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| Compounded medicines and good manufacturing practice (GMP) |
| Guide to the interpretation of the PIC/S guide to GMP for compounded medicinal products |
| Version 3.0, September 2020 |

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## Introduction

This guidance is for TGA licensed manufacturers of extemporaneously compounded medicines. It provides an interpretation of the requirements of the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products PE009* (PIC/S guide to GMP) and explains expectations for compliance when manufacturing extemporaneously compounded medicines.

It may also be used by persons who are exempt from the requirement to hold a TGA licence to manufacture under Schedule 8 of the *Therapeutic Goods Regulations 1990* (the Regulations).

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| Information | Clause numbers referenced in this guidance are from [PIC/S Guide to Good Manufacturing Practice for Medicinal Products, PE009-14, 01 July 2018](https://www.tga.gov.au/publication/manufacturing-principles-medicinal-products). |

### Purpose

The TGA (we) have adopted the PIC/S guide to GMP as the manufacturing principles for the manufacture of medicines, including extemporaneously compounded medicines.

This guidance document provides specific interpretation of PIC/S guide to GMP clauses and describes how you may meet compliance requirements. Where no specific guidance is provided, comply fully with the requirements of PIC/S guide to GMP clause(s).

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| Information | Comply with the requirements of the marketing authorisation unless the medicine you manufacture is exempt from Part 3-2 of the *Therapeutic Goods Act 1989*.In all cases, [default standards](https://www.tga.gov.au/pharmacopoeias) apply to the manufacture of extemporaneously compounded medicines as defined under the *Therapeutic Goods Act 1989*. |

### Development of this guidance

This document has been developed by the TGA’s Manufacturing Quality Branch, in relation to the PIC/S guide to GMP for Medicinal Products PE 009-14, 01 July 2018, following consultation with stakeholders, including licensed manufacturers and product sponsors.

### Disclaimer

This guidance is not mandatory or enforceable under law. It is not intended to be restrictive. We recommend following this guidance document to facilitate meeting regulatory obligations. The guidance describes a way that a manufacturer may operate to demonstrate compliance with the relevant manufacturing principles (PIC/S guide to GMP).

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| Information | Guidance documents are not intended to establish a minimum standard of practice for inspection purposes. |

### Related information

* [TGA interpretation and expectations for demonstrating compliance](https://www.tga.gov.au/publication/pe009-13-pics-guide-gmp-medicinal-products) PE009-14, the PIC/S guide to GMP for medicinal products
* ISO 14644 (2015) Cleanrooms and associated controlled environments - Part 1: Classification of air cleanliness by particle concentration and Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration
* [ICH guideline Q10](https://www.tga.gov.au/ws-sg-index?search_api_views_fulltext=EMA%2FCHMP%2FICH%2F214732%2F2007&items_per_page=10&=Search) on pharmaceutical quality system
* ISO 13408-2:2018 Aseptic Processing of Healthcare Products – Part 2: Sterilising filtration
* [Uniform recall procedure for therapeutic goods (URPTG)](https://www.tga.gov.au/publication/uniform-recall-procedure-therapeutic-goods-urptg)
* [Manufacture of sterile radiopharmaceuticals labelled with fluorine-18](https://www.tga.gov.au/publication/manufacture-sterile-radiopharmaceuticals-labelled-fluorine-18)
* Pharmacy Board of Australia [Guidelines on compounding of medicines](https://www.pharmacyboard.gov.au/codes-guidelines.aspx)

### Sections of PE009-14 that apply

In general, follow the principles of Part I of PE009-14, and in addition, all annexes relevant to your operation, such as:

* Annex 1 (manufacture of sterile medicinal products)
* Annex 2 (manufacture of biological medicinal products for human use)
* Annex 7 (manufacture of herbal medicinal products)
* Annex 8 (sampling of starting and packaging material)
* Annex 9 (manufacture of liquids, creams and ointments)
* Annex 11 (computerised systems)
* Annex 13 (manufacture of investigational medicinal products)
* Annex 15 (qualification and validation)
* Annex 17 (real time release testing and parametric release)
* Annex 19 (reference and retention samples)

### Definitions

**Compounding**

The preparation (mixing, assembling, altering, packaging, and labelling) of a medicine, medicine-delivery device or device in accordance with a doctor’s prescription or initiative in the course of professional practice based on the doctor, patient, pharmacist, compounder relationship.

Compounding includes the following:

* preparation of medicine dosage forms for both human and animal patients
* preparation of medicines or devices in anticipation of prescription medicine orders based on routine, regularly observed prescribing patterns
* reconstitution or manipulation of commercial products that may require the addition of one or more ingredients
* preparation of medicines or devices for the purposes of, or as an incident or, research (clinical or academic), teaching, or chemical analysis
* preparation of medicines and devices for a doctor’s premises use where permitted by Commonwealth and State law
* synthesis of a radiopharmaceutical medicine, (e.g. radiolabelling of a ligand with a radioisotope).

**Dispensing**

The manipulation of a commercially available product, in accordance with the manufacturer’s instructions, in order to produce a medicine in a ‘ready to administer’ form. Examples include reconstitution of oral antibiotic mixtures and aseptic transfer to a sterile device.

Where a manufacturer’s instructions are **not** followed, for example, a different diluent is used, this is considered compounding.

**Biological medicines**

For the purpose of this guidance, biological medicines or products refers to biologically derived therapeutic goods applicable to Schedule 1 Part 1 of the [*Therapeutic Goods (Manufacturing Principles) Determination*](https://www.legislation.gov.au/Series/F2020L00864).

## General requirements

### Appropriate circumstances for compounding medicines

Only prepare a compounded medicine in circumstances where:

* an appropriate commercial product is not available
* a commercial product is not suitable (e.g. if a patient experienced an allergy to an excipient in the commercial product), or
* when undertaking research sanctioned by a recognised human research ethics committee.

The compounding of a medicine (whether prescribed or not) should **not** take place when it would both:

* be a close formulation to an available and suitable commercial product
* would not be likely to produce a different therapeutic outcome to the commercial product.

In this situation, notify the prescriber that this medicine cannot be compounded under these circumstances.

### TGA manufacturing licence and the Australian Register of Therapeutic Goods (ARTG)

Holding a manufacturing licence and including a therapeutic goods in the ARTG are separate matters.

If you are engaged in the manufacture of therapeutic goods in Australia, you must generally either:

* hold a TGA issued manufacturing licence, or
* be exempt from the requirement.

In addition, before therapeutic goods may be imported, exported, manufactured or supplied in Australia, they must be included in the ARTG, unless the goods are exempt under one of the exemptions provided for under the legislation.

## Pharmaceutical quality system (PQS)

The principle of the Pharmaceutical Quality System (PQS), formerly called Quality Management System (QMS), is to ensure medicinal products:

* are fit for their intended use
* comply with relevant authorisation requirements
* do not place patients at risk due to inadequate safety, quality or efficacy

To comply, your PQS should incorporate GMP and Quality Risk Management (QRM) principles and be:

* designed comprehensively
* documented fully
* implemented correctly
* monitored for effectiveness
* adequately resourced and fully supported by senior management.

### Manufacturing authorisation

You must hold a valid manufacturing authorisation (Manufacturing Licence) issued by us before undertaking steps in manufacture. The licence must authorise your site for the production of compounded medicines and therapeutic goods for clinical trials (where relevant).

#### Quarterly notification to Secretary (Schedule 5A item 5 condition (c))

You must notify the Secretary every quarter (within 15 days from the end of that quarter) of the goods manufactured for that quarter and who they were supplied to, if you manufacture and supply extemporaneously compounded medicines in accordance with Schedule 5A, item 5 of the *Therapeutic Goods Regulations 1990*.

Email these reports to the TGA Experimental Products Section (eps@tga.gov.au).

#### Marketing authorisation

Manufacture goods in full accordance with the conditions of the applicable Marketing Authorisation (MA) in place. (Part I, Chapter 1, Principle).

Where there is no MA in place, for example, where the product is exempt from the requirement to be included in the Australian Register of Therapeutic Goods (ARTG), formulate the product in line with the formally received clinician order and any [default standards](https://www.tga.gov.au/pharmacopoeias) relevant to the production of the medicine.

Ensure the product formulation is derived by appropriately qualified and experienced personnel, with extensive knowledge of the active substance, its therapeutic use and expected dosing practices - this is usually a qualified pharmacist. The person assessing the formulation must be capable of identifying incorrect, incompatible or potentially unsafe formulations or dosages.

Maintain a list of ‘approved formulas’ for each product type and ensure these formulations align with established stability data for each product. Capture these formulations in the formal batch record or hold electronically in a validated system.

Ensure that the order and formulation are not the same as a product that is available commercially for each compounded medicine manufactured.

#### Exemption to compounded & supply medicines not included in the ARTG

Community pharmacists are exempt, in certain circumstances, from the requirement to hold a manufacturing licence under Item 2 of Schedule 8 of the Regulations. For example, when therapeutic goods (other than biologicals) are (i) produced by the pharmacist in the pharmacy where they practice and the pharmacy is open to the public and (ii) the goods are supplied on or from those premises (other than by wholesale).

