

CHAPTER 2.3.5.

MINIMUM REQUIREMENTS FOR ASEPTIC PRODUCTION IN VACCINE MANUFACTURE

SUMMARY

This chapter provides requirements for aseptic production in the manufacture and quality control of veterinary vaccines in accordance with Chapter 1.1.8 Principles of veterinary vaccine production and Chapter 2.3.4 Minimum requirements for the production and quality control of vaccines. Manufacturers should use the recommendations as a basis for the elaboration of specific rules adapted to their individual needs.

The manufacture of vaccines should be carried out in clean areas with controlled entry for personnel, equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air that has passed through filters of an appropriate efficiency. Component preparation, product preparation and filling should be carried out in separate areas within the clean area. Manufacturing operations are conducted aseptically at some or all stages.

Clean areas for the manufacture of vaccines are classified into four grades according to the characteristics of the required environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimise the risks of particulate or microbial contamination of the product or materials being handled. In order to meet operational conditions these areas should be designed to reach certain specified air-cleanliness levels in the resting state. The resting state is the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present. The operational state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working. The operational and resting states should be defined for each clean room or suite of clean rooms.

The chapter sets out specific requirements for air quality, use of isolators, aseptic preparation, personnel, building design, equipment, sanitation, processing of materials, sterilisation and finishing of products.

SPECIFIC REQUIREMENTS FOR ASEPTIC PREPARATION

1. Principle

Most vaccines are injectable products, sterile or aseptically prepared. Their production should meet the following additional requirements for aseptic preparation.

Sole reliance for sterility or other quality aspects must not be placed on finished product test.

2. General

- i) The manufacture of vaccines should be carried out in clean areas entry to which should be through airlocks for personnel or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air that has passed through filters of an appropriate efficiency.

- ii) The various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area. Manufacturing operations are conducted aseptically at some or all stages.
- iii) Clean areas for the manufacture of vaccines are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimise the risks of particulate or microbial contamination of the product or materials being handled.
- iv) In order to meet “in operation” conditions these areas should be designed to reach certain specified air-cleanliness levels in the “at rest” occupancy state. The “at-rest” state is the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present. The “in operation” state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.
- v) The “in operation” and “at rest” states should be defined for each clean room or suite of clean rooms.
- vi) For aseptic preparations four grades can be distinguished.
- a) *Grade A*: The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 to 0.54 m/s (guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated.
- A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes.
- b) *Grade B*: For aseptic preparation and filling, this is the background environment for the Grade A zone.
- c) *Grade C and D*: Clean areas for carrying out less critical stages in the aseptic preparation.

3. Clean room and clean air device classification

- i) Clean rooms and clean air devices should be classified in accordance with EN ISO 14644-1. Classification should be clearly differentiated from operational process environmental monitoring. The maximum permitted airborne particle concentration for each grade is given in the following table.

Maximum permitted number of particles per m ³ equal to or greater than the tabulated size				
Grade	At rest		In operation	
	0.5 µm	5.0µm	0.5 µm	5.0µm
A	3520	20	3520	20
B	3520	29	352,000	2900
C	352,000	2900	3,520,000	29,000
D	3,520,000	29,000	Not defined	Not defined

- ii) For classification purposes in Grade A zones, a minimum sample volume of 1 m³ should be taken per sample location. For Grade A the airborne particle classification is ISO 4.8 (as defined in ISO 14644-1) dictated by the limit for particles ≥5.0 µm. For Grade B (at rest) the airborne particle classification is ISO 5 for both considered particle sizes. For Grade C (at rest and in operation) the airborne particle classification is ISO 7 and ISO 8 respectively. For Grade D (at rest) the airborne particle classification is ISO 8. For classification purposes EN/ISO 14644-1 methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest considered particle size and the method of evaluation of the data collected.
- iii) Portable particle counters with a short length of sample tubing should be used for classification purposes because of the relatively higher rate of precipitation of particles ≥5.0µm in remote sampling systems with long lengths of tubing. Isokinetic sample heads shall be used in unidirectional airflow systems.

