Australian Government
Department of Health
Therapeutic Goods Administration

Compounded medicines and good manufacturing practice (GMP)

Guide to the interpretation of the PIC/S Guide to GMP for compounded medicinal products

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TGA Health Safety Regulation

Contents

Introduction

The following guidance is provided to assist in the interpretation of the PIC/S GMP requirements when manufacturing compounded medicines. Clause numbers referenced are from PIC/S "Guide to GMP for Medicinal Products" PE 009-8 15 Jan 2009.

Preamble

The purpose of this document is to clarify the PIC/S Guide to GMP for Medicinal Products PE-009 requirements for the manufacture of extemporaneously compounded medicines. This document is only applicable to licensable manufacturers, although may be used as guidance for pharmacists performing compounding that are considered exempt from licensing under the *Therapeutic Goods Regulations 1990.*

This document has been developed in relation to the PIC/S Guide of GMP for Medicinal Products PE-009-8 15 January 2009, following consultation with stakeholders.

Definitions

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

Interpretation of the basic GMP requirements

Where a clause number or an Annex is not listed, there is no specific interpretation provided for manufacture of extemporaneously compounded products.

Please note:

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

Interpretation

Quality management – chapter 1

Topic	PIC/S clause	Interpretation
Marketing Authorisation	1.1, 1.2, & 1.3	As there is no Marketing Authorisation, as such, the product formulation must be in line with the order supplied. If the order is not clear enough, then it should be clarified with the customer. The product formulation is normally derived by appropriately qualified and experienced personnel, usually a qualified pharmacist. The manufacturer should maintain a list of 'approved formulas' for each product type; these are normally translated to the formal batch record. In some cases, these formulas are held electronically. For products supplied under Schedule 5A, Item 5 of the *Therapeutic Goods Regulations 1990,* the manufacturer is required to ensure that the product is not substantially similar to a product that is available commercially.
Order	1.2	Orders can be received in any format (phone/fax/email), but normally in written form (including a prescription), with the order then used as part of the final release check. Any changes made to the order should follow and established process to ensure appropriate documentation and approval of any change to avoid any mix-up. Manufacture in anticipation of an order: Where products are manufactured under the provisions of Schedule 5A manufacture may proceed in anticipation of an order. However, all other conditions of Schedule 5A item 5 must be met. Where products are manufactured under the provisions of Schedule 5, item 6, there needs to be an identified patient at the time of the compounding. Manufacture may proceed in anticipation of an order where the manufacturer holds evidence that the identified patient is undergoing a defined course of treatment.

Topic	PIC/S clause	Interpretation
Batch release	1.3	The order (in written format) must be available at the time of performing the final check for product release. It can be an authorised photocopy of the original order. The final product release must include an independent check against the original order. This is to include a physical check of the final product/s to be dispatched including any secondary labelling that is applied. This check must be recorded on the batch record. Any discrepancies should be investigated and appropriate corrective action taken before the product is released to the patient. Where the batch is made in advance, the release should include verification that the QC 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.
GMP	1.2	Trending and formal reviews should be performed for environmental monitoring results, complaints, and deviations.
Product Quality Review	1.4	Product Quality Reviews should be performed with the aim of assessing the suitability of existing operations, whether manufacturing processes are in control, and should address all relevant aspects of clause 1.4. It is recognised that compounding encompasses a broad range of different formulations, strengths, and presentations in the products it produces and as such manufacturers may wish to group products or similar presentations for the purposes of generating a Product Quality Reviews. Any grouping applied to the products manufactured should be justified in accordance with risk management principles.
Quality Risk Management	1.5 & 1.6	Risk management principles have been embodied in PIC/S PE009 as a means of assessing suitability of operations and justifying how requirements are to be met. Risk management should be utilised to identify how GMP requirements are being met. It should not be used to justify how requirements set out in the PIC/S Guide to GMP can be reduced.

