AP(+): POST-ASEPTIC PROCESSING TERMINAL TREATMENT AND ITS POTENTIAL USE FOR PARAMETRIC RELEASE

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Outline

I. Aseptic processing and terminal sterilization

II. Parametric release

III. Limitations of the sterility test

IV. QbD and regulatory flexibility

V. Sterility assurance levels and AP(+)

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Definitions

Aseptic Processing – “the drug product, container, and closure are first subjected to sterilization methods separately, as appropriate, and then brought together.”

- FDA’s Aseptic Processing Guidance - 2004

Terminal Sterilization – “A process whereby product is sterilized within its sterile barrier system.”

-PDA TR-1 and ISO/TS 11139:2006,

“Any manual or mechanical manipulation of the sterilized drug, components, containers, or closures prior to or during aseptic assembly poses the risk of contamination…A terminally sterilized drug product, on the other hand, undergoes final sterilization in a sealed container, thus limiting the possibility of error.”

- FDA’s Aseptic Processing Guidance - 2004

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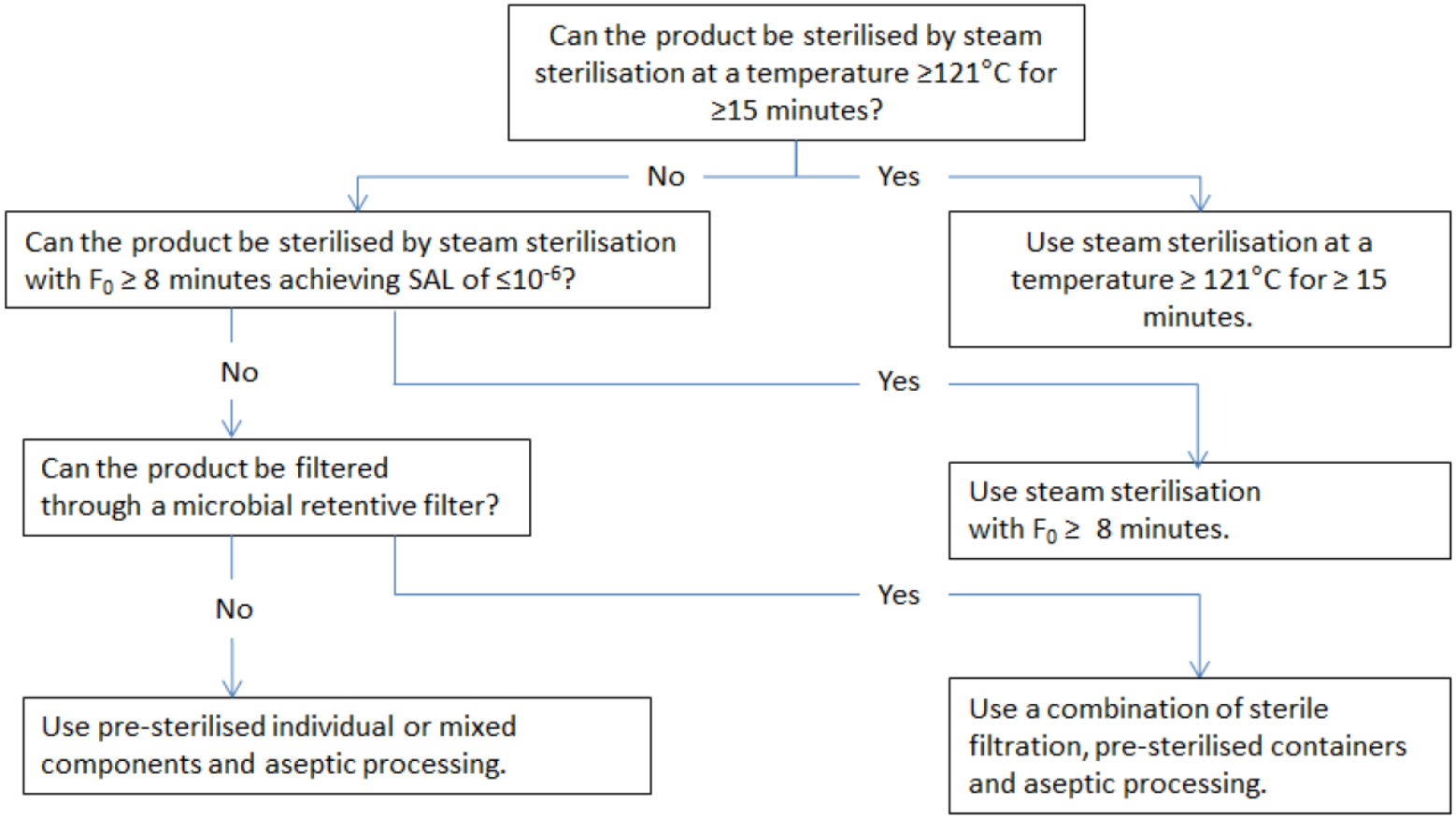
A Preference for TS