Pharmacists and TGA licensed manufacturers are exempt, in particular circumstances, from the requirement to include therapeutic goods in the ARTG under Item 6 Schedules 5 of the Regulations. For example, where the goods are dispensed or extemporaneously compounded for a particular person for therapeutic application to that person. This exemption does not permit manufacture in advance of an order, nor does it permit bulk manufacture of multiple units for later dispensing.

In addition, TGA licensed manufacturers are exempt, in particular circumstances, from the requirement to include therapeutic goods in the ARTG under Item 5 Schedules 5A of the Regulations. For example, where goods or a batch of goods are produced for a Public Hospital, Private Hospital or Public Institution for supply to patients of the specific institution.

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| Information | This guidance is not intended to be a complete and comprehensive presentation of the legal framework for the supply of exempt/unapproved therapeutic goods. You must consult the legislation and ensure that all legislative requirements and conditions for the supply of unapproved/exempt goods are met. |

### Order management

You can receive orders in any format (phone, fax, email), but record them in written form. Ensure that the order for the compounded medicine has been received:

* in an appropriate format
* from an appropriately qualified medical practitioner or prescriber, that is authorised to request and receive the compounded medicine.

If the order is not clear enough, clarify with the customer prior to commencement of manufacture.

Follow an established process to ensure appropriate documentation and approval of any change made to the written order.

Provide the written order to the Authorised Person performing the final product release check.

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| Information | For **products** supplied under Schedule 5A, Item 5 of the Regulations, be aware of the specific conditions of supply, and ensure that the product is not substantially similar to a product that is available commercially. (See [Determination of ‘substantially similar’](#_Determination_of_‘substantially) for guidance of what to consider).For **orders** for products supplied under Schedule 5, Item 6 of the Regulations, ensure that a specific patient(s) is identified within the order prior to performing any steps in manufacture. |

#### Manufacture in anticipation of an order

Manufacture may proceed in anticipation of an order where products are manufactured under the provisions of Schedule 5A of the Regulations. However, all other conditions of Schedule 5A item 5 must be met.

You need to be in possession of an order identifying a specific patient before compounding may commence where products are manufactured under the provisions of Schedule 5, item 6.

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| Information | Manufacture for individual patients may only proceed in anticipation of an order where you hold evidence that the identified patient is undergoing a defined course of treatment. |

### Trending of data

Perform trending and formal reviews for:

* environmental monitoring results
* complaints, and
* deviations.

### Product quality reviews

Perform product quality reviews with the aim of assessing the suitability of existing operations. Address all relevant aspects of clause 1.10 in reviews.

You may group products or similar presentations for the purposes of generating product quality reviews, as compounding encompasses a broad range of different formulations, strengths, and presentations in the products produced. Justify in accordance with risk management principles any grouping applied to the products manufactured.

### Quality Risk Management (QRM)

Use the risk management principles embodied in PIC/S guide to GMP as a means of:

* assessing suitability of operations
* identify how GMP requirements are being met, and
* justifying how requirements are to be met.

It is not be used to justify how requirements set out in the PIC/S guide to GMP can be reduced.

## Personnel

### Required expertise

Compounded goods are most commonly supplied as unapproved/exempt goods, and they are not subject to any pre-market clinical or safety assessments prior to supply. Therefore compounding of unapproved goods requires particular expertise to ensure that product and process risks are understood and managed. Manufacturers have a responsibility to ensure the safety of products manufactured and supplied. Staff should have adequate knowledge and experience to readily identify requests for potentially harmful products, e.g. those with atypical routes of administration, unusual levels of potentially toxic active ingredients or containing incompatible ingredients.

To ensure staff can perform assigned duties and functions at an acceptable level, ensure all personnel involved in the manufacture of extemporaneously compounded medicines have the appropriate:

* education
* training
* experience
* skills
* or any combination of these elements.

Deliver specific training in the complexities and risks associated with compounding and maintain records of training (clause 2.10 & 2.11).

Adequate microbiology expertise, either on or off site, is needed to support the provision of acceptable quality (including sterility assurance and environmental monitoring programs).

### Senior management

The roles and responsibilities of senior management, who have ultimate control over manufacturing facilities and activities, are emphasised in Chapter 2 of PIC/S guide to GMP.

Senior management are accountable for ensuring appropriate resources are available to support the relevant manufacturing activities. Senior management are to define roles, responsibilities, and authorities for key management personnel (clause 2.5).

### Authorised persons

The person performing the release for supply activity should be appropriately qualified and experienced. Normally, they have a pharmacy qualification, but this is not mandated.

Ensure that the Authorised Persons performing release have sufficient and relevant GMP experience and have a comprehensive understanding of:

* the specific dosage form
* manufacturing processes
* controls, and
* relevant GMP requirements.

Name any persons performing the release for supply function in the PQS.

Persons performing the release function should be independent from the production function. If the number of personnel at the manufacturer is too few to allow for this, then the person performing releasing duties should not release products that they have personally manufactured, that is, been involved in the order processing, dispensing, compounding, or labelling operations. Clearly document the separation of job functions within the site’s PQS.

The person named in the licence as responsible for Quality Control should have adequate oversight of this function.

### Training

Ensure that operator training and validation programs for manual processes involved in compounding are sufficient to demonstrate that they deliver products of a suitable quality.

Include training and assessment of operator competency in critical tasks and processes in training programs, for example:

* dispensing accuracy
* correct operation of critical equipment
* correct performance of in-process checks, and
* understanding of critical process parameters and their relationships to critical quality attributes of the final product.

## Documentation

### Manufacturing formula and processing instructions

Approved manufacturing formula and processing instructions are required, in writing, for each product to be manufactured. It is common for these to be included in one concise document. Apply the basic requirements of Chapter 4 of the PIC/S guide to GMP.

Include in your batch records details of all equipment, items and materials used in the manufacture of each product, or a reference to a Bill of Materials which includes each materials uniquely identifiable batch number. Maintain adequate records to allow traceability of all materials and equipment.

Include a statement of the expected final yield with the acceptable limits, and yields for relevant intermediates where applicable, in the manufacturing formula (clause 4.17d).

### Retention of documentation

Keep records relating to the preparation of the dosage for at least:

* one year after expiry date of the batch to which it relates, or
* five years after certification of the batch

whichever is the longer.

Keep records relating to personnel training, equipment, validation, risk assessments, for the period they are in use (lifetime) or one year after the expiry of medicines to which these records relate (whichever is the longer period).

### Starting material specifications (clause 4.14)

Provide a specification identifying the key requirements for each starting material (clause 4.14).

For starting materials that are registered therapeutic goods, provide a specification identifying the key requirements, including (as a minimum):

* item name
* approved supplier and manufacturer, and
* ARTG number.

We encourage you to include a photo to assist the identification of the item being received and approved for use, where registered goods are used as starting materials.

We expect full compliance with GMP requirements for management of raw materials and suppliers where starting materials consist of APIs and excipients, for example, clinical trial manufacture (chapter 5 and Annex 13).

Have a complete knowledge of the supply chain for each starting material.

### Finished product specifications (clause 4.16)

Compounded medicines are not exempt from meeting the quality standards set out in the *Therapeutic Goods Act 1989*.

The finished product specifications for compounded medicines should reflect:

* relevant monographs from the BP, EP or USP
* requirements of any relevant Therapeutic Goods Orders (TGOs) (e.g. TGO 100 for microbial quality).

For [BP](https://www.tga.gov.au/acronyms-glossary#id_950) and [EP](https://www.tga.gov.au/acronyms-glossary#id_1043): comply with the general monographs applicable to the dosage form (for example, tablets, parenteral preparations, unlicensed medicines). In addition, comply with any specific monographs for the formulated preparation.

For [USP](https://www.tga.gov.au/acronyms-glossary#id_1341): Comply with the relevant general monographs applicable to the dosage form (for example, injections). In addition, comply with any specific monographs for the formulated preparation.

The requirements of individual monographs apply throughout the period that the formulation is expected to be satisfactory for use.

The batch record may fulfil the requirement of a finished product specification where all aspects of a product specification form part of the master batch template.

Clearly define where product release requires the results from prospective testing.

## Production

### Prevention of cross-contamination

Base controls for the prevention of cross-contamination on multiple factors including (but not limited to):

* implementing a combination of technical and organisational controls as outlined in PIC/S Chapter 5
* using dedicated or closed systems of manufacture
* gowning practices
* use of filtered air supplies and cleanrooms
* pressure cascades
* isolator technology
* use of validated cleaning methods, and
* segregation of production of differing molecules by physical location and time.

Implement a thorough risk assessment of the range of products manufactured, and document and monitor the controls necessary to effectively avoid cross-contamination.

Perform manufacture of potent or sensitising molecules in separate areas and using dedicated equipment where toxicological data does not support a controllable risk (e.g. allergenic potential from highly sensitising materials, such as β-lactams).

Have a validated cleaning program to demonstrate that the risks of cross contamination are effectively controlled for potent or sensitising molecules.

Carry out the preparation of biological medicines (for example, monoclonal antibodies) with similar strategies to avoid cross-contamination.

Give specific attention to the risks associated with clinical trial materials where the toxicological profile of new molecules may be poorly understood.

