Insights from a Former Regulator

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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 final product
  - Holistic Contamination Control Strategy (CCS) in facility and equipment design and process controls
  - A risk based approach to PUPSIT
- Innovative technologies
  - The use of RABS, Isolators, Robotic systems
  - Single-Use systems
  - Rapid/alternative methods

Contamination Control Strategy (CCS)

- A knowledge and risk based approach:
  - Product, process and microbiological knowledge starting with process/product development
  - Knowledge on manufacturing science & technology
  - Facility, Utility, equipment design
  - Define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organizational) and monitoring measures employed to mitigate risks
  - Quality risk management is applied in the development and maintenance of the CCS, to identify, assess, reduce/eliminate, and control contamination risks

Considerations for CCS Implementation

- Understanding of product and process
  - Open vs. closed operations
  - Equipment design (SS vs SUT, dedicated vs shared)
  - Bioburden controlled vs. sterile products
- New vs existing facilities
  - Facility's prior experience
  - Evaluate and integrate existing contamination control measures
- Establish a robust Quality System
  - Healthy quality culture and personal awareness
  - Actively review and update to drive continual improvement of the manufacturing and control methods
- What data can help the manufacturers to evaluate the CCS?
  - Cannot solely rely on the release testing to ensure product is safe of contaminant.

Quality Risk Management

- Quality Risk Management Principles
  - The evaluation should be based on scientific knowledge and ultimately link to the protection of the patient; and
  - The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.
- 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
- A risk based approach to PUPSIT
  - An alternative approach may be taken with a thorough risk assessment and appropriate controls

Innovative Technologies

- Barrier Technologies, e.g. RABS, Isolators, robotic systems
  - The use of different technologies should be based on process and product risks
  - The use of robotic systems to reduce/eliminate human interventions
    - Robotic environmental monitoring
    - Robotic filling operations
    - Comply with regulatory requirements?

- Single-Use Systems
  - Supplier/material qualification
  - Complexity of the assembly and manual operations
  - Leachables and Extractables
  - Leaks

Rapid/Alternative Methods

- Rapid detection of potential contamination in the product and the environment
  - Rapid microbial methods
  - Continuous monitoring systems

- Full validation of non-compendial methods
  - Demonstrate their equivalency or superiority to the compendial methods for the product and process.

Implementation of Annex 1 in the US

- FDA's existing guidance for sterile drug manufacturing is largely aligned with Annex 1
- FDA has no plans to enforce EU's GMPs Annex 1 in the US
  - Has their own national laws and guidances
  - Are not obligated to comply with Annex 1
- For similar reasons, FDA will not be enforcing PUPSIT
  - PUPSIT continues to be a challenge topic
  - FDA's guidance provides risk based approaches to filter integrity testing

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