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Update on PDA TR22 Revisions for Aseptic Process Simulations

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Agenda

- **Definition TR22**
- **Why the revision**
- **What's Changing**
- **Conclusions**
- **Acknowledgements**



Definition of TR22

- **Initial version published in 1996, replaces:**
 - **Technical Monograph No. 2, *Validation of Aseptic Filling for Solution Drug Products*, 1980;**
 - **Technical Report No. 6, *Validation of Aseptic Drug Powder Filling Processes*, 1984**
- **Provide a valuable guide to industry in the area of process simulation testing**
- **Addresses the validation of aseptic processing during formulation and filling activities**
- **An APS is a simulation of the entire aseptic formulation and filling process, which substitutes a microbiological growth medium for a sterile product.**



Why the Revision

- **Periodic Review – originally published in 1996**
- **Develop a modest revision / expansion of PDA TR#22,**
- **Update / clarify coverage of interventions.**
- **Address personnel participation in a meaningful and coherent fashion.**
- **Include an accountability discussion.**
- **Clarify application to aseptic steps in the drug compounding process.**
- **Outline execution practice in greater detail.**
- **Maintain consistency with regulatory guidance (especially FDA's 2004 AP guide).**



Important Points to Consider

- **APS demonstrates capability, does not determine an SAL.**
- **Interventions are either:**
 - **Inherent – a integral part of the process**
 - **Corrective – performed to fix problems**
- **Interventions must be the focus of the discussion, because contamination is largely associated with them.**
- **Aseptic process simulation, is not just media filling.**



Purpose of the APS

- **Demonstrate as part of an overall process validation approach, the capability of the aseptic process to produce sterile drug products.**
- **Evaluate proficiency of aseptic processing personnel.**
- **Comply with current Good Manufacturing Practice requirements.**
- **Confirm the appropriateness of operating practices used in support of aseptic processing.**



What's Changing – Section 2

PROCESS SIMULATION CONCEPTS AND PRINCIPLES

- **No change to typical six month interval**
- **Providing clarity around worst case conditions**
 - **Present a reasonable challenge to the system without forcing unintentional failure**
 - **Duration is equal to a maximum production run including**
 - **Shifts**
 - **Room/equipment time**
 - **Extremes of container sizes and rates**



What's Changing – Section 2

RISK ASSESSMENT ADDITION

- **A risk assessment may be performed to determine, identify, and rate the aseptic process steps and interventions, which can potentially adversely affect the sterility assurance of the product.**
- **These process impacting steps and interventions should be included in the process simulation study.**
- **Other steps and interventions which do not affect the sterility assurance of the product may be included in the study at the discretion of the company.**



What's Changing – Section 3

PROCESS SIMULATION TEST

DOCUMENTATION

- **Media fills do not support the filtration validation of the product / process being simulated, so differences in filtration area, filter media, etc are acceptable**
- **Expanded content for aseptic compounding steps and recommend that processes requiring the addition of sterile powders employ an acceptable placebo material in containers identical to those utilized in the process being evaluated**
- **Anaerobic media would be appropriate where strict anaerobic conditions are present**
- **NOTE: The aseptic production of sterile bulk pharmaceuticals is addressed in PDA's TR #28**



What's Changing – Section 6

ELEMENTS OF PROCESS SIMULATION TESTS

- **Created Section 7 to discuss intervention identification and management**
- **Recommend that the frequency of intervention during APS be related to the frequency of occurrence in production.**
- **Recommend that the APS duration be long enough to stress the process, the supporting environment and the operators**
- **Recommend that the number of units filled during each manual process simulation study represent the maximum production lot size.**
- **Incubate for a minimum of 14 days unless supported by a validated approved alternative method (Rapid Methods)**



What's Changing – Section 6

ELEMENTS OF PROCESS SIMULATION TESTS

- **Added Section for Unit Accountability and Reconciliation**
 - **Recommend an accurate count of integral media-filled containers be performed**
 - **An accurate unit count may be obtained by one of the following methods:**
 - **Use of a calibrated counter with demonstrated accuracy**
 - **A nested or divided tray configuration**
 - **A verified physical count**
 - **Complete unit accountability of the APS is the goal**



What's Changing – Section 7

INTERVENTION MANAGEMENT – *New Section*

- **Created to discuss intervention identification and management**
- **Provides Guidance for:**
 - **Study Design**
 - **The human operator is by far the greatest source of microbial contamination during an aseptic process.**
 - **To demonstrate aseptic processing capability, process simulation programs should include all the inherent (part of the process) and corrective (problem resolution) activities that occur during an aseptic filling process**
 - **May accommodate similar configurations**
 - **Frequency**
 - **At least once annually**



What's Changing – Section 7 INTERVENTION MANAGEMENT, continued

- **Inherent Interventions**

- An integral part of the aseptic process required for either set-up, routine operation and/or monitoring, e.g., aseptic assembly, container replenishment, environmental sampling, etc. Inherent interventions are required by batch record, procedure, or work instruction for the execution of the aseptic process.

- **Corrective Interventions**

- Performed to correct or adjust an aseptic process during its execution. These may not occur with the same frequency (or at all) in the aseptic process. Examples include such activities as: clearing component jams, stopping leaks, adjusting sensors, and replacing equipment components. Corrective measures should be taken to reduce their extent and frequency.



What's Changing – Section 7 INTERVENTION MANAGEMENT, continued

- **Monitoring**
 - **The documentation in the batch record will allow for identification, cataloging and trending**
- **Incubation of Interventions Related Containers**
 - **If written procedures and batch documentation are adequate to describe an associated clearance, the intervention units removed during media fills do not need to be incubated**



What's Changing – Section 8

PERSONNEL QUALIFICATION – *NEW SECTION*

- **Complete training that provides an understanding of:**
 - **Basic microbiological concepts**
 - **How contamination is generated and spread**
 - **Control of contamination risks (eg. gowning, behavior)**
 - **An appreciation of the consequences of a patient receiving a non-sterile product.**
- **Recommend that operators are qualified with an off-line individual test to confirm that they understand and can execute basic aseptic techniques**
 - **Set-up and other complex interventions are excluded from off-line qualification.**
- **Recommend that Operators work under direct supervision until they have achieved the required proficiency to perform independently.**



What's Changing – Section 10

ONGOING ASSESSMENTS

- **Re-titled Maintenance to convey that the process of assessing a state of control must be an ongoing process**
- **Utilize Risk Management Tools to assess needs**
 - **Not strictly time driven, although 6 months is typical**
 - **Not strictly event driven, controlled maintenance activities may be allowed**
 - **Assess new container closure systems through previously qualified systems**
 - **Equipment preparation and assembly modifications**
- **An aseptic process simulation *must not be used* to justify practices that pose unnecessary contamination risk**



What's Changing – Appendix 2 and 3

- **Two new appendices:**
 - **Appendix 2 – Media Preparation and Sterilization**
 - **Outlines alternatives**
 - **Allows for variation from process**
 - **Does not validate process filtration**
 - **Appendix 3 – Aseptic Process Simulation Execution Sequence**
 - **Outline for sequencing of APS activities included**



Conclusions

- **No major changes to the approach or intent**
- **Added clarifications for:**
 - **Worst case conditions**
 - **APS durations and design**
 - **Application of Risk Assessment Tools**
- **Added new sections for:**
 - **Intervention Management**
 - **Personnel Qualification**
- **PDA submitted for Regulatory Review to:**

FDA	EMA
Health Canada	TGA
Koseisho	PIC/S



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