

Auditing an Aseptic Sterile Area

Goals

When you have completed this unit, you should be able to:

- Perform an audit of an aseptic/sterile processing area
- Access and understand aseptic/sterile manufacturing requirements
- Understand worldwide regulatory agency requirements for aseptic/sterile processing
- Use a range of information tools, from the contents of this module to the Intranet in support of an aseptic/sterile processing audit
- Recognize compliance or non-compliance of areas to regulations pertaining to aseptic/sterile processing requirements.

Definitions

Action levels: established microbial or particle levels that, when exceeded, should trigger an appropriate investigation and corrective action based on the investigation.

Air Lock: a small room with interlocked doors, constructed to maintain air pressure control between adjoining rooms (generally with different air cleanliness standards). The intent of an air lock is to preclude ingress of particulate matter and microorganism contamination from a lesser controlled area.

Alert levels: established static and operational microbial or particulate levels giving early warning of potential drift from normal operating conditions which are not necessarily grounds for definitive corrective action but which require follow-up investigation.

Alert levels (environmental monitoring): established static and operational microbial or particulate levels giving early warning of potential drift from normal operating conditions which are not necessarily grounds for definitive corrective action but which require follow-up investigation.

Alert levels (media fill): an established number of media filled units which indicate the presence of microbial growth (e.g. positive units). The cause of the growth should be investigated, but is not necessarily a reason for definitive corrective action.

Aseptic filling: a process by which the drug or biological product, container, and closure are sterilized separately then assembled under strict environmental conditions.

Bioburden: the total number of microorganisms associated with a specific item prior to sterilization.

Cleanroom: a room designed, maintained, and controlled to prevent particle and microbiological contamination of drug products using high efficiency particulate air filters (HEPA). Air from the filters may either flow down (vertical) or across (horizontal) the surface to be kept clean.

Compounding: a process in which one bulk drug substance is combined with another bulk drug substance and/or one or more excipients to produce a drug product.

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Aseptically produced products

The same formulation principles as for terminally sterilised products apply except that a cleaner environment is utilised. The bulk solution is then filtered both to remove particles and to remove all microorganisms to render the product sterile. The sterile bulk solution is filled into washed, sterilised containers under conditions that minimise the potential for microbial contamination of the product. The environment standards of cleanliness are required to be higher for aseptic manufacturing than for products to be terminally sterilised.

As the actual sterilisation step is the filtration step the bioburden must be kept to an absolute minimum and there must be a good understanding of the types of microorganisms present. Solutions should be protected from contamination and holding times kept to a minimum. The choice of filter must be carefully considered to be compatible with the product and process conditions. Filter validation conditions should be equivalent to ordinary process use. Effective filtration depends on the integrity of the whole system not only on the filter itself.

Regular media fills are performed in order to verify the consistent manufacture of sterile products using the process of choice. The overall microbiological vulnerability of the aseptic manufacturing process is assessed. A nutrient media shown to promote microbial growth replaces product. Media fills should be performed in the same way as ordinary filling, however there may be practical limitations (e.g. powder filling). Filled and sealed containers are incubated to microbial growth (bacterial and fungi over a range of temperatures). Contaminants, which may have penetrated the integrity of the process and entered into the containers, will then be visible. Incubated containers are inspected for turbidity and the level of contamination is compared with published standards. Media fills are performed as part of the initial validation and thereafter on a regular basis. Each filling line as well as all operators involved needs to be qualified by media fills.



Dry heat steriliser with the door open. Equipment used may be sterilised by dry heat. Product containers will be sterilised by dry heat. In large scale production sterilisation tunnels attached to the washing machine are often used.

Container Integrity

The consequences of a problem in the quality of sterile products are so significant that 100% inspection is necessary. The EU GMP guide requires 100% leak testing of containers closed by fusion and 100% inspection of parenteral products for particulate contamination. Leak testing is usually performed by methods of dye batch testing and/or electrostatic testing, the later is preferred. Such a non-destructive high voltage inspection method allows defects as pinholes

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made in personal hygiene and correct wearing of special, non-shedding, gowning, people account for over 80% of all particulate contamination in the clean room and virtually all the microbiological contamination.

The garment should be comfortable to wear and made using antistatic fabric of minimum pore size (prevent passage from the person to the environment but allow passage of moisture). There should be tight seals around neck, wrists and ankles. Additionally it should be possible to wash and sterilise them (if used in grade A/B). Separate laundry is desirable.

