



**Australian Government**  
**Department of Health**  
Therapeutic Goods Administration

# PE009-13, the PIC/S guide to GMP for medicinal products

TGA interpretation and expectations for  
demonstrating compliance

Version 1.0, December 2017

**TGA** Health Safety  
Regulation



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## About PE009-13



The TGA is adopting version PE009-13 of the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products* (PIC/S Guide to GMP), excluding Annexes 4, 5 and 14, as the manufacturing principles for:

- medicines and active pharmaceutical ingredients
- biologicals that comprise or contain live animal cells, tissues or organs

PE009-13 is available from the [PIC/S website](#), and will take effect on 1 January 2018 as [communicated on the 13 September 2017](#). TGA have published a notice about the [transition to new GMP requirements for medicinal products](#).



PE009-13 does **not** apply to:

-  medical devices
-  biologicals that comprise, contain or are derived from human cells or human tissues

## This guidance

This guidance explains the TGA's interpretation and expectations for compliance with specific sections of the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products*, PE009-13. The content is based on questions and feedback received from industry stakeholders and replaces the questions and answers on GMP previously published by the TGA.



This guidance is not mandatory or enforceable under law. It is not intended to be restrictive. It describes a way that a manufacturer may operate to demonstrate compliance with the PIC/S Guide to GMP.

This information is provided for guidance only and has been developed on the basis of current knowledge of the subject matter. It should not be relied upon to address every aspect of the relevant legislation.

For legislative requirements, refer to:

- [Therapeutic Goods Act 1989](#)
- [Therapeutic Goods Regulations 1990](#)

For technical requirements, refer to:

- [PIC/S Guide to GMP for medicinal products](#)

For more TGA guidance:

- [Manufacturing medicines](#)

## Further questions

If you have further questions, or you require further clarification of a particular requirement, you can email your questions to the [Manufacturing Quality Branch](#).

## Australian legislation and the manufacturing principles

For medicines and other therapeutic goods that are not medical devices, section 36 of the [Therapeutic Goods Act 1989](#) applies.



Section 36(1): The Minister may, from time to time, determine written principles to be observed in the manufacture of therapeutic goods for use in humans.

The manufacturing principles are determined in a [therapeutic goods \(manufacturing principles\) determination](#).

## Periodic changes

Good Manufacturing Practice requirements change over time due to various reasons, such as to:

- provide guidance for the management of new technologies
- address gaps or clarify existing compliance requirements
- manage risks identified through inspections and regulation
- facilitate continuous improvements in the way medicines are manufactured

The TGA uses internationally harmonised manufacturing standards to allow manufacturers to operate in an international environment. The TGA maintains its GMP standards in line with updates issued through PIC/S. Regular updates are necessary to:

- maintain mutual confidence with international regulators
- promote quality assurance of inspections
- promote harmonisation of technical standards and procedures with international inspection standards for the production and testing of medicinal products

Australian manufacturers benefit from reduced regulatory burden where the TGA is able to adopt harmonised international standards and establish mutual recognition agreements and cooperation arrangements with comparable international assessment bodies.

## Adoption of PE009-13

### PIC/S guide to GMP is mandatory

Under provisions of section 36, *Therapeutic Goods Act 1989* the PIC/S Guide to GMP PE009-13 will be adopted as the mandatory standard for the manufacture of medicinal products, replacing PE009-08. This means that the requirements outlined in the PIC/S Guide to Good Manufacturing Practice PE009-13 will be legally enforceable following adoption.

## Timing of adoption

PE009-13 is to be adopted on 1 January 2018 with a transition period up to 1 January 2019, and will replace PE009-08 as the manufacturing principles. TGA commences inspecting against the requirements of PE009-13 from 1 January 2018. However, there will be a transitional period and expectations for compliance are outlined in the [transition plan](#). Compliance with all elements of the PIC/S GMP guide is mandatory from 1 January 2019.

## Implication for imported products

The adoption of PE009-13 has no impact on imported products cleared by GMP certificates and other evidence of GMP compliance as outlined in the [GMP Clearance Guidance](#). Following introduction of the PE009-13, the TGA will conduct its overseas inspections according to the new standard.

## The main changes introduced by PE009-13

The changes between the PE009-08 and PE009-13 *PIC/S Guide to GMP* are clarifications of existing expectations. Some of these changes may require manufacturers to revise or modify their approach to compliance.

