Save the Date PDA Metro Chapter Day Symposium
Tuesday, March 28, 2017 Auditing - 2017
Details soon at PDA.org, Chapters, Metro

Success with Manual Aseptic Processing

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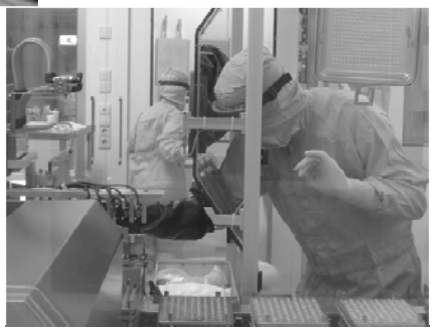
Commercial Aseptic Filling



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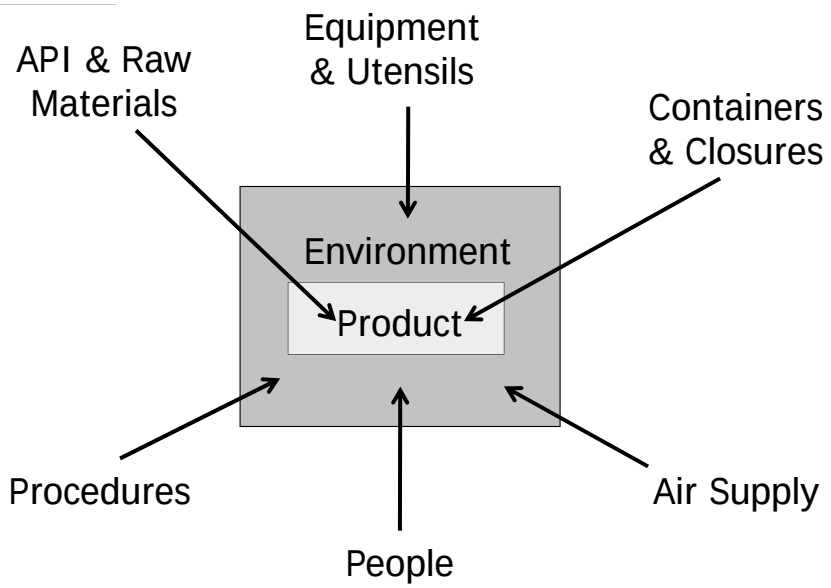
Sterility by Design

- Best practice in aseptic processing is the application of a 'Sterility By Design' concept where the design & controls needed for success are selected to minimize the contamination risk.
- This is more difficult with manual aseptic processing because the operator performs nearly all of the process and the ability to separate the operator from the sterile materials and surfaces is limited.

Influences on Aseptic Processing



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Aseptic Processing Definition

- "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."

- PDA, TR# 22, 2011 revision

Personnel & Contamination

- "It is useful to assume that the operator is always contaminated while operating in the aseptic area. If the procedures are viewed from this perspective, those practices which are exposing the product to contamination are more easily identified."

- Hank Avallone – 1988

Manual Aseptic Processing Differs

- Aseptic processing on a commercial scale evolved substantially over the last 100 years.
- The operator's adverse impact has largely been mitigated by technological advances primarily in the areas of automation (reducing the need for operator intervention) and separation (the operator is moved farther away from sterile items).
- However there are many aseptic processes where the operator plays a central role in the manipulation of sterile items.

Manual Aseptic Processes

- Some are performed only at IND or early stage only; while others are full commercial!
- It takes many forms. In some cases of these can be partially automated or closed.
  - Manufacturing (formulation)
    - Powders, ointments, combination products, assembly.
    - Cell therapy, wound treatment, some compounding .
  - Compositing (many units into one)
    - Common in vaccine / biological production, pharmacy
  - Aseptic filling / subdivision (one unit into many)
  - Sampling (partial removal of contents)
  - Transfer (change in container)