Personnel – chapter 2

Topic	PIC/S clause	Interpretation
Personnel	Chapter 2	The person performing the release for supply activity should be appropriately qualified and experienced. These persons should have a comprehensive understanding of the specific dosage form, manufacturing processes and controls and relevant GMP requirements. Normally, they have a pharmacy qualification but this is not mandated. It is important that they have sufficient and relevant GMP experience. Any persons performing the release for supply function should be named in the Quality System. 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, i.e. been involved in the dispensing, compounding, or labelling operations. The separation of job functions should be clearly documented within the site's QMS. As normally expected, the person named in the licence as responsible for QC should have adequate oversight of this function.

Premises and equipment – chapter 3

Topic	PIC/S clause	Interpretation
Sanitisation of items for transfer into clean areas		For sterile preparations, see below under "Manufacture of Sterile Medicines" For non-sterile preparations, appropriate controls should be in place to ensure that all equipment and materials used in production areas are adequately sanitised to prevent contamination and cross contamination.
Environmental monitoring		For sterile preparations, see below under "Manufacture of Sterile Medicines" For non-sterile medicines, environmental monitoring should be undertaken periodically to demonstrate that the manufacturing environment is appropriate. Monitoring methods and frequencies should be justified based on a risk assessment and data from the qualification of the production environment.
Prevention of cross-contamination	3.6	Manufacture of cytotoxics and antibiotics should be performed in separate areas where toxicological data does not support a controllable risk, e.g. allergenic potential from highly sensitising materials much as β-lactams; or (for non-sensitising molecules) there should be a validated cleaning program to demonstrate that there is no cross contamination. Similarly, preparation of biological medicines (e.g. monoclonal antibodies) should be carried out with similar strategies to avoid cross-contamination. In all cases where dedicated equipment is not used, a risk assessment should be available that shows the mitigation steps that should be implemented.

Documentation – chapter 4

Topic	PIC/S clause	Interpretation
Record retention periods	4.9	Records relating to the preparation of the dosage should be kept for at least 1 year after expiry date. Records relating to personnel training, equipment, validation, risk assessments etc., should be kept for the period they are in use (lifetime) or 1 year after the expiry of medicines to which these records relate, (whichever is the longer period)
Starting material specifications	4.11	Each starting material should be supported by a specification identifying the key requirements, as per clause 4.11. However, for starting materials that are registered therapeutic goods a specification identifying the key requirements, including (as a minimum) the following should be available: • Item name • approved supplier and manufacturer • ARTG number Where registered goods are used, inclusion of a photo is encouraged as a means to assist the identification of the item being received and approved for use. Where starting materials consist of APIs and excipients, e.g. clinical trial manufacture, full compliance with GMP requirements for management of raw materials and suppliers would be expected (Chapter 5 and Annexes 8 & 13). Manufacturers should also have a complete knowledge of the supply chain for each starting material.

Topic	PIC/S clause	Interpretation
Finished product specifications	4.13	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 the relevant monographs from the BP/EP or USP, including relevant standards on microbial quality. For BP/EP: Compliance with the general monographs applicable to the dosage form is expected, e.g. Tablets, Parenteral Preparations, Unlicensed Medicines. In addition, compliance with any specific monographs for the formulated preparation is expected. For USP: Compliance with the relevant general monographs applicable to the dosage form, e.g. Injections, is expected. In addition, compliance with any specific monographs for the formulated preparation is expected. Individual monographs are intended to apply throughout the period for which the formulation is expected to be satisfactory for use. The batch record may fulfil the requirement of a finished product specification in some circumstances. Where product release requires the results from prospective testing, this should be clearly defined.
Batch and packaging instructions and records	4.14 - 4.18	The requirements of the PIC/S Guide to GMP still apply, although it is common for these to be included in one concise document. All items which are part of the final pack should be included in the Bill of Materials (BOM) with their batch number. Where a separate BOM is not used, these items should be listed on the batch record.