- iv) “In operation” classification may be demonstrated during normal operations, simulated operations or during media fills as worst-case simulation is required for this. EN ISO 14644-2 provides information on testing to demonstrate continued compliance with the assigned cleanliness classifications.
- v) Clean rooms and clean air devices should be routinely monitored in operation, for the full duration of critical processing, except where justified by contaminants in the process that would damage the particle counter or present a hazard, e.g. live organisms. In such cases, monitoring during routine equipment set up operations should be undertaken prior to exposure to the risk. Monitoring during simulated operations should also be performed.
- vi) Airborne particle monitoring systems may consist of independent particle counter; a network of sequentially accessed sampling points connected by manifold to a single particle counter; or a combination of the two.
- vii) The sample sizes taken for monitoring purposes using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of clean rooms and clean air devices.
- viii) The particle limits given in the table for the “at rest” state should be achieved after a short “clean up” period of 15–20 minutes (guidance value) in an unmanned state after completion of operations.
- ix) The monitoring of Grade C and D areas in operation should be performed in accordance with the principle of quality risk management. The requirements and alert or action limits will depend on the nature of the operations carried out, but the recommended “clean up period” should be attained.
- x) Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard.
- xi) Examples of operations to be carried out in the various grades include:

Grade	Examples of operations for aseptic preparations
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

- xii) Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations. Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitisation.

Recommended limits for microbiological monitoring of clean areas during operation:

Recommended limits for microbial contamination ^(a)				
Grade	Air sample CFU/m ³	Settle plates (diameter 90 mm) CFU/4 hours ^(b)	Contact plates (diameter 55 mm) CFU/plate	Glove print five fingers CFU/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

^(a)These are average values. ^(b)Individual settle plates may be exposed for less than 4 hours.
CFU= colony-forming unit

- xiii) Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded operating procedures should prescribe corrective action.

4. Isolator technology

- i) The use of isolator technology to minimise human interventions in processing areas may result in a significant decrease in the risk of microbiological contamination of aseptically manufactured products from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment should be designed so that the required air quality for the respective zones can be realised. Isolators are constructed of various materials more or less prone to puncture and leakage. Transfer devices may vary from a single door to double door designs to fully sealed systems incorporating sterilisation mechanisms.
- ii) The transfer of materials into and out of the unit is one of the greatest potential sources of contamination. In general the area inside the isolator is the local zone for high risk manipulations, although it is recognised that laminar air flow may not exist in the working zone of all such devices.
- iii) The air classification required for the background environment depends on the design of the isolator and its application. It should be controlled and for aseptic processing it should be at least Grade D.
- iv) Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example the quality of the air inside and outside (background) the isolator, sanitisation of the isolator, the transfer process and isolator integrity.
- v) Monitoring should be carried out routinely and should include frequent leak testing of the isolator and glove or sleeve system.

5. Aseptic preparation

- i) Components after washing should be handled in at least a Grade D environment. Handling of sterile starting materials and components, unless subjected to sterilisation or filtration through a microorganism-retaining filter later in the process, should be done in a Grade A environment with Grade B background.
- ii) Preparation of solutions that are to be sterile filtered during the process should be done in a Grade C environment; if not filtered, the preparation of materials and products should be done in a Grade A environment with a Grade B background.
- iii) Handling and filling of aseptically prepared products should be done in a Grade A environment with a Grade B background.
- iv) Prior to the completion of stoppering, transfer of partially closed containers as used in freeze drying should be done either in a Grade A environment with Grade B background or in sealed transfer trays in a Grade B environment.

6. Specific requirements for personnel working in clean areas

- i) Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processing.
- ii) All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of vaccines. This training should include reference to hygiene and to the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.
- iii) Staff who have been engaged in the processing of animal tissue materials or of cultures of micro-organisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined entry procedures have been followed.
- iv) High standards of personal hygiene and cleanliness are essential. Personnel involved in the manufacture of aseptic preparations should be instructed to report any condition that may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be

taken about personnel who could be introducing undue microbiological hazard should be decided by a designated competent person.