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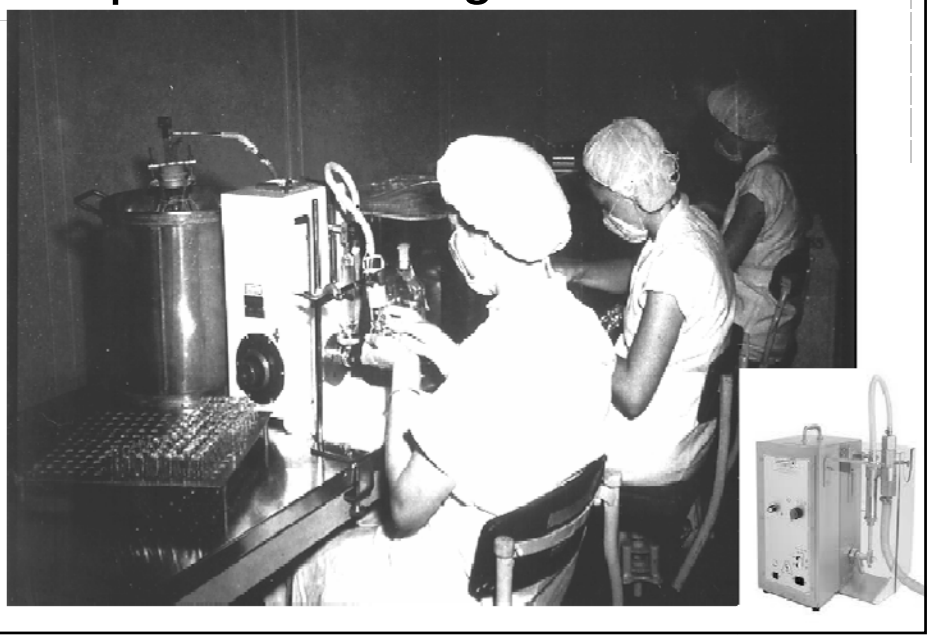
It's not machine based filling

- The intervention (inherent and corrective) based focus and approach that works for machine based aseptic filling of containers isn't a great fit.
- Manual aseptic processes require extensive human manipulation. The manual aseptic process is basically a lengthy inherent intervention from beginning to end.
- Process design becomes all important.

Aseptic Processing – circa 1930?



Manual Aseptic Processes

The Proper View of Interventions

- The ‘perfect’ intervention is the one that is eliminated from the process!
- In aseptic manufacturing where human intervention is required throughout the execution how can this be addressed?
- Concepts from aseptic filling work only to a limited extent. They are poorly suited to non-filling activities which require extensive operator activity.

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Aseptic Manufacturing

- A process for the preparation / handling of sterile materials where extensive operator interaction is required. On a small scale this can be performed in a LFH/BSC, but in some cases they will be executed in a larger laminar flow system. Depending upon the specifics of the process horizontal flow may be preferable.
- A BSC should only be used where worker safety is a meaningful concern.

Aseptic Process Design

- The process to use must be identified in detail from start to finish including all sampling, inspection and other activities.
- The goal should be to maintain the sterile materials in closed systems at all times minimizing exposure to personnel and the background environment.
- The ideal process takes place entirely in closed systems and there is no direct human intervention.

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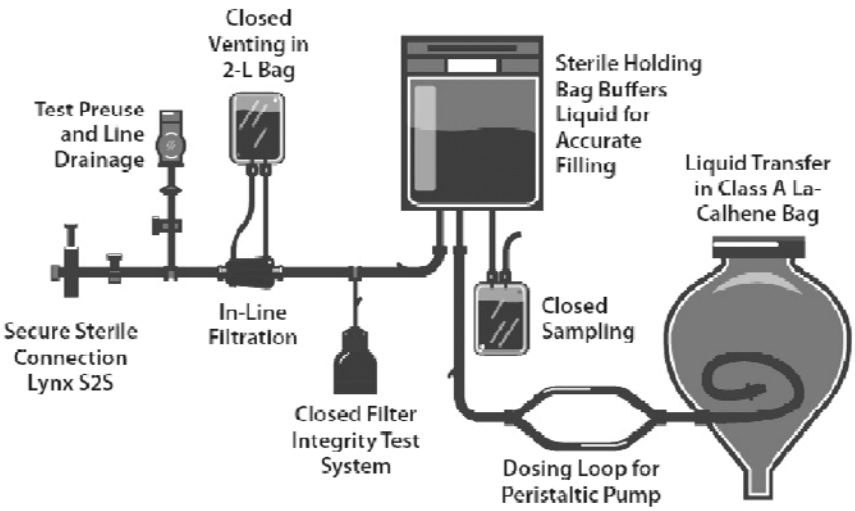
Closed Systems

- A "closed" system is specifically designed to prevent the ingress of micro-organisms. A "closed" system can be more easily and accurately defined by characteristics of its operation than by a description of its physical attributes.

