Current Trends in Media Fill

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Disclaimer

The opinions expressed herein are personal and not those of my employer. Information contained herein does not provides any kind of legal or other opinion. Please consult appropriate expert for business advice.

Quality can not be tested in the product, it must be built in each unit

References

- Guidance for Industry-Sterile drug products produced by Aseptic processing –Current Good manufacturing practice – September 29th, 2004 by US Food and Drug Administration).
- Pharmaceutical Inspection and Convention, PI007-04. 01 January 2010.
- EudraLex, Volume 4, EU guideline for, good manufacturing practices for medicinal products for Human and Veterinary use Annex 15: "Qualification and Validations", March 2015 (Page No. 02 to 06).
- PDA Technical report No.22 (revised 2011) Process simulation for aseptically filled products.
- WHO Guideline "A WHO guide to Good Manufacturing Practice (GMP) requirements, Part 2: Validation, January 1997 (Page No. 11 to 35).
- Schedule M (Part IA) Requirements for Manufacture of Parenteral & Ophthalmic Preparation.



Observations

Our inspection found that your Quality Unit (QU) did not take appropriate steps prior to resumption of aseptic manufacturing after a shutdown that included multiple significant activities that compromised cleanroom control. Your QU allowed manufacturing operations to resume for (b)(4) filling operations without performing an aseptic process simulation (i.e., media fill) as indicated by your procedure. Your firm manufactured and shipped several batches of (b)(4) to the U.S. market after this deviation.

Your investigation into contaminated media fill units is inadequate in that it did not include scientifically supported conclusions, it lacked corrective actions and preventive actions (CAPA), and it failed to address all potentially compromised lots.

Inadequate Media Fills

Media fills should accurately simulate commercial operations. Our inspection found that interventions and other operations simulated during media fills were not sufficiently representative of commercial aseptic manufacturing.

Observations

Regarding the aseptic processing simulation of the ^{(b) (4)} process, not all media filled vials are subject to the ^{(b) (4)} steps in that the media filled vials that are exposed during the fill room operators' manual interventions are removed from the batch of the media filled vials. In addition;

The interventions performed during media fills are not based on historical data from filling operations. Media fills are not reflective of routine operation. Inherent interventions are not tracked or trended in routine production. Only corrective and critical interventions are documented.

Not all media filled vials are subject to the incubations, steps in that the media filled vials that are exposed during the fill room operators manual interventions are removed from the batch of the media filled vials.

During media fill batch due to mechanical failure of the conveyor in the filling machine. At the time of the mechanical failure 3,696 integral vials has been filled. These vials were not incubated and media fill was invalidated. During routine production the portion filled prior to a mechanical failure would be release as a sub lot.

Observations

- Media fill practices / interventions are different than the commercial batches
- Video recording of Media filling is not meaningful
- Anaerobic Media filling with anaerobic conditions not performed
- Recording of interventions By supervisor in Media fill and by operator in commercial batches
- Removal of integral units from incubation
- Poor aseptic practices observed in media filling
- Trending of interventions during sterile manufacturing does not take into consideration packaging configuration (i.e. vial size and run speed)

Why Media Fill ?

- To evaluate Capability of the aseptic processing activity-machine, people and facility environment.
- To evaluate Engineering and manufacturing controls.
- To evaluate Environmental controls.
- To evaluate People practices, equipment and facility design.
- To identify Potential threat to the process/sterility assurance.
- Helps in operation to build an approach on Interventions during routine commercial production.
- Helps in establishing the hold times.
- Regulatory Requirement
- Prevents Batch Failures, Market complaints, recalls due to lack of sterility assurance



When to perform Media Fill

- New Facility / New line / New introduction of any aseptic production process / Introduction of new aseptic processing equipment - 3 media fill runs
 - 3 Media fills with smallest container with widest mouth and highest speed
 - 3 Media fills with largest container with widest mouth and slowest speed
 - Water trial is recommended
- After major modification (addition of new tank, change in aseptic connections).
- Sterility failure, depending upon investigation outcome
- Continuous environmental failure.
- New Pack introduction based on assessment
- Change in machine and or machine design
- Bracketing / Matrix approach One run for intermediate size of container closure
- Periodic Frequency (Six Months)
- Closing Media fill after last commercial batch before major shut down

