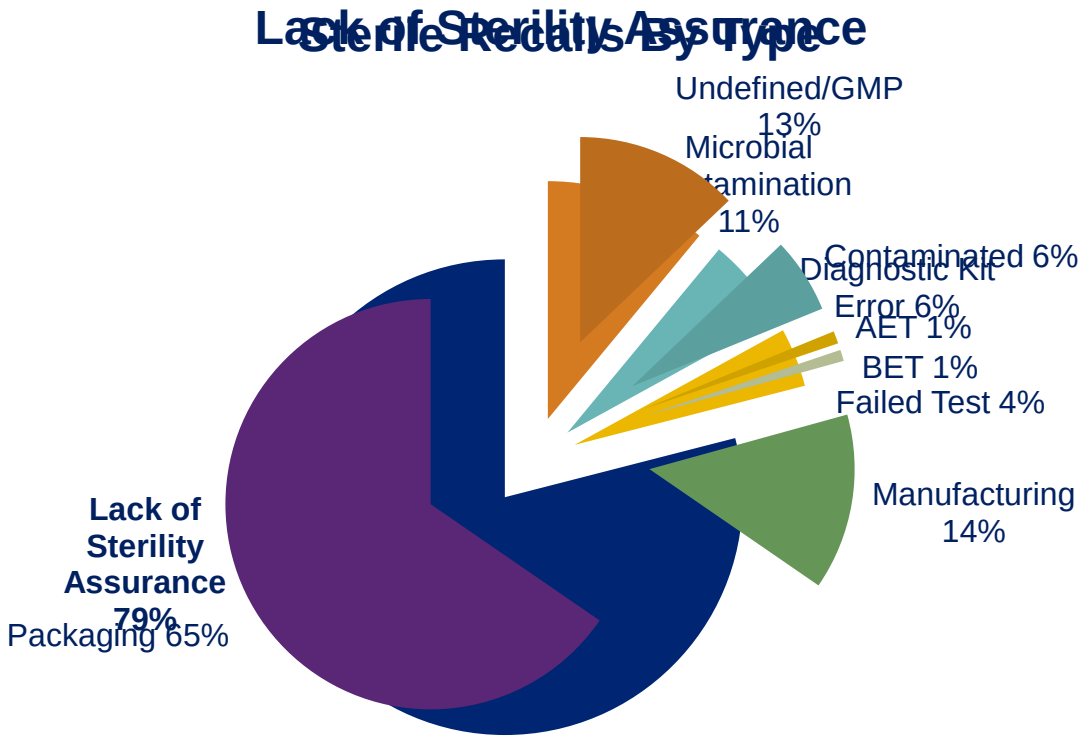
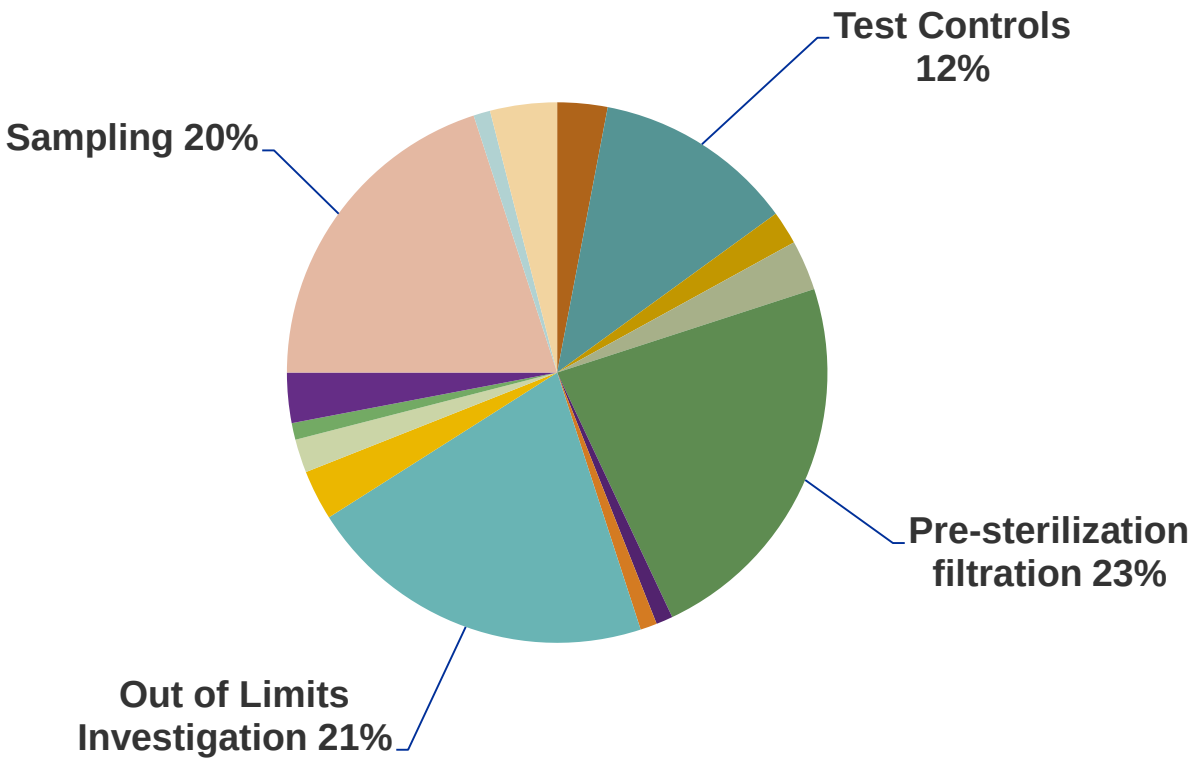
Sterile Manufacturing - Product Quality Risks From Microbial Hazards

