MEDIA FILLS

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Media Fills aka Process Simulation

Why does your company perform Media Fills???

We have to

We want to

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WHY DO AUTHORITIES WANT YOU TO DO MEDIA FILLS?

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FDA's 2004 Aseptic Processing Guidance

"To ensure the sterility of products purporting to be sterile, sterilization, aseptic filling and closing operations must be adequately validated. The goal of even the most effective sterilization processes can be defeated in the sterilized elements of a product (the drug formulation, the container and the closure) are brought together under conditions that contaminate any of those elements."

Do media fills ensure sterility of products purporting to be sterile?

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EU Annex 1

For any run size, intermittent incidents of microbial contamination may be indicative of low-level contamination that should be investigated. Investigation of gross failures should include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.

Does a failure of a media simulation necessarily implicate product in the field?

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Japanese Pharmacopeia (17)

The media fill test is one of the process validations employed to evaluate the propriety of the aseptic processing of pharmaceutical products using sterile media, etc. instead of actual products.

Does a media fill evaluate the propriety (correctness) of aseptic processing?

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PDA TR: Points to Consider for Aseptic Processing, Part 2 (2016)

The aseptic process simulation provides additional but not absolute assurance of process control on a periodic basis. While part of the overall approach to process validation, process simulation is inly one of the may tools or approaches designed to evaluate the processing steps for aseptic manufacture.

What does PDA mean by additional but not absolute assurance of process control?

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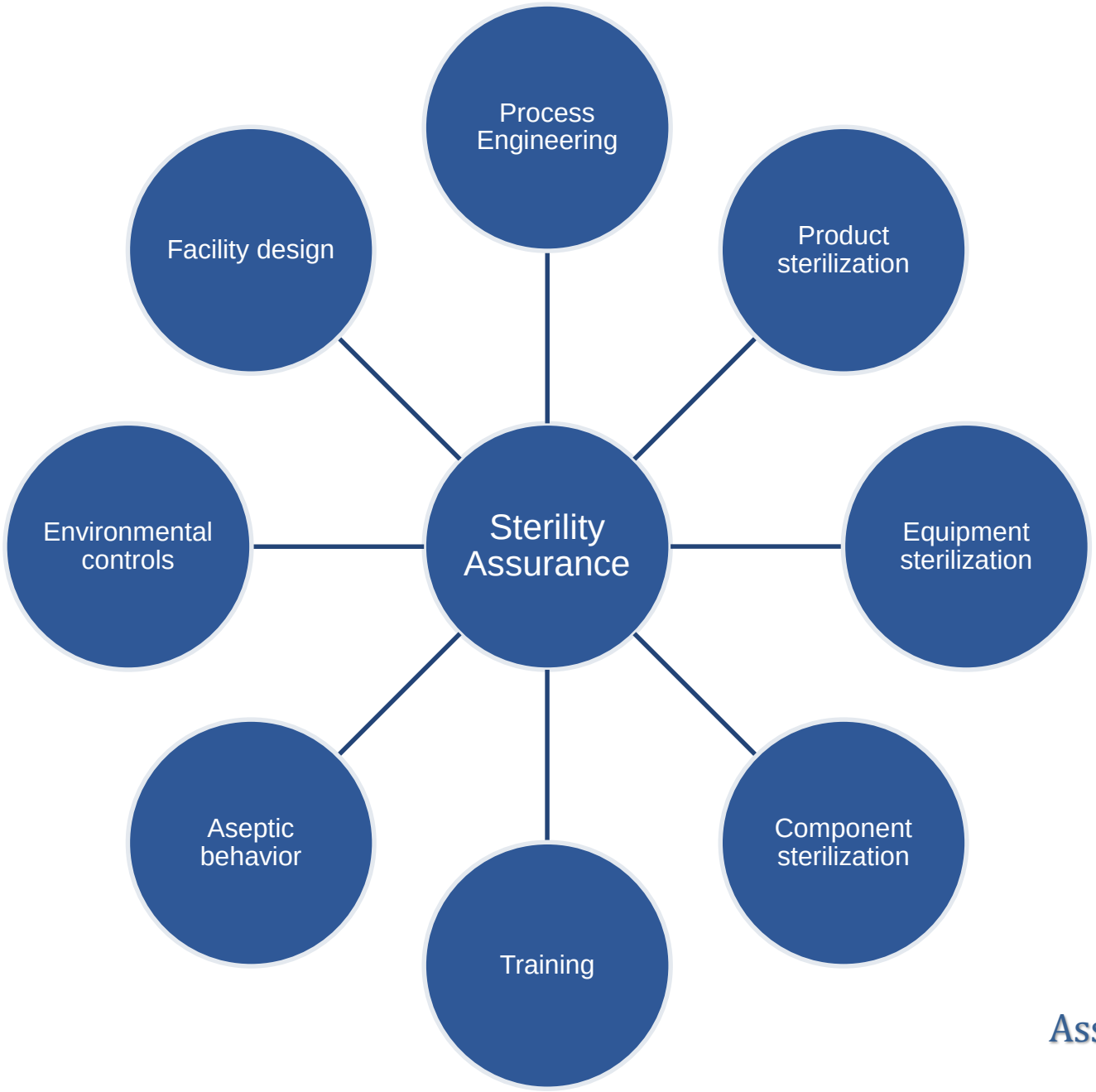
Aseptic Manufacturing



