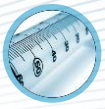
Connecting People, Science and Regulation®

Recommended Practices for Manual Aseptic Processes



PDA Technical Report

Technical Report Scope

Build upon & supplement, published guidance which is generally more focused on automated large-scale operations.

Out of Scope

Human intervention into an otherwise automated filling process. Examples include:

- Reach-ins to remove a toppled vial from the filling line or to obtain a container for quality testing
- Aseptic connection made during set-up
- Corrective activities during line stoppages

Blanket Statement

- When manual aseptic processing of sterile dosage forms is required, special consideration must be given to sterility and verification of processing accuracy:
  - Training of Personnel involved in Sterile Preparation Processes
  - Environmental Control and Monitoring Requirements
  - Specifications for Sterile and non-Sterile Ingredients and Components
  - Release Criteria for Sterility and Pyrogen Testing.

Note: *Refer to the following documents 2004 FDA Guidance on Aseptic Processing, EU GMP – Annex 1, Ph Eur 5.01.01 "Methods of Preparation of Sterile Products", and USP Chapters "Pharmaceutical Compounding – Sterile Preparations– Sterile Preparations" and "Radiopharmaceuticals for Positron Emission Tomography – Compounding"*

Definition: *Aseptic Processing*

Handling sterile materials in a controlled environment, in which the air supply, facility, materials, equipment and personnel are regulated to control microbial and particulate contamination to acceptable levels.

What makes MAP special? (1)

- Manual aseptic processing (MAP) operations differ from automated operations
- These differences pose unique operational and evaluation challenges
- These challenges must be considered thoroughly when designing the evaluation procedure or protocol for the MAP operation

What makes MAP special? (2)

MAP involves a human operator performing, at a minimum, the container and/or closure movements → MAP relies heavily on individual operators' basic understanding of microbiology proficiency

Personnel must be individually qualified

People - the Usual Suspects! (1)

The greatest sources of microbial contamination during MAP are operational personnel and their activities.

Image courtesy of Cleanroom Technology

People - the Usual Suspects! (2)

Human performance deviations or failures are linked to:

- Complex aseptic processing tasks
- The continuous span of time during which an operator carries out repetitive aseptic activities
- The expected rate of activity
- Change in personnel

Goal of Aseptic Processing Evaluation

Prevent the contamination of sterile materials during their processing

- Demonstrate that aseptic processing can be achieved and maintained successfully under the specified operational configuration, activities, and conditions
- Same goals for manual or automated aseptic operations and for small-scale or large scale operations

Common Equipment Used

Unidirectional Air Flow Hood (UAFH)

- A cabinet designed to protect materials from operator and environmental contamination

Isolator

- ISO 5 decontaminated systems that isolate their interior from the surrounding environment

UAFH

- Air supplied to the UAFH is High Efficiency Particulate Air (HEPA) filtered


Image courtesy of Hugh Fox

- Air flow flows from the UAFH (and the critical manufacturing areas) exiting to the surrounding environment

HEPA: High efficiency particulate air filter with minimum 0.3 *µm* particle retaining efficiency of 99.97 percent.

Isolators

Closed isolator

- Only allows air exchanges with the surrounding environment through microbially retentive filters

Open isolator

- May transfer air directly to the surrounding environment through openings ("mouseholes") that prevent microbial contamination

Image courtesy of Amercare, Ltd.

Supporting Clean Environment

- Clean environment outside the critical zone/ cabinet/UAFH is typically ISO 7
- Use of isolator may relax the requirements of surrounding environment
  - New manufacturing installations may employ ISO 8 background environment *(2004 FDA Aseptic Processing Guidance)*

ISO 7: Environmental operating conditions defined in ISO 14644-1, "Cleanrooms and associated controlled environments."
(Note: For total particulates, ISO 7 approximates Class 10,000 from the now obsolete Federal Standard 209.)

Other Points

- Personnel performing the manual processes are located in the surrounding clean area
- Appropriate gowning facilities are required *(consistent with the background environment requirements)*
- Execution of the MAP is usually supported by sterilization equipment and processes for materials
- Overall flow of MAP facility, personnel and equipment is consistent with large scale environments

Personnel Training & Qualification

People are the most critical operational variable in manual aseptic processing

Therefore personnel training and qualification becomes critical to success

Photo courtesy of www.uthsc.edu

Elements of Training Requirements

Knowledge Alone is Insufficient

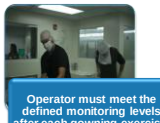
Operators must be able to:

- ✓ Apply classroom learning to real world
- ✓ Excel in aseptic gowning, assembly and technique
- ✓ Consistently perform without contamination

Gowning Qualification Practical Exercises

- Repetitive gowning in full aseptic garb
- Monitoring of gown surfaces
- Monitored gown surfaces: gloves, forearms, and chest area

Gowning Qualification



Operator must meet the defined monitoring levels after each gowning exercise.

Conduct periodic gowning certifications to confirm operators maintain consistent practices.

Access to aseptic core after initial gowning certification for continued aseptic processing instruction.

Note: Following a long term absence, adverse trend or out of limits in gowning results (and based on investigation) operators should be requalified for gowning.

Risk Management

MAP frequently involves greater risks than automated aseptic processes. → **A risk-based quality management system is necessary.**

"Quality risk management can be an effective method of identifying and reducing aseptic processing risk, thus improving the assurance of sterility, endotoxin control, and subsequent patient safety." (*PDA Technical Report 44)*

APS

- Requires operators to perform aseptic interventions during the simulation that are typically conducted during manufacturing
- Operators will assemble the sterilized equipment prior to the media fill

Importance of APS

- **MAP are more susceptible to human contamination than automated aseptic processing**
- **Interventions during MAP are frequent; may be complicated by suboptimal equipment design.**

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

Manual Aseptic Interventions

- Frequent and may be complicated
- Individuals must demonstrate proficiency in rigorous MAP requirements regardless of technology used
  - Various challenge tests where operator directly handles sterile equipment and materials
  - Representative of the actual process steps

Intervention: An aseptic manipulation or activity that occurs within the critical area. This technical report regards interventions as either corrective or inherent.

