Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs

GUI-0119

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Canada

Annex 1 to the *Good manufacturing practices guide* – Manufacture of sterile drugs (GUI-0119)

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Disclaimer

This document does not constitute part of the *Food and Drugs Act* (the Act) or its regulations and in the event of any inconsistency or conflict between the Act or regulations and this document, the Act or the regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the regulations and the applicable administrative policies.

Ce document est aussi disponible en français.

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About this document

1. Purpose

This document provides guidance for fabricating and packaging/labelling sterile drug products.

It is an annex to the current edition of the *Good manufacturing practices guide for drug products (GUI-0001)*. It will help you understand and comply with good manufacturing practices (GMP) for sterile products.

The interpretations in this document have been adopted from those published by the Pharmaceutical Inspection Cooperation Scheme (PIC/S) in *Guide to Good Manufacturing Practice for Medicinal Products Annexes*.

The international norms referenced in this document (e.g. ISO standards) were applicable at the time it was drafted. Future revisions of these norms do not automatically apply to this document. Relevant updates will be reflected in a future version of this document.

2. Scope

These guidelines apply to these types of sterile drugs:

- pharmaceutical
- radiopharmaceutical
- biological
- veterinary

The scope of this document does not include establishment licensing. To understand how to comply with GMP requirements in order to get an establishment licence, see *Guidance on Drug Establishment Licences and Drug Establishment Licensing Fees (GUI-0002).*

Guidelines for active pharmaceutical ingredients (APIs) are described in Health Canada's *Good Manufacturing Practices Guidelines for Active Pharmaceutical Ingredients (GUI-0104)*.

3. Introduction

These guidelines interpret the requirements for manufacturing sterile products in Part C, Division 2, section C.02.029 of the Food and Drug Regulations (the Regulations).

Health Canada is an active participating member of the Pharmaceutical Inspection Cooperation Scheme (PIC/S). In working towards international harmonization, Health Canada has adopted interpretations from those published by PIC/S to support the manufacture of sterile drugs. Future revisions adopted by PIC/S may be reflected by Health Canada in this guidance document.

Guidance documents like this one are meant to help industry and health care professionals understand how to comply with regulations. They also provide guidance to Health Canada staff so that the regulations are enforced in a fair, consistent and effective way across Canada.

The Health Product Compliance Directorate in the Regulatory Operations and Regions Branch at Health Canada inspects establishments to assess their compliance with the *Food and Drugs Act* (the Act) and associated regulations. When we conduct an inspection, we will use this document as a guide in assessing your compliance with GMP requirements for sterile products.

These guidelines are not the only way GMP regulations can be interpreted, and are not intended to cover every possible case. Other ways of complying with GMP regulations will be considered with proper scientific justification. Also, as new technologies emerge, different approaches may be appropriate.

Guidance documents are administrative and do not have the force of law. Because of this, they allow for flexibility in approach. So use this guide to help you develop specific approaches that meet your unique needs.

Guidance

4. Manufacture of sterile drugs

Sterile products

C.02.029

In addition to the other requirements of this Division, a drug that is intended to be sterile shall be fabricated and packaged/labelled

(a) in separate and enclosed areas;

(b) under the supervision of personnel trained in microbiology; and

(c) by a method scientifically proven to ensure sterility.

Rationale

Manufacturing sterile products is subject to special requirements, to minimize risks of microbiological contamination and particulate and pyrogen contamination.

A lot depends on the skill, training and attitudes of the personnel involved. Quality assurance is particularly important. This type of manufacture must strictly follow carefully established and validated methods of preparation and procedure. You must not rely only on a terminal process or finished product test for sterility or other quality aspects.

The guidance that follows has been adopted from "Annex 1: Manufacture of sterile medicinal products" in the Pharmaceutical Inspection Cooperation Scheme (PIC/S) document *Guide to Good Manufacturing Practice for Medicinal Products Annexes (PIC/S)*.

Interpretation

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.

