Aseptic Process Challenges: The Threat of Underperforming Disinfectants for cGMP Applications

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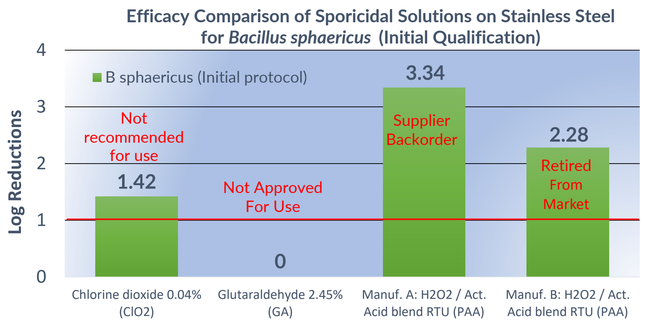
Introduction

Disinfectant Efficacy Matters: Resilient Spores, Sterility Risks, and Supply Challenges

This poster reviews Disinfectant Efficacy Tests (DET) for sporicidal solutions in aseptic manufacturing, guided by USP <1072>, across initial and CAPA-driven assessments following a Sterility Failure. It addresses inherent resistant spore formers and market supply challenges that impact disinfection strategies.

Background

1. A conventional aseptic parenteral and ophthalmic manufacturing site conducted a study to evaluate the efficacy of both approved and prospective sporicidal solutions.
2. Since USP <1072> alignment was still under evaluation, internal acceptance criteria were defined, requiring at least a 1-log reduction. Disinfectants that demonstrated higher log reductions will be selected for routine sporicidal use.
3. Three sporicidal chemistries were assessed and challenged with *Bacillus sphaericus* (predominant spore-forming plant isolate):
   A. Chlorine Dioxide (ClO_2): Historical Sporicidal Use
   B. Glutaraldehyde (GA): Historical Sporicidal Use
   C. Hydrogen Peroxide/Acetic Acid RTU (PAA, two manufacturers)



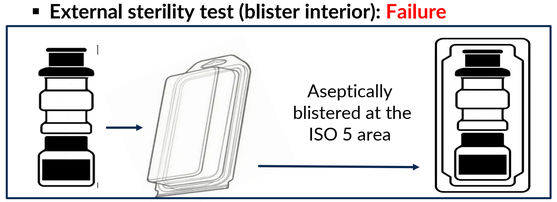
4. Based on results, *PAA was implemented* as the sporicidal agent (primary & back-up), ***ClO_2 was retained (even when not recommended)***, and GA was removed from the portfolio.

Implementation Impact & Market Supply Challenges: Prompting the use of Chlorine Dioxide.

1. Within one year of implementation of the new disinfection program, **isolation frequency** for **spore formers, molds**, and Gram-positive cocci was **reduced** by approximately **60%.** During this time, **ClO_2 was not used** to support commercial activities.
2. Approximately 18 months later, PAA Manufacturer B retired its product from the market. Additionally, PPA Manufacturer A reports a product shortage, triggering supply disruptions that cut the sporicidal portfolio by 67%, prompting the use of Chlorine Dioxide .0.04%.

The Aseptic Failure

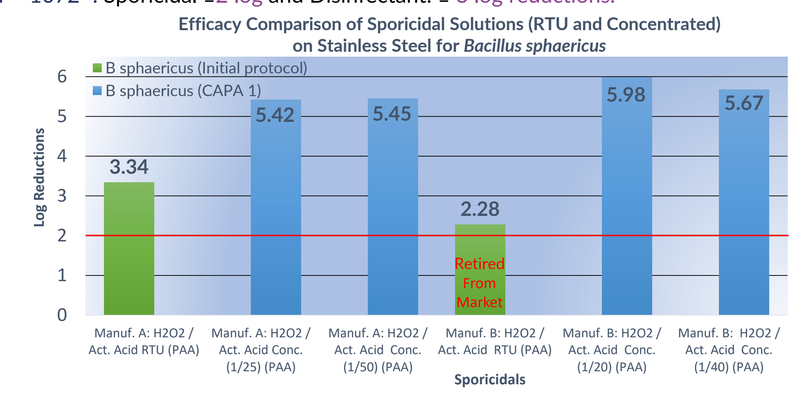
1. An Ophthalmic product Sterility Failure was reported shortly after reinitiating the use of Chlorine dioxide 0.04% (ClO_2) to support manufacturing activities as a sporicidal.
   - **Internal product sterility test (vial with product): Pass – Sterile**
   - **External sterility test (blister interior): Failure**



