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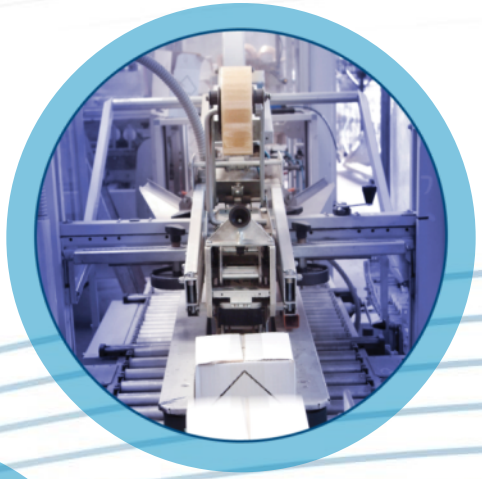
Best Practices in Aseptic Processing Simulations



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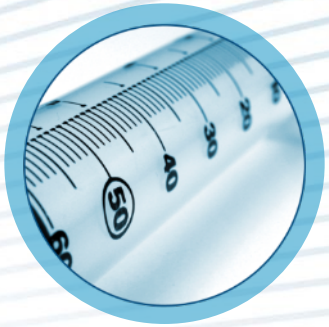


Overview about Presentation

- Basic Concepts and Regulatory Framework about APS
- Best Practices in Media Fill for Finished Dosage Forms and API
  - TR 22 and TR 28 (Survey results)
- My “Hot Topics”: Definitions of Worst Case Criteria & Categorization of Interventions
- Operator Qualification & Media Fill

What is an APS/ Media Fill ?

What is the purpose ?

What are the limitations ?

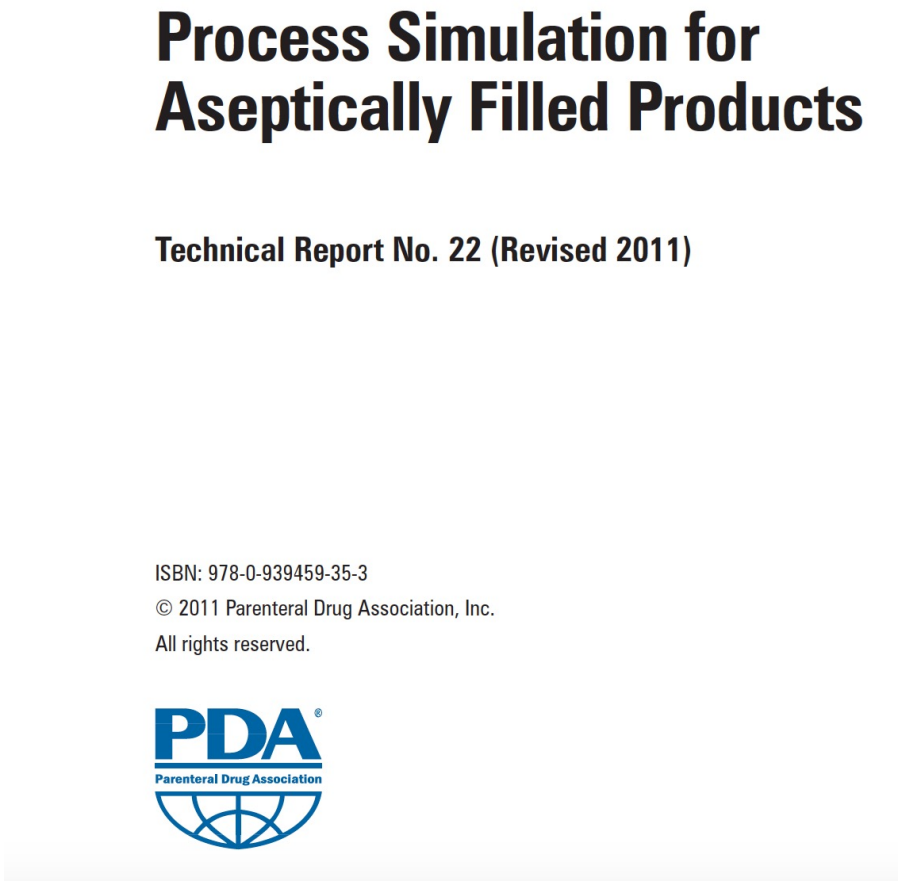
EU Annex 1 (2022)

Aseptic Process Simulation (APS) – A simulation of the entire aseptic manufacturing process in order to verify the capability of the process to assure product sterility. Includes all aseptic operations associated with routine manufacturing, e.g. equipment assembly, formulation, filling, lyophilization and sealing processes as necessary.

