Regulatory Assessment of Contamination Control Strategy

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Highlights of the Revised EU Annex 1

- Expanded Scope of products
  - The principles may be used for products other than sterile products, e. g., bioburden controlled drug substances
- Quality Risk Management
  - Introduction of QRM principles to prevent contamination in the product
  - Holistic Contamination Control Strategy (CCS) in facility and equipment design and process controls
- Innovative technologies
  - The use of RABS, Isolators, Robotic systems
  - Single-Use Systems
  - Rapid/alternative methods

CCS Implementation Considerations/Challenges

CCS Implementation-General

- CCS is a high-level document that addresses how manufacturers plan to address and mitigate the risk of contamination to their products.

- CCS is not anything new, but rather formalizes efforts to get manufacturers to set out a plan for controlling contamination.

- General understanding of CCS
  - Practical knowledge on contamination controls
  - Limited experience in CCS development and implementation
  - What manufacturers should prepare to implement the CCS?

CCS Implementation-General

- Fully in compliance or a risk based approach
- Internal cross functional decision making process:
  - SME vs. decision maker
  - Business vs regulatory impact
- Global HA requirements vs. local safety regulations
- Global Health Authorities' expectations (What is in compliance?)
  - Inspector's expectations

CCS Implementation- Quality Risk Management

- The evaluation should be based on scientific knowledge and ultimately link to the protection of the patient
  - New facilities vs. existing facilities
- In some cases, use of quality risk management does not obviate industry's obligation to comply with regulatory requirements.
  - Inadequate design of facility and process
  - Critical product quality or process defects

CCS Implementation- Documentation

- Whether manufacturers should have a formalized CCS document?
- Develop and formalize a plan for contamination controls
  - Summarize current state of contamination controls
  - Conduct a new risk assessment and incorporate changes in the CCS
- Identify and mitigate the risk of contamination
  - What elements should be included?
    - Follow Annex 1
  - Periodic review and PAC impact assessment
    - As an independent document
  - CCS effectiveness assessment?
  - When should a CCS document be ready for a new facility?
    - Prior to GMP manufacturing?

CCS Implementation- Facilities, Equipment, and Utilities

- An effective CCS development for new facilities
  - Lack of data and/or experience to support CCS
    - Understanding of product and process
      - Risk based approach
      - Existing GMP requirements and guidelines
    - EM program development
- CCS for existing facilities
  - Will historical data be sufficient to demonstrate an effective CCS?
  - Equipment/Part design/upgrade to meet “new” requirements
    - Sterilization vs. decontamination
- Annex 1 requirements vs. other regional safety regulations
  - How to manage different requirements?

CCS Implementation- Equipment Sterilization and Decontamination

- Direct and indirect product contact parts should be sterilized
  - Limitation on equipment sterilization
- Assembly of sterilized equipment inside of filling line
  - Potential exposure of non-grade A environment
  - Should sterilized parts be covered during set ups?
- VHP decontamination
  - Where decontamination methods are used to render certain product contact surfaces free of viable organisms, a minimum of a six-log reduction should be demonstrated using a suitable biological indicator.
- Risk of spraying sterile disinfectants inside of a filling line?
  - Sterility
  - Impurities

Do Manufacturers Need to Retrofit Filling Lines/Areas?

- Regulatory compliance status and requirements
  - Under a warning letter/critical observations
- Impact on process and product quality
  - Contamination risks
- Business needs
  - New applications
  - Scale up
- A new car or an older car?

CCS Implementation- Environmental Monitoring

- Risk assessments should be performed in order to establish a comprehensive environmental monitoring program
  - Knowledge of the process and product, the facility, equipment, historical monitoring data, air visualization studies
  - Sampling locations, frequency of monitoring, monitoring methods
  - Appropriate alert and action limits for viable and total particle monitoring
- Procedures for investigation of exceeding alert and action limits, periodic EM trending and assessment of risk to product quality.
  - Excursion root cause investigations and CAPA
  - Impact of historical data on CCS
  - Impact on process and quality
- How to update CCS based on EM trending data?

