



# ASEPTIC PROCESS SIMULATION (MEDIA FILL)

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# ASEPTIC PROCESS SIMULATION (MEDIA FILL)

## AGENDA

1. **DESCRIPTION AND PURPOSE OF APS**
2. **CONCEPTS, PRINCIPLES AND REGULATORY EXPECTATIONS**
3. **RISK ASSESSMENT AND WORST CASE SCENARIOS**
4. **STUDY DESIGN**
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6. **POINTS TO CONSIDER – INTERVENTIONS.**
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# ASEPTIC PROCESS SIMULATION (MEDIA FILL)

## WHAT IS ASEPTIC PROCESS SIMULATION (APS)?

- ▶ It is a tool to evaluate the capability of aseptic processing activities, using microbiological growth promoting media in place of product. APS simulates the aseptic process from the product and component sterilization to final sealing of the container. The media is made to contact all product contact surfaces of the equipment chain, container closure, critical environment and process manipulations which the product itself will undergo.
- ▶ Media is then incubated and inspected for microbial growth. This information is used to assess the potential for product units to become contaminated during the aseptic processing operations.



# ASEPTIC PROCESS SIMULATION

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## PURPOSE OF MEDIA FILLS-

To assess the capability of the aseptic process to produce sterile products reproducibly. Assess the contamination risk factors of the process and hence the state of control.

Assess vulnerability to microbial contamination.

Demonstrate that the aseptic operating practices and procedures are appropriate.

Evaluate the aseptic processing personnel practices.

Qualify/requalify/disqualify personnel.

Compliance with Good Manufacturing Practices and regulatory expectations.



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## CONCEPTS, PRINCIPLES AND REGULATORY EXPECTATIONS

### NUMBER AND FREQUENCY OF APS

The number and type of APS should be based on Risk Assessment of the aseptic process.

- a. Qualification/validation of a new facility or new production process. APS is performed after facility, process, equipment, facility decontamination, personnel training, room qualification and EM program implementation is complete. APS is one of the last steps in the validation process. Typically a minimum of three (3) APS are a regulatory expectation.
- b. Semi-annual APS are a regulatory expectation for a qualified line/ process.
- c. Any major changes to facility or aseptic process – perform Risk Assessment to determine if APS is needed and how many.



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## RISK ASSESSMENT AND WORST CASE SCENARIOS

Definition of Risk – combination of a hazard and its likelihood of occurring and harming the patient. In aseptic processing this is loss of sterility assurance.

- ▶ Risk assessment can be used to determine the worst case manufacturing scenarios, holistic approach –
  - operating conditions-including personnel
  - interventions
  - container closure – size and configuration
  - line speed
  - batch size

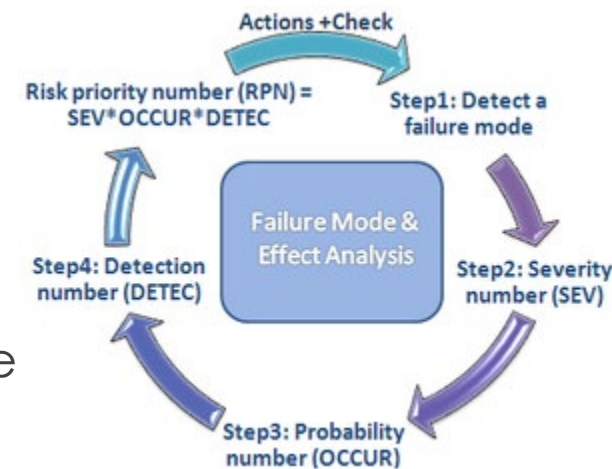
The Risk Assessment should be documented and used as the basis for the design of the APS study.