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 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 drugs 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 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

Clean room and clean air device classification

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 1.0: Maximum permitted airborne particle concentration (by grade)

Grade	Maximum permitted number of particles/m³ equal to or greater than the tabulated size			
	At rest		In operation	
	0.5µm	5.0µm	0.5µm	5.0µm
A	3,520	20	3,520	20
B	3,520	29	352,000	2,900
C	352,000	2,900	3,520,000	29,000
D	3,520,000	29,000	not defined	not defined

5. For classification purposes in Grade A zones, a minimum sample volume of 1m³ 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.

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 should be used in unidirectional airflow systems.

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.

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.

9. For Grade A zones, particle monitoring should 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.

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.

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.

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.

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.

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.

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.

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.

17. Examples of operations to be carried out in the various grades are given in the tables below (see also paragraphs 28 to 35):

Table 2.1: Examples of operations for terminally sterilised products

Grade	Examples of operations for terminally sterilised products (see para. 28-30)
A	Filling of products, when unusually at risk
C	Preparation of solutions, when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling

Table 2.2: Examples of operations for aseptic preparations

Grade	Examples of operations for aseptic preparations (see para. 31-35)
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

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.

19. Recommended limits for microbiological monitoring of clean areas during operation:

Table 3.0: Recommended limits for microbial contamination [(a)]

Grade	Air sample cfu/m³	Settle plates (diam. 90 mm), cfu/4 hours [(b)]	Contact plates (diam. 55mm), cfu/plate	Glove print 5 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.

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.

Isolator technology

21. The utilisation 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.

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.

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.

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.

25. Monitoring should be carried out routinely and should include frequent leak testing of the isolator and glove/sleeve system.

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.

27. Because of this special technology particular attention should be paid to, at least the following:
    a. equipment design and qualification
    b. validation and reproducibility of cleaning-in-place and sterilisation-in-place
    c. background clean room environment in which the equipment is located
    d. operator training and clothing

e. interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

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.

29. Filling of products for terminal sterilization should be carried out in at least a grade C environment.

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 sterilization.

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.

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.

33. Handling and filling of aseptically prepared products should be done in a grade A environment with a grade B background.

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.

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.

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.

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 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.

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.

40. Wristwatches, make-up and jewellery should not be worn in clean areas.

41. 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.

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.

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 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.

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 risk of shedding of particles.

Premises

46. 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.

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.

48. False ceilings should be sealed to prevent contamination from the space above them.

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.

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.

51. 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.

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.

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.

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 particle generating person, operation or machine to a zone of higher product risk.

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.

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).

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.

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.

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.

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.

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 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.

63. Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

Processing

64. Precautions to minimise contamination should be taken during all processing stages including the stages before sterilisation.

65. Preparations of microbiological origin should not be made or filled in areas used for the processing of other drugs; however, vaccines of dead organisms or of bacterial extracts may be filled, after inactivation, in the same premises as other sterile drugs.

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.

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 take into account various interventions known to occur during normal production as well as worst-case situations.

68. 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.

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:
        i. One (1) contaminated unit should result in an investigation, including consideration of a repeat media fill;
        ii. Two (2) contaminated units are considered cause for revalidation, following investigation.
    - When filling more than 10,000 units:
        i. One (1) contaminated unit should result in an investigation;
        ii. Two (2) contaminated units are considered cause for revalidation, following investigation.

70. 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.

71. Care should be taken that any validation does not compromise the processes.

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.

For more information on the validation of aseptic processing, please see *Process Validation: Aseptic Processes for Pharmaceuticals (GUI-0006)*.

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.

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.

75. Containers and materials liable to generate fibres should be minimised in clean areas.

76. Where appropriate, measures should be taken to minimise the particulate contamination of the end product.

77. Components, containers and equipment should be handled after the final cleaning process in such a way that they are not recontaminated.

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.

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.

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.

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.

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.

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 (or other relevant) 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.

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 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.

86. Validated loading patterns should be established for all sterilisation processes.

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.

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.

89. Sterilisation records should be available for each sterilisation run. They should be approved as part of the batch release procedure.

Sterilisation by heat

90. 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 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.

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.

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.

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 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 sterilising agent at the required temperature for the required time.

