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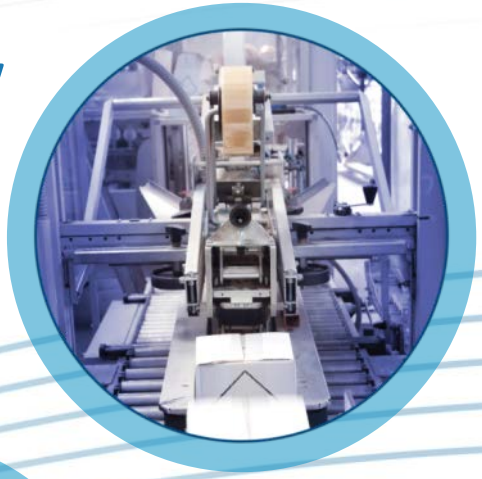
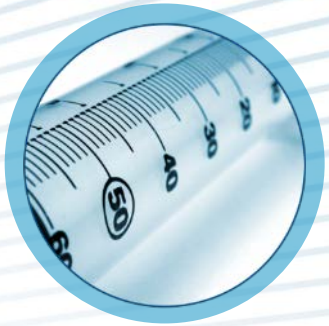
Media Fills – General Overview and Hot Topics





By Guenther Gapp

Overview about Presentation

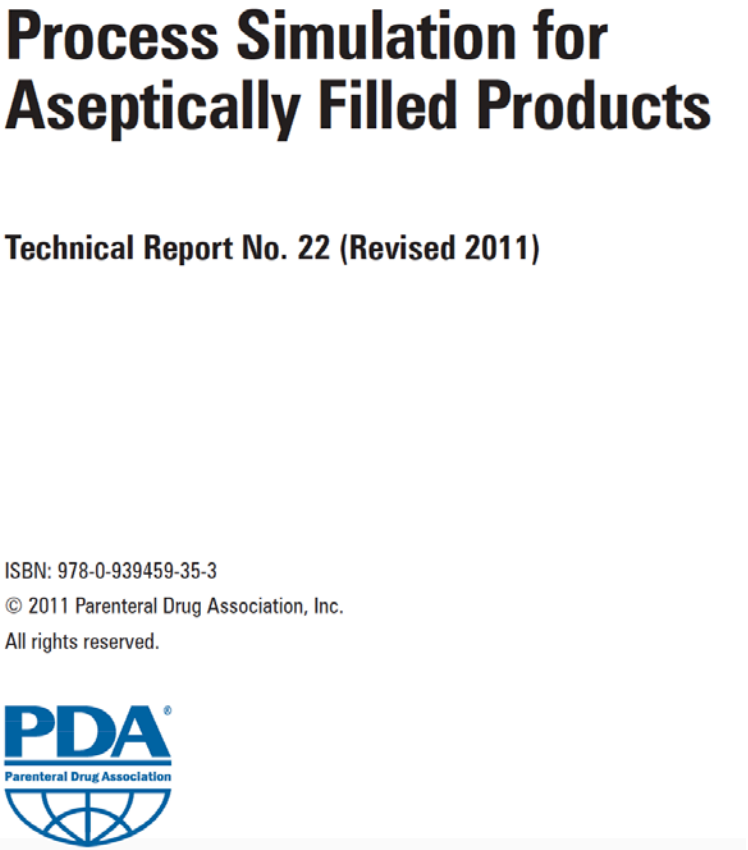
- Glossary
- Selected Topics from PDA TR 22
- Hot Topics : Definitions of Worst Case Criteria & Interventions
- Operator Qualification
- Process Simulation for Bulk Products / PDA TR 28

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.

PDA TR 22


Process Simulation for Aseptically Filled Products
Technical Report No. 22 (Revised 2011)
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PDA
Parenteral Drug Association

Definitions

- PDA TR 22 : Process Simulations of Aseptically Filled Products (2001)

Aseptic Processing Simulation (APS)

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

Note: Aseptic processing simulations are understood to be synonymous with media fills, process simulations, simulated product fills, broth trials, broth fills, etc.