	Frequent	Likely	Occasional	Seldom	Unlikely
Catastrophic	EH				
Critical		Hi			
Marginal			Mod		
Negligible					Low

EH = Extremely High

Likely or Frequent Catastrophic Event

Frequent Critical Event



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## STUDY DESIGN

Ensure that the APS study/program incorporates risk factors and assesses the state of process control. APS should simulate manufacturing operations including “worst case” activities and conditions as identified during risk assessment. Some factors to be simulated/evaluated during APS are

### Aseptic Compounding

- ▶ The entire aseptic compounding process should be simulated including all aseptic additions. APS can be stand alone for the compounding step or integrated with filling.
- ▶ Filling
- ▶ Longest duration of run on an aseptic processing line.
- ▶ Interventions – inherent (routine) and corrective (non-routine)
- ▶ Aseptic assembly-line set up

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- ▶ **Number of personnel – duration and activities, shift changes, breaks**
- ▶ **Number of aseptic additions/transfers**
- ▶ **Connections/disconnections**
- ▶ **Processes such as Lyophilization**
- ▶ **Line speed and configuration**
- ▶ **Container closure types/systems**
- ▶ **Inert gassing**
- ▶ **Number of units filled**
- ▶ **Frequency and number of runs**



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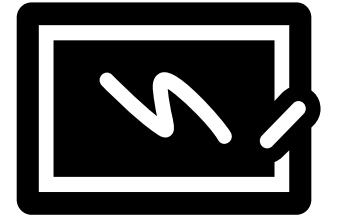
## DOCUMENTATION

Documentation of every step of the APS is very important. The documentation will serve as record of the rationale for APS design and its performance.

Documentation should include step by step instructions of the performance of the APS, acceptance criteria, all results obtained, any deviation.

An aseptic simulation policy/procedure should be prepared which gives an overall comprehensive list of requirements and rationale for APS studies.

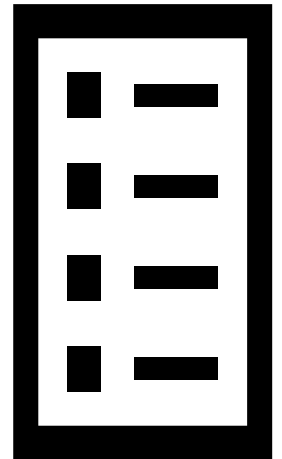
The following documentation procedure is recommended.



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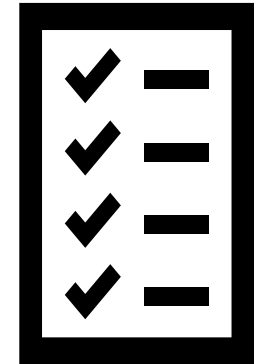
## PROTOCOL

- ▶ An approved APS protocol should be in place prior to starting the study. Information/instructions in the protocol should include at a minimum
- ▶ Responsible groups for execution, testing
- ▶ Rationale for “worst case” scenarios
- ▶ Identification of room, filling line, equipment, process flow.
- ▶ Types of container closure to be used
- ▶ Fill volume
- ▶ Minimum number of units to be filled and rationale
- ▶ Line speed(s)
- ▶ Type of media to be used with rationale



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- ▶ **Number and types of interventions**
- ▶ **Number, identity and roles of personnel**
- ▶ **Environmental monitoring to be performed**
- ▶ **Accountability of units filled**
- ▶ **Incubation conditions and durations**
- ▶ **Inspection of units – pre-incubation, post incubation and intermediate**
- ▶ **Acceptance criteria**
- ▶ **Conditions of exclusion of vials from incubation (this should be rare)**
- ▶ **Growth promotion**
- ▶ **Conditions for invalidating/cancelling – decision making authority**



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- ▶ **Personnel training requirements**
- ▶ **Details about batch record to be used**
- ▶ **Documentation requirements for the final report**

## **Batch Record**

A detailed batch record (BR) written in the same format as the production BR with the same data recording and verification/sign off requirements should be in place.

An additional section detailing the step by step performance of the Interventions should be a part of this BR. All interventions performed (planned and unplanned) with details such as time, operators involved, duration, the identity of the tray filled, any line stoppages, sample units removed, should be clearly documented.