Microbiologically-Related Product Recalls 2004-2011[1]



Sterile Manufacturing - Product Quality Risks From Microbial Hazards

Microbiologically-Related Warning Letters 2001-2011[2]



Recalls & Warning Letters - Themes & Conclusions

- Lack of sterility assurance continues to be a cause of product recalls
- Packaging, manufacturing, microbial contamination all major reasons for product recalls
- Significant numbers of warning letters linked to microbial control
  (79 companies, 11 observations)
- Sampling, OOL investigations, pre-sterilization filtration are all major causes of microbial-related warning letters

Terminal Sterilized Products - Product Quality Risks From Microbial Hazards

- *Cleanroom Guidance*
- *Quality System Improvements – Risk-Based Controls*

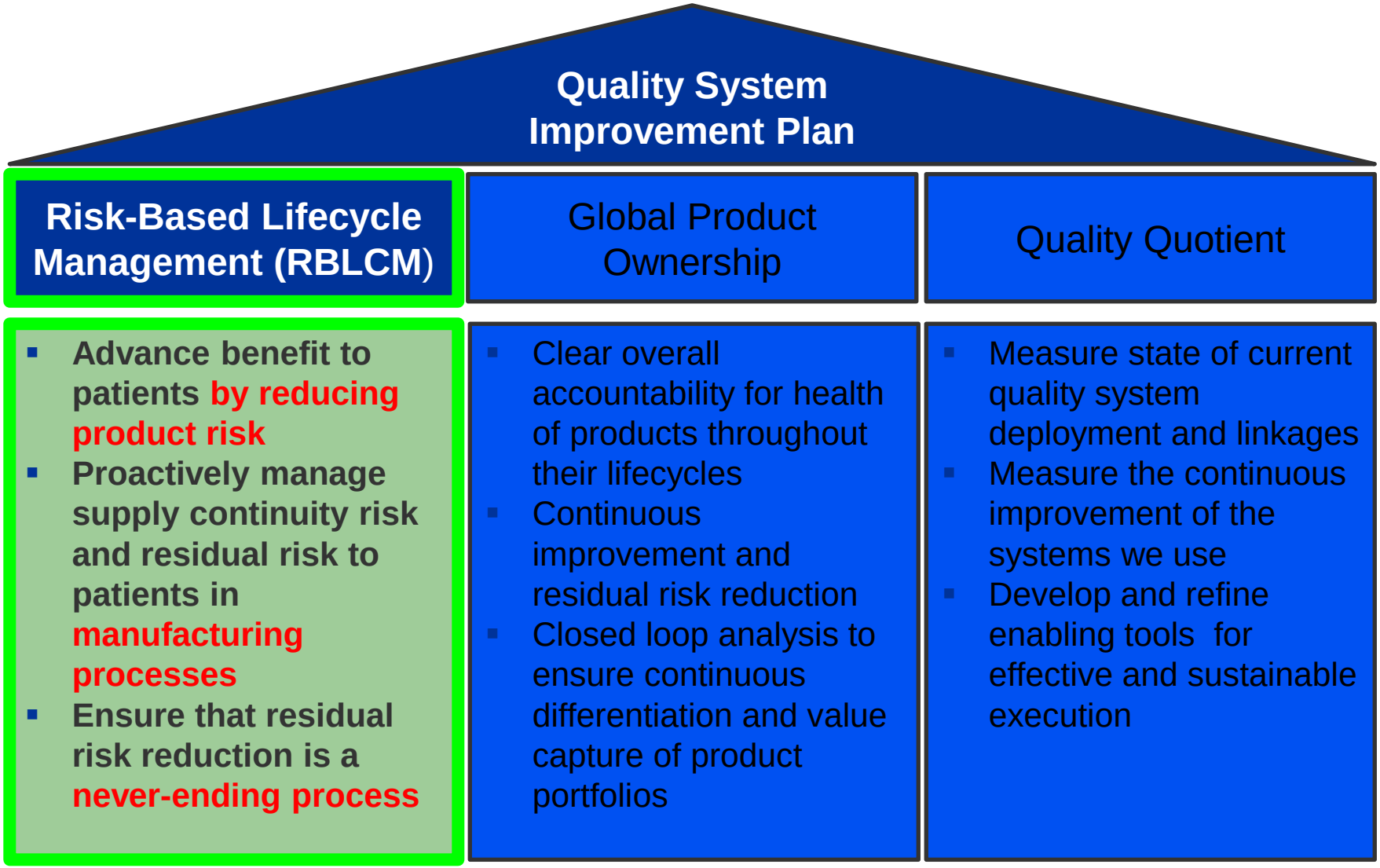
Guidance Recommendations For Terminally Sterilized Product Cleanrooms

