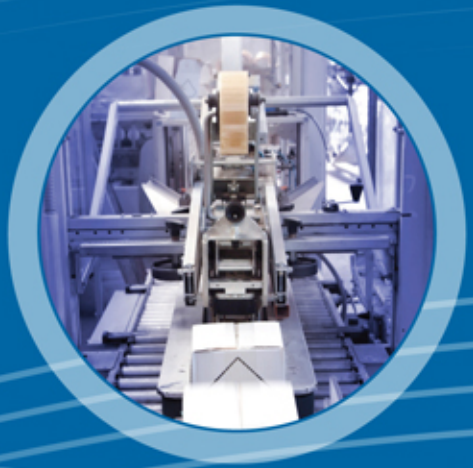
Connecting People, Science and Regulation

PDA Parenteral 2014
Munich Conference

Contamination Control: Particles, Bio-contamination, Bioburden and Endotoxins in Aseptic manufacturing.



James Drinkwater
F Ziel Head of Aseptic processing technologies & GMP Compliance.
Chairman of PHSS.

Contents

Contamination Control & Cross Contamination Control.

What's new in Industry, Pharmacy requirements

< WHATS NEW >
In knowledge
In GMP

What's new in regulatory expectations and initiatives

Contamination Control: Particles, Bio-contamination, Endotoxins: Strategies, Principles, Disinfection, Techniques, Procedures.

Environmental monitoring, Bioburden, Sterility, Endotoxin testing Through phases of establishing control to formal state of control

Initiatives: following on from QMS, QbD, QRM, PAT, CPV and Q-Metrics the EU GMP Annex 1 is in process for revision. Under review for Annex 1 are Control Strategies for manufacturing Sterile Drug products/ substances.

Best Practice Guidance:
The PHSS have published a Bio-contamination 'Life cycle' Technical monograph – reviewed by the MHRA before publication.
The PDA are preparing a Technical Report on Cleaning and Disinfection.

What's New: Knowledge

Photographs courtesy of F Ziel GmbH.

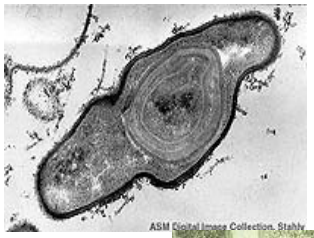
- **Gowned operators generate microorganisms so following Quality by Design principles a physical separation barrier** between the process/ product and the most contaminating source 'people' e.g. with Isolators, RABS is required particularly in Aseptic processing that is increasing with new biological products.

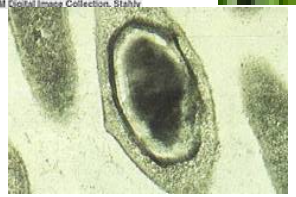
- **Environmental monitoring is limited in recovery with limited sample sizes and sample areas/ volumes** meaning we only have an indication not absolute values on contamination levels; trends (much data) are needed to indicate state of control. A single measuring event has little value on its own.

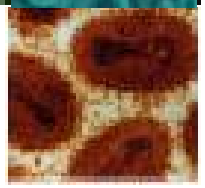
- **We are still learning about disinfection and developing new approaches: Manual, Semi-automatic and Automatic**. Isolators are typically decontaminated with vH_2O_2 – VHP (bench mark), other automated gaseous disinfection processes may apply, and still there is not widespread knowledge in this area: An understanding of Science, Process and Microbiology are key to efficacy, efficiency and GMP compliance.

- Despite being an established process **the industry still has problems with Moist heat sterilisation**

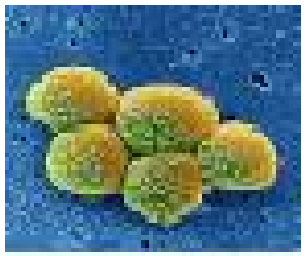
Challenges of Resident and Transient micro-flora in Controlled Environments





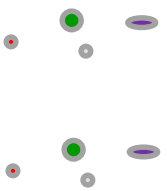


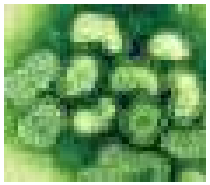
Microflora on Materials in transfer

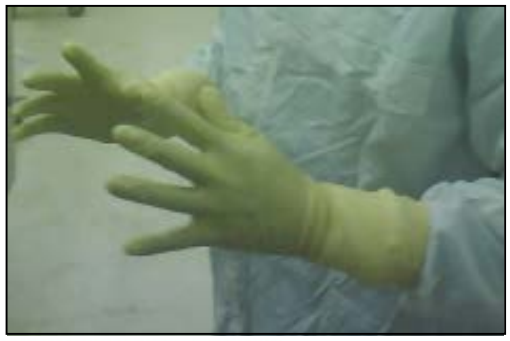


Microflora on Hand transfer

Microflora transfer from Surrounding Environment







Controlled Environment

Controlled Zones

Containment & Cross Contamination control

Pharmaceutical Containment Hierarchy

1
- **Biological safety rooms and cabinets: Biological safety Levels Rooms BL1,2,3,4 & Class 1,2,3 cabinets**
- Containment of Biologically hazardous, toxic, pathogenic organisms, products/substances for operator protection. Requirements detailed in Biosafety standards.

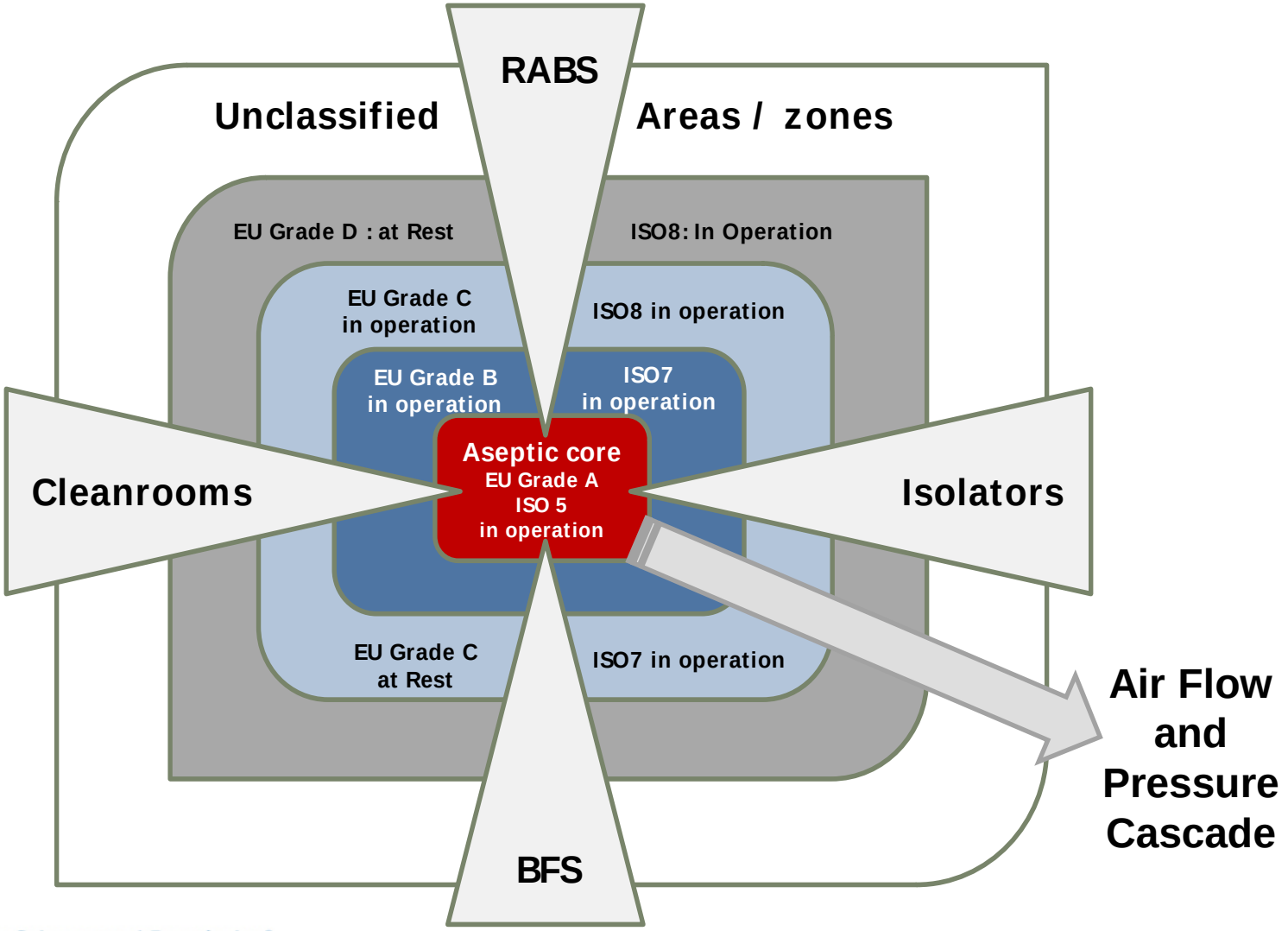
2
- **AP1 – Active Pharmaceutical Ingredient containment: API Powder containment including non sterile products**
- Containment levels referenced in API micro-grams by cubic metre for operator protection. Powder containment in Isolators (turbulent flow) and closed systems.