A nearly 'closed' filling system



A "closed" system -1

1. Is constructed, installed and qualified in a manner which demonstrates integrity is maintained throughout the full range of operating conditions, and over a time period inclusive of the longest expected usage (i.e., manufacturing campaign). The qualification is done according to a formal protocol, following generally accepted engineering principles, and is documented.

- This includes the entire system over the course of the complete aseptic process. It should include media hold and/or manipulation as necessary to simulate the use of the system. Accomplished by initial qualification of the system and supported by appropriate process simulation of the batch (or campaign) use of it.

A "closed" system - 2

2. Is sterilized-in-place or sterilized while closed prior to use using a validated procedure.

- This should embrace the entire system extending to (and perhaps slightly beyond) the boundary's of the system that are potentially exposed to sterile materials (whether they are actually in physical contact with the materials is not a consideration).

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Sterility Test in BSC

A "closed" system – 3, 4 & 5:

3. Can be utilized for its intended purpose without compromising the integrity of the system.
4. Can be adapted for fluid transfers in and/or out while maintaining asepsis.
5. Is connectable to other closed systems while maintaining integrity of all closed systems (e.g., Rapid Transfer Port, steamed connection, etc.).

- As demonstrated by the process simulations performed encompassing the extremes of processing and all additions / removals of material from the system over the course of the batch (or campaign) duration.

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A "closed" system - 6:

6. Is safeguarded from any loss of integrity by scheduled preventive maintenance.

- A formal program for calibration and preventive maintenance is required. The system and support utilities must of course be subject to change control.

A "closed" system - 7:

7. Utilizes sterilizing filters that are integrity tested and traceable to each product lot for sterilization of process streams.

- Filter sterilization must be demonstrated. Integrity of filters after 'worst case' sterilization as a part of the initial validation is recommended.
- Filter integrity for process filters must be confirmed at the conclusion of the batch (or campaign).
- Vent filter integrity should be confirmed in accordance with the intended use period which may be more than one batch and extend to the full campaign duration.

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Closed Process Train / Machine

- A series of pressure vessels specifically configured for execution of the process internally.
- Commonly used for sterile bulk powders, liposomes and other materials.
- Installation need not be in an aseptic area.
- Sterilized-in-place using with steam or gas as one unit, or with overlapping segments.
- The last steps of the process train may transition into a closed isolator system.
- Usually only for large scale operations.

Closed Isolator System

- A closed system surrounding an otherwise open process.
- Equipment can be placed within for small scale process. For larger scale processes, only material access ports to/from the equipment would be inside the isolator.
- Generally quite flexible in design to accommodate a variety of simple processes.
- Performance excellent; turnaround and flexibility are trouble areas.

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Sterile Single Use Disposable

- The use of these is increasingly common in biotechnology and fill-finish operations.
- Adaptation to liquid handling is extremely simple especially when used in conjunction with the many sterile connector systems now available.
- Can be easily combined for use with closed process train or isolator designs.
- Materials compatibility and flexibility of operation are concerns.

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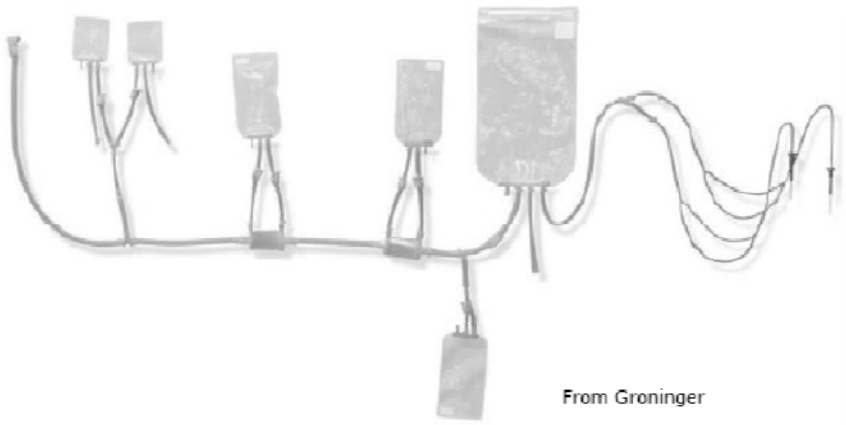
Single Use Filter/Fill Set



Working without a Closed System

- Review the process stepwise in detail looking closely at all activities where sterile materials are exposed to personnel.
- Consider the following questions:
  - Can the step be eliminated?
  - Can a closed system design be used instead?
  - Can the activity be simplified or streamlined to reduce the contamination risk.