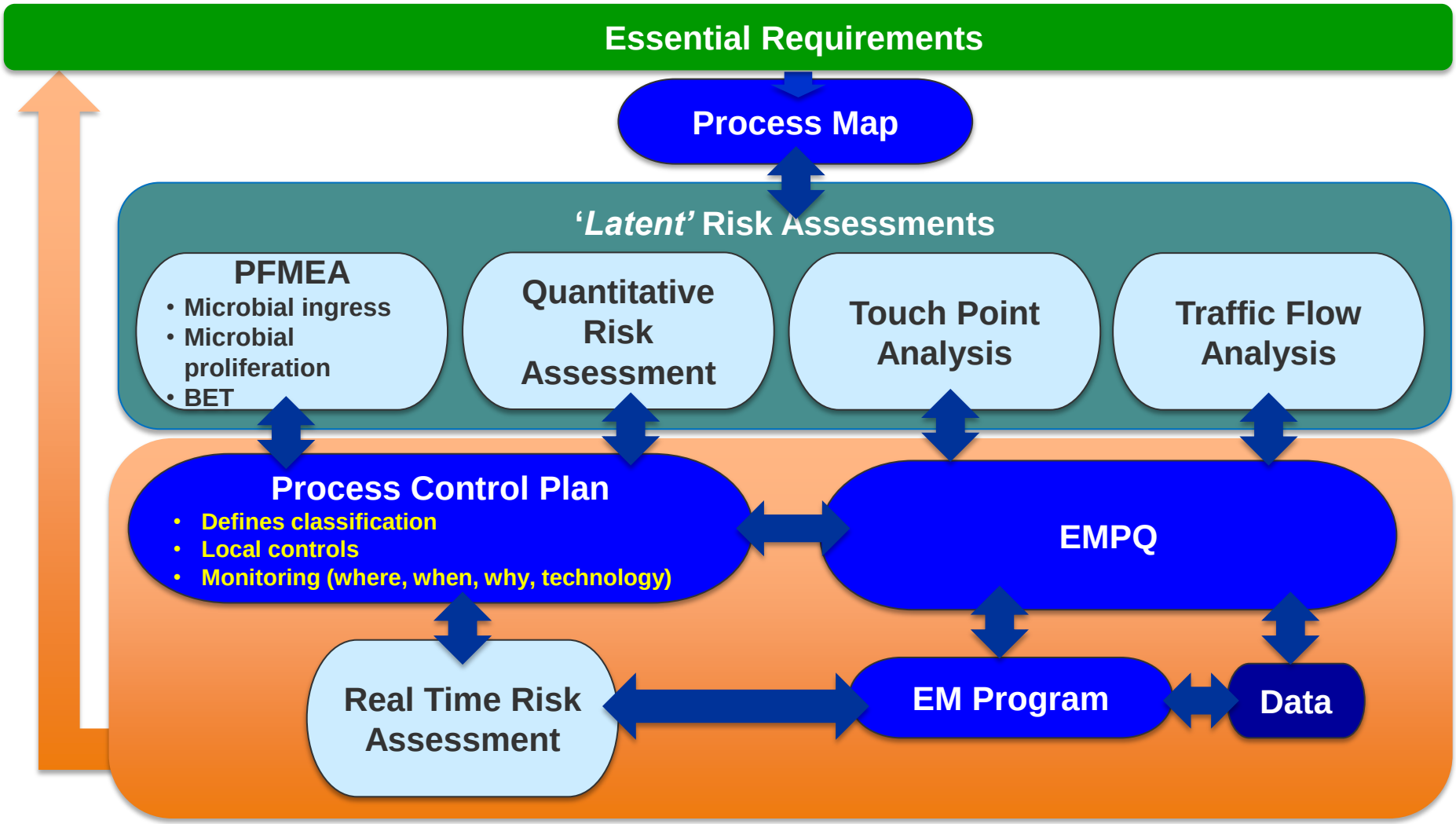
Reference	Cleanroom Standards & Controls
EU GMP, Annex 1	At least a **grade C environment** Where the product is at **unusual risk** of contamination …. filling should be done in a **grade A zone with at least a grade C background**
FDA, Guidance for Industry Sterile Drug Products Produced by Aseptic Processing	Terminal sterilization usually involves filling and sealing product containers under **high-quality environmental conditions**. Products are filled and sealed in this type of environment to minimize the microbial and particulate content of the in-process product and to help ensure that the subsequent sterilization process is successful.
United States Pharmacopoeia 35 <1116>	Perform a **risk analysis to determine the appropriate environmental control classification**. Microbial monitoring should reflect the microbiological control requirements of manufacturing and processing activities.

Parametric Release Guidance – Environmental Controls

FDA Guidance for Industry[3]

'Demonstrated reliability of the production terminal sterilization cycle, **microbiological control** and monitoring and control of production cycle parameters….'


Quality System
Improvement Plan
Risk-Based Lifecycle Management (RBLCM)
Global Product Ownership
Quality Quotient
Advance benefit to patients by reducing product risk
Proactively manage supply continuity risk and residual risk to patients in manufacturing processes
Ensure that residual risk reduction is a never-ending process
Clear overall accountability for health of products throughout their lifecycles
Continuous improvement and residual risk reduction
Closed loop analysis to ensure continuous differentiation and value capture of product portfolios
Measure state of current quality system deployment and linkages
Measure the continuous improvement of the systems we use
Develop and refine enabling tools for effective and sustainable execution


Essential Requirements
Process Map
'Latent' Risk Assessments
PFMEA
• Microbial ingress
• Microbial proliferation
• BET
Quantitative Risk Assessment
Touch Point Analysis
Traffic Flow Analysis
Process Control Plan
• Defines classification
• Local controls
• Monitoring (where, when, why, technology)
EMPQ
Real Time Risk Assessment
EM Program
Data

A New Tool – Quantitative Risk Assessments

- *What is Quantitative Risk Assessment?*
- *Microbial Ingress Technology – Qualification & Validation*
- *Microbial Ingress Technology – Mapping Microbial Contamination Risks*

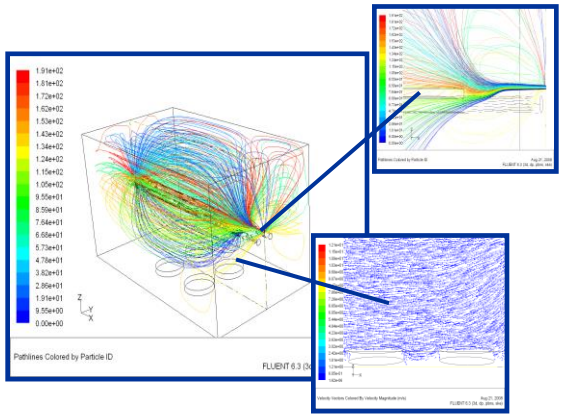
What is Quantitative Risk Assessment?