Selected Topics from TR 22

3.2 Worst Case

A useful technique in the validation of pharmaceutical processes is the employment of "worst case" scenarios. The use of "worst case" situations is intended to challenge the process under conditions that may be on the edge of normal operating conditions. If, under the circumstances of the worst case challenge, acceptable results are achieved, then there is greater confidence in the reliability of the system under more routine conditions. Worst case does not mean creation of artificial conditions or environments which exceed allowed operating conditions and which can force a system failure.

Worst case conditions vary depending on the operations or risk being considered. For example, executing the APS using the maximum number of personnel may be worst case at certain times as gowned personnel are the greatest source of microbial contamination in an aseptic process. In other situations worst case may include executing the process with fewer people if this results in more movement by the process operators.

Selected Topics from TR 22

Other examples of "worst case" practices may include:

- Using room/equipment at the maximum time period after completion of sanitization/sterilization (clean hold time)
- Using the slowest fill speed for the largest container (maximum opening)
- Using the highest fill speed for the smallest container (handling difficulty)

The worst case conditions selected for inclusion in an APS should be predefined based upon characteristics of the operation. The identification of appropriate worst case conditions should be accomplished by conducting an assessment of the APS covering the relevant variables and their microbiological impact on the process. Such assessments can benefit from the application of risk management principles. The assessment conclusion should outline the variables selected as worst case and considerations/rationale for their selection.

Selected Topics from TR 22

5.2 Protocol/Procedure Preparation

A formal written protocol or procedure should be prepared, approved, and issued prior to the start of the study. The document should be identified for traceability and should be approved prior to execution by representatives of the Quality Unit. Other stakeholders may review and approve the document at the discretion of the company. The document should include but not be limited to the following information:

- Groups responsible for execution, microbial testing, and approval of study
- Rationale for the "worst case" parameters chosen as appropriate simulation of routine operations
- Identification of the process to be simulated
- Identification of the room or rooms to be used
- Identification of the filling line and equipment to be used including fluid path configuration details if multiple configurations are available
- Type of container/closure to be used
- Line speed
- Minimum number of units to be filled
- Number and type of interventions and stoppages
- Identification of units to be excluded from incubation and rationale
- Number, identity and specific roles of people participating
- Media to be used

Selected Topics from TR 22

- Volume of medium to be filled into the containers
- Incubation time, temperature and duration for the filled units
- Environmental monitoring to be performed
- A copy of the batch record to be used
- Accountability requirements
- Acceptance criteria for all activities
- Description of the documentation required for the final report
- Duration of the aseptic process simulation
- Duration of routine production fills being simulated
- Definition of conditions that may cause the simulations to be invalidated and decision-making authority.

Other factors may have to be considered due to the nature of the process to be simulated. The protocol should require that prior to execution of the process simulation study critical support system qualifications and process validations have been verified to be successfully completed and approved.

Selected Topics from TR 22

Process simulation should be carried out using the routine environmental monitoring operating procedures and sampling requirements. This should include the set-up period, set-up interventions and set-up personnel. Any changes to the routine environmental monitoring requirements during process simulation (e.g., additional sampling or change in sampling location) should be explained and documented.

The results of the environmental and personnel monitoring are used to assess whether suitable processing conditions were maintained during the process simulation. Additionally, environmental and personnel monitoring results obtained during process simulation can aid in the identification of root cause if the process simulation yields any positives (See Sectio**n 11.0**).

Environmental Monitoring excursion investigations should be completed and approved. Failure to meet established routine monitoring levels should be addressed according to routine monitoring investigation procedures and actions taken according to those procedures. Environmental monitoring excursions are not an automatic cause to reject the results of an APS; rather any decision should be based on the investigation results.

Note that "passing" an aseptic process simulation with environmental monitoring results that exceed action limits does not mean that the aseptic process may be routinely performed in such an environment and should not be used as justification for doing so.

