Aseptic Process Simulation (APS) Program Risk Assessment Implementation: One Year Later

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Agenda

- Background
- Process
- Implementation- Positive Outcomes and Case Study 1
- Implementation- Constructive Learnings and Case Study 2
- Conclusions
- Q&A

Background

- **EU Annex 1**

  "*Process simulation tests should be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC-system, equipment, process and number of shifts.*"

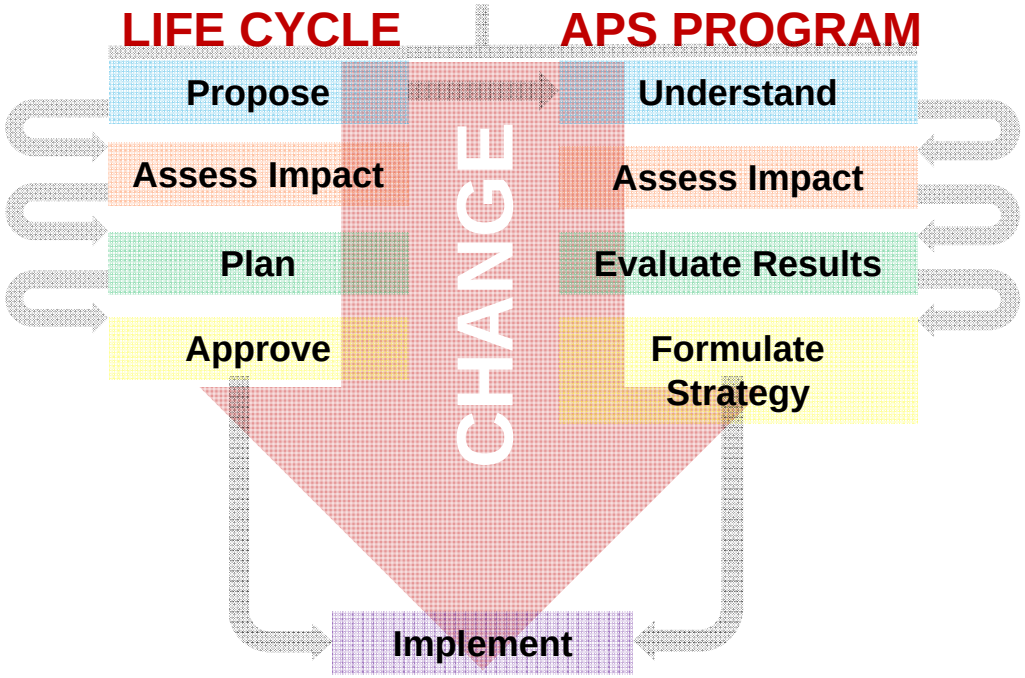
- **FDA Guidance for Industry**

  "Each change to a product or line change should be evaluated using a written change control system. Any changes or events that have the potential to affect the ability of the aseptic process to exclude contamination from the sterilized product should be assessed through additional media fills. For example, facility and equipment modifications, line configuration changes, significant changes in personnel, anomalies in environmental testing results, container closure system changes, extended shutdowns, or end product sterility testing showing contaminated products may be cause for revalidation of the system."

How do you apply the regulatory guidance…

1. Scientifically
2. Systematically
3. Consistently

Process



Process

Understand the change…

- QUESTION 1: Does the change result in impact within the sterile boundary or to a container closure system?
  - If NO…further assessment is not required
  - If YES…continue to QUESTION 2
- QUESTION 2: Is the change challenged by the current aseptic process simulation program?
  - If YES…further assessment is not required
  - IF NO…proceed to the next phase

Assess the impact (risk assessment)…

- Determined level of sterility assurance risk to the following APS elements (1= Low, 2 = Medium, 3 = High):
  - [A] *Process / Personnel*
  - [B] *Environment / Facility*
  - [C] *Equipment*
  - [D] *Container Closure System*
- Document rationale for each individual risk score

Calculate final risk score:

[A] X [B] X [C] X [D] = Final Risk Score

Process

Evaluate results…

There are 15 distinct Final Risk Scores that can be obtained when each of the four APS Elements is rated 1, 2, or 3.

