EU GMP Annex 1 Implementation: Contamination Control Strategy (CCS)

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Annex 1 Implementation

- General considerations for CCS implementation
- Challenges and Opportunities
  - Facilities, Equipment, and Utilities
  - Materials, personal, facility Monitoring
  - CCS documentation and effectiveness check
- Impact of EU Annex 1 in China

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

Considerations for CCS Implementation

- 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

- Fully in compliance or risk based approaches
- Internal cross functional decision making process:
  - Expert vs. decision maker
  - Business vs regulatory impact
- Global HA requirements vs. other local safety regulations
- Global Health Authorities' expectations
  - Inspector's expectations

CCS Implementation

CCS documentation

- Whether manufacturers should have a formalized CCS document?
- Develop and formalize a plan for controlling contamination
  - 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
    - 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

- 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?

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

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
- Rise based EM locations and frequencies
  - Definition of 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

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?

Equipment Sterilization or Decontamination

- EU Annex 1:
  - 5.5 For aseptic processes, direct and indirect product contact parts should be sterilized. Direct product contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that do not contact the product, but may come into contact with other sterilized surfaces, the sterility of which is critical to the overall product sterility (e.g. sterilized items such as stopper bowls and guides, and sterilized components).

- FDA Aseptic Processing Guidance:
  - Filling Line Sterilization: To ensure sterility of product contact surfaces from the start of each operation, the entire path of the sterile processing stream should be sterilized. In addition, aseptic processing equipment or ancillary supplies to be used within the isolator should be chosen based on their ability to withstand steam sterilization (or equivalent method). It is expected that materials that permit heat sterilization (e.g., SIP) will be rendered sterile by such methods. 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.

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

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

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 (existing facilities)
  - Critical product quality or process defects

CCS Implementation

CCS effectiveness check

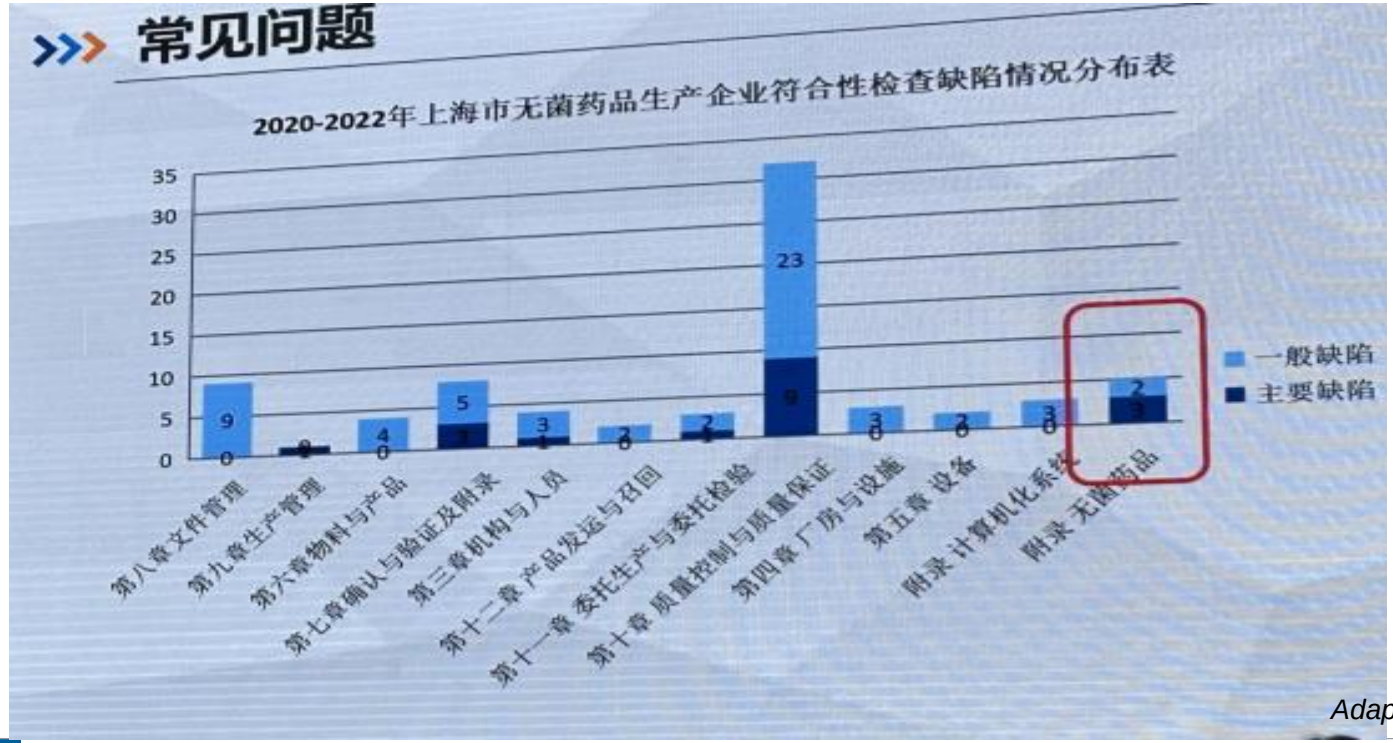
- Incorporate in existing periodic assessment including APQR
- Initiate a new process for CCS assessment
- CCS assessment
  - Real-time vs. annually
- Criteria for an effectiveness check?
  - # of Grade A excursions?
  - An isolated event or a systematic issue?
- What data can help the manufacturers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