- Design, process and operationally focused tool
- Structured, objective, systematic quantification of microbiological contamination risks
- Uses well defined and qualified microbial ingress assessment technology
- Models worst case contamination rates – design space
- Design space data applied to real world manufacturing variables to determine contamination risks
- Microbial contamination risk data used to optimize environmental and process controls

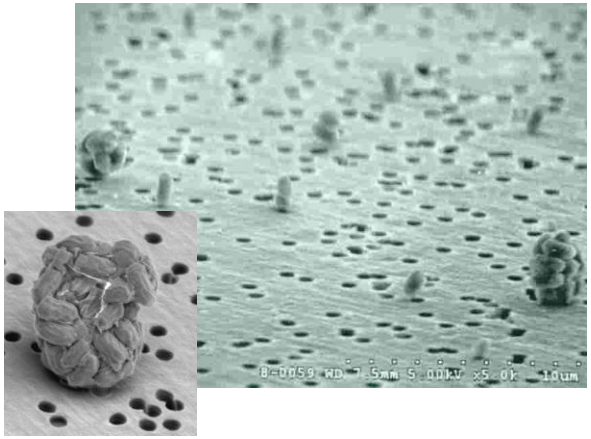
Microbial Ingress Technology – Qualification & Validation

- Microbial ingress test chamber
- Optimized aerosolization
- Fully qualified -

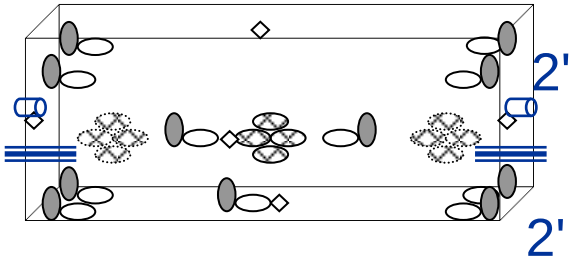
Computational Fluid Dynamics



Witness Plates – dispersal and agglomeration

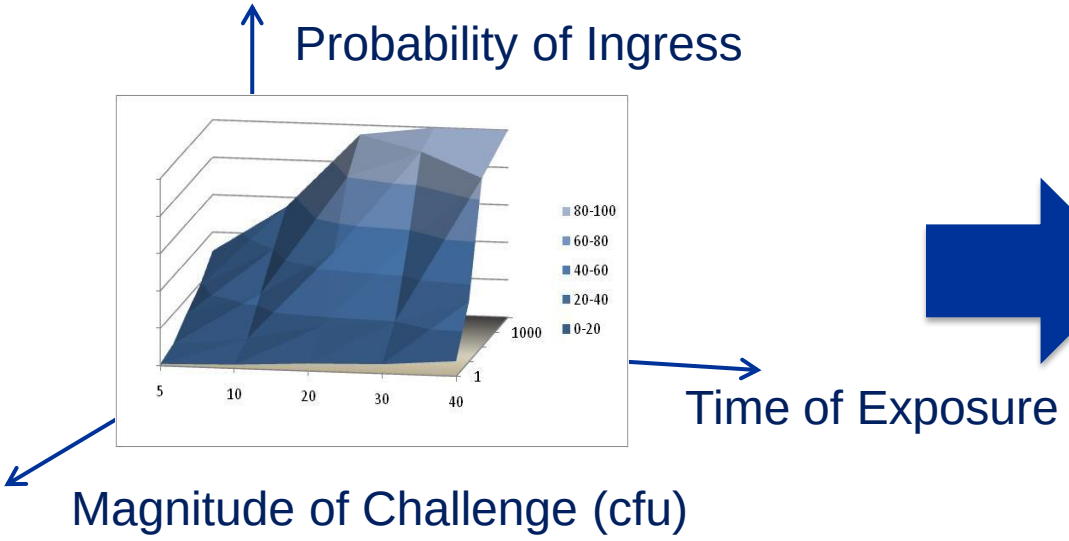


Plates & Active Air Mapping



Microbial Ingress Technology – Maps Microbial Contamination Risks

- Microbial ingress test chamber
- Loaded with media filled containers
- Microbial aerosol challenge
- Variety of different conditions
- Maps the design space for risk of microbial contamination



- Apply manufacturing variable
- Fill speed, container apertures
- Worst case environmental conditions
- Generates quantitative contamination rate – use to optimize controls

A New Tool - Real Time Risk Assessment (RTRA)

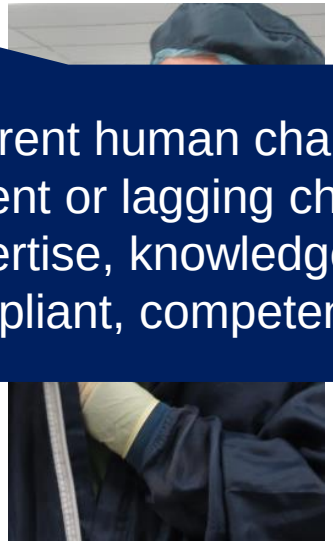
- *Relevant 483s*
- *What is RTRA*

Terminal Sterilized Products - Product Quality Risks From Microbial Hazards

FDA 483s

Employee practices do not align with written procedures and are not assessed for their impact upon manufacturing efficiency and/or product quality. Examples include:

No procedure or means of tracking employees' practice of storing plastic films for use in the fa[illegible]tion of 500 ml and 1000 ml bags



Human behaviors	– inherent human characteristic
Documentation	– absent or lagging change
Oversight	– expertise, knowledge, communication
Culture	– compliant, competent in microbial risk assessment?

