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Global Implementation of System-Based Microbial Control For Parenteral Manufacture



Baxter

Ed Tidswell

Baxter – Public Information

Drug & Device Manufacturing – Local & Global Challenges



SUPPLY

- Supply chain
- Base costs
- Linking lab to market

FDA	ISO	European Commission
21 CFR 210 & 211 Current Good Manufacturing Practices (cGMP)	**ISO 9001:2008** Quality management system requirements	**European Commission GMP**
21 CFR 820 Current Good Manufacturing Practices (cGMP)	**ISO 13485:2003** Quality management system requirements for medical devices	**Medical Devices Directive (MDD)**

REGULATIONS

- Global
- Regional
- Complexity & diversity



PROCESS & PORTFOLIO DIVERSITY

- Personalized care
- Therapies
- Technologies

Drug & Device Manufacturing – Needs & Necessities



SUPPLY

- Flexible production
- Increased agility
- Minimal downtown
- Self-detection, self-correction

FDA	ISO	European Commission
21 CFR 210 & 211 Current Good Manufacturing Practices (cGMP)	**ISO 9001:2008** Quality management system requirements	**European Commission GMP**
21 CFR 820 Current Good Manufacturing Practices (cGMP)	**ISO 13485:2003** Quality management system requirements for medical devices	**Medical Devices Directive (MDD)**

REGULATIONS

- Effective QS integration
- Flexible
- *Commensurate* compliance



PROCESS & PORTFOLIO DIVERSITY

- Improved knowledge
- Flexible processes
- Systems

Regulations – Complexity & Diversity

EU Annex 1 & PIC/s Annex 1 Manufacture of Sterile Medical Products	**ISO 14644** Cleanrooms and Associated Controlled Environments	**FDA 21 CFR 211**	**FDA Guidance for Industry** Guide to Sterile Drug Products Produced by Aseptic Processing
Adjacent rooms of different grades should have a pressure differential of **10 – 15 Pa** (guidance values) (Item 53)	The pressure…should lie typically in the range of **5 Pa to 20 Pa** (Section A.5.3)	Aseptic processing, which includes as appropriate: (iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or non laminar	For example, a positive pressure differential of at least **10-15 Pa** should be maintained between adjacent rooms of differing classification (with doors closed)

Identical intent - Adjacent rooms of different grades should have a positive pressure differential

10-15 Pa	**5–20 Pa**	**None**	**10–15 Pa**

Regulations – Complexity & Diversity

Annex 1 Guidance

Grade A: The **local zone** for **high risk operations**, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. **Normally** such conditions are provided by a **laminar** air flow work station. Laminar air flow systems **should** provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (**guidance value**) at the working position in open clean room applications. The maintenance of **laminarity should** be demonstrated and validated

Intent

Assure that air flow (first air) over and around high risk aseptic operations protects the product by preventing ingress and sweeping away contamination by proven (validated) mechanics and mechanism of HEPA filtered air

Regulations –

- **Effective QS integration**
- **Flexibility**
- **Commensurate compliance**

Global Quality Requirement establishes **intent**

Global & Regional

Should guidance values be outlined globally?

Yes

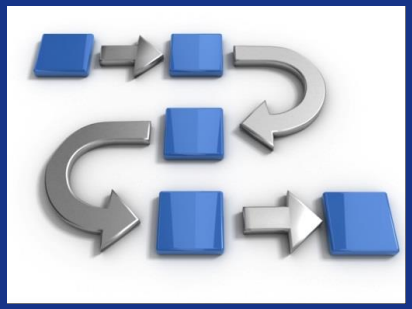
No

Local

Systems-based microbial control

What is System-Based Microbial Control?

- **System** – A group of interdependent items that interact regularly to perform a task



- **Logic** – The principles and reasoning permitting sound decision



System-Based Microbial Control

- The systematic and logic driven management process for the control of microbial hazards and risks during the drug and device manufacturing life-cycle; assuring the provision of products meeting specifications
- System-based microbial control is a self-detecting, self-correcting system
- Systems thinking is not one thing, not a new SOP but a set of habits or practices
- A framework that is based on the recognition that the component parts of a system are best understood as in relationships with each other rather than in isolation

Why System-Based Microbial Control?