3
- **Aseptic and Toxic containment in Aseptic processing of sterile medicines, drugs and drug substances.** Using Isolator technology with Safe Change Filter barrier containment and CIP / decontamination features
- Product and operator protection to O.E.L. including containment for cross contamination control

4
- **Aseptic and non pathogenic biological product containment in Aseptic processing of sterile medicines, drugs and drug substances.**
- Product protection and containment for cross contamination control using Isolator barriers.

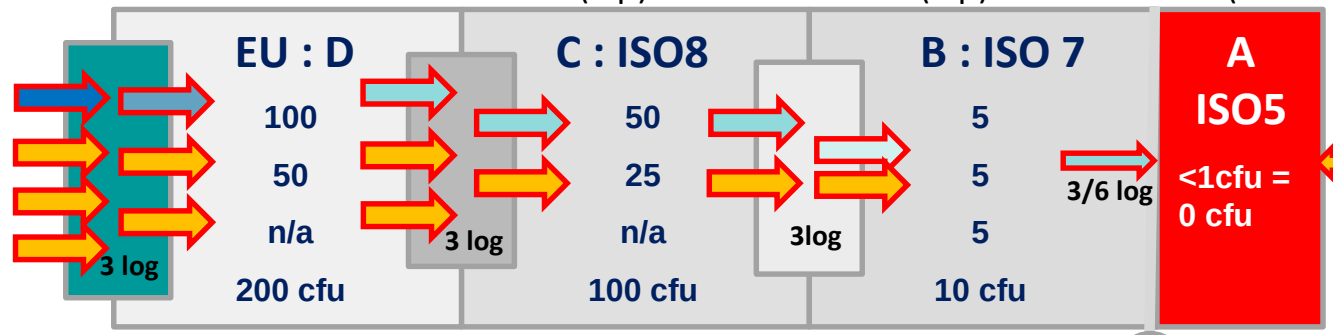
5
- **Aseptic processing with product protection**
- Product protection using Barrier Separation Technology (Isolators and RABS).

Classified Area Zonation



Control Targets: Total particulate & Microbiological levels

GMP Annex 1 > ISO 14644 Parts 1 & 2



Microbiological Contamination as colony forming units > (cfu)

- Settle plates max cfu.
- Contact plates max cfu.
- Glove prints max cfu.
- Active air cfu / cubic metre.

In Operation>

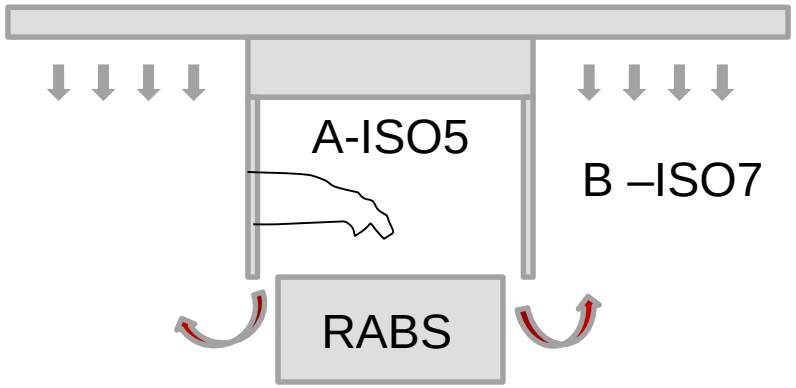
ISO 14698

FDA guidance.

USP<797> & <1116>

Air flow & Pressure Cascade direction

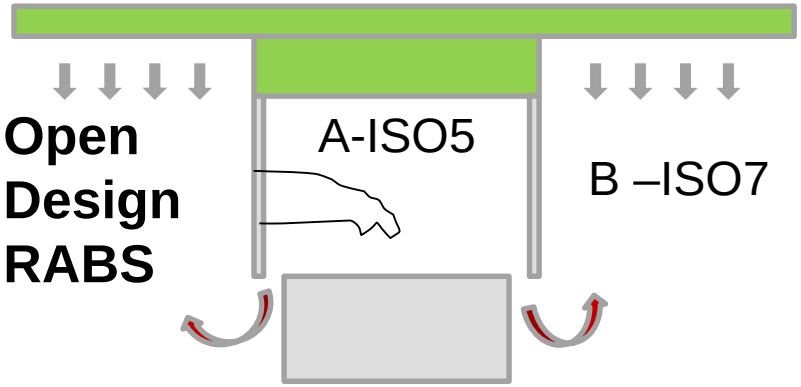
What's New in Contamination Control :Barrier Separation Technology



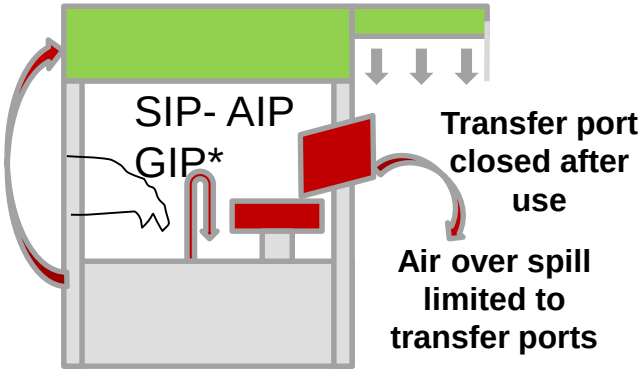
- **Do we really understand what the differences are between Isolators and RABS** with all the configuration variants and what is best for a given application.
- **Do we understand the Contamination control attributes of Barrier Separation Technology** and how they are applied for contamination control.
- **Do we understand how containment applies for Pharmaceutical applications**, other than APIs; powder particle containment that are well characterized.
- **Could we finally be making progress with implementation with RMM/ RTM?**

Open & Closed Design RABS
Open & Closed Operation RABS

RABS: Combination or Physical and Aerodynamic barrier. Passive or Active Air management



Active Air management +ve



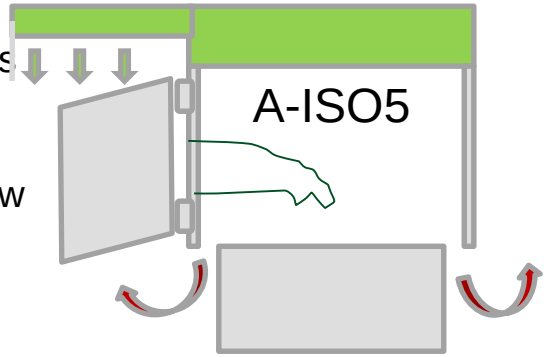
*VHP-GIP possible.

