GMP-Z Annex 1 - Fabricage van steriele geneesmiddelen

Inleiding

In de ziekenhuisapotheek worden steriele geneesmiddelen gemaakt door middel van terminale sterilisatie, aseptisch bereiden en via aseptische handelingen. Aseptisch bereiden wordt onderverdeeld in aseptisch bereiden zonder naverhitten en aseptisch bereiden met naverhitten (30 min 100 ^{o}C). Aseptisch bereiden met naverhitten komt niet voor in Annex 1 van de GMP en wordt daar waar van toepassing aangevuld in dit GMPz hoofdstuk.
Aseptische handelingen worden in hoofdstuk Z3 behandeld.

GMP item	Richtsnoer GMP-Z	Toelichting GMP-Z
Principle		
The manufacture of sterile products is subject to special requirements in order to minimize risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance is particularly important, and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.	GMP	
General		
1. The manufacture of sterile products should be carried out in clean areas entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.	GMP	
2. The various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area. Manufacturing operations are divided into two categories; firstly those where	GMP	

the product is terminally sterilised, and secondly those which are conducted aseptically at some or all stages.		
3. Clean areas for the manufacture of sterile products 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. 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. The “in operation” and “at rest” states should be defined for each clean room or suite of clean rooms. For the manufacture of sterile medicinal products 4 grades can be distinguished. 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 – 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	GMP	

<table>
<tr><td>boxes.
Grade B: For aseptic preparation and filling, this is the background environment for the grade A zone.
Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.</td><td></td><td></td></tr>
<tr><td>Clean room and clean air device classification</td><td></td><td></td></tr>
<tr><td>4. 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:
<table>
<tr><td></td><td colspan="4">Maximum permitted number of particles per m^3 equal to or greater than the tabulated size</td></tr>
<tr><td></td><td colspan="2">At rest</td><td colspan="2">In operation</td></tr>
<tr><td>Grade</td><td>0.5 µm</td><td>5.0µm</td><td>0.5 µm</td><td>5.0µm</td></tr>
<tr><td>A</td><td>3520</td><td>20</td><td>3 520</td><td>20</td></tr>
<tr><td>B</td><td>3520</td><td>29</td><td>352000</td><td>2900</td></tr>
<tr><td>C</td><td>352000</td><td>2900</td><td>3520000</td><td>29000</td></tr>
<tr><td>D</td><td>3520000</td><td>29000</td><td>Not defined</td><td>Not defined</td></tr>
</table></td><td>GMP</td><td></td></tr>
</table>

5. For classification purposes in Grade A zones, a minimum sample volume of 1m^3 should be taken per sample location. For Grade A the airborne particle classification is ISO 4.8 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 & 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.	GMP	
6. 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.	GMP	
7. “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.	GMP	
Clean room and clean air device monitoring		
8. Clean rooms and clean air devices should be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices.	GMP	
9. For Grade A zones, particle monitoring should	9Z. Voor de situaties waarbij binnen de	

be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, e.g. live organisms and radiological hazards. 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. The Grade A zone should be monitored at such a frequency and with suitable sample size that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of ≥5.0 µm particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.	ziekenhuisfarmacie een klasse A-ruimte wordt gebruikt met klasse D achtergrond, wordt niet gedurende het proces van aseptische handelingen continu deeltjestelling verricht.	Een klasse A-ruimte kan als achtergrond een klasse B hebben, maar ook een klasse D. Beide situaties komen in de ziekenhuisfarmacie voor. De wijze waarop monitoring van aseptische handelingen plaatsvindt, wordt beschreven in hoofdstuk Z3 Voor de monitoring van individuele aseptische bereidingen en aseptische voorraadbereidingen met naverhitten wordt verwezen naar 35.
10. It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased. The importance of the particle monitoring system should be determined by the effectiveness of the segregation between the adjacent Grade A and B zones. The Grade B zone should be monitored at such a frequency and with suitable sample size that changes in levels of contamination and any system deterioration would be captured and alarms triggered if alert limits are exceeded.	GMP	

11. Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points connected by manifold to a single particle counter; or a combination of the two. The system selected must be appropriate for the particle size considered. Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing must be considered in the context of particle losses in the tubing. The selection of the monitoring system should take account of any risk presented by the materials used in the manufacturing operation, for example those involving live organisms or radiopharmaceuticals.	GMP	
12. 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.	GMP	
13. In Grade A and B zones, the monitoring of the ≥5.0 µm particle concentration count takes on a particular significance as it is an important diagnostic tool for early detection of failure. The occasional indication of ≥5.0 µm particle counts may be false counts due to electronic noise, stray light, coincidence, etc. However consecutive or regular counting of low levels is an indicator of a possible contamination event and should be investigated. Such events may indicate early failure of the HVAC system, filling equipment failure or may also be diagnostic of poor practices during machine set-up and routine operation.	GMP	

<table>
<tr><td>14. 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.</td><td>GMP</td><td></td></tr>
<tr><td>15. The monitoring of Grade C and D areas in operation should be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended “clean up period” should be attained.</td><td>GMP</td><td></td></tr>
<tr><td>16. 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.</td><td>GMP</td><td></td></tr>
<tr><td>17. Examples of operations to be carried out in the various grades are given in the table below (see also paragraphs 28 to 35):
<table><tr><th>Grade</th><th>Examples of operations for terminally sterilised products. (see paragraphs 28-30)</th></tr><tr><td>A</td><td>Filling of products, when unusually at risk</td></tr><tr><td>C</td><td>Preparation of solutions, when unusually at risk. Filling of products</td></tr><tr><td>D</td><td>Preparation of solutions and components for subsequent filling</td></tr></table>
<table><tr><th>Grade</th><th>Examples of operations for aseptic preparations. (see paragraphs. 31-35)</th></tr><tr><td>A</td><td>Aseptic preparation and filling</td></tr><tr><td>C</td><td>Preparation of solutions to be filtered.</td></tr><tr><td>D</td><td>Handling of components after washing</td></tr></table></td><td>GMP, met als uitzondering dat het uitvullen van producten die in de uiteindelijke container worden gesteriliseerd in een klasse D ruimte mogelijk is (in plaats van in klasse C) mits aan voorwaarden is voldaan (zie 29Z)</td><td>In de praktijk is aangetoond dat er in de ziekenhuisapotheek kan worden afgevuld in een klasse D ruimte. Het aantal (niet zichtbare) deeltjes in het product blijkt laag te zijn evenals de initiële contaminatie [1].</td></tr>
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<table>
<tr><td>18. 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.</td><td>GMP</td><td>De eisen bij aseptische handelingen worden beschreven in hoofdstuk Z3.</td></tr>
<tr><td>19. Recommended limits for microbiological monitoring of clean areas during operation:
<table>
<tr><th></th><th colspan="4">Recommended limits for microbial contamination (a)</th></tr>
<tr><th>Grade</th><td>air sample cfu/m^3</td><td>settle plates (diameter 90 mm) cfu/4 hours (b)</td><td>contact plates (diameter 55 mm) cfu/plate</td><td>glove print 5 fingers cfu/glove</td></tr>
<tr><td>A</td><td>< 1</td><td>< 1</td><td>< 1</td><td>< 1</td></tr>
<tr><td>B</td><td>10</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>C</td><td>100</td><td>50</td><td>25</td><td>-</td></tr>
<tr><td>D</td><td>200</td><td>100</td><td>50</td><td>-</td></tr>
</table>
Notes
(a) These are average values.
(b) Individual settle plates may be exposed for less than 4 hours.</td><td>GMP</td><td></td></tr>
<tr><td>20. 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.</td><td>GMP</td><td></td></tr>
<tr><td>Isolator technology</td><td></td><td></td></tr>
</table>

21. The utilisation of isolator technology to minimize 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 sterilization mechanisms.	GMP	
22. 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.	GMP	
23. 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.	GMP	
24. 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.	GMP	
25. Monitoring should be carried out routinely and should include frequent leak testing of the isolator and glove/sleeve system.	GMP	
Blow/fill/seal technology		