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| Information | Where the risks associated with cross-contamination are unacceptable or poorly understood, for example, investigational medicinal products, take a conservative approach to effectively avoid cross-contamination. |

### Sampling and management of starting materials

#### Vendor assurance (clause 5.27)

All suppliers of starting materials (including packaging materials) should be qualified under your PQS and in accordance with QRM principles. Take account of the following when validating starting materials (Annex 8.3):

* manufacturer and supplier understanding of GMP requirements of the pharmaceutical industry
* quality assurance system of the manufacturer
* manufacturing conditions
* nature of the starting material and the medicinal products in which it will be used.

The vendor assurance program for starting materials that are registered or listed therapeutic goods is normally limited to ensuring that products are sourced from a suitably authorised wholesaler, via approved supply routes.

For all other starting materials please refer to the [Requirements for starting materials that are APIs](#_Requirements_for_starting).

#### Inspection of starting & packaging materials (clause 5.5)

Implement systems for:

* supplier approval and qualification
* material receipt
* incoming inspection and testing
* approval for use
* storage
* status labelling
* expiry dating.

Quarantine each delivery of materials physically or by equivalent means, until it has been verified against specification.

Where the component is an approved or licensed finished human medicinal product, purchase it directly from a manufacturer without repacking or other alteration since initial manufacture, or purchase from a distributor that certifies that it has not been subject to repacking or other alteration since initial manufacture.

Use primary containers that are medical devices included in the ARTG for the manufacture of sterile compounded goods.

Maintain a record of incoming materials into the facility.

Perform an incoming inspection against the approved specification. This would normally be a visual inspection looking for:

* approved supply chain
* integrity of the unit
* compliance with the specification
	+ including sterility for containers, closures and devices
* indications that the goods may be counterfeit.

Investigate and reject any component not meeting acceptance requirements.

If the starting material is an API then additional requirements apply. See Requirements for starting materials that are APIs.

#### Requirements for starting materials that are APIs

If APIs are received, including those to be used for manufacture of clinical trial products, then full compliance with the PIC/S guide to GMP requirements relating to vendor assurance, supply, supply chain integrity, sampling and testing is expected, this includes conducting audits of API manufacturers.

Prepare approved specifications for API starting materials. Reflect any available pharmacopoeial monograph. If no recognised official monograph is available, then base the specification on the supplier’s specification and include test for identification, assay, and all critical tests, as a minimum. Ensure starting materials are tested by TGA licensed laboratories using appropriately validated methods.

Sample every container of starting materials on receipt. Reduced sampling is only permitted in cases where the supplier has undergone a detailed qualification and evaluation, and the sampling procedure has been validated (Annex 8.2-8.3).

Fully justify any reduction in testing in accordance with QRM principles and considering (Annex 8.3):

* results of the assessment
* qualification of the supplier, and
* supply history.

Have available certificates of analysis, from the manufacturer and evidence of the appropriate GMP status of the API manufacturer, for all API starting materials.

Refer also [Quality Control](#_Quality_control) below.

#### Starting material traceability (clause 5.37)

There should be a unique identifier for all materials, including:

* APIs
* excipients
* finished product components
* packaging components
* consumables.

Use the unique identifier throughout the manufacturing systems and documents for identification and traceability in the event of a notified problem or recall.

#### Process gasses

Sampling of gases purchased from commercial sources and used during production is not expected. The approval for use of these gases may be performed based on supplier approval and certificates of analysis.

#### Sampling areas for starting materials

A separate sampling area is required for starting materials that are APIs. Where sampling is performed and materials are exposed to the environment, conduct sampling in such a way as to prevent contamination or cross-contamination of the material and environment (clause 3.22).

### Labelling (clauses 5.55 & 5.59)

Check labels for readability and compliance with GMP at the time of generation and record the check on the batch record.

Labels applied to compounded goods must meet the requirements of the relevant [Therapeutic Goods Orders (TGOs)](https://www.tga.gov.au/therapeutic-goods-orders).

### Reconciliation (clause 5.61)

Put in place a system for the reconciliation of all materials, labels and components used, and partly used, during the compounding operation, prior to release of the batch and before destruction of the used and empty containers.

Put checks in place to ensure the correct quantities have been used, for example, weight or volume checks. The compounding operator followed by an independent operator should check the additions in the room prior to addition and reconciled afterwards. Secondary checks may be performed by a second operator or suitably validated electronic system (Annex 11 of the PIC/S guide to GMP for requirements).

Put adequate controls in place, where relevant (for example, liquids production), for the:

* pre-dilution of multiple containers prior to use (e.g. antibiotics), and
* practice of sharing starting materials across batches.

Check the reconciliation processes to ensure that the appropriate control exists for these operations due to the risk of mix-up.

To minimise the risk of a mix-up, adequately control equipment used to

* manufacture
* transfer prepared or reconstituted product to the final container, and
* add diluents

Adequately identify such devices (such as a system to mark or label) and consider as part of the reconciliation exercise.

## Quality control

### Testing

Perform the testing of starting materials and each batch of product manufactured in accordance with any:

* conditions of a Marketing Authorisation (where relevant)
* TGOs
* [default standards](https://www.tga.gov.au/pharmacopoeias)

relevant to the material or product. Validate all test methods used in the analysis of starting materials and finished products before use (clause 6.15).

The requirements for finished product testing should be commensurate with patient risk. Take into account the intended use of the product, and the methodology of manufacture.

|  |  |
| --- | --- |
| Information | All tests for extemporaneously compounded medicines made from raw materials that are NOT included in the ARTG (for example, from APIs) must be performed before the product can be supplied. |

#### **Testing of starting materials that ARE finished therapeutic goods included in the ARTG** (clause 6.17)

Where products are compounded from ‘starting materials’ that are licensed finished goods registered on the ARTG, the default requirements will be compliance with the attributes listed on the specification (for example, item name, ARTG #, label, approved manufacturer and supplier).

Perform a formal check to determine whether the goods show evidence of being falsified or counterfeit.

No additional testing of the starting material is expected.

#### Testing of starting materials that are NOT finished therapeutic goods included in the ARTG (clause 6.17)

Meet all GMP requirements where products are compounded from ‘starting materials’ that are APIs and excipients. For example:

* identity testing on all containers for both the API and excipients
* full testing of the materials in accordance with the relevant pharmacopoeial monograph
* a review of the manufacturer’s and supplier’s CoA against the company’s specification
* assessing and obtaining GMP evidence for the manufacturer and supplier of the API.

#### Material specifications

Prepare a specification for the testing requirements for each starting material and finished good and document in the PQS. Where specifications are not derived from a default standard, include a clear justification for the test regime in the specifications for finished products.

Extemporaneously compounded **sterile** medicines produced from starting materials that ARE included in the ARTG can be dispatched before formal completion of all tests; however, outline in the specification the mandatory tests required to be conducted before the product is released for supply (that is, administration into patients).

### Chemical testing

#### Compounded medicines produced from starting materials that ARE included in the ARTG

Where manufacture solely involves the use of starting materials that ARE finished therapeutic goods included in the ARTG, and these goods are prepared in a manner consistent with the PI we do not expect routine chemical testing of the finished product. However, it is expected that the medicine meet any relevant label claim and pharmacopoeial standards if tested, and therefore validation of manufacturing processes is critical.

Where manufacture involves the use of starting materials that ARE finished therapeutic goods included in the ARTG, and your manufacturing process involves modification of the product in a manner inconsistent with the PI, we expect routine chemical testing of the finished product. Perform a risk assessment of the manufacturing process and required critical quality attributes for the finished product, and undertake appropriate finished product testing, relevant to the specific dosage form and in accordance with relevant pharmacopoeial or equivalent standards.

#### Compounded medicines produced from starting materials that ARE NOT included in the ARTG

Where manufacture involves or includes the use of starting materials that are NOT finished therapeutic goods included in the ARTG (e.g. APIs or excipients) we expect that appropriate finished product testing, relevant to the specific dosage form and in accordance with relevant pharmacopoeial or equivalent standards, will be performed (for example, ID testing, assay, critical physical testing). Perform chemical testing for each batch manufactured and ensure results are available before batch release for supply.

### Microbiological testing

Put in place appropriate microbiological testing of starting materials and products to demonstrate compliance with TGO 100 requirements, including test for sterility and endotoxins in sterile products. A risk based approach to testing may be taken based on the nature of the dosage form and the manufacturing process utilised, and the resultant risk of microbiological contamination of the product.

Ensure that all methods utilised are validated for the specific product formulation.

Put controls in place for microbiological culture media that include supplier evaluation and the availability of a CoA. Verify the suitability of each lot of media before use, either by performing growth promotion testing of each delivery of each lot of media received, or alternatively, by validating the transport system used to ensure that media deliveries are routinely transported under appropriately controlled conditions.

### Reference and retention samples (clause 1.9(viii) & Annex 19)

Take retention samples where products are compounded on a batch basis, that is, 10 or more units of the same product in the same session. Determine the size of the retention sample kept following risk management principles and ensure sufficient samples to permit repeat testing of samples in case of complaint or quality incident.

Keep reference samples for products where manufacture involves a discrete bulk manufacturing step, that is, products are produced using APIs or excipients as starting materials.

Include samples of finished product labels and any other printed items used as part of batch documentation.

