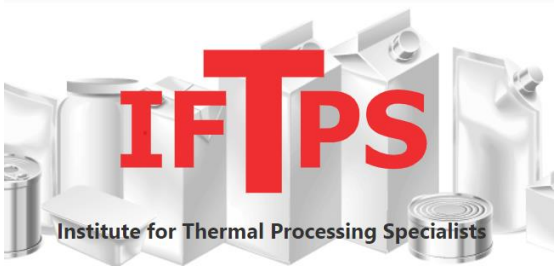

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA Views on Surrogate Selection & Calibration

Nate Anderson

FDA

IFTPS Autumn Symposium

Principles and Practices in the Use of Surrogates in Process Evaluation

September 14-15, 2021

Outline

- Validation definition
- Establishing performance standards
- Historical case study
- Bacterial surrogates

Validation within FSMA

- Preventive controls need to be validated.

21 CFR 117.160

- Validation must include **collecting and evaluating scientific and technical information (or … conducting studies)** to determine whether the preventive controls, when properly implemented, will effectively control the hazards.

21 CFR 117.160 (b)(1), (b)(2)

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Establishing Performance Standards

Identification of target pathogen

- Resistance to mode of inactivation (thermal, chemical, etc.)
  - Process efficacy is **process** *and* **product** dependent
- Likelihood and severity of adverse effect
- Uncertainties

[1]*Principles and guidelines for the conduct of microbiological risk assessment CAC/GL-30 (1999)*

Identification of surrogate organism

"The test organism should have a sufficiently high resistance to the sterilization process being validated to demonstrate the desired log reduction of the target organism."

(IFTPS G.005.V1)

IFTPS Institute For Thermal Processing Specialists

Document G.005.V1

GUIDELINES FOR MICROBIOLOGICAL VALIDATION OF THE STERILIZATION OF ASEPTIC FILLING MACHINES AND PACKAGES, INCLUDING CONTAINERS AND CLOSURES

Establishing Performance Standards

- Setting level of treatment required
  - Surrogate vs. organism of concern
  - Target log reduction
  - Initial bioburden
- Biological validation
  - Count reduction
  - End Point

CASE STUDY: HYDROGEN PEROXIDE

Aseptic packaging sterilant

Hydrogen Peroxide

- Early evaluations by FDA only considered *Clostridium botulinum.*

  "Testing may involve…food contact surfaces inoculated with micro-organisms at least as resistant to hydrogen peroxide exposure as *C. botulinum*."

Davis, R.B. and Dignan, D.M. 1982. Use of hydrogen peroxide sterilization in packaging foods. Assoc. of Food and Drug Officials.

Hydrogen Peroxide

- A 12D process would reduce the *C. bot* load per container to 10^{-12}.
- The spore load for a 1L carton was taken as ~1.0. A ratio of ~one *C. bot* spore per 1 million spores in the general population was assumed. Therefore, ~10^{-6} *C. bot* spores per container.
- A 6D treatment of the *packaging material* would yield a similar probability of failure as the product.

Microbiological Requirements

- 6-log reduction of *Clostridium botulinum*
- *A minimum* 4-log reduction (4D) of Bacillus atrophaeus (previously named *Bacillus subtilis, Bacillus subtilis var. niger or Bacillus globigii.)*

Mode of Inactivation

- The target pathogen may differ using a different lethal treatment, e.g., heat vs. chemical, H_2O_2 vs. PAA.
- The target pathogen may require more (e.g., HPP) or less (e.g., LACF) treatment than spoilage microorganisms.

Peracetic Acid

- Spores tested in aqueous solution showed an order of sensitivity (least to greatest) to PAA:

Bacillus cereus > B. subtilis > C. botulinum

Blakistone et al. Journal of Food Protection, Vol. 62, No. 3, 1999, Pages 262–267

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News Release

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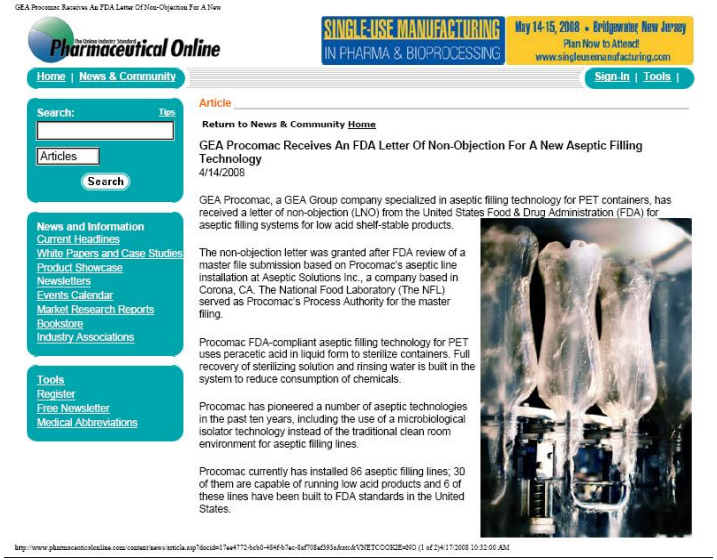
FMC Clarity™ Becomes First Peracetic Acid Sterilant to Receive Low-Acid Acceptance and Letter of Non-Objection from FDA