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.

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.

Sterilisation by radiation

98. Radiation sterilisation is used mainly for the sterilisation of heat sensitive materials and products. Many drugs 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.

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.

100. Biological indicators may be used as an additional control.

101. Validation procedures should ensure that the effects of variations in density of the packages are considered.

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.

103. The total radiation dose should be administered within a predetermined time span.

Sterilisation with ethylene oxide

104. This method should only be used when no other method is practicable. During process validation 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.

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 minimise the time before sterilisation.

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.

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.

109. After sterilisation, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to reduce to the defined level. This process should be validated.

Filtration of drugs 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.

111. Due to the potential additional risks of the filtration method as compared with other sterilisation 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.

112. Fibre-shedding characteristics of filters should be minimal.

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.

114. The same filter should not be used for more than one working day unless such use has been validated.

115. The filter should not affect the product by removal of ingredients from it or by release of substances into it.

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.

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.

118. 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.

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.

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.

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.

122. Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimising direct human interventions into the capping operation.

123. Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.

124. 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.

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.

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.

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. for 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.

5. GMP Annex 1 Revision 2008

Interpretation of most important changes for the manufacture of sterile medicinal products

The guidance in this section has been adopted from the Pharmaceutical Inspection Cooperation Scheme (PIC/S) document GMP Annex 1 Revision 2008: Interpretation of most important changes for the manufacture of sterile medicinal products (PIC/S).

Clean room / clean air device classification

General interpretation: The GMP Annex 1 Revision distinguishes very clearly between clean room / clean air device classification which is described in sections 4 to 7, and clean room monitoring, which is described in sections 8 to 20.

Section 3 defines at rest and in operation states, which is not new. However, it should be noted that the company needs SOPs to define at rest and in operation states, which might be specifically required per production room. These SOPs should include a definition of equipment to be installed and running, number of operators to be present.

In general, clean room / clean air device classification is required to be performed according to EN ISO 14644-1 with the applicable limits for particle counts defined in the table in section 4 of GMP Annex 1. Probe-locations should be chosen in order to demonstrate the homogeneity across the room. A classification report should be prepared according to section 4.4 of ISO 14644-1 and section B.1.4 of ISO 14644-3.

Monitoring, on the other hand, does not need to be performed according to EN ISO 14644-1. It can be performed for a reduced number of sampling points and sampling volumes. A formal risk analysis study based on experiments and analysis of the monitoring data (over at least 6 month operation) should provide a basis for the determination of frequencies and limits. Frequencies and limits should be process- based and the results of the initial qualification and ongoing monitoring should be taken into account when setting operational alert and action limits. These limits and sample locations should be periodically reviewed for on-going validity of the risks initially considered.

Those frequencies and limits should be process-based and the results of the qualification should be taken into account.

Section 4

New text: 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.

Interpretation

Classification of clean rooms / clean air devices should be done according to provisions in EN ISO 14644-1. Compared with the prior version, the values for maximum permitted particles have been changed in this section. Especially the values for the maximum permitted number of 5 µm particles / m^3 for grade A have been changed from 1 to 20. For grade A, the corresponding ISO class is 4.8, based on the 5 µm counts.

For grade D, no in operation limits are defined; the company should establish in operation limits based on a risk analysis and on historical data where applicable

Section 5

New text: For classification purposes, EN/ISO 14644-1 methodology defines both the minimum number of sampling locations and the sample size.

Interpretation

Minimum amount of sampling points and sampling volume and also interpretation of the results are defined in EN ISO 14644-1 (confidence interval). See also provisions for outliers in appendix B 6.2 of EN ISO 14644-1.

ISO 14644-1 Annex f has an informative section on the use of sequential sampling techniques for non-viable particle monitoring. This technique may be useful in reducing the time needed for sampling very large clean-room areas, at rest. This method would not be considered suitable for "in operation" classification.

The application of this method may be acceptable but it is unlikely to be the preferred method since most pharmaceutical facilities do not normally have the very large clean rooms of the type discussed in Annex f and therefore it is unlikely that significant time would be saved.