Open & Closed Operation

Using Open or Closed Design RABS.

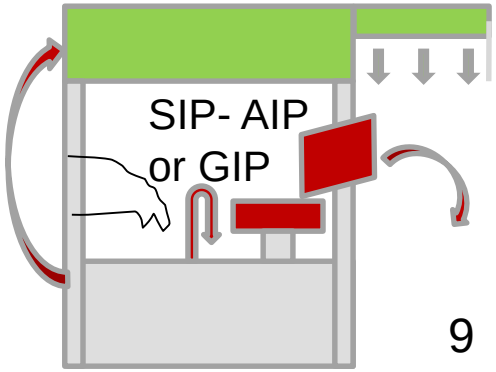
Open Operation RABS

Open barrier door operator interventions are risk assessed, justified, controlled and monitored. Airflow protection at open door.



Best practice: Closed Operation RABS

After set up and last Bio-decontamination step barrier doors remain **closed** for complete aseptic processing **operation**. Interventions only by barrier gloves for operators & controlled access ports for materials.



SIP=Sterilise in place. AIP= Aseptic/assembly-GIP=Gassing in Place.

Hierarchy of Biological Reduction

Biological Reduction Hierarchy

1
- **Sterilisation: Moist Heat, Dry Heat Gamma irradiation, ETO**
- Penetrative processes fully referenced in pharmacopeia's delivering a defined sterility assurance level (SAL)

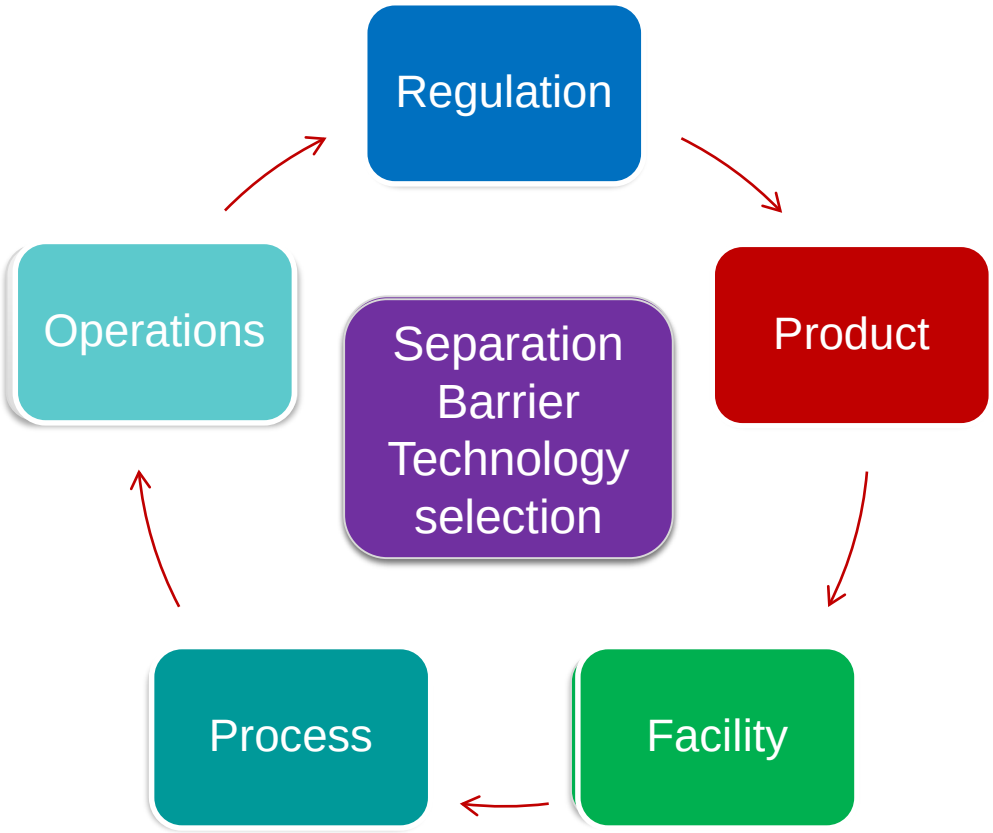
2
- **Automated Surface Sterilisation**
- Non-chemical based automated surface sterilisation
- Chemical based automated Gaseous Surface Sterilisation in combination with residue free cleaning to prevent chemical contamination transfer to products

3
- **Automated Gaseous Disinfection (airborne and surfaces)**
- examples include Hydrogen peroxide vapour –vH_2O_2/ VHP

4
- **Semi-automated aerosol/ fogger disinfection (airborne and surfaces)**
- examples include Dry fog, nebulisers

5
- **Surface Manual Disinfection Processes;** In-process efficacy qualification
- **Surface Manual Disinfection Procedures:** Laboratory qualified efficacy. in-process qualification of agent application via procedures (SOPs). EM used to monitor impact on microbial control

Holistic Decision making –
Separation Barrier Technology selection

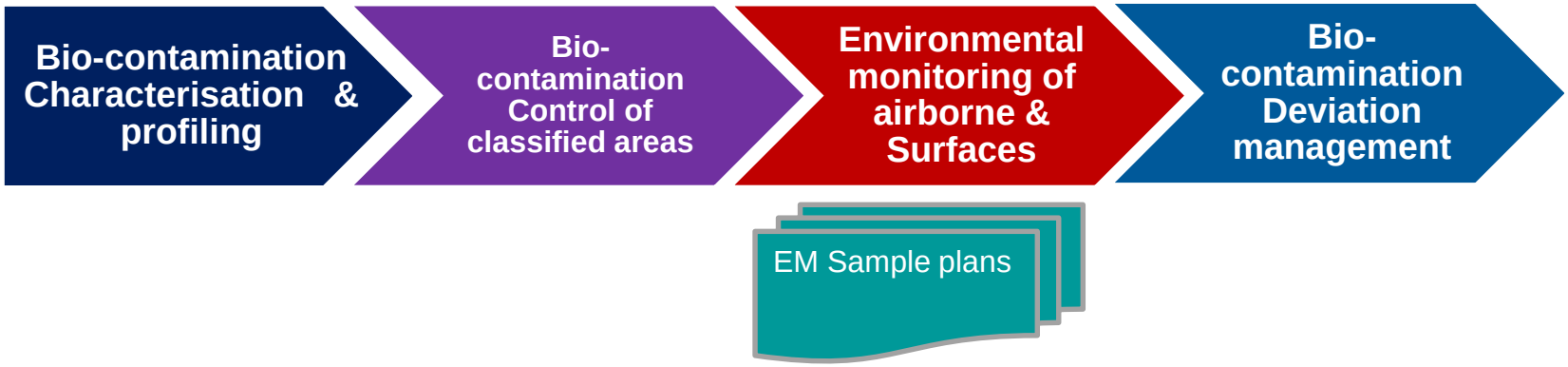


Use a control strategy to consider each area for key requirements / issues that influence the Barrier Technology: Isolator or RABS selection.

Contamination Control

PHSS Bio-contamination Monograph Structure

Guidance on best practice including 'how to do', 'how to achieve compliance' and examples – not just principles;



The monograph is intended as a key reference on Best practice and training resource and reference for SOP development
A major reference for Indian companies.