In grade A/B areas sterilised full suits and hoods are used as well as special boots/footwear (sterilised or disinfected), sterile gloves and face masks (goggles). Gowning is changed every work session or at least daily. Two-piece suits should not be used in grade A/B areas.

In grade C areas non-shedding full suits, gloves and shoes as well as complete hair and beard cover are used.

In grade D areas general protective suits are worn as well as hair and beard cover and shoes/overshoes.

Visual inspection

Visual inspection of parenterals may be performed manually or automatically using camera vision systems. Pharmacopoeias provide information on how viewing units should be designed when performing manual inspections.

Personnel should undergo frequent eyesight checks and be trained in identification of defect types and the expected standards. Frequent breaks and rotation of tasks should be allowed. The premises used must be quiet and allow personnel to work separate from pass ways and noisy production areas. Appropriate lighting should be provided.

Walk through

During an aseptic/sterile processing audit, the auditor must observe the facility/area, process and personnel. The walk through is a critical part of any aseptic/sterile processing audit. In some of the cleanest areas you may not be allowed access due to the risk of contamination. It may however be possible to observe through a window. If you cannot observe work being carried out it may be very difficult to draw any conclusions. The issue has to be discussed/resolved. External personnel should not be breaching sterile area unless validated by site. If you cannot see into area in operation adequately you need to challenge how the company manage the area.

This must include examination of the appearance of the floors, walls, ceilings, housekeeping, operator activities during operations, movement of materials and people, manufacturing processes and the microbiology laboratory. You must take your time and if necessary observe these operations several times during your audit. If possible, the walk through must coincide with the shift changeover in order to observe two groups of operators. This allows the auditor to determine if behaviors and practices are consistent across both shifts. Inconsistent behaviors may suggest underlying training deficiencies. Prior to performing the walk through, obtain reference as-built diagrams of the following:

- Facility layout
- Personnel and material flow
- HVAC, room classifications, air pressure differentials; commissioning documents **must** be available to clearly demonstrate that the area as-built delivers the appropriate environment
- Production water systems
- Environmental sampling sites

We recommend that you verify that the various room classifications and air pressure differentials are compliant with the relevant regulations. During the walk through you must

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- Inspect the component preparation area.
 - Ensure that sterilization equipment (autoclave, dry heat oven, sterilizing tunnel) has been validated and is properly maintained.
 - Ensure that equipment used to wash/rinse containers and closures has been properly validated and maintained.
 - Ensure the required water quality is used for washing/rinsing
 - Ensure that there are approved procedures for departmental processes, operation of/and maintenance of equipment. Verify that operating procedures reflect those used during validation.
 - Observe personnel to determine if they are appropriately gowned.
 - Ensure that there is a documented training program in place for operators in this area.
- Inspect the microbiology laboratory.
 - Review sterility testing program, performance and test results.
 - Review all investigations for completeness and lot disposition decisions.
 - Determine if there are any trends regarding false positive test results and the root cause.
- Review the Media Fill Procedure.
 - Ensure there is a defined, approved program.
 - Ensure that the media fill program is compliant with the applicable regulations and site Policy/Guideline requirements.
 - Ensure that all operators have participated in a media fill within the year.
 - Ensure that media fills are performed for every aseptic filling line for every shift semi-annually.
 - Verify the number of units filled during a media fill and assure that the media fill is representative of the filling process. (For example: size and duration of fill; line speed; incubation (14 days and adequate temperature to detect organisms and examination of each filled unit)
 - Ensure that **all staff** that might be involved in the aseptic filling process participates in the media fill.
 - Review media fill performance documentation and all associated deviation reports.
 - Ensure that the number of units filled during the media fill trial is equivalent to the number of units placed on incubation. Ensure that any variances in number are documented.
- Review the Environmental Monitoring Program.
 - Ensure that there is a defined, approved program.
 - Review training records for staff performing program sampling and testing.
 - Ensure that the program is compliant with all worldwide regulatory and site policy/guideline requirements.
 - Ensure that there are established alert and action limits that are appropriate.
 - Review test results and associated investigations.
 - Ensure that the program requires review of test results prior to release of product batches.
 - Ensure that data is tracked for trends and reviewed by QC unit on a regular basis.