Introduction

- EU Annex 1 was last revised in 2008. The new version was published August 22, 2022.
- Deadline for coming into operation is August 22, 2023.
  - The 2008 version was only 16 pages long. The new revision is 59 pages long.
  - https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en
- The new version strongly emphasizes the use of robust risk assessments, pharmaceutical quality systems (PQS) and Quality Risk Management (QRM).
  - All decisions and rationales must be scientifically justified.
- LOTS of increased expectations around facilities and equipment
  - As technologies have improved and are readily available, we are expected to start using them.

Introduction

- Many of the changes are clarifications/enhancements around existing specific requirements in addition to new requirements.
  - Some “standard industry practice” has been included.
- This presentation will focus on the major aspects of the new revision that will impact your environmental monitoring (EM) program.
  - Some excerpts from the new revision are included in this presentation.

New Requirement: Contamination Control Strategy (CCS)

- A documented, facility-wide CCS is now expected.
- A CCS is a holistic program that encompasses design, procedural, organizational, technical control measures and the monitoring measures employed to manage risks to product quality and safety.
  - Requires the microbiologist to think more holistically
  - Intended to provide robust assurance of contamination prevention

New Requirement: Contamination Control Strategy (CCS)

- A Contamination Control Strategy (CCS) should be implemented across the entire facility to
  - Define all critical control points
  - Assess the effectiveness of all the controls and monitoring measures used to manage contamination risks
- The CCS should be actively reviewed and updated and drive continuous improvement.

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New Requirement: Contamination Control Strategy (CCS)

- The CCS should consider all aspects of contamination control with ongoing and periodic review.
- Updates within the quality system should be made as needed and as appropriate.
  - Any changes to the systems in place should be assessed for any impact to the CCS both before and after implementation.
- The manufacturer should take all steps and precautions required to ensure the sterility of its products.
  - "Sole reliance for sterility or other quality aspects should not be placed on any terminal process or finished product test."

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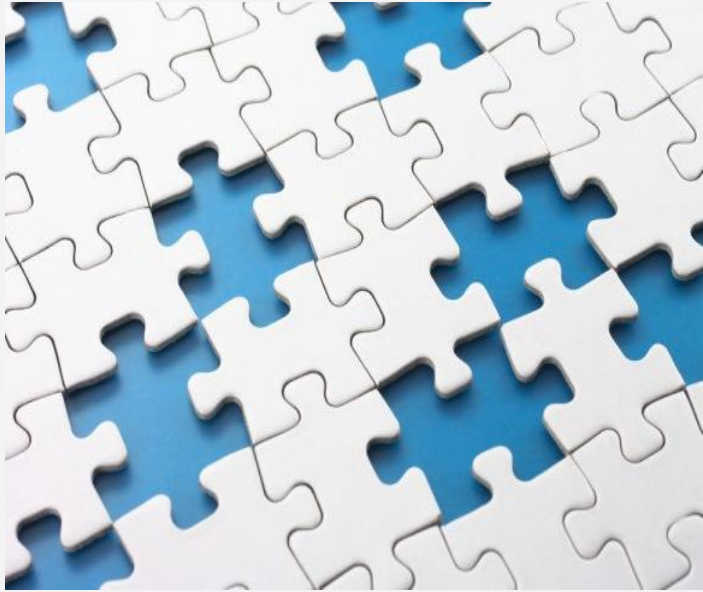
New Requirement: Contamination Control Strategy (CCS)

- Where existing control systems are in place and are appropriately managed, these may not require replacement but should be referenced in the CCS.
- Collective effectiveness of all contamination control steps and measures should be considered together.
- The associated interactions between systems should be understood.