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What's the point

- There's a reason why media fills come after process development. They test the assumptions and actions taken to identify and mitigate critical quality attributes, critical processing parameters, critical operating parameters
- Media fills assess the confluence of all of the various Quality System processes that affect sterility assurance
- Arguably: Media Fills are not there to fulfill a compliance requirement. They're there to help us better understand our processes

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WHAT CAN GO WRONG?

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Production (Compounding Facility)

- WL
  - The investigators noted that your firm continued to produce commercial products prior to the successful completion of your media fill validation protocol which included xxx media fill failures due to xxx and turbidity of growth media.
  - Your firm failed to perform media fills for your automated vial filling machine which has been used to fill sterile drug products for commercial production

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Recommendation

- Follow USP 797
  - Media-fill testing is used to assess the quality of the aseptic skill of compounding personnel. Part of skills training.
  - Performed at least annually by each person under conditions that closely simulate the most challenging or stressful conditions encountered during compounding for low risk (e.g. single transfer), medium risk (e.g. pooling/dispensing material) and high risk (e.g. filtration of nonsterile materials)
  - Incubate 14 days. Turbidity = failure

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Investigations

- 483
  - The firm has not adequately investigated all discrepancies associated with aseptic process simulation xxxx. For example, personnel monitoring action limits were exceeded by an operator performing the media fill. The firm failed to investigate or evaluate this discrepancy as required per their media fill protocol and EM procedure
- 483
  - The firm has failed to complete or invalidated 33% of media fills attempted in filling room xxx since it has been converted to an aseptic filling area

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Investigations: Recommendation

- All of the normal “rules” of aseptic manufacturing, including gowning, sterilization, EM, apply to media fills. The firm’s SOPs support the MF protocol, and therefore all “normal” deviations must be investigated per SOP
- As with any validation/qualification, all discrepancies must be investigated and documented.
  - How often does this happen in real life?
  - Can we assess the potential impact to the outcome of the study and/or assess the risk to product quality?

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Training

- 483
  - The media filled vials are inspected for turbidity and visible particulates following the initial 7 day and final 14 day incubation periods. However, the Supervisor confirmed that there is no specific document that describes the requisite training for the individuals who perform the visual inspection.

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Recommendation

- Those who read media fills should be trained in what to look for
- What about those materials that are filled into semi-opaque containers?
- Media fills are seen by some as the ultimate training proficiency exam for operators – focus changes from process to the individual
  - Compounding pharmacies
  - Cell/gene processes that are highly manual
  - Must be properly documented in the training program

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Reconciliation

- Warning Letter
  - Your media fill reconciliation records failed to include a specific description of the reason why your firm rejected vials from each batch. Although a significant number of media-filled units were rejected with no written justification, you found the media fill runs in the following table acceptable