Health Authority	Quote
TGA	"Where possible, heat sterilization is the method of choice"
Health Canada	"…terminal moist heat sterilization, when practical, is presently considered the method of choice to ensure sterility."
FDA	"It is a well-accepted principle that sterile drugs should be manufactured using aseptic processing only when terminal sterilization is not feasible"
EMEA	"Where possible, finished product should be terminally sterilized, using a validated and controlled sterilization process, as this provides a greater assurance of sterility than a validated and controlled sterile filtration process and/or aseptic processing. "Where it is not possible for a product to undergo terminal sterilization, consideration should be given to using terminal bioburden reduction steps, such as heat treatments (e.g. pasteurization), combined with aseptic process to give improved sterility assurance."

The Problem With TS



EMEA Sterilisation Guideline - 2019

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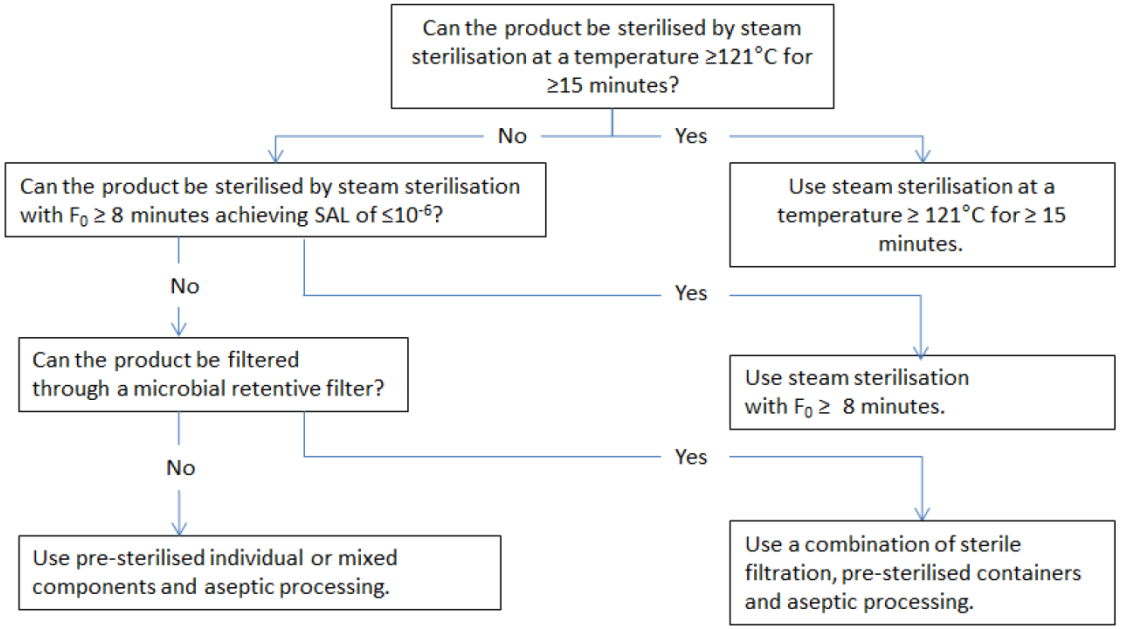
The Problem With TS



F_o <8 min	Post-aseptic processing terminal heat treatment	1 2, 3, 5, 7, 8	0 CFU/100ml, aseptic filtration and processing prior to terminal heat treatment (routine)

EMEA Sterilisation Guideline - 2019

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Parametric Release

Definition:

"A sterility assurance release program where demonstrated control of the sterilization process enables a firm to use defined critical process controls, in lieu of the sterility test"

- FDA PR Guidance

Requirements:

Control Strategy:
- CPPs
- Methods for CPP monitoring
- Acceptance criteria
- Micro. monitoring plan

Risk Assessment:
- Consistency of TS
- Environment, cycle, and cc variables
- Experience/prior knowledge

Documentation:
- Cycle description
- CPPs
- Adherence to CPPs vs. sterility test
- Description of the sterilization load monitor
- Exposure verification
- COA

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Benefits of PR

1. Regulators get improved QbD and risk-based manufacturing approaches

2. Manufacturers avoid the sterility test

3. Consumers get safe available products

The Sterility Test

- Tests a maximum of 20 units/batch
- Verified sensitivity ≤100 CFU of healthy ATCC organisms
- Requires sampling of a portion of the container contents
- Slow and wasteful
- Technically challenging, expensive, false positives
- Does not build quality into the product!