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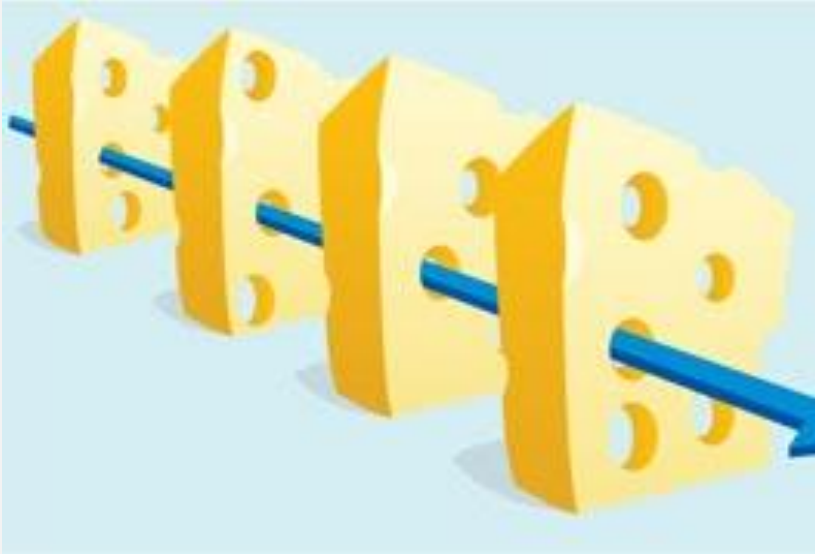
James Reason’s “Swiss Cheese” Model

- The “Swiss Cheese Model of Accident Causation" was developed by Professor James T. Reason at the University of Manchester about 25 years ago.
- Each slice of cheese represents a system component.
- The holes in the Swiss cheese represent weaknesses of system components.
- In most cases, each component compensates for the weaknesses of another, and covers the holes.
- Where the holes align, the system fails.



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New Requirement: Contamination Control Strategy (CCS)

- Elements to be considered within a CCS should include (but are not limited to):
  - Design of both the plant and processes including the associated documentation
  - Premises and equipment
  - Personnel
  - Utilities
  - Raw material controls – including in-process controls
  - Product containers and closures
  - Vendor approval

New Requirement: Contamination Control Strategy (CCS)

- Management of outsourced services and availability/transfer of critical information between parties
- Process risk management
- Process validation
- Validation of sterilization processes
- Preventative maintenance (planned and unplanned maintenance)
- Cleaning and disinfection
- Monitoring systems, including assessing feasibility of scientifically sound, alternative methods for optimal environmental contamination detection.

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New Requirement: Contamination Control Strategy (CCS)

- Prevention mechanisms
  - trend analysis
  - investigation and root cause analysis, including the use of comprehensive investigational tools
  - corrective and preventive actions (CAPA)
- The information gathered from the aforementioned areas should be used to drive continuous improvement.

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Risk-Based EM

- Risk assessments should be performed in order to establish a comprehensive environmental monitoring program and determine
  - sampling locations
  - frequency of monitoring
  - monitoring methods
  - incubation conditions
- Additional information (e.g., airflow visualization studies) should be considered in these assessments.
- Microbiologists are expected to scientifically justify these parameters as they relate to their products and processes and document accordingly in the CCS.

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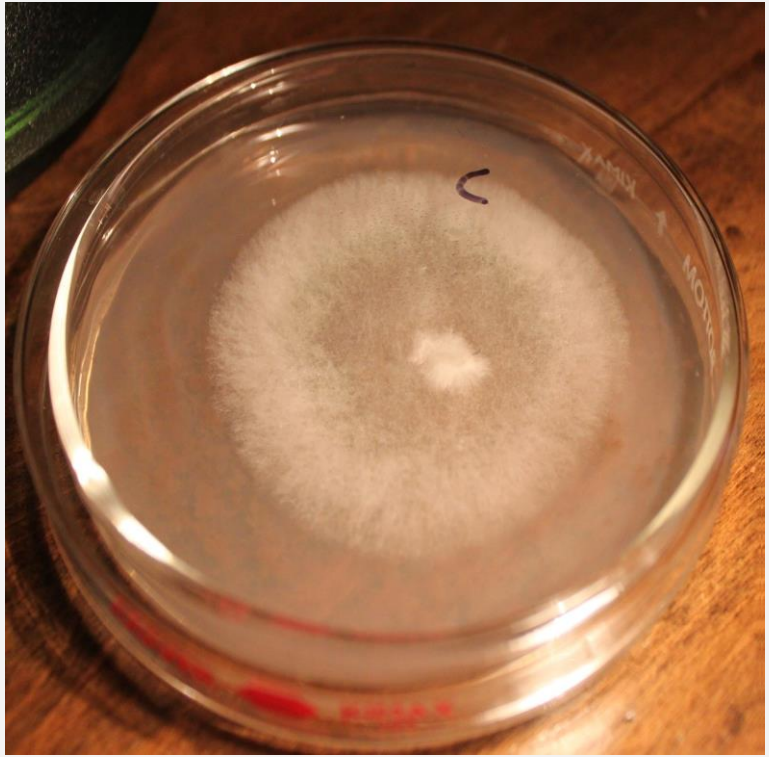
Media Qualification



- "Media used for environmental monitoring and APS should be tested for growth promotion before use, using a scientifically justified and designated group of reference microorganisms and including suitably representative local isolates."
- "Media quality control testing should normally be performed by the end user. Any reliance on outsourced testing or supplier testing of media should be justified and transportation and shipping conditions should be thoroughly considered in this case."

