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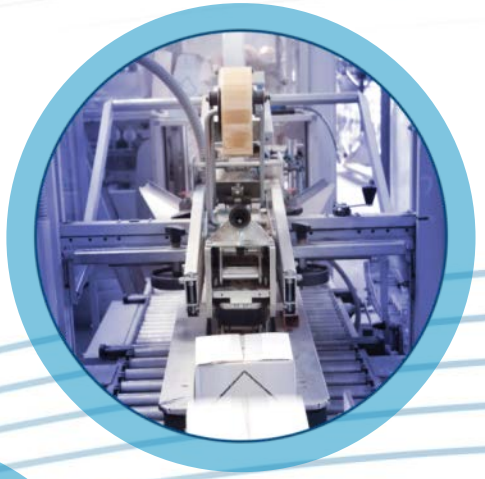
Best Practices in Aseptic Processing Simulations



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On line

19 Oct 2021

Overview about Presentation

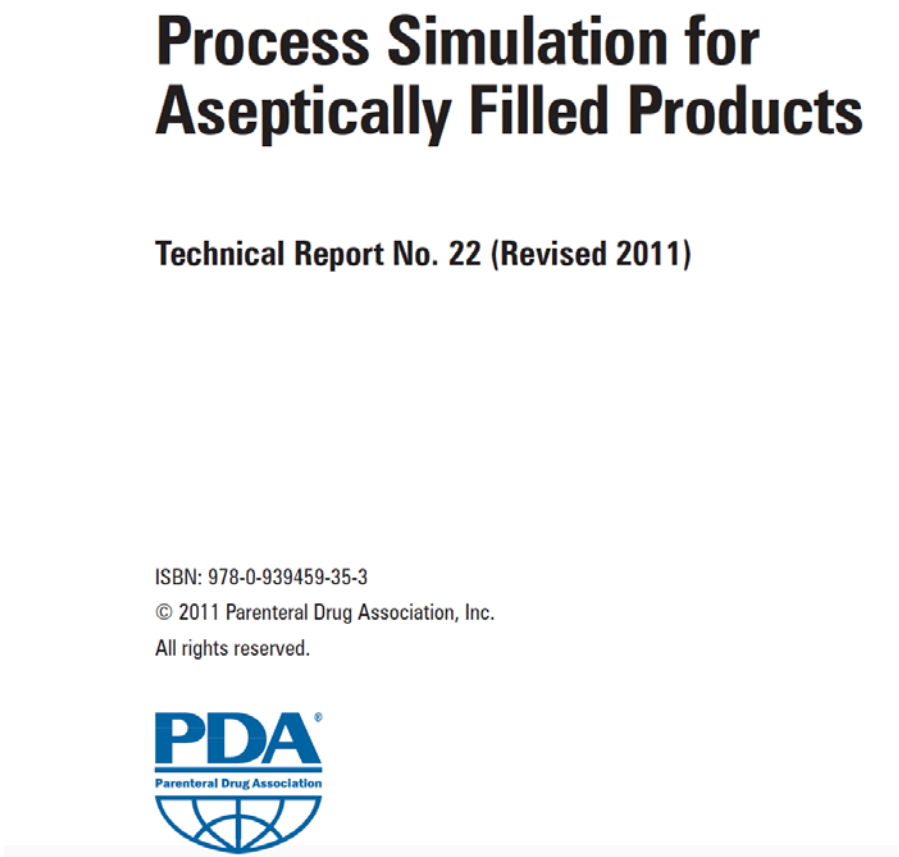
- Definitions
- Design of a Media Fill and worst case conditions
- My “Hot Topics”: Definitions of Worst Case Criteria & Interventions
- Operator Qualification & Media Fill
- EU Annex 1 Rev 2020
- Back-Up: References from PDA TR 22

What is a Media Fill ?

What is the purpose ?

What are the limitations ?

PDA TR 22 (Revision TF will start Q3 / 2019)



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 : ….)