Aseptic process simulation (APS) (also known as media fill)

9.32 Periodic verification of the effectiveness of the controls in place for aseptic processing should include an APS using a sterile nutrient media and/or surrogate in place of the product. The APS should not be considered as the primary means to validate the aseptic process or aspects of the aseptic process. The effectiveness of the aseptic process should be determined through process design, adherence to the pharmaceutical quality system and process controls, training, and evaluation of monitoring data. Selection of an appropriate nutrient media and/or surrogate should be made based on the ability of the media and/or surrogate to imitate physical product characteristics assessed to pose a risk to product sterility during the aseptic process. Where processing stages may indirectly impact the viability of any introduced microbial contamination, (e.g. aseptically produced semi-solids, powders, solid materials, microspheres, liposomes and other formulations where product is cooled or heated or lyophilized), alternative procedures that represent the operations as closely as possible should be developed. Where surrogate materials, such as buffers, are used in parts of the APS, the surrogate material should not inhibit the growth of any potential contamination.

PDA TR 22 (under revision)



Definition of Media Fill / Aseptic Process Simulation

- PDA TR 22 (2001):

Media Fill: A means for establishing the capability of an aseptic process as performed using a growth medium.

Note: Media Fill is understood to be synonymous with aseptic processing simulations, process simulations, simulated product fills, broth trails, broth fills, etc.

Definitions

- FDA Guide 2004 :

An aseptic processing operation should be validated using a microbiological growth medium in place of the product. This *process simulation,* also known as a *media fill,* normally includes exposing the microbiological growth medium to product contact surfaces of equipment, container closure systems, critical environments, and process manipulations to closely simulate the same exposure that the product itself will undergo. The sealed containers filled with the medium are then incubated to detect microbial contamination. Results are then interpreted to assess the potential for a unit of drug product to become contaminated during actual operations (e.g., start-up, sterile ingredient additions, aseptic connections, filling, closing). Environmental monitoring data from the process simulation can also provide useful information for the processing line evaluation.

Purpose

The purpose of a Media Fill is to:

- assess the capability of an aseptic process under a given manufacturing environment and process controls

- evaluate the proficiency of aseptic processing personnel

- demonstrate compliance with current GMP

- demonstrate the appropriateness of operating practices used in support of aseptic processing

- challenge the aseptic process for microbial contamination vulnerabilities.

Design of Media Fill I

A Media Fill program should incorporate the contamination risk factors that occur on a production line, and accurately assesses the state of process control. *(…. e.g. set- up)*

The establishment of Media Fill requires in-depth knowledge of the routine aseptic processing operations process, material and personnel flow, adjacent environmental and quality controls and more.

The Media Fill should imitate as closely as possible the routine aseptic manufacturing process and include all critical manufacturing steps.

Important: for all steps of the Media Fill prepare an overall Risk Assessment that – as the outcome- provides a “Rationale” for the approach.

Design II : Identification of worst case conditions

The outcome of the assessment should justify the variables selected.

- Determining the representative sizes of container/closure combinations to be used for validation. Bracketing or a matrix approach can be considered for initial validation of the same container/closure configuration.

- The volume filled per container, which should be sufficient to ensure that the media contacts all equipment and component surfaces that may directly contaminate the sterile product.

- Maximum permitted holding times for sterile product and associated sterile components exposed during the aseptic process.

- Ensuring that any contamination is detectable. (Example : ….)