26. Blow/fill/seal units are purpose built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow/fill/seal equipment used for aseptic production which is fitted with an effective grade A air shower may be installed in at least a grade C environment, provided that grade A/B clothing is used. The environment should comply with the viable and non viable limits at rest and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products which are terminally sterilised should be installed in at least a grade D environment.	GMP	
27. Because of this special technology particular attention should be paid to, at least the following: • equipment design and qualification • validation and reproducibility of cleaning-in-place and sterilisation-in-place • background clean room environment in which the equipment is located • operator training and clothing • interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.	GMP	
Terminally sterilised products		
28. Preparation of components and most products should be done in at least a grade D environment in order to give low risk of microbial and particulate contamination, suitable for filtration and sterilisation. Where the product is at a high or unusual risk of microbial contamination, (for example, because the product actively supports microbial growth or must be held for a long period before sterilisation or is necessarily processed not mainly in closed vessels), then preparation should be carried out in a grade C environment.	GMP	

29. Filling of products for terminal sterilisation should be carried out in at least a grade C environment.	29Z. Geneesmiddelen die in de uiteindelijke container worden gesteriliseerd kunnen in een klasse D- ruimte worden uitgevuld, mits door middel van validatie en inproces-controles is aangetoond en wordt bewaakt dat het aantal (niet zichtbare) deeltjes in het product laag is.	In de praktijk is aangetoond dat er in de ziekenhuisapotheek kan worden afgevuld in een klasse D ruimte. Het aantal (niet zichtbare) deeltjes in het product blijkt laag te kunnen zijn evenals de initiële contaminatie [1].
30. Where the product is at unusual risk of contamination from the environment, for example because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing, the filling should be done in a grade A zone with at least a grade C background. Preparation and filling of ointments, creams, suspensions and emulsions should generally be carried out in a grade C environment before terminal sterilisation.	GMP	
	Aseptische voorraadbereidingen met nabehandeling 100^{0}C 30 min	
	30A-Z De aseptische voorraadbereiding met naverhitten 100 ^{0}C 30 min. wordt uitgevoerd indien sterilisatie in de uiteindelijke container niet mogelijk is vanwege een te grote ontleding of doordat de verpakking er niet tegen bestand is. Er moet aan de volgende randvoorwaarden wordt voldaan: • Voorzorgen conform GMPz voor in de uiteindelijke container gesteriliseerde bereidingen. • Volledige bereiding (oplossen, uitvullen en sluiten) uitvoeren in de LAF kast, veiligheidswerkbank of isolator. Indien niet mogelijk, dan kunnen niet-kritische stappen (bijvoorbeeld het afwegen en oplossen van grondstoffen) buiten de LAF-kast worden uitgevoerd. • Zo veel mogelijk gebruik maken van steriele halffabrikaten. • Sterielfiltratie 0,2 microm aan het eind van	De ziekenhuisfarmacie kent naast de aseptische voorraadbereiding de aseptische bereiding met naverhitten 100 ^{0}C 30 min. De SAL 10^{-3} wordt als volgt onderbouwd: - Een kiemgetal voorafgaand aan de thermische kiemreducerende nabehandeling moet minder zijn dan 1 KVE per 10 geproduceerde eenheden. - Uit de literatuur blijkt dat 1 op de 100 bacteriën een sporenvormer is, welke thermische kiemreducerende nabehandeling van 100 ^{0}C 30 min kan overleven [2]. - Alle niet sporenvormers overleven de thermische kiemreducerende nabehandeling niet.

	de vullijn. • Kiemgetal na filtratie en voor naverhitten <0,1 KVE per container. • Bewaarcondities: koelkast. • Microbiologische validatie.	
Aseptic preparation		
31. 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 micro-organism-retaining filter later in the process, should be done in a grade A environment with grade B background.	GMP	
32. Preparation of solutions which 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.	GMP	
33. Handling and filling of aseptically prepared products should be done in a grade A environment with a grade B background.	GMP	
34. 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.	GMP	
35. Preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a grade A environment, with a grade B background, when the product is exposed and is not subsequently filtered.	GMP	
	Aseptische individuele bereidingen	
	35A Z De aseptische individuele bereiding wordt uitgevoerd, indien sterilisatie in de uiteindelijke container en verhitting 100 ^{0}C 30 min niet	De ziekenhuisfarmacie kent naast de aseptische voorraadbereiding de aseptische individuele bereiding. De eisen bij aseptische handelingen

