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Track: Sterility Assurance Expectations for Generic and Biosimilar Sterile Products

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Regulatory-Ready Sterility Assurance for Generic and Biosimilar Sterile Products

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Disclaimer

The content expressed in this presentation are personal views/opinions of the speaker and should not be construed as advice or recommendations on behalf of Cipla Ltd.

Presentation Overview

Achieving regulatory-ready sterility assurance

- Critical Factors
- Study-Specific Key Considerations

Benefits of regulatory-ready sterility assurance

Achieving Regulatory-Ready Sterility Assurance:

Critical Factors

Make the submission easy to understand, navigate, and to review

Write clear, complete and consistent narrative summaries

- Clearly explain the "what," "why," "how" of each study
- Provide sufficient operational details (e.g., equipment, filling line identification, and room numbers etc)
- Ensure consistency across the submission. No conflicting information (e.g., among summaries, supporting documents and different modules)
- Provide a clear scientific justification wherever needed (e.g., if bracketing approach used)

Reference: Guidance for Industry: M4Q: The CTD — Quality

Achieving Regulatory-Ready Sterility Assurance:

Critical Factors (continued..)

Commercial Process is the Target : *Validate What You Propose to Use*

- Focus on validation of manufacturing process **proposed** for commercial production
- Do not limit the assessment to process that **was used** for exhibit batches

Key Takeaway

Always **cross-check** the validation package **against** the proposed commercial Batch Records (BMR) to ensure complete alignment.

Achieving Regulatory-Ready Sterility Assurance:

Critical Factors (continued..)

Validation vs Commercial

Provide a **comparison of the parameters** used during **validation vs proposed** for commercial

Requalification Program

Describe **Requalification program**, including:

- frequency of requalification
- number and type of runs performed (e.g., HD or HP study, with or without BI)

Recent Qualification Data

- If data is outdated (>2 years old), provide additional data from **recent** validation runs

Achieving Regulatory-Ready Sterility Assurance:

Critical Factors (continued..)

Biological Indicators

BI Description

- Provide complete description of BIs used for validation studies, including:
  - genus/species, D-value, manufacturer, lot number, expiry
  - manufacturer's stated spore concentration and
  - **confirmed spore concentration**

Post-sterilization exposure conditions

- Provide post-sterilization exposure conditions for BI, including **temperature** and **duration**

Controls

- Provide details related to positive control and negative control

Reference: FDA Guidance for Industry: *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (NOV 1994)

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Terminal Sterilization – Key Considerations

Surrogate solution

- Clearly identify the solution used during TS validation
- If a surrogate solution (e.g., WFI) used instead of the drug product solution:
  - ➢Provide a scientific justification

Selection of appropriate BI

- Select a BI appropriate for the specific sterilization process and validation objective
- For Heat Penetration TS validation of **solutions**:
  - ➢BI strips are not suitable
  - ➢Instead, BI spore suspensions or self-contained BI ampules are recommended

BI resistance and challenge

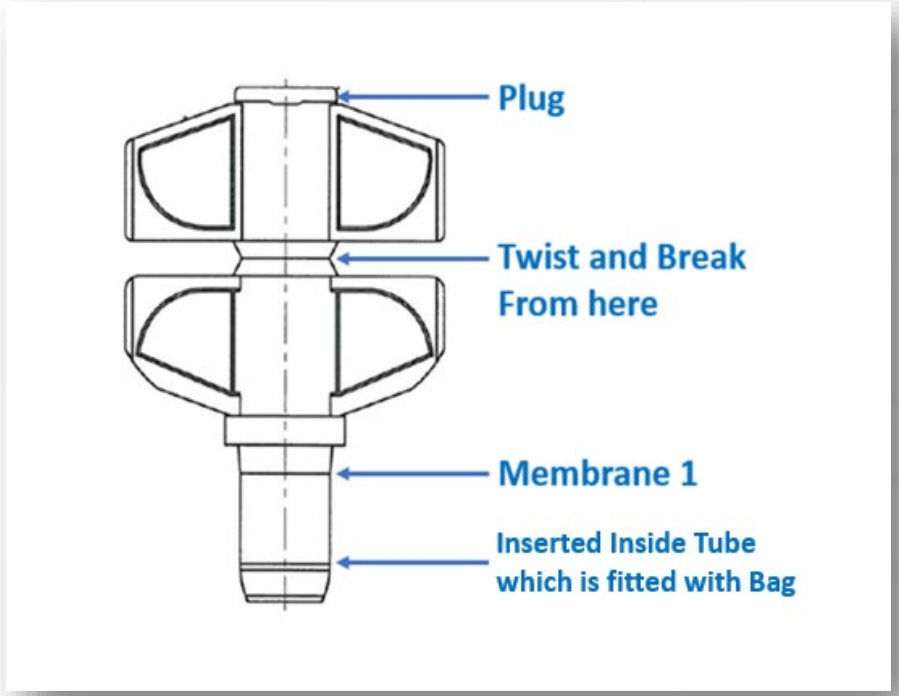
- Evaluate BI resistance against product bioburden and sterilization-cycle lethality
- Ensure the selected BI provides an appropriate microbiological challenge for validation