Selected Topics from TR 22

7.3 Media Selection and Preparation

The most common medium for process simulation is Soybean-Casein Digest Medium (SCDM). SCDM is a general purpose growth medium well suited for the recovery of aerobic microorganisms of the types commonly associated with human borne contamination. It is very similar to SCDA which is widely utilized for microbial recovery in aseptic areas for the same reason. Replacement of the products, diluents, and buffer solutions with media is customary when performing process simulation studies.

Aseptic processing conducted in a strict anaerobic environment (one which maintains less than 0.1% oxygen throughout the process) should be evaluated with alternate Fluid Thioglycollate Medium (FTM) or other suitable medium, in addition to aerobic evaluation. An anaerobic media fill may also be considered for a typically aerobic process if anaerobic microorganisms are consistently recovered during periodic environmental monitoring (for anaerobes), or if facultative anaerobes are detected exclusively in FTM sterility test medium. In either case, oxygen is excluded from processing and parameters such as container fill volume and inert gassing may require modification to provide a true anaerobic environment for the aseptic process simulation study. (See **Appendix 13.2** for additional detail)

Selected Topics from TR 22

7.4 Inert Gassing

Nitrogen or other inert gases are used to provide a low oxygen environment for oxygen-sensitive products. They are also used to provide positive pressure for solution transfer. Nitrogen (or other gases) for these uses does not provide a true anaerobic environment (less than 0.1% residual oxygen is needed for anaerobic conditions). In these instances, filter sterilized air should be utilized in lieu of an inert gas for process simulation studies. Air should replace the inert gas and be delivered by the same delivery system thus assuring the purge/transfer set-up and delivery considerations are fully considered in the simulation.

The sterility of the inert gas system is confirmed through filter validation, integrity testing, and sterilization of connecting lines downstream of the filter, not by means of the process simulation. The use of an inert gas with Soybean-Casein Digest Medium may inhibit growth. If it is necessary to use an inert gas for simulation of an oxygen free process, testing should confirm the ability of the inert gas/medium combination to support microbial growth.

Selected Topics from TR 22

7.5 Container Size

In general, process simulation trials should entail at least the filling of the largest and smallest containers on a given filling line based on a facility established matrix. Exceptions to this general rule occur when the same filling machine, on the same filling line is used for different product presentations. In these instances, the flexibility of the filler may make it necessary to evaluate more than one set of large and small containers, because the filling set-ups are so different. For example, if filling another size container results in a process which is significantly changed (e.g., additional manipulation or fill parts), then that size container should be included in the study.

7.7 Filling Speed

In general, the fill speed to be used for most containers should be set at the production filling speed range for that size container in commercial production. Where production filling speeds on a line are variable, if higher or lower speeds in the speed range result in the potential for greater interventions or other adverse impact such as increased product exposure to environment, that speed can be considered 'worst case' and should be considered when selecting process simulation parameters (See **Section 3.2**).

Selected Topics from TR 22

7.8 Fill Volume

The container need not be filled to its normal fill volume. The fill volume must be controlled and monitored as performed during routine filling. Where partial fills are employed, the fill speed should follow the advice given in **Section 7.7.** Regardless of the actual fill volume, the process simulation should include a fill weight/volume adjustment using methods identical to those employed during production.

While the specific amount of medium utilized in a partial fill may not be critical, there are two general criteria. First, there must be enough medium in the container to contact all the container-closure seal surfaces when the container is inverted and swirled. Second, there must be enough medium in the container to allow for the detection of microbial growth.

The volume of headspace should be considered in the growth promoting capability of the media to support aerobic microorganisms (See **Section 7.16**).

Selected Topics from TR 22

7.10 Duration and Number of Units Filled

The duration and number of units filled for an aseptic process simulation should be sufficient to adequately challenge the aseptic process, the operators that perform interventions, and the capability of the processing environment to provide appropriate conditions for the manufacture of a sterile product. Inherent interventions that occur during processing, such as loading of components, environmental monitoring and equipment set-up, are an integral part of each aseptic process simulation. The frequency of inherent interventions during the APS is generally consistent with the frequency during routine production (See **Section 7.9** for discussion on risk). The duration of the APS should be long enough to capture the potential microbiological impact of performing those interventions. Corrective interventions should be performed at a frequency defined in the aseptic process simulation model. If the production process is run on a campaign basis, the aseptic process simulation should be conducted in a consistent manner (See **Section 7.11**).