Self-Detecting Self-Correcting Systems

Sustained continuous improvement, preventative corrections and improved process control require systems that self-detect and self-correct

Improved Process Control

Improved process control increases product performance, efficiency and economy, reduces scrap and product recalls

Increased Flexibility & Compliance

Patient safety is based upon sound reasoning (logic) for decision. Without documented logic decision becomes arbitrary and compliance driven by strict adherence to rules, reducing flexibility, patient safety and increasing costs

Enhances & Grows Competency

Focuses on facts, data and underpinning science and engineering. Fosters evaluation of data and controls from all elements and parts of quality assurance cohesively geared to patient safety

Microbial Monitoring & Control – *Jenga* Towers That Support Product Quality



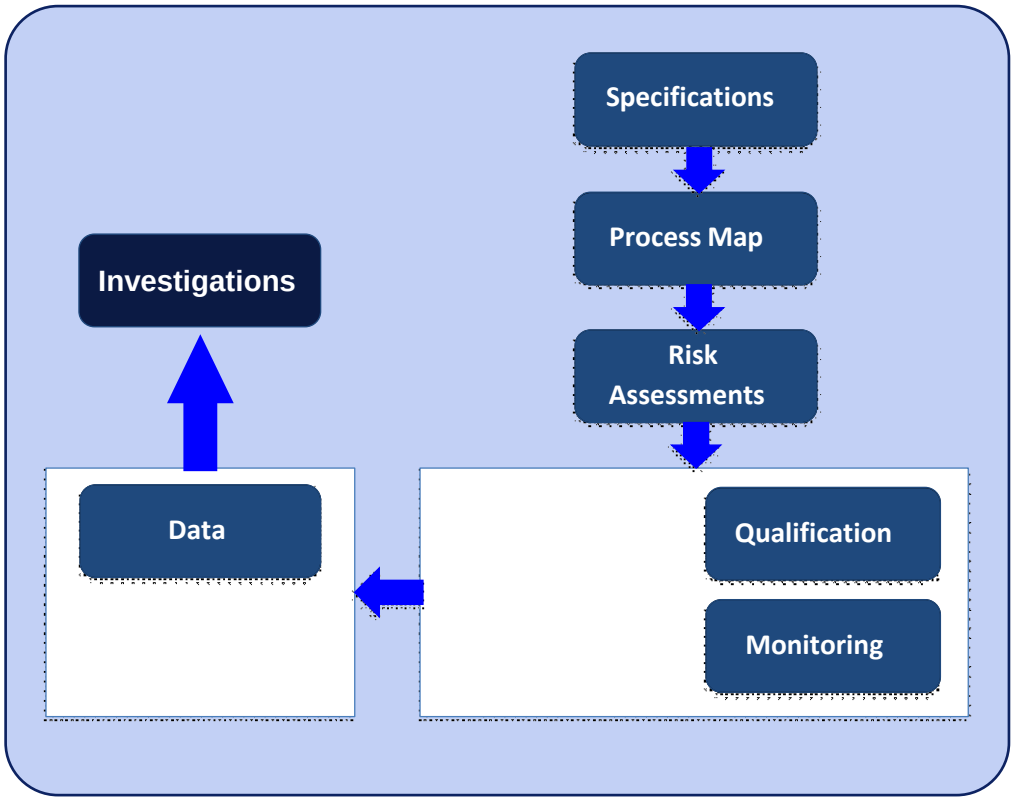
- Built from add on specific requirements or instructions
- No documented or easily explained logic to the selection of controls and monitoring
- Costly through excessive or poorly targeted testing and controls and monitoring
- Difficult to change through inability to predict, detect and correct
- Uncertain control of product quality assurance
- Does not permit flexible self-determined patient safety compliance

System-Based Microbial Control



- Systematic construction of controls
- Designed on easily understandable and documented logic of controls and monitoring
- Efficient through value-adding testing and controls
- Easier to change through increased predictability, self-detection and self-correction
- Certain control of product quality assurance
- Permits flexible self-determined patient safety compliance