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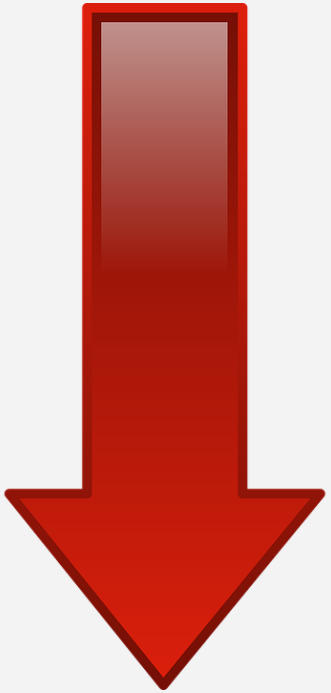
Alert Levels and Action Limits: Revised Definitions

- "Action limit – An established relevant measure (e.g., microbial, or airborne particle limits) that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation."
- "Alert level – An established relevant measure (e.g., microbial, or airborne particle levels) giving early warning of potential drift from normal operating conditions and validated state, which does not necessarily give grounds for corrective action but triggers appropriate scrutiny and follow-up to address the potential problem. Alert levels are established based on routine and qualification trend data and periodically reviewed. The alert level can be based on a number of parameters including adverse trends, individual excursions above a set limit and repeat events."

Alert Levels and Action Limits

- Appropriateness of action limits must be scientifically justified as part of the CCS.
  - Action limits, when set appropriately, should be exceeded occasionally as they are intended to provide an early warning to a potentially catastrophic failure.
  - Therefore, action limits more stringent than the maximum limits listed in the guidance may need to be implemented as determined within the CCS. Applies to Grades A-D.
  - PDA TR-13 "Fundamentals of Environmental Monitoring" (Revised 2022) provides some suggested methods for calculating both alert and action limits.
- "If action limits are exceeded, operating procedures should prescribe a root cause investigation, an assessment of the potential impact to product and requirements for corrective and preventive actions."



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Alert and Action Limits

- "Alert levels for both total particle and viable particles should be established based on results of cleanroom qualification tests and periodically reviewed based on ongoing trend data."
- "If alert levels are exceeded, operating procedures should prescribe assessment and follow-up, which should include consideration of an investigation and/or corrective actions to avoid any further deterioration of the environment."

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New Text on Trending

- "Monitoring procedures should define the approach to trending. Trends should include, but are not limited to:
  - Increasing numbers of excursions from action limits or alert levels
  - Consecutive excursions from alert levels
  - Regular but isolated excursion from action limits that may have a common cause, (e.g., single excursions that always follow planned preventative maintenance)
  - Changes in microbial flora type and numbers and predominance of specific organisms.
    - Particular attention should be given to organisms recovered that may indicate a loss of control, deterioration in cleanliness or organisms that may be difficult to control such as spore-forming microorganisms and moulds."

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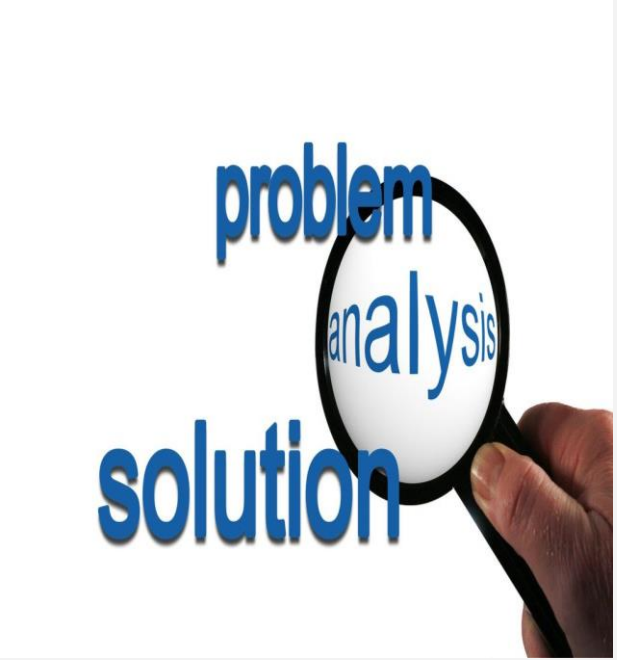
New Text on Trending