	mogelijk zijn vanwege te grote ontleding of doordat de verpakking er niet tegen bestand is. Er moet aan de onderstaande randvoorwaarden wordt voldaan: • Bereidingsruimte klasse A met minimaal achtergrond klasse D met de daarbij horende monitoring • Persoonlijke hygiëne, kleding en training conform GMP • Volledige bereiding (oplossen, uitvullen en sluiten) uitvoeren in de LAF kast, veiligheidswerkbank of isolator. Indien niet mogelijk, dan kunnen niet-kritische stappen (bijvoorbeeld het afwegen en oplossen van grondstoffen) buiten de LAF-kast worden uitgevoerd. • Werk zoveel mogelijk met (bijna) gesloten systemen en ga indien mogelijk uit van steriele halffabrikaten • Neem extra maatregelen als niet-steriele grondstoffen moeten worden gebruikt, bijvoorbeeld een tweede filtratiestap. • Microbiologische validatie. • Bewaartermijn in microbiologisch opzicht: maximaal 24 uur bij kamertemperatuur en 72 uur in de koelkast.	worden beschreven in hoofdstuk Z3. Een microbiologische houdbaarheid van 24 resp. 72 uur is nog net haalbaar in deze zorgsituaties. Gezien de uiterst kleine kans op besmetting en de groeisnelheden van micro-organismen zijn deze termijnen verantwoord.
Personnel		
36. Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processing. Inspections and controls should be conducted outside the clean areas as far as possible.	GMP	
37. 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 sterile products. This training should include reference to hygiene and to the basic elements of	GMP	

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.		
38. 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.	GMP	
39. High standards of personal hygiene and cleanliness are essential. Personnel involved in the manufacture of sterile preparations should be instructed to report any condition which 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.	GMP	
40. Wristwatches, make-up and jewellery should not be worn in clean areas.	GMP	
41. Changing and washing should follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean	GMP	
42. 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.	GMP	
43. The description of clothing required for each grade is given below: • 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	GMP	

contamination coming from outside the clean area. • 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. • 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.		
44. 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.	GMP	
45. Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants which 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	GMP	

risk of shedding of particles.		
Premises		
46. In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.	GMP	
47. 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.	GMP	
48. False ceilings should be sealed to prevent contamination from the space above them.	GMP	
49. Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.	GMP	
50. 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 backflow.	GMP	
51. Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize 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	GMP	

should be provided only in the first stage of the changing rooms.		
52. Both airlock doors should not be opened simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.	GMP	
53. 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 which 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. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. Decontamination of facilities and treatment of air leaving a clean area may be necessary for some operations.	GMP	
54. 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 particlegenerating person, operation or machine to a zone of higher product risk.	GMP	
55. 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.	GMP	
Equipment		

56. 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).	GMP	
57. 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.	GMP	
58. When equipment maintenance has been carried out within the clean area, the area should be cleaned, disinfected and/or sterilised where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the work.	GMP	
59. 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. Water for injections should be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70°C.	GMP	
60. 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.	GMP	
Sanitation		
61. 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	GMP	

undertaken regularly in order to detect the development of resistant strains		
62. Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.	GMP	
63. Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.	GMP	
Processing		
64. Precautions to minimize contamination should be taken during all processing stages including the stages before sterilisation.	GMP	
65. Preparations of microbiological origin should not be made or filled in areas used for the processing of other medicinal products; however, vaccines of dead organisms or of bacterial extracts may be filled, after inactivation, in the same premises as other sterile medicinal products	GMP	
66. 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.	GMP	
67. 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	GMP	

