

COLLABORATION SESSION

Panel Prep Meeting | August 27, 2026

NOVEMBER 2-4, 2026

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Breakout session description

This session will explore evolving scientific approaches and regulatory expectations for sterility assurance submissions supporting generic and biosimilar sterile products, including drug-device combination products. Panelists will discuss current expectations for application content, format, and level of detail, as well as how tools such as Remote Record Assessments are shaping regulatory review and sponsor preparedness. The session will also address emerging issues such as low endotoxin recovery, plunger movement studies, vaporized hydrogen peroxide controls where applicable, and differing expectations for terminally sterilized and sterile-filtered products.

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Breakout Session Outline

Title: Sterility Assurance Expectations for Generic and Biosimilar Sterile Products

Time/Date: Monday, November 2, 2026, 10:45 a.m. - 12:00 p.m.

Participants

- **Ravi Harapanhalli, PhD (moderator/presenter)- Session Overview, PUPSIT, LER**
  Senior Vice President- Global Regulatory Affairs, R&D Operations, Amneal Pharmaceuticals
- **Shannon Heine, PhD (presenter)- Remote Regulatory Assessments and Expectations**
  Senior Pharmaceutical Scientist, DPMAI, OPMA, OPQ, CDER, FDA
- **Krishna Venkatesh, PhD (presenter)- Barriers, Isolators, VHP controls**
  Global Head of Product Development, Dr. Reddy's Laboratories
- **Rumit Shah, MPharm (presenter)- Modern deterministic toolsets, CCIT, Devices**
  Associate Director Product Development, Apotex
- **Arvind Mathuria, M.S. (presenter)- Trends in Agency queries on sterility assurance**
  Associate Director, Regulatory Affairs, Cipla
- **Moderated discussion** and Q/A (30 minutes)

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Sterility Assurance- Holistic Approach

- By far the most critical requirement for sterile pharmaceutical products
  - Controlling bioburden/endotoxins upstream
  - Maintaining sterility downstream
- Main challenges: Human Factors, Complexity of manufacturing and testing equipment and maintenance, Strict environmental controls
- Good aseptic practices: sequencing, environmental control, hand hygiene, maintenance of aseptic fields, and use of personal protective equipment (PPE)
- Cleanrooms- ISO 14644-1 from ISO 1 (cleanest) to ISO 9 (ordinary room air) based on the maximum number of airborne particles allowed per cubic meter
- Enclosures: RABS (open, closed, active, passive). Isolators (Completely sealed)
- Aseptic filters:
  - Sterile, hydrophobic auxiliary filters on gas feed lines and vent ports to block environmental microbes from entering the manufacturing line and test assembly.
- Sterilization Validation: Need for independent validation of product sterility, containers/device components, manufacturing equipment and accessories.

PUPSIT (Pre-Use Post-Sterilization Integrity Testing)

- Basic question: Are sterilized product filters intact and fully functional at the point of use?
- A vital validation step for product filters used in sterile filling
- Verifies filter is undamaged and properly installed before product filtration begins
- Detects cracks, tears, or seal leaks caused during sterilization or assembly before product contact, where particulate or microbial foulants clog a damaged filter during use, allowing it to falsely pass
- Helps prevent batch losses from undetected filter defects
- Avoids the effort of negotiating regulatory challenges
- Future-proofs filling lines
- Core Test Methods:
  - Bubble point test
  - Diffusive flow/Forward flow test
  - Pressure hold/Decay test

Adequacy of Sterile Filtration Controls

- **Traditional Approach**:
  - Validated constant-flow peristaltic pumps operating at validated low flow rates e.g. <150 mL/min to ensure likelihood of pressure-induced membrane deformation, fouling, or breach
  - Ensure low-shear, non-pulsatile, and low-pressure flow to minimize stress on filters
  - Post-use filter integrity testing
  - Compliant environmental and aseptic processing controls
  - Assurance of no filtration interruptions, integrity failures, bioburden excursions
  - Bacterial retention validation >30 psi using *B. diminuta*
  - Sterility testing
- Question: Does the flow rate alone serve as an adequate surrogate for filtration pressure?
- Answer: No. filter blockage may result in increased pressure without corresponding changes to the flow rate upstream of it.
- **Additional Expectations – Control strategy enhancement**:
  - Implementing pressure monitoring upstream of filters to ensure max upstream and differential pressure across filter doesn't exceed the validated pressure during filtration
  - Identifying filter pressure as a CPP
  - Configuring filtration train assembly with dual filters with one pressure monitor upstream and one in between
  - Choice of non-product contacting pressure sensors

Low Endoxin Recovery (LER)

- A critical analytical and patient-safety concern
- LER is a time-dependent masking or inactivation effect rather than immediate, constant assay interference (Not a destruction or removal)
- Detectable endotoxin activity in a drug product may progressively decrease over time, resulting in a spiked recovery of less than 50% of the expected value using LAL assays.
- The FDA expects biological and pharmaceutical manufacturers to evaluate and address LER during product and assay development, particularly for BLAs containing protein formulations, chelating agents, and surfactants.
- Formulation components like buffers, chelators (which remove divalent cations), and surfactants (like polysorbate) can disassemble natural lipopolysaccharide (LPS) aggregates, hiding the endotoxin from detection by standard Limulus Amebocyte Lysate (LAL) tests
- It is critical to develop and validate methods for storing and handling samples to prove the stability of assayable endotoxin content and demonstrate the absence or mitigation of LER
- Guidance on hold time studies to rule out or mitigate LER:
  - *FDA's Pyrogen and Endotoxins Testing Q and A Guidance- March 2026*
  - *PDA Technical Report No. 82*

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LER Mitigation Strategies

- Hold –time Studies
  - Reverse spiking study comparing the results of DP samples with water samples spiked to the same final endotoxin concentration as the DP samples and at the same time points (hours, day 0-7, weeks) and showing recoveries ≥50%RT
  - Conducted at 2-8^{o}C and RT
- Buffering and Demasking Agents
  - Utilize alternative buffers, divalent cation adjustments (e.g., magnesium chloride or magnesium sulfate), specialized demasking technologies (such as heat or chemical treatments), or modified BET protocols to restore endotoxin detectability

Questions to Ponder Over

- EU GMP Annex 1 for aseptic processing mandates PUPSIT. FDA and WHO are considering it as part of good manufacturing practices. Does FDA also mandate this testing?
- What are some challenges faced by Industry in setting up PUPSIT?
- Do the extra resources needed to install a setup conducive to PUPSIT justify adopting PUPSIT or alternative traditional approaches suffice?
- How many batches are considered required to validate PUPSIT?
- What are some areas of technical impossibility that preclude PUPSIT?
- What level of justification is typically needed in precluding PUPSIT?
- Have you seen LER in your product formulations? If so, how have you mitigated it?
- Is product reformulation necessary to overcome LER?