Production – chapter 5

Topic	PIC/S clause	Interpretation
Vendor assurance	5.26	There should be a vendor assurance program in place based on risk management principles. 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 section titled "Requirements for starting materials that are APIs"
Inspection of starting & packaging materials	5.5	Each delivery of materials should be quarantined, physically or by equivalent means, until such time as it has been verified against specification. Where the component is an approved/licensed finished human medicinal product it should be purchased directly from a manufacturer without repacking or other alteration since initial manufacture, or purchased from a distributor that certifies that it has not been subject to repacking or other alteration since initial manufacture. There should be a record of incoming materials into the facility. The incoming inspection should be performed against the approved specification; this would normally only be a visual inspection looking for approved supply chain, integrity of the unit, compliance with the specification, including sterility for containers/closures/devices and indications that the goods may be counterfeit. However, if the starting material is an API then additional requirements apply. Refer below. Any component not meeting acceptance requirements must be investigated and rejected.

Topic	PIC/S clause	Interpretation
Requirements for starting materials that are APIs	5.25-5.31	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 is expected. It is expected that there are systems in place for supplier approval and qualification, material receipt, incoming inspection and testing, approval for use, storage, status labelling, expiry dating, etc. There should be approved specifications for API starting materials. These should reflect any available pharmacopoeial monograph. If there is no recognised official monograph available then the specification should be based on the supplier's specification and include at least test for identification and assay, as a minimum. Certificates of analysis, from the manufacturer, should be available for all API starting materials. Refer also Quality Control below.
Starting material traceability	5.29	For all materials, including APIs, excipients, finished product components, packaging components, consumables, there should be a unique identifier for each which should be used for identification and traceability throughout the manufacturing systems and documents in the event of a notified problem/recall.
Checks for auto-compounders (sterile production)		Checks on the correctness of set-up should include: · 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 (e.g. barcode linking). Replenishment of starting solutions throughout the process should be similarly verified. · Volume delivery checks. · Independent check on the required volume for each solution. · Reconciliation of starting solutions at the end of the compounding session. · Details of remaining manual additions. The mechanism for setup and checking is extremely important. Validation of any new equipment should also include a risk assessment.

Topic	PIC/S clause	Interpretation
Reconciliation	5.56	There should be a system in place for the reconciliation of all materials and components used, and partly used, during the compounding operation, prior to release of the batch and before destruction of the used/empty containers. There should be checks in place to ensure the correct quantities have been used, e.g. weight or volume checks. The additions are checked by the compounding operator and an independent operator in the room prior to addition and reconciled afterwards. Secondary checks may be performed by a second operator or suitably validated electronic system, (Refer Annex 11 of the PIC/S GMP guide for requirements) There should be adequate controls for the pre-dilution of multiple containers prior to use, e.g. antibiotics, and the practice of sharing starting materials across batches. Reconciliation processes should be checked to ensure that the appropriate control exists for these operations due to the risk of mix-up. Syringes used to aseptically transfer reconstituted product to the final container, addition of diluents, etc., must be adequately controlled to minimise the risk of mix-up. Such devices must be adequately identified (such as a system to mark, label or identify them) and considered as part of the reconciliation exercise.
Labelling	5.41 & 5.50	Labels should be checked for readability and compliance with GMP at the time of generation and the check recorded on the batch record.
Computerised Systems	Annex 11	Full compliance is expected.

Topic	PIC/S clause	Interpretation
Validation	Annex 15	In general, full compliance to this Annex is expected. Due to the nature of the batch sizes some flexibility is allowed with respect to process validation. Operations relating to the compounding of patient specific units should be validated in terms of dispensing accuracy. This should be performed for each device/manipulation combination. A model analyte such as NaCl can be used for the purposes of validation, as the content of the compounded medicine may be analysed and quantified e.g. by titration. Process validation for products made from APIs or batch manufacture is expected to be performed in full accordance with Annex 15.
Media fills (Process Simulation Tests)	Annex 1, 66-70	Process simulation tests should be performed for aseptically produced sterile products as part of initial validation and repeated at 6 monthly intervals and should be representative of the batch sizes manufactured. Operator media fills must be performed 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 the worst case manufacturing process identified as well as non- routine interventions and events. Usually a matrix approach is taken and this is acceptable. New processes, changes to existing processes, scale of activity, etc. must be assessed to ensure that the previous media fills remain valid. Batch scale “process simulation” exercises are not the same as “end of session media fills”, the latter of which are used in lieu of performing the test for sterility and can be an abbreviated form of a media fill. For the matrix approach, the process simulation should include the worst case attributes of the products covered by the simulation, including factors such as types of manipulations, number of compounded units, and length of the process and container type.

