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

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Aseptic Processing Workshop:
July 2014; Indore

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 to 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")

Commercial Consequences – Routine Media Fills

Day 0 – begin Media Fill

Day 14 – confirm contamination in Media Fill. *Stop all further manufacture*
Quarantine product
Start Investigation

Day 17 – obtain Identification of contaminants

Day 25 – finalise investigation by confirming root cause

Day 30 – CAPA agreed and confirmed. Order placed for parts

Day 35 – Parts fitted and tested

Days 36-38 Confirmatory Media Fills set up

Days 50-52 Obtain Media Fill Results

Day 53 – Resume Manufacture

Day 67 – Resume Releasing Product

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***

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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

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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.***

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Case Study

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***

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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 former***

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Case Study

This indicates the following :

1. Improper aseptic practices

2. Improper equipment design

3. Improper systems

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Case Study

Conjecture	Conclusion	Direct Evidence	Indirect Evidence / Comment
There were lapses in performing aseptic manipulations	This conjecture is correct	Video of media fill activities shows , operator leaning over open vials at many occasions.	Supervisor has not observed this in 1st run and did not inform the operator/s
There were process or equipment deficiencies which could account for all media fill failures	The conjecture is definitely correct	Steam trap mounted horizontally on drain line (not self draining) No barrier filter on drain line	No validation of CIP Done to ensure absence of TSB from the line. SIP not thermometrically and biologically validated at low point (drain)
The contamination in all 3 batches originated from the same source	The conjecture is most probably incorrect	The types of microorganisms recovered from Batch A were distinctly different from those recovered from Batch B and C The fluid path was visibly contaminated in Batch C at all sample pints from the product drain downstream, but there were no such indications for Batch A.	The types of contaminants in Batch B were intermediate between those identified for Batches A and C. It would appear that something may have happened in the system after its first exposure to TSB when running Batch A, which led to the fluid path contamination seen in Batch C.
The process is conducted in a closed system, subject to SIP.	The conjecture is incorrect	The drain was not adequately protected from possible microbiological ingress into the system	A diaphragm valve and a horizontally mounted steam trap do not present an anti-microbial barrier.

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Case Study

Conjecture	Conclusion	Direct Evidence	Indirect Evidence / Comment
The source of contamination of the fluid path (Batch C) is downstream of the holding vessel	The conjecture is most probably correct	Visible contamination in Batch C throughout the system from the drain point to all points downstream	Contamination observed in all samples and vials
The contamination of the fluid path in Batch c resulted from a failure in the SIP	The conjecture is possibly correct	The contaminants from Batch C were aerobic spore formers which would be expected to be somewhat heat resistant.	SIP records were all in order SIP was not thermometrically and biologically qualified at drain
The contamination in Batch A arose at point of fill	The conjecture is most probably correct	The microorganisms identified in Batch A were all common environmental and human types, the same as or similar to those found in routine monitoring.	Poor aseptic techniques
The contamination in Batch C did not arise at point of fill	The conjecture is most probably correct	The fluid path was visibly contaminated within a few days of starting Batch C at all points in the system downstream of the drain. The microorganisms identified in Batch C had never been identified in routine environmental or personnel monitoring	It is unlikely that contamination would move upstream against the flow of product over this distance in such a short time. It is unlikely that this concentration of contaminants could have developed from incidental environmental sources

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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.

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Thank You

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