New Zealand Code of
Good Manufacturing Practice
for Manufacture and Distribution
of Therapeutic Goods

Part 3
Compounding and Dispensing

Annex 1:
Compounding of Sterile Pharmaceutical Products
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of Therapeutic Goods

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This Annex should be read in conjunction with
Part 3: Compounding and Dispensing for those pharmacies
engaged in the preparation of sterile and aseptic products.
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Susan Peacock  Pharmacy Guild of NZ
Ursula Egan  Pharmaceutical Society of NZ
Melissa Whitbrook  Hospital Pharmacist
Alex Yung  Hospital Pharmacist
Naina Panchia  Hospital Pharmacist
Bruce Laird  Community Pharmacist
Eleanor Hawthorn  Community Pharmacist
Warren Flautney  Community Pharmacist
Melissa Young  Ministry of Health
Peter Pratt  Ministry of Health

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INTRODUCTION

Principle

The compounding of sterile preparations has special requirements in order to minimise 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 of particular importance, and compounding must strictly follow carefully established and validated methods of preparation and procedures.

The practices outlined in this document are considered general guidelines and may be adapted to meet individual needs. The equivalence of alternate approaches should be validated.

Application

Issues relating to protection of personnel preparing or handling hazardous pharmaceuticals, such as cytotoxic medicines, are not addressed in this annex.

This annex is primarily intended for use by pharmacists involved in the preparation and dispensing of sterile products but should also be applied by others involved in this work. It does not apply to licensed manufacturers of sterile products, nor does it apply to preparation of medicines for administration to patients in a medical emergency.

Sterile products should be prepared and dispensed to individual patients, as and when required. Batch preparation of sterile products for stock should be avoided wherever possible (unless premises are licensed to manufacture sterile products). However, it is recognised that batch preparation for stock may be necessary in some circumstances, particularly over weekends and holiday periods. The following guidelines should be applied in these circumstances:

- No more than one week's supply should be prepared in anticipation of demand.
- All ingredients must be sterile ingredients prepared by licensed manufacturers.
- Products should be given expiry dates based on stability data.
GLOSSARY

Definitions given below apply to the words as used in this code. They may have different meanings in other contexts.

Airlock
An enclosed space with two or more doors, and which is interposed between two or more rooms, eg. of differing class of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock designed may be for and used by people or goods.

Anteroom
A room attached to a clean area, providing access to the clean area for personnel, equipment, and operating components.

Aseptic preparation area
A room or area designated for the preparation of sterile products. This area includes the critical area and may include a clean area.

Aseptic preparation/technique
The use of procedures in the preparation of sterile products which minimise or prevent the introduction of micro-organisms.

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.
Note: The classification of environmental cleanliness is given in Table 1 below.

Critical area
A grade A area intended to protect sterile products manufactured within the area from any secondary microbial contamination.

Hepa filter
A high-efficiency particulate air (HEPA) filter. HEPA filters are used as a component of a horizontal or vertical laminar airflow hood or room.

Isolator
A self-contained enclosed apparatus which provides a clean working environment for the handling of materials which require protection from contamination or require containment for personal and background environment protection. It consists of a work zone which maintains specified air purity and one or more transfer devices which isolate the work zone from the background environment. Manipulation within the work zone is performed through fitted glove ports.

Laminar airflow
An airflow in which the entire body of HEPA filtered air within a defined area moves in a uniform and uni-directional manner.

Sterile
The absence of living organisms.

Sterile alcohol
Sterile 70% isopropyl alcohol or sterile 70% ethanol.

Table 1: CLASSIFICATION FOR ENVIRONMENTAL CLEANLINESS

<table>
<thead>
<tr>
<th>Grade</th>
<th>Class</th>
<th>Max. permitted number of particles per m$^3$ equal to or above</th>
<th>Max. permitted number of viable microorganisms per m$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>10</td>
<td>3,500</td>
<td>none</td>
</tr>
<tr>
<td>B</td>
<td>100</td>
<td>3,500</td>
<td>none</td>
</tr>
<tr>
<td>C</td>
<td>10,000</td>
<td>350,000</td>
<td>2,000</td>
</tr>
<tr>
<td>D</td>
<td>100,000</td>
<td>3,500,000</td>
<td>20,000</td>
</tr>
</tbody>
</table>

* Low values are only reliable when a large number of air samples are taken

Notes:
- Laminar airflow systems should provide a homogenous air speed of 0.30 m/s for vertical flow and 0.45 m/s for horizontal flow.
- In order to reach the B, C and D grade areas, the number of air changes should generally be higher than 20 per hour in a room with a good airflow pattern and appropriate HEPA filters.
- It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress, due to generation of particles or droplets from the product itself.
CHAPTER ONE

COMPOUNDING OF STERILE PRODUCTS

1.1 Aseptically-prepared products (products prepared by aseptic technique, not subjected to terminal sterilisation in their final container) should be prepared in a Grade A environment. Such an environment exists in a certified horizontal or vertical airflow hood, or a certified isolator. The airflow hood or isolator should be kept running continuously, or turned on for the period specified by the manufacturer before work begins.

