Defining the processes
Typical process steps for sterile products (1)

- Dispensing
- Compounding
- Sterile filtration
- Container preparation
- Stopper preparation
- Transfer of components and equipment into aseptic area
Typical process steps for sterile products (2)

- Filling and stoppering
- Transfer of partially stoppered and uncrimped vials within aseptic area
- Lyophilization (this step is not applicable for terminally sterilized products)
- Capping and crimping
- Terminal sterilization
- Inspection
- Packing
Aseptic process flow diagram (ISPE)
Terminally sterilised product process flow diagram (ISPE)
Dispensing or weighing
Non-sterile materials dispensing or weighing
Compounding or formulation
Compounding general considerations for an aseptic product

• A Grade C area is generally required.
• If, for product reasons, an aseptically processed product cannot be sterile filtered after compounding (suspension), then the charging of raw materials should be performed in a Grade A aseptic environment within a Grade B aseptic processing area.
• If highly potent materials are handled extra measures such as a closed charging systems or an isolator may be required to protect the operators during charging of raw materials.
Compounding or formulation

- Formulation in a Grade C room
- Local ISO5 UDAF protection if OPEN process, and if product is susceptible to contamination
- Utility requirements
- Cross contamination risks
- Sampling
- Cleaning and storage of cleaning supplies
- Flows
  - people,
  - clean and dirty equipment,
  - materials,
  - product,
  - waste
Compounding/Formulation Area Some Design considerations

- Utility requirements
- Cross contamination risks
- Sampling
- Cleaning and storage of cleaning supplies
- Flows
  - people,
  - clean and dirty equipment,
  - materials,
  - product,
  - waste
Compounding/formulation area disposable systems for sampling
Filtration sterilisation
Sterile filtration - decisions

- Aseptic process integrity
- Clean assembly and sterilization of the filter in place (SIP) (closed)
- Autoclave filter sterilization, and aseptic assembly (open).
- Filter compatibility validation
- Single OR double filtration
- Filter wetting
- Filter integrity testing (before and after use)
- Product flushing of the filter
Main Regulatory references

- EU CPMP (CPMP/QWP/486/95)
  - Normally bio-burden NMT 10cfu/100ml
  - If necessary use a pre-filter to obtain this bioburden
  - Pore sizes 0.22µm or less are acceptable for sterile filtration
- PIC/S GMP Annex 1
  - Nominal pore size 0.22µm or less
  - Second filtration via a further sterilised micro-organism retaining filter, immediately prior to filling may be advisable
  - Final sterile filtration should be carried out as close as possible to the filling point
Usual interpretation of regulatory guidance

- Pre-use Integrity testing of filters should ideally take place after sterilisation of the filter
- Integrity testing of filters should ideally be performed in-situ
  (Pre use cartridge in original housing with housing in place in process line, post use cartridge in original housing on or off process line)
- Routine bioburden testing prior to processing
- Filter ‘process validation’ refers to a product / process specific bacterial retention test at a minimum of $1 \times 10^7$ cfu/cm$^2$ of an appropriate organism
Possible filter locations in a sterile manufacturing process - 1

• **Single stage sterilising filter system.**
  • Bioburden in feed to A below 10cfu/100ml
  • Filter A to produce sterile product for hold tank
  • Filter A process validated
  • Filter A integrity tested pre- and post use
  • Vent filter must be sterilised and integrity tested pre and post use
  • May involve risks e.g tank integrity, distance between tank and filling head.

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[Image: Diagram illustrating the flow of a sterile manufacturing process with filter locations.]
Possible filter locations in a sterile manufacturing process - 2

- **Double sterilising filter**
  - Bioburden in feed to A below 10cfu/100ml
  - Both A and B are sterilising grade filters
  - Filters A and B process validated
  - Both filters sterilised and integrity tested before and after use
  - Vent filter must be sterilised and integrity tested pre and post use
  - May involve risks e.g tank integrity, distance between tank and filling head.
Possible filter locations in a sterile manufacturing process - 3

- **Single stage sterilising filter**
  - Bioburden in tank below 10cfu/100ml
  - Integrity test pre-use and post-use
  - Filter process validated
  - May involve risks e.g. distance between filter and filling head.
Possible filter locations in a sterile manufacturing process - 4

- **Double stage ‘redundant’ sterilising filter system**
  - Bioburden in tank below 10cfu/100 ml
  - Single stage filtration adequate to meet process sterility requirement
  - A & B process validated singly
  - Filter A and B integrity tested pre-use.
  - One filter (A or B) integrity tested post use. If that filter fails, integrity test the second filter. If the second filter then passes, OK
  - May involve risks e.g distance between integral filter and filling head.