### Allocation of expiry dates

#### General

Where a finished product manufactured by you is included in the ARTG, apply the approved expiry date included in the product registration or listing. Notify us if changes to expiry dates for products in the ARTG are required. Refer to the relevant Australian regulatory guideline for details.

You hold all responsibility for determination of the product expiry date(s) where the product manufactured is exempt from inclusion in the ARTG, for example, under schedule 5 or 5A of the Regulations.

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| Information | Expiry dates for exempt medicines are not assessed by us prior to supply, and are reviewed only during post-market surveillance activities, for example, during inspections. |

Base stability information primarily on actual trials using the unique combinations of active, diluents and packaging components and secondly on available literature. Document your justification to its approach for each product.

Data used to assign product expiry must be:

* derived using stability indicating analytical methods, and
* relevant to the proposed product formulation and container closure system.

Preservative efficacy testing may be required to support in-use stability.

Base product expiry on a scientific rationale, including test data. Laboratories used to generate this data should operate an appropriate quality system and be subject to your company’s supplier approval system.

Cover physical, chemical and microbiological stability in test data in order to demonstrate that the product remains in specification throughout the labelled shelf life. Base testing used to support expiry dates on international standards or use adequately validated ‘in-house’ methods.

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| Information | The expiry date applied to a product should be as short as possible, and only sufficient to allow the product to be manufactured, supplied and administered to the patient.The application of periods longer than the minimum necessary or extended expiry dates for economic reasons is not permitted. |

Include a margin of safety to the assigned shelf life from the stability data available.

Test data may be obtained from literature searches, provided that the literature is relevant to the product formulation and container and closure system proposed.

Support expert opinion on product shelf life with a documented rationale and test data if available.

For multiple use containers the expiry date or time for the container starts when it is first opened.

Include in stability summaries data relating to the suitability (including compatibility) of the container and closure system used.

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| --- | --- |
| Information | We are aware that not all devices (e.g. syringes) are intended to be used as closed container storage systems for medications. Reduced potency has been reported in some cases when medications are pre-filled and stored in plastic syringes. |

#### Expiry dates when starting materials ARE included in the ARTG

The expiry of the compounded medicine should not be greater than the shelf life of the starting material prior to reconstitution, when starting materials are registered therapeutic goods.

#### Expiry dates when starting materials ARE NOT included in the ARTG

We expect that all starting materials are within the current shelf life at the time of manufacture, for products manufactured from starting materials that are API and excipients.

#### Expiry dates for compounded sterile medicines

In addition to the above considerations, base expiry dates for compounded sterile products on scientific data that is directly relevant to the specific starting materials, formulation, container and closure used in the compounding of products.

Generate additional stability data, demonstrating compliance with critical microbiological product attributes, for example, sterility and endotoxins, over the shelf life of products.

#### Expiry dates for compounded non-sterile medicines including dose administration aids (DAAs)

The [general requirements](#_General) above apply with additional guidance available from:

* [Australian Pharmaceutical Formulary](https://www.psa.org.au/media-publications/australian-pharmaceutical-formulary/) – Principles of Compounding, and
* Pharmacy Board of Australia – [Codes, Guidelines and Policies](https://www.pharmacyboard.gov.au/Codes-Guidelines.aspx)

#### Extended expiry dates

We do not endorse the application of extended expiry dates to compounded medicines due to the risks associated with microbial contamination and proliferation.

You must support the application of an expiry date greater than 24 hours by performing appropriate assessment of the overall risk of microbiological contamination, if extended expiry is required.

You must document a justification for the expiry period and to support the expiry period, hold at least one of the following information and data:

* Results of preservative efficacy tests that involve repeated microbial challenges of the compounded medicine over the expiry period. You can use a modification of a pharmacopoeial preservative efficacy test (preferably the EP or BP preservative efficacy test) that includes rechallenges of the medicine with reduced numbers of challenge organisms (compared with the initial challenge).

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| Information | Guidance can be obtained from the normative part of the International Standard ISO 14730 Ophthalmic optics - Contact lens care products - Antimicrobial preservative efficacy testing and guidance on determining discard dating, which describes a test procedure and performance criteria for preservative efficacy over an open shelf life period of 28 days. |

* Results of preservative efficacy tests on the contents of containers of the medicine after preparation.

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| Information | The application of an expiry date greater than 24 hours is only acceptable where there is a clear justification or need for the longer expiry, for example, where a longer expiry is required to meet clinical needs. |

#### Expiry dates for compounded biological medicines

Give special attention to shelf lives assigned and the methodology used for biologically derived products such as monoclonal antibodies (MABs).

Generally, biological products have a complex set of structural properties (for example, amino acid sequence, glycosylation, folding) essential to their intended effect and are very sensitive to changes to their manufacturing process, including but not limited to any manipulation outside of their approved container-closure systems and storage conditions. Therefore, compounding of such products could adversely affect the safety and effectiveness of the medicine.

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| Information | Where possible, information regarding the stability of the compounded biological medicine should be discussed with the product sponsor to ensure that stability data generated by the manufacturer and the allocated shelf-life are not contradicted by stability data held by the sponsor. |

Support expiry dates applied to product with sufficient stability test data demonstrating acceptable; identity, purity, potency and accurate detection of degradation changes during storage.

Adequate characterisation of the product is likely to involve a suite of analytical testing tailored for each specific product. Consider other risks in studies such as the formation of protein aggregates and extractables or leachates from packaging.

We require real-time stability data for all extemporaneously compounded biological medicines, as the degradation of biological medicines is not usually amenable to kinetic analysis and extrapolation from accelerated testing. Applied shelf lives cannot be longer than the real-time data available to support them.

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| Information | * It may not always be possible to establish degradation pathways and identify decomposition products formed in significant amounts.
* The use of only compendial methods is not acceptable unless it has been demonstrated that the methods used are able to detect critical degradation pathways for that product.
* The use of only physicochemical assay techniques, such as chromatographic methods for decomposition products, may not always be appropriate for biological medicines.
 |

### Ongoing stability testing (clauses 6.26-6.36)

Conduct an ongoing stability programme when routinely manufactured formulations have an expiry greater than 24 hours. Where scientifically justified, grouping of formulations for such a program can be acceptable.

Perform stability testing for extemporaneously compounded medicines in accordance with the principles of clauses 6.26-6.36. Ensure stability data addressing each product, formulation and presentation is available for each product supplied. Represent the range of strengths of each product supplied in stability testing, for example, including batches manufactured at the highest and lowest concentrations.

Base stability information primarily on actual trials using the unique combinations of active, diluents and packaging components and secondly on available literature. Prepare a documented justification to its approach for each product.

We require additional stability to support the shelf life and storage conditions for any additives or stabilisers added to the formulated preparation to assure the chemical and microbiological quality of the finished product.

#### Stability of radiopharmaceutical preparations

Conduct an ongoing stability programme for all products manufactured, including for goods with a shelf-life <24 hours.

Perform stability testing for radiopharmaceuticals in accordance with the principles of Part I Clauses 6.26-6.36. Stability data addressing each product, formulation and activity level should be available for each product supplied. Stability testing should represent worst-case conditions, for example, include batches manufactured at the upper activity concentration.

Additional stability is required to support the shelf-life and storage conditions for any additives or stabilisers added to the formulated preparation to assure the chemical and microbiological quality of the finished product.

#### Ongoing stability evidence and data

Hold evidence of both chemical and microbiological stability of the dosage units for the period of storage up to and including the labelled shelf life. That is, they need to comply with Part 3-1 of the Act, which would mean compliance to the BP, EP or USP monographs and TGOs relevant to the formulation and dosage forms.

Base the literature review on known published journals when using literature-based evidence. Verify the source material is about a suitably similar product, for example, in terms of device, diluent, formulation, dosage form or presentation.

Regularly review, at least annually, available stability data to ensure that the data meets contemporary standards and continues to support allocated expiry dates. We expect an annual review of available literature to verify the relevance of contemporary publications where stability is based on literature reviews.

## Release for supply

### Batch release

Make the written order available to the Authorised Person performing the final product release check. It can be a photocopy of the original order.

Include in the final product release an independent check against the original order. This check must include a physical check of:

* the final product(s) to be dispatched
* any secondary labelling that is applied.

Record this check on the batch record. Investigate any discrepancies and take appropriate corrective action before the product is released to the patient.

Where the batch is made in advance, include in the release verification that the Quality Control testing results comply with the specification for those batches which are manufactured from API and excipients.

Product release is a real time activity; any subsequent review is a quality review tool and not a component of the release process for a given batch. Closely align the release for supply process with real time release testing (RTRT) requirements outlined in Annex 17 and, in particular, with RTRT strategies defined in clauses 3.2 and 3.3. Support the real time release of product with on-going scientific evidence based on material, product, environment and process knowledge.

### Procedure for release for supply

Establish a written procedure detailing the assessment of production and analytical data and include an exact and detailed description of the whole release procedure including the responsibilities of the involved personnel and the continuous assessment of the effectiveness of the PQS. Follow the written procedure and demonstrate compliance before dispatching the batch.

In the release procedures, clearly outline the production and quality control data to be reviewed before the product is dispatched.