- This is about critical analysis of the EM data. What do your results *mean* with respect to things like
  - Risk to product and processes/batch impact
  - Impact to the CCS
    - *Why* are you seeing a trend?
    - If it is a repeat or extended trend, have your CAPAs been effective?
    - Are your alert levels and action limits set appropriately?
    - Has anything changed with respect to your processes or processing environment, cleaning and disinfection, equipment or materials that could account for the trends?
    - Are all components of the CCS as robust as they need to be?

Greater Emphasis on Control of Grades C & D

- "The monitoring of Grade C and D cleanrooms in operation should be performed based on data collected during qualification and routine data to allow effective trend analysis."
  - Grades C & D usually lead into Grades B & A.

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Organism Identification in Grade C & D

- "Consideration should also be given to the identification of microorganisms detected in Grade C and D areas (for example where action limits or alert levels are exceeded or following the isolation of organisms that may indicate a loss of control, deterioration in cleanliness or that may be difficult to control such as spore-forming microorganisms and moulds and at a sufficient frequency to maintain a current understanding of the typical flora of these areas."

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EM During Set-up Activities

- Continuous EM during set-up is expected for both viable air and total particulate in Grade A. Personnel EM is also expected where applicable.
  - This is in addition to the continuous EM already expected in Grade A during critical processing activities.
  - The rationale for this is that any contamination introduced during set-up is likely to be transferred downstream during processing.
  - Continuous EM (including set-up EM) should also be considered for Grade B cleanrooms based on risk of impact.

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Total Particulate Monitoring

- "Where the nature of the process etc. may damage the particle counter or present a hazard (powder and radiation hazards), a monitoring frequency and strategy should be employed to assure the environmental classification is maintained both prior to and post exposure to the risk."
  - Additional viable particle monitoring should be considered.
  - Approach should be defined in the CCS
- A minimum flow rate of 28 litres (1ft^3) per minute should be employed.
- The sample volume for EM does not need to be the same as that used for formal classification of cleanrooms and clean air equipment (i.e., 1 m^3) but does need to be justified.

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Total Particulate Monitoring

- Alarms should be triggered if alert levels are exceeded in Grade A. Procedures should define the actions to be taken in response to alarms including the consideration of additional microbial monitoring.
- It is recommended that a similar system be used for the Grade B area although the sample frequency may be decreased. Frequency should be justified in the CCS.

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Viable Particulate Monitoring

- The method of sampling used should be justified within the CCS and should be demonstrated not to have a detrimental impact on Grade A and B airflow patterns.
  - Portable samplers in general can cause issues such as turbulence and particle generation, and cannot be effectively sterilized.
- Viable particle monitoring should also be performed within the cleanrooms when normal manufacturing operations are not occurring and in associated rooms that have not been used.
  - To detect potential incidents of contamination which may affect the controls within the cleanrooms
- In case of an incident, additional sample locations may be used as a verification of the effectiveness of a corrective action (i.e., cleaning and disinfection).

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Personnel Monitoring

- A risk assessment should evaluate the locations, type and frequency of personnel monitoring based on the activities performed and the proximity to critical zones.
- Personnel monitoring should be performed following involvement in critical interventions and on each exit from the cleanroom.
- Gloves and/or gowns should be replaced after sampling.
- Where operations are manual in nature (e.g., aseptic compounding or filling), increased emphasis should be placed on microbial monitoring of gowns. This should be justified within the CCS.
- Where monitoring is routinely performed by manufacturing personnel, this should be subject to regular oversight by the quality unit.

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Alternative Monitoring Methods

- The adoption of suitable alternative monitoring systems such as rapid methods should be considered to expedite the detection of microbiological contamination issues.
  - Especially for cell and gene therapy products and/or other products with a very short turnaround time.
  - Validation must demonstrate equivalency or superiority to the established methods.
  - Alternative sampling methods can be used provided they meet the intent of providing information across the entire critical process where product is at risk of contamination.
- Supporting data for the recovery efficiency of the sampling methods chosen should be available.
- If different or new technologies are used that present results in a manner different from colony forming units (CFU), the manufacturer should scientifically justify the limits applied and correlate them to CFU where possible.