Interventions

INHERENT	CORRECTIVE
Required for set-up or routine operation and/or monitoring	An intervention that is performed to correct or adjust an aseptic process during its execution.
Inherent interventions are required by batch record, procedure, or work instruction for the proper conduct of the aseptic process	

Equipment, Components & Container/Closure

MAP is similar to automated lines, but on a smaller scale:

Sealed package is supplied to the APA after depyrogenation/ sterilization	Requires validated depyrogenation/ sterilization methods
	Prep methods prior to depyrogenation/ sterilization similar to automated AP, but smaller scale
	If sterilization/ depyrogenation processes cannot be used, validated sanitization process must be performed
	When sterile containers/closures are purchased from a commercial source, procedures should be in place and implemented to ensure the sterility of these items are maintained when introduced into an aseptic environment and used in production.

Process Time Limitations (1)

MAP time limitations more critical than for Automated AP

- Short/non-repetitive processes time may be of little relevance
- "Worst case" fatigue evaluation = APS ≥ duration of longest period of uninterrupted task performance
- APS at the end of a normal day's production can evaluate the effect of fatigue on the operator's aseptic technique

Repetitive tasks for long periods fatigue must be considered in both routine operation and the APS.

The operator's aseptic technique may deteriorate with the passage of time.

Process Time Limitations (2)

Additional time limits to validate

- Holding dirty/clean/sterile equipment
- Holding sterile/depyrogenated components
- Mix-to-sterilize times (filtration considering grow-through)
- Holding sterile bulk through usage

Note: Topics further discussed PDA TR 22.

Design of Manual Aseptic Processes

- Sterility assurance to mitigate contamination requires a holistic approach that encompasses the following:
  - Facility
  - Equipment
  - Process design
  - Aseptic practices/validation
  - Risk Assessment
- Manual Aseptic Processes should be designed to minimize the impact of personnel
  - Process design reduces contamination risk

Aseptic Filling: The part of aseptic processing where a pre-sterilized product is filled and/or packaged into sterile containers and closed

MAP Design Principles: Unidirectional Air Flow Hood (1)

- Adequate space to perform the work
- Exposed product and product-contact components remain in First Air
- Aseptic manipulations made in First Air
- Decontaminate or change gloves on a frequent basis

First Air (First Work Location): The work location first in the path of HEPA filtered air

MAP Design Principles: UAFH (2)

- Primary operator(s) performs the critical aseptic manipulations
  - Hands remain in the ISO 5 environment at all times
  - Gloves and sleeves are changed or gloves re-sanitized before reentry to ISO 5 environment
- Secondary operator(s) acts as the support person to minimize the potential of primary operator touching non-sterile surfaces
  - Put on sterile gloves/ sleeves prior to:
    - Any activity inside ISO 5 environment
    - Transfer of items to/from primary operator

Sterile: Absence of life; usually refers to absence of viable microorganisms.

MAP Design Principles: UAFH (3)

- Introduce sterilized items by aseptic removal of the final wrap
- Sterilize extra subassemblies and utensils to be available as needed
- Use sterile tools and utensils
  - Avoid direct contact with the operator's hands
  - Sterile supports for tools or hangers inside environment to minimizes contact between tools and surfaces
- Process designed to minimize contamination risk
  - Withdraw samples from a sterile container in a single step; then subdivide samples as required in another location
  - Use residual left in the original container post-production as the test sample

MAP Design Principles: UAFH (4)

- Pre-measure introduced materials into tightly sealed containers prior to sterilization and addition
- Electrical equipment and controls should be located outside the processing environment
- Equipment which exhausts air that could contaminate the environment needs special attention
- Use peristaltic pumps for liquid transfers outside the aseptic environment, not automatic pipettes
- Pre-mark containers to indicate the amount of material to transfer

MAP Design Principles: UAFH (5)

Preserve environmental integrity	Moving items in/out	Sanitization
• Perform as much of the process inside the ISO 5 environment as possible • Minimize removal and re-entry of sterile items • Small equipment may be included within the environment	• Items should be aseptically wrapped in pre-sterilized covering • Minimize exposure of critical surfaces to less clean surrounding environments. • Items into ISO 5 environment: overwrap is removed and discarded	• APA is sanitized when empty • Non-sterilizable items or equipment is sanitized as introduced or re-introduced • Do not introduce large items mid-process

MAP Design Principles: UAFH (6)

- ✓ ISO 5 Environment Strategies
  - ✓ Product contact surfaces shall be sterilized
  - ✓ Protective layers removed as materials are moved to cleaner environments
  - ✓ Sterilized items pre-assembled: avoid aseptic assembly
  - ✓ Perform steps not required to be aseptic outside the ISO 5 environment

Sterilization: Validated process used to render a product free of viable microorganisms.

Environmental Monitoring

- Similar to methods for other highly controlled (ISO 5/7) environments
- Same cautions on monitoring in other systems apply
- Sampling activities must not introduce contamination
- Smaller environmental systems require monitoring methods based on lack of impact

Environmental Monitoring Program: Defined documented program that describes the routine particulate and microbiological monitoring of processing and manufacturing areas.

Execution of Simulation

- An observer is recommended who properly documents process simulation activities
- Use a batch record specifically for simulation
- Automated filling or sterile bulk chemical methods and principles can be utilized with minor modifications