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Adapted from a 483

Media Fill	Fill suite	Fill date	Filled vials	Defective Vials	Assignable cause for discarded vials
1	?	2/13	6357	1652 (26%)	Not specified
2	?	7/13	10675	382 (3.6%)	Not specified
3	?	7/13	10653	334 (3.1%)	Not specified
4	?	8/13	12002	1826 (15.2%)	Not specified
5	?	10/13	10736	622 (5.8%)	Not specified
6	?	10/13	10190	63 (0.6%)	Not specified
7	?	1/12	6470	114 (1.8%)	Not specified
8	?	7/12	11673	242 (2.1%)	Not specified

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Recommendation

- Reconciliation requires the following:
  - Number of units filled
  - Number of units rejected; reasons for rejection (tied back to normal operations)
  - Number of units incubated
  - Number of units inspected after incubation
  - Number of units positive (turbid)

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Recommendation

- All integral vials incubated
- Non-integral vials may be excluded but must be accounted for with reasons consistent with standard SOPs
- Cosmetic or other issues that do not impact integrity should be incubated
- If the SOP calls for vials to be cleared from the line after certain types of intervention, then they may be cleared – but no more than allowed or required by SOP
- Incomplete run may be invalidated or aborted
- Complete run with positives = failed run

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Duration

- WL
  - Your procedure, xxxxx, states that each operator must remain in the cleanroom for no more than 6 hours without exiting or regowning. There is no study performed during your media fills to validate this practice.
  - Your firm's xxxx media fill states that the duration of the fill time is xxxx. However, production lots xxxx and xxxx exceeded these fill times.

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Recommendation

- The issue is that all boundaries are tested. Longer does not necessarily mean that there are more problems as contamination is due to events, not time.
- Duration long enough to test
  - List of inherent and corrective Interventions
  - Shift changes (personnel activity)
  - Any equipment swap outs
  - Sufficient numbers of vials to incubate

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Human Fatigue

- Human fatigue may result in mistakes and additional corrective interventions.
- What contributes to fatigue? Very often it's poor process and/or facility design:
  - Sequence of tasks
  - Logistics of cleanroom and equipment layout/design
  - Temperature/humidity controls
  - Lack of training
  - Ergonomics
  - Lack of attention to shift changes/rest periods

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Types of Interventions

- Inherent – the normal routine – prescriptive in the batch record
  - Aseptic set up
  - Aseptic connections
  - Environmental Monitoring
  - Refill stopper hopper
- Corrective – Variable – based on history
  - Clearing jams
  - Mopping up spills
  - Keep track of corrective interventions and assure that they are included in the simulation protocol

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Interventions

- 483
  - They do not simulate any interventions.
- 483
  - During the aseptic simulation of line xx you do not record or simulate all activities/interventions which occur during routine sterile processing operations. For example, the frequency for the activities you classify as “inherent interventions” such as loading stoppers, fill volume checks, traying vials, etc. are not accounted for during your aseptic fill operations
-

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Interventions

- WL
  - Sampling was inadequate. Normal production of xx uses xx on each xx in the ISO 5 cleanroom. For each run in this validation, only xx was taken from one of the xx.
  - Number of inherent interventions in the APS does not equal the number in a “normal” run
  - BR does not require interventions to be recorded

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Interventions

- 483
  - The interventions performed during media fills are not based on historical data from filling operations. Media fills are not reflective of routine operation.
  - Media fill runs do not include executing the same number of reoccurring manual interventions and for the same length of time as performed during routine filling operations

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Recommendation

- Normal batch records should identify inherent interventions and should track corrective interventions
- Quality and Operations should be able to produce a list of recurring interventions
  - Investigations?
  - CAPA
- Repeating inherent and corrective interventions should be repeated at the maximum levels
- Protocols should reflect both inherent and corrective interventions

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Questions:

- Is sampling an intervention?
- Why are the regulatory agencies so hung up on interventions?

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Documentation

- 483
  - There were no predefined acceptance criteria or monitoring performed for viable organisms
- WL
  - You have not defined the following:
    - Routine and non-routine interventions
    - Factors associated with the longest permitted run on the processing line that can pose a contamination risk
    - Normal fill time or duration of aseptic processing operations, thus it is unknown if the media fills represent routine or worst case production activities

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Documentation

- WL (continued)
  - Number of personnel allowed in the clean room, number of shift changes and the activities to be performed
  - Mechanism in place to track all personnel who are authorized to enter the specific aseptic processing room during manufacturing
  - Normal production speed
  - Reconciliation requirements

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Documentation

- Media fill validation xxxx performed in cleanroom xxx lacks objective evidence to support the study design or validation protocol requirements being met.

