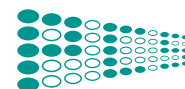
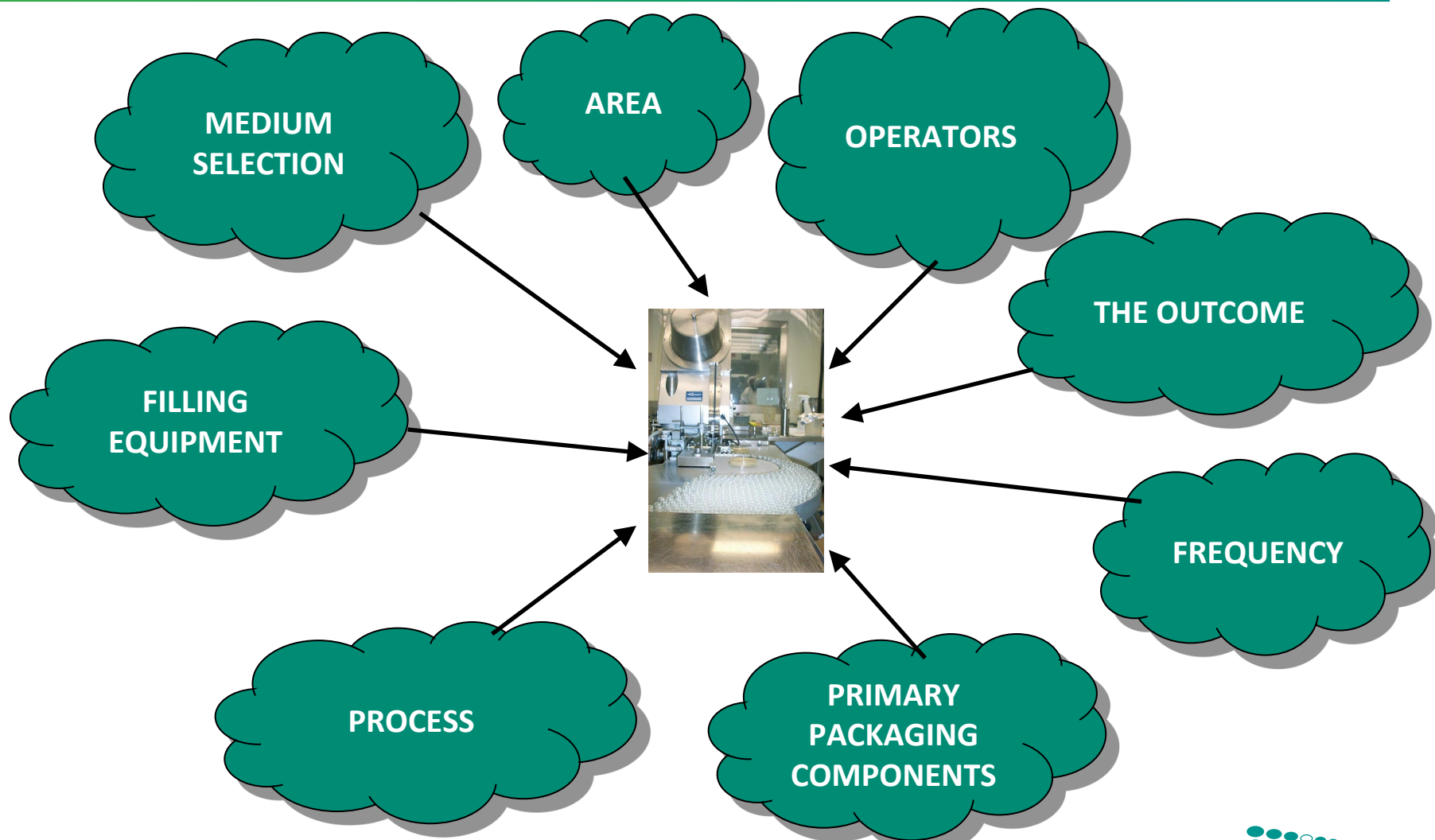


PHARMACEUTICAL
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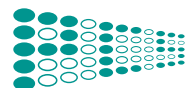
MEDIA FILLS

Jaap Koster

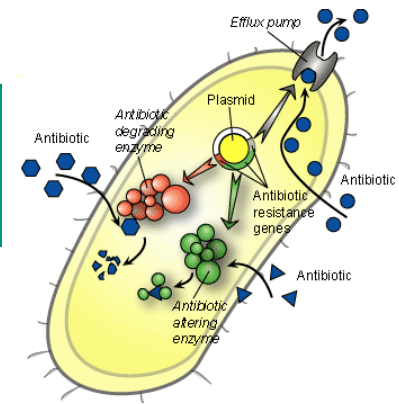


MEDIUM SELECTION

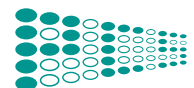
- The medium should be able to support the growth of a wide range of microorganisms.
- The medium should be suitable from a process perspective to perform as product (e.g. it should be filterable, if the product is normally also filtered).
- The medium should be clear in order to be able to observe any turbidity caused by growth.
- The medium should be prepared according to manufacturer's instructions.