Make available the order for the product (in written format) at the time of performing the final check for product release. It can be an authorised true-copy of the original order. Include an independent check against the original order in the final product release and record this check on the batch record. Investigate any discrepancies and take appropriate corrective action before the product is released for administration to the patient.

Describe in this procedure the measures to be taken if unsatisfactory (out-of-specification) test results are obtained after release for supply and before expiry. Investigate and document out-of-specification events, including the relevant corrective actions taken and preventative actions put in place to prevent future events.

### Separation between production, quality control and release person

The testing of an extemporaneously compounded medicine should be by a separate individual from the person who manufactured the batch. Likewise, an Authorised Person who was not involved in the manufacture or testing of the product, should perform release for supply (clause2.5).

However, under exceptional circumstances, this may not always be possible. Address these situations in the release procedures. When a single person is responsible for manufacturing, testing and release of a batch, have an independent person perform a review of the testing results and release of that batch at the earliest opportunity, ideally within 24 hours.

## Outsourced activities

Fully comply with Chapter 7 requirements. Assess, define and cover by a written contract all outsourced GMP-related activities that may have an impact on product quality.

Examples of outsourced activities include, but are not limited to:

* contract manufacturing and analysis
* maintenance and calibration services
* providers of critical consumables (e.g. gowns, sterilised componentry)
* suppliers and manufacturers of raw materials, packaging materials and printed artwork
* provision of training and consulting services
* validation services associated with facilities, equipment, utilities, process and product design, qualification and validation
* provision of transport and logistical services for products
* contract cleaning and waste management services
* contract pest control services
* agencies that provide temporary or contract personnel

Ensure contracts are in place between the site of manufacture and the entity receiving the goods for example, private hospital, public hospital, public institution, clinician, medical imaging centre. (See [**Determining ‘public institutions’**](#_Determination_of_‘public) to determine if an entity is a public institution).

## Complaints & recalls

Report all suspected or serious adverse reactions related to compounded medicines to [us](https://www.tga.gov.au/reporting-adverse-events).

In addition, in circumstances where the manufacturer is made aware of any quality issue that would have resulted in recall of products, report these events to the TGA recalls coordinator, irrespective of whether any units are recoverable. For example, following identification of out-of-specification testing results, (e.g. retrospective sterility testing failures) or significant environmental monitoring excursions that indicate an unacceptable risk to process integrity or product quality.

Follow the guidance given in [Uniform Recall Procedure for Therapeutic Goods (URPTG)](https://www.tga.gov.au/publication/uniform-recall-procedure-therapeutic-goods-urptg) for recall actions.

## Manufacture of sterile products

### Design of aseptic processes

Design processes to include a minimum number of aseptic manipulations. Perform all aseptic manipulations under unidirectional airflow that meet Grade A requirements.

Personnel performing manipulations in the Grade A environment should be dedicated to this activity for the duration of the work session, and remain in the Grade A environment throughout. Process design should prevent ‘swapping’ of roles (for example, with other Grade B operators) as this could create disturbance and potential contamination to the Grade A environment.

### Clean room and clean air devices

Carry out the manufacture of sterile products in clean areas. There are four Grades of clean area, A, B, C and D, classified according to required environmental characteristics of the area (Annex 1.3, 1.4 & 1.19). Air supplied to clean rooms or clean air devices should pass through filters of an appropriate efficiency.

#### Clean-air devices

Clean air devices such as laminar air flow cabinets, Cytotoxic Drug Safety Cabinets or isolator technology used for the production of extemporaneously compounded sterile medicines should be carefully designed and located so that the:

* required air quality for the respective zones can be achieved in accordance with Annex 1.3 & 1.17
* risk of contamination from the environment of aseptically manufactured products is effectively minimised
* Meet the grade requirements from the following table.

Grade requirements

| Grade | Examples of operations for manufacture of sterile compounded medicines |
| --- | --- |
| A | Aseptic preparation and filling |
| B | Background or adjacent environment for the grade A zone (e.g. transfer hatch between grade C and grade A environments) |
| C | Preparation of solutions prior to sterile filtration.Fully closed and automated operations |
| D | 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 |

#### Classification

Classify clean areas under both **in-operation** and **at-rest** conditions in accordance with EN ISO 14644-1. Find detailed environmental characteristics in Annex 1.4–1.5 of the PIC/S guide to GMP.

#### Monitoring of clean air device and clean rooms (Annex 1.8-1.20)

Monitor clean areas under both in-operation and at-rest conditions in accordance with EN ISO 14644-2. Find detailed environmental characteristics in Annex 1.8–1.20 of PIC/S guide to GMP. Follow QRM principles when determining the ongoing environment monitoring programme; justify the selection of sampling locations, frequencies and methods based on risk to product quality (Annex 1.8).

Sufficient information should be available from the environmental monitoring (EM) program to identify any loss of control in a timely manner and to enable appropriate remedial actions.

Commence monitoring of the Grade A zone for both non-viables and viables at the start of each work session (during set-up) and continue for the full duration of the session. Continuous particle monitoring within the grade A area is required.

Perform the environmental monitoring of lower grade areas in accordance with Annex 1 requirements.

Monitor and trend environmental results.

|  |  |
| --- | --- |
| Information | We expect a higher rate of monitoring in newly established facilities or where historic test data is not available. |

#### Assessing results

Generally, for sterile medicines, the use of closed systems should reduce the risk of microbial ingress to the product, but only if all precautions have been taken such as an effective decontamination program and adherence to good aseptic techniques including observing ‘first air’ principles, etc.). ‘First air’ is defined as the undisrupted air coming directly from a HEPA filtration source. However, assess your specific manufacturing processes for potential risks from microbial contamination.

You need to set appropriate alert and action limits for the environmental results of particulate and microbiological monitoring, in alignment with Annex 1. Prescribe in your operating procedures corrective action for if these limits are exceeded.

Take the impact of any out-of-specifications or out of trends into consideration in determining whether released product is of the appropriate quality and if any corrective action is required (Annex 1, sections 8-20).

During release of products manufactured in that session, consider:

* non-viable results for the session
* the impact of any historical out-of-specifications or out of trends for viable results in determining whether the manufacturing environment is in control, any subsequent impact on product quality and if any corrective action needs to be taken.

For traditional microbiological monitoring methods, the data is retrospective and is less useful for batch-specific actions. Most products will have been released before the information is available.

|  |  |
| --- | --- |
| Information | We encourage the application of rapid microbial monitoring methods as these methods provide more timely data regarding critical environmental control. |

Document the basis on which you are confident to continue with release, if a potential problem with environmental control is identified when reviewing EM data for operations where the reporting of results is retrospective.

If multiple batches are compounded in a single session, consider any excursion for its overall impact on all manufacturing operations and sessions in the area implicated.

#### Identification policy

Routinely identify all microorganisms in Grade A areas to species level. Ensure staff performing identification tests are adequately trained and experienced.

Identify isolates from Grade B to at least genus level, except when:

* high individual counts are recovered
* negative trends indicating a deterioration in environmental control emerge
* recovery of potentially objectionable organisms.

In these cases, perform additional identification of organisms (at least to species level) to aid in investigation and rectification of the event.

Verify identified isolates from the Grade A areas against the EM validation database to ensure that the currently employed validated decontamination programme remains valid. Include typical local isolates as part of the validation for cleaning and EM programs.

#### Controls

Perform reading and incubation of any microbiological plates in a location and in a manner that does not present a risk to manufacturing operations.

Media and their containers (such as agar plates) used in grade A and B areas must be sterile before use.

### Entry to clean areas

Access to clean manufacturing areas should be via a separate gowning area and restricted to authorised personnel. High standards of personal hygiene and cleanliness are essential.

Personnel, equipment and materials are to enter clean areas through appropriately designed, controlled and operated airlocks. Suitably clean, decontaminate and sanitise all equipment and materials transferred into clean areas in order to prevent contamination of the grade into which the item is transferred. Include the use of a sporicidal agent in decontamination and sanitisation processes and validate for effectiveness, (Annex 1.61, 1.62, 1.64, 1.76, & 1.81).

### Clothing

Clothing and its quality should be appropriate for the process and the grade of the working area. Wear clothing in a way to protect the product from contamination (Annex 1.42). Find a description of clothing required for each grade in Annex 1.43.

Choose clothing to match the grade in which it is used. For example, low-linting sterilised gowns and gloves are required for personnel entering the Grade A and B areas of the facility.

#### Gowning training and qualification

Provide and record training in appropriate gowning processes. For aseptic areas, operators should undergo an initial qualification and periodic assessment of ability to correctly gown. Perform monitoring of the gown surfaces and gloves worn in Grade A and B areas frequently, for example, each session, in accordance with risk management principles (Annex 1.8).

Include all set up processes related to the manufacturing operations for Grade A Operator gowning qualifications. Exclude operators who do not demonstrate compliance with the environmental monitoring limits from aseptic operations until such time they have demonstrated consistent reproducible compliance. Investigate any out-of-limit results to determine possible impact on product quality.

#### Single use of sterile gowns

For every worker in a Grade A and B area, provide clean sterile protective garments (including masks and gloves) at each working session. A working session can be considered to be the maintenance of a period of the same operational conditions, that is, personnel, process, and environment. Hence, movement from, or exiting the Grade B cleanroom, would necessitate a gown change for re-entry.