1.2 A horizontal or vertical airflow hood should be placed in a Grade D background or better.

1.3 Terminally sterilised products (products subjected to sterilisation procedures in their final container) should be manufactured in a grade C environment in order to give low microbial and particulate counts, suitable for filtration and sterilisation. It could be allowed in a Grade D environment, provided additional steps are taken in order to minimise the contamination, such as the use of closed vessels.

1.4 Clean areas should be maintained to an appropriate standard of cleanliness and supplied with air which has passed through filters of an appropriate efficiency. Clean areas for compounding of sterile products are classified according to the required characteristics of the air, in Grades A, B, C and D. The air characteristics are given in Table 1 in the Glossary, on page 11.

CHAPTER TWO

PERSONNEL

2.1 An appropriately qualified person with sufficient training and/or experience should be responsible for sterile production operations. The designated person should be knowledgeable in the following areas:

- aseptic technique and contamination factors
- environmental monitoring, facilities, equipment and supplies
- parenteral routes of drug administration, methods and equipment for administration of drugs
- procedures for preparation, compounding, distribution and storage of sterile products
- chemical, pharmaceutical and clinical properties of all ingredients in a sterile product
- documentation, general quality control and assurance procedures.

2.2 The designated person should ensure that all sterile products have the identity, strength, quality and purity purported for the preparation.

2.3 Only the minimum number of personnel required should be present in clean areas. Personnel who are required to be in the area should be properly attired.

2.4 Personnel involved in sterile preparation should maintain high standards of personal hygiene and cleanliness.

2.5 Personnel with any health condition which may adversely affect the safety and quality of sterile products should be assessed and exempted from responsibilities in the area if necessary.

2.6 Wrist watches and jewellery (including smooth wedding bands) should not be worn in clean areas and cosmetics should not be used.
CHAPTER THREE
FACILITIES

3.1 The aseptic preparation area should be designed, operated and managed so as to minimise microbial and particulate contamination.

3.2 The aseptic preparation area should be a limited access area that is separated from other operations. Unrelated activities should not take place in the aseptic preparation area.

3.3 Eating, drinking, chewing, smoking, and storing food, drink, smoking materials and personal items in the production and storage areas should be prohibited. Any unhygienic practices (e.g., ear piercing, cholesterol testing, pregnancy testing) within the aseptic preparation area or any other area where the product might adversely be affected, should be forbidden.

3.4 The aseptic preparation area should be clean (to the appropriate cleanliness standard), and should be of sufficient size and well lit. Premises should be designed and maintained in a manner which will prevent entry of insects and migration of extraneous material from outside.

3.5 The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn by staff.

3.6 Floors, walls, partitions and ceilings of the aseptic preparation area should be non-porous and washable. All exposed surfaces should be maintained as smooth, impervious and unbroken surfaces to minimise the shedding or accumulation of particles or microorganisms and to permit the repeated applications of cleaning agents and disinfectants.

3.7 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. Pipes and ducts should be installed so that they do not create recesses which are difficult to clean. Doors should be carefully designed to avoid uncleanable recesses; sliding doors are undesirable for this reason.

3.8 Sinks and drains should be avoided and should be excluded from aseptic preparation areas. Where installed they should be designed, located and maintained so as to minimise risks of microbial or foreign material contamination generated during sink usage.
CHAPTER FOUR
EQUIPMENT

3.9  An adjacent support area (eg, anteroom and change room) is desirable. This should be separated from the aseptic preparation area by a barrier (eg, wall, partition, floor length plastic curtain). Appropriate activities for the support area include handwashing, gowning, gloving, removal of packaging and cardboard items, and disinfecting supplies before placing these items in the clean area.