take into account various interventions known to occur during normal production as well as worst-case situations.		
68 Process simulation tests (for validation of aseptic processing; see 66) 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.	68Z Processimulatietesten voor de validatie van aseptisch bereide en uitgevulde producten (al dan niet met naverhitten 30 min. 100°C) worden uitgevoerd op een worst-case proces, dat door middel van risicoanalyse wordt vastgesteld. Als initiële validatie worden drie achtereenvolgende simulaties met goed resultaat uitgevoerd. De simulatietesten worden minimaal twee keer per jaar herhaald en na iedere significante wijziging aan het HVAC systeem, de apparatuur of het proces.	Binnen de ziekenhuisfarmacie hebben we vaak een grote diversiteit aan producten en processen zodat gekozen wordt voor validatie van het worst-case product per procestype als processvalidatie van aseptisch uitvullen met naverhitten 30 min. 100°C.
69. 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 growth and the following should apply: • When filling fewer than 5000 units, no contaminated units should be detected. • When filling 5,000 to 10,000 units: a) One (1) contaminated unit should result in an investigation, including consideration of a repeat media fill; b) Two (2) contaminated units are considered cause for revalidation, following investigation. • When filling more than 10,000 units: a) One (1) contaminated unit should result in an investigation; b) Two (2) contaminated units are considered cause for revalidation, following investigation.	GMP	
70. For any run size, intermittent incidents of microbial contamination may be indicative of	GMP	

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.		
71. Care should be taken that any validation does not compromise the processes.	GMP	
72. 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.	GMP	
73. 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.	GMP	
74 Microbiological contamination of starting materials should be minimal. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.	74 Z De microbiologische contaminatie van grondstoffen moet voldoen aan de monografie dan wel hoofdstuk 5.1.4 van de Ph Eur.	In de PH. Eur. worden in monografieën van een groot aantal grondstoffen criteria genoemd (als kve/g of kve/ml). Grondstoffen geleverd van een betrouwbare leverancier dienen hier aan te voldoen.
75. Containers and materials liable to generate fibres should be minimised in clean areas.	GMP	
76. Where appropriate, measures should be taken to minimize the particulate contamination of the end	GMP	

product.		
77. Components, containers and equipment should be handled after the final cleaning process in such a way that they are not recontaminated.	GMP	
78 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.	78Z Standtijden van gesteriliseerde utensiliën worden bepaald conform de NEN steriliseren en steriliteit van medische hulpmiddelen.	Gewassen infuuscontainers worden in de ziekenhuisfarmacie binnen een werkdag gebruikt in het bereidingsproces.
79 The time between the start of the preparation of a solution and its sterilisation or filtration through a micro-organism-retaining filter should be minimised. There should be a set maximum permissible time for each product that takes into account its composition and the prescribed method of storage.	GMP	De processen binnen de ziekenhuisfarmacie zijn zo kleinschalig, dat de bereidingprocessen van oplossen tot en met de terminale sterilisatie of aseptisch kiemfiltratie, binnen een werkdag plaatsvinden.
80. The bioburden should be monitored before sterilisation. There should be working limits on contamination immediately before sterilisation, which are related to the efficiency of the method to be used. Bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilised products. Where overkill sterilisation parameters are set for terminally sterilised products, bioburden might be monitored only at suitable scheduled intervals. For parametric release systems, bioburden assay should be performed on each batch and considered as an in-process test. Where appropriate the level of endotoxins should be monitored. All solutions, in particular large volume infusion fluids, should be passed through a micro-organism-retaining filter, if possible sited immediately before filling.	GMP	

81. 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 which achieves the same objective of not introducing contamination. Non-combustible gases should be passed through micro-organism retentive filters.	GMP	
82. 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.	GMP	
Sterilisation		
83. All sterilisation processes should be validated. Particular attention should be given when the adopted sterilisation method is not described in the current edition of the European Pharmacopoeia, or when it is used for a product which is not a simple aqueous or oily solution. Where possible, heat sterilisation is the method of choice. In any case, the sterilisation process must be in accordance with the marketing and manufacturing authorisations.	GMP	
84. 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	GMP	

should be kept of the results.		
85. 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.	GMP	
86. Validated loading patterns should be established for all sterilisation processes.	GMP	
87. Biological indicators should be considered as an additional method for monitoring the 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.	GMP	
88. There should be a clear means of differentiating products which have not been sterilised from those which 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.	GMP	
89. Sterilisation records should be available for each sterilisation run. They should be approved as part of the batch release procedure.	GMP	
Sterilisation by heat		
90. Each heat sterilisation cycle should be recorded on a time/temperature chart with a sufficiently	GMP	

large scale or by other appropriate equipment with suitable accuracy and precision. The position of the temperature probes used for controlling and/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.		
91. Chemical or biological indicators may also be used, but should not take the place of physical measurements.	GMP	
92. 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.	GMP	
93. 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	GMP	
Moist heat		
94. 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	GMP	