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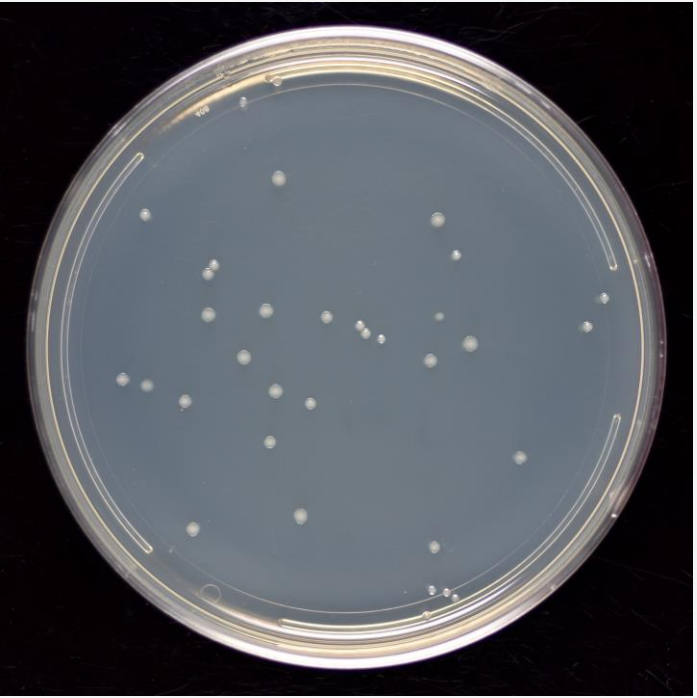
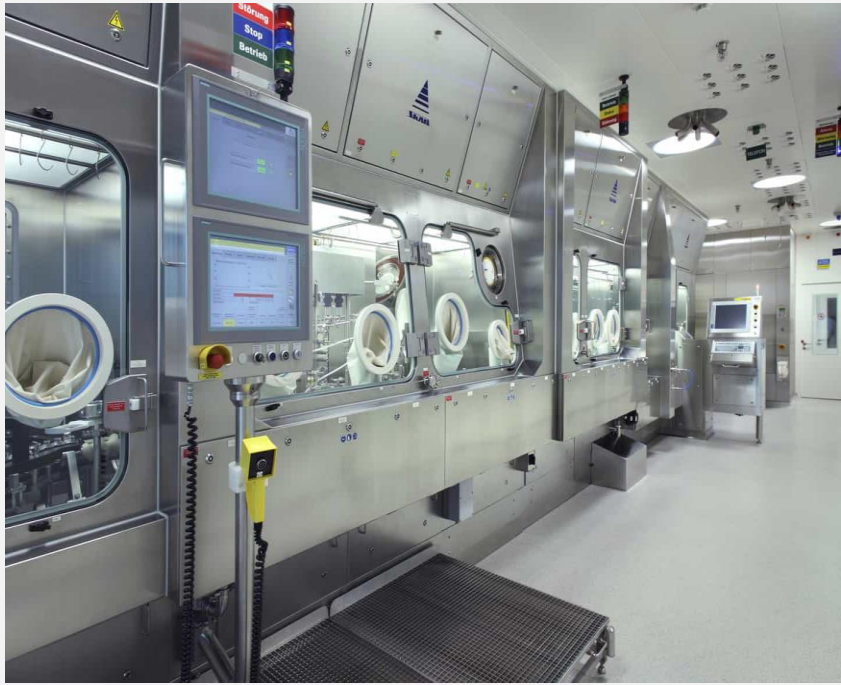
Settle Plates



- Settle plates should be exposed in Grade A and B areas for the duration of operations (including equipment set-up).
- Exposure time should be baed on validation including recovery studies.
- For Grade C and D areas, exposure time and frequency should be based on QRM.
- Maximum exposure time is still 4 hours for all grades.

Aseptic Process Simulations (APS)

- "The APS should not be considered as the primary means to validate the aseptic process or aspects of the aseptic process. The effectiveness of the aseptic process should be determined through process design, adherence to the pharmaceutical quality system and process controls, training, and evaluation of monitoring data."
- Alternative procedures that represent the operations as closely as possible should be developed where microbial viability is a concern.
- Surrogate materials should not inhibit the growth of any potential contamination.



