ISPE Annex 1 Symposium Hot Topics

Marsha Steed

CEO & Founder, Steed MicroBio LLC

Consultant JYA

EMA Update Annex 1 ATMPs

Robert Conocchia (EMA)

Background

- AMTP Part IV of th GMP guidelines addresses ATMPs, published 2017 as a standalone guidance for ATMPs
- The rationale was to allow academia, developers and manufactures to achieve consistent production of high quality ATMPs across the European Union

Revision was considered needed by IWG due to:

- Scientific and technological progress
- Alignment with Annex 1
- Innovative manufacturing approaches
- To remove ambiguity and inconsistencies

Scope Limitations and Boundaries

- Revision limited mainly to sterile manufacturing and contamination control
- Many sections will remain largely unchanged
- Part IV remains standalone guidance

European Commission

EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines

Consultation Process & Timeline

Concept paper was drafted by the WG and published on the European Commission webpage (May 2025)

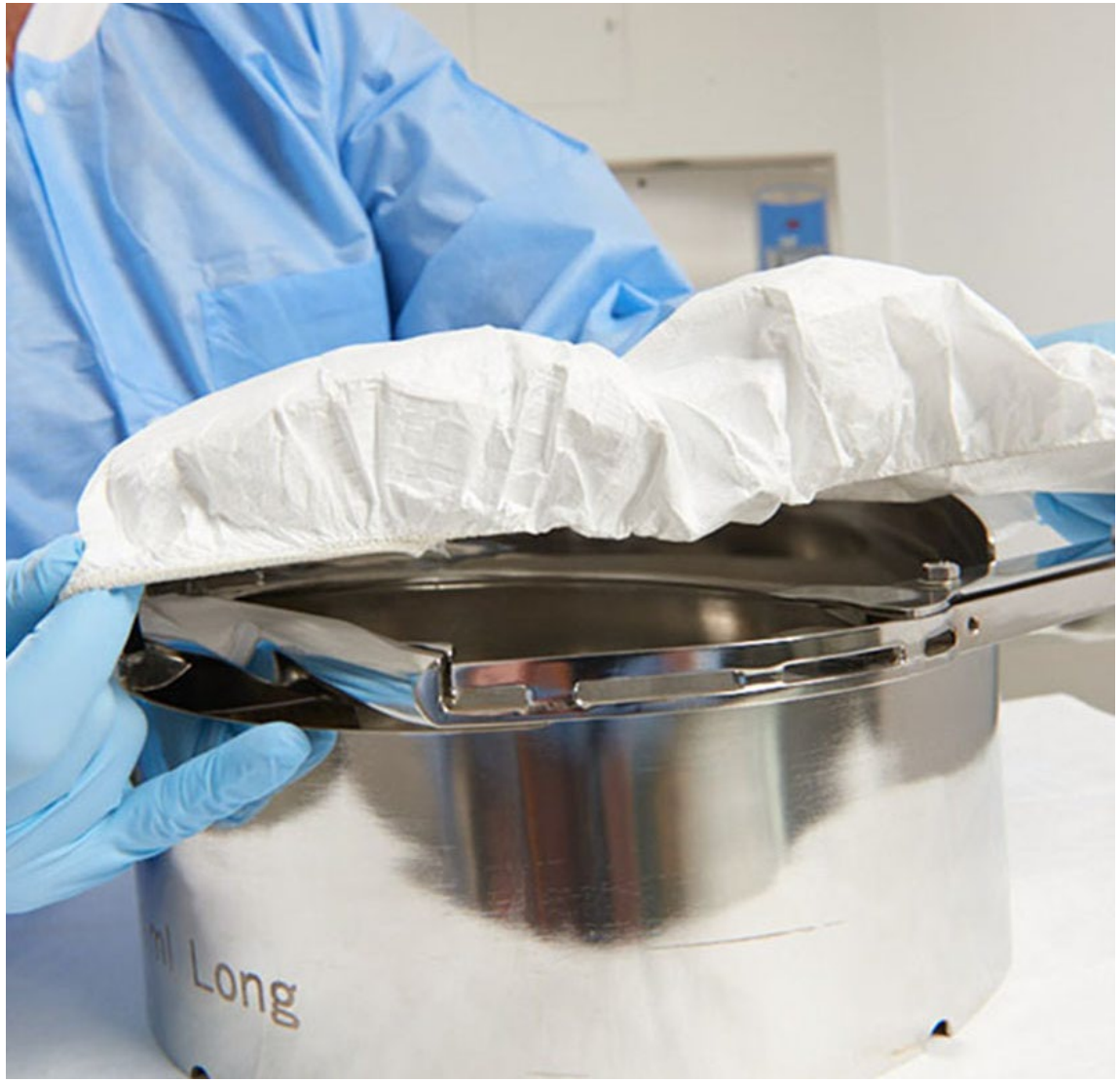
Public consultation was opened for 2 months

Next steps: draft guideline, further consultation, finalization

Aseptic Processing – Sterile Parts

Annex 1 (Clauses 5.5)

- For aseptic processes, direct and indirect product contact parts should be sterilised. Direct product contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that do not contact the product, but may come into contact with other sterilised surfaces, the sterility of which is critical to the overall product sterility (e.g. sterilised items such as stopper bowls and guides, and sterilised components).