Terminal Sterilized Products - Product Quality Risks From Microbial Hazards

FDA 483s

Employee practices do not align with written procedures and are not assessed for their impact upon manufacturing efficiency and/or product quality. Examples include:

No written procedures for employees' practice of using ZZZ and YYY at multiple points on and in the machines that place 500 ml and 1000 ml bags into overwraps to prevent ja[illegible] and possible damage to overwrap pouches and/or bags

Human behaviors	– inherent human characteristic
Documentation	– absent or lagging change
Oversight	– expertise, knowledge, communication
Culture	– compliant, competent in microbial risk assessment?

Terminal Sterilized Products - Product Quality Risks From Microbial Hazards

FDA 483s

Employees engaged in the manufacture and processing of a drug product lack the **training (?)** required to perform their assigned functions. For example:

Filling nozzle on the filler was observed to be misaligned resulting in product solution spilling over the edge of the respective vials being filled. This in turn resulted in product solution pooling in a catch basin beneath the vial conveyor system and forming puddles on the floor and an indention in a wall as the conveyor system trans[illegible] spilled product solution from the filling machine to the capping machine

Equipment design	– human factors, aging infrastructure
Equipment adjustment	– inappropriate, regularity, expertise and know-how
Facility	– aging infrastructure, maintenance
Environment	– risk mitigation activities absent
Culture	– compliant, competent in microbial risk assessment?

Terminal Sterilized Products - Product Quality Risks From Microbial Hazards

FDA 483s

Buildings used in the manufacturing and processing of a drug product are not maintained in a good state of repair, specifically:

> Caulking material around multiple ceiling tiles was observed to be cracking and degrading in the Filling Area where 500 ml and 1000 ml bags are filed and seal[illegible] At least one ceiling tile was observed to have displaced slightly upwards [illegible] interstitial space above

Facility	– aging infrastructure
Facility	– appropriate modification/repair, expertise, risk management
Facility	– conformance to standards
Environment	– risk mitigation activities absent
Culture	– compliant, competent in microbial risk assessment?

Terminal Sterilized Products - Product Quality Risks From Microbial Hazards

FDA 483s

Buildings used in the manufacturing and processing of a drug product are not maintained in a good state of repair, specifically:

A brick, metal beams and large metal cogs were among the objects used to weigh down ceiling tiles as observed from the interstitial space directly above the filling areas

Facility – aging infrastructure
Facility – appropriate modification/repair, expertise, risk management
Facility – conformance to standards
Culture – compliant, competent in microbial risk assessment?

Terminal Sterilized Products - Product Quality Risks From Microbial Hazards

FDA 483s

Equipment and utensils are not cleaned and maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product. For example:

> Inspection revealed numerous HEPA filters, HEPA filter supporting grid work, HEPA filter screens and HEPA filter screen tracks possessed varying amounts of discolored [illegible] chipping paint, multicolored coalescing droplet, and clumps of dark materi[illegible]

Facility – aging infrastructure
Facility – regular assessment, repair, expertise, risk management
Facility – conformance to standards
Culture – compliant, competent in microbial risk assessment?

Key Compliance Root Cause Themes

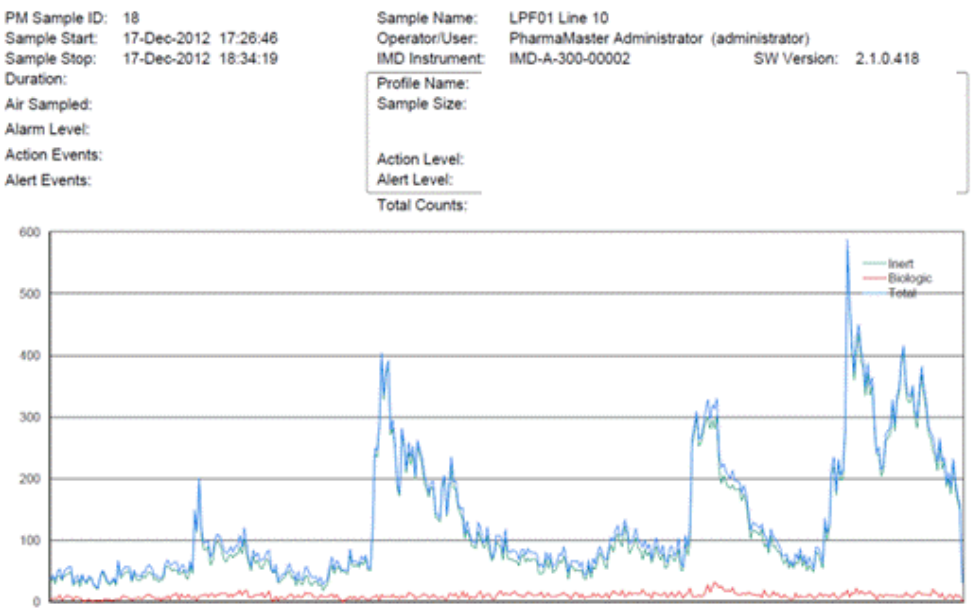
Employee behaviors	– inherent human characteristic
Documentation	– absent or lagging change or behavior
Oversight	– expertise, knowledge, communication
Culture	– compliant, competent in microbial risk assessment?
Equipment design	– human factors
Equipment adjustment	– appropriate, regularity, expertise and know-how
Environment	– risk mitigation activities absent
Facility/equipment	– aging infrastructure
Facility	– modification/repair, conformance to standards, risk management

What is RTRA?