The main differences between the PE009-8 and PE009-13 are:

1. clarified requirements for the pharmaceutical quality system used to manage the manufacture and/or testing of medicinal products including:
  - inclusion of changes aligned with ICH Q10 principles Pharmaceutical Quality System
  - clearer definition of the scope and design of the quality system
  - the introduction of the need to perform management reviews
  - requirements for the manufacturer to develop a quality policy
2. clearer expectations for the evaluation of supply chains used for active pharmaceutical ingredients as part of Product Quality Reviews (PQRs)
3. clarification of the application of quality risk management principles
4. specifying the roles and responsibilities for senior management involved in the operation and management of manufacturing sites
5. clearer expectations for the management of all outsourced activities that have the potential to affect product quality
6. clarification on existing GMPs and new technologies used in the manufacture of biological medicinal substances and products for human use (Annex 2)
7. updates to Annex 3, regarding the manufacture of radiopharmaceuticals, specifically in relation to the application of GMP and clarification of the requirements for sterile products
8. updates to the Annex 11, regarding computerised systems, to align with current expectations regarding system validation and management
9. several modifications to requirements for the manufacture of investigational medicinal products in Annex 13
10. modifications to Annex 15, regarding qualification and validation, including modification of requirements for process and cleaning validation and clarification of requirements for validation of transportation methods

For more information, refer to:

- [Transition to new GMP requirements for medicinal products](#)

## Implications of PE009-13 adoption for current TGA guidance

TGA will be working with industry representatives and manufacturers to update all technical guidance documents to reflect any modified or clarified requirements as a result of the adoption. These documents will be completed and available during the transition phase (i.e. prior to 1 January 2019).

In the interim period, TGA inspectors will accept compliance with existing [guidance documentation](#) published on the TGA website. However, manufacturers are expected to:

- review the requirements of PE009-13
- assess the required modifications to their Pharmaceutical Quality Systems
- implement changes in line with the [transition plan](#)

## Application of PE009-13

### Sections of PE009-13 that apply

The sections of the PIC/S Guide (PE009-13) that apply will be determined by the nature of your operations and the types of products or dosage forms you manufacture. In general:

- Manufacturers of **finished dosage forms** should follow the principles of Part I of PE009-13, and in addition, all annexes relevant to their operations and dosage forms. Generally speaking, these manufacturers should meet the requirements of Annex 1 (for sterile API/product manufacturers), Annex 8 (sampling), Annex 11 (computerised systems), Annex 15 (qualification and validation) and Annex 19 (reference and retention samples)
- Manufacturers of **active pharmaceutical ingredients** (APIs) should follow the principles of Part II of PE009-13, and in addition, all annexes relevant to their operations, (e.g. annexes 1, 2, 3, 7, 12, 14). Note that annexes 6, 8, 9, 10, 11 and 15 do not directly apply to the manufacture of APIs as specific guidance for APIs is provided within Part II of the guide; these annexes may however, be used as supplementary guidance without introducing additional requirements.
- Guidance within annexes for specific dosage forms or product types should be read in conjunction with the relevant part of PE009-13 (Part I or II), e.g.:
  - a manufacturer of herbal liquid products should meet the requirements of Part I and annexes 8, 9, 11, 15 and 19
  - a manufacturer of sterile injectable products should meet the requirements of Part I and annexes 1, 8, 9, 11, 15, 17 and 19

### Data management and data integrity

TGA has specific guidance relating to [data management and data integrity](#). Refer to:

- [Data Management and Data Integrity \(DMDI\) Guidance](#)

## TGA inspections of veterinary medicines

The Australian Pesticides and Veterinary Medicines Authority (APVMA) will continue to accept TGA inspections of veterinary manufacturers. The TGA and the Australian Pesticides and Veterinary Medicines Authority (APVMA) have a [Memorandum of Understanding \(MoU\)](#) for cooperation on medicinal products manufactured in Australia for veterinary use.

For information about APVMA-TGA cooperation, refer to:

- [Australian manufacturing licences and overseas GMP certification](#)

Requests for inspections of veterinary medicinal products in addition to human medicinal products **must** be conveyed to the APVMA by the manufacturer.

For inspections of veterinary medicines manufacturers that also hold a TGA licence to manufacture, inspections are restricted to the equipment and facilities used for the common production of human and veterinary medicines. Areas used solely for the manufacture of veterinary medicines, and that are not for the purpose of exporting to EU under the MRA, are outside the scope of the TGA inspection. However, if there are concerns about the impact of these areas on the manufacture of human therapeutic goods, these areas may be reviewed.

PIC/S GMP Annexes 4 and 5 have not been adopted by the TGA. However, if a domestic veterinary manufacturer is inspected by the TGA under the [European Community - Australia Mutual Recognition Agreement](#), the TGA will use the relevant parts and annexes of PE009-13, including Annex 4 and Annex 5.