Microbial Monitoring & Control – Typical Environmental Control



System-Based Microbial Control – Environmental Control

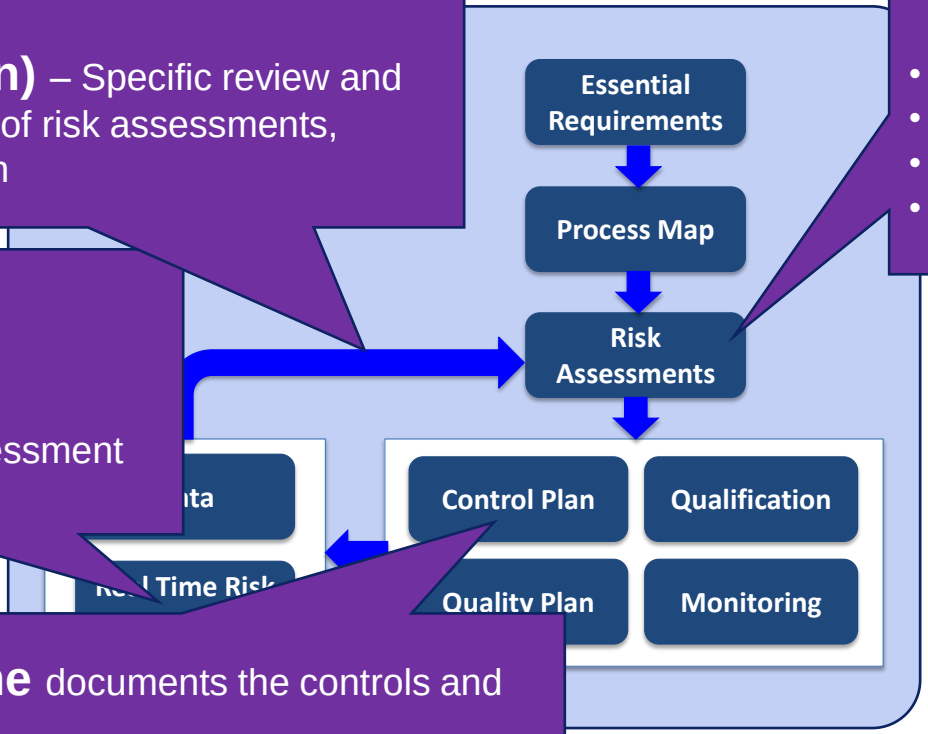
Triggers (detection) – Data, trends and observations trigger specific actions

Actions (correction) – Specific review and decision tree evaluations of risk assessments, qualifications, control plan

Real Time Risk Assessments
Real time in situ risk assessment

Risk Assessments

- pFMEA (process stream)
- Traffic flow
- Touch point
- Quantitative



Control Scheme documents the controls and monitoring and logic

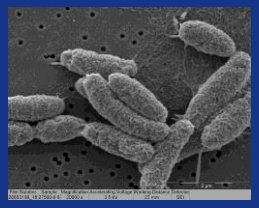
Quality Plan documents the schedule of improvements and logic for the schedule

System-Based Environmental Microbial Control – Key Points Risk Assessments

pFMEA





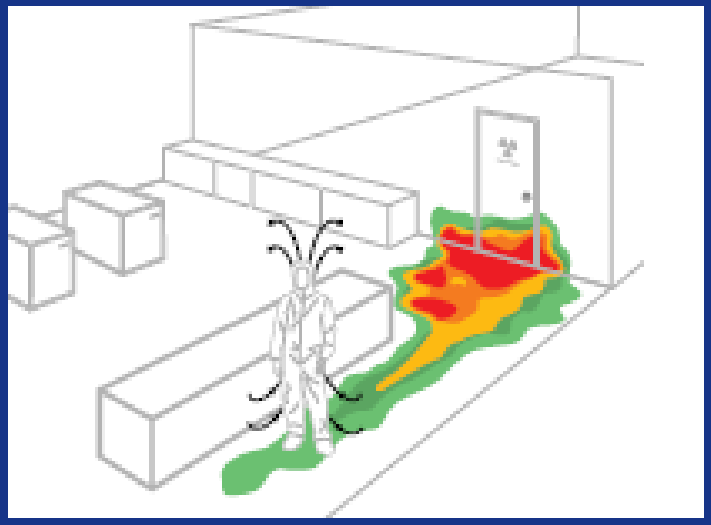




- **Microbial Ingress** –assessment of probability and severity of microbial ingress in to the process
- **Microbial Proliferation** – assessment of probability and severity of microorganisms replicating at that point in the process
- **Microbial Retention** – assessment of probability and severity of microorganisms remaining, staying, adhering to that part of the process
- **Pyrogens** – applying the above same failure modes