CCS Implementation- Personnel Aseptic Qualification

- The requirement to change socks to facility socks for entry to Grade C and above
  - Fully in compliance or a risk based approach?
- Electronic devices used in cleanrooms (e.g. mobile phones and tablets) should be designed to permit cleaning and disinfection
- The requirement for clean room garments used in Grade A/B areas
  - Criteria on designing, monitoring and trending?
- Risks associated with ATMP process
  - No sterile filtration or terminal sterilization
  - Extensive manual manipulations
- Routine monitoring of aseptic techniques
  - QA with microbiology background

CCS Implementation- Materials, personal, facility Monitoring

- Impact of monitoring excursions on CCS
  - Lack of definitive root causes
  - CAPA effectiveness
- Impact on product quality
  - Routine monitoring data
- Use CCS for SUS material and suppler management
  - Method reliability
  - High cost
- Risk based EM locations and frequencies
  - Define high risk areas?
  - Product contact surfaces?
- Microbiological testing for Materials
  - Frequencies and sample sizes

CCS Implementation- Single-Use Systems

- Supplier/material qualification
  - Testing methods: sensitivity and reliability
  - Shipping risk
- Complexity of the assembly and manual operations
  - Operator qualification
  - Open vs. closed operations
- Leachables and Extractables
  - Regulatory expectations (LM vs. SM)
- Leaks
  - Impact on process and quality
- Process segregation
  - Pre- and post- viral segregation

CCS Implementation- Effectiveness Check

- Effectiveness Check process
  - Incorporate in existing periodic assessment including APQR
  - Initiate a new process for CCS assessment
- CCS assessment
  - Real-time vs. annually
- Criteria for an effectiveness check?
  - # of Grade A excursions?
  - An isolated event or a systematic issue?
- What data can help the manufacturers to evaluate the CCS?
  - Cannot solely rely on the release testing to ensure product is safe of contaminant

PUPSIT: Pre-Use, Post-Sterilization Integrity Testing

Annex 1: 8.87 The integrity of the sterilized filter assembly should be verified by integrity testing before use (PUPSIT), to check for damage and loss of integrity caused by the filter preparation prior to use. It is recognized that PUPSIT may not always be possible after sterilization due to process constraints (e.g. the filtration of very small volumes of solution). In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of a non-integral filtration system. Points to consider in such a risk assessment should include but are not limited to:

- In depth knowledge and control of the filter sterilization process to ensure that the potential for damage to the filter is minimized.
- In depth knowledge and control of the supply chain to include:
  - Contract sterilization facilities.
  - Defined transport mechanisms.
  - Packaging of the sterilized filter, to prevent damage to the filter during transportation and storage.
- In depth process knowledge such as:
  - The specific product type, including particle burden and whether there exists any risk of impact on filter integrity values, such as the potential to alter integrity-testing values and therefore prevent the detection of a non-integral filter during a post-use filter integrity test.
  - Pre-filtration and processing steps, prior to the final sterilizing grade filter, which would remove particle burden and clarify the product prior to the sterile filtration.

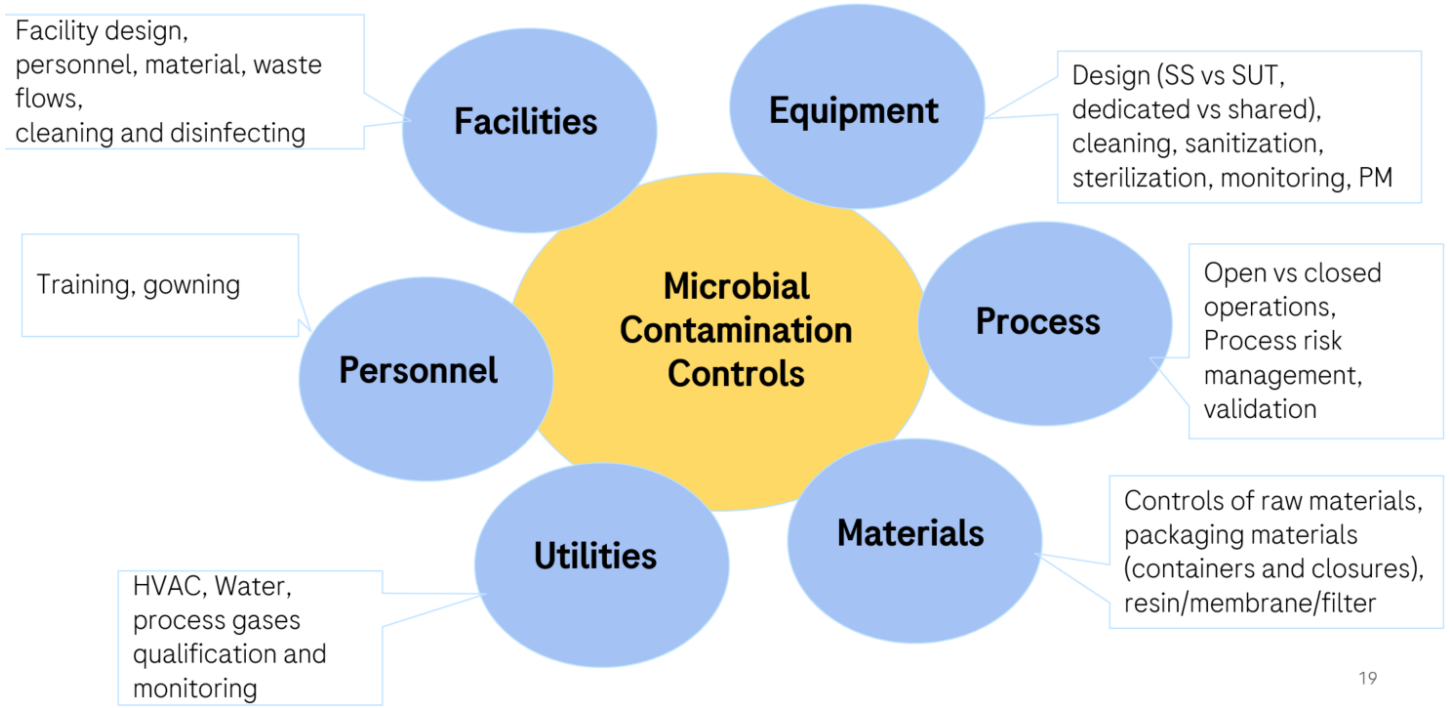
Why Use or Not Use PUPSIT?