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.		
95. The items to be sterilised, other than products in sealed containers, should be wrapped in a material which allows removal of air and penetration of steam but which prevents recontamination after sterilisation. All parts of the load should be in contact with the sterilizing agent at the required temperature for the required time.	GMP	
96. Care should be taken to ensure that steam used for sterilisation is of suitable quality and does not contain additives at a level which could cause contamination of product or equipment.	GMP	
Dry heat		
97. 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 should be used as part of the validation.	GMP	
Sterilisation by radiation		
98. 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	GMP	

absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not normally an acceptable method of sterilisation		
99. During the sterilisation procedure the radiation dose should be measured. For this purpose, dosimetry indicators which 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.	GMP	
100. Biological indicators may be used as an additional control	GMP	
101. Validation procedures should ensure that the effects of variations in density of the packages are considered.	GMP	
102. Materials handling procedures should prevent mix-up between irradiated and nonirradiated materials. Radiation sensitive colour disks should also be used on each package to differentiate between packages which have been subjected to irradiation and those which have not	GMP	
103. The total radiation dose should be administered within a predetermined time span.	GMP	
Sterilisation with ethylene oxide		
104. This method should only be used when no other method is practicable. During process validation	GMP	

it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material.		
105. Direct contact between gas and microbial cells is essential; precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.	GMP	
106. Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimize the time before sterilisation	GMP	
107. Each sterilisation cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.	GMP	
108. For each sterilisation cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration and of the total amount of gas used. The pressure and temperature should be recorded throughout the cycle on a chart. The record(s) should form part of the batch record.	GMP	
109. After sterilisation, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to	GMP	

reduce to the defined level. This process should be validated.		
Filtration of medicinal products which cannot be sterilised in their final container		
110. Filtration alone is not considered sufficient when sterilisation in the final container is possible. With regard to methods currently available, steam sterilisation is to be preferred. If the product cannot be sterilised in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilised container. Such filters can remove most bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment	GMP	
111. Due to the potential additional risks of the filtration method as compared with other sterilization processes, a second filtration via a further sterilised micro-organism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point	GMP	
112. Fibre-shedding characteristics of filters should be minimal.	GMP	

113. The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from this during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals.	113Z Een filterintegriteitstest wordt direct na gebruik uitgevoerd met een voor dat filter geschikte methode. Filters die gassen filtreren worden getest indien het gas in contact komt met het product in de eindverpakking.	Het testen van een productiefilter voor filtratie is voor het proces niet nodig. Immers als blijkt dat een filter na filtratie niet voldoet zal het product worden vernietigd. Uit financieel oogpunt is het wel zinvol het filter voor filtratie te controleren , zodat bij het gebruik van een onjuist of niet-integer filter de partij niet hoeft te worden vernietigd. Het meten van het drukverval over het filter tijdens uitvullen is niet nodig, gezien de productie batchgrootte klein is en daarmee de filtertijd kort in verhouding tot industriële batchgroottes.
114. The same filter should not be used for more than one working day unless such use has been validated	GMP	
115. The filter should not affect the product by removal of ingredients from it or by release of substances into it.	GMP	
Finishing of sterile products		
116. Partially stoppered freeze drying vials should be maintained under Grade A conditions at all times until the stopper is fully inserted.	GMP	
117. 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.	GMP	
118. The container closure system for aseptically filled vials is not fully integral until the aluminium	GMP	

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.		
119. 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.	GMP	
120. 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.	GMP	
121. 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.	GMP	
122. Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimising direct human interventions into the capping operation.	GMP	
123. Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.	GMP	
124. Filled containers of parenteral products should be inspected individually for extraneous	GMP	

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.		
Quality control		
125. The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. The test should be validated for the product(s) concerned.	GMP	
126. In those cases where parametric release has been authorised, special attention should be paid to the validation and the monitoring of the entire manufacturing process.	GMP	
127. Samples taken for sterility testing should be representative of the whole of the batch, but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, e.g.: a. for products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant intervention, b. or products which have been heat sterilised in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.	GMP	

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