3.10  Where an area is designated as a clean area (Grade D or better):

a)  It should have sufficient airflow (as specified in Table 1 in Glossary) and a positive pressure differential relative to adjacent controlled and uncontrolled areas. The pressure gradient between successive pressurised areas should not be less than 15 pascals.

b)  Changing rooms should be designed as airlocks and used to provide separation of the different stages of changing and so minimise microbial and particulate contamination of protective clothing. They should be effectively flushed with filtered air.

c)  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.

d)  A filtered air supply should maintain a positive pressure relative to surrounding areas under all operational conditions and should flush the area effectively. 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 contacting the product are exposed. The various recommendations regarding air supplies and pressure differentials should be modified where it becomes necessary to contain some materials, eg, cytotoxics. Decontamination facilities and treatment of air leaving a clean area may be necessary for some operations.

e)  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 daily or before each work session.

4.1  Large pieces of equipment such as tanks, carts, tables, etc, used in the aseptic preparation area, should be made of material that is easily cleaned.

4.2  The parts of production equipment that come into contact with the product should not be reactive, additive, or absorptive to such an extent that it will affect the quality of the product and present any hazard.

4.3  As far as possible, 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 after complete reassembly wherever possible.

4.4  When equipment maintenance has been carried out within the clean area and if the required standards of cleanliness and/or asepsis have not been maintained during the work, the area should be cleaned, and disinfected where appropriate, before processing recommences. The aseptic preparation area should be validated for cleanliness and air flow after maintenance is completed.

4.5  All equipment including sterilisers, air-filtration systems, water treatment systems including stills should be subject to planned maintenance and validation.

4.6  Equipment surfaces that come into direct contact with sterile preparations should be properly sterilised before being introduced into the critical area. This includes such items as tubing, filters, reservoirs and other processing equipment.

4.7  Equipment surfaces that do not come into direct contact with sterile preparation should be properly cleaned and disinfected before being placed in the critical area.
CHAPTER FIVE
SANITATION

5.1 All surfaces in the aseptic preparation area should be disinfected and cleaned regularly in accordance with written protocols. Disinfectants should be regularly rotated.

5.2 Disinfectants and detergents should be selected and used to prevent microbial contamination. Diluted solutions should be kept in previously cleaned containers. They should not be stored for long periods unless sterilised and chemical stability has been established. Partly emptied containers should not be topped up.

5.3 Cleaning materials (eg, mops, sponges) should be dedicated for use in aseptic preparation areas. They should be made of materials that generate a low level of particulate matter.

5.4 An appropriate method of disposing of waste, including needles, should be established. Waste materials should not accumulate in the aseptic preparation area.

5.5 Clean area clothing should be laundered or cleaned in such a way that it does not gather additional particulate contaminants which can later be shed. Separate laundry facilities for such clothing are desirable. Cleaning and sterilisation procedures for clothing should follow written protocols.

CHAPTER SIX
STORAGE AND HANDLING OF MATERIALS

6.1 Raw materials used in the preparation of sterile products and packaging materials in direct contact with the sterile product should be of pharmacopoeial grade.

6.2 Every component of a sterile product and the finished product itself should be stored and handled in such a way that the physical and chemical integrity is maintained.

6.3 Pharmaceuticals, equipment and containers used to prepare sterile products should be stored under conditions which ensure cleanliness, prevent contamination and deterioration, and allow easy inspection and rotation.

6.4 Pharmaceuticals, equipment and containers used in the preparation of sterile products should be inspected before use for expiry date, contamination or damage to packaging. Expired, contaminated or damaged items should not be used.

6.5 Pharmaceuticals, equipment and containers should be removed from their outer shipping cartons prior to their introduction into the aseptic preparation area.
CHAPTER SEVEN
PROTECTIVE CLOTHING

7.1 Clothing should be appropriate for the areas where personnel will be working:

- Isolators:
  - sterilised non-powdered gloves disinfected regularly with sterile alcohol.

- Clean Areas:
  - clean, low particle generating gowns or overalls which retain particles shed by the body
  - head and facial hair covering
  - face mask
  - sterilised non-powdered gloves, disinfected regularly with sterile alcohol
  - appropriate disinfected footwear or overshoes should be worn.

7.2 Personnel should don the appropriate clothing before entering clean areas and remove it upon exiting the area.

7.3 Personnel working in the aseptic preparation area should be provided with clean protective garments at each work session, or at least once a day if monitoring results justify this. Gloves should be regularly disinfected during operations and masks and gloves should be changed at least at every working session.

CHAPTER EIGHT
ASEPTIC PRODUCT PREPARATION

8.1 Changing and washing should follow a written procedure. Personnel should wash hands with a suitable anti microbial skin cleanser for an appropriate length of time at the beginning of work and when re-entering the aseptic preparation area. Skin cleansers should be regularly rotated unless monitoring justifies this as not necessary.

If hands are dried then a sterile non linting cloth should be used for this purpose.