Manufacture of sterile medicine products – annex 1

Topic	PIC/S clause	Interpretation
Design of aseptic processes	Principle	Processes should be designed to include the minimum number of aseptic manipulations necessary. All aseptic manipulations should be performed under unidirectional airflow that is grade A. Personnel performing manipulations in the Grade A environment should be dedicated to this activity for the duration of the work session. Process design should prevent "swapping" of roles (e.g. with other Grade B operators) as this could create disturbance to the Grade A environment.
Environmental Monitoring frequencies and locations	8-20	Monitoring of the Grade A zone for both non-viables and viables should commence at the start of each work session and continue for the full duration of the session. Non-viable results for a session should be considered for release of products manufactured in that session. Viable results should be monitored and the impact of any out of specifications or out of trends considered in determining whether released product is of the appropriate quality and/or if any corrective action needs to be taken. The monitoring of lower grade areas should be performed in accordance with Annex 1 requirements.
Changing and storage of gowns	42-45, 51	The PIC/S Guide to GMP requires that for every worker in a Grade A/B area, clean sterile protective garments (including masks and gloves) should be provided at each working session. A working session can be considered to be maintenance of the period of the same operational conditions i.e. personnel, process, and environment. Hence, movement from, i.e. exiting the Grade B cleanroom would necessitate a gown change for re-entry. Storage of sterile cleanroom garments (including hoods, gowns and boots) beyond a working session is not acceptable. Monitoring of gloves and garments used in Grade A and Bareas is required to ensure that microbial load conforming to requirements is maintained.

Topic	PIC/S clause	Interpretation
Use of ampoules	76	Ampoules should only be used for a single withdrawal immediately after opening and discarded. The contents of glass ampoules should be filtered prior to dispensing into the final dosage container to ensure any glass particulates have been removed.
Control of "pooling" operations	64, 66-70	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". Aseptic pooling of sterile materials should be minimised and only used where this activity reduces the risk of errors in compounding. The use of aseptic pooling should be justified 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). Aseptic pooling should be treated as a batch operation, which is validated by media fill, described in SOPs and recorded in a batch manufacturing records. Each batch should undergo assessment and release and in the case of pools for immediate use, this release may be concurrent with finished product release. Any aseptic pool should be given a maximum shelf life, as justified and demonstrated through appropriate validation/media fill studies, and should not be transferred between different work sessions.

Topic	PIC/S clause	Interpretation
Sanitisation of items for transfer into clean areas	61, 62, 64, 76, 81	The nature of aseptic compounding requires that numerous components including consumables such as syringes, needles, caps together with injection vials, ampoules and intravenous solution bags are introduced into the final preparation area which is normally a Grade A LAF or CDSC. For consumables these are normally enclosed in a primary packet which is opened in a Grade A environment. 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 particulates into the Grade A preparation zone poses a risk of contamination of the final product. Standard practice in compounding is to surface sanitise with suitable disinfectants in a manual process of either "spray" and/or "spray and wipe". The effectiveness in reducing particulates to an "acceptable" level relies on a number of aspects which must be consistently applied. These include adequate exposure to appropriate disinfectants (exposure time and coverage) and adequate wiping with suitable cleaning materials. It is considered that a sanitisation step be performed at each transfer through each of the final grade changes. i.e. Grade C to B, Grade B to A. Procedures should be in place to detail exposure time to sanitant, control of materials used for wiping, preparation details for sanitants, in use period for sanitants, wipes and any other cleaning aids, wiping technique. Sanitants used for early sanitisation steps should be of an appropriate level of bioburden, preferably sterile, and used in such a fashion as to prevent contamination. Wipes used should not shed particles and be sterile when used at the last stage of transfer for aseptic products. Sanitants and cleaning solutions for use in Grade B and A areas should be sterile. The minimum expectation is that there are two discrete decontamination steps with a spray and wipe performed at both steps and the first decontamination steps should use a sporicidal agent. Manufacturers should ensure that the sanitising agents and processes used do not adversely affect the product and are do not leave any residues that may present any risk of harm to the patient