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Manual Aseptic Process Design - 1

- Include microbiology & process experts in the review process.
- Begin with a preliminary process design including all sampling, monitoring and other activities.
- Determine whether all of the steps are required in order to streamline the process.
- If a step can be closed or eliminated, do so.
- Define the planned execution sequence, materials and equipment to be used for the remaining open steps in the process.

Manual Aseptic Process Design - 2

- Plan the order of entry for materials and their internal placement.
- Typically items are introduced in reverse of their order of use and positioned so that 'first air' principles are maintained.
- Always prepare and introduce spare items in case of handling mishap, or other problem.

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Preparing for the Aseptic Process




Manual Aseptic Process Design - 3

- The process begins with an empty decontaminated workspace.
- Organize the critical zone to eliminate excessive contact with materials.
- Develop a detailed execution sequence for each step minimizing the exposure risk.
- Moving materials from one side to the other during the process usually works well.

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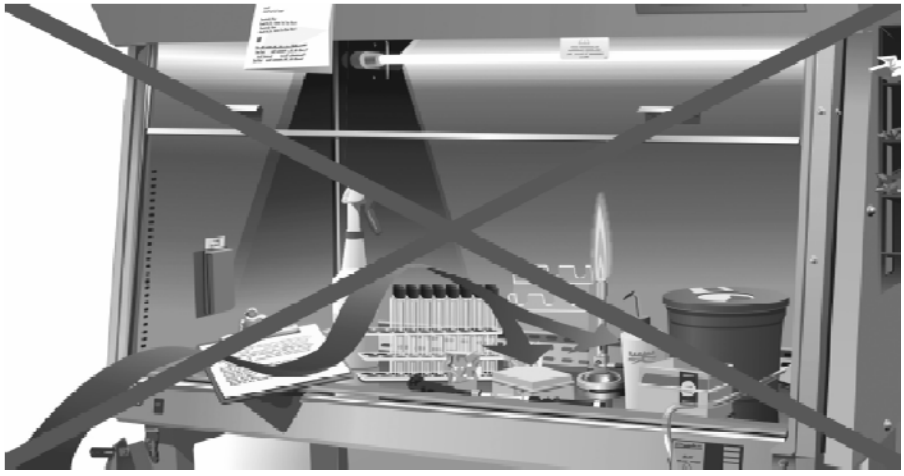
Manual Aseptic Process Design - 4

- Execute the process using water or other placebo materials with the equipment.
- Update the manufacturing instructions to provide a detailed process sequence.
- Refine the process as necessary to reduce exposure.
- Use video and still photographs to document process sequence and details.
- Train any additional staff in the process.
- Perform process simulation studies following PDA TR #28 or PDA #62.

Bad Design Practices



Manual Aseptic Processing Details

Use a Laminar Flow Hood!!

- Laminar flow units protect the product best.
- Biological Safety Cabinets (BSC) are designed to protect operators and the external environment from infected or dangerous materials inside the cabinet. Since air flows into the BSC from the surrounding environment, bio-safety cabinets should be used **only** when worker safety or environmental hazard due to the material being handled is a meaningful concern.