Parameter	Fact
Isolated microorganism	***Paenibacillus alvei* (bacterial spore former)**
***P. alvei* EM isolation frequency**	**0.04% – extremely low (36 months)**
Special EM monitoring	*P. Alvei was also* **isolated** from an **SS chair** inside the **filling room (ISO 5)**
Investigation Root cause	**No** definite **root cause** identified. Most probable root cause: **Inefficient material transfer/room disinfection** → after corresponding fencing and product impact assessment: Batch was rejected.
CAPA	Two CAPA records were assigned to the QC Microbiology Laboratory
CAPA Details	1.Expand sporicidal portfolio to strengthen contamination control. 2.Assess ClO_2 efficacy specifically against *P. alvei*

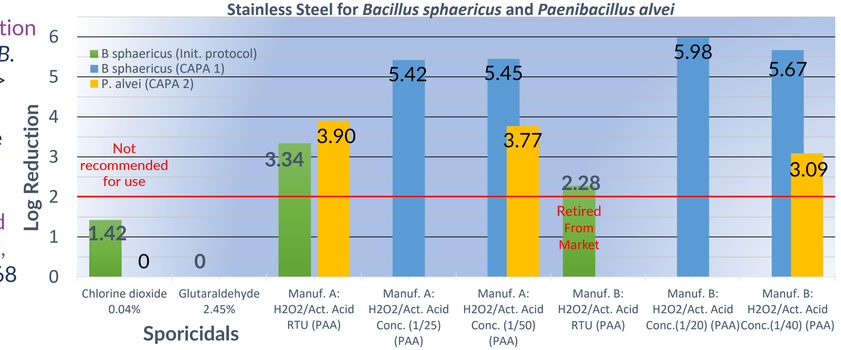
CAPA 1: Expand approved sporicidal portfolio

1. Concentrated/Like PAA formulations from Manufacturers A and B were selected for evaluation. A second DET protocol assessed multiple dilutions, aiming to reduce irritant fumes while preserving sporicidal efficacy, following alignment with regulatory expectations according USP <1072>: Sporicidal ≥2 log and Disinfectant: ≥ 3 log reductions.
2. Effective Against *B. sphaericus* – Evaluated use-dilutions successfully inactivated *B. sphaericus*, performing equal to or better than initially tested sporicidals.
3. Comparable Performance – Differences among PAA dilutions were ≤0.5 log; the highest dilution was advanced for testing against *P. alvei.*



CAPA 2: Evaluate the efficacy of Chlorine Dioxide and new PAA against *Paenibacillus alvei*

1. Concentrated PAA formulations from Manufacturers A and B, along with Chlorine Dioxide (ClO_2), were evaluated under USP <1072> criteria: Sporicidal ≥2-log reduction and Disinfectant ≥3-log reduction, ensuring alignment with regulatory expectations.
2. Chlorine Dioxide (ClO_2): No inactivation of *P. alvei* (0 log) versus 1.42 log on *B. sphaericus*—both below USP <1072> criteria.
3. RTU PAA: Comparable performance against both organisms, with only a 0.56 log difference.
4. Concentrated PAA: *P. alvei* exhibited greater resistance than *B. sphaericus*, with log reductions ranging from 1.68 to 2.58.



Observations/Conclusions

- **Balanced Selection** – Choosing the right disinfectant requires weighing empirical efficacy, product presentation, and supply reliability. USP <1072> criteria ensure a safety buffer against inherently resistant species.
- **Species-Level Resistance** – Resistance varies by organism; *Paenibacillus alvei* showed higher resistance *than Bacillus sphaericus* when tested with ClO_2 and concentrated PAA.
- **Adaptability Required** – Preferred disinfectants must be replaced if they fail to meet efficacy standards, regardless of prior approval.
- **Market Impact** – Supply shortages and product withdrawals can force reliance on underperforming agents, risking ineffective control of inherent resistant spores (>1.42 log).