## GMP for specific medicine types

### Sunscreens

Sunscreens with a Sun Protection Factor (SPF) claim of 4 or more are required to be manufactured in compliance with GMP and so will be required to be compliant with PE009-13. More details are in the [Australian Regulatory Guidelines for Sunscreens](#).

The [technical GMP guidance](#) for listed complementary medicines are baseline documents, elements of which can also be applied to other listed medicines (such as sunscreens) if justified.

### Medicinal gases

The implications of the adoption of PE009-13 for medicinal gas manufacturers are similar to those for other medicines manufacturers.

Technical Guidance for manufacturers of medicinal gases can be found within the [Guide to interpretation of the PIC/S Guide to GMP – 15 January 2009; applicable to the manufacture of medicinal gases](#). This guidance will be revised to reflect PE009-13. However, in the interim period, the TGA will accept compliance with the principles in the current TGA guidance.

### Export-only medicines

For medicines listed in the ARTG as 'export only':

- Medicines that would require registration on the ARTG for domestic supply (i.e. contain substances, quantities of substances or labels without mandatory warning statements required for supply in Australia) should be manufactured in accordance with the GMP applicable to registered medicines
- Medicines that can be listed in the ARTG (i.e. contain substances that are included in the [Catalogue of permitted ingredients for use in listed medicines](#)) should be manufactured in accordance with the GMP applicable to listed medicines, with consideration to any TGA [GMP guidance](#) relevant to the manufacture of listed medicines

# Quality management (Chapter 1)

## Terminology for quality management

### Pharmaceutical Quality System

In the latest PIC/S Guide to GMP, the terminology 'Quality Management System' has been replaced with the term 'Pharmaceutical Quality System' (PQS). This is in line with ICH Q10 global harmonisation efforts, PIC/S Harmonisation efforts and to align the GMP guide with contemporary principles of quality systems management. The new terminology better reflects the specific design elements and requirements for a quality system used to manage the manufacture of medicinal products. The Pharmaceutical Quality System approach described within PIC/S Guide to GMP (PE009-13) is applicable to the manufacture of all therapeutic goods to which the PE009-13 applies.

### Manufacturing authorisation

The term 'manufacturing authorisation', generally refers to the *Licence to Manufacture Therapeutic Goods* issued by the TGA to domestic manufacturers. For manufacturers located overseas, this would refer to the *Certificate of GMP Compliance* issued following an inspection.

### Marketing authorisation

A marketing authorisation, (MA) is the approval given to supply a therapeutic good in Australia, and, in most cases, involves entry on the Australian Register of Therapeutic Goods (ARTG).

The marketing authorisation includes the details of the product in the Australian Register of Therapeutic Goods (ARTG), as well as all other matters in relation to product registration, listing or inclusion agreed in writing between the TGA and the sponsor, and any other requirements imposed by a relevant Delegate of the Secretary upon ARTG entry.

Examples of regulatory requirements include, but are not limited to:

- compliance with standards and registered formulations
- special storage and transportation conditions
- shelf life
- packaging and labelling
- batch release testing requirements

Manufacturers are responsible for ensuring their Pharmaceutical Quality Systems are designed and operated to ensure all relevant requirements of the marketing authorisation are observed during the manufacture of medicines.

### Holder of the marketing authorisation

The holder of the marketing authorisation is the product sponsor.

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## Change management

### Regulated changes

Manufacturing changes that affect the product registered details are regulated and are included as requirements for the marketing authorisation of therapeutic goods:

- prescription medicines ([ARGPM](#))
- OTC medicines ([ARGOM](#))
- complementary medicines ([ARGCM](#))
- biologicals ([ARGB](#))

These requirements are mandatory and are in addition to the requirements of the PIC/S Guide to GMP (PE009-13). The requirements within the PIC/S Guide to GMP (PE009-13) in relation to change control and risk assessment apply to both regulated and other changes.

### Change control applies to all GMP-related activities

Change control is included in Chapter 1 (Clause 1.4 xii, xiii), PE009-13. This clarifies the existing expectation that change control does not just apply to validation activities, but to all GMP-related activities undertaken by a manufacturer.

Any changes to existing processes, systems, facilities, equipment, products, documents, etc. should be evaluated through a change control process. The effort and extent of change control processes should be commensurate with the nature of the change and based on risk management principles.

All changes implemented should be verified for their effectiveness following implementation.

## Managing deviations

There are no changes to the expectations for managing deviations and other similar events (Clause 1.4 xiv). However, PE009-13 now provides clarity regarding the expectations for the investigation of deviations, including adequate root-cause-analysis and identification