Topic	PIC/S clause	Interpretation
Sanitisation of items for transfer into clean areas (continued)	61, 62, 64, 76, 81	During any transfer activity measures should be in place to avoid any re-contamination of sanitised articles. Where items are packed in multiple protective layers, such as agar plates, needles, syringes and diluent bags, the inner most sterile layer should only be removed at the Grade B/A interface. Management and handling in the Grade A zone after final sanitisation should minimise the likelihood of recontamination and reflect good aseptic practice. For example, orientation of critical surfaces to a clear stream of HEPA filtered air. During sanitisation, particular attention should be paid to the rubber septa of vials and break lines of ampoules, which should be subjected to all stages of the sanitisation treatments. Over-seals should therefore be removed at the first sanitisation stage (in Grade C). Extended storage time of sanitised components is considered to be a risk factor and therefore the storage times of items held between sanitisations steps should be supported by appropriate validation data. Steps should be taken to minimise the exposure of items supplied as sterile prior to entering the Grade A work zone. Sanitant solutions should be subject to an ongoing monitoring program to demonstrate their suitability. The effectiveness of sanitants should be validated before use. Sanitants should be demonstrated to be effective against the normal flora encountered in the facility and on process materials. Sanitisation processes should be validated and used as the basis for sanitisation procedures. Periodic verification of sanitisation effectiveness should be carried out at a frequency based on a risk assessment. Training to maintain sound practices is required.

Topic	PIC/S clause	Interpretation
Use Of "Partial" Vials		Some injectable products are intended for single use only, however, often the full (reconstituted) contents of a container may not be used for a compounded product batch and when another batch is to be made/dispensed for the same product, the reconstituted vial may be retained for subsequent use. This may occur to avoid wastage. The use of partial vials may be acceptable if the following are met: · A risk assessment of the process is conducted to determine the need to utilise partial vials and all controls in place to mitigate any risks associated with their use. · The container is a vial closed with an elastomeric stopper and is held / stored under appropriate conditions at all times. The vial should not be stored in an area classified less than Grade C and there should be an appropriate and validated* mechanism to return it to the Grade A cabinet. · Ampoules should not be reused once opened. · The product is manufactured as a campaign with the patient doses prepared one after the other. The product **cannot** be left in the cabinet when other different products are being manufactured. · 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. · Appropriate checks on the volume drawn up for each patient at the time of manufacture are carried out to ensure that the correct dose is supplied for each patient. · The use of 'partials' including all manipulations is to be validated via the media fill program. · The stability (and sterility) of the partial vial has been established based on stability studies. · The product is not used outside the conditions stated in the 'product information'.

Topic	PIC/S clause	Interpretation
Use Of "Partial" Vials (continued)		*The use of partials should be validated taking into consideration the following: · The transfer process · Container closure integrity · Closure type · Penetration device · The septum is appropriate for multiple entries (usually using a closed system transfer device) · The product formulation · Eradication of any sources of contamination
Performing the "test for sterility"	125, 126	Refer "Quality Control" below.
Container/closure integrity	117	Integrity of the container/closure system must be performed to verify its ability to maintain the quality of the finished drug product and sterility over the expiry period.