Section 6

New text: 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 µm in remote sampling systems with long lengths of tubing.

Interpretation

This section implies that old central particle counters with long tube lengths will no longer be acceptable for clean room classification, as they absorb too many particles (especially 5 µm particles). Therefore, modern portable particle counters with short tubes or (even preferable when possible) those without tubes should be used for classification purposes. The certificate of calibration of the particle counter should mention the tube length and nature of material (inox or polymer). When calibration of the particle counter is performed outside by an external laboratory, the particle counting system should be qualified on site with a comparative measurement with an isokinetic probe. For impact on monitoring, see also section 11.

Section 7

New text: EN ISO 14644-2 provides information on testing to demonstrate continued compliance with the assigned cleanliness classifications.

Interpretation

This provision concerns clean room re-qualification. The company may choose to perform re-qualification of clean rooms according to provisions in EN ISO 14644-2 (including the proposed frequencies). For re-qualification of grade A areas, it is generally expected to carry out the following activities also performed during initial classification: air velocity, filter integrity, differential pressure every 6 months. Other examples for frequencies: grade B: every 6 months at rest, once a year in operation; other grades: once a year, with maximum delay defined. If the company takes another approach, this should be justified, e.g. based on monitoring data.

Clean room / clean air device monitoring

Section 8

New text: 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.

Interpretation

Frequency, location and number of monitoring locations should be based on a formal risk assessment and not on ISO 14644-1. Data obtained during classification and previous monitoring data should be considered. Critical locations should be covered.

Section 9

New text: For grade A zones, particle monitoring should 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. 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.

Interpretation

In critical areas with exposed product continuous monitoring, covering the duration of the operations is expected. Continuous means that the system must be able to pick up any potentially occurring event of an unusual number of particles, including an event that occurs for a short time only. Manifold systems might not be suitable for Grade A Zone monitoring due to a lack in responsiveness. It is important that monitoring in grade A comprises equipment assembly, because there is a high impact of the human operator. An SOP should be present defining alert levels and pre-defined corrective measures in cases of alerts and interventions.

Section 10

New text: It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased. 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.

Interpretation

Continuous monitoring (see definition under interpretation to section 9) is expected while not fully integral containers are handled in the B zone, e.g. partially stoppered vials within a laminar air flow mobile unit prior to lyophilisation. Manifold systems might not be suitable for Grade B Zone monitoring due to a lack in responsiveness.

Section 11

New text: 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 radii of any bends in the tubing must be considered in the context of particle losses in the tubing.

Interpretation

This section addresses concerns especially for the sedimentation of 5 µm particles in remote systems (as a rough example, s-shaped bent tubing of 1.5 m length can already absorb about 30% of the 5 µm particles.). The company must qualify their particle sampler and sampling system for both particle sizes, 0.5 µm and 5 µm.

Section 12

New text: It is not necessary for the sample volume to be the same as that used for formal classification

Interpretation

The important point for sampling during monitoring is to be able to sample quickly (especially in critical areas), to be able to link a particle excursion to an actual event and to be able to generate an alarm so that operators are immediately aware of the alarm situation. Thus sampling of 1 m^3 (which often takes 30 minutes) could be inadequate during monitoring of an A zone during operation.

Section 15

New text: 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.

Interpretation

The number of sampling points and the sampling frequency are to be determined by at least a risk assessment, including risk identification, risk analysis and risk evaluation (see also GMP Annex 20). There is no need for a continuous monitoring. However, the frequency should be higher than that of Re-Qualification of these areas.

Microbiological monitoring

There are no changes to the provisions for microbiological monitoring (sections 18 and 19).

However, it is important to note that for critical sampling locations in grade A areas where aseptic operations are performed, every found microorganism should result in a thorough investigation, the microorganism has to be identified and impact on batch release should be considered. An additional comment should be made on the limits for settle plates. These limits are interpreted as limit per settle plate. Also, the same limits apply when sampling time is less than 4 hours, e.g. for operations being shorter than 4 hours.