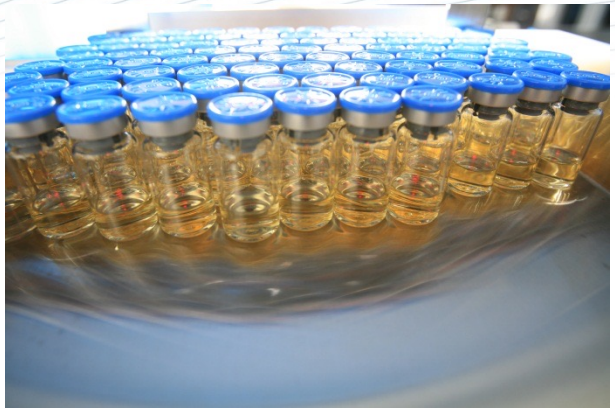
Design III : Identification of worst case conditions

- The requirement for substitution of any inert gas used in the routine aseptic manufacturing process by air, unless anaerobic simulation is intended.

- The duration of Media Fill run to ensure it is conducted over the maximum permitted filling time. If this is not possible, then the run should be of sufficient duration to challenge the process, the operators that perform interventions, and the capability of the processing environment to provide appropriate conditions for the manufacture of a sterile product.

- The Media Fill should mimic the routine production procedures, activities and conditions that provide a challenge to aseptic operations. By this simulation it can be demonstrated that the routine process itself is capable of producing aseptically filled products, ensuring the sterility assurance of a specific product. However, a Media Fill should not be used to validate bad working practices or events (e.g. to simulate power failures), that may pose a microbial contamination risk to the product.

Media Fills



- Initial Qualification
  - 3 Consecutive SUCCESSFUL media fills
- 1 Media Fill performed every six months (minimally) .. per line
- Should accurately simulate process
  - Routine (Inherent/Corrective) interventions should be included
  - Number of units filled/ duration

Hot Topics about Media Fills / my learnings from 2012

- Form 483 *„ ...* ***not all approved interventions are simulated yearly in the Media Fills*** *“* . Background: have not occurred in the routine, however these interventions must be performed.

- FDA: *„How can you release batches without simulating these interventions in a Media Fill ? “* Sound arguments have been provided that these (not in the Media Fill performed interventions) are very similar and comparable to the performed interventions in the Media Fill.

- The problem was: there has been a too long list of many potential interventions from the past, several of them did not occur over months, and therefore not been simulated in Media Fills for some years.

- Advise: Keep your „routine intervention list/ approved intervention list “ as short as possible, only with relevant interventions !

„My“ Hot Topics about Media Fills

- Kind of interventions: All approved Cat 1/ A critical) must be performed during each Media Fill, and all Cat 2/ B (less critical) interventions must be simulated at least once a year.
- Number of interventions: based on a Risk Assessment, e.g. the maximum number of interventions, which occurred during the routine production within a time period, should be performed during the Media Fills.
- Important is the accurate documentation and counting of the routine batch production interventions. Based on this the number of required interventions will be defined for the upcoming Media Fill.
- Exceeding the number of „approved interventions“ in the routine leads to a deviation. Occurrence of a corrective interventions in routine, not validated in a Media Fill ? E.g. Stoppage for Cat 1, for Cat 2 requires a deviation notice and a risk assessment ... ?
- GPT should be done within the primary packaging material, e.g. not to use an aliquot sample of media
- Good reconciliation of filled/ removed units (Warning Letters)
- Media Fill plans for operators (e.g. Grade A/ B operators, Set-Up, …) – which interventions must be simulated

„My“ Hot Topics about Media Fills since > 10 years

- Important is to have a **Risk Assessment / Rationale/ Justification** in advance to each Media Fill run
  - Assessment/ Justification about the format used in the upcoming Media Fill (e.g. bracketing)
  - Number and kind of interventions
  - Number and names of involved operators, and related interventions to these operators to (re)qualify in detail (e.g. distinction between Grade A or Grade B operators, involved during set-up and/or filling
  - Number of involved shifts and filling time (maximum time)
  - Defined maximum storage time of (packaged) components and filling equipment
  - Filling speed
  - composition of nutrient / Placebo usage
  - ... (dedicated Interventions for each operator/ mechanic)

New: APS design should be based in a Risk Assessment

- TR 22- Team is just working on it

Key Questions to clarify and to assess in the Risk Assessment :

- Does your APS design appropriately reflect all stages of the manufacturing process (this is particularly linked to assessing / providing justification as to where does APS begins)?
- Is your MF design able to "challenge process capabilities" for Sterility Assurance, and identify deficiencies of process and people ?
- are your selected and simulated "worst case criteria" appropriate, and do not pose a risk for product sterility ?
- does your APS design meets regulatory and industry guidance requirements ?=

„My“ Hot Topics about Media Fills

- **NOTE :** Media Fill requires full duration QA oversight (physically) or prepare a video for a later review by QA !