It is not acceptable to re-use sterile cleanroom garments (including hoods, gowns and boots) beyond a working session. Monitoring of garments presented to the Grade A work zone is required to ensure that microbial load conforming to requirements for Grade A is maintained. (Annex 1, sections 42-45, 51)

### Aseptic processing

Perform process simulation tests for aseptically processed sterile products as part of initial validation and repeated at six monthly interval tests. Process simulation tests to be representative of the batch sizes manufactured.

Perform operator process simulation tests twice per year, for every operator involved in aseptic manipulations. These assessments are typically separate from process simulation tests.

Process simulation tests should mimic the number, type and complexity of manipulations taking place in both:

* the worst case manufacturing process identified
* non-routine interventions and events.

A matrix approach to process simulation tests may be utilised where scientifically justified.

For the matrix approach, in the process simulation, include the worst case attributes of the products covered by the simulation, including factors such as types of manipulations, number of compounded units, length of the process and container type. Cover all parts of the aseptic process in the process simulation, including all aseptic manipulations that should be validated by successful studies. This is normally achieved by substituting the aseptically produced product with a sterile nutrient medium, that is, media fill (Annex 1.66).

Perform process simulation tests for each processing area (for example, cabinet) in use, in accordance with Annex 1 requirements.

You must assess new processes, changes to existing processes or scale of activity, in light of existing media fill data, to determine whether previous media fill studies are valid. Where indicated by risk assessment, conduct additional media fills or revalidation of processes following changes.

Batch scale ‘process simulation’ exercises are not the same as ‘end of session media fills’. End of session media fills are used in lieu of performing the test for sterility and can be an abbreviated form of a media fill.

### Terminally sterilised products, materials and intermediates

Comply fully with Annex 1 requirements for validation, control and monitoring of terminally sterilised products, materials and intermediates.

### Manufacturing controls

#### Sanitisation of items into clean areas (Annex 1.61, 62, 64, 76, 81)

The nature of sterile production requires that numerous components including consumables such as:

* syringes
* needles
* caps
* injection vials
* ampoules
* intravenous solution bags

are transferred from lower grade areas into higher grade areas, before introduction into the final preparation area which is normally a Grade A laminar air flow or Cytotoxic Drug Safety Cabinets.

It is critical to implement appropriately validated and controlled decontamination steps to effectively prevent contamination of critical areas by transferred materials. Sterile consumables are normally enclosed in a primary packet which are opened within the Grade A environment. Products used in aseptic compounding are commonly packed within glass vials or ampoules. The outer surfaces of these packets and containers are usually not sterile and may be contaminated with both viable and non-viable particulates. Introduction of such contaminants into the Grade A preparation zone poses a risk of contamination of the final product.

The effectiveness in reducing contaminants (for example, particulates and microorganisms) to an ‘acceptable’ level relies on a number of aspects, which must be consistently applied. These include both adequate:

* exposure to appropriate disinfectants (exposure time and coverage)
* wiping with suitable cleaning materials.

Surface sanitise with suitable, sterile disinfectants in a manual process of either “spray” or “spray and wipe”. Whatever methods is applied, appropriate data to demonstrate the efficacy of the disinfectant is required, both in vitro and in the specific manner in which it is used.

Perform a sanitisation step at each transfer through each of the grade changes, that is, Grade C to B, Grade B to A. Put procedures in place, as determined during validation, to detail:

* the control of materials used for wiping
* preparation details for sanitants
* in use period for sanitants, wipes and any other cleaning aids
* wiping technique
* critical process parameters, such as required exposure time to sanitise.

Use an appropriate quality sanitant for early sanitisation steps in grades D and C with a minimal bioburden, preferably sterile. Use in such a fashion as to prevent contamination.

Wipes used should not shed particles and should be sterile when used at the last stage of transfer for aseptic products. Use sterile sanitants and cleaning solutions in Grade B and A areas.

The minimum expectation is that there are discrete decontamination steps as materials transfer across differing grades. The transfers from C to B and B to A respectively require decontamination performed at both steps and the first decontamination steps must use an effective sporicidal agent.

Ensure that the sanitising agents and processes used do not adversely affect the product and do not leave any residues that may present any risk of harm to the patient.

During any transfer activity, put in place measures to avoid any re-contamination of sanitised articles. Where items are packed in multiple layers (for example, triple wrapped, irradiated goods such as agar plates, needles, syringes and diluent bags) only remove the inner most layer at the B to A interface. Minimise the likelihood of recontamination and reflect good aseptic practice in management and handling in the Grade A zone after final sanitisation. For example, orientation of critical surfaces to a clear stream of HEPA air.

During sanitisation, pay particular attention to the rubber septa of vials and break lines of ampoules, subject these to all stages of the sanitisation treatments. Therefore, remove over-seals at the first sanitisation stage (in Grade C).

Extended storage time of sanitised components is considered a risk factor and therefore implement subsequent steps prior to transfer into the Grade A zone. Similarly, take steps to minimise the exposure of items supplied as sterile prior to entering the Grade A work zone.

Implement an ongoing monitoring program for sanitant solutions to demonstrate their suitability. Validate the effectiveness of sanitants before use. Sanitants should be effective against expected and normal flora encountered in the facility and on process materials.

Validate sanitisation processes and use as the basis for sanitisation procedures. Carry out periodic verification of sanitisation effectiveness with frequency based on a risk assessment.

Training to maintain sound practices is required.

#### Bioburden monitoring

Comply fully with requirements for bioburden monitoring of Annex 1 when sterile products are either:

* produced from APIs
* manufactured by terminal sterilisation.

#### Sterilising filtration

Validate the sterilising filtration processes (Annex 1.83) and ensure data to demonstrate the ability of the sterilising filter to sterilise the specific product formulation is available prior to product release.

Data from sterilising filter validation to meet the requirements of Annex 1.110 – 115, and include:

* data to demonstrate the bacterial retention capabilities of the filter assembly
* data to demonstrate the compatibility of the product-contact parts of the filter to ensure that the filter does not affect the solution and vice-versa
* data to establish the integrity testing values used to demonstrate filter integrity.

Additional guidance: ISO 13408 2:2018 Aseptic Processing of Healthcare Products – Part 2: Sterilising filtration.

#### Filter integrity testing

Confirm the post-use integrity of the sterilising filter using a validated filter integrity test, as soon as practicable and prior to batch release.

Record and retain filter integrity test data with the batch record.

#### Use of ampoules (Annex 1.76)

Only use ampoules for a single withdrawal immediately after opening, then discard.

Filter the contents prior to dispensing into the final dosage container to ensure any glass particulates have been removed.

#### Control of “pooling” operations (Annex 1.64, 66-70)

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| Information | Pooling definition: “the bulk transfer of multiple original containers of a sterile staring material into a new (pre-sterilised) container without changing the formulation or concentration of the original starting material”. |

Minimise aseptic pooling of sterile materials. Only use where this activity reduces the risk of errors in compounding. Justify the use of aseptic pooling by a risk assessment, which considers the risk to the finished product from the additional aseptic manipulations required for the production of the pool(s).

Treat aseptic pooling as a batch operation, which is:

* validated by media fill
* described in SOPs, and
* recorded in a batch manufacturing records.

Undertake assessment and release of each batch and in the case of pools for immediate use, this release may be concurrent with finished product release.

Give a maximum in-use shelf life to any aseptic pool, as justified and demonstrated through appropriate validation or media fill studies. Do not transfer in-use shelf life between different work sessions.

#### Use of “partial” vials

Some injectable products are intended for single use only, however, it is recognised that the full (reconstituted) contents of a container may not be used for a compounded product batch. When another batch is to be made or dispensed for the same product, you may retain the reconstituted vial for subsequent use. This may occur to avoid wastage.

The use of partial vials is not encouraged due to risks associated with microbial contamination; however, if used, meet the following minimum requirements:

* Do not use the product outside the conditions stated in the ‘product information’.
* Conduct a risk assessment of the process to determine the need to utilise partial vials and put in place all controls to mitigate any risks associated with their use.
* Generate validation data to demonstrate that the elastomeric closure meets the requirements of the ‘self-sealing test’ as descried in the current edition of the BP monograph for Rubber Closures for Containers for Aqueous Parenteral Preparations, (or equivalent)
* Use the vial in the manufacture of similar products in the same session (campaign) with the patient doses prepared one after the other. Do not leave the vial in the cabinet when other products consisting of different starting materials are being manufactured, due to the risks of product mix-up.
* The container is a vial closed with an elastomeric stopper and is held or stored under appropriate conditions at all times. Ampoules cannot be reused once opened.
* If the partial vial is removed from the grade A cabinet, package it to protect from external contamination. It cannot be stored in an area classified less than Grade C between uses.
* Batch records must reflect the actual manufacturing process carried out with the appropriate line clearance steps between the manufacture of individual patient doses as required.
* Perform appropriate checks on the volume drawn up for each patient at the time of manufacture to ensure that the correct dose is supplied for each patient.
* Validate via the media fill program, the use of ‘partials’ including all manipulations.
* Establish the stability (and sterility) of the partial vial, based on stability studies.
* Put in place an appropriate and validated process to return partial vials to the Grade A cabinet once removed, without affecting the quality of the contents of the partial vial or the environment within the cabinet.