All methods indicated for a specific grade in the table of section 19 should be used for monitoring the area of that specific grade. If one of the methods is not used, this should be justified.

Media simulations

The provisions for media simulations (sections 66-71) are now fully harmonized with FDA aseptic guide. This should not give rise to problems. Section 7 includes a need for media fills to be done under worst-case conditions.

Bioburden monitoring

Section 80

New text: 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 assays 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.

Interpretation

General: The contribution to bioburden of the various raw materials and packaging materials together with the manufacturing processes prior to the sterilisation step should be understood and controlled. A monitoring and control strategy including periodic monitoring and trending of bioburden prior to any bioburden reduction step should be established and justified on the basis of process risks. Volumes sampled should be justified and take account of the expected level of contamination

The bioburden should at least be determined for the product prior to the final sterilization step. Acceptance criteria for bioburden must be based on the sterilising step, a sterility assurance level of

10^{-6} must be met. The results of the bioburden assays must be present before release (unless an overkill cycle is used for terminal sterilisation). This favours the use of rapid micro-methods.

A risk assessment should be performed in order to determine the need for endotoxin studies. When needed, endotoxins should be determined also for the units of product that were filled the last.

Terminal sterilisation: For terminal sterilisation the F_o value has to be taken into account. The sampling should be performed on filled containers prior to sterilisation. For overkill sterilisation processes for terminally sterilized products, the company must justify the intervals chosen for bioburden testing.

Aseptic operations: For sterile filtration, filter efficacy studies must be taken into account when determining the acceptance criteria for the bioburden prior to filtration. This means that if two subsequent filtration steps are used, product has to be sampled prior to the last filtration step, if technically possible, e.g. first filtration into bulk tank, second filtration immediately prior to filling. However, if a system of two filters with redundancy is used (the second filter is used for security, if one fails the required SAL is still achieved), sampling should be performed upstream of these filters in order not to compromise the filtration step. The company has to justify its approach if sampling is done before the first filtration step.

Provisions for environmental conditions for the handling of aseptically filled vials after leaving the aseptic processing area up until final sealing

Interpretation

General: These provisions are valid not only for freeze-dried vials but for all aseptically filled vials. If crimp-capping is done as a "clean process" (see section 120) these provisions define requirements for the environment for vials from the moment they leave the aseptic processing area until the crimp cap has been crimped into place on the stoppered vial. Grade A air supply is required for conveyor tunnels connecting the aseptic processing area with the crimp capping machine for liquid products and powder, and the transport of freeze-dried vials from the freeze dryer to the crimp capping machine and the crimp capping machine itself.

Grade D classification is considered to be the minimal requirement for the clean room in which the crimp-capping machine is located. The company has to justify their approach for choosing the appropriate room class.

It is important to note that in order to avoid contamination of the product at this stage, not only one but several factors are important such as the design of the vial stopper combination, a thoroughly validated detection systems of misplaced or missing stoppers, restricted access of operators, good training of operators, thorough procedures for manual interventions and follow-up actions and adequate environmental conditions.

Section 116

New text: Partially stoppered freeze drying vials should be maintained under grade A conditions at all times until the stopper is fully inserted.

Interpretation

There should be no problem with this point, which is basically equivalent with the provisions in section 12 of the prior version of the Annex.

Section 118

New text: 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.

Interpretation

This is to be used as a definition. It does not mean that the product is considered open prior to crimp capping and therefore it is not a requirement for aseptic conditions up to crimp capping. However, for more detail on specific requirements see section 120.

Section 120

New text: Vial capping can be undertaken as an aseptic process using sterilized 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.

Interpretation

For lyophilized products: product transfer from filling machine to freeze dryer should be done under grade A conditions (e.g. laminar air flow mobile unit) with grade B surroundings. Transfer to the crimp-capping machine should be done under grade A air supply. For liquid products and powders: transfer from the aseptic processing area to the crimp capping machine should be done under grade A air supply. For all products: Crimp capping should be done under grade A air supply. Sterilization of crimp caps is only mandatory, when crimp capping is performed in the aseptic core.