The APS should also be of sufficient duration to include a representative number of interventions which might occur during an actual production filling operation. Where they are part of normal operations, gown changes, breaks and shift changes should be simulated. Justification of the selected number of units filled, duration and yield should be included in the process simulation study design.

The following are general approaches to define aseptic process simulation fill duration and number of units. Uniquely small or large batch sizes may require modification from the approaches listed below. Each company must determine appropriate rationale and approaches applicable to their unique operations.

Selected Topics from TR 22

7.9 Interventions

As a general rule during routine aseptic processing, interventions (inherent and corrective) should be minimized. Interventions that would represent an unreasonable risk of contamination should not be included in either process simulation or routine production. The choice of interventions to be considered for an APS can benefit from the use of formal risk assessment and quality risk management principles. Anticipated interventions should be assessed to determine the amount of micro- biological risk their performance poses to the product or process. Where an intervention, even if rarely performed, poses a higher risk to the product or process due to its complexity and infrequent execution, the company may consider including the intervention at a higher than normal frequency in the APS.

Intervention assessments should include the activities which occur during an aseptic filling process that could affect the sterility of the product (e.g., inherent interventions, such as weight adjustments and container/closure re-supply) as well as any permitted corrective interventions (e.g., correct for equipment and container breakage, closure jams, misalignment or part replacement). (See **Section 8.0** for expanded detail.)

Selected Topics from TR 22

8.2.1 Inherent Interventions

Inherent interventions are normal and planned activities that occur during an aseptic filling process (e.g., equipment set-up, weight adjustments, closure re-supply, container re-supply, EM sampling, etc.). Inherent interventions are not corrections to events that occur on the filling line. Rather they are a planned and documented part of the overall process and are performed during the APS at a defined frequency or point of the filling operation. While these activities may not be specifically documented within the routine production batch record; they should be recorded as interventions during an aseptic process simulation.

8.2.2 Corrective Interventions

Corrective interventions are performed to correct or adjust an aseptic process during its execution. While not part of the planned aseptic process, they are well understood operations and are recognized to sometimes occur during processing. Corrective interventions include: container break- age, tip-over of a container, stopper jam, change in filling needle, change in filling equipment, dose adjustments/samples, clearing automatically rejected units, etc. Since corrective interventions are unplanned, they should be clearly identified and documented in the associated records. The APS should include a defined and representative number of corrective interventions that can be expected to occur during an actual production filling operation. Inclusion of corrective interventions in successful process simulations can demonstrate acceptable aseptic technique and control.

A new corrective intervention (e.g., one not included in the firm's process simulation program) performed during a routine aseptic fill must be evaluated. The intervention may be determined acceptable if it is similar to a previously simulated intervention and was performed with proper aseptic tech-

Selected Topics from TR 22

8.3 Intervention Procedures

There should be an approved list of allowed interventions, both inherent and corrective, which may occur during production and in the APS. Procedures should be established that describe the methods for performance of these interventions. The procedures listing the types of inherent and corrective interventions and how to perform them should be updated, as necessary, to ensure consistency with actual manufacturing activities.

In the conduct of an intervention that requires removal of units from the process, the units to be removed must be designated by a specific number and/or location (e.g., all units from the turntable to the first fill head). This facilitates process execution where the line may not be fully populated and a fixed number of units relevant to the intervention can not be identified and removed.

Acceptance Criteria : Ptc 1

Topic A: Acceptance Criteria

Problem Statement

What are the acceptance criteria for aseptic process simulations?

Recommendation

The objective of the aseptic process simulation (APS) is to produce zero contaminated units, irrespective of run size. Therefore the target involving such simulations should be zero positive units.

