Session 2: Qualification/validation of aseptic techniques – dos and don’ts

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Purpose of GMP

• Generally, good GMP-compliance is based on good understanding

• When you understand the reasons for a particular GMP requirement, the chances are high that you will be able to comply with it – in procedures, records and actions

• In this session we will understand what GMP intends to gain from media fills

Why Media Fill?

• The basic idea is that we run an aseptic process, substituting a microbiologically inert placebo for product

  – And then test every unit for microbiological contamination

• It has been convenient that liquid microbiological media serve as placebo

  – This is because we can inspect each filled unit by eye for visible growth

The Underlying Principle

• In aseptic processing it is intended that a product and its containment system (separately sterilized) are brought together without them becoming microbiologically contaminated

• The media fill is an investigative tool which can show us if the aseptic process actually does what it is intended to do
Simulation

- In other words we are simulating the aseptic process in order to find out if it is safe.
- Commercial airline pilots are trained on flight simulators to ensure that they are safe to be in charge of aircraft.
- Commercial airline pilots are also trained for emergency landings on flight simulators because obviously you cannot practice crash landings in real situations.

Media Fill Simulation

- The unsatisfactory part of media fill simulation is this:
  - There are lots of reasons why unsafe aseptic processes could still give perfect media fill results (zero contaminants)
    - Media does not support growth
    - Media Fill done in “best conditions” which do not reflect reality
    - Routine risks omitted (accidentally or deliberately)
  - The only way media fills give us any useful information about our aseptic processes is when they fail, we investigate, we find a fault in the process, and then we fix the faults.

Media Fill Failure

- Only “failed” media fills trigger the process improvement cycles –
  - Investigate
  - Find root cause
  - Fix root cause
  - Confirm “fix” was correct
- However there are severe commercial and regulatory consequences from “failed” media fills
  - Therefore triggering the process improvement cycle through failed media fills has disproportionate costs.

Commercial Consequences-Validation Media Fills

- At validation we know very little about the performance of a new line (or new size):
  - We do not know very much about the equipment except what the supplier tells us (the best for the price)
  - We have limited experience of working with the equipment (what are its difficulties?)
  - We have had little practice working in new surroundings
- Therefore we perform media fills on every size and in replicates
  - Failure helps us “de-bug” any problems before they turn up in commercial production.
Commercial Consequences – Validation Media Fills

- We prepare our protocol from a tentative "Study Design" to help us find out if there is anything going to go wrong that we need to get fixed.
  - Because it is better to do it in validation than discover it in routine operation.
    - In validation it may delay release of the line but it has no other costs to the patient or the commercial supply chain.
- The tentative Study Design is the list of interventions tested at worst case which could lead to contamination on the line.
  - We should make the tentative Study Design as tough as possible because the regulatory submissions will be scrutinised and inspected to ensure we have done this.

Commercial Consequences – Routine Media Fills

- We are required to repeat media fills on each line at 6 month intervals.
- In routine media fills, failure means we have either:
  - Missed something out when we did the Validation Media Fill, or
  - Some aspect of the equipment or facility has "broken down" or changed, or
  - Our personnel have begun to do something differently, or
  - We are experiencing bad luck (but inspectors do not acknowledge "bad luck").

Routine Media Fills

- So ... the routine media fill is NOT A SAFE SIMULATION.
  - It is not like the commercial airline pilot’s emergency landing simulation which is completely safe.
- But can we make it safe?
Making Routine Media Fills Safe!

1. **We can “cheat”**.
   - But cheating might give us an unsafe process and we might be endangering the patient!
   - If we get caught cheating it will cost us more than 6-8 weeks lost production.

2. We can make sure that we discover and **address every risk BEFORE** we test the process by media fill: this is sensible **Risk Management**.

Compliance with Media Fill Requirements

- **Observe the process and correct all areas of doubtful control**
- **Create a Study Design** for Media Fills including the worst risks we have identified but have been unable to correct.
- **Replicate worst risks in every media fill Protocol** and include all other risks.
- Ensure that a “worst case” process is included each 6-months in Routine Media Fill Matrix.
- Ensure that any Investigation of media fill failure is intensively done and comprehensively documented.

Case Study

A firm filled 3 media fill batches and on daily observation found:

- **Batch “A”** – all containers OK after 7 days
- **Batch “B”** – all containers Ok after 5 days
- **Batch “C”** – All containers **contaminated after 2 days**.

Investigation begins:

- **Identification of the contaminating organism** started.
- **During the process 26 contaminations observed in Batch “A” after 12 days and 6 contaminants were observed in Batch “B” also after 10 days**.
Case Study

Initials information and investigations suggest that:

- Batch “A” is contaminated at point of fill by environmental flora
- Batch “B” is contaminated at point of fill by environmental flora and surviving spore formers
- Batch “C” is contaminated at point of fill by environmental flora and surviving spore formers also the filling path was contaminated with spore formers

This indicates the following:

1. Improper aseptic practices
2. Improper equipment design
3. Improper systems

Conjecture

<table>
<thead>
<tr>
<th>Initials</th>
<th>Case Study</th>
<th>Conclusion</th>
<th>Direct Evidence</th>
<th>Indirect Evidence</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>There were lapses in performing aseptic manipulations</td>
<td>The conjecture is correct</td>
<td>Nurse of media fill operators reported filling errors at many occasions.</td>
<td>The nurse also noted that the operators were not consistently following aseptic practices.</td>
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<td>There were process or equipment deficiencies which could account for all media fill failures</td>
<td>The conjecture is definitely correct</td>
<td>The filling path was visibly contaminated in Batch C at all points from the product drain downstream.</td>
<td>The fluid path was visibly contaminated in Batch C at the drain point and all points downstream.</td>
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<td>The contamination in all 3 batches originated from the same source</td>
<td>The conjecture is most probably correct</td>
<td>The microorganisms identified in Batch A were all common environmental and human types, the same as or similar to those found in routine environmental monitoring.</td>
<td>The contamination in Batch A was due to poor aseptic techniques</td>
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<td>The process is conducted in a closed system, subject to SIP.</td>
<td>The conjecture is demonstrated</td>
<td>The operators were not adequately protected from potential microbiological exposures to the system.</td>
<td>The contamination in Batch A was due to the operator's exposure to the microbial barrier.</td>
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<td>The contamination of the fluid path in Batch C resulted from a failure in the SIP</td>
<td>The conjecture is probably correct</td>
<td>The contaminants from Batch C were aerobic spore formers which would be expected to be somewhat heat resistant.</td>
<td>SIP records were all in order</td>
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<td>Visible contamination in Batch C throughout the system from the drain point to all points downstream.</td>
<td>SIP was not thermometrically and biologically qualified at drain</td>
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Case Study

• Considering this Hypothesis, process simulation studies were conducted after
  – Correction in equipment design
  – Correction of product path
  – Training of operating personnel
  – Requalification of the system
• This resulted into a successful simulation of the aseptic process.

Thank You