The new revision of Annex 1 mentions a new term, Grade A air supply, but no definition of this new term is given in the revised Annex. Inspectors and Industry therefore need an interpretation of this term, especially as a provision of a grade A air supply is one of the most significant changes in Annex 1.

The term grade A air supply is specifically used to describe a supply of air which is HEPA filtered, and at the point of supply meets when tested, the non-viable particulate requirements of a grade A area, as defined in paragraph 4 of the revised Annex 1. It is important to differentiate between the terms grade A air supply and grade A area. A grade A air supply should be qualified and monitored as follows:

Qualification requirements:

- Qualification is done only under at rest conditions: For the crimp-capping machine the at-rest state is achieved when the air supply is switched on, the crimp-capping machine is operating (feeding of vials and crimp caps is not considered necessary) and there is no interference by operators. For the conveyor tunnel for liquid products the at-rest state is achieved when the air supply is switched on, the conveyor belt is switched on and there is no interference by operators.
- Non-viable particles should be measured and are expected to meet grade A requirements. The probe should be located at the point of supply of the filtered air.
- Smoke studies should be performed. Whilst unidirectional air flow is not required, efficient protection of the vials should be demonstrated and the absence of air entrainment from the surrounding room should be demonstrated.
- Limits for air velocity should be in place and justified.

Monitoring requirements:

- Monitoring requirements for non-viable particles and microbiological contamination should be defined by the company following a risk assessment.

Section 121

New text: 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 vials and to minimise microbial contamination.

Interpretation

It is essential that there is a robust system, capable of detecting with a very high probability displaced or missing stoppers prior to capping. These vials should be rejected prior to capping. For thoroughly validated systems, a physical ejection of rejected vials after the capping station is acceptable although physical ejection prior to capping is preferred. The better the controls are for correctly set stoppers and demonstration of integrity, the lower the dependence is for the monitoring of the capping environment. If there is no such detection and rejection system in place, capping must be performed as an aseptic process rather than as a clean process.

Procedures must be in place defining manual interventions, avoiding unnecessary contamination and measures in case of manual interventions. This is true also for the handling of the transport tunnel for liquid products.

Section 122

New text: Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimising direct human interventions into the capping operation.

Interpretation: The use of RABS or isolators is not a direct requirement; human impact can be reduced by other means as well.

Appendices

Appendix A – Glossary

Acronyms

API: Active pharmaceutical ingredient

GMP: Good manufacturing practices

ICH: International Council on Harmonisation

MRA: Mutual recognition agreement

NOC: Notice of compliance

OOS: Out of specification

PIC/S: Pharmaceutical Inspection Cooperation/Scheme

RABS: Restricted access barrier systems

SOP: Standard operating procedure

VICH: Veterinary International Council on Harmonisation

WFI: Water for injection

WHO: World Health Organization

Terms

These definitions explain how terms are used in this document. Definitions quoted from other documents are identified in brackets at the end of the definition. If there is a conflict with a definition in the *Food and Drugs Act* or Food and Drug Regulations, the definition in the Act/Regulations prevails. More applicable definitions can be found in the *Good manufacturing practices guide for drug products (GUI-0001)*.

Airlock – "An enclosed space with two or more doors, and which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the air-flow between those rooms when they need to be entered. An air-lock is designed for and used by either people or goods." (PIC/S)

Aseptic area – A zone or zones within a clean area where Grade A or B (see table in Section C.02.029 of these guidelines) conditions are maintained.

Aseptic process – A process for compounding and assembling sterile bulk drugs or raw materials with sterile packaging components under Grade A or B conditions to produce a sterile product (see table in Annex 1 to the Good Manufacturing Practices Guide – Manufacture of sterile medicinal products).

Clean area – "An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area." (PIC/S)

Critical area – Area in which the sterilized drug product, containers, and closures are exposed to environmental conditions that must be designed to maintain product sterility. Activities conducted in this area include manipulations, such as aseptic connections, sterile ingredient additions, filling and closing operations.