CCS Implementation

Regulatory expectations

- Annex 1 is largely aligned with FDA's guidance for sterile drug manufacturing
  - FDA Aseptic Processing Guidance
- Will the FDA enforce EU's GMPs Annex 1?
  - FDA is not obligated to comply with Annex 1
  - FDA will not be enforcing PUPSIT

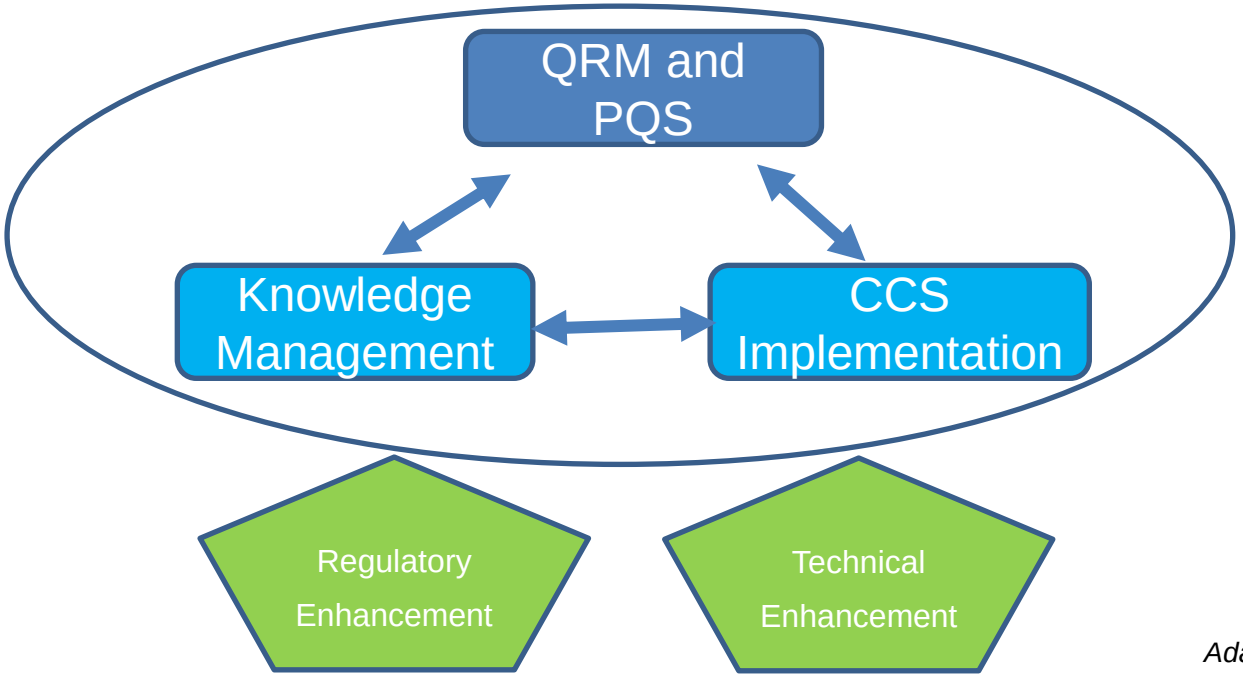
Impact of EU Annex 1 in China



Adapted from China PDI 2023

Impact of EU Annex 1 in China

Proposed revision of China's Annex 1 of GMP for sterile products



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Thank You!