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Recommendation: Documentation

- Signature Page
  - All stakeholders including Quality
- Purpose (WHY are we doing this)
- Scope (What products/processes are covered)
- Background (How did we get here. Semi annual challenge? Change control?)
- Acceptance Criteria
- JUSTIFY all study design decisions and criteria

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New Technology Challenges

- As technology advances, we need to 1) understand the current issues and questions regarding media fills 2) adapt our thinking and 3) evolve our thinking.
- For example: Autologous immunotherapy has a very small lot size: often n=1. Allogeneic immunotherpay may have lot sizes of 500-1000 vials.
- How does one perform a media fill?
- Must understand the philosophy behind media fills and adjust to the situation.
  - Explain carefully in the protocol

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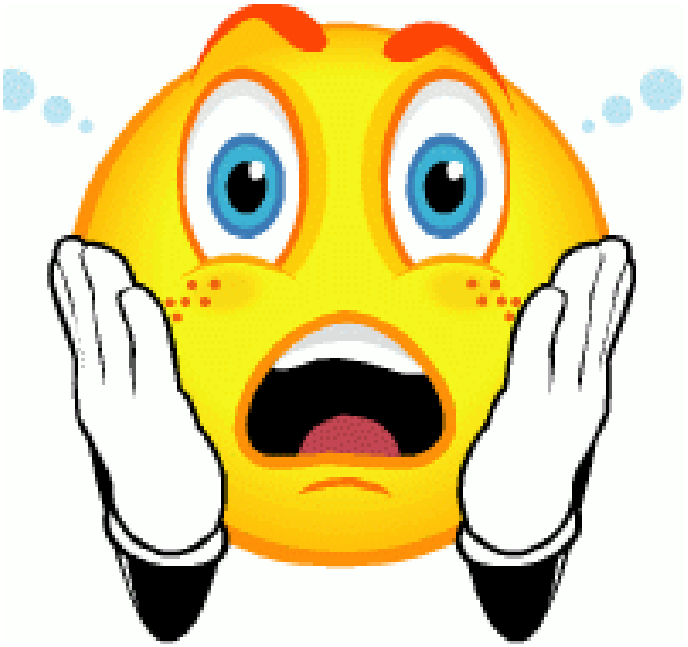
OOPS

- A firm filled, incubated and inspected 10,000 vials
- After the final inspection (no turbids), the vials were discarded in a bin, but no one called for the bin to be removed
- A few days later (day 17 after the media fill) an analyst decided to use some of the filled vials in a container/closure integrity study.
- Guess what…



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You Guessed It!

- Now what???????

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Failures

- If we assume that the following is correct:
  - The deviation/CAPA management system is a measure of the robustness of the Quality System
  - The Change Management system is a measure of the stability of the Quality System
- Investigation of failures should not be limited to the event but rather understands an understanding of process.
  - It should include an assessment of deviation/CAPA (have we seen an increase in problems that could lead to positives)
  - It should include an assessment of changes to the process – could there have been unintended consequences of changes that could have led to positives

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Rules and Regulations Regarding Serendipity – Dr. Frederik Bang

- Serendipity = combination of chance and sagacity (keen mental discernment/good judgment and often collaborative)
- Rules
  - Take a fresh look at old phenomena
  - Remain naïve but carry the knowledge of past experience
  - Ask new questions and seek new answers
- “Although the cost of serendipity is moderately high and failure is not infrequent, the benefits are many times greater than those that follow the regular procedure that results from the completion of forms…”

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Parting Thoughts

1. Taking Dr. Bang's thoughts into account, has this "Media Simulation" process become an exercise in "how" (carefully choreographed filling out of forms) or "what" (dependence on filled in fields) we do rather than "why" we do it (processing understanding to assure patient safety).
2. Have we stopped asking questions for fear of failure and/or compliance complications?

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THANK YOU!

Questions?

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