- v) Wristwatches, make-up and jewellery should not be worn in clean areas.
- vi) Changing and washing should follow a written procedure designed to minimise contamination of clean area clothing or carry-through of contaminants to the clean areas.
- vii) The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.
- viii) The description of clothing required for each grade is given below:
 - a) Grade D: Hair and, where relevant, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.
 - b) Grade C: Hair and where relevant beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.
 - c) Grade A/B: Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilised, non-powdered rubber or plastic gloves and sterilised or disinfected footwear should be worn. Trouser-legs should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.
- ix) Outdoor clothing should not be brought into changing rooms leading to Grade B and C rooms. For every worker in a Grade A/B area, clean sterile (sterilised or adequately sanitised) protective garments should be provided at each work session. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least for every working session.
- x) Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants that can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibres and may increase the risk of shedding of particles.

7. Specific requirements for clean areas

- i) In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimise the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.
- ii) To reduce accumulation of dust and to facilitate cleaning there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be designed to avoid those uncleanable recesses; sliding doors may be undesirable for this reason.
- iii) False ceilings should be sealed to prevent contamination from the space above them.
- iv) Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean.
- v) Sinks and drains should be prohibited in Grade A/B areas used for aseptic manufacture. In other areas air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade clean rooms should be fitted with traps or water seals to prevent back-flow.
- vi) Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimise microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at-rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and

leaving clean areas is sometimes desirable. In general hand washing facilities should be provided only in the first stage of the changing rooms.

- vii) Both airlock doors should not be opened simultaneously. An interlocking system or a visual or audible warning system should be operated to prevent the opening of more than one door at a time.
- viii) A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of 10–15 Pascals (guidance values). Particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which a product and cleaned components that contact the product are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials, e.g. live viruses or bacteria. Decontamination of facilities and treatment of air leaving a clean area may be necessary for some operations.
- ix) It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particle-generating person, operation or machine to a zone of higher product risk.
- x) A warning system should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly or otherwise documented.

8. Equipment

- i) A conveyor belt should not pass through a partition between a Grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilised (e.g. in a sterilising tunnel).
- ii) As far as practicable equipment, fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. If sterilisation is required, it should be carried out, wherever possible, after complete reassembly.
- iii) When equipment maintenance has been carried out within the clean area, the area should be cleaned, disinfected or sterilised where appropriate, before processing recommences if the required standards of cleanliness or asepsis have not been maintained during the work.
- iv) Water treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity.
- v) All equipment such as sterilisers, air handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems should be subject to validation and planned maintenance; their return to use should be approved.

9. Sanitation

- i) The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains.
- ii) Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should be stored and labelled according to specifications and expiry. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.

10. Processing

- i) Preparations of microbiological origin should not be made or filled in areas used for the processing of other vaccines; however, vaccines of dead organisms or of bacterial extracts may be filled, after inactivation, in the same premises as other sterile medicinal products after appropriate cleaning.

- ii) Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilisation of the nutrient medium.
- iii) The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. It should also take into account various interventions known to occur during normal production as well as worst-case situations.
- iv) Process simulation tests should be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC-system, equipment, process and number of shifts. Normally process simulation tests should be repeated twice a year per shift and process.
- v) The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth¹. For any run size, intermittent incidents of microbial contamination may be indicative of low-level contamination that should be investigated. Investigation of gross failures should include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.
- vi) Care should be taken that any validation does not compromise the processes.
- vii) Water sources, water treatment equipment and treated water should be monitored regularly for chemical and biological contamination and, as appropriate, for endotoxins. Records should be maintained of the results of the monitoring and of any action taken.
- viii) Activities in clean areas and especially when aseptic operations are in progress should be kept to a minimum and movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.
- ix) Microbiological contamination of starting materials should be within a pre-specified range. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.
- x) Containers and materials liable to generate fibres should be minimised in clean areas.
- xi) Components, containers and equipment should be handled after the final cleaning process in such a way that they are not re-contaminated.
- xii) The interval between the washing and drying and the sterilisation of components, containers and equipment as well as between their sterilisation and use should be minimised and subject to a time-limit appropriate to the storage conditions.
- xiii) Components, containers, equipment and any other article required in a clean area where aseptic work takes place should be sterilised and passed into the area through double-ended sterilisers sealed into the wall, or by a procedure that achieves the same objective of not introducing contamination. Non-combustible gases should be passed through micro-organism retentive filters.
- xiv) The efficacy of any new procedure should be validated, and the validation verified at scheduled intervals based on performance history or when any significant change is made in the process or equipment.