Terminal Sterilization – Key Considerations (continued...)

TS of Drug-device Combination Products - Sterilization of Twist-off Port of Infusion Bags:



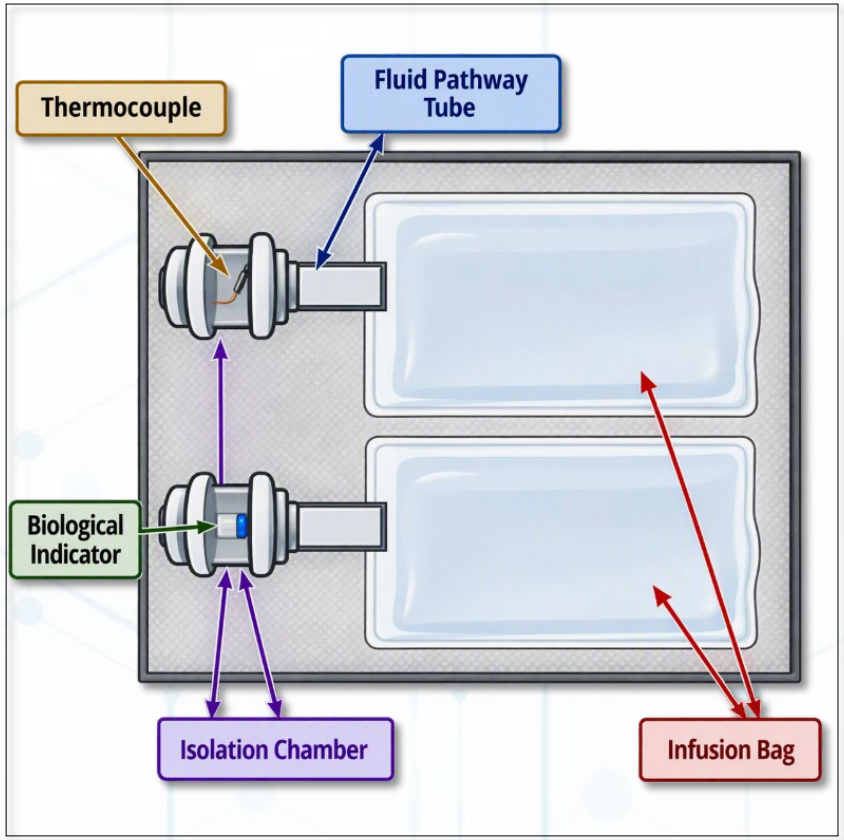
Infusion bag



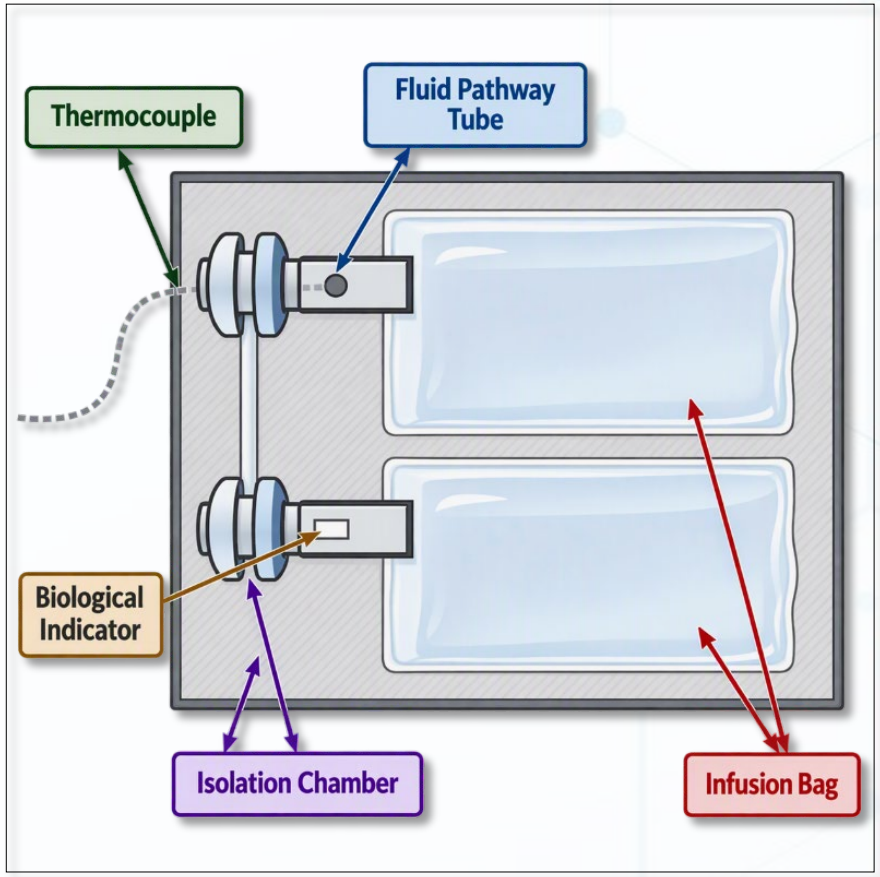
Twist off port

Terminal Sterilization – Key Considerations (continued...)

Thermocouples and BIs location in isolation chamber of twist off port



Thermocouples and BIs location in fluid pathway of infusion bag



Media Fill – Key Considerations

Media Fill Should Represent the Commercial Aseptic Process

Filling Duration

- Simulate the **maximum filling duration** proposed for commercial production (e.g., scaled up commercial batch size)

Filling speed

- Challenge the proposed **filling speed range**

Operation

- Simulate all aseptic operations (e.g., loading partially stoppered vials into lyophilizer)

Equipment

- Use the same equipment proposed for commercial, including the filling line, filling room, and associated equipment (e.g., multiple lyophilizers proposed)

Reference: FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice (2004)

Container Closure Integrity Testing – Key Considerations

Method Sensitivity

- Establish and justify the **sensitivity / limit of detection (LOD)** of the CCIT method
- Provide a **summary of validation data** supporting the established detection capability

Commercial Container-Closure System

- Use the **same container-closure system and interface** proposed for commercial
- Justify if any alternative is used

Representative Process Exposure

- Expose test units to the **proposed commercial manufacturing process conditions** before CCIT
- Include relevant worst-case process stresses, such as **terminal sterilization**

Positive and Negative Controls

Include controls to demonstrate the discriminatory capability of the method:

Positive control: Known-leak units

Negative control: Intact, conforming units

Hold Times - Key Considerations

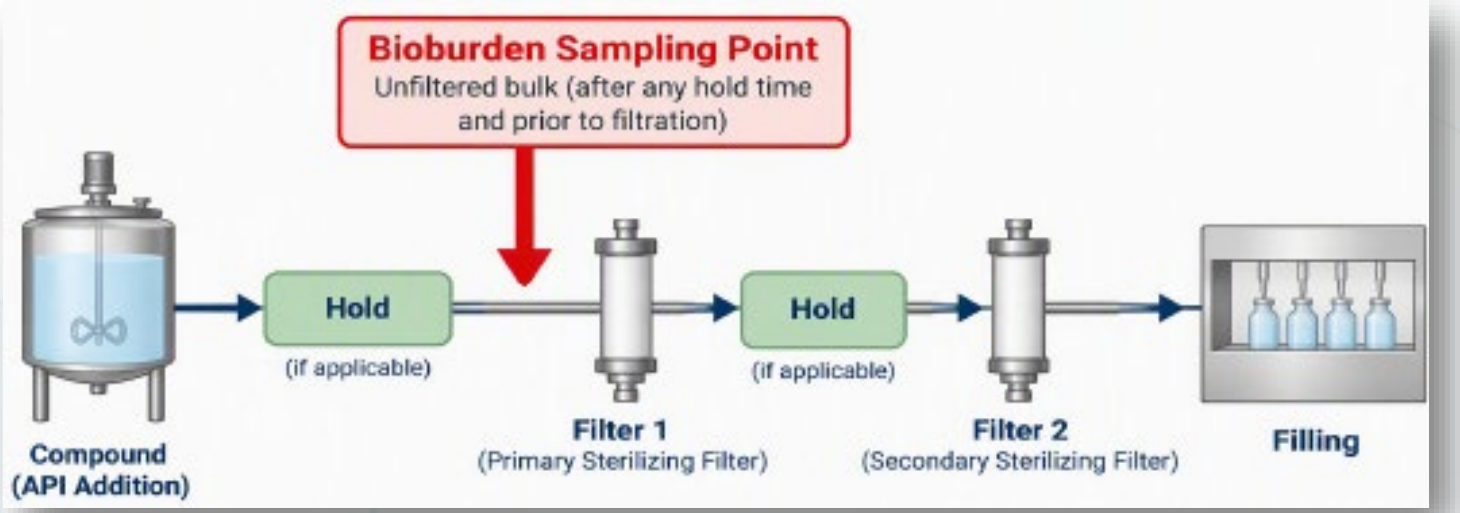
Maximum Filling Duration

- Ensure that the proposed **maximum filling duration** for commercial is **not based solely** on the time required for batch filtration/filling and bulk hold time study
- It should also be adequately supported by the relevant validation studies, including:

Filter validation studies	Filter/ tubing extractable / leachable studies	Media fill
duration evaluated for filter compatibility, integrity, bacterial retention	maximum product-contact duration evaluated	maximum filling duration simulated

Bioburden Sampling of the Bulk Solution

Sampling for bulk bioburden testing should be done on unfiltered bulk (i.e., after any hold time and prior to filtration)



Sampling at this stage

- provides an accurate assessment of the microbial load
- assess the potential risk associated with microbial proliferation during bulk holding and thus potential microbial metabolites and/or toxins in the bulk drug solution
- microbial metabolites can pass through the filters

BET Specification - Key Considerations

Maximum dose

- Calculate based on **proposed label's** maximum dose and duration of dosing:
  - Worst case dose may be **pediatric**
  - **USP specification** may not meet specification requirements

Drug Combination Product

- For a drug combination product with multiple APIs:
  - consider endotoxin burden from each API

Co-Packaged combination product

- For a co-packaged combination product:
  - consider endotoxin burden from each product

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Benefits of Regulatory-Ready Sterility Assurance

Better submissions → More efficient reviews → Timely patient access

A win for all stakeholders

Applicants: Fewer deficiencies, less review cycles

Reviewers: more efficient and faster review

Patients: faster access to necessary drug products

References

1. Guidance for Industry (1994): Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.
2. Guidance for Industry (2004): Sterile Drugs Products Produced by Aseptic Processing - Current Good Manufacturing Practice
3. Question-based Review (QbR) for Sterility Assurance of Terminally Sterilized Products: Frequently Asked Questions
4. Question-based Review (QbR) for Sterility Assurance of Aseptically Processed Products: Quality Overall Summary Outline
5. Guidance for Industry: Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products
6. USP <85> Bacterial Endotoxins Test
7. USP <1207> Package Integrity Evaluation - Sterile Products



Thank You