- Behavior, operationally focused tool
- Structured, objective assessment of cleanroom microbiological risks
- Regularly executed during shifts (in real-time)
- Performed and overseen by Microbiologists
- Identified risks are mitigated as far as possible at time of discovery (real-time)
- Risks are reported to Manufacturing, Quality, Engineering management
- Focus alters with improved performance - *evergreen*
- Mean of continuous improvement on cGMP
- Can Incorporate real time environmental monitoring (IMD-A Technology)

Real Time Environmental Monitoring With IMD Technology

- Standardized measurement using IMD-A technology
- Immediate assessment of cleanroom air bacteria and mold levels
- Instant data prevents product or compliance risks
- Continuous improvement



Road Map for Developing / Sustaining RTRA

- EMPQ (Environmental Monitoring Performance Qualification)
- Risk Assessment
- Traffic Flow
- Worst Case Locations

Review Data

Process Review

Involve SMEs

Brainstorming

Implement RTRA per Quality system

Perform RTRA on a regular basis

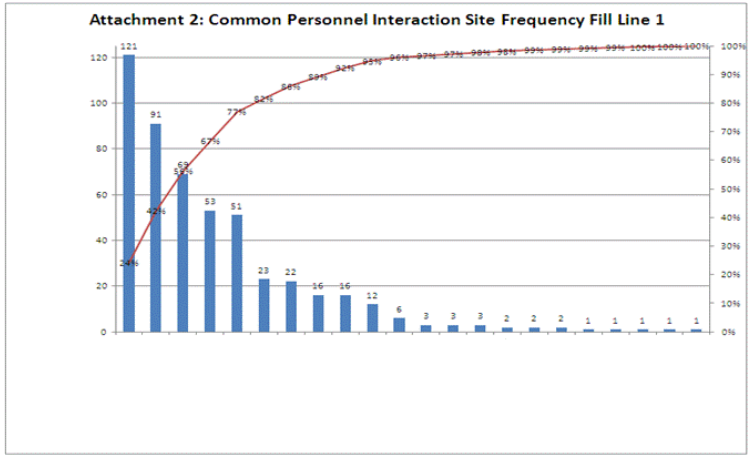
- Microbiologists perform
- Report results regularly

Continuous Improvement

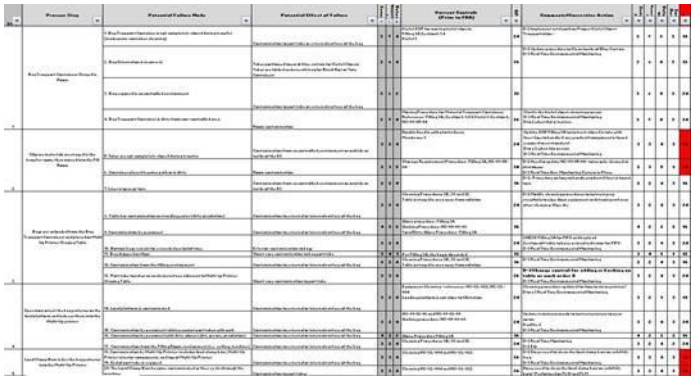
- Corrective Actions
- Preventative Actions
- Knowledge Transfer

Microbiological Process Review

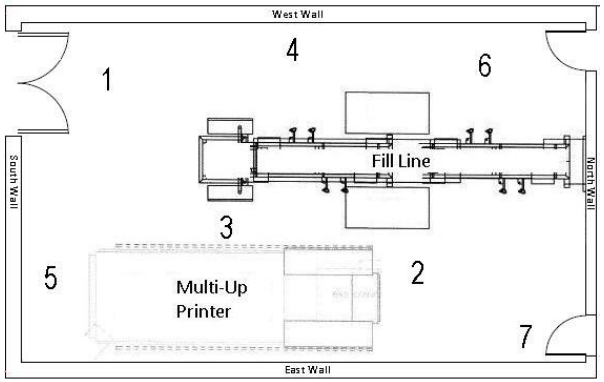
Personnel Traffic Flow Chart



Process Contamination Risk Assessment



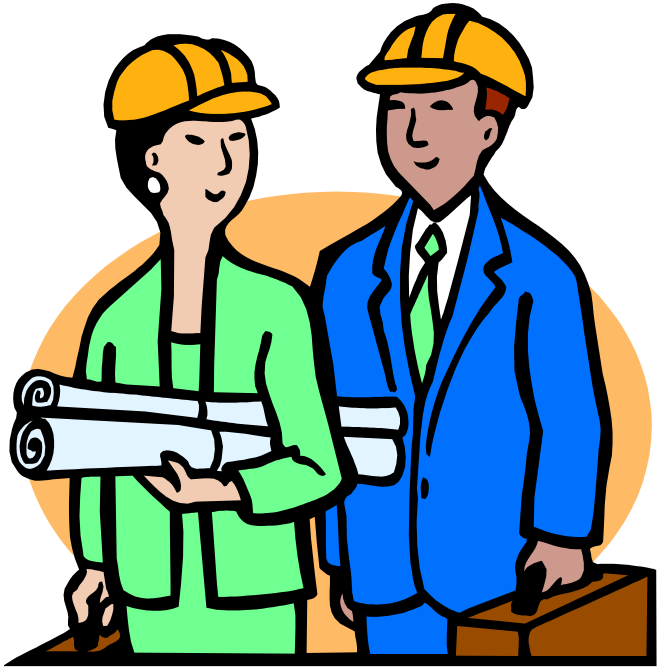
Worst Case Monitoring Locations



Who is to be involved in development?