MEDIUM SELECTION

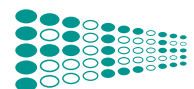


- Medium tested on House Flora
 - *Meaning: House Flora determined as a prerequisite*
- Growth Promotion Property tests with the correct amount of microorganisms (10 – 100 or less CFU/unit)
- GPP test performed either after processing or in parallel; growth within 5 days
- Typically, TSB is an all-purpose medium that fulfils all criteria.



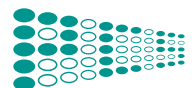
AREA – GENERAL PRINCIPLES

- Media fills should be performed in the same areas as product fills (this includes being in and out a freeze-dryer, if applicable!).
- If the same process is carried out in another clean room, this should also be validated.
- Each filling line to be validated twice per year
- Bracketing principles can be applied to reduce number of fills.
- Worst case principles can be applied to reduce number of fills.



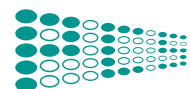
FILLING EQUIPMENT – GENERAL PRINCIPLES

- The same equipment that is used for product fills should be used for media fills.
- If inert gases are normally used in the process, filtered air should be applied during media fills not to prohibit growth of microorganisms. (If anaerobic microorganisms are found during routine E.M., the use of inert gases should also be considered.)
- All aseptic holding vessels should be part of a regular process simulation test, unless a validated pressure hold or vacuum hold test is routinely performed.



PROCESS – GENERAL PRINCIPLES

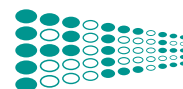
- The media fills should simulate the complete product fill situation as far as equipment, processes, Environmental Monitoring, personnel involved, areas and time taken for both filling and holding.
- The media fill should represent a “worst case” situation compare to a normal fill with respect to manipulations and interventions.
- If filling takes place for over 24 hours, the media fills should extend to the same time, unless the validity of the media fill is not compromised by running the fill for less time.



PROCESS – GENERAL PRINCIPLES

PLANNED INTERVENTIONS

- Media fills should include all interventions normally expected during product filling.
- Unplanned interventions should reflect actual experience with the filling process.
- Simulating interventions defines the validated envelope
 - *Excursions outside validated envelope, batch failure as default*



PROCESS – GENERAL PRINCIPLES

PLANNED INTERVENTIONS

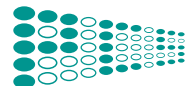
- Normal actions associated with the process, e.g. stopper bowl filling
- Normal occurrences, e.g. needle exchange, line stoppage
- Abnormal occurrences determined from deviations noted during previous runs

All the above to be incorporated into a “script” for the media fill.



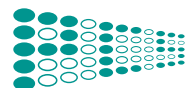
ADDITIONAL REMARKS

- Operator versus allowable interventions by him/her to be defined
- During normal operation, after intervention: removal of possible contaminated vials; that is allowable for Media Fill as well.
- Only discarding of vials as it is usually done.



MEDIA FILLS – DURATION

- ISO: “sufficient duration to cover most manipulations”
- EU: “sufficient to enable a valid evaluation”
- PIC: “Over the whole of the standard filling period”
- FDA: “Duration of commercial aseptic process best and preferred for larger simulations”



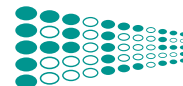
PRIMARY PACKAGING COMPONENTS – GENERAL PRINCIPLES

- Primary packaging components should be prepared as for regular production.
- When normally opaque containers are used, these should be used for media fills as well. The examination of growth though should be performed by transferring the whole contents.



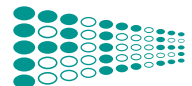
PRIMARY PACKAGING COMPONENTS – POINTS TO CONSIDER

- Primary packaging components should be the same as for normal production runs (amber vs clear vials?)
- Primary packaging components should be prepared the same as for normal production runs (washing and sterilisation)
- Media fill volume should be sufficient to cover, when the vial is inverted, the whole inner surface.



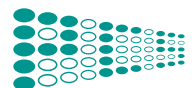
FREQUENCY – GENERAL PRINCIPLES

- Start-up simulation is applicable to new processes, new equipment or after critical changes to environment, equipment, process or significant personnel changes.
- Start-up simulation should consist of three consecutive, satisfactory runs with the same shift of people.
- Ongoing simulations should happen normally twice a year per shift and per process (unless there were changes to the product process or action limits exceeded).