- **<u>Practices / Examples that cannot be validated in a Media Fill</u>**
  - Power failures during filling
  - Disruption of UDF above open containers/ closures without rejection of containers/ closures
  - Pressure drops in cleanrooms and reduced air velocities
  - Contacting of product contact surfaces with gloved hands
  - Isolators: validate of pinholes in gloves or isolator - non integrity
  - Deviations in EM program (cleanroom/ personnel)
  - Introduction of non properly sterilized or sanitized materials/ equipment into the cleanroom / isolator
- What I commonly see in a few companies: incubate „intervention vials“

EU Annex 1 / Some sections selected :

8.16 There should be an authorized list of allowed and qualified interventions, both inherent and corrective, that may occur during production (see paragraph 9.34). Interventions should be carefully designed to ensure that the risk of contamination of the environment, process and product is effectively minimized. The process of designing interventions should include the consideration of any impact on air-flows and critical surfaces and products. Engineering solutions should be used whenever possible to minimize incursion by operators during the intervention. Aseptic technique should be observed at all times, including the appropriate use of sterile tools for manipulations. The procedures listing the types of inherent and corrective interventions, and how to perform them, should be first evaluated via risk management and APS and be kept up to date. Non-qualified interventions should only be used in exceptional circumstances, with due consideration of the risks associated with the intervention and with the authorisation of the quality unit. The details of the intervention conducted should be subject to risk assessment, recorded and fully investigated under the manufacturer's PQS. Any non-qualified interventions should be thoroughly assessed by the quality department and considered during batch disposition.

EU Annex 1 / Some sections selected :

7.4 The personnel accessing grade A and B areas should be trained for aseptic gowning and aseptic behaviours. Compliance with aseptic gowning procedures should be confirmed by assessment and periodic reassessment at least annually, and should involve both visual and microbial assessment (using monitoring locations such as gloved fingers, forearms, chest and hood (facemask / forehead). See paragraph 9.30 for the expected limits). The unsupervised access to the grade A and grade B areas where aseptic operations are or will be conducted should be restricted to appropriately qualified personnel, who have passed the gowning assessment and have participated in a successful APS.

Operator Qualification ….Final Step in most companies: Media Fill

7.5 Unqualified personnel should not enter grade B cleanrooms or grade A in operation. If needed in exceptional cases, manufacturers should establish written procedures outlining the process by which unqualified personnel are brought into the grade B and A areas. An authorized person from the manufacturer should supervise the unqualified personnel during their activities and should assess the impact of these activities on the cleanliness of the area. Access by these persons should be assessed and recorded in accordance with the POS.

EU Annex 1 / Some sections selected :

9.34 The APS should take into account various aseptic manipulations and interventions known to occur during normal production as well as worst-case situations, and take into account the following:

i. Inherent and corrective interventions representative of the routine process should be performed in a manner and frequency similar to that during the routine aseptic process.

ii. The inclusion and frequency of interventions in the APS should be based on assessed risks posed to product sterility.

INTERVENTIONS: What is „MY Concept“ in simple words .

How to start: design the process to prevent interventions , ….

Many Filling Lines: design problems !

Sterile Bulk Manufacturer ?

- Only very few manufacturer are left
- TR 28 might be applicable for Cell-Culture / Low Bioburden
- What is it ?
- Flipchart ?

PDA TR 28

Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals

Technical Report No. 28 Revised
Supplement
Vol. 60, No. S-2
2006

2021 there was an industry survey .

Survey will be published soon

Results Survey

- Brief summary, if requested

Questions to APS ?

END