Upon discovery of any positive units, an investigation including a comprehensive risk assessment should be performed to assess any potential root causes, implementation of Corrective and Preventative Actions (CAPAs), and respective documentation.

In addition to other qualification requirements, it may be advisable to include multiple process simulation runs to verify the robustness[1] of the implemented corrective actions with consideration of the following:

(a) Potential for multiple root causes

(b) Introduction of CAPAs may inherently introduce unintended consequences which are otherwise not sufficiently challenged; or may represent a departure from the original qualified state.

Investigations which determine a definitive and readily identifiable root cause might provide grounds for a reduced number of repeat run(s). However, CAPAs should be put in place to avoid such issues and deviations to studies and processes from reoccurring.

In all cases, the execution of additional run (s) without the undertaking of a comprehensive risk based investigation to identify and correct any potential root causes is not acceptable.

[1]Robustness in this case refers to the maintenance of sterility.

Rationale for Recommendation

Process simulation contamination rates resulting in zero positive units should be achievable in well designed and operated production lines.

Operator Qualification: Ptc 1

Topic B: Aseptic Personnel Qualification Program

Problem Statement

What is the process to qualify personnel to work in or access the aseptic processing area (Grade A/B area)?

Recommendation

There should be a formal aseptic personnel qualification program that is designed to minimize the risk of contamination from human activities, interventions, and inadequate aseptic techniques. The program should include prerequisites, qualification procedures, and disqualification procedures.

Personnel working in the cleanroom must be capable of adequately performing their job functions. Capability is achieved through work function training. Personnel must be qualified to perform those functions. The requirements for the qualification of cleanroom personnel should be written in a formal procedure and the results should be documented. These persons should have a thorough understanding of the process and the potential contamination risks.

The qualification prerequisites and training should include but are not limited to the following:

- Basic GMP training
- Impact of personal hygiene and health
- Basic microbiology education or background
- Proper aseptic techniques
- Appropriate cleanroom behavior
- Patient safety hazards posed by a contaminated product
- Gowning training and certification
- Specific cleanroom operation and function as well as relevant intervention procedures training

Operator Qualification: Ptc 1, ctd.

Initial Qualification:
In addition to the above requirements, they should demonstrate their proficiency in aseptic technique by:

- Successfully completing a qualification test involving manual media manipulation not associated with an Aseptic Process Simulation

or

- Successfully participating in an aseptic-process simulation run in which they perform the same function(s) to the same extent as they will perform the function(s) during actual production, as applicable

Operator Qualification: Ptc 1, ctd.

Periodic Qualification:
Operators and others qualified to work in the cleanroom should participate in a successful aseptic-process simulation run in which they perform the same function(s) to the same extent as they will perform the function(s) during actual production (as applicable) at least once per year.

It is recommended that individuals requiring access to the aseptic area be periodically (annually) requalified. This requalification process includes demonstrating knowledge of successful gowning and microbial monitoring limits.

EU Annex 1 Proposal- PDA response

4.4 The personnel working in a grade A/B cleanroom should be trained for aseptic gowning and aseptic practices. Compliance with aseptic gowning procedures should be assessed and confirmed and this should be periodically reassessed at least annually and should involve both visual and microbiological assessment (using additional locations such as arms and chest). Only trained personnel who have passed the gowning assessment and have participated in a successful aseptic process simulation (APS) test, during which they performed their normal duties, should be authorized to enter any grade A/B area, in which aseptic operations will be conducted, or are being conducted, whilst unsupervised. The microbial monitoring of personnel in the grade A/B area should be performed to assess their aseptic behaviour. This monitoring should take place immediately after completion of a critical intervention and upon each exit from the cleanroom. It should be noted that there should also be an ongoing continuous monitoring program for personnel including some consideration of periodic monitoring under the supervision of the quality unit.

