Media Fill (or Aseptic Process Simulations)

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Scope

- Regulatory Guidance and Standards
- Principles
- Procedure
- Summary

Regs and guidance

- USFDA “Guide to Aseptic processing” 2004

- An aseptic processing operation should be validated using a microbiological growth medium in place of the product. This process simulation, also known as a media fill, normally includes exposing the microbiological growth medium to product contact surfaces of equipment, container closure systems, critical environments, and process manipulations to closely simulate the same exposure that the product itself will undergo. The sealed containers filled with the medium are then incubated to detect microbial contamination. Results are then interpreted to assess the potential for a unit of drug product to become contaminated during actual operations (e.g., start-up, sterile ingredient additions, aseptic connections, filling, closing). Environmental monitoring data from the process simulation can also provide useful information for the processing line evaluation.

Regs and guidance

USFDA “Guide to Aseptic processing” 2004

1. Study Design
2. Frequency and Number of Runs
3. Duration of Runs
4. Size of Runs
5. Line Speed
6. Environmental Conditions
7. Media
8. Incubation and Examination of Media-Filled Units
9. Interpretation of Test Results

Very similar to Annex 1 9.36

Regs and guidance

USFDA “Guide to Aseptic processing” 2004

A written batch record, documenting production conditions and simulated activities, should be prepared for each media fill run. The same vigilance should be observed in both media fill and routine production runs. The firm’s rationale for the conditions and activities simulated during the media fill should be clearly defined.

Media fills should not be used to justify practices that pose unnecessary contamination risks.

Regs and guidance

2022 Annex 1

Aseptic process simulation (APS) Section 90.

9.32 Periodic verification of the effectiveness of the controls in place for aseptic processing should include an APS using a sterile nutrient media and/or surrogate in place of the product. The APS should not be considered as the primary means to validate the aseptic process or aspects of the aseptic process. The effectiveness of the aseptic process **should be determined through process design,** adherence to the pharmaceutical quality system and process controls, training, and evaluation of monitoring data. Selection of an appropriate nutrient media and/or surrogate should be made based on the ability of the media and/or surrogate to imitate physical product characteristics assessed to pose a risk to product sterility during the aseptic process. Where processing stages may indirectly impact the viability of any introduced microbial contamination, (e.g. aseptically produced semi-solids, powders, solid materials, microspheres, liposomes and other formulations where product is cooled or heated or lyophilized), alternative procedures that represent the operations as closely as possible should be developed. Where surrogate materials, such as buffers, are used in parts of the APS, the surrogate material should not inhibit the growth of any potential contamination.

9.35 APS should not be used to justify practices that pose unnecessary contamination risks.

9.41 Filled APS units should be agitated, swirled or inverted before incubation to ensure contact of the media with all interior surfaces in the container. All integral units from the APS should be incubated and evaluated, including units with cosmetic defects or those which have gone through non-destructive in-process control checks. If units are discarded during the process simulation and not incubated, these should be comparable with units discarded during a routine fill, and only if production SOPs clearly specify that units must be removed under the same circumstances (i.e. type of intervention; line location; specific number of units removed). In no case should more units be removed during a media fill intervention than would be cleared during a production run. Examples may include those that must be discarded during routine production after the set-up process or following a specific type of intervention. To fully understand the process and assess contamination risks during aseptic setup or mandatory line clearances, these units would typically be incubated separately, and would not necessarily be included in the acceptance criteria for the APS.

9.46 The target should be zero growth. Any contaminated unit should result in a failed APS and the following actions should be taken:

Principles

Definition

- Aseptic Process Simulation (APS) – A simulation of the entire aseptic manufacturing process in order to verify the capability of the process to assure product sterility. Includes all aseptic operations associated with routine manufacturing, e.g. equipment assembly, formulation, filling, lyophilization and sealing processes as necessary.

Worst case – but do not try to validate bad practice of just in case scenarios

Principles

- Media prep and sterilisation – Filtration or heat
- Filling line set up Filling process :
  - Equipment and product sterile hold times (Worst case)
  - Line speed
  - Duration
  - Numbers
  - Interventions
  - EM (extra)?
- Personnel
- Post fill inspection
- Incubation
- Post incubation inspection
- Positive controls
- Results
- Report

Study design considerations

- Do you need to spilt the process up e.g. bulk hold
- How do you simulate different product e.g. ointment, or cream or powder
- What about non-transparent containers

- Filling line set up (normal or matrix)
- Filling process (can be a matrix approach) :
- Equipment and product sterile hold times (Worst case) (but not bad practice)
- Duration - Length of maximum fill to cover all shifts (normal regulatory expectation for a liquid fill is no more than 24hours)
- Numbers can be less that maximum fill but still need to mimic empty units, water filled units jus stop the line (unfortunately not just one solution)
- Interventions Numbers and type need to link back to routine production (and vice versa) (but not bad practice)
- Critical or otherwise (do operators do all or just some) Planned and unplanned
- EM (extra)? At least routine (key intervention) but may want more in case of investigation)

Personnel

- Environmental monitoring personnel (if different)
- Engineering (if they may intervene during a fill)
- QA? (if present during filling)
- Operators All