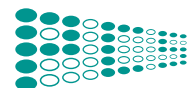
THE OUTCOME – GENERAL PRINCIPLES

- Incubation is normally 14 days at 20 – 25°C or sometimes 7 days at 20 – 25°C followed by 7 days at a higher temperature (<35° C).
- Containers should be inverted prior to incubation so that all surfaces are wetted by the medium.
- When inspecting for growth, a known sterile container should be used as comparison.
- Alert and actions limits should be previously established.
- Even if not alert nor action limit was exceeded, microorganisms should be identified.



THE OUTCOME - REQUIREMENTS

- The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be **zero** growth and the following should apply:
 - When filling fewer than 5000 units, no contaminated units should be detected.
 - When filling 5,000 to 10,000 units:
 - 1 contaminated unit should result in an investigation, **including consideration of a repeat media fill**;
 - 2 contaminated units are considered cause for revalidation – ***JK: meaning failure of simulation*** - , following investigation.
 - When filling more than 10,000 units:
 - 1 contaminated unit should result in an investigation;
 - 2 contaminated units are considered cause for revalidation, following investigation.

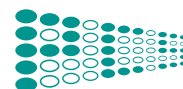


MEDIA FILLS – OOS

- There are not detailed indications from regulations, except:
 - Each contamination must be investigated.
 - Repeat media fill or repeat validation, after investigation, depending on the level of contamination and the run size.
- There is not distinction between initial validation and routine revalidation

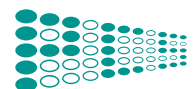
Also, guidelines and/or PDA (e.g. #22 are not very specific:

- “The root cause and the corrective action will dictate the number of process simulations required to demonstrate that the process is operating within the expected parameters”.
- In any case, the result of the investigation will be the key element for deciding how to address a media fill failure.



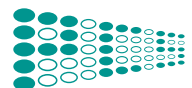
INVESTIGATION STEPS

- A basic checklist for performing a media fill investigation can be derived from guidelines (e.g. PDA) and other publications/presentations on this topic, example:
 - Identification of the organism(s) in the contaminated units and in the environment (air, surfaces, personnel) and check for matching.
 - Check of media fill process documentation (batch records, deviations, filter integrity testing, cleaning, sanitization and sterilization records) for anomalies.
 - Check of critical systems (HVAC and pressure cascade, HEPA filters, WFI/ PW, Compressed gasses, Clean Steam) and their maintenance/calibration records.
 - Verification of personnel training and aseptic qualification records.
 - Check of Validation and Change management records of the equipment and systems involved in the process, including holding times of sterilized materials.



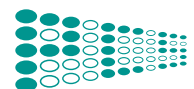
ADDITIONAL INVESTIGATION TIPS

- In addition to the “standard” investigation steps, in some cases important indications can be obtained by analysing the distribution of the contaminated units during filling.
- This is mainly valid in case of massive contamination, not so infrequent during validation of new filling lines/processes.



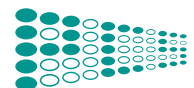
MEDIA FILLS—POINTS TO CONSIDER IN SUMMARY

- Duration of longest run
- Worst case environmental conditions
- Number and type of interventions, stoppages, adjustments, transfers
- Aseptic assembly of equipment
- Number and activities of personnel
- Number of aseptic additions
- Shift breaks, changes, multiple gownings
- Number/type of aseptic equipment disconnections and connections
- Aseptic samples
- Line speed/configuration
- Manual weight checks
- Operator fatigue
- Container/Closure types run on the line
- Temp/Relative humidity extremes
- Conditions permitted before line clearance
- C/C surfaces which contact formulation during aseptic process



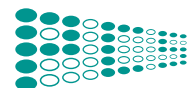
MEDIA FILLS – TYPICAL INSPECTION CONCERNS

- Inadequate investigation of media fill failure
- Inadequate training of employees after media fill failure
- Media fills did not follow SOP
- Media fill aborted due to high particulate counts, but inadequate investigation into reasons for high counts
- Media fill did not start at point after product had been sterilized
- Defective vials discarded prior to incubation and not counted as failures
- Number of units filled too small
- Media fills did not simulate what was documented in batch records
- Certain environmental data not collected during fill

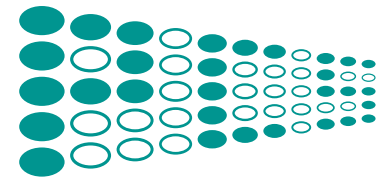


OPERATORS TRAINING/QUALIFICATION

- Training Plan must be available (authorized by QA),
- Beside on-the-job training: surveillance how persons are behavior in Class A/B conditions,
- Operator, Supervisor should have been adequately trained as well as the manager in Aseptic Considerations
 - Interventions (allowable and non-allowable)
 - SOP: removal of product during interventions
 - GMP
 - Guidelines
 - Hygiene
 - Cleanroom behavior
- Manager and Supervisor should have oversight over training plan and performance,
- QC AND Maintenance persons: almost same requirements.



THANK YOU FOR YOUR ATTENTION



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