Control Strategies – Sterile Products Manufacturing: PHSS White Paper

phss

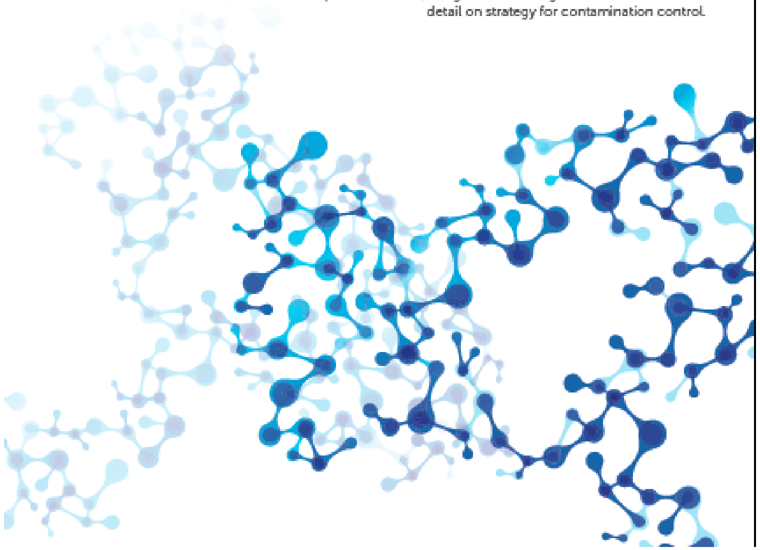
over 25 years of advancing pharmaceutical and healthcare sciences

Control Strategy

In manufacture of Sterile Pharmaceutical/ Drug products.

PHSS 'White paper' on principle considerations for a Control Strategy including additional detail on strategy for contamination control.

Guidelines to create and manage a control strategy in pharmaceutical manufacturing processes need to be better defined. This PHSS White paper communicates principle considerations for a Control Strategy in sterile pharmaceutical/ drug manufacturing and includes additional detail on strategy for contamination control.



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Control Strategy Content

1.0 Principle components of a Control Strategy

As outlined the Control Strategy should be considered in three component parts all of which are inextricably linked:

- Manufacturing control strategy.
- Quality control strategy.
- Contamination control strategy.

Manufacturing of sterile Pharmaceutical/ Drug products, substances and constituents requires a risk based approach, in design; Quality by Design (QbD principles) and in quality under the auspices of a Pharmaceutical Quality System including Quality Risk Management following ICH Q10 integrated in EU GMP Part I Chapter 1.

The setting of control strategies in manufacturing combines manufacturing control, quality control and contamination control to deliver the specified product quality, efficacy and patient safety.

Each aspect of manufacturing, quality and contamination control needs consideration in setting a Control Strategy. This White paper sets out principle considerations for the Manufacturing and Quality control strategies with more detail around the Contamination control strategy as the main focus of this White paper.

2.0 Manufacturing Control Strategy

The Manufacturing control strategy should include considerations on the follow areas together with a defined approach set out how a specified level of control will be achieved/ implemented:

- Whether the product is to be manufactured by terminal sterilization (preferred for risk management in patient safety) or by aseptic processing (justified for product type). For some product types that may be impacted by overkill terminal sterilization processes it may be possible to justify suboptimal sterilization cycles that deliver the required Sterility assurance level (SAL) over aseptic processing.

Control Strategies

- A Control Strategy should be considered to include: All are inextricably linked.
- **Manufacturing control strategy;** based on product type, demand, process and risk.
- **Quality control strategy;** based on understanding of risk with control of Critical Quality Attributes (CQAs) in a manufacturing process meeting regulatory requirements.
- **Contamination control strategy** including cross contamination control that may include requirements for containment/ product segregation.

A PHSS white paper on Control Strategy for Manufacture of Sterile Products has been released.

Characteristics of a Control Strategy

- **Key characteristics of a control strategy for contamination control would be considered as:**
- **Product and process knowledge and skills in pharmaceutical product manufacturing and GMP/ cGMP compliance critical to an effective risk based approach to control.**
- **Under the auspices of a Pharmaceutical Quality System (PQS) together with initiatives of Quality by Design (QbD) and Quality Risk Management (QRM).**
- **All changes as a result of increasing knowledge, process improvements are subject to a change control process.**
- **Dynamic and iterative throughout the product life cycle.**
- **Holistic and proactive.**
- **Based on targeted/ risk based measures of contamination avoidance**
- **Uses key performance indicators (KPIs) to assess status of contamination control**
- **Includes a defined strategy for deviation management: investigations and CAPA.**

Contamination Control in Isolator Barriers: Aseptic – Containment Filling

Personnel Gowning monitoring

Photo: Courtesy of Pharmagraph

Concept courtesy of F Ziel

Clean/ Sterilize Vials

Biological Product

Sterile Caps & Stoppers

Sterile Vial In feed

Filling

Buffer

Rapid Decon VHP

EM plates & parts

Track & Trace Bar-coded EM Plates

Finished Product

Active mouse hole with Filter barrier

Cap 1.

Cap 2.

Lyo Interface 1.

Lyo Interface 2.

Lyo 1

Lyo 2

Isolator/ RABS Leak Integrity Classes

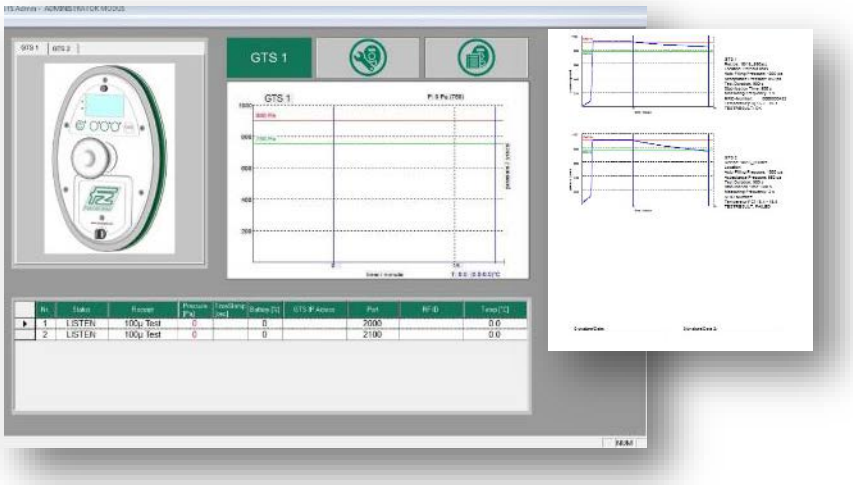
Table 1 *Leak integrity acceptance criteria.*

Barrier system Leak rates specified as % volume per hour	Reference for acceptance criteria: Isolators or RABS. Also reference PHSS RABS monograph no 15.	Pressure decay measured values from test pressure (1.5x) to (2x) operating pressure	Application – Typical but not limited to:
0.25% volume per hour	ISO 10648-2 Class 2	25pa pressure decay in 6 minutes.	Negative pressure operation small scale barrier isolators or hotcells used for processing radiopharmaceuticals.
1% volume per hour	ISO 10648-2 Class 3	25pa pressure decay in 1.5 minutes.	Positive pressure operation small scale and negative pressure large scale barrier isolators.
2% volume per hour	Reference from this monograph for Isolators. PHSS RABS Class 1 leak integrity.	50pa pressure decay in 1.5 minutes.	Suitable for Isolators and Closed design RABS barrier integrity and H2O2 sporicidal gas/vapour OEL/ containment in small scale Isolators.
3% volume per hour	Reference from this monograph for Isolators.	75pa pressure decay in 1.5 minutes. Typically method limited to 3% vol/hr. Pressure decay / time can vary to suit barrier.	Suitable for large scale Isolators barrier systems barrier integrity and H2O2 sporicidal gas/vapour: OEL containment and compliance.
5% volume per hour	PHSS RABS Class 2 leak integrity. Reference from this monograph for Isolators.	Pressure hold test: Leak volume flow rate to hold test pressure.	Suitable for Closed design RABS sporicidal gas/vapour containment and large scale Isolator systems.
10% volume per hour	PHSS RABS Class 4 leak integrity. This class does not apply to Isolators.	Pressure hold test: Leak volume flow rate to hold test pressure.	Construction test for RABS barrier (if required by risk assessment). Not applied to Pharmaceutical Isolators.