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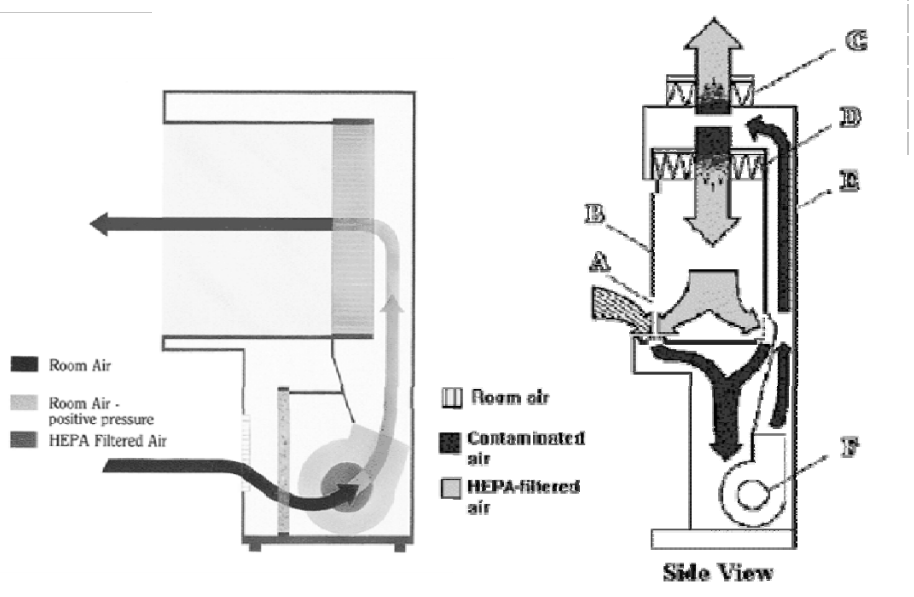
or Use a Biological Safety Cabinet

- Laminar Flow Cabinets (LFCs) are not suitable for the preparation of hazardous drugs. Biohazard safety cabinets (BSCs) should be used instead, with a vertical downward air flow exhausting vertically from the cabinet and not towards the operator.
- Preparation under negative pressure, protecting operator and environment from contamination should only be used for the preparation of hazardous pharmaceuticals (e.g. cytotoxic drugs, radiopharmaceuticals and radio labelled blood products), together with appropriate precautions against contamination of the medicinal product (e.g. appropriate background room air quality, positive pressure airlock systems).

PIC/S Guide to good practices for preparation of medicinal products in healthcare establishments- April 2008 http://www.picscheme.org/.

LFH vs. BSC



PDA TR#62 – Table of Contents

Design Principles for LFH/BSC - 1

- All exposed product and product-contacting components remain in First Air.
- Aseptic manipulations made in First Air.
- The operators should decontaminate or change their gloves on a frequent basis.
- The hands of the primary operator stay in the ISO 5 at all times. The secondary operator(s) dons new sterile gloves / sleeves prior to any activity inside the ISO 5 environment, or in transfers of items to/from the primary operator.

Design Principles for LFH/BSC - 2

- Anytime the primary operator leaves ISO 5, gloves should be changed or re-sanitized prior to reentry to ISO 5.
- Sterilized items should be introduced to the aseptic processing area by aseptic removal of the final wrap around the item as it is being introduced.
- Extra subassemblies and utensils should be sterilized and available for immediate use in the event a replacement is needed.

Define the Operator Attire




Design Principles for LFH/BSC - 3

- Sterile tools and utensils should be employed rather than the direct contact with the operator gloves. There should be sterile supports for tools inside the ISO 5 to minimize contact between the tool and surfaces of the workspace.
- Samples should be taken with minimal risk of contamination. It is preferable to take all desired samples from a container in a single step, and then subdivide that sample as required.

Design Principles for LFH/BSC - 4

- Alternatively, the residual in the original container post-production can be used as the test sample. The use of technologies such as sterile septum or connectors should be considered to minimize the risk of sampling.
- Wherever possible materials being introduced into the process should be pre-measured into a tightly sealed container prior to sterilization, transfer into ISO 5 and use in the process.

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Flu Virus Research

Design Principles for LFH/BSC - 5

- Electrical equipment and controls should be located outside the processing environment. If that is not possible a second operator (not the primary operator) should adjust equipment settings as necessary.
- Pay special attention to equipment which exhausts or disturbs air flow patterns that could contaminate the environment.

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Design Principles for LFH/BSC - 6

- Liquid transfers should use peristaltic pumps, rather than automatic pipettes. To minimize equipment movement and contamination, pre-mark containers to indicate the amount to transfer.
- Perform as much of the process inside the ISO 5 as possible in order to minimize the removal and re-entry of in-process materials in suitable containers. This may require the placement of small equipment within the environment.

BSC with RTP

Design Principles for LFH/BSC - 7

- When containers must be removed, and returned to ISO 5 they should be wrapped in a pre-sterilized covering which is removed prior to reentry. Alternatively, the exterior of the container(s) can be re-sanitized prior to reentry.
- Sanitize the ISO 5 operating area when empty, and sanitize non-sterilizable item/ equipment as introduced and transferred into the aseptic processing environments.