What are Prerequisites to Media fill

- All equipment/Utilities should be qualified.
- LAFs / Filling line qualification
- Disinfectant qualification
- Cleaning and sanitization program
- Area Qualification including HVAC
- Environment monitoring program (Viable / Non-viable)
- Personnel gown qualification / training
- Air flow pattern / Smoke study
- Approved Protocol/BMR.
- Vendor qualification for the media
- Visual inspector qualification
- Review of past deviations, CAPA for any recommendations of intervention/hold time simulations.
- Water trial for new line to derive interventions

Documents associated with media fill

Below are the main guiding documents for media fill -

- 1. SOP on media fill procedure
- 2. Protocol on media fill
- 3. Report after media fill is concluded
- 4. Quality Risk Assessment

The media fill BMR contains minimum following details:

- The details of the equipment to be used
- Details of the media and packing material to be used
- The cleaning and sterilization details of the equipment
- List of the execution team
- Detailed step wise unit processes
- Reconciliation
- Incubation details
- Unit inspection details
- Hold time details
- Interpretation of results

Different Aseptic Processes and Media

Types (Process)	Media
Liquid	3% Liquid SCDM
Dry Powder	Lactose/Manitol followed by Liquid media
Ophthalmic	Liquid media with Color indicator
Suspension	Different parts are filtered followed by aseptic dispensing of lactose /Manitol and aseptic manufacturing
Lyophilization	3% Liquid media filling with half stoppering and full stoppering in the lyophilizer
Emulsion	Using 3% liquid media

Why SCDM used for Media Fill?

- Easily soluble.
- Easy to filter through 0.22-micron filters.
- It support broad spectrum of microbial flora (Aerobic, Anaerobic, Mold, Fungi)
- Growth is easily visible.
- Easy to remove post media filling
- Use of media with color indicator is recommended to avoid any error during inspection (Essential for translucent plastic containers)



Media Fill Process Flow



Interventions

- <u>Routine</u> Interventions are normal and planned activities that occur during an aseptic manufacturing, filtration and/ or filling process, lyophilization process.
- <u>Non-Routine</u> Interventions are performed to correct or adjust an aseptic process; they are well understood operations and are recognized to sometimes occur during processing.
- <u>Worst case</u> Worst case situations/ simulations are those in which no manual interventions are done inside the grade A, but activity happen in surrounding room of Grade A and hence the risk to the product is minimal.
- Build Engineering solution / design to avoid intervention, rather than simulation



Interventions

Routine (Inherent)

- Machine Parts assembling
 In-process weight checks simulation.
- **O**Fill weight adjustment
- Prime the filling needle to remove entrapped air
- Sampling of bulk from filtration vessel
- ©Environmental Monitoring
- Charging of rubber stoppers

Non-Routine (Corrective)

- clearing track jamming **O**How to decide the interventions in new line? **O**Based on the water trial, experience, machine design **O**Removal of Fallen rubber stoppers **O**Clearance of stuck rubber stopper from rubber stopper bowl • Needle adjustment
- (Centering)

Worst

Maximum persons in filling room simulation
Lunch and dinner break simulation
Operator fatigue
Shift change over simulation
Room door opening
Dynamic Pass Box opening

Hold time

Hold time study is done/performed by simulating in at least three media fills. Examples of various hold times-

- Sterilized stoppers, seals, filling machine parts
- Filtered Bulk
- Assembled filling machine parts
- Assembling duration
- Filling duration
- Maximum allowable break/stoppage duration.
- Aseptic dispensing duration
- Garments hold time

Note - Hold Time are established for any exigencies, not to plan the work accordingly