- Filter manufacturing, transport and usage are insufficiently controlled, and there is a risk that filter flaws could be masked
- Filter flaw masking: certain flaws that would allow microbiological contamination to pass during filtration and may be blocked or clogged by fluid contaminants or components during the filtration process and remain undiscovered during post-use integrity test.
  - must be small enough not to be uncovered during initial testing,
  - yet able to become large enough to pass microbiological contamination after sterilization, and
  - yet again, small enough to be closed by clogging.
  - Additionally, the product being filtered must have the ability to clog the filter.

- Risk associated with performing PUPSIT may greatly outweigh the risk of product contamination as a result of the masking effect.
  - The exposure of the downstream portions of the sterile product transport line poses a risk to maintaining the sterility of the filtered product.
  - A complex process, requires additional manipulations of a sterilized system
- The risks of filter flaws are generally to be considered low, due to filter manufacturing, handling and use controls in place to prevent filter flaws and failures and use of pre-sterilization testing.
- Product characteristics: masking study
  - The conditions do not represent a typical filtration process or fluid in commercial pharmaceutical manufacturing
- Data Mining:
  - approximately 2,080 data sets have been collected and statistically analyzed from a multitude of different 0.2µ and 0.45µ filters used with different fluid streams. The data mining showed that a pre- and post-use bubble point value shift is extremely rare.

Application CMC Assessment

CMC Assessment: Contamination Control Strategy



CMC Assessment: Contamination Control Strategy

- Raw material controls and testing for microbial quality
- Identify, control, and monitor potential microbial entry points (facilities, equipment, utilities, raw materials, process, and personnel)
- Control/reduce/eliminate bioburden at critical steps in the process
  - Minimize hold steps, when possible
  - Use closed system and operations, when possible
- Validate critical manufacturing steps (CIP/SIP) to eliminate and prevent microbial ingress
- Process Proformance Qualification and Continued Process Verification
- Periodic review and update control strategy

CMC Assessment: Contamination Control Expectations

- The process should be designed to prevent microbial contamination and monitored to assure final product meets all quality attributes
- A risk based testing program for raw materials and packaging materials
- Monitoring of intermediates and pools for bioburden and endotoxin prior to filtration
- Column pools and/or loads should typically be filtered to reduce bioburden
- Concurrent validation protocols to monitor resin/membrane reuse
- In-process hold conditions should be validated microbiologically at scale
- Establish bioburden and endotoxin limits at critical steps prior to filtration
  - Liquid Bulk DS (2-4 °C): <1 CFU/10mL
  - Frozen Bulk DS: 10 CFU/10mL or less
- PPQ data supporting process consistency and microbial controls

CMC Assessment: Manufacturing Process Controls (DP)