Design Principles for LFH/BSC - 8

- Avoid the introduction of large items into mid-process.
- After introduction of items, sterile gloves/sleeves should be changed.
- Product contact surfaces must be sterilized. Sterility is assured by protective layers which are removed as materials are transferred.
- Significant aseptic assembly in ISO 5 should be avoided through the use of sterilized pre-assembled items. This will reduce the extent of manual assembly required.

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Connections in LFH/BSC

Design Principles for LFH/BSC - 9

- Non-aseptic steps should be performed outside the ISO 5 environment by other operator(s).
- The operators should work as a team. The primary operator(s) should perform all tasks inside the ISO 5 environment. The secondary operator(s) assists in the introduction/ removal of items from the ISO 5 environment, and may assist the primary operator(s) with less critical tasks inside that environment.

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Design Principles for LFH/BSC - 10

- Additional support operator(s) may be necessary to support activities exclusively in the surrounding environment.
- The primary operator must wear sterile gloves and never contact a non-sanitized or non-sterilized item.
- The process design should be rehearsed several times and documented in air flow studies using all of the required items and placebo materials to refine the steps, location of items, etc.

Sterility Testing (Vertical Hood!)

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Design Principles for LFH/BSC - 11

- This ensures the process is practical and reduces contamination risk.
- The manufacturing process should be documented in sufficient detail to allow operators to understand and conform to the desired practices. The secondary or support operator(s) should complete the batch record.
- Environmental monitoring practices should be non-intrusive in order to avoid potential for contamination in the ISO 5 environment.

Design Principles for LFH/BSC - 12

- Air sampling during processing may be performed with specially designed equipment that does not compromise the environment and may include settling plates. Surface monitoring should be performed using contact plates or swabs after processing has been completed.

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Aseptic Technique

Pharmacy Compounding

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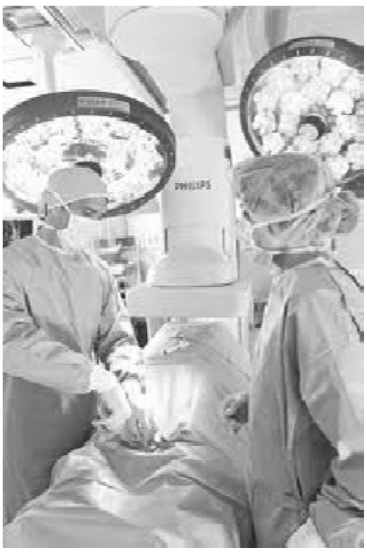
It starts with aseptic technique

- The human activities & practices that reduce the risk of infections by decreasing the likelihood that microorganisms will enter the product during processing.
- It includes concepts adapted from operating room & microbiology laboratory practices for use in a pharmaceutical setting.
- The microbiology laboratory methods are likely “best practices”, because they have been proven successful.

The ‘Sterile’ Field

- In surgical terms - the ‘*sterile’* field is an area created by placing sterile towels or surgical drapes around the procedure site and on the stand that will hold sterile instruments and other items needed during the procedure.
- It is roughly equivalent(?) to the critical zone / area in the aseptic process.



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Maintaining the 'sterile' field

- Place only sterile items within the 'sterile' field.
- Do not contaminate sterile items when opening, dispensing, or transferring them.
- Do not allow sterile personnel to reach across non-sterile areas or to touch non-sterile items.
- Recognize that a sterile or high-level disinfected barrier that has been penetrated (wet, cut, or torn) is considered contaminated.

Aseptic Technique Basics

- Follow 'first air' principle at all times.
- Remove or kill microorganisms from /on hands and objects.
- Employ sterile instruments and other items.
- Reduce risk of exposure to microorganisms at all times.

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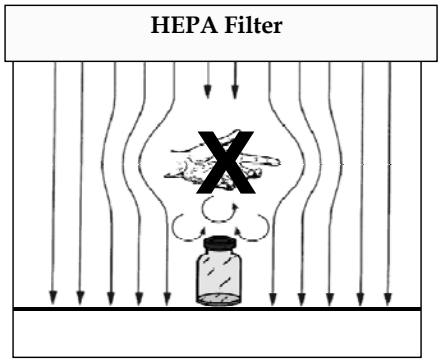
First Air

- Critical surfaces must see "**First Air**"
- Hands or other objects should not pass over an exposed sterile surface or item.