- A Final Risk Score of 1 can only be obtained if all APS Elements are rated as "Low Risk", and as such correlate to an impact of "*little to no expected risk to sterility assurance*".
- The remaining 14 Final Risk Scores are qualitatively distributed as follows:

    1) Scores of 2, 3, 4, and 6 are all obtained if at least two of the four APS Elements are rated as "Low Risk", and not more than one APS Element is rated as "High Risk" – these scores are correlated to "*LOW expected risk to sterility assurance*".

    2) Scores of 8, 9, 12, 16, 18, and 24 are divided such that the lower half correlates to "*MEDIUM expected risk*" and the upper half correlates to "HIGH expected risk" to sterility assurance.

    3) Scores of 27, 36, 54, and 81 result from combinations of risk ratings that are indicative of a change with sufficient complexity/criticality/risk such that the existing APS validation program no longer represents the validated state of sterility assurance.

If the Final Risk Score is…	Then…	The recommended aseptic process simulation strategy is…	Rationale
1	There is **LITTLE TO NO EXPECTED** risk to sterility assurance	1X single shift APS	The scope of the change should be challenged by a 1X single shift to ensure there are no unintended / unanticipated consequences to sterility assurance.
2 3 4 6	There is a **LOW** expected risk to sterility assurance as a result of the change.	1X full duration APS	The change should be challenged by a 1X full duration APS to ensure that any associated sterility assurance risk is represented across all shifts within a contiguous filling operation.
8 9 12	There is a **MEDIUM** expected risk to sterility assurance as a result of the change.	3X single shift APS	The scope of the change should be challenged by 3X single shift duration APS's to ensure that any associated sterility assurance risk is represented across multiple filling equipment setups to demonstrate consistency and repeatability.
16 18 24	There is a **HIGH** expected risk to sterility assurance as a result of the change.	2X single shift APS and 1X full duration APS	The scope of the change should be challenged by a 1X full duration APS and 2X single shift duration APS's. This will ensure that any associated sterility assurance risk is represented across a full contiguous filling operation as well as multiple filling equipment setups.
27 36 54 81	The change is significant enough that the current APS validation program is no longer representative of the validated state of sterility assurance	3X full duration APS	The scope of the change requires full line revalidation and should be challenged by a 3X full duration APS's.

Process

Formulate the strategy…

- APS strategy and challenge parameters
  - Number of APS challenge(s)
  - Duration of APS challenge(s)
- Document rationale
- Approval by:
  - Engineering
  - Technical Services / Manufacturing Science (TS/MS)
  - Operations
  - Quality Assurance

Implementation

Post Implementation Examples

- Line Speed Increase/Decrease
- Stopper Equivalency
- Sterilization Wrap Change Impacting Sterile Equipment
- Equipment Modifications/ Decommissioning
- Introduction of New Container Closure Systems/Components
- Campaigning
- Area Reclassification
- Flavor Management
- Clinical Trial Molecule Introduction
- Pre-Use Post- Sterilization Integrity Testing

Positive Outcomes

- Removed the “it feels like” conversation
- Impacted functions provide input/agreement up front
- Positive global Quality internal inspection review
- Approach has facilitated a standardized approach for risk evaluation
- Has forced that details of change are well understood and documented
- Has facilitated right size APS responses to changes

Case Study 1

PUPSIT

Positive Outcome Example

Case Study 1

Understand the change…

- DESCRIPTION: Implement Pre-Use Post-Sterilization (PUPSIT) for Aseptic Filling Lines A and B.
- QUESTION 1: Does the change result in impact within the sterile boundary or to a container closure system? YES- Impact to the equipment/process used to establish the sterile boundary.
  - If NO…further assessment is not required
  - If YES…continue to QUESTION 2
- QUESTION 2: Is the change challenged by the current aseptic process simulation program? NO- There are no APS validations challenging the PUPSIT process and associated equipment for Filling Lines A and B.
  - If YES…further assessment is not required
  - IF NO…proceed to the next phase

Case Study 1

Assess the impact (risk assessment)…

- Determined level of sterility assurance risk to the following APS elements (1= Low, 2 = Medium, 3 = High):

  [A] *Process / Personnel* – **3**

  - Impacted- Process used to establishment of the sterile boundary (i.e. set-up sequence, manipulations of new equipment/aseptic connections).
  - Not impacted- Intervention program, durations and processing times, line speeds, filling/stoppering/plungering processes, personnel (numbers and fatigue shift challenges), maximum sterile equipment holds

  [B] *Environment / Facility* - **1**; No change in environmental classifications or control strategies

  [C] *Equipment* – **3**; New FTR, new aseptic connector, new filtration assembly.