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The Sterility Test

Frequency of contaminated units in the batch	Probability of failing Sterility Test with the current sample size
0.001	0.0198–2%
0.005	0.0952–9.5%
0.01	0.1813–18%
0.05	0.6321–63.2%
0.1	0.8647–86.5%
0.5	1.0000–100%

- Sutton, S. 2011. Sterility Tests IN Rapid Sterility Testing J. Moldenhauer (ed) PDA/DHI Publ pp 7-24

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Quality by Design

"…quality cannot be tested into products; i.e., quality should be built in by design."	ICH Q8 - 2005
"…quality cannot be tested into products; it should be built-in or should be by design."	FDA PAT Guidance - 2004
"quality must be built in; it cannot be tested in."	Janet Woodcock, The Concept of Pharmaceutical Quality. American Pharmaceutical review, 2004
"Good quality must be built in during the manufacturing process; it cannot be tested into the product afterwards."	World Health Organization – Essential medicines and health products. GMP Questions and Answers.
"Quality should be built into the product, and testing alone cannot be relied on to ensure product quality"	FDA Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations - 2006.
"Quality, safety, and efficacy are designed or built into the product…Quality cannot be adequately assured merely by in-process and finished-product inspection or testing"	FDA Guidance for Industry - Process Validation: General Principles and Practices 2011
"Sterility is a critical quality attribute for all sterile substances, products and containers. Sterility cannot be assured by testing, it needs to be assured by the use of a suitably designed, validated and controlled manufacturing process."	EMA Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container - 2019

Regulatory Flexibility

"…the demonstration of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided."	**ICH Q8 and ICH Q11**
"…knowledge can be gained in a structured manner by, for example, applications of formal experimental designs, PAT concepts, or risk management tools (e.g. failure mode effect analysis or FMEA) and can allow regulatory agencies to develop more flexible regulatory approaches, for example, to…implement real time quality control, leading to a reduction of end-product release testing"	**FDA GMPs for the 21st century**
"effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight."	**ICH Q9**
"Regulatory approaches for a specific product or manufacturing facility should be commensurate with the level of product and process understanding, the results of quality risk management, and the effectiveness of the pharmaceutical quality system."	**ICH Q10**
"The extent of operational and regulatory flexibility is subject to product and process understanding (ICH Q8 and Q11), application of risk management principles (ICH Q9), and an effective pharmaceutical quality system (ICH Q10)." Q12	**ICH Q12**
"There are many development strategies that can be used to identify optimal formulations and processes. The knowledge acquired in these development programs is the foundation for product and process design. This knowledge base can help to support and justify flexible regulatory paths for innovation in manufacturing and post-approval changes."	**FDA PAT guidance**

Probability of a Non-Sterile Unit

$$\log N_u = -F_0/D + \log N_0$$

N_u = PNSU

F_0 = equivalent time (minutes) at 121°C (lethality)

D = decimation (log reduction) value of the natural bioburden at 121°C.

N_0 = bioburden population of the container of product

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Media Fill Failures

Date of for 483	Organism(s)	Organism Description	Typical Environment
6-February-2019	Sphingobacterium multivorum	G (-) non-spore forming rod	Ubiquitous in nature, e.g., soil
	Cellulosimicrobium cellulans	G (+) non-spore forming rod	Ubiquitous in nature, e.g., soil
	Pseudomonas stutzeri	G (-) non-spore forming rod	Soil
	Stenotrophomonas species	G (-) non-spore forming rod	Soil, water, plants
21-December-2018	Staphylococcus epidermidis	G(+) non-spore forming cocci	Human skin
	Brevundimonas diminuta/vesicularis	G (-) non-spore forming rod	Soil, sediment, water
	Stenotrophomonas maltophila	G (-) non-spore forming rod	Soil, water, plants
19-July-2017	Propionibacterium acnes	G(+) non-spore forming rod	Human skin
19-May-2017	Stenotrophomonas maltophila	G (-) non-spore forming rod	Soil, water, plants
1-December-2016	Staphylococcus cohnii	G(+) non-spore forming cocci	Human skin
19-July-2016	Chaetomium subaffine	Fungus	Soil, plant decay, air
10-August-2015	Penicillium commune	Fungus	Indoor environments, food.
22-May-2015	Bacillus species*	G (+) spore forming rod	Ubiquitous in nature, e.g., soil
	Staphylococcus species	G(+) non-spore forming cocci	Human skin