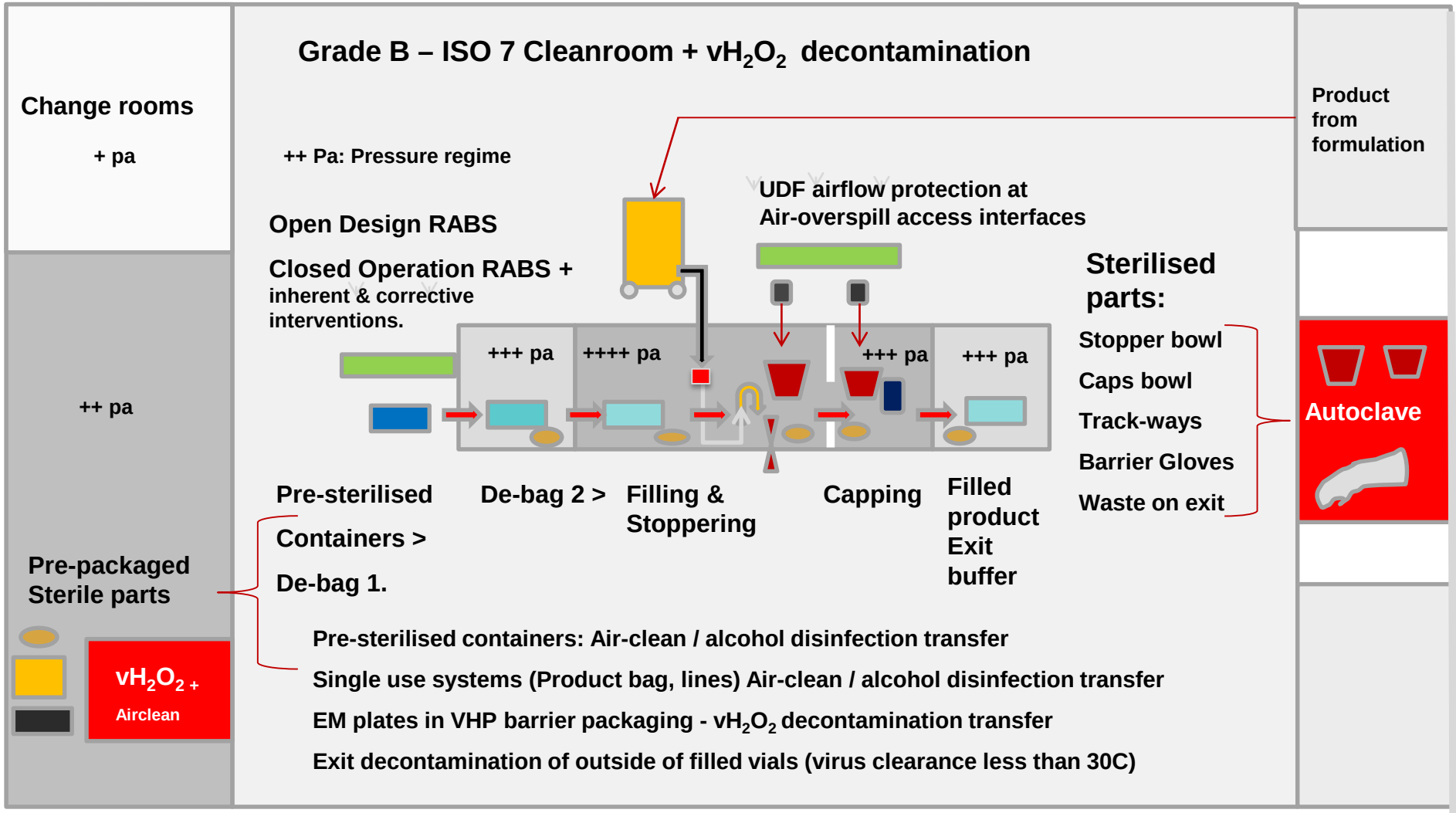
Isolator Glove Leak integrity Testing: in-situ

- Wireless Glove Testing now best practice.
- Limit of detection improving from 100 to 70 micron with new developments.
- Many gloves tested in same time frame: 15 minutes.
- Test Ports use inflatable seal technology to avoid false failures.
- Pressurising pumps are fully integrated and battery operated (with separate charging station).
- RFID tags on Glove test port and Isolator Glove port record position and Glove in test.
- Compliant electronic data capture and reporting.
- Glove hole impact research in progress: microbiological challenge testing.

W-LAN Glove Testing Systems



RABS Filling of Clinical trial batches of virus based product in Vials



Manual Cleaning & Disinfection

Manual Disinfection of classified and controlled areas

There is no consensus on definition of the terms disinfection and sanitisation.

- **Qualification of manual disinfection/ sanitisation processes that have an in-process efficacy challenge or procedures that use laboratory qualified agents and qualified procedures of application with EM used to monitor impact on contamination control .**
- **Qualification of disinfectant:**
- **Standard European approach**
- **Standard U.S. approach**

A PHSS recommended practice for laboratory testing of a disinfectant for use in manual disinfection is included in the Bio-contamination monograph

The approach is based on an adaption of standard (generic) approaches for specific use in pharmaceutical and hospital GMP/ cGMP Classified and controlled areas.

A new PDA Cleaning and Disinfection TR is in final stages of review.

Semi automated aerosol (fogger) disinfection technology

Semi-automated disinfectant aerosol systems termed as Foggers, Dry foggers, atomisers, have a role in cleanroom and controlled area disinfection to improve the distribution, uniformity in application of disinfection agents for large volumes / surfaces over that of the manual application of agents.

There are process, efficacy and compatibilities challenges to consider in selection.

Automated Gaseous Disinfection

- Automated Gaseous Disinfection, under validated conditions, provides repeatable and robust biological decontamination of controlled areas/ zones; airborne and surfaces at relatively low temperature conditions, typically below 30 degrees Celsius.

- It should be noted that Gaseous disinfection is a finishing step and areas also require pre-cleaning to remove soiling layers that would protect microorganisms from the surface disinfection process. Also only surfaces that are exposed to the gaseous disinfection agent will be disinfected.

- The Gaseous disinfection agents may vary but there is a more limited choice when considering issues of material compatibility, requirements for a residue free process together with operator/ personnel and environmental safety.

Single Use Systems (SUS) used in Barriers

Photograph courtesy of Millipore Bioprocess division

- **Consider disinfectant compatibilities, particularly oxidising agent (VHP) compatibility** with biological products e.g. ingress through packaging during transfer into an aseptic manufacturing environment.
- **Consider the challenge of transfer into pre-gassed Isolator – RABS** without microbiological compromise of the classified environment.
- **Validate bio-compatibility with Disinfection process - manual or Gaseous and product or validate avoidance of contact/ peameation.**.
- **Consider maintaining sterile integrity of SUS through the supply chain to point of use**, including manipulation in set up after sterile outer packing is opened.

Hydrogen peroxide Vapour (VHP) Automated Gaseous Disinfection selection

Key considerations in selecting Automated Gaseous Disinfection for the Barrier System (Isolators or Closed Design RABS)

H_2O_2/ VHP disinfection optimised by: Rapid kill – with targeted H_2O_2 molecule delivery mechanisms. Rapid Aeration – without over saturation minimum dosage.

