Regulatory Assessment of Contamination Control Strategy

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Highlights of the Revised EU Annex 1

- Expanded Scope of products
  - Principles may be applied for products other than sterile products, where the control and reduction of contaminants are important (e. g., bioburden controlled drug substances)
- Quality Risk Management (ICH Q9 R1) & (ICHQ10)
  - Introduction of QRM principles to prevention of product contamination
  - Holistic **Contamination Control Strategy** (CCS) in facility and equipment design, and process controls
- Appropriate design of facility, equipment, and processes
  - Consideration for use of innovative technologies -
    - RABS, Isolators, Robotic systems, Single-Use Systems
    - Rapid/alternative methods

CCS Implementation Considerations/Challenges

Purpose of the CCS

- Proactive identification of risks and mitigation
- Defines critical control points
- Collective effectiveness checks of all control points
- Monitoring system to demonstrate correct implementation of design and procedures, and risks management
- Establish robustness of contamination prevention
- Frequent reviews and update where appropriate

CCS Implementation-General

- It's not new - A formalized high-level scheme that describes how manufacturers plan to address and mitigate the risk of contamination to their products
- Requires general understanding of CCS
  - Practical and comprehensive knowledge on contamination controls
  - Limited experience in CCS development and implementation
- How should manufacturers prepare to implement the CCS?
  - Internal cross functional decision-making process:
    - SME vs. decision makers
    - Business vs regulatory impact
  - Global HA/Annex I requirements vs. local/regional safety regulations
    - Global Health Authorities' expectations
    - Inspector's expectations

CCS Implementation- Quality Risk Management

- QRM emphasis
  - facility, equipment, and process design
  - Implementation of well thought out controls and risks mitigation procedures
  - Monitoring systems
- Scientific knowledge-based evaluations with the ultimate goal of safe products for patients
  - New facilities vs. existing facilities
- In some instances, use of QRM does not release manufacturer's obligation to comply with regulatory requirements.
  - Inadequate facility design and process
  - Critical product quality or process defects

CCS Implementation- Risk Assessment

- Avoiding pitfalls –
  - Good understanding of the manufacturing process for risk assessment and management
  - Should include complete information for process flows, descriptions, and risk evaluations
  - Scope should not be limited by focusing only on certain known risks
  - Should not include too many scopes into the same risk assessment
  - Assessment should not be subjective, but be objective and non-bias, considering all potential aspects

CCS Implementation- Consideration and Challenges

- Develop and formalize a plan for contamination controls (existing facility)
  - Summarize current state of contamination controls
  - Perform a gap assessment
  - Conduct a new risk assessment and incorporate changes in the CCS
  - Manage contamination risks

- Identify and mitigate contamination risks (new facility)
  - Manufacturing processes mapping
  - Identify, assessment and mitigation of risks
  - Elements described in Annex 1 – plus process-specific elements

- Periodic review and post-approval change impact assessment
- Collective CCS effectiveness assessment

CCS Implementation- Facilities, Equipment, and Utilities

- When should a CCS document be ready for a new facility?
  - Prior to GMP manufacturing?
- 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
      - QRM knowledge during product development
      - 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

CCS Implementation- Equipment Sterilization and Decontamination

- Direct and indirect product contact parts should be sterilized
  - Limitation on equipment sterilization
- Assembly of sterilized equipment on the filling line
  - Potential exposure to 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 a filling line?
  - Sterility of disinfectants
  - Impurities from residues

CCS Implementation- Environmental Monitoring

- Risk assessments 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

CCS Implementation- Personnel Aseptic Qualification

- Requirement to use facility socks for entry to Grade C and above
- The requirement for clean room garments used in Grade A/B areas (high necks)
  - Criteria on designing, monitoring and trending?
    - Number of washes and wear, checks for wear and tear
    - Vendor qualification and monitoring
- Electronic devices used in cleanrooms (e.g. mobile phones and tablets) should be designed to permit cleaning and disinfection
- Routine monitoring of aseptic techniques (by personnel with microbiology training)
- Risks associated with ATMP process
  - No sterile filtration or terminal sterilization
  - Extensive manual manipulations