  [D] *Container Closure System* – **1**; No change to current container closure systems/ introduction of new container closure systems.

- Calculate final risk score:

  [A] X [B] X [C] X [D] = **9**

Case Study 1

Evaluate results…

There are 15 distinct Final Risk Scores that can be obtained when each of the four APS Elements is rated 1, 2, or 3.

- A Final Risk Score of 1 can only be obtained if all APS Elements are rated as "Low Risk", and as such correlate to an impact of "*little to no expected risk to sterility assurance*".
- The remaining 14 Final Risk Scores are qualitatively distributed as follows:

    1) Scores of 2, 3, 4, and 6 are all obtained if at least two of the four APS Elements are rated as "Low Risk", and not more than one APS Element is rated as "High Risk" – these scores are correlated to "*LOW expected risk to sterility assurance*".

    2) Scores of 8, 9, 12, 16, 18, and 24 are divided such that the lower half correlates to "*MEDIUM expected risk*" and the upper half correlates to "HIGH expected risk" to sterility assurance.

    3) Scores of 27, 36, 54, and 81 result from combinations of risk ratings that are indicative of a change with sufficient complexity/criticality/risk such that the existing APS validation program no longer represents the validated state of sterility assurance.

If the Final Risk Score [3] determined in Section 2 is	Then	The recommended aseptic process simulation strategy is	Rationale
1	There is **LITTLE TO NO EXPECTED** risk to sterility assurance	1X single shift APS	The scope of the change should be challenged by a 1X single shift to ensure there are no unintended / unanticipated consequences to sterility assurance.
2 3 4 6	There is a **LOW** expected risk to sterility assurance as a result of the change.	1X full duration APS	The change should be challenged by a 1X full duration APS to ensure that any associated sterility assurance risk is represented across all shifts within a contiguous filling operation.
8 9 12	There is a **MEDIUM** expected risk to sterility assurance as a result of the change.	3X single shift APS	The scope of the change should be challenged by 3X single shift duration APS's to ensure that any associated sterility assurance risk is represented across multiple filling equipment setups to demonstrate consistency and repeatability.
16 18 24	There is a **HIGH** expected risk to sterility assurance as a result of the change.	2X single shift APS and 1X full duration APS	The scope of the change should be challenged by a 1X full duration APS and 2X single shift duration APS's. This will ensure that any associated sterility assurance risk is represented across a full contiguous filling operation as well as multiple filling equipment setups.
27 36 54 81	The change is significant enough that the current APS validation program is no longer representative of the validated state of sterility assurance	3X full duration APS	The scope of the change requires full line revalidation and should be challenged by a 3X full duration APS's.

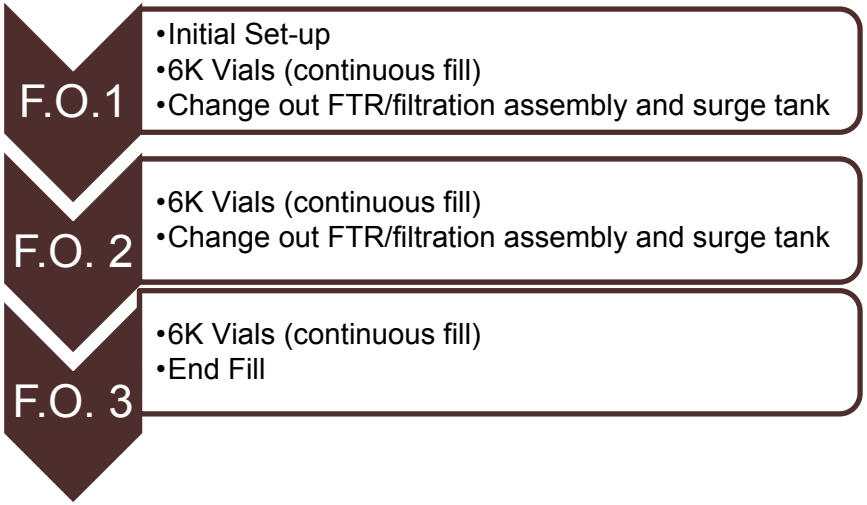
Case Study 1

- Key characteristic of the assessment- ensuring the risk is represented across multiple equipment set-ups.
- Does multiple equipment set-ups = individual batches in this case?
- Can an alternative approach be taken (3X batch vs 3X representation)?
- Can this alternative approach be used at the site/global network?