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| Information | Validate the transfer of partials, taking into consideration the following:* product stability
* container closure integrity
* closure type
* penetration device
* the septum is appropriate for multiple entries (usually using a closed system transfer device)
* product formulation
* effectiveness of decontamination processes to reduce external microbial and particulate contamination
* expected external pre-decontamination cleanliness and bioburden.
 |

#### Preparation of sterile starting materials that ARE included in the ARTG

Perform the preparation (reconstitution, dilution, mixing) of sterile starting materials in accordance with the instructions within the relevant Product Information. Variations from the PI instructions should be avoided; however, where absolutely necessary, any variation from the PI must be scientifically justified and supported by comprehensive stability data, and where necessary safety and efficacy data.

#### Fractionation of vials

The practice of ‘fractionating’ or splitting of product vials for later use is strongly discouraged due to risks associated with microbial contamination and dosing errors or variations. Fractionation is not a practice endorsed or supported within the Product Information. However, if used, adopt a similar approach for the use of partial vials in order to fully risk assess the process and validate the practice over the full life cycle of the fractionated vials.

Perform comprehensive stability testing for all fractionated products.

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| Information | Due to the significant increased risks relating to fractionation of starting materials, manufacturers undertaking fractionation are expected to hold scientific evidence from the sponsor of the starting material demonstrating the safety, stability and suitability of proposed fractionation processes. |

#### Reconstitution of radiopharmaceutical cold-kits and “super-loading”

Perform the preparation (reconstitution, dilution, mixing) of cold-kits in accordance with the instructions within the relevant Product Information. Variations from the PI instructions should be avoided; however, where absolutely necessary, any variation from the PI must be scientifically justified and supported by comprehensive stability data, and where necessary safety and efficacy data.

Test the reconstituted cold-kit in accordance with the quality control methods specified by the cold-kit sponsor.

‘Super-loading’ is a term used in nuclear medicine compounding that refers to the reconstitution of cold kits with additional radioactivity beyond the PI recommendation in order to increase the number of doses from a kit. Super-loading is not endorsed as it is considered to be using the product outside the conditions stated in the ‘product information’.

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| Information | Due to the increased risks relating to super-loading of cold-kits, manufacturers undertaking super-loading are expected to hold scientific evidence from the sponsor of the starting material demonstrating the safety, stability and suitability of any proposed super-loading processes. |

#### Checks for auto-compounders

Auto-compounders are commonly used to automatically dispense and combine multiple differing products into a single final formulation. The processes for setup and routine checks is critical to ensure the correct product and quantities are dispensed.

Checks for the correct set-up and operation should include:

* Verification that the correct starting material is connected to the correct line. This check should be independent of set-up, and may be either a second operator or automated verification (for example, barcode linking). Verify replenishment of starting solutions throughout the process similarly.
* Volume delivery and accuracy checks.
* Independent check of the required volume for each solution dispensed.
* Reconciliation of starting solutions at the end of the compounding session.
* Details of remaining manual additions.

### Finished products

#### Visual inspection

Visually inspect, all filled containers of parenteral products individually for extraneous contamination or other defects (Annex 1.124).

Validate the inspection process through operator training and check the performance of the inspection equipment and operators at defined intervals. Record results of the validation and routine inspection results.

Operators performing visual inspection of filled containers should pass regular eye-sight examinations, and wear corrective lenses where required, (Annex 1.124). Retain records of eye-sight examinations.

#### Product yield

Document and trend yield results and investigate any significant deviation from the expected yield, as this may be indicative of a process issue that may impact product quality. (clause 5.44).

#### Container integrity

Perform validation to support the integrity of each container-closure configuration and system to verify its ability to maintain the quality of the finished drug product and sterility over the expiry period (Annex 1.117).

### Quality control testing of sterile compounded medicines

#### Sterility testing

Put in place a documented sterility test programme, which includes consideration of all process variables and risks. Design the program to ensure that variables such as product and operators are adequately monitored and controlled.

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| Information | We expect a higher rate of monitoring and sterility testing in newly established facilities or where historic test data is not available. |

Determine the frequency for sterility testing by the nature of the starting materials used in manufacture:

* For products manufactured from starting materials that are registered therapeutic goods:
	+ Minimum expectation is one sterility sample per operational work station per week.
	+ The requirement for sterility testing may be off-set by the use of a suitably designed ‘end of session media fill simulation’ as part of an ongoing monitoring programme. Align the frequency of this with the minimum requirements for performing the test for sterility, that is, minimum of one simulation per operational work station per week.
	+ Evaluate all types of aseptic manipulation in end of session media fills, and variables such as product and operators cyclically covered on a rolling basis. Document the processes to achieve this in the PQS.
* For products manufactured from starting materials that are NOT registered therapeutic goods:
	+ Perform a formal test for sterility. In the case of product with an expiry exceeding one month, use the sterility test results for batch release. In shorter dated stock, use the sterility test results for trending purposes.

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| Information | The application of rapid sterility test methods is encouraged where these methods provide more timely information regarding product sterility. |

Irrespective of what method is used, monitor each work station at least weekly.

Take samples for sterility testing representative of ‘worst case’. Refer Annex 1, section 127.

In performing the test for sterility, the use of a ‘simulated product’ will be accepted as long as it is processed using the same steps and conditions for testing and replicates worst case scenarios.

Inactivate antimicrobials if present in the product formulation, for example, multi-use vials.

Due to the relatively small batch size of extemporaneously compounded sterile medicines, full compliance with the sample number and volume requirements specified in TGO 100 is not expected. Justify sampling plans and test volumes in accordance with QRM principles.

Using QRM and validation principles, you may be able to justify the accumulation of sterility samples over a period of several working days (up to a week) before shipment for sterility testing. However, perform sterility testing be as soon as practicable when:

* any quality issues are identified that indicate any possible impact to product sterility for batches awaiting testing
* changes to the manufacturing process, materials or environment indicate the need for expedited testing
* a newly qualified operator has commenced production of product for commercial supply and clinical use

The pooling of sterility samples across multiple batches is not encouraged, but may be permissible where justified by risk assessment. If pooling is conducted, you must fully investigate all batches (and starting materials) implicated by a sterility failure.

#### Endotoxin testing

Perform endotoxin testing on each batch before release for products:

* manufactured from starting materials that are not products registered on the ARTG, and
* produced by terminal sterilisation.

Test endotoxin samples from each batch as discrete samples (that is, not pooled).

Ensure endotoxin samples are representative of the whole of the batch. Justify sampling plans and test volumes in accordance with QRM principles.

## Manufacture of non-sterile products

Although not as prevalent as compounding of sterile products, there are instances where non-sterile medicines are compounded or dispensed in accordance with GMP.

### Production environment

In all cases, it is your responsibility to ensure that thorough qualification, validation and monitoring processes are in place to justify heating, ventilation, and air conditioning design and demonstrate that the air quality is sufficient for non-sterile manufacturing areas.

You are required to demonstrate that the manufacturing environment for non-sterile products affords appropriate protection to the products, and prevents contamination. Use a risk-based approach to determine the required air quality and associated controls, based on a thorough understanding of:

* the manufacturing processes
* the nature of the product handled
* risks of contamination and cross-contamination
* risks to product quality

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| Information | As a minimum expectation:* define air quality requirements (physical and microbiological) during system design and demonstrate compliance through qualification and on-going monitoring.
	+ air filters used in manufacturing areas where product is exposed to be at least EU7 grade or equivalent
* higher efficiency air filters may be required for products or processes that present a contamination risk
* define pressure differentials and air flows, they must be appropriate.
 |

Additional guidance in relation to recommended levels of air filtration: World Health Organisation's [Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms](https://www.who.int/medicines/areas/quality_safety/quality_assurance/SupplementaryGMPHeatingVentilationAirconditioningSystemsNonSterilePharmaceuticalDosageFormsTRS961Annex5.pdf)

### Manufacturing controls

#### Sanitisation of items used in production

For non-sterile preparations, put in place appropriate controls to ensure that all equipment and materials used in production areas are adequately sanitised to prevent contamination and cross contamination. Training to maintain sound practices is required.

#### Environmental monitoring

For non-sterile medicines, undertake environmental monitoring periodically to demonstrate that the manufacturing environment is appropriate. Justify monitoring methods and frequencies based on a risk assessment and data from the qualification of the production environment.

#### Product yield

Document and trend yield results and investigate any significant deviation from the expected yield, as this may be indicative of a process issue that may impact product quality. (clause 5.44).

## Use of computerised systems

Full compliance with the requirements of Chapter 4 and Annex 11 is expected.

Consider and meet expectations for [Data Management and Integrity](https://www.tga.gov.au/data-management-and-data-integrity-dmdi).

## Qualification and validation

### General

In general, full compliance to Annex 15 is expected.

### Process validation

Due to the nature of the compounded product batch sizes, we allow some flexibility with respect to process validation.

Validate operations relating to the compounding of patient specific units in terms of dispensing accuracy. Perform this for each dosage form, device and manipulation combination. Generate validation data to support the suitability and accuracy of manual and automated compounding operations. The design of the validation study to be directly relevant to the dosage form and formulation produced. In some cases, a surrogate model analyte such as NaCl can be used for the purposes of validation, as the content of the compounded medicine may be readily analysed and quantified, for example, by titration.

