Aseptic Process Simulation (APS) Program Risk Assessment

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Agenda

- Background
- Process
- Case Studies
- 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.*"

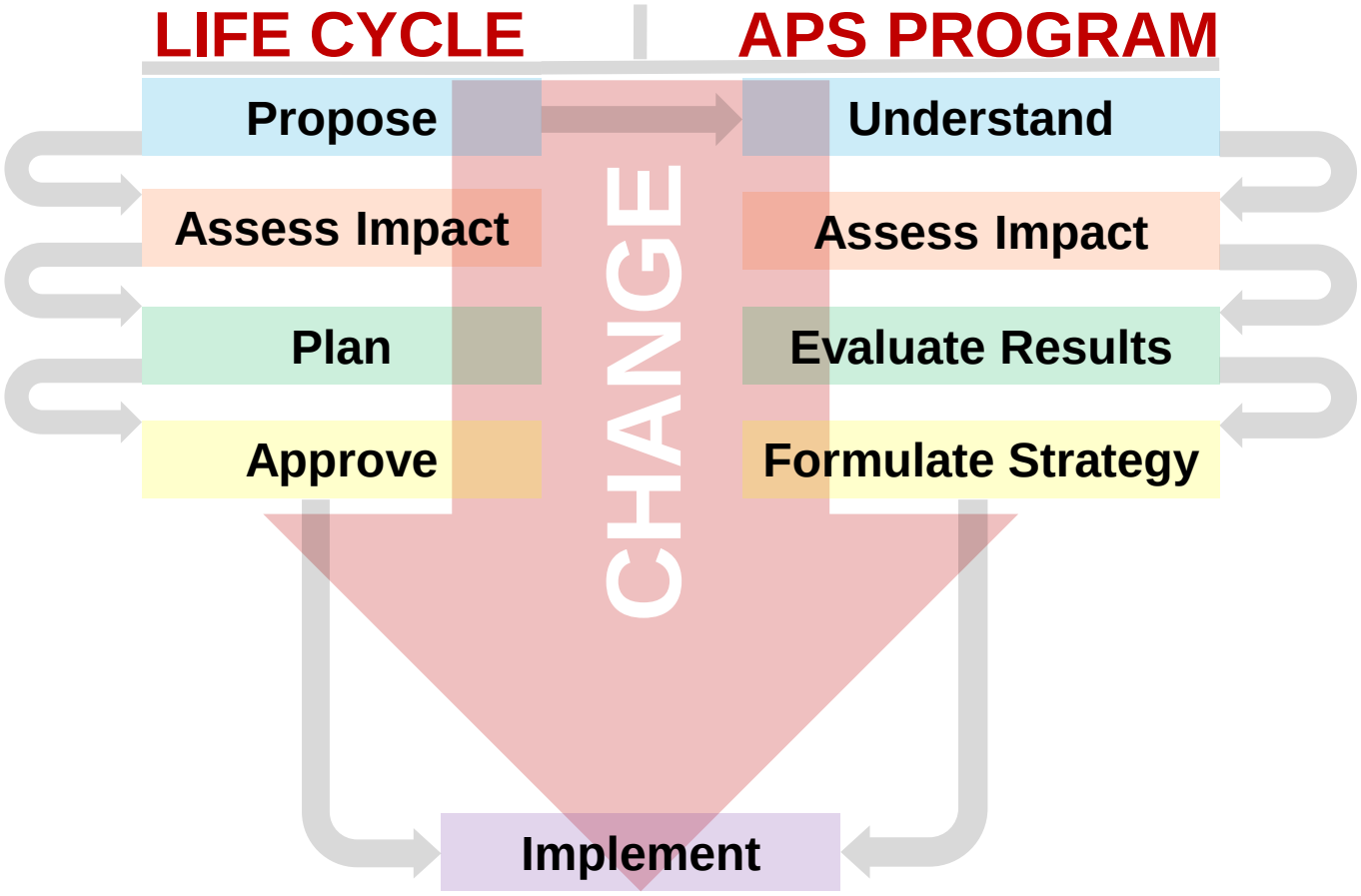
- **FDA Guidance for Industry**

  "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

Process

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

Case Study 1

Filling Line Speed Change

Case Study 1

Understand the change…

- DESCRIPTION: The slowest filling line speed for the largest vial processed on Fill Line A will be reduced.
- QUESTION 1: Does the change result in impact within the sterile boundary or to a container closure system? YES
  - 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
  - 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**; Introduction of a new line speed outside of validated range supported by the media fill program

  [B] *Environment / Facility* - **1**; No change in environmental classifications / controls or facility modifications

  [C] *Equipment* - **1**; No modifications to existing equipment/introduction of new equipment

  [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] = **3**

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 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

Formulate the strategy…

- APS strategy and challenge parameters
  - Number of APS challenge(s) - 1; Does not represent a significant, fundamental change in process, equipment, facility or container closure systems, such that the APS program is no longer representative of validated state of sterility assurance
  - Duration of APS challenge(s) – Full Duration; Ensures that the media fill evaluates the cumulative effect of prolonged exposure of sterile product and container closure across the maximum fill duration of a batch
- Approval by:
  - Engineering
  - Technical Services / Manufacturing Science (TS/MS)
  - Operations
  - Quality Assurance

Case Study 2

New Container Closure System

Case Study 2

Understand the change…

- DESCRIPTION: A new 5.0 mL Cartridge Container Closure System (i.e., Cartridge Barrel / Plunger / Disc Seal) will be utilized on a Cartridge Fill Line.
- QUESTION 1: Does the change result in impact within the sterile boundary or to a container closure system? YES
  - 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
  - If YES…further assessment is not required
  - IF NO…proceed to the next phase

Case Study 2

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* – 2; There is a change in process as the new container closure configuration will impact line set-up; there are no changes to personnel.

  [B] *Environment / Facility* - 1; No impact to the environment classification or facility design/modification(s).

  [C] *Equipment* - 3; There will be new set-up equipment, plunger/disc seal insertion stations, Human Machine Interface / Recipe changes.

  [D] *Container Closure System* - 3; This is a new container closure system that has not been previously utilized on the Cartridge Fill Line.

- Calculate final risk score:

  [A] X [B] X [C] X [D] = 18

Case Study 2

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.

Case Study 2

Formulate the strategy…

- APS strategy and challenge parameters
  - Number of APS challenge(s) – 3X; This will ensure any associated sterility assurance risk is represented across multiple filling equipment setups to demonstrate *consistency* and *repeatability*.
  - Duration of APS challenge(s) – 1X; Full Duration and 2X single shift APS. This will ensure that any associated sterility assurance risk is represented across a full contiguous filling operation as well as multiple filling equipment setups.
- Approval by:
  - Engineering
  - Technical Services / Manufacturing Science (TS/MS)
  - Operations
  - Quality Assurance

Q&A