- Manufacturing operations
  - Critical operations
    - Transfer of sterilized container or closure to the aseptic filling areas
    - Aseptic filling using barrier and isolator systems
  - Sterilizing filter (supplier, size, membrane material, membrane surface area, etc.) and filtration parameters
  - Concerning holding periods
    - Between formulation or bulk thaw and/or pooling and filtration
    - Between filtration and filling
    - Microbial limits pre-sterile filtration
- Microbiological monitoring of the environment
  - Microbiological methods (EM sampling)
  - Locations based on risk assessment (product contact surfaces)
  - Limits and assessment

CMC Assessment: Process Validation and/or Evaluation

- Sterilization process validation of sterile product contact containers, closures, equipment and components
  - At scale studies, worst-case conditions
- Aseptic process validation, including,
  - Procedures and specifications for media fills, including EM results
  - At least 3 recent runs representing the proposed commercial CCS, filling speed, duration, and commercial manufacturing process or worst-case, types of interventions
  - Actions concerning products when media fill fails.
- PPQ runs (Process Validation –product specific), includes sterile filter performance specifications, processing times in the commercial facility, for BLAs only.

CMC Assessment: Control of Drug Product

- Bioburden (USP <61>), Sterility (USP <71>), and Bacterial Endotoxin (USP< 85>)
  - Qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate.
  - Provide full validation of non-compendial microbial methods.
- Low Endotoxin Recovery Qualification (PDA TR 82)
  - Low endotoxin recovery studies using DP, Biotech products only. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> Bacterial Endotoxin Test (BET). The effect of hold time on endotoxin detection should be assessed for recoverable endotoxin over time.
- Rabbit Pyrogen Testing (USP< 151>)
  - The Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).
  - A request to waive the Rabbit Pyrogen Test may be made for certain products by providing a scientifically justifiable rationale.

Facility Assessment and Inspections

Inspection Coverage: Contamination Control

- Understanding of contamination risks:
  - Use animal-derived components
  - Microbial or cell culture based system
  - Pre- and post-viral activities
  - Upstream and downstream operations
  - Open vs. closed operations
  - Process equipment design (SS vs SUT, dedicated vs shared)
  - In-process holds
  - Bioburden controlled vs aseptic process
  - Design of facilities, utilities, and equipment
  - Effective Preventative Maintenance and Calibration Program in place

Inspection Coverage: Contamination Control-DP

- Observing the manufactuing process and equipment
  - Filling line set ups, Filling operations and interventions
  - Environmental Monitoring
- Personnel training in aseptic techniques
  - Media fill vs. routine production
- Major production equipment qualification
  - Aseptic Processing Equipment: RABS, Isolators, conventional filling room
  - Sterilizers, Lyophilizers, Depyrogenation equipment
  - Visual Inspection/Automated Inspection Equipment
- Media fills design and summary of all media fills performed
  - Investigation and impact assessment
- Visual inspection of injectable products (100% and AQL)
  - personnel qualification/requalification, and equipment qualifications
  - defect categories and investigation and impact assessment of visible particulates

Inspection Coverage: Environmental Monitoring

- Risk assessments should be performed in order to establish a comprehensive environmental monitoring program
- Knowledge of the process and product, facilities, equipment, historical monitoring data, air visualization studies
- Sampling locations (direct and indirect product contact surfaces), frequency of monitoring, and monitoring methods
- Alert and action limits for viable and total particle monitoring
- Procedures for investigation of exceeding alert and action limits, periodic EM trending and assessment of risk to product quality.
- Conditions of incubation, types of media used etc.

Inspection Coverage: Personnel Training

- How to assess an aseptic process personnel training program?
  - Should be designed to minimize personnel interventions
  - Training program (initial and ongoing) should include aseptic technique, cleanroom behavior, microbiology, hygiene, gowning, patient safety hazards
  - Contact sterile materials only with sterile instruments
  - Move slowly and deliberately
  - Keep the entire body out of the path of unidirectional airflow (first air) that does not compromise sterility of the product
- An aseptic gowning qualification/requalification program
  - To maintain the quality of the gown after performance of gowning procedures
  - Microbiological surface sampling of critical locations

Inspection Coverage: Facilities

- Facility design to minimize cross contamination risks
  - How to address flaws, issues, or modifications for existing facilities?
  - Material, personnel, product, and waste flows
    - Unidirectional flows?
    - Material and personnel airlocks?
- Effective facility cleaning and disinfection program
  - How to validate a cleaning and disinfection process?
- Environmental Monitoring Program
  - How to design an adequate environmental monitoring program?
  - How to respond to sub-action level trends ?