Surface Sterilization: (GIP) Gassing-in-place requires special considerations in cleaning validation to prevent chemical contamination of products

Managing the VHP condensable vapour in process design is critical to VHP cycle performance and optimum (short) cycle times

Biological products can be impacted by VHP residuals so cycle end points become critical – HRP analysis can be used in studies for bio-compatibility

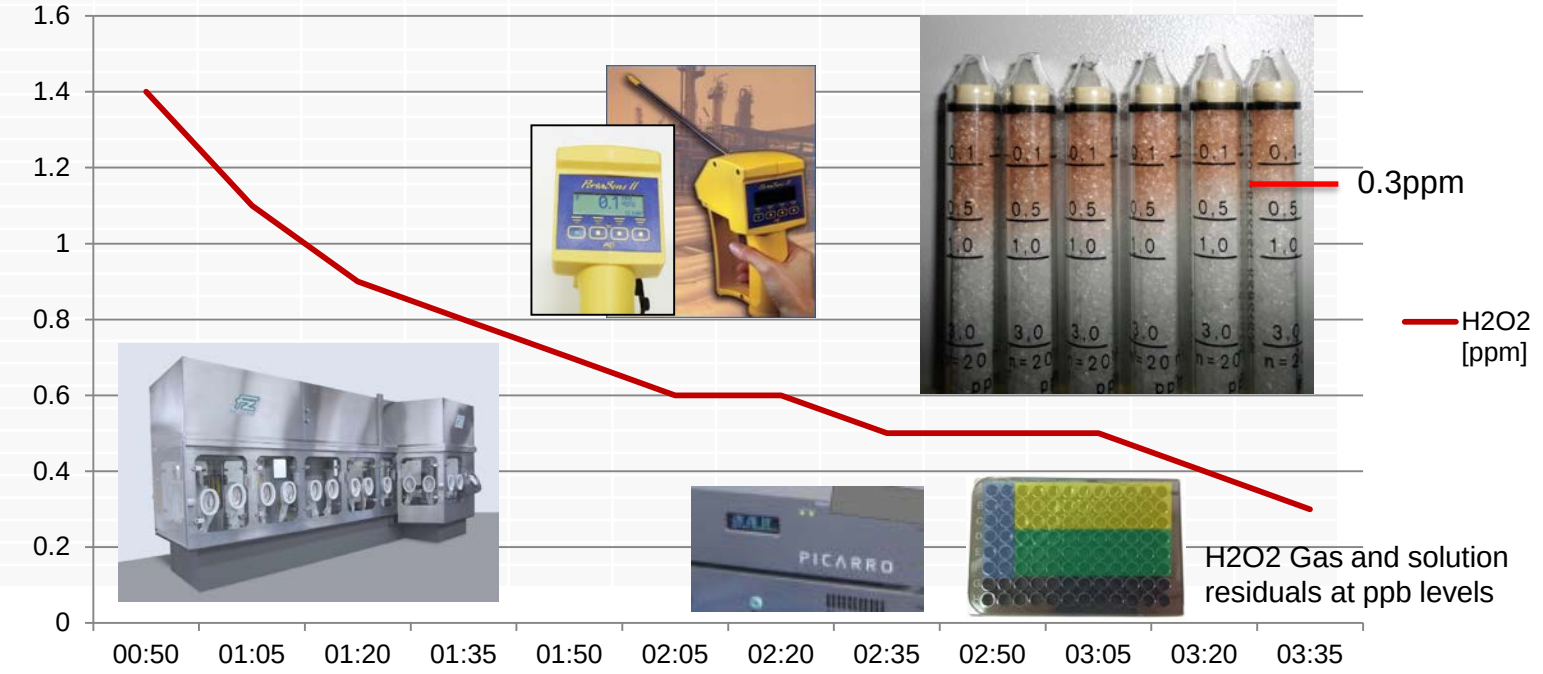
Target is for as short as possible production down time and optimum turnaround through cleaning and disinfection stages

VHP cycle end points for Biological products

Case study results; VHP graphical presentation of concentration reduction over time.

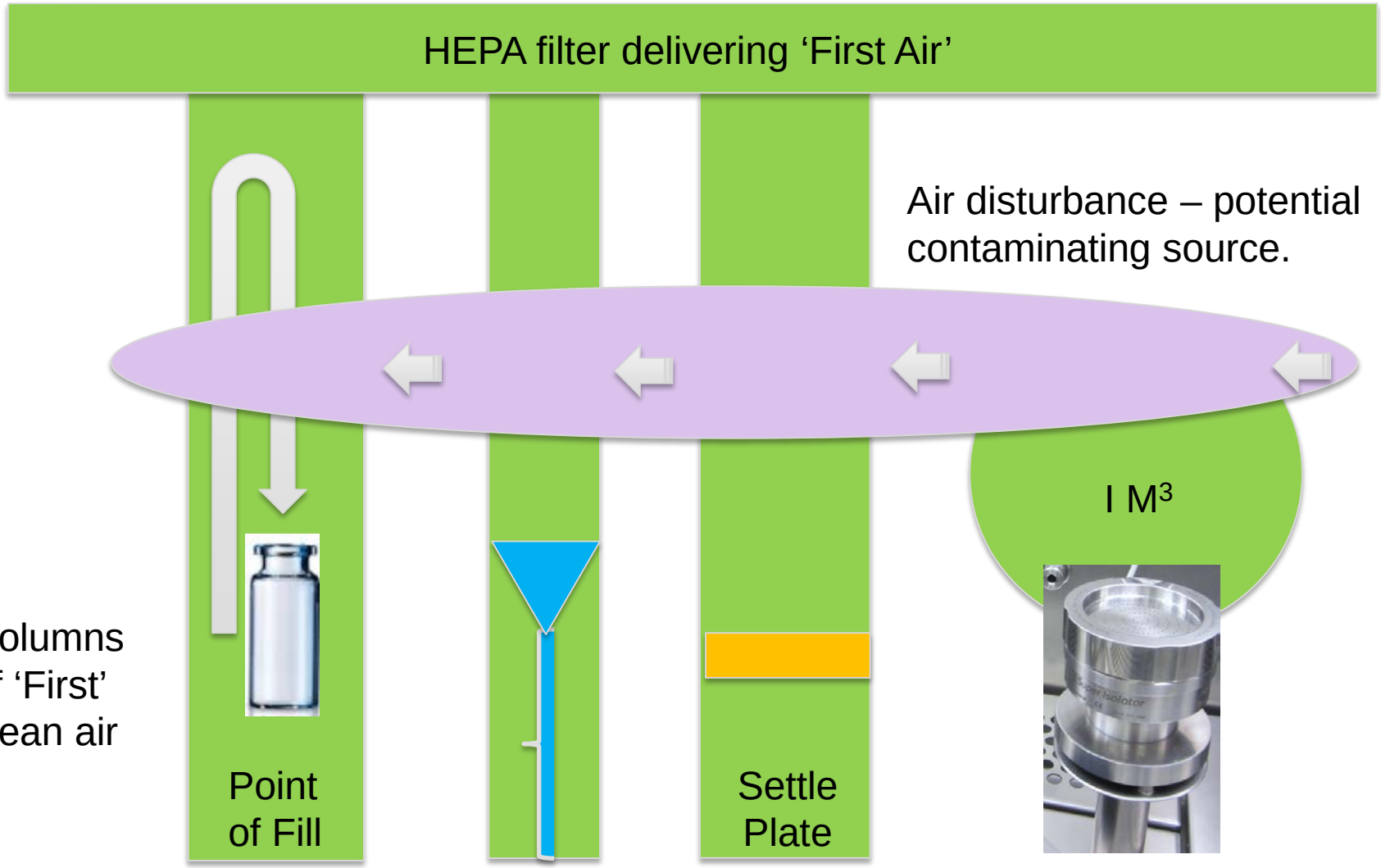
By Design of Barrier critical to cycle time:
Total VHP cycle time to 1ppm 2hours 12 minutes
to 0.3 ppm 4hours 30 minutes >>>> 0.03ppm

Time	Aeration Time	H_2O_2 [ppm] Sensor
11:45	00:50	1.4ATI
12:00	01:05	1.1ATI
12:15	01:20	0.9ATI
12:30	01:35	0.8ATI
12:45	01:50	0.7ATI
13:00	02:05	0.6ATI
13:15	02:20	0.6Dräger
13:30	02:35	0.5Dräger
13:45	02:50	0.5Dräger (+)
14:00	03:05	0.5Dräger (-)
14:15	03:20	0.4Dräger
14:30	03:35	0.3Dräger