Regulatory Findings – HOT NEW NEWS

Annex 1 – Major Finding (HPRA) May 2025

- The aseptic processes in the X and X areas at the site were not adequately designed to minimize the risk of potential and EM monitoring was not effectively implemented to detect potential contamination. The following deficiencies in the area were identified:
- The design of the fluid pathway and the aseptic intervention for needle-to-tubing attachment did not afford maximum protection to product filled in the X isolator of the X area
- The filling needles were not sampled as part of the EM monitoring program
- There was no air monitoring performed in the Grade A zone, during open door set-up of the filling line
- There was no continuous particulate monitoring or continuous viable air monitoring in the Grade A (e.g., air sampling or settle plates) during aseptic/equipment set-up
- There was no EM of the Grade C and D cleanrooms in operation during the aseptic set-up

Regulatory Findings – HOT NEW NEWS

FDA 483 - January 2025 PAI PFS Filling Line - Ireland

- Observation 1a – Failed to maintain sterility of the stoppering equipment steam sterilized by autoclave during its introduction into the isolator, and instead you rely on sanitization of the plunger stopper component contact equipment (e.g., plunger stopper bowl and plunger stopper rods) with sterile 70% IPA followed by VHP, or VHP alone to render it ready for aseptic fill-finish
- Observation 1b – Failed to sanitize the isolator doors upon closure into Grade A space from Grade C space for each door closure event. Additionally, you failed to conduct smoke studies for the stoppering system installation open door interventions.

Regulatory Findings – HOT NEW NEWS

FDA 483 - January 2025 PAI PFS Filling Line - Ireland

- Observation 2a – An operator was observed using a sanitized isolator glove during assembly of the steam sterilized filling needles clip holders to sanitize SS mounting bracket …. Blocking first air (unidirectional laminar airflow) over the needles with the sanitized isolator glove
- Observation 2b – The stainless-steel fill needle mounting bracket located directly over the open syringes during manufacturing is a sanitized surface, not sterile.

Regulatory Findings – HOT NEW NEWS

FDA 483 - January 2025 PAI - Germany

- Observation 1a – Inadequate aseptic processing technique was observed during the activities performed in X in Building X during post VHP set-up and filling operations. Non-sterile isolator gloves were used to handle the silicon and Teflon tubing and the filling needles during their connection and installation. Additionally, during this process, first air was blocked above the exposed filling needles.
- Observation 1b – Failed to sanitize the isolator doors upon closure into Grade A space from Grade C space for each door closure event. Additionally, you failed to conduct smoke studies for the stoppering system installation open door interventions.

1b - (EXACT SAME WORDING AS IRELAND SITE)

Regulatory Findings – HOT NEW NEWS

What Are They Doing About It?

- Updated their Annex 1 Gap Assessment Action Plan (Gap Assessment)
- ~ 700k Euro CAPEX Investment
- Internal and External SME reviews
- EM during line set-up in-progress

Aseptic Behaviors Training

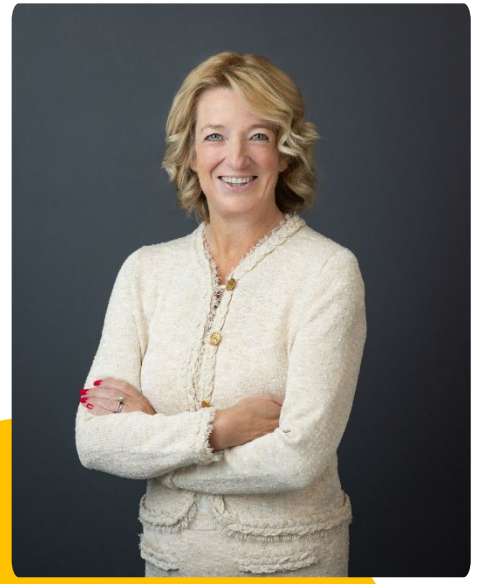
Critical to have **GOOD** aseptic behaviors training

- Operators
- QA
- QC Microbiology

Isolators – It Is NOT a Magic Box

STEED MicroBio

THANK YOU



Contact Info

Marsha Steed

949-412-6683

marsha@steedmicrobio.com

www.steedmicrobio.com