21 CFR 211.113
Validation of Aseptic Processing and Sterilization

- Process Simulation / Media Fill
- Filtration Efficacy
- Sterilization of Equipment, containers and closures
What is Media Fill?

Includes exposing the microbiological growth medium to product contact surface of equipment, container closure systems, critical environments, and process manipulations to closely simulate the same exposure that the product itself will undergo.
What should be considered for a media fill?

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
1. STUDY DESIGN

a. Factors associated with longest permitted runs
b. Interventions
   i. Routine
   ii. Non routine
c. Lyophilization, when applicable
d. Aseptic assembly of equipment
e. Number of personnel
f. Aseptic additions/transfers
j. Shift changes
k. Gown changes
l. Aseptic sample collection
m. Line speed and configuration
n. Weight checks
o. Container closure system
p. Written procedures
2. FREQUENCY AND NUMBER OF RUNS

a. Initial Qualification of line
   i. To be repeated enough times
   ii. Atleast three consecutive separate successful runs required

b. Subsequent routine qualification
   i. Semi-annual for each line
C. Additional qualification required in case of
i. Facility and equipment modification
ii. Line configuration changes
iii. Significant changes in personnel
iv. Anomalies in environmental testing results
v. Container closure system changes
vi. Extended shut downs
vii. End point sterility failures
d. Post failure media fill

- Cause detected
- Cause not detected

Three consecutive successful runs required
3. DURATION OF RUNS

a. Full Batch size and duration is the ideal run

b. Manual filling/closing

c. Extensive Manual manipulation

d. Fully automated procedure
4. SIZE OF RUNS

a. For a batch size of less than 5,000 units
   Atleast equal to the maximum batch size

a. For a batch size of 5,000 units or more
   Generally acceptable starting point 5,000 to 10,000 units
Factors affecting run size

- Actual batch size
- Type of operation manual/mechanical
- Time consumed
- Type of facility open/isolated
5. LINE SPEED

- Range of line speeds addressed
- One media fill one line speed
6. ENVIRONMENTAL CONDITIONS

- Actual Conditions

- Stressful conditions inline with SOPs
7. MEDIA

Routine: Soybean caesin digest medium
Exceptional: Fluid thioglycollate medium

Growth promotion demonstration
Bacteria
Gram +ve
Gram-ve
Yeast and mold
Size of inoculum
Less than 100 CFU

Failure of growth promotion and origin of contamination during simulation be investigated and media fill to be repeated
8. INCUBATION AND EXAMINATION OF MEDIA-FILLED UNITS

Temperature 20-35°C
Set temperature ± 2.5°C of target temperature

Time
Lower temperature 7 days
Higher temperature 7 days
Examination

Pre-incubation
Integral units to be incubated
Units lacking integrity to be rejected

After-Incubation is underway
Selection/Rejection of damaged units to be justified

Written procedure for aseptic intervention should be clear and specific
9. INTERPRETATION OF TEST RESULTS

Contaminated units to be considered objectionable.
Microorganism to be identified to species level.
Contamination indicative of potential sterility assurance problem, regardless of run size.
<table>
<thead>
<tr>
<th>Batch Size</th>
<th>Number of contaminated units</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 5000</td>
<td>zero</td>
<td>OK</td>
</tr>
<tr>
<td></td>
<td>One</td>
<td>Revalidation</td>
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<tr>
<td>5000 to 10,000</td>
<td>zero</td>
<td>OK</td>
</tr>
<tr>
<td></td>
<td>One</td>
<td>Investigate and consider repeat</td>
</tr>
<tr>
<td></td>
<td>two</td>
<td>Revalidation</td>
</tr>
<tr>
<td>More than 10,000</td>
<td>zero</td>
<td>OK</td>
</tr>
<tr>
<td></td>
<td>One</td>
<td>Investigate and consider repeat</td>
</tr>
<tr>
<td></td>
<td>two</td>
<td>Revalidation</td>
</tr>
<tr>
<td>Observed number of failures</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>-----------------------------</td>
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<td>---</td>
</tr>
<tr>
<td>Upper 95% confidence limit</td>
<td>3</td>
<td>4.74</td>
</tr>
</tbody>
</table>
Contamination rate =
Upper confidence limit/Number of filled units
X 100%

Accepted contamination rate should be less than 0.1% with a 95% confidence level
CONSIDERATIONS FOR EACH DOSAGE FORM

Liquid products

Injectable Powder products

Suspension products

Freeze Dried products
Semi-Solid products

Clinical trials material and small batch size products

Biological and Biotechnology products

Sterile Bulk Pharmaceuticals

Blow Fill Seal Packed products
SOURCES OF CONTAMINATION

Aseptic practices
Poor aseptic connections
Poor sanitization
Construction
Poor gown design
New line’s HVAC installation
Velocity thru HEPA filters
Mechanical failure
References

21 CFR 211.63
21 CFR 211.65
21 CFR 211.67

21 CFR 211.84 (c)
21 CFR 211.100(a)
21 CFR 211.113(b)
Thank You