Media Fill - Acceptance Criteria

Commercial Batch Size	Media Fill Batch Size	Acceptance Criteria
Less Then 5000	Equal to Batch size	Nil Contamination
5000 to 10000	Equal to Batch size	 unit which calls for investigation, consideration for revalidation units revalidation
More then 10,000	Equal to commercial batch size /not less then 10,000	1 unit, calls for investigation 2 units, revalidation

Note – Even if there is one vial contaminated, thrust for investigation shall be there to identify the cause

Sampling During Media Fill

Sr. No.	Details	Reasons
1	рН	To ensure that it support growth
2	Empty sterilized vials	To prove that vials are not contaminated
3	Rubber stoppers from hopper	To prove that stoppers are not contaminated
4	Seals	To ensure that seals are not contaminated
5	Liquid Media for GPT	To ensure that liquid media is supporting the growth
6	GPT Post incubation	To ensure that media remains growth supportive throughout incubation period
7	CCIT	To ensure that container closure is not leaking
8	Compressed air	To ensure that air quality is meeting the acceptance criteria

Operator Participation

- Line wise qualification— PFS/Cartridge/Vial
- All critical interventions like- Filling needle change, tube change, aseptic set up should have been done by the same operator in media fill as well.
- Requalification frequency of operator- 06 months is preferred, 1 year is must.
- Operator should do the same work in media fill , the way he is supposed to do in product manufacturing.



VISUAL INSPECTION

- Only integrity breach units need to be discarded e.g.
 - Empty units
 - Crack units
 - Broken units
 - Without stopper vial/unit
- Do not discard any unit having-
 - Cosmetic defects like Crimping defects
 - Less/High fill volume,
 - Foreign particle like fibers
- Reconciliation at the stage of incubation inspection should be 100 %



INCUBATION

- Post inspection, the media filled units should be kept for incubation ASAP (Normally within 08 hours).
- $\circ\,$ Incubation 07 days at 20- 25 °C and next 07 days 30-35 °C
- Incubation -07 days inverted and next 07 days in upright condition
- Post incubation Microbiologist should inspect (Preferred)
- Once the units kept under incubation, no unit/vial can be removed from the media fill tally.



Media Fill Abort

- Media Fills can be aborted only for reasons extrinsic to the process
- <u>Rare occurrence</u> Only under circumstances when commercial batch would also be equally handled
- Investigated and CAPA shall be initiated
- Following circumstances Media fill shall be considered as aborted
 - Major Machine breakdown
 - Major power failure (AHU/LAF stoppages)
 - Leakage and / or damage in the filling assembly
 - Any typical event which has direct impact on sterility assurance



POST Media filling

- Area is heavily exposed to the growth promoting media
- Special cleaning and sanitization of the area- complete cleaning & sanitization, fogging etc.
- Extra Monitoring for viable and non-viable particle counts.— different locations.

Note - Batch failure after media fill is common

- Restart of production depends----- Waiting/Not waiting results.
- Cleaning sample of the filling machine parts/tanks etc. (pH, Conductivity, TOC, Bioburden)

Do's and Don'ts

- $\circ~$ Conduct all the routine interventions more or at least in similar intervals
- Label each tray after capping / sealing with media fill no, tray no, date, time.
- Use Nitrogen only if we observe anaerobes in the facility (EM/Gas/Sterility test).
- Use the clear glass vial for media fill in place of Amber color vial used for routine commercial production.
- $\circ\,$ pH of liquid media should be 7.1 to 7.5
- Do not perform Extra/special cleaning and sanitization for media filling
- Do not design Interventions to justify poor process and would represent an unreasonable risk
- \circ Do not reject filled integral units (Even stoppered)



Media fill failure investigations

- Investigation Team Quality Assurance, Production, Engineering, Microbiology
- Identification of microorganisms up to the species
- Review Environmental records for manufacturing and testing area for temperature, relative humidity, differential pressure and non-viable air born particle counts.
- Sterilization record of garments, filters, machine parts etc. Bowie Dick and leak test records of steam sterilizer
- Filter integrity record.
- Cleaning and sanitization records
- Batch record of process simulation runs.
- Review of Video CD, will be part of investigation.
- If the root cause is assignable, a single successful media fill run has to be taken.
- If the root cause is not assignable If any gap is found, carry out three successful media fill runs before undertaking any production run.