Principles - 1

- Only sterile objects and personnel(??) may be allowed within the 'sterile' field.
- Only sterile items are free of potentially harmful microorganisms.
- Once a sterile object comes in contact with a non-sterile object or person or with dust or other airborne particles, the object is no longer sterile.
- Do not touch your hood, mask or cleanroom clothing while in the aseptic area.

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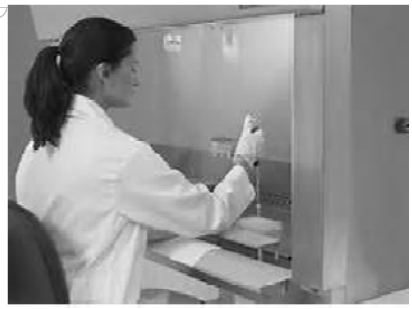
Aseptic Technique



Principles - 2

- If even one non-sterile object or person enters the 'sterile' field, the field is no longer sterile.
- When in doubt about whether something is sterile, consider it contaminated.
- A well thought out training program for aseptic technique should focus on safety and accuracy.
- Arrange objects in a manner to get full benefit of the unidirectional flow of air.

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Principles - 3

- A direct path must be maintained between the filter and the area inside the hood where the manipulations are being performed. Air downstream from non-sterile objects (such as solution containers, hands etc.) becomes contaminated from particles blown off these objects.
- The hands should never obstruct airflow.

Aseptic Transfer

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Principles - 4

- Always minimize clutter.
- Waste and other items should never enter the ‘sterile’ field nor the surrounding critical zone /area.
- All calculations should be done outside the critical zone and preferably by someone else entirely.

Principles - 5

- Outer pouches and wraps should be removed at the edge of the ‘sterile’ field as the sterile contents are pulled into it. Never bring these items into the ‘sterile’ field.
- Remember that hand cleanliness is further reduced each time more items are handled, so frequent glove disinfection is required.

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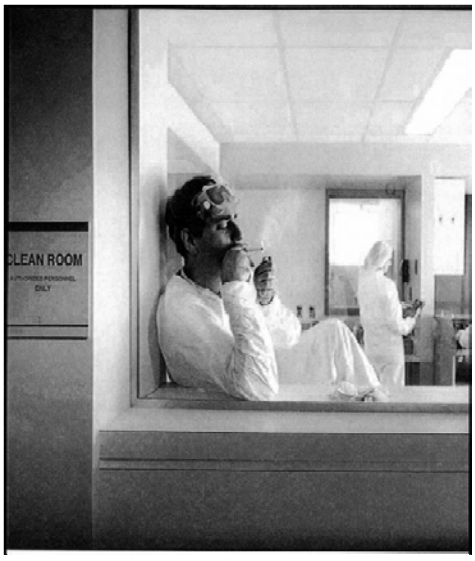
Principles - 6

- It is possible to disturb the airflow by a strong reverse current produced by coughing, quick movements, talking, etc.
- Keep all of these to a minimum in order to maintain an aseptic environment.
- Do not cough or sneeze into the 'sterile' field.
- Minimize conversation in the background environment.

Putting it into Perspective

- Make the process as easy as possible.
- Success of the operator's 'worst day', not their best.
- The outcome always depends upon the weakest link in the system.



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Aseptic Processing – circa 1905?

Some closing thoughts

- Manual aseptic processes are considered generally safe provided there's good aseptic technique and the design principles are followed.
- In the future, we should see increased use of closed systems (either single use or isolators), but LFH / BSC processes aren't going away anytime soon.
- Sound process design is important
- Good aseptic technique is always going to be critical to success.

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Many THANKS for YOUR Attention
Dziękuję Ďakujem dhanya-waad Дякую
bedankt תודה go raibh maith agat
tesekkürle Спасибо شكرًا Thank yu
Merci köszi díky tack så mycket
Thank you faleminderit
Shukriyâ Danke hvala kiitos
takk Obrigada Mulţumesc nandri
Grazie anugurihiitosumi
Ευχαριστώ dhanya-waad köszönöm
tack
Muchas gracias ačiû Terima Kasih
aitäh děkuji vam mange tak salamat