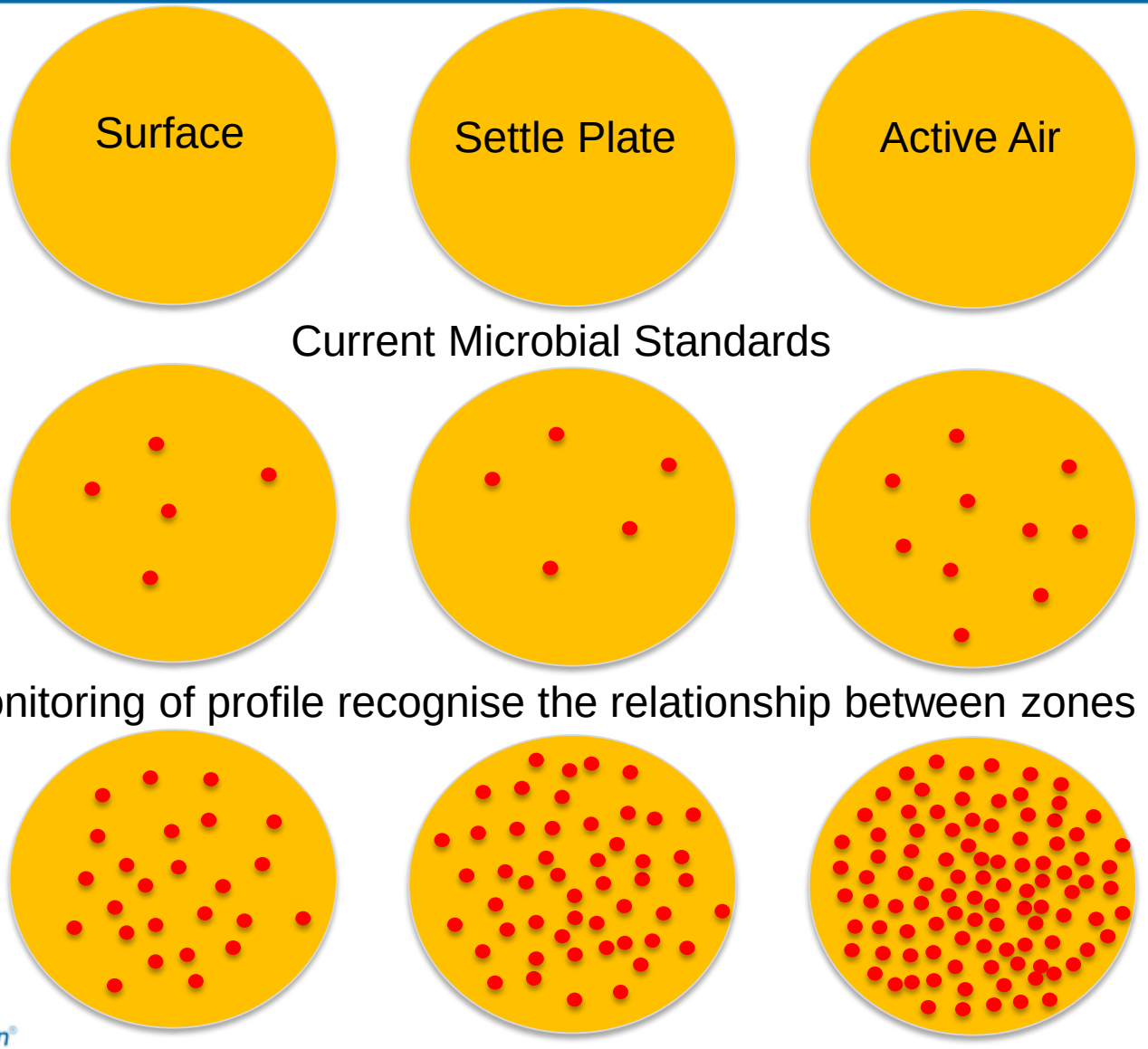
Monitoring the performance and deviation in Contamination Control

Risk based Sample Locations
Value of sampling location?



Holistic monitoring of the microbiological profile to detect and respond to escalation in bio-contamination transfer risk to Grade A.

Move from reactive to proactive Bio-contamination risk management



Microflora groups

The microbiological monitoring ‘microflora’ profile groups defined in the PHSS Bio-contamination Monograph are:

- *Bacilli*
- Gram negative rods: related to endotoxin risks.
- Human commensals
- Moulds and yeasts
- Others; including environmental non-sporing rods
- Defined; atypical microorganisms.

Gram Negative microorganisms would be considered objectionable in environments close to where products are manufactured/ exposed.

Bio-contamination Risk Profile table

Bio-contamination Risk profiling table			
EU Grade D	**EU Grade C**	**EU Grade B**	**EU Grade A**
Cfu levels • Reference • Actuals (range). % incidence of deviation.	Cfu levels % incidence of deviation.	Cfu levels % incidence of deviation.	Cfu levels % incidence of deviation.
Flora profile	Flora profile	Flora profile	Flora profile
1. Reference 2. Harmful & objectionable. 3. Trends groups.	1. Reference 2. Harmful & objectionable. 3. Trends groups	1. Reference 2. There would be an expectation not to detect any spores or moulds/ fungi in Grade B areas.	There should be no detectable microorganisms in Grade A hence all are objectionable.

Microflora characterisation through establishing control to formal state of control

The relative percentage change of one microbiological group to another will shift inherently through transition of establishing control into a control state.

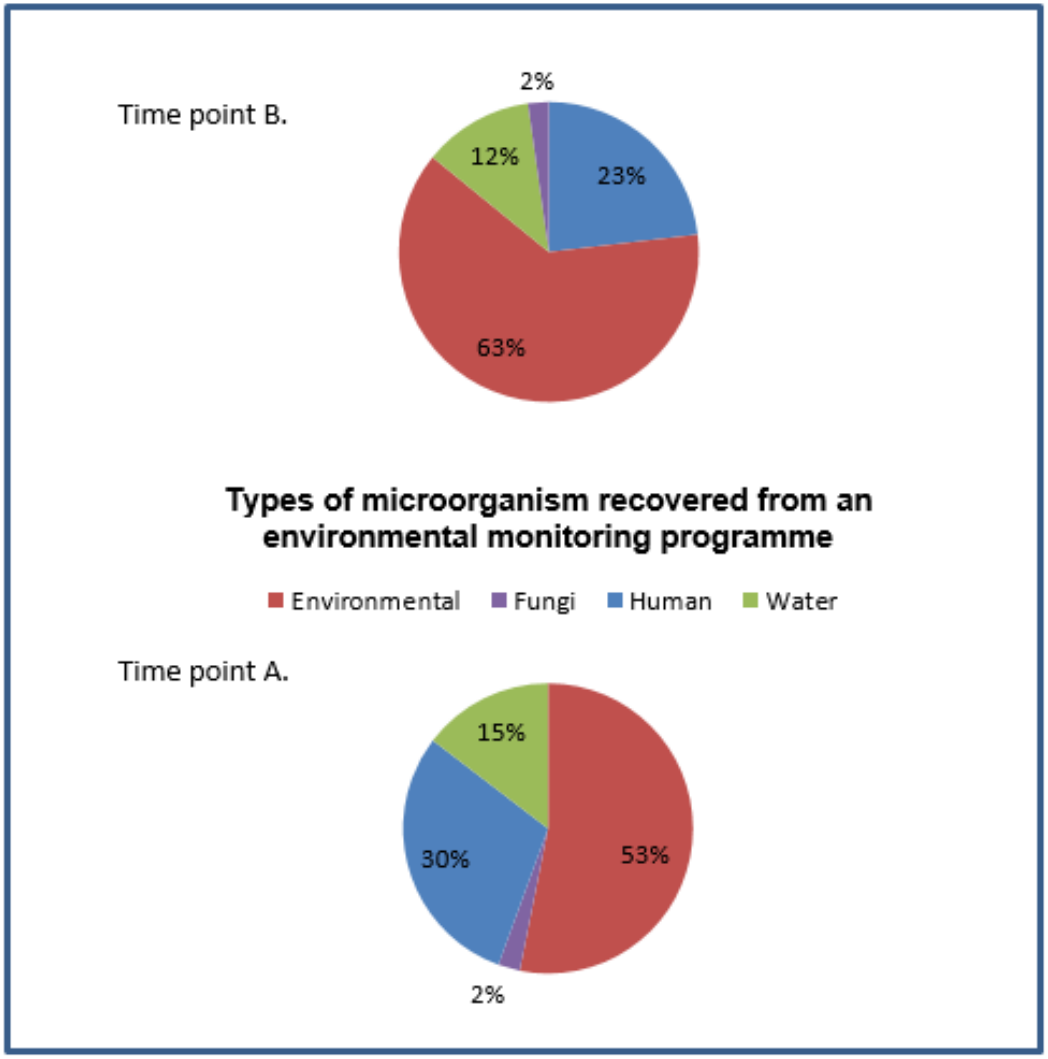
Thereafter there may be seasonal changes or as a result of other influences, possibly changes related to external facility activities.