Perform process validation for products made from APIs or batch manufacture in full accordance with Annex 15.

### Distribution and storage

Perform appropriate validation studies to adequately justify how the proposed shipping conditions represent the worst case shipping scenario (based on both time and likely external temperature exposure) for product being distributed around Australia.

Cover the validation of shipping container the worst case shipping scenario.

Ensure the data for justifying any temperature excursions during shipping includes real time studies of the proposed excursion, followed by return to the normal storage conditions for the remainder of the shelf life.

## Investigational medicinal product manufacture

Where the product is intended for use as an investigational medicinal product (IMP), Annex 13 - Manufacture of investigational medicinal products, is applicable to manufacture of extemporaneously compounded medicines.

Manufacture IMPs in accordance with the PIC/S guide to GMP, but note that there is an exception for the manufacture of IMPs when used in [initial experimental studies in human volunteers](https://www.tga.gov.au/book-page/investigational-medicinal-products-annex-13). Take into account other guidelines where relevant and as appropriate to the stage of development of the product.

**Dose Administration Aids (DAAs)**

This section has been prepared to provide general information to manufacturers of Dose Administration Aids (DAA). DAA manufacturers typically use automated and semi-automated dose packaging systems to prepare and pack medicines into single and multi-dose formats for use by patients.

In addition to the requirements of the Commonwealth therapeutic goods legislation, a person involved in the manufacture of DAAs should consider applicable state and territory requirements, including the [Health Practitioner Regulation National Law](https://www.ahpra.gov.au/about-ahpra/what-we-do/legislation.aspx), as in force in each state and territory. These include the requirements set out in the Pharmacy Board of Australia’s [Guidelines on dose administration aids and staged](http://www.pharmacyboard.gov.au/Codes-Guidelines.aspx) [supply of dispensed medicines.](http://www.pharmacyboard.gov.au/Codes-Guidelines.aspx)

Where permitted by applicable federal, state and territory legislation, a pharmacist may engage the services of a third party to manufacture a DAA on their behalf. The third party should ensure that it holds appropriate authorisation to perform the packaging operation, including any requisite manufacturing licence.

Third party pharmacists should note that, in circumstances where the federal legislation applies, the supply of DAAs to another pharmacy may be considered for supply by way of ‘wholesale’ for the purposes of the *Therapeutic Goods Act 1989/ Therapeutic Goods Regulations 1990*; in which case the third party pharmacist must, where applicable, hold an appropriate manufacturing licence issued by the TGA. In general, the expectations outlined in this guidance for non-sterile medicines is applicable to licenced manufacturers of DAAs.

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| Information | The DAA should be supplied to the patient from the supply pharmacy as they have the prescription and have contracted out the packaging. |

## Interpretation of the basic GMP requirements

The tables below reference the section in this guidance that refers to a particular clause or Annex. Only the clauses and annexes with a specific interpretation for extemporaneously compounded medicines are listed in the tables.

### Interpretation of PE009-14 Part I

| Clause(s) | Page\* | Interpretation |
| --- | --- | --- |
| Chapter 1 - Principle | 1 | [Pharmaceutical Quality System](#_Pharmaceutical_quality_system) |
| 1.4, 1.8, & 1.9 | 1 | [Comply with marketing authorisation requirements](#_Marketing_Authorisation) |
| 1.4xv, 1.9vii | 3, 5 | [Release for supply](#_Release_for_supply)[Procedure for release for supply](#_Procedure_for_release) |
| 1.9ii | 5 | [Starting material](#_Sampling_and_management) |
| 1.9viii | 5 | [Reference samples](#_Reference_and_Retention) |
| 2.5, 2.9 | 9 – 10 | [Separate testing and release person](#_Separation_between_production,) |
| 3.22 | 15 | [Sampling areas for starting materials](#_Sampling_areas_for) |
| 4.17(d), 5.44 | 22, 34 | [Product yield](#_Product_yield) |
| 5.33 | 32 | [Starting material collection and testing](#_Testing) |
| 5.63 | 36 | [Release for supply](#_Release_for_supply) |
| 5.66 | 36 | [Rejected and waste materials](#_Reconciliation_(Clause_5.56)) |

\*: Page in Part I of the PIC/S guide to GMP

### Interpretation of PE009-14 annexes

| Clause(s) | Page\* | Interpretation |
| --- | --- | --- |
| Annex 1 - Principle | 1 | [Sterile Products](#_Manufacture_of_Sterile) |
| Annex 1.9 | 3 | [Monitoring of clean air device and clean rooms](#_Clean_room_and) |
| Annex 1.66 | 11 | [Media fills](#_Aseptic_processing) |
| Annex 1.80 | 12 | [Bioburden monitoring](#_Bioburden_monitoring) |
| Annex 1.113 | 16 | [Filter integrity tests](#_Filter_integrity_testing) |
| Annex 1.124 | 17 | [Visual inspection](#_Visual_inspection) |
| Annex 1.125-1.127 | 17 | [Sterility testing](#_Sterility_testing) |
| Annex 1.125-1.127 | 17, 18 | [Endotoxin testing](#_Endotoxin_testing) |
| Annex 8.3 | 82 | [Validation of starting materials](#_Sampling_and_management) |
| Annex 13 | 99 | [Investigational medicinal product manufacture](#_Investigational_medicinal_product) |
| Annex 17 | 145 | [Real time release testing](#_Batch_release) |
| Annex 19 | 152 | [Reference samples](#_Reference_and_Retention) |

\*: Page in the Annexes of the PIC/S guide to GMP

### Determination of ‘public institution’

The key questions to consider in determining whether an entity is a ‘public institution’ in the application of item 5c, Schedule 5A and item 3, Schedule 8 of the [*Therapeutic Goods Regulations*](https://www.legislation.gov.au/Series/F1996B00406)[*1990*](https://www.legislation.gov.au/Series/F1996B00406) are in the table below.

Considerations in determining a public institution

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| Key questions to consider | Could be considered a ‘public institution’ if all three criteria below are met | Probably not be considered a ‘public institution’ if any of the criteria below are met |
| How is the entity controlled? | The institution is controlled by the government or other public entity.AND | It is controlled by private individuals, an independent, commercial company, or a corporate body. |
| How is the entity funded? | The institution is funded by the government or other public entity; andAny profits are directed towards the services the institution provides to the public.AND | The institution is established by a private entity and/or is for profit of particular individuals. |
| Who has access to its services? | The institution serves the public generally or a large proportion of the public. | The institution only serves or is accessible by a small portion of the public.Individuals are selected for reasons of private concern or as members of some private class. |

###

### Determination of ‘substantially similar’

Whether there are listed or registered goods on the ARTG that are substantially similar, in all relevant respects, to the medicines for which the Schedule 5A exemption is said to apply, requires a relative assessment. It is a factual question to be decided on a case by case basis having regard to the relevant essential characteristics of those two therapeutic goods.

The TGA therefore makes an assessment of whether the medicines for which the exemption is said to apply are substantially similar, in all relevant respects, to listed or registered goods, by considering a number of factors that characterise the essential features of therapeutic goods, including but not limited to, whether these goods have:

* a different formulation, composition or design specification; or
* a different strength or size (disregarding pack size); or
* different dosage form; or
* different indications; or
* different directions for use; or
* a different type of container (disregarding container size).

The exemption applies if the listed or registered goods are not similar, to a considerable degree, to medicines in question.

To fulfil the requirement of the exemption one of the criteria is that the private hospital or the public hospital in a State or territory, or the public institution, must be able to specify the full formulation of each product, including active ingredients, excipients and their quantities. If the product to be packed into final packaging is already registered or listed on the ARTG, this criterion could be met by providing the ARTG listing or registration number of the medicine.

For example, a manufacturer or pharmacy is engaged by an institution to repackage a medicine presently registered on the ARTG with container types (e.g. bottles or blister packs) into DAA packs or sachets. The benefit of the DAA packs or sachets to the institution, in terms of its capacity for more efficient and effective control over the administration of the medicine, particularly one that reduces the likelihood of administration error, is of such significance that the registered medicine would not be substantially similar to the repackaged medicine. The latter would, therefore, be exempt from the ARTG, provided all other criteria and conditions of item 5, Schedule 5A of the *Therapeutic Goods Regulations 1990* are met.

If the listed or registered goods are substantially similar, in all relevant respects, to the medicines in question, the latter must be entered onto the ARTG before they can be lawfully supplied.

## Version history

| Version | Description of change | Author | Effective date |
| --- | --- | --- | --- |
| V1.0 | Original publication | Manufacturing Quality Branch | 01/05/2017 |
| V 2.0  | Minor editing and update to provide clarification of requirements.  | Manufacturing Quality Branch  | 29/05/2017 |
| V3.0 | Restructured and updated to be consistent with PE009-14, PIC/S guide to GMP. Additional guidance on expiry dates of compounded medicinal productsInclusion of radiopharmaceutical considerationsInclusion of information previously available in GMP information for manufacturers of compounded medicines and DAAs | Manufacturing Quality Branch | TBC 2020 |

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| Reference/Publication # D19-6249472 |