Inspection Coverage: Utilities

- Utilities should be designed, installed, qualified, operated, maintained and monitored in a manner to ensure that the utility system functions as expected
- The impact of utilities on product quality should be assessed:
  - How to define product contact utilities?
    - Directly contact product
    - Contact materials that will ultimately become part of the product.
    - Contact surfaces that come into contact with the product.
- How to establish adequate limits, controls and monitoring program for WFI, Purified Water, Steam, Gas?
  - A three-tier limit: alert level, action limit, monograph specification?
  - Is routine EM data sufficient to demonstrate adequate control?
  - Do only action level results require investigation (including ID) and CAPA?

Inspection Coverage: Materials

- How to develop relevant raw material specifications?
  - the risk profile of the origin material
  - the material's manufacturing process
  - the level of quality needed for the drug manufacturing process
- How to develop a risk based microbiological control and testing program for raw materials and packaging materials?
  - Vendor/material qualification
  - Set microbial, particulate and endotoxin/pyrogen limits and sampling frequency, quantity, and location to obtain the most representative samples
  - Limits should be aligned with the intended final product specification and dosage use

Inspection Coverage: Equipment

- Equipment should be designed to reduce process contamination risk and for its intended use
  - Is the equipment designed as a closed system wherever possible?
  - Are parts designed to be sterilized as a unit to minimize connections during setup?
  - Is the equipment designed to provide ease of access and to prevent operators leaning over open product or components during aseptic operations?
- Cleaning and Sterilization of critical equipment should be validated
  - Are all product contact surfaces sterilized (direct or indirect)?
  - Clear definitions of direct and direct product contact parts?
- Effective Requalification, Preventative Maintenance and Calibration Program in place
  - A risk based requalification program?

Inspection Coverage: Manufacturing Process

- Three main microbial contamination considerations for the risk assessment:
  - Microbial Ingress: What are the sources of contamination and how are they gaining access to the manufacturing environment?
  - Proliferation: Are there environmental factors or processing conditions that may increase the risk or extent of a contamination?
  - Persistence: Are the cleaning, sanitization/sterilization, and monitoring programs appropriate to ensure bioburden is being eliminated or kept in check?
- Consider that microorganisms may enter the manufacturing process from multiple sources: from incoming raw materials, facility design and inputs, open and closed drug substance manufacturing, and culminating in the final packaging of drug product.
  - Additional testing early in the process for risk-mitigation
  - Viral and mycoplasma contaminations

Inspection of Injectable Products for Visual Particles

- USP General Chapter <1> states that "[t]he inspection process should be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates" as defined in USP General Chapter <790>.
  - The term essentially free means that when injectable drug products are inspected, no more than the specified number of units may be observed to contain visible particulates.
- A visual inspection program should ensure that any visible particulates present in the batch at the time of release are only those that have a low probability of detection because they are of a size approaching the visible detection limit.
  - Establish procedures for inspecting the product (100% Visual Inspection)?
  - Statistical sampling plan (AQL testing)?
  - Acceptance/rejection criteria (Critical or Major)?
  - Training and Qualification (equipment and operators)?
  - Investigation/reinspection?

Quality Risk Assessment of Visual Particles

- Conduct a risk assessment to ensure product quality and to limit patient risk
- Risk considerations based on the category of particulates:
  - Inherent particulates are particulates that are an innate product characteristic.
    - Consider as part of the quality target product profile if they are a property of the product and product release specifications are met
    - Monitor time-dependent changes during stability testing
  - Intrinsic particulates are particulates that are derived from the manufacturing equipment, product formulation, or container system.
    - Establish process controls
    - Assess impact on manufacturing process, equipment and facilities
    - Evaluate trends to monitor and controls, time-dependent particle formation
  - Extrinsic particulates are particulates that originate from the manufacturing environment and are foreign to the manufacturing process.
    - Negatively impact on process, product quality and sterility assurance

Final Thoughts

- Scientific knowledge of the process and technical knowledge of preventing contamination are the foundations of the CCS
- Employ quality risk management (QRM) principles when designing manufacturing processes and facilities.
- Establish a robust Quality Systems to actively review and update to drive continual improvement of the manufacturing and control methods
- The health of the quality culture and level of personnel awareness have a direct and significant impact on the success of the CCS
- Where existing control systems are in place and are appropriately managed, these may not require replacement but should be referenced in the CCS and the associated interactions between systems should be understood.
- The CCS principles can be applied to any drug manufacturing or compounding process.

Thank You!