Microbiologists/Quality

Engineers

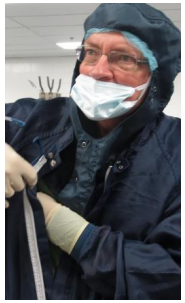


Manufacturing

Developing RTRA - Brainstorm - Results

- Mitigate moisture in clean room (reduce microbial proliferation)
- Interventions and techniques (reduce contamination probability)
- Equipment / Facility / Housekeeping conditions (vectors of contamination)
- Aseptic technique / Traffic Flow / Behavior (vectors of contamination)
  - Use as “teaching moment” to operators/personnel





What Does An RTRA Look like?

- Protocol in three parts

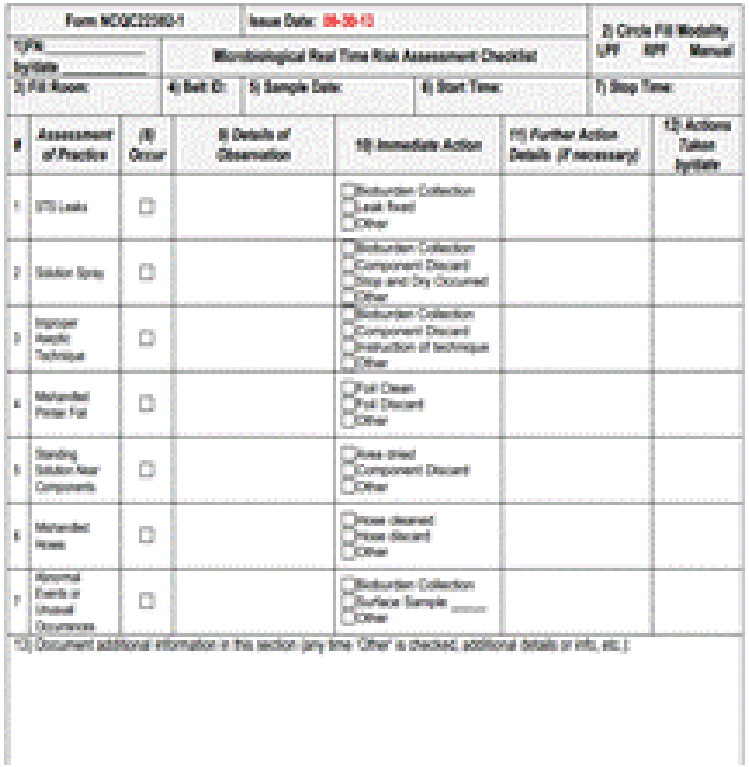
    1) Listed potential or anticipated risks, and recommended actions if observed
    2) New, un-anticipated or previously un-recorded microbial risks
    3) IMD-A testing

- Risks are evaluated *in situ* and potential mitigation decisions made immediately

- This output permits the prioritization for risk reduction and risk mitigation activities

- The protocol and process is maintained ‘evergreen’ – as risk are retired the risk list adjusts to focus on new or higher priority risks, assuring continuous improvement

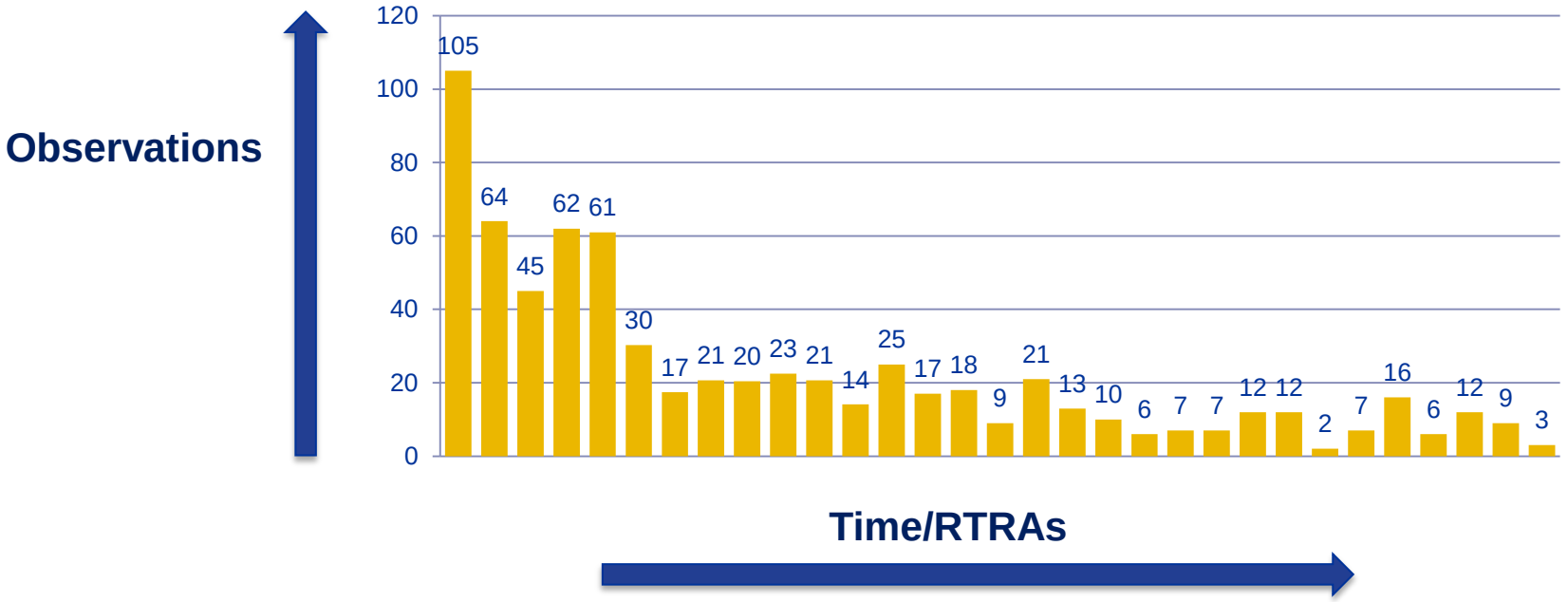
- Fundamentally RTRA realizes all the concepts in ICH Q9 – especially risk communication