Quality control – chapter 6

Topic	PIC/S clause	Interpretation
Environmental Monitoring data	6.7, 6.9	As microbiological data is generally retrospective it is less useful for batch- specific actions for products with a very short shelf-life. Most products will have been released before the information is available. However, environmental monitoring data should be considered as part of batch release for those products with longer shelf-lives that permit the evaluation of data prior to release.Multiple batches are compounded in a single session so any excursion cannot be readily traced or tied to a single batch but rather implicate a number of batches. 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, use of good aseptic techniques including 'first air' principles, etc.) If, when reviewing EM data, a potential problem with environmental control is identified, the basis on which the manufacturer is confident to continue with release should be documented for operations where the reporting of results is retrospective. Sufficient information should be available from the EM program to identify any loss of control in a timely manner and to enable appropriate remedial actions.
Microbiology		Adequate microbiology expertise, either on or off site, is needed to support the provision of acceptable quality, (including sterility assurance and environmental monitoring programs). For sterile products, the identification of all microorganisms in grade A areas should routinely be to species level. Staff performing identification test should be adequately trained and experienced. Isolates from Grade B should be identified 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

Topic	PIC/S clause	Interpretation
		In these cases, additional identification of organisms (at least to species level) should be performed to aid in investigation and rectification of the event. Typical local isolates should also form part of the validation for cleaning and EM programs. Reading of any plates should be performed in a location and in a manner that does not present a risk to manufacturing operations. For non-sterile products, appropriate microbiological testing of starting materials and products should be in place to demonstrate compliance with TGO 77 requirements. A risk based approach may be taken to testing based on the nature of the dosage form and the manufacturing process utilised, and the resultant risk of microbiological contamination of the product. Controls in place for media should include supplier evaluation and the availability of a CofA. The suitability of each lot of prepared media should be verified 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 by qualified pre-prepared media suppliers to ensure that media deliveries are routinely transported under appropriately controlled conditions.
Testing of starting materials that are NOT finished therapeutic goods listed on the ARTG	6.17	Where products are compounded from 'starting materials' that are APIs and/or excipients, all GMP requirements should be met. For example: · An 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/supplier's CoA against the company's specification.

Topic	PIC/S clause	Interpretation
Testing of starting materials that ARE finished therapeutic goods listed on the ARTG	6.17	Where sterile products are compounded from 'starting materials' that are sterile finished goods registered on the ARTG, the default requirements will be compliance with the attributes listed on the specification (item name, ARTG #, label, approved manufacturer/supplier, etc.) There should also be 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 finished products	6.3	The requirements for finished product testing should be commensurate with patient risk, taking into account the intended use of the product, and the methodology of manufacture. Where manufacture involves the use of starting materials that ARE finished therapeutic goods listed on the ARTG the TGA does not expect routine chemical testing of the finished product. However, it is expected that the medicine meets any relevant label claim and pharmacopoeial standards if tested. Where manufacture involves the use of starting materials that are NOT finished therapeutic goods listed on the ARTG e.g. APIs or excipients, there is an expectation that finished product testing will be performed; ID testing, assay and, in addition, for sterile products, the test for sterility and endotoxins.
Reference and Retention Samples	6.14 & Annex 19	Where products are compounded on a batch basis i.e. 10 or more of the same product in the same session, then retention samples need to be taken. The size of the retention sample kept should be determined following risk management principles and take into consideration potential need for retesting. Reference samples are expected for products where manufacture involves a discrete bulk manufacturing step, i.e. products are produced using APIs or excipients as starting materials'. Samples of Finished Product labels and any other printed items used are to be included as part of batch documentation.
Expiry date		Product expiry should be based on a scientific rationale, including test data. Laboratories used to generate this data should operate an appropriate quality system and be subject to the company's

Topic	PIC/S clause	Interpretation
		supplier approval system. · Test data may be obtained from literature searches, provided that the literature is relevant to the product formulation and container/closure system proposed. · Expert opinion on product shelf life must be supported with a documented rationale and test data if available. · Test data needs to cover physical, chemical and microbiological stability (i.e. remain sterile through the labelled shelf life). · For products manufactured from starting materials that are registered therapeutic goods the expiry of the resulting product should not be greater than the shelf life of the input product prior to reconstitution. · For products manufactured from starting materials that are API and excipients it is expected that all these are within the current shelf life at the time of manufacture. · For multiple use containers, the expiry date/time of the container starts when it is first opened. Data used to assign product expiry must be derived using stability indicating analytical methods, and be relevant to the proposed product formulation and container closure system. Preservative Efficacy Testing may be required to support in-use stability. · The assigned shelf life must include a margin of safety from the stability data available. · Special attention should be given to shelf lives assigned and the methodology used for biologically derived products such as MABs. · Stability summaries should include data relating to the suitability (including compatibility) of the container/closure system used. TGA is 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 syringes.