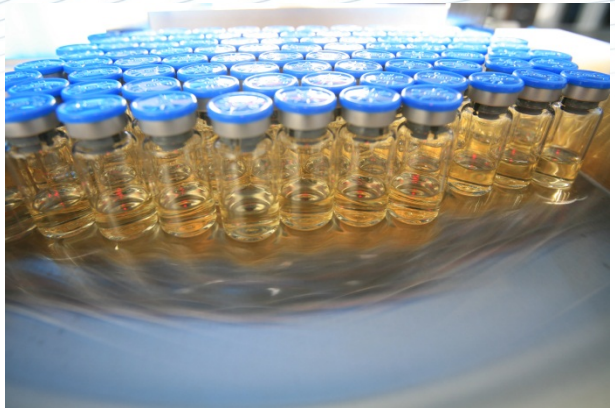
Design III : Identification of worst case conditions

- 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

- Important is to have a **Risk Assessment / Rationale/ Justification** in advance to each Media Fill run
  - Assesment/ 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)

„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 many companies: incubate „intervention vials“

Operator Qualification

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PDA TR 28

Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals

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

2021 was an industry survey .

TR under Revision

EU Annex 1 (2020 Draft) / Some sections selected :

9.36 The process simulation testing should take into account various aseptic manipulations and interventions known to occur during normal production as well as worst case situations, including:

i. Inherent interventions representative of the routine process at the maximum accepted frequency per number of filled units (e.g. loading of vials into a lyophilizer).

ii. Corrective interventions, that occur frequently during routine production, in a representative number and with the highest degree of acceptable intrusion (e.g. correcting jammed stoppers).

EU Annex 1 (2020 Draft) / Some sections selected :

9.38 In developing the process simulation test plan, consideration should be given to the following:

i. Identification of worst case conditions covering the relevant variables, such as container size and line speed, and their impact on the process. The outcome of the assessment should justify the variables selected.

ii. Determining the representative sizes of container/closure combinations to be used for validation. Bracketing or matrix approach may be considered for validation of the same container/closure configuration for different products where process equivalence is scientifically justified.

iii. 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. The volume used should provide sufficient headspace to support potential microbial growth and ensure that turbidity can be detected during inspection.

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

v. The method of detection of microbial contamination should be scientifically justified to ensure that any contamination is detectable.

vi. The selected nutrient media should be capable of growing a designated group of reference microorganisms as described by the relevant pharmacopeia and suitably representative local isolates and supporting recovery of low numbers of these microorganisms.

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

EU Annex 1 (2020 Draft) / Some sections selected :

occasional anaerobic simulations as part of the overall validation strategy should be considered (refer to paragraph 9.35 point iii).

viii. The process simulation should be of sufficient duration to challenge the process, the operators that perform interventions, shift changes and the capability of the processing environment to provide appropriate conditions for the manufacture of a sterile product.

ix. Where the manufacturer operates different shifts then the APS should be designed to capture specific factors (e.g. for those manufacturing during a night or extended shift, fatigue should be considered).

x. Simulating normal aseptic manufacturing interruptions where the process is idle (e.g. shift changeovers, recharging dispensing vessels, introduction of additional equipment, etc.).

xi. Ensuring that environmental monitoring is conducted as required for routine production, and throughout the entire duration of the process simulation.

xii. Where campaign manufacturing occurs, such as in the use of Barrier Technologies or manufacture of sterile active substances, consideration should be given to designing and performing the process simulation so that it simulates the risks associated with both the beginning and the end of the campaign and demonstrating that the campaign duration does not pose any risk. The performance of "end of production or campaign APS" may be used as additional assurance or investigative purposes; however, their use should be justified in the CCS and should not replace routine APS. If used, it should be demonstrated that any residual product does not negatively impact the recovery of any potential microbial contamination.

EU Annex 1 (2020 Draft) / Some sections selected :

9.40 Process simulation tests should be performed as part of the initial validation, with at least three consecutive satisfactory simulation tests that cover all working shifts that the aseptic process may occur in, and after any significant modification to operational practices, facilities, services or equipment (e.g. modification to the HVAC system, equipment, major facility shut down, changes to process, number of shifts and numbers of personnel etc.). Normally, process simulation tests (periodic revalidation) should be repeated twice a year (approximately every six months) for each aseptic process, each filling line and each shift. Each operator should participate in at least one successful APS annually. Consideration should be given to performing an APS after the last batch prior to shut down, before long periods of inactivity or before decommissioning or relocation of a line.

Operator Qualification …. Media Fill

Slides for audience as back-up and references

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.

END