Media fill failure case study 1

During visual inspection of media fill batch after 7 days incubation completion, microbial growth (contamination) was observed in 02 vials collected in Lyo Loading Tray No.: 36 (Collection Tray No.: 01), which was last tray of media fill run. Total incubated vials: 8256 Nos.

Investigation revealed that newly introduced open door intervention i.e. Clutch Setting was performed in this media fill run for lyophilization process simulation. During execution of intervention, half stoppered vials were present on the conveyor belt which were further transferred & loaded into lyophilizer in which full stoppering done. Hence, it might be possible that the specific half stoppered vials present in vicinity of newly performed intervention location got contaminated. One media fill run (Lyophilized process) was successfully executed in which intervention of 'Clutch setting' was performed with closed door from backside of vial filling machine to avoid direct exposure of half stoppered vials.

Media fill failure case study 2

Microbial growth observed in the leftover bulk solution which was collected after filling from 'Product Tank (Buffer tank) and microbial growth was also observed in all the incubated units (11541 Nos.). One of the non-routine interventions (i.e. replacement of manifold tubing) was different from the previous media fill runs. There was media leakage observed from junction of male-female HFC connector connected between product tank (buffer tank) and manifold. This open-door intervention 'Replacement of Manifold inlet tubing' was performed to rectify the solution leakage. The observed organism (Staphylococcus haemolyticus) was a part of In-house Environment monitoring isolate and same organism was identified from environment monitoring samples collected during media fill activity from different locations. This intervention resulted into microbial contamination of the media solution.

Media fill failure case study 3

Turbidity was observed in the bulk media samples (Collected at the end of filling from buffer tank for Growth Promotion Test (GPT) & sterility assurance and remaining media solution from buffer tank for incubation).

Investigation revealed that the 'Teflon part' of 'Low level sensor port' in manifold was fallen on aseptic area floor during assembling operation of the batch. Filling operator cleaned and sanitized the Teflon part instead of sterilization and reassembled in manifold. Contact of media solution with cleaned and sanitized (non-sterilized) surface of Teflon part during filling process resulted into microbial contamination in samples collected from the buffer tank, left over bulk (collected from manifold) and filled units (7602 Nos.) of the batch.



Questions to be asked to help prevent issues

- Have written procedures that are clear and specific enough to ensure consistent operations that meet all GMP requirements? Conduct periodic assessments?
- Adequate training of personnel on written procedures
 and aseptic practices
- How do you monitor your employee behavior and aseptic practices to ensure procedures are followed?
- Periodically review your written procedures to ensure they are still adequate? Do you do a good review?
- Do you interview your operators to get feedback from them on how the procedure could be improved? Are there instructions that they do not follow, and why?

Conclusion

- Media fill is not a magic validation to support wrong Practices/Failures/Design Flaws
- Power failure should not be simulated in Media fill
- High risk aseptic intervention, technique or practice is not acceptable and can not justify to use during production of commercial batches
- Exposure of Machine parts in grade B can not be accepted based on media fill simulation.
- Manual aseptic processing involves greater risk than the automated aseptic process (properly designed engineering solution)
- Water trial is recommended to determine the interventions for any new line
- Vials are falling excessively on turn table/Track and same is simulated in media fill but not corrected.
- Accepting failing EM counts during batch as it was failing during media filling and MF was passing.
- Media fills can be aborted only for the reasons extrinsic to the process.
- Media fill run should be aborted only when commercial lots would be equally handled
- Any single positive unit in the media fill shall be thoroughly investigated
- Colour indicating Media shall be used for translucent plastic containers
- Quality Risk Assessment of the Aseptic filling line would help to identify the potential failure modes (Risk) and mitigation of the risks
- Perform trending of interventions to determine the frequency and duration of the interventions for simulation is subsequent media fills





Quality is never an accident; it is always the result of high intention, sincere effort, intelligent direction and skillful execution; it represents the wise choice of many alternatives.

(William A. Foster)

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