![Diagram showing possible filter locations](image)
Possible filter locations in a sterile manufacturing process - 5

- Combination of sterilising and bioburden reduction 0.22µm or less rated filters
  - Bioburden in tank above CPMP limit
  - Filter A reduces bioburden to <10cfu/100ml.
  - Filter B adequate to meet process sterility requirement
  - Single stage B process validated
  - Filter A and B integrity tested pre- and post use.
  - Both must pass integrity
  - A for bioburden control
  - B for sterility
  - May involve risks e.g. distance between sterilising filter and filling head.
**Double - Serial sterilising filter system**
- Bioburden in tank below 10cfu/100ml
- Both stages (A & B) process validated together or singly
- Filter A and B integrity tested pre- and post use.
- Both must pass integrity
- May involve risks e.g distance between sterilising filter B and filling head.
Possible filter locations in a sterile manufacturing process - 7

- **Double stage sterilising filter system**
  - Input to A must be <10cfu/100ml
  - Filter A to produce sterile product for hold tank
  - Both filters A and B process validated
  - Filters A and B integrity tested pre- and post use.
  - Both must pass integrity
  - Vent filter must be sterilised and integrity tested pre and post use
  - May involve risks e.g. distance between sterilising filter B and filling head.

[Diagram of sterilisation process showing filters A and B, sterile tank/product, and filling head]
Component and parts preparation
Closure/stopper preparation

• Extraneous particulates and chemicals are removed by washing and rinsing.
• Detergent is often used for endotoxin load reduction and to aid cleaning.
• Stoppers can be siliconized for smooth insertion of stoppers into vials.
• Stoppers must receive a final WFI rinse prior to sterilisation.
Closure/stopper preparation

- Storage and transfer to filling machine in closed containers or under Grade A conditions (called Grade A continuity).
- Increasing trend to source stoppers as “ready to use” = sterile or “ready to sterilise” = pre-washed.
  - This results in a reduction in the process equipment required, and complexity of the facility design.
Stopper preparation

- Wash and sterilise in a dedicated processor (pass-through design)
Stopper preparation

Wash and sterilise in an autoclave

Grade B – Aseptic side

Grade D or C preparation/loading side
Stopper preparation

Wash and sterilise in a dedicated processor (pass-through design)
Product contact parts preparation

- Cleaned with detergent to remove residues – concern regarding residual detergent.
- Sometimes change parts may be product-dedicated
- Cleaned using an ultrasonic cleaner
- Final rinse with WFI
- Parts are wrapped in a “sterilization wrap” and steam sterilized
Product contact parts preparation

- Cleaned with detergent to remove residues – concern regarding residual detergent.
- May be product-dedicated
- Cleaned using an ultrasonic cleaner
- Final rinse with WFI
- Parts are wrapped in a “sterilization wrap” and Steam Sterilized
Post sterilisation - control of components and change parts

- For equipment which cannot be sterilized in place (SIP), wherever possible equipment and materials should be sterilized through double ended sterilizers, which open directly into a Grade A zone.
- Where sterilizers are not directly adjacent to the location where aseptic operations are performed, Grade A continuity should be maintained for the transfer of materials from the sterilizer to the place of storage or use.
Post sterilisation - control of components and change parts

- It is possible to use “clean air” protected carts.
- Where autoclave and oven loads are withdrawn from the sterilizer chamber into a Grade B room, there should be localized unidirectional Grade A airflow protection at the chamber outlet so items may remain under these controlled conditions until the load has cooled.
- Then, need to consider how the goods are transferred to the filling line.
Post sterilisation - control of components and change parts

• Where Grade A protection cannot be provided for autoclaved materials and components, the items should be sterilized double wrapped in coverings that permit air removal/steam entry and condensate removal while maintaining the sterile integrity of the contents.

• Items which are pre-sterilized by other methods such as Gamma irradiation or ethylene oxide should be protected with appropriate wrappings to maintain their sterile integrity while outside the Grade A environment.
Final container preparation

Contamination that must be controlled is:

- Bioburden
- Endotoxin
- Particulates
- Extraneous chemicals (such as glass mold release compounds)
Final Container Preparation

- Extraneous particulates and chemicals are removed by washing and rinsing.
- Containers must be subjected to a final rinse with Water-For-Injection (WFI).
- Bioburden is inactivated and endotoxin is degraded during de-pyrogenation, either in a dry heat oven or a continuous de-pyrogenation tunnel.
- Endotoxins can also be called pyrogens.
Container preparation

Very common! Example of automated glass washer feeding a de-pyrogenisation tunnel (sometimes called a compact line).
Filling
Filling and stoppering