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Aseptic Process Simulations (APS)

- Separate simulations of individual unit operations should be avoided.
  - "Any use of individual simulations should be supported by a documented justification and ensure that the sum total of the individual simulations continues to fully cover the whole process."
- APS should not be used to justify practices that pose unnecessary contamination risks.
- Justification for the number of units to be filled should be clearly documented in the CCS.

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Aseptic Process Simulations (APS)

- APS should be performed as part of the initial validation, with at least three consecutive satisfactory simulation tests.
  - Revalidation should be performed every 6 months.
  - Each operator should participate in one APS annually.
- Where the manufacturer operates different or extended shifts, the APS should be designed to capture factors specific to those shifts that are assessed to pose a risk to product sterility.
  - Example: the maximum duration for which an operator may be present in the cleanroom, and for individual garment wear.
- Consideration should be given to performing an APS after the last batch prior to shut down, before long periods of inactivity or before decommissioning or relocation of a line.

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Aseptic Process Simulations (APS)

- Where manual operation (e.g., aseptic compounding or filling) occurs, each type of container, container closure and equipment train should be initially validated with each operator participating in at least 3 consecutive successful APS.
- Revalidation should occur with one APS approximately every 6 months for each operator.
- "APS should be carefully observed by personnel with specific expertise in aseptic processing to assess the correct performance of operations and address inappropriate practices if detected."

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Aseptic Process Simulations (APS)

- Materials that contact the product contact surfaces but are then discarded (e.g., product flushes) should be simulated with nutrient media and be incubated as part of the APS, unless it can be clearly demonstrated that this waste process would not impact the sterility of the product.
- "Filled APS units should be incubated without unnecessary delay to achieve the best possible recovery of potential contamination."
- "The selection of the incubation conditions and duration should be scientifically justified and validated to provide an appropriate level of sensitivity of detection of microbial contamination."
- The method of detection of microbial contamination should be scientifically justified to ensure that contamination is reliably detected.

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Aseptic Process Simulations (APS)

- Upon completion of incubation, filled containers should be inspected by personnel who have been appropriately trained and qualified for the detection of microbiological contamination.
- Samples of the filled containers should undergo growth promotion testing with an appropriate battery of reference organisms and appropriately representative local isolates.

Aseptic Process Simulations (APS)

- The target should be zero growth. Any contaminated unit should result in a failed APS.
  - The allowance for one container when filling more than 5,000 vials is gone.
- The following actions should be taken:
  - An investigation to determine the most probable root cause(s)
  - Determination and implementation of appropriate corrective and preventative measures
  - A sufficient number of successful, consecutive repeat APS (normally a minimum of 3)

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Aseptic Process Simulations (APS) (continued)

- "A prompt review of all appropriate records relating to aseptic production since the last successful APS."
  - "The outcome of the review should include a risk assessment of potential sterile breaches in batches manufactured since the last successful APS."
  - "All other batches not released to the market should be included in the scope of the investigation. Any decision regarding their release status should consider the investigation outcome."
- "All products that have been manufactured on a line subsequent to a process simulation failure should be quarantined until a successful resolution of the process simulation failure has occurred."

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Summary

- The new Annex 1 relies heavily on sound quality risk management and documented risk assessments.
- A holistic, comprehensive and facility-wide Contamination Control Strategy (CCS) will need to be developed and documented.
- Rationale and justification for all environmental monitoring parameters, including but not limited to:
  - Methods, locations and frequencies for sampling
  - Choice of media and incubation parameters (for both EM and APS)
  - Determination of alert and action limits
  - Trending methods

needs to be documented and justified in the CCS as they relate to YOUR facility, processes and products.

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Summary

- Increased emphasis on continuous monitoring or increased monitoring of Grade B areas
- Increased emphasis on monitoring and trending of Grade C&D areas
- Trending needs to be MEANINGFUL.
  - e.g., increased emphasis on organism identification and EM in Grades C & D
- A lot of what was considered “standard industry practice” has been incorporated into the guidance.
- All critical decisions (in general) should be based on risk, be scientifically justified and tie back into the CCS.
- Operational procedures also need to tie back into the CCS and include specific steps to be taken for example, when an excursion occurs and for performing trending.

Thank you for your kind attention!

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