Topic	PIC/S clause	Interpretation
Ongoing stability	6.23-6.33	Where formulations are manufactured routinely and have an expiry greater than 24 hours then an ongoing stability programme should be conducted. Where justified, grouping of formulations for such a program is acceptable. Stability information should be based primarily on actual trials using the unique combinations of active, diluents and packaging components and secondly on available literature. The manufacturer should have a documented justification to its approach for each product. There should be available to review at inspection 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 or USP monograph for Parenteral Preparations. When using literature-based evidence the literature review needs to be based on known published journals. Manufacturers should verify the source material in terms of device, diluent etc.
Test for Sterility	Annex 1: 125, 126, 127	A documented sterility test programme must be in place, which includes consideration of all process variables and risks. The program should be designed to ensure that variables such as product and operators are adequately monitored and controlled. The TGA expects a higher rate of monitoring in newly established facilities or where historic test data is not available. The frequency for sterility testing is determined by the nature of the starting materials used in manufacture. For products manufactured from starting materials that are registered therapeutic goods: · The 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. The frequency of this should be in line with the minimum requirements for performing the test for sterility, i.e. minimum of one simulation per operational work station per week. · End of session media fills should evaluate all types of aseptic manipulation, and variables

Topic	PIC/S clause	Interpretation
		such as product and operators cyclically covered on a rolling basis. The processes to achieve this should be documented in the QMS. For products manufactured from starting materials that are NOT registered therapeutic goods: · A formal test for sterility should be performed. In the case of product with an expiry exceeding one month, the results of the sterility test should be used for batch release. In shorter dated stock, the test for sterility results should be used for trending purposes. Samples taken for sterility testing should be representative of 'worst case'. Refer Annex 1 § 127. In performing the test for sterility, the use of a 'simulated product' may be accepted where scientifically justified and as long as it is processed using the same steps and conditions . routinely used for production. Worst case scenarios should be replicated when manipulating simulated product. The testing of simulated product is not permitted for products manufactured from starting materials that are NOT registered therapeutic goods. If antimicrobials are present in the product formulation (e.g. multi-use vials) then these need to be inactivated.

Contract manufacture and analysis – chapter 7

Topic	PIC/S clause	Interpretation
Contract Manufacture and Analysis	Chapter 7	Full compliance is expected. In addition, to comply with the requirements of Schedule 5A, there should be a contract between the licensed manufacturer and the private hospital/public hospital/public institution.

Complaints and recalls – chapter 8

Topic	PIC/S clause	Interpretation
Complaints and Recalls	Chapter 8	It is expected that all suspected or serious adverse reactions related to compounded medicines will be reported to the TGA. In addition, in circumstances where the manufacturer is made aware of any quality issue that would have resulted in recall of products these events are reported to the TGA recalls coordinator, irrespective of whether any units are recoverable, e.g. following identification of retrospective sterility testing or environmental monitoring failures.

Self inspection – chapter 9

Topic	PIC/S clause	Interpretation
Self Inspection	Chapter 9	No additional requirements/interpretations at this time

Distribution and storage – 1.1viii, 1.2ix, 5.58, 5.60

Topic	PIC/S clause	Interpretation
Distribution and Storage	1.1viii, 1.2ix, 5.58, 5.60	No additional requirements/interpretations at this time

Computerised systems – annex 11

Topic	PIC/S clause	Interpretation
Computerised Systems	Annex 11	No additional requirements/interpretations at this time

Licensing and regulatory/reporting requirements – schedule 5A item 5 condition (c)

Topic	PIC/S clause	Interpretation
Licensing and regulatory/reporting requirements	Schedule 5A item 5 condition (c)	The licence holder is required to 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 for. These reports are to be sent to the TGA Experimental Products Section eps@tga.gov.au.

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

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

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