System-Based Environmental Microbial Control – Key Points Risk Assessments

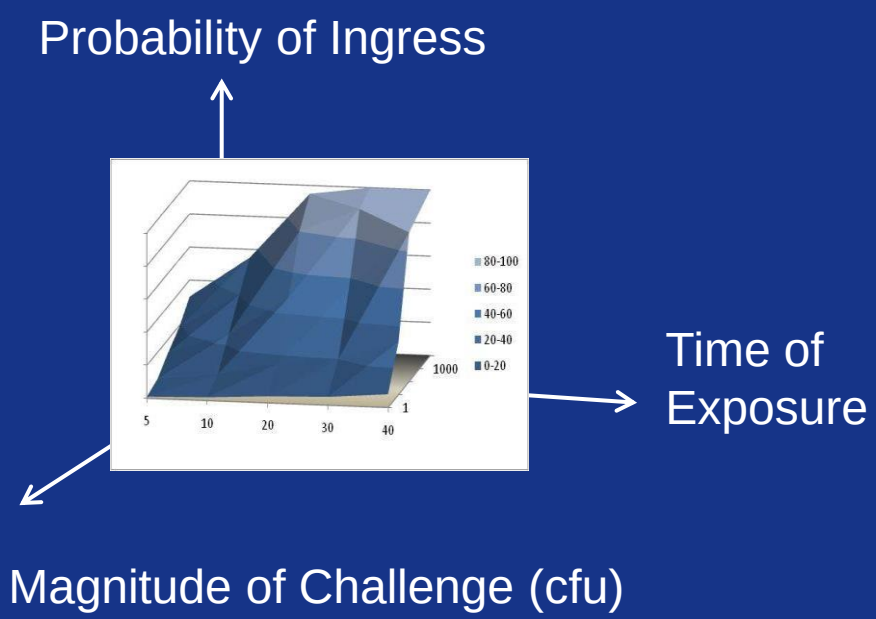
Traffic Flow & Touch Points



- **Personnel**
- **Product**
- **Waste**
- **Components**
- **External to Area** - Consider traffic flow outside the immediate areas where common touch points can occur from items that never enter the cleanroom or environment under evaluation

System-Based Environmental Microbial Control – Key Points Risk Assessments

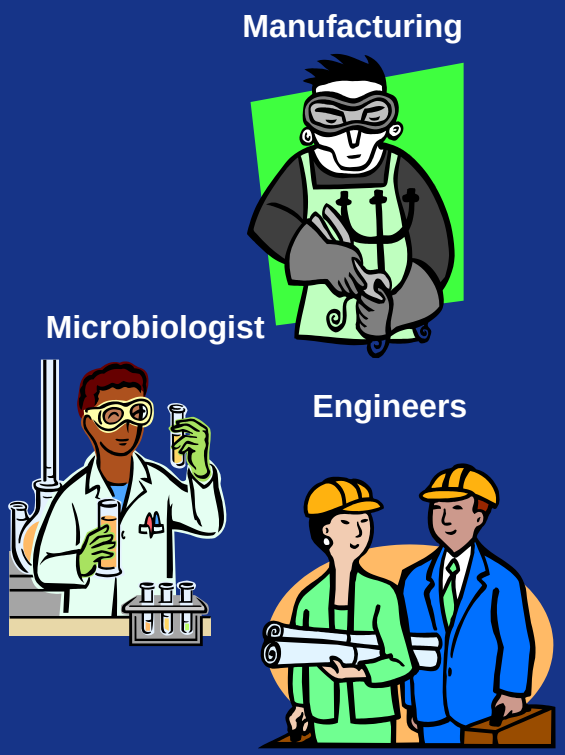
Quantitative Risk Assessments



- **Air-borne ingress –** for open process steps or open containers air borne ingress can be quantified
- **Mechanics of air flow –** air flows and contamination rates are quantifiable as likely units contaminated with at least 1 cfu
- **QbD** – quantitative assessment of contamination risk maps design space in a surface response model permitting QbD principles to be applied

System-Based Environmental Microbial Control – Key Points Risk Assessments

Real Time Risk Assessments



- 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

System-Based Environmental Microbial Control – Key Points Triggers



Triggers

- Set to avoid ‘nuisance or noise’ responses
- Consider rolling time, certain SPC rules
- Recovery rates and hit rates
- Define risk profile or minimum species profile and ‘index microorganisms’ to respond to
- Inspection, audit observations
- Control fails (e.g. growth promotion)

System-Based Environmental Microbial Control – Key Points Example Triggers

Main Categories of Microorganism Recovered From Cleanrooms*

Microorganism	Grade B	Grade C	Grade D
Gram positive cocci	81%	63%	41%
Gram positive non-sporing rods	3%	14%	12%
Gram positive sporing rods	13%	10%	19%
Gram negative rods	2%	12%	20%
Fungi, yeasts, mold	1%	1%	8%