Grade A air supply – "A supply of air which is HEPA filtered, and at the point of supply meets when tested, the non-viable particulate requirements of a Grade A area." (PIC/S)

Growth promotion – A test in which prepared media is challenged with pre-selected organisms to assure that the media is capable of supporting growth.

Radiopharmaceutical – "A drug that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons." (C.03.201)

Room classification – Room classification is part of the initial qualification of a facility and is also normally performed during routine re-qualification. Both, classification activities and the final / to be achieved classification status for clean rooms / clean air devices are meant. This Annex directly links to clean room / clean air device classification according to ISO 14644. For qualification and validation and re-qualification see also PIC/S GMP Guide Annex 15. (PIC/S)

Sterile – Free from viable microorganisms.

Terminal sterilization – The sterilizing of a drug in its final closed container.

Appendix B – References

Food and Drugs Act
http://laws.justice.gc.ca/en/F-27

Food and Drug Regulations
http://laws.justice.gc.ca/en/F-27/C.R.C.-C.870

Good manufacturing practices guide for drug products (GUI-0001)
www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php

GMP Annex 1 Revision 2008: Interpretation of most important changes for the manufacture of sterile medicinal products (PIC/S)
https://www.picscheme.org/layout/document.php?id=159

Guide to Good Manufacturing Practice for Medicinal Products Annexes (PIC/S)
https://www.picscheme.org/layout/document.php?id=127

Process Validation: Aseptic Processes for Pharmaceuticals (GUI-0006)
www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/app-papp-eng.php

ISO standards
www.iso.org/iso/home/store/catalogue_ics.htm

- ISO 14644-1: 1999. Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness by particle concentration
- ISO 14644-2: 2000. Cleanrooms and associated controlled environments - Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1
- ISO14644-3: 2005. Cleanrooms and associated controlled environments — Part 3: Test methods
- ISO 14644-4: 2001. Cleanrooms and associated controlled environments – Part 4: Design, construction and start-up
- ISO 14644-5: 2004. Cleanrooms and associated controlled environments – Part 5: Operations

The ISO standards referenced in this document were applicable at the time of drafting. Future revisions of these standards do not automatically apply to this document. Relevant updates will be reflected in a future version.

Appendix C – Questions and answers

1. **Does the supervisor of a sterile product manufacturing facility need to have a degree in microbiology?**

   Section C.02.029 (b) "Sterile Products" of the Food and Drug Regulations requires that "…a drug that is intended to be sterile shall be produced under the supervision of personnel trained in microbiology…". The expression "trained in microbiology" does not mean that this person must have a university degree in microbiology. However, the person must have taken university courses in microbiology.

2. **If water that has already been used in compounding is later found to contain endotoxins, what actions need to be taken?**

   Water can be used for production before obtaining microbiological test results, but the results of these tests must be available before final release of the product. Good manufacturing practices permit release only after raw material and finished product testing is completed and results show the product complies with its specifications.

   The appropriate action would include an investigation into:

   - the potential sources of endotoxins
   - the sanitation and maintenance of the water system

3. **Are sterile products in amber glass and plastic ampoules exempt from 100% visual inspection?**

   No. You must visually inspect each final container of injections. The 100% visual inspection test does not limit itself to particulate matter. It also includes sealing defects, charring, glass defects, underfills and overfills, missing print, etc. Please see interpretation 124. For parenteral products, there are more requirements for packaging (e.g. the immediate container must be of a material and construction that allows visual or electronic inspection of the drug). Please see section C.01.069 "Limits of Variability" in the Food and Drug Regulations.

4. **What are the requirements in terms of monitoring/testing for the release of sterile gowns to be used in a controlled environment (Grades A or B), when they are obtained from a supplier?**

   There are no specific requirements in this document for the sterility testing of protective garments to be worn in Grades A and B areas. However, the sterility cycle used by an outside supplier to sterilize these garments should have been validated according to scientifically sound procedures. Also, the integrity of the outside wrapping (to maintain sterility) should be demonstrated.

5. What are the room classification requirements for preparing containers and other packaging materials to be used in fabricating sterile products?

