India Chapte



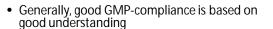
:Session 2: Qualification/validation of aseptic techniques – dos and don'ts

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Aseptic Processing Workshop: July 2014; Indore

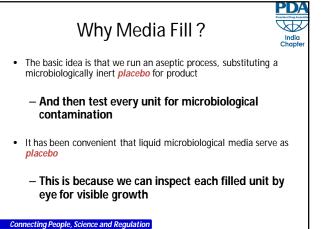
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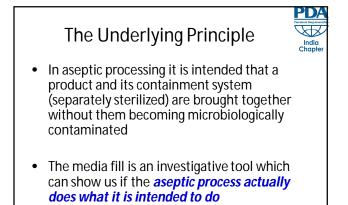
Purpose of GMP



- 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

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- 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
 - Failure helps us "de-bug" any problems before they turn up in commercial production

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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

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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")

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Commercial Consequences -**Routine Media Fills Routine Media Fills** India Day 0 - begin Media Fill • So ... the routine media fill is NOT A SAFE Day 14 – confirm contamination in Media Fill. Stop all further manufacture Quarantine product SIMULATION Start Investigation Day 17 - obtain Identification of contaminants - It is not like the commercial airline pilot's Day 25 - finalise investigation by confirming root cause emergency landing simulation which is completely Day 30 - CAPA agreed and confirmed. Order placed for parts Day 35 - Parts fitted and tested safe Days 36-38 Confirmatory Media Fills set up Days 50-52 Obtain Media Fill Results Day 53 – Resume Manufacture • But can we make it safe? . Day 67 – Resume Releasing Product ecting People, Science and Regulation Connecting People, Science and Regulation

Making Routine Media Fills Safe !

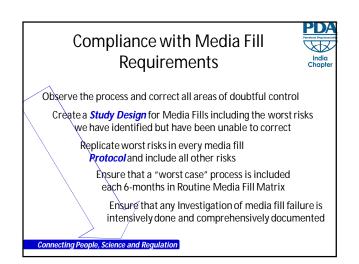


1. We can "cheat".

- 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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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 <u>contaminated</u> after 2 days.

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:

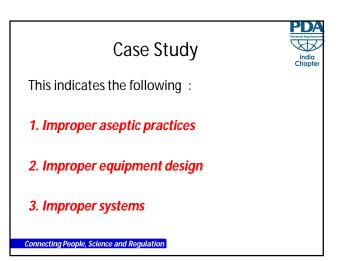
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- Batch "A" is contaminated at point of fill by environmental flora
- Batch "B" is contaminated at point of fill by environmental flora and surviving spore formers
- Batch "C" is contaminated at point of fill by environmental flora and surviving spore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

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Case Study				
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 1 st 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 Band C The fluid path was visibly contaminated in Batch Ca at all sample pits from the product drain downstream, but there were no such indications for Batch A.	The types of contaminants in Batch 8 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 TS8 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.	

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 o product over this distance in such a short time. It is unlikely that this concentration of contaminants could have developed from incidental environmental sources

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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