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All results should be a part of the batch record including –

- ▶ Environmental and personnel Monitoring results
- ▶ Number of units filled, number of units incubated, full accountability
- ▶ Number of units rejected pre-incubation with cause for rejection
- ▶ Results of inspection – number of units positive for growth, tray identity, detailed investigation with root cause and corrective/preventive actions
- ▶ Growth Promotion of media after incubation
- ▶ Record of activities and occurrences during the APS
- ▶ Any deviations/OOS
- ▶ A Final Report which evaluates the entire media fill and formulates a conclusion on the acceptability of the APS is required.
- ▶ Quality unit oversight of the entire process including observation in real time



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## POINTS TO CONSIDER FOR APS

1. **Number of APS – for new line/process a minimum of three (3) APS are required. For ongoing requalification – minimum semi-annual. If different processes are performed on the same line, each process has to be re-evaluated semi-annually.**
2. **Container closure – if multiple sizes of containers of the same type and in same process are used, a bracketing approach (smallest-largest) may be used.**
3. **Filling speed-generally should be set at production filling range. However if higher or lower speeds present “worst case” conditions those maybe used. Eg. Bracketing approach of highest speed with smallest unit (operational challenge-PM generation) or slowest speed with largest vial (larger neck size – maximum exposure) may be used.**

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4. **Fill volume-** container need not be filled to full capacity. Amount of media should be sufficient to contact all container –closure surfaces when inverted and allow for detection of microbial growth.
5. **Media used** – most common medium used is Soybean Casein Digest Medium (SCDM). This medium is capable of supporting the growth of aerobic microorganisms commonly found in the clean room environment and personnel samples. If the process being validated is anaerobic then Fluid Thioglycollate Medium (FTM) may be used.
6. **Inert gassing** – Typically Nitrogen or other inert gases are used to protect oxygen-sensitive products and also to provide positive pressure for transfer. For APS the Nitrogen should be replaced by air using the same method of delivery and at the same steps.

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**Duration and number of units filled** – the **duration** should simulate the longest fill or be representative of routine operations. The duration should be sufficient to allow all interventions and process steps to be executed. **Number of units** filled during APS should be based on contamination risk and sufficient to simulate the process. Generally 5,000-10,000 units are considered acceptable for average production runs.

- For production batches less than 5,000 units, the APS batch should be equal to the production batch size.
- For production batches 5,000 to 10,000 units, the APS batch should be comparable size (5,000-10,000 units).
- For production batches >10,000 units, the APS batch should be > 10,000 units with several approaches to the batch size and filling process.

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## **Interventions-**

**Activities performed by personnel in proximity to the aseptic fill zone are called Interventions. Some of these are unavoidable and part of the process. However, Interventions in aseptic processes should be kept to a minimum. The Risk Assessment performed should be used to record and evaluate the contamination risk posed to the product due to each intervention.**

- **Identification of Interventions-** the type and frequency of each intervention must be identified. Hence a list of interventions with the frequency of occurrence is to be maintained and re-evaluated.
- **The interventions are grouped into two categories – inherent (routine) and corrective (non-routine).**

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## **Inherent (routine) Interventions-**

- **These are normal planned activities that occur during an aseptic filling process. Some examples are**
- **Equipment set up – aseptic assembly**
- **Fill weight checks and adjustments**
- **Recharging stoppers and other closures**
- **Environmental Monitoring sampling**
- **Shift changes, breaks, duration of personnel activity**



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## **Corrective (non-routine) interventions**

**These are performed to correct an aseptic process during execution. They are not a part of the normal aseptic process but they are well defined and recognized as occurring on infrequent occasions. Some examples-**

- **Container breakage and picking up fallen units**
- **Correcting stopper jams**
- **Changing out filling needles or equipment**
- **Pulling samples**
- **Clearing rejected units**
- **Maintenance work – line stoppage**
- **Changing out of filters, tubing, pumps**

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## **List and process for Interventions-**

**There should be an approved list of interventions. This list is to be re-evaluated at pre-determined intervals or if any unusual events occur during production runs.**

**There should be established procedures that describe how to perform these interventions.**

**Only personnel trained/qualified in the interventions should be permitted to perform them.**

**During an APS these interventions should be incorporated to represent the type and frequency of each type on the approved list.**

**During routine production operations, any interventions performed should be documented and frequency noted. If any unusual interventions are performed they should be evaluated and a Risk Assessment performed as necessary. Based on the risk/evaluation they should be incorporated into the approved list of interventions for APS.**

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## PROCESS QUALIFICATION

Lyophilized Products – most are aseptically filled and then transferred to a pre-sterilized lyophilization chamber and subject to lyophilization.