- Grade A (ISO 5) (Class 100) Conditions
- Machine must be set up aseptically unless it is a Clean-in-Place/Steam-in-Place (CIP/SIP) setup.
- Ampoules can be open or closed
- Small batch sizes often require some form of transfer system from the depyrogenization oven.
- Humidity control required for sterile powder filling
- Vial transfer and product fill
- Nitrogen purge of head-space may be required?
- Application of stoppers to vials
- Stopper bowl is a critical area hence care in loading stoppers into the bowl
- Lyophilized stoppering uses a different design of stopper compared with liquid filled product (to allow vapour release).
Filling

- Vial filling machine

- Blow-fill-seal forming and filling machine

- These machines can both do aseptic filling, but have very different facility needs
Filling equipment design

- Non-corrosive/non-reactive product contact parts
- Parts withstand repeated cleaning and sterilization
- Fill accuracy (Impacts Dose i.e. product CQA)
- Moving parts contained in housings to reduce particulate generation
- No lubricants in the aseptic core area
- Design to support unidirectional air flow
- Adjust machine without reaching over open vials
- Demountable stopper bowls for cleaning and sterilization.
- Ease of aseptic assembly.
Blow fill seal (BFS) process

1. Extruding a parison by extruding plastic granulate
2. Forming of the container in the mold
3. Filling the container with product
4. Sealing the container
5. Ejecting the container and checking the container integrity

Note: This figure is reproduced with the kind permission of Weiler Engineering
BFS technology advantages

- Very short exposure of the container to the environment, compared to conventional filling into preformed containers.
- The container can be designed more freely, e.g., it is possible to include stoppers if a multidose presentation is desired.
- Operator interventions are kept to a minimum.
- Barrier-protected aseptic environment is maintained around the filling zone.
BFS technology special considerations

- The process is not as fast as glass-vial filling machines. Batch times are therefore generally longer.
- Format change requires different moulds to be fitted.
- The process is relatively specialised and, therefore, is suited to firms that can develop “centre of excellence” capability in the technology.
Lyophilisation
Lyophilization or freeze drying
Lyophilization
Lyophilization

- Freeze drying
- Aseptic process in Grade A (ISO 5) UDAF cleanzone
- Manual or automated loading
Lyophilization process sequence

- Cleaning of chamber
- Sterilisation of chamber
- Loading
- Freezing
- Primary drying/sublimination
- Secondary drying/desorption
- Backfill
- Stoppering
- Aeration
- Unloading
- Defrosting
- Cleaning/CIP
- Filter integrity test
- Leak testing
Lyophilization general issues

• Provide a system to transfer vials from the filler to the shelves in the lyophilizer under Grade A conditions.
• May consider an automated loading system.
• Most lyophilizers will seat the stoppers in vials by shelf compression.
• If stoppers are not seated, then unloading must also occur under Grade A conditions.
• Lyophilisation cycle times can be very long – 72 hours is not uncommon.
Some specific Annex 1 requirements
Capping and crimping (vials)

- Secures the inserted stopper in the vial neck and thereby helps assure the long term integrity and sterility of the vial. For aseptic products stoppers should be fully seated in the ISO5 environment
  - Cappers are Particulate Generators
  - Uncapped vials on the capper in-feed are protected by local HEPA filtered air – a stopper may not be fully seated until it passes through the capper
  - Automated stopper detection can find and eject vials with missing partially seated stoppers
Capping/sealing vials

- Less critical process
- Can be an aseptic or clean manipulation
- Clean air protection with ISO 5 (Grade A “air supply” designated in EU GMP Annex 1).
If stoppered vials exit an aseptic processing zone or room prior to capping, appropriate assurances should be in place to safeguard the product, such as local protection until completion of the crimping step. Use of devices for on-line detection of improperly seated stoppers can provide additional assurance.
Vial capping can be undertaken as an aseptic process using sterilised caps or as a clean process outside the aseptic core.

Where this latter approach is adopted, vials should be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a Grade A air supply until the cap has been crimped.
As the equipment used to crimp vial caps can generate large quantities of non-viable particulates, the equipment should be located at a separate station equipped with adequate air extraction. (don’t interpret this literally – means separate the particle source from open containers).

The capping station may not be able to meet Grade A conditions for non-viable particles in the “in operation” condition but should meet the microbiological requirements.
Typical leak detection methods

- Vacuum method
- Dye challenge test
- Pinhole detector/high voltage detector
- Pressure decay or head space analysis
There is a lot in the guide that help you to consider the requirements, and develop an appropriate facility design.
Conclusion

- Understand purpose of different types of process equipment in manufacturing process steps
- Ensure link to CQAs and facility design
- Ensure process enables contamination to be minimised
Thank you for your time.
Questions?

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