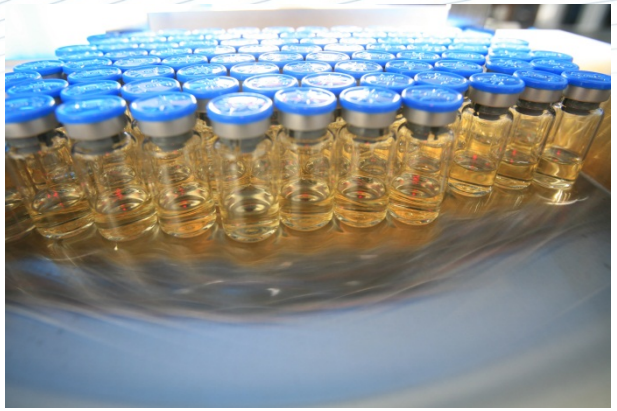
EU Annex 1 Proposal- PDA response

Comment: Section 4.4 requirement for personnel to participate in a successful aseptic process simulation as a prerequisite for unsupervised entry to the Grade A/B is unnecessary and in conflict with PDA published positions, in PDA Technical Report 22 (2011) and Aseptic Processing Points to Consider Part 1 (2015). Each person entering the aseptic processing area has the potential to introduce microbiological contamination; however, the risk to product may vary with the specific job function. Personnel within an aseptic processing area present the greatest potential of microbial contamination and as such require extensive training, monitoring and on-going training to reduce the likelihood of viable particulate shedding/contamination. The critical aspects of qualification involve the ability of personnel to understand and perform their job functions, and should assure that aseptic processing area personnel have the proper training and knowledge for their respective functions. Testing through Aseptic Process Simulation is not sensitive enough to fully qualify personnel to work in the Grade A/B area. Participation in media fills does not provide additional assurance of adherence to proper clean room behavior. And mere adherence to this requirement may result in clean room personnel allowed to work in the Grade A/B area without proper knowledge and demonstration of clean room behavior. Instead we recommend an emphasis on training and monitoring, as noted in the aforementioned Technical Report and Points to Consider. In addition, as currently written, the requirement would be burdensome and limiting for certain ATMP (Advanced Therapy Medicinal Product) aseptic processes.

EU Annex 1 Proposal- PDA response

	Proposed change: "4.4 Only trained, qualified personnel who have passed the gowning assessment and have demonstrated their proficiency in aseptic technique by either successfully performing a qualification test entailing manual media manipulation not associated with a full aseptic process simulation (APS), or have participated in a successful aseptic process simulation test, in both cases simulating or performing their normal duties, should be authorized to enter any grade A/B area, in which aseptic operations will be conducted, or are being conducted, whilst unsupervised."

Media Fills



- Initial Qualification
  - 3 Consecutive SUCCESSFUL media fills
    - Following Failure or Requalification
- 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

My Hot Topics about Media Fills / 2012

- Form 483 *„ ... **not all approved interventions** are simulated yearly in the Media Fills“ ....* even if not occured in the routine: these interventions must be performed.
- But: FDA Guidance 2004 states explictely : ONLY a „representative number of aseptic additions (e.g. charging of containers ..) or transfers“ is required
- 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.

- **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 (more critical) must be performed during each Media Fill, all Cat 2 (less critical) interventions must be simulated at least once a year.

•**Number of interventions**: The maximum number of Cat ½ interventions, which occured during the routine production within a time period before, must be performed during each Media Fill.

•**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.

•**Nonroutine (corrective) interventions, not validated in a Media Fill, how to react ?** Stoppage for Cat 1, for Cat 2 requires a deviation notice and a risk assessment ... ?

„My“ Hot Topics about Media Fills

- **NOTE :** Media Fill requires full duration QA oversight (physically or a later review of videos also possible) !

- **<u>Practices / Examples that cannot be validated in a Media Fill</u>**
  - Power failures during filling
  - Disruption of undirectional airflow 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

My Hot Topics about Media Fills

- Important to have a **Risk Assessment / Rationale/ Justification** in advance to each Media Fill run
  - Justification about the format used in the upcoming Media Fill
  - Number and kind of interventions
  - Number of involved personnel
  - 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
  - …

Class- room Discussion / Benchmarking

- How to you perform „Operator Qualifiacation“ ?
- Holding Time of vessels/ closed equipment validated ?
- Anaerobic Media Fills
- ...