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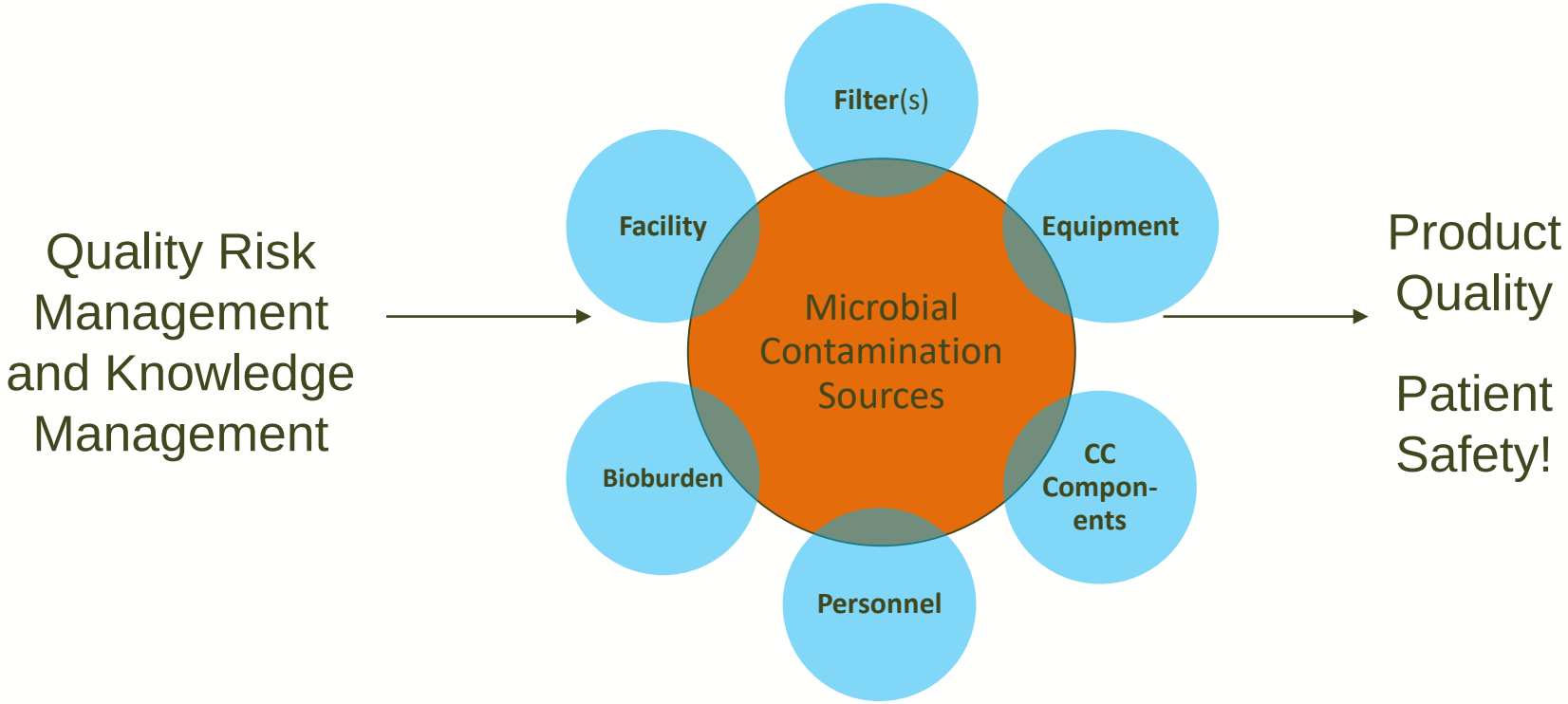
FDA form 483 observations from 2015-2019 (source: FDAzilla).

* Bacillus species were also present in the manufacturing area

AP(+)

- Aseptic processing plus a limited amount of terminal treatment – improve sterility assurance while limiting impurities
- Uses risk management techniques to identify and control sterility assurance risks



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Questions?

1. Are we fooling ourselves with continued reliance on the sterility test?

2. 100 years from now, will we still be reliant on the sterility test?

"I believe that you have to be willing to be misunderstood if you're going to innovate"

- Jeff Bezos

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Thank you!

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Parametric Release Discussion Group

https://www.linkedin.com/groups/13881053/?msgControlName=reply_to_sender&msgConversationId=6687955392669995008&msgOverlay=true

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