11. Sterilisation

- i) All sterilisation processes should be validated. Particular attention should be given when the adopted sterilisation method is not described in the current editions of Pharmacopoeias, or when it is used for a product that is not a simple aqueous or oily solution. Where possible, heat sterilisation is the method of

1 A rationale to this topic can be found in the PIC/S guideline (PIC/S, 2014).

choice. In any case, the sterilisation process must be in accordance with the marketing and manufacturing authorisations.

- ii) Before any sterilisation process is adopted its suitability for the product and its efficacy in achieving the desired sterilising conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.
- iii) For effective sterilisation the whole of the material must be subjected to the required treatment and the process should be designed to ensure that this is achieved.
- iv) Validated loading patterns should be established for all sterilisation processes.
- v) Biological indicators should be considered as an additional method for monitoring sterilisation. They should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls. If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination from them.
- vi) There should be a clear means of differentiating products that have not been sterilised from those that have. Each basket, tray or other carrier of products or components should be clearly labelled with the material name, its batch number and an indication of whether or not it has been sterilised. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilisation process, but they do not give a reliable indication that the lot is, in fact, sterile.
- vii) Sterilisation records should be available for each sterilisation run. They should be approved as part of the batch release procedure.

11.1. Sterilisation by heat

- i) Each heat-sterilisation cycle should be recorded on a time/temperature chart with a sufficiently large scale or by other appropriate equipment with suitable accuracy and precision. The position of the temperature probes used for controlling or recording should have been determined during the validation, and where applicable also checked against a second independent temperature probe located at the same position.
- ii) Chemical or biological indicators may also be used, but should not take the place of physical measurements.
- iii) Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilising time-period is commenced. This time must be determined for each type of load to be processed.
- iv) After the high temperature phase of a heat-sterilisation cycle, precautions should be taken against contamination of a sterilised load during cooling. Any cooling fluid or gas in contact with the product should be sterilised unless it can be shown that any leaking container would not be approved for use.

11.1.1. Moist heat

- i) Both temperature and pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator. The reading of the independent temperature indicator should be routinely checked against the chart recorder during the sterilisation period. For sterilisers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position, throughout the sterilisation period. There should be frequent leak tests on the chamber when a vacuum phase is part of the cycle.

- ii) The items to be sterilised, other than products in sealed containers, should be wrapped in a material that allows removal of air and penetration of steam but that prevents recontamination after sterilisation. All parts of the load should be in contact with the sterilising agent at the required temperature for the required time.
- iii) Care should be taken to ensure that steam used for sterilisation is of suitable quality and does not contain additives at a level that could cause contamination of product or equipment.

11.1.2. Dry heat

- i) The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins could be used as part of the validation.

11.2. Sterilisation by radiation

- i) Radiation sterilisation is used mainly for the sterilisation of heat-sensitive materials and products. Many medicinal products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not normally an acceptable method of sterilisation.
- ii) During the sterilisation procedure the radiation dose should be measured. For this purpose, dosimetry indicators that are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the irradiator. Where plastic dosimeters are used they should be used within the time-limit of their calibration. Dosimeter absorbances should be read within a short period after exposure to radiation.
- iii) Biological indicators may be used as an additional control
- iv) Validation procedures should ensure that the effects of variations in density of the packages are considered.
- v) Materials handling procedures should prevent mix-up between irradiated and non-irradiated materials. Radiation sensitive colour disks should also be used on each package to differentiate between packages that have been subjected to irradiation and those that have not.
- vi) The total radiation dose should be administered within a predetermined time span.

12. Finishing

- i) Partially stoppered freeze drying vials should be maintained under Grade A conditions at all times until the stopper is fully inserted.
- ii) Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.
- iii) The container closure system for aseptically filled vials is not fully integral until the aluminium cap has been crimped into place on the stoppered vial. Crimping of the cap should therefore be performed as soon as possible after stopper insertion.
- iv) 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.
- v) 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.

- vi) Vials with missing or displaced stoppers should be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology should be used to prevent direct contact with the vials and to minimise microbial contamination.
- vii) Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimising direct human interventions into the capping operation.
- viii) Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.
- ix) Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.

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NB: FIRST ADOPTED IN 2016.