Microbiological Real Time Risk Assessment Checklist

#	Assessment of Practice	(8) Occur	9) Details of Observation	10) Immediate Action	11) Further Action Details (if necessary)	12) Actions Taken by/date
1	STO Leaks	☐		☐Bioburden Collection ☐Leak fixed ☐Other		
2	Solution Spray	☐		☐Bioburden Collection ☐Component Discard ☐Stop and Dry Occurred ☐Other		
3	Improper Aseptic Technique	☐		☐Bioburden Collection ☐Component Discard ☐Instruction of technique ☐Other		
4	Mishandled Portion Foil	☐		☐Foil Clean ☐Foil Discard ☐Other		
5	Standing Solution Near Components	☐		☐Area dried ☐Component Discard ☐Other		
6	Mishandled Hoses	☐		☐Hose cleaned ☐Hose discard ☐Other		
7	Abnormal Events or Unusual Occurrences	☐		☐Bioburden Collection ☐Surface Sample ☐Other		

13) Document additional information in this section (any time 'Other' is checked, additional details or info, etc.):

RTRA Observations (Fill Rooms A & B)

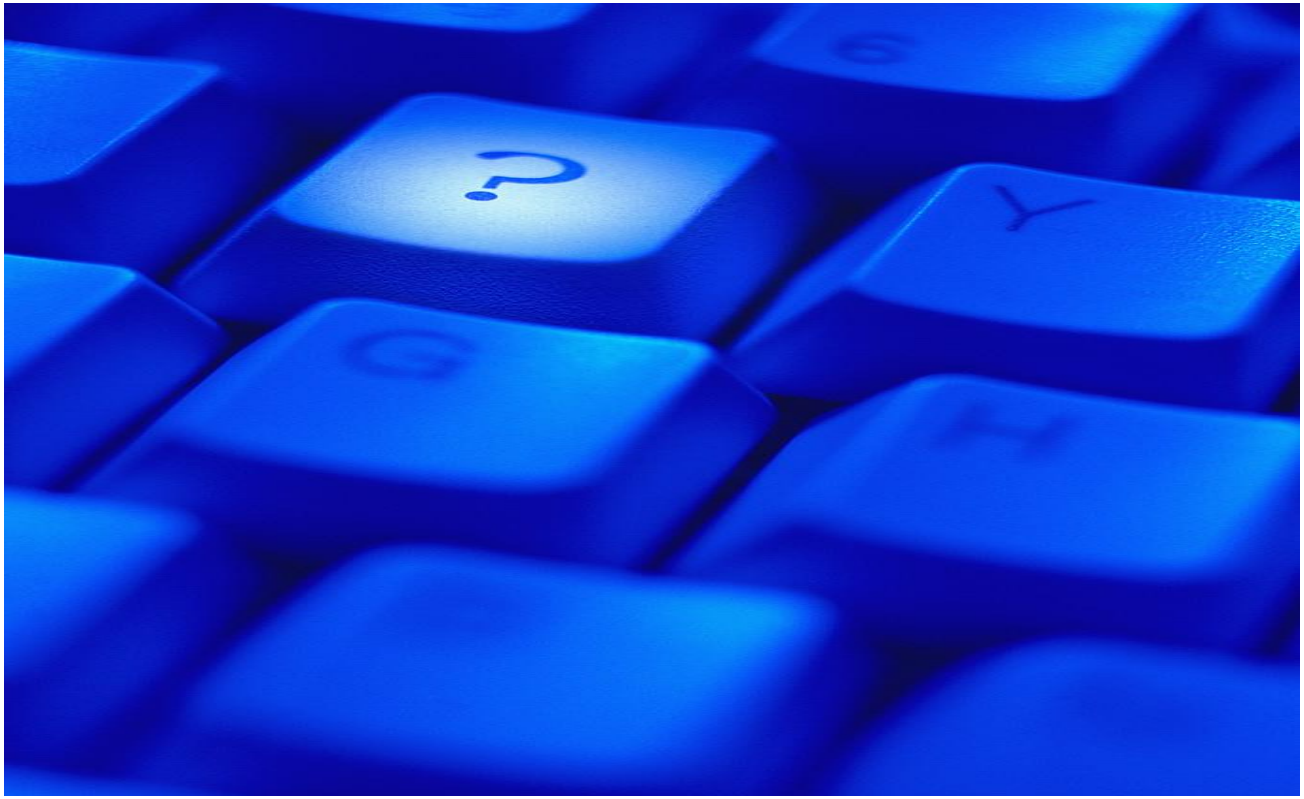


Advantages of RTRA

- Drives continuous improvement of the microbiological state of manufacturing environment and associated practice (cGMP's)
- Fosters Open Communication at a Cross-Functional Level
- Positively alters the culture
- Change from a reactive microbiological quality system to a proactive quality system
- Science-based process for quality decisions
- Data are easily trended and the impact of improvements visualized
- 'Evergreen' process
- Helps meet the guidance for terminal sterilized product manufacture
- Is a 'stepping stone' to raise competency cross functionally

References

1. Sutton., S, Jimenez , L. (2012) A Review of Reported Recalls Involving Microbiological Control 2004-2011 with Emphasis on FDA Considerations of “Objectionable Organisms”. American Pharmaceutical Review. 15, 42-57.
2. Sandal, T. (2012) Review of FDA warning letters for microbial bioburden issues (2001-2011). Pharma Times, 44 (12), 29-30.
3. Food and Drug Administration (CDER, CVM, CBER) "Guidance for Industry for the Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes", February, 2010.



Thank You!