Bulk Media Fill – my background and experience ...

PDA TR 28

Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals

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

PDA SM
Parenteral Drug Association

PDA TR 28- „Placebo“

4.2. Placebo Material Simulation

A placebo material is substituted for the production materials and handled in a representative manner. The placebo material can be sampled for microbial count or sterility testing depending upon the acceptance criteria requirements of the protocol.

Media Fill: Bulk Pharmaceuticals

„My“ Hot Topics about Media Fills

- **Sterile Bulk Pharmaceutical Manufacturing**
  - Bulk Pharmaceuticals Media Fills must be a very different approach, because :
  - campaign production may last over weeks in huge plants (vessels cannot be flooded with TSB over weeks)
  - Media Fill after a campaign with product residues left: e.g. antibiotics inhibit microbial growth and must be inactivated, or may not be dissolved in nutrient
  - bigger Bulk primary packaging materials (bags/ containers)/ huge vessels/ pipings / huge filling isolators: Bulk Aseptic Filling cannot be simulated 1:1 like a vial or syringe filling operation
  - **Microbiological Growth Promotion Testing problems :** Media Fills in huge vessels or containers may lead to problems in microbial growth recovery (probably also based on „sensum quorum“ effects)

  - How do validate a Sterile Bulk Pharmaceutical Manufacturing plant ?
    - **„IS A MUST“**: compliant/ valid Media Fills are a regulatory requirement to assure the Sterility of the Sterile API plant !
  - **Approach**
    - **Part 1** Aseptic Processing/ Filling Validation (= „Solid Media Fill“)
    - **Part 2** : Interior Production Line / Vessels Sterility (= „Liquid Media Fill“)

Sterile API Media Fills

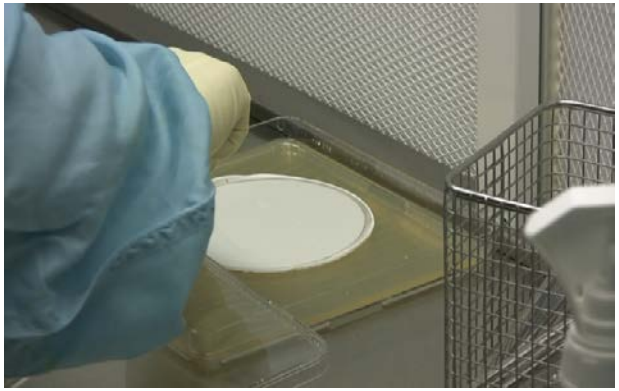
- Simulation of Aseptic Processing Steps: **„Solid Media Fill“**

  - Different approaches are possible , e.g. flask fill approach with funnel (see slide before)
  - Can be a) after a campaign or b) with a clean/ sterile production line
  - For Powder filling: as Placebo might be „sterile Mannitol/ Lactose ; osmotic effects may be critical !
  - Several worst case „manipulations“ are required
  - Important: primary packaging material must be included
  - Maximum storage of equipment/ primary packing included
  - Enhanced Environmental Monitoring / Sterility testing as usual
  - Requirement: all Media Fill units must be „Sterile“
  - **Bacteriostatis/ Fungistasis** Studies required, and not only after incubation (inhibition of bacteriostatic product may be critical)

Sterile API Media Fills

Simulation of Production Processing Steps: **„Liquid Media Fill“**

- Rinse with xxL sterile buffer solution or **WFI** (but not flood with TSB)
- Is easy (regarding cleaning)
- **Choices** a) after a campaign or b) after SIP in clean/ sterile production line
- Important: the interior surface must come in contact with the rinse fluid
- Worst Case: maximum production time of production line
- Rinse solution is membrane filterered and tested with the requirement: „Sterile“ or „0 cfu“ (depends if filter cartridge or membrane filter is used)
- Important are **„Microbiological Survival studies“**



3 TAKE HOME Messages