The process of loading the partially stoppered units into the lyophilizer, lyophilization process and the final unloading of the chamber must be captured during an APS. This can be done as follows-

- Load /unload with shortened hold time and partial vacuum.
- Simulated lyophilization- where the units are held under partial vacuum for the full duration of the cycle.
- In both cases sterile air is used to vent the chamber instead of Nitrogen.
- APS is used to qualify and requalify the aseptic steps of the lyophilization process.

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## PERSONNEL QUALIFICATION

The requirements and the process for the qualification of personnel should be documented in a procedure and results documented and records maintained per each person.

Pre-requisite – all relevant training such as gowning qualification, clean room and aseptic behavior training, GMP training, procedure training,

Initial Qualification- Personnel should participate in a successful APS in which they perform activities which they would normally perform.

Periodic Qualification- Personnel should participate in a successful APS in which they perform activities which they would normally perform once per year at a minimum.

Disqualification can occur if the personnel fail to participate in periodic qualification, fail gown certification repeatedly, participate in a failed APS whose failure was directly attributed to their poor aseptic technique.

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## **Pre-incubation inspection**

**After the completion of the filling and sealing process, the exact unit count is recorded and verified.**

**The units are subject to pre-incubation inspection. The purpose is to remove all non-integral units which would have been removed during normal product inspection. Once again count of units proceeding for incubation is documented and verified.**

**Some examples of units which maybe removed are units with cracks, misaligned or missing stoppers, poor crimps- units with compromised container closures. These would also be removed during routine inspection of product.**

**No unit maybe removed due to cosmetic defects.**

**The number of units removed and the cause should be documented and verified.**



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## **Incubation conditions**

**Incubation conditions should be suitable for the recovery of bioburden and environmental isolates. It should be in the range of 20-35° C.**

**Incubation time should be not less than 14 days.**

**A single incubation temperature for 14 days or two temperatures for 7 days each may be used. If two incubation temperatures are used it is recommended to start incubation at the lower temperature.**

**Prior to start of incubation all units should be inverted or manipulated so that the media comes into contact with all internal surfaces.**

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## **Post –incubation inspection**

**After completion of incubation, all APS units are inspected visually for the presence of microbial growth.**

**Personnel trained to detect low/high levels and different types of microbial growth should perform the inspection.**

**The count of units is performed and verified after inspection.**

**If non-integral units are found an investigation should be performed as these should have been detected during pre-incubation inspection.**

**All these activities should have the oversight of the Quality unit.**

**Growth Promotion should be performed after final inspection. In addition to ATCC cultures the most common environmental isolates should be used.**

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## Acceptance Criteria

The target acceptance criteria for APS study is zero contaminated units.

Per FDA Guidance for Aseptic Processing

When filling <5000 units – one contaminated unit is cause for revalidation

When filling 5000 to 10,000 units-

- one contaminated unit – investigation and possible repeat media fill
- two contaminated units- revalidation following investigation

When filling > 10,000 units-

- one contaminated unit – investigation
- two contaminated units- revalidation following investigation

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## Investigation of an APS positive/contamination

A thorough investigation should be performed and documented with root cause and corrective/preventive actions clearly identified. At a minimum, the investigation should include the following-

- Species level identification of the contaminant and comparison to EM/personnel isolates
- Holistic look at all systems and engineering controls
- Environmental trend and recovery review
- Personnel activities and qualification
- Sanitization process review
- Review of batch record, sterilization processes and any deviations
- Tracing the location of the contaminant and correlating to any interventions
- Trend review of previous APS

# ASEPTIC PROCESS SIMULATION (MEDIA FILL)

## REFERENCES

1. FDA Guidance for Industry- “Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practices.” September 2004.
2. PDA Technical Report No. 22 – “Process Simulation for Aseptically Filled Products.” 2011.
3. EU GMP Annex 1: Manufacture of Sterile Medicinal Products. 2009

(EudraLex The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use)