Post fill inspection

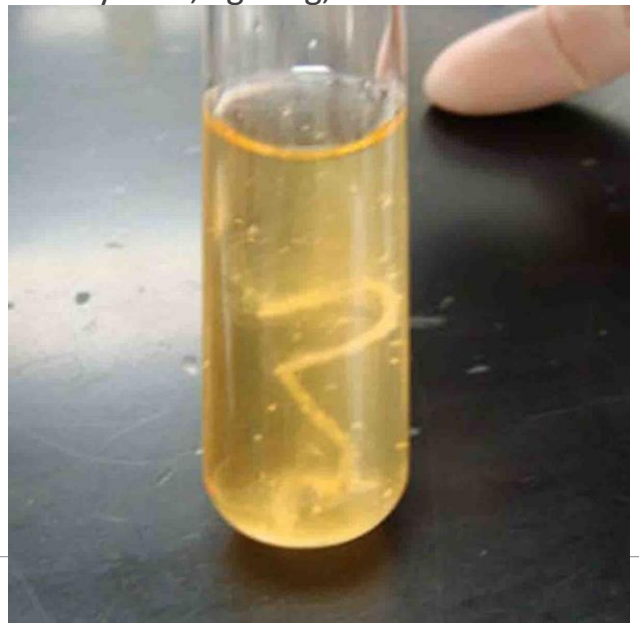
- Do you do a post fill “routine inspection”?
- Try not to delay incubation
- What rejects are allowed (only where the container closure has been breached and only what you would normally reject)
- What do you do with rejects

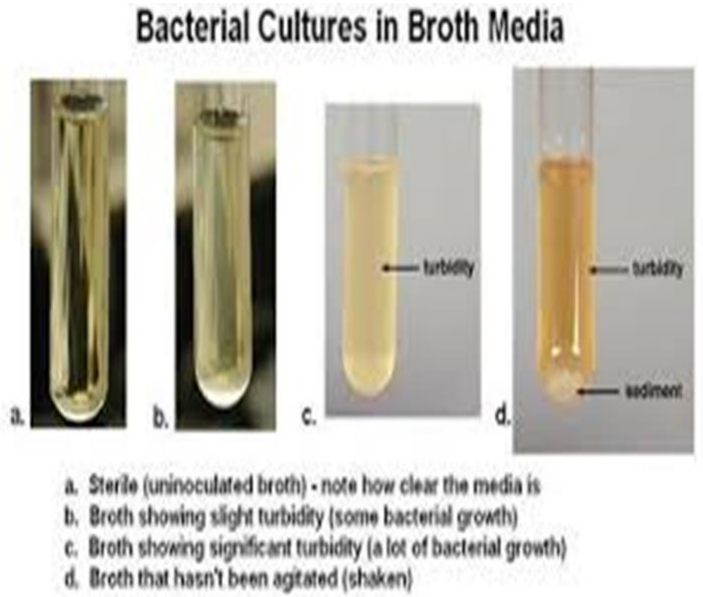
Incubation

- Units inverted etc.
- What temperatures (guidance speaks to 25 to 35°C with tolerance ± 2.5) so need to decide (what suits our process, does it need to be anaerobic)
- If dual which way around (low then high)
- Duration minimum of 7 days at each temperature if dual, of 14 days if single

Post incubation inspection

- Who does it (conflict of interest, QA oversight)
- What training (Different types of growth, flocculant, turbid etc.)
- What qualification (test kits, eye tests etc.)
- Where do they do it, lighting, no distraction etc.





Positive controls

- Samples from worst case position (e.g. BME)
- Not until incubation completed
- Using pharmacopeial orgs to include also types
- Environmental organisms (whatever that means?)

Results

Results

- Bracket (what?)
- Quarantine (anything made, still on site APS or under our control) since last successful medial fill) or may be even further back
- Investigate
- Impact assess
- Review of complaints, previous EM , sterility data and media fills (but be careful)
- Need quick interim assessments (these need to be updated as more information is gathered)
- Capture and document everything you do (actions and decisions)
- Act on your final outcome
- It's micro so not always a "smoking gun"
- Need to act on your potentials as well as your true root cause
- CAPA plan
- Your decision and your report will be scrutinised
- Again
- And again
- And again

Report

- The media fill is not complete until the report is authorised, all batches still in companies control that are linked to the media fill process should be on hold
- May need an interim release form/report/process
- Executive summary is always useful

- You must have a procedure
- You must also have a risk assessment (linked to the CCS)

- These documents support
- But must include:
- Rationale for what you do (process incubation, what why where and when)
- Frequency (6 months ± 1 month) what happens if you exceed the time?
- What to do in the event of a failure:
  - Bracket
  - Quarantine
  - Recall
- Report timelines
- Aborted runs
- Invalid run

Aborted runs

- A run you stop either before or during filling.
- You have to be able to show that if the same thing were to happen in routine running the same outcome would occur (i.e. batch would stop).
- Any filled units may need to be incubated.
- Needs to be captured in the QMS

Invalid run

- A run that is completed and incubated but has not followed the correct process e.g.
- Positive controls don't grow (but any contaminated units still count)
- Incubators fail
- The operation did not follow the prescribed process (but why)

Summary

- Clearly document your rationale for what you are doing (link it to the CCS)
- Perform every six months (all shifts and all personnel)
- Interventions need to be linked to the “real process”
- Need a good procedure
- When it all goes wrong don’t panic but have a clear strategy
- Be aware of the limitations of the media fill, do not validate bad practice

Thank you and any questions