Aseptic Manufacturing Cleanroom Recovery Rates**

Room Classification	Active Viable Air (%)	Passive Viable Air (%)	Surface Sample (%)	Glove or Garment (%)
Isolator/Closed RABS (ISO 5 or better)	< 0.1	< 0.1	< 0.1	< 0.1
Grade B	< 1	< 1	< 1	< 1
Grade C	< 5	< 5	< 5	< 5
Grade D	< 10	< 10	< 10	< 10

*Derived from Sandal, T. (2011). A Review of Cleanroom Microflora: Types, Trends, and Patterns., *PDA J. Pharm. Sci and Tech*., **65**, 392-403.
** USP <1116>

System-Based Environmental Microbial Control – Key Points Actions



Action

- Risk assessment review – root cause or failure mode included? Add if missing…
- If root cause or failure mode included was it risk assessed appropriately? Re-assess with improved knowledge…
- If risk assessment was appropriate were the controls adequate? Adjust, amend, add as necessary and include on **Quality Plan**
- Review control plan – were the cohesive controls and monitoring program appropriate. Adjust, change as necessary **Control Plan**
- Review qualifications (environmental monitoring performance qualification). Adjust, add as necessary and include on **Quality Plan**
- Action instill continued improvement in know-how, competency, knowledge and keeps the system ‘evergreen’

System-Based Environmental Microbial Control – Key Points Control Plan



Control Plan

- Describes holistic microbiological controls, and monitoring
- Rationale for cohesive set of controls and monitoring
- Single source document for risk-based microbial controls
- States the logic, science and engineering reasons
- Permits a holistic view of cohesive controls
- Can be used to change sampling and controls
- A swift and easy means for non-facility personnel to evaluate the ‘health’ of the facility
- Reviewed upon triggers and therefore assists continued improvement in know-how, competency, knowledge and keeps the system ‘evergreen’

System-Based Environmental Microbial Control – Key Points Quality Plan



Quality Plan

- Describes environmental control improvements
- Cohesive holistic plan and schedule of actions and improvements
- States the logic and rationale for the sequence and schedule
- Includes ‘bridging’ actions
- Maintained ‘evergreen’ to sustain a genuinely continuum of systematic and cohesive improvements
- Regularly reviewed and approved by Quality and manufacturing

Global Implementation



71 ‘entities’
4 regions
26 Countries

Terminally sterilized
Aseptic
Compounding

LVPs
SVPs
Devices

Varying competency
Not in current QMS
Significant paradigm change

Global Implementation - Strategy



Design process
Pilot at multiple entities and use to grow SMEs
Asses impact at 80-100% entities

Embed in QMS
Global requirements & multiple tools

Prioritize implementation outside QMS process
Communication at multiple venues – top down, bottom up

Regional SME deploy
Align regional and entity SMEs through personal objectives
Flexible deployment pattern

Global Implementation - Strategy



Design process
Pilot at multiple entities and use to grow SMEs
Asses impact at 80-100% entities

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Global Implementation - Assistance



- Supporting Documentation – additional information, reinforcing learning
- Compile feedback on draft quality system documents and use as learning tool
- FAQ – collect during pilot impact assessments
- Program of presentations
- Encourage facility-facility partnering, interaction within a community
- Develop champions from early adopters, pilot facilities to lead
- Provide best practices, lessons learned and supporting literature
- Single location for resources and community

Global Implementation - Learning



Wide variety in competency
Over communicate
Use multiple means of assisting
Ideal implementation sequence rare
Quality Plan first if not all elements in place
Control plan forces conversations on logic
Control plan forces clarity on state of control
Generally positive feedback from MOHs

System-Based Environmental Microbial Control – Summary

Challenges

- Supply/shortage. Regulations and standards complex. New processes, new technologies, new products

Needs

- Agility, flexibility, speed. Commensurate compliance, global integration. Systems thinking with improved know-how

Systems-based Microbial Control

- Structured way of operating
- Genuine science and engineering foundation for patient safety
- Instill continuous improvement and improved competency
- Documents genuine current state and provides clear logic of road map for the future state – because we all have legacy and aspire to improve


Baxter
Thank You!

Let us meet again..

We welcome you all to our future conferences of OMICS International

2nd International Conference and Expo on

Parenterals and Injectables

On

October 24-26, 2016 at **Istanbul, Turkey**

http://parenterals-injectables.pharmaceuticalconferences.com/