CCS Implementation- Materials Monitoring

- Use CCS for SUS material and supplier management -
  - Test method reliability, costs/supply chain
  - Shipping risk
  - Durability of system/structural integrity at POU
- Microbiological testing for Materials – frequencies, sample sizes, established limits (bioburden, endotoxins/pyrogens)
- Complexity of the assembly and manual operations
  - Operator qualification
  - Open vs. closed operations
- Leaks
  - Impact on process and quality
- Process segregation
  - Pre- and post-viral activities

CCS Implementation- Effectiveness Check

- Effectiveness Check process
  - Incorporate existing periodic assessment including APR
  - 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?
  - Should not solely rely on release testing to ensure product is safe of contaminants

Facility Assessment and Inspections

Inspection Coverage: Contamination Control (DS)

- Understanding of contamination risks:
  - animal-derived components - cell culture based system
  - upstream downstream operations
  - pre- and post-viral activities
  - open/closed operations
  - process equipment design (dedicated or shared re-usable ss vs SUS)
  - hold times/process times
  - bioburden controlled vs aseptic processes

Inspection Coverage: Contamination Control-DP

- Observing the manufactuing process and equipment set-up
- Personnel training in aseptic techniques
  - Media fill vs. routine production
- Media fills design and summary of all media fills performed
  - Investigation and impact assessment
- Major production equipment qualification
- Visual inspection of injectable products (100% and AQL)
  - Personnel/equipment qualification/requalification
  - defect categorization
  - product impact assessment of visible particulates

Inspection Coverage: Environmental/Personnel Monitoring

- Risk assessments performed to establish a comprehensive environmental monitoring program
- EMPQ and identification of EM locations, frequencies etc.
- Environmental Monitoring Program
  - Does the environmental monitoring program adequately address risks to products?
  - How do you respond to sub-action level trends ?
- How to assess an aseptic process personnel training program?
- Aseptic gowning qualification/requalification program
  - To maintain the quality of the gown after gowning
  - Microbiological surface sampling of critical locations

Inspection Coverage: Facilities/Utilities

- Facility design to minimize cross contamination risks
- Effective facility cleaning and disinfection program
- Design space and room air cleanliness appropriate for process operation
- IOPQ, monitoring, and maintenance of utilities to ensure that the systems function as expected
- Establish adequate limits, controls and monitoring program for WFI, Purified Water, Steam, Gas
- The impact of utilities on product quality should be assessed:
  - 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

Inspection Coverage: Materials

- How to develop relevant raw material specifications?
  - risk profile of the material's origin
  - material's manufacturing process
  - 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/interventions?
- Cleaning and Sterilization of critical equipment should be validated
  - Are all product contact surfaces sterilized (direct or non-direct)?
  - Clear definitions of direct and non-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: e.g. raw materials, facility design and inputs, open and closed system of DS manufacturing; to the final product package, and human interactions.
  - Additional testing early in the process for risk-mitigation
  - Viral and mycoplasma contaminations

Conclusion

- The foundation of the CCS should be based on scientific and technical knowledge of the process and contamination prevention
- QRM principles should be used when designing manufacturing processes and facilities, procurement of equipment and components.
- A robust Quality System needs to be established to actively review and update the CCS for continual improvement of the manufacturing and control methods
- The quality culture and level of personnel awareness in contamination controls and prevention have a direct and significant impact on the success of the CCS
- Replacement systems may not be required when appropriately managed existing control systems are in place. However, these should be referenced in the CCS and the interactions between these systems should be understood
- The CCS principles can be applied to any drug manufacturing or compounding process
- The CCS is a living document that requires continuous update and improvement

Thank You!