PHILADELPHIA, December 17, 2007 -- FMC Corporation and Kan-Pak LLC announced that the FDA Office of Food Safety has issued a Letter of Non-Objection for Clarity™ sterilant, FMC's new peracetic acid based sterilant for use in aseptic packaging of low acid products at Kan-Pak.


GEA Procomac Receives An FDA Letter Of Non-Objection For A New

Pharmaceutical Online

SINGLE-USE MANUFACTURING IN PHARMA & BIOPROCESSING — May 14-15, 2008 • Bridgewater, New Jersey — Plan Now to Attend! www.singleusemanufacturing.com

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GEA Procomac Receives An FDA Letter Of Non-Objection For A New Aseptic Filling Technology
4/14/2008

GEA Procomac, a GEA Group company specialized in aseptic filling technology for PET containers, has received a letter of non-objection (LNO) from the United States Food & Drug Administration (FDA) for aseptic filling systems for low acid shelf-stable products.

The non-objection letter was granted after FDA review of a master file submission based on Procomac's aseptic line installation at Aseptic Solutions Inc., a company based in Corona, CA. The National Food Laboratory (The NFL) served as Procomac's Process Authority for the master filing.

Procomac FDA-compliant aseptic filling technology for PET uses peracetic acid in liquid form to sterilize containers. Full recovery of sterilizing solution and rinsing water is built in the system to reduce consumption of chemicals.

Procomac has pioneered a number of aseptic technologies in the past ten years, including the use of a microbiological isolator technology instead of the traditional clean room environment for aseptic filling lines.

Procomac currently has installed 86 aseptic filling lines; 30 of them are capable of running low acid products and 6 of these lines have been built to FDA standards in the United States.

Bacterial Surrogates

Sterilization method	Application(s)	Food	Test microorganism	Notes	References
Bacterial surrogates					
Moist Heat/ Steam	Autoclave/Retort	Low-acid canned foods	*Clostridium sporogenes* P.A. 3679; *Geobacillus sterothermophilus* NCA1518 (ATCC 7953, DSM 5934);	Widespread use of PA 3679 resulted in genetic diversity of strains. Formerly *Bacillus sterothermophilus*	(Stumbo et al., 1950, Donk, 1920, Schill et al., 2016, Bigelow and Esty, 1920, Bigelow et al., 1920, Bigelow, 1921, Goldblith et al., 1961)
Dry heat	Dry heat sterilization	Contact surfaces	*Geobacillus sterothermophilus* NCA1518 (ATCC 7953, DSM 5934)		(Donk, 1920, Murrell and Scott, 1966)
Hydrogen Peroxide	Packaging equipment and materials		Bacillus atrophaeus ATCC 9372 Baciullus subtillus SA 22 NCA 72-52 (SA22),	Formerly *Bacillus subtilis* A or B. *subtilis var. globigii*	(Ito et al., 1973)
Thermal processes	Thermal processing, roasting, extrusion	Almonds, cocoa beans, pistachios, seasonings, chicken meat powder, pet food, oat flour, wheat flour	*Enterococcus faecium* NRRL B-2354	Formerly *Pediococcus* sp NRRL B-2354	(Rachon et al., 2016, JEONG et al., 2011, Verma et al., 2018, CEYLAN and BAUTISTA, 2015, Bianchini et al., 2014, Liu et al., 2018, Tsai et al., 2019)
Chemical	Propylene oxide (PPO)	Cashews, Macadamia nuts	*Enteroccus faecium* ATCC 8549; *Pediococcus acidilactici* ATCC 8042		Saunders et al., 2018

Ceylan, Erdogan, et al. "Guidance on validation of lethal control measures for foodborne pathogens in foods." *Comprehensive Reviews in Food Science and Food Safety* 20.3 (2021): 2825-2881.

Appropriate Statistical Procedures

- FDA BAM MPN--Most Probable Number from Serial Dilutions

"Not all possible outcomes of a given experiential design are equally likely; on the contrary, some outcomes may have an extremely low probability of occurring…"

Moruzzi, G., Garthright, W., and Floros, J. 1999, Food Control, 11, 57-66.


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