Normally, you would prepare (clean, wash, etc.) containers and packaging materials in a "clean" room (Grades C or D). Afterwards, for drugs sterilized by filtration (and not further subjected to terminal sterilization in their final containers), you must depyrogenate and sterilize (using double-ended sterilizers or any other validated method) the containers and materials used before introducing them into aseptic rooms. The depyrogenation step can be done using pyrogen-free water for injection (WFI) for the last rinse before sterilization, or by performing the depyrogenation and sterilization in one operation using a dry heat oven. Filling of these products normally takes place in a Grade A area with a Grade B background.

For products that are terminally sterilized, you do not have to use containers and packaging materials that are sterile. However, those in direct contact with the product should be free of pyrogen. This is usually done by using pyrogen-free WFI for the last rinse of these materials, unless they are later depyrogenated by another method (for example, using a dry heat oven).

Also, the initial bioburden of these materials should meet pre-established limits, based on sound science. Keep the risk of contamination during their introduction in filling areas to a minimum.

6. For the validation of moist heat sterilization cycles, will the new standards include the use of prions as the organism of choice (instead of Bacillus stearothermophilus)?

At the present time, the scientific and pharmaceutical community recognizes the spores of Bacillus stearothermophilus as the organisms of choice for validating moist heat sterilization cycles. The use of prions (infectious proteins) could be inadequate because their detection and quantification—which is based on animal models—is very difficult. Also, these proteins are very hard to destroy and could present a danger should they accidentally be spread in a plant.

7. According to the monograph on parenteral products (0520) of the 4th edition (2002) of the *European Pharmacopoeia* (Ph. Eur.), injections for veterinary use with a volume dose of less than 15 mL are exempted from bacterial endotoxins/pyrogen testing by the European Union (EU). Is this interpretation correct? If so, would this EU exemption be applicable in Canada?

Yes, this interpretation is correct. But this exemption does not apply in Canada.

As per section C.01.067 (1) "Limits of Variability" in the Regulations, each lot of a drug for parenteral use must be tested for the presence of pyrogens using an acceptable method. Each lot must be found to be non-pyrogenic. The Bacterial Endotoxins and Pyrogen test methods described in the *United States Pharmacopeia* (USP) and Ph. Eur. are considered acceptable methods for that purpose.

For all parenteral drug products, the Bacterial Endotoxins test should be preferred over the Pyrogen test, unless the latter is shown to be justified (more appropriate) or has been approved by a review directorate. So the specification of all drug products for parenteral use intended for the Canadian market should include a test for Bacterial Endotoxins or Pyrogens, and the current EU "15 mL exemption" does not apply in Canada.

The only acceptable exemptions are those provided in section C.01.067 (2) “Limits of Variability.” In other words, not testing a parenteral drug product for the presence of pyrogens would be considered acceptable only if documentation is available to show that the parenteral drug product is inherently pyrogenic or that it cannot be tested by any of the methods.

8. For radiopharmaceuticals, can it be acceptable to verify the integrity of the sterilizing filter only after use, and to not perform the pre-filtration integrity testing?

As per Interpretation 113, the integrity of the sterilizing filter must be verified before and after use.

However, the pre-filtration integrity testing for radiopharmaceuticals could lead to radioactive contamination (as a result of the venting process of the filter assembly that must be performed before the start of product filtration). This would pose an unacceptable health risk for the operators and could result in disruption of production until the facility is decontaminated.

It is therefore acceptable to use two filters of a minimum filter rating of 0.22 micron, and to verify the integrity of the sterilizing filters after use only for these products. However, data should be available from the filter manufacturer that the filters are supplied pre-assembled and individually integrity tested by the filter manufacturer.

9. What is Health Canada’s position on pooling of samples within the same batch (e.g. seven samples in one pool) for testing for sterility? The *European Pharmacopoeia* (Ph. Eur.) does not mention explicitly a pooling of samples for testing for sterility.

It is acceptable to pool samples for sterility testing with the membrane filtration method. But it is not acceptable to pool samples if you use the direct inoculation method. Exceptions can be tolerated when the volume of the sample pool does not exceed 10% of the culture medium volume.