Once ‘typically found’ micro-flora is understood in the control state, then deviation from the characterised and expected flora;

- by cfu levels,
- by incidence rates,
- by micro-flora group type,

can be defined as a risk escalation to contaminating Grade A facilitating a proactive response.

Presenting data: Micro-flora 'Pie chart' profiles



Risk Profiling and Proactive Response - RPPR

Increased risk to Grade A by Bio-contamination transmission through D>C>B to A

Risk profiling
- cfu levels - holistic
- Microbiological flora

D > C > B > A

Holistic Monitoring

D > **C*** > B > A

Proactive response to profile change & increased risk to A

Investigate root cause to change in microbiological profile

CAPA – Corrective & Preventative Action

C* = Increase bio-contamination control and monitoring in Grade C.

Profile the measurable cfu's in Grade C to detect increased risk to Grade A.

Less emphasis on Grade A where zero cfu is expected and deviations are reactive – possibly with loss of batch

Challenges of characterising a microbiological profile as ‘typical flora’ in Grade C areas

Challenges in monitoring in Grade C areas will include the following:

- There will need to be an increase in environmental monitoring (EM) resource. Focus where the greatest challenges are.
- Grade C areas are not aseptically controlled in the same way as Grade A or B so there is more variation of flora.
- Water may be present.
- By necessity, equipment operates that is not fully enclosed or sterilised.
- Non-sterile materials are handled.
- A higher number of operators are present compared to Grade B rooms.

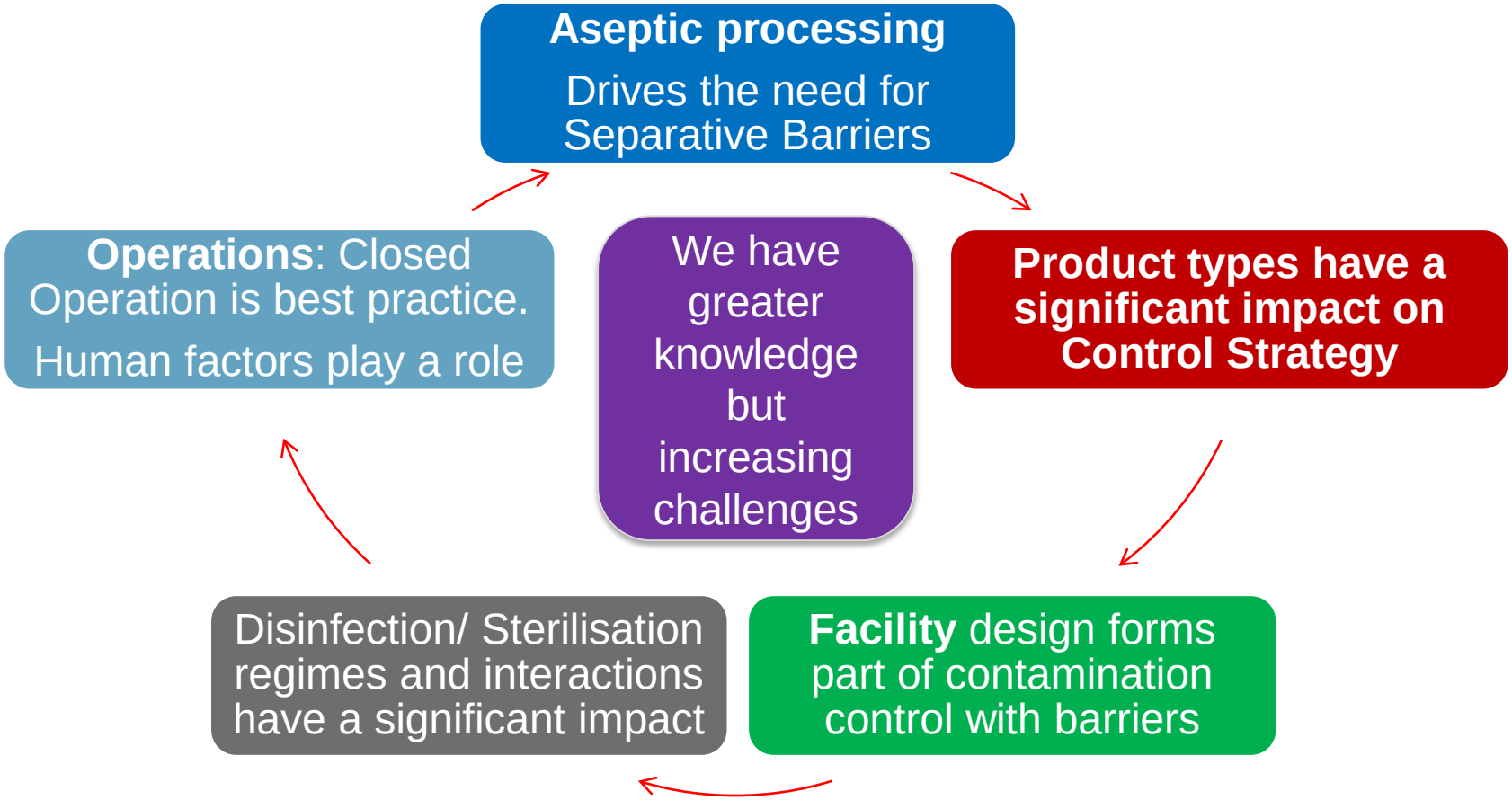
Given the above, the micro-flora is continuously changing in numbers and species.

- Determining ‘typical flora’ could be difficult, but once established then the holistic profile and deviation from the characterised expected profile in microbiological flora becomes a key performance indicator (KPI).

Benefits of RPPR initiative

- Reduces the bio-contamination risk to both patients and sterile products
- Detection of a changing environmental profile and taking appropriate controlling or intervening action to re-establish control before the Grade A/ISO5 barrier is compromised or beached improves contamination control performance and risk management**.**
- RPPR profiles are a Leading KPIs – Key performance indicators relating to bio-contamination control.
- Reduces costly and largely inconclusive root cause investigations.
- Improves regulatory compliance.
- Gain more knowledge about the changing environment in the Grade C/ISO8 zones and understanding of how to better control it.
- Reduces risk of batch loss due to non-compliance in bio-contamination monitoring results and potentially sterility.

SUMMARY
Contamination Control



EU GMP annex 1 is changing to reflect new knowledge, changing product profiles. Increasing complexity drives the need for Control Strategies .