8.2 Personnel should don appropriate clothing.

8.3 All necessary materials and equipment essential for processing the product should be placed in the critical area prior to processing. No other material should be in this area.

8.4 All non sterile item surfaces should be disinfected with sterile alcohol or other suitable anti microbial agent before being placed into the critical area.

8.5 Materials should be arranged in a laminar airflow hood so as not to interrupt the airflow between the HEPA filter, critical surfaces and areas where sterile components, raw materials or drug products are exposed.

8.6 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 vigorous activity.

8.7 Precautions to minimise microbial and particulate contamination should be taken during all processing stages. Any processes which generate or disseminate particles within the aseptic preparation area during processing should be minimised or eliminated.

8.8 The efficacy of any new procedure should be validated, and the validation repeated at regular intervals thereafter, or when any significant change is made in the process or equipment.
CHAPTER NINE
STERILISATION

9.1 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 British or
other relevant pharmacopoeia, or when it is used for a preparation that is not a simple
aqueous or oily solution. Where possible and practicable, heat sterilisation is the method of
choice.

9.2 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. This work should be repeated at scheduled intervals, at least
annually, and whenever significant modifications have been made to the equipment. The
results should be kept on record.

9.3 For effective sterilisation, the process must be designed to ensure that the whole of the
material is subjected to the required treatment.

9.4 Biological indicators should be considered only as an additional method for monitoring the
sterilisation. If they are used, strict precautions should be taken to avoid transferring
microbial contamination from them.

9.5 There should be a clear means of differentiating products which have not been sterilised
from those that have.

CHAPTER TEN
EXPIRY DATE

10.1 Expiry periods should be established for each type of sterile product. Chemical stability,
and incompatibilities should be considered. Sterility at end of life should be validated.

10.2 Every product should be clearly labelled with an expiry time or date.

10.3 Determining expiry periods should be based on the following:
• manufacturers' recommendations
• pharmaceutical compendia
• professional literature
• in-house stability and/or sterility studies.
CHAPTER ELEVEN
LABELLING

11.1 Labels should be legible and firmly affixed to the primary container.

11.2 Intermediate or in-process products should be clearly labelled and, where appropriate, labelled to indicate the stage of production or status of contents (e.g. quarantined, accepted, rejected).

CHAPTER TWELVE
PROCESS VALIDATION

12.1 It is important to have in place documented validated procedures and equipment, so that the sterility of the final product can be assured.

12.2 Laminar airflow hoods and isolators should be recertified by a certified contractor at least once a year or when they are relocated, to ensure operational efficiency and effectiveness.

12.3 Automated compounding devices should be calibrated and where possible certificates of accuracy documented.

12.4 Integrity testing of the filter should be performed after sterilising by filtration in order to detect any filter leaks or perforations that may have occurred during filtration.

12.5 There should be a validation process performed on each person performing aseptic technique. This should be conducted during training and repeated on a regular basis (at least yearly), or more often if problems arise (see 2.9).

12.6 Depending on the procedure performed, process validation may include direct observation, media fills or microbiological monitoring of work surfaces.

12.7 Maximum microbial and particulate levels should be established along with the corrective course of action if limits are exceeded.
CHAPTER THIRTEEN
DOCUMENTATION

13.1 All documentation should be clearly written.

13.2 Written standard operating procedures should be followed for sterile pharmaceutical preparation. In particular standard operating procedures should be available for the following activities:
   a) process validation
   b) cleaning procedures, with particular attention to areas requiring specialised cleaning or where design makes cleaning difficult
   c) operation and maintenance of equipment
   d) disposal of waste materials
   e) product preparation.

13.3 Documentation of all validation, cleaning, and maintenance procedures should be kept and reviewed on a regular basis.

13.4 Records of compounding should be kept and master formulae should be used where appropriate.

13.5 It is recommended that documents be readily retrievable for a period of one year following the expiration of the final product.

CHAPTER FOURTEEN
FINISHED PRODUCT TESTING

14.1 Products should be individually inspected in accordance with written procedures. Inspection should be undertaken immediately after compounding.

14.2 Products should be inspected against a well-lit background for visual particles and foreign matter, container-closure integrity and any other apparent visual defect.

14.3 If products are not distributed immediately after preparation, a pre-distribution inspection should be conducted to ensure that products with defects such as precipitation, cloudiness and leakage are not distributed.

14.4 All products should be checked against the original prescription or master formulae, for accuracy of the label and volumes and quantities of ingredients.

14.5 Where appropriate, products should be quarantined and a representative sample of the product subjected to sterility and pyrogenicity testing (eg, products made from non sterile ingredients, or batch prepared products).