Case Study 1

Formulate the strategy…

- Number of APS challenge(s) - 1; Represents a medium risk change in the process/equipment that can be challenged as part of three PUPSIT-specific equipment installations (i.e. set-ups) to demonstrate consistency and repeatability via equipment change outs.
- Duration of APS challenge(s) – Single shift; Durations are not impacted.

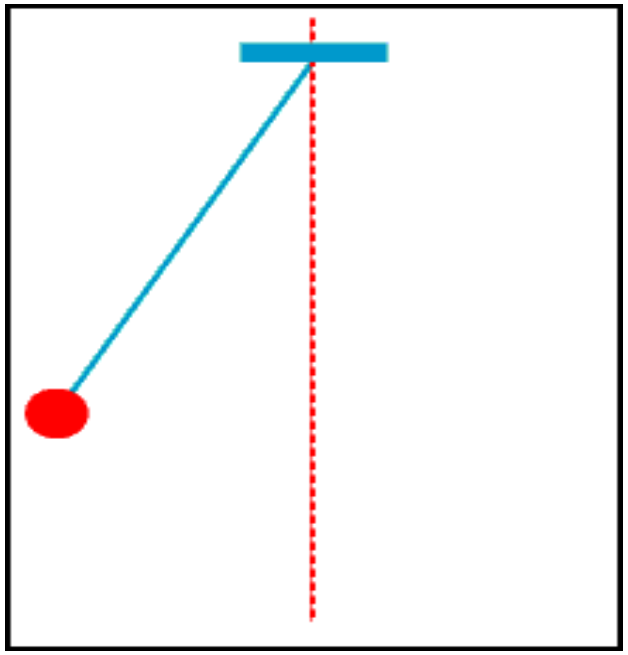


Use of the process saved Lilly Indianapolis Parenteral Manufacturing 8 individual MF batches across 4 aseptic filling lines!

Constructive Learnings

- Long term drive for consistency
  - Future tool development with examples of high, medium, and low risk examples within each APS element
- Learning curve of supporting functions
- Flexibility

The Pendulum Swing



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- Flavor Management
- Non-aseptic Manufacturing Changes
- Clinical Trial Resupply
- Introduction of New Clinical Trial Molecules

Case Study 2

Introduction of New Clinical Trial Molecule

Constructive Learning Example

Case Study 2

Understand the change…

- DESCRIPTION: Introduction of Clinical Trial Molecule 1 (CT1) to Filling Line A
- QUESTION 1: Does the change result in impact within the sterile boundary or to a container closure system? YES- While the APS program does not perform product-specific APS, CT1 proposed processing parameters must be evaluated to determine if the current validated aseptic processes/parameters support manufacture of the product.
  - If NO…further assessment is not required
  - If YES…continue to QUESTION 2
- QUESTION 2: Is the change challenged by the current aseptic process simulation program?
- The form was being used in 3 ways-
  - NO- There are no APS validations challenging parameter(s) required for CT molecule manufacture
  - YES- APS program clearly support CT molecule manufacture
  - YES- only if scenarios…
  - **Form could be of limited added value to the business in certain situations. Re-evaluation was performed.**

Right Sizing The Response

Lilly

Guidance Revision

- If it can be clearly assessed there is no impact to or within the sterile boundary or container closure system or the change is supported by the current APS program, then the assessment can be directly documented as part of the change.
- If there is impact and change is not challenged by the current APS program, the assessment is required to further assess risk of change.
- Similar verbiage for was implemented for new CT molecule introduction.

Conclusions

- The APS risk assessment process has proven to be a powerful addition to the Indianapolis Parenteral Manufacturing Sterility Assurance Technology program.
- It has been utilized to right size the APS response based on risk, facilitating the development of alternative, compliant approaches, allowing us to return additional line time back to production.
- Cross functional learning curves must be a consideration in implementation.
- Post implementation evaluation allowed the team to make changes, removing non- value added work, providing additional flexibility in how the process is used.
- Periodic reviews should be performed to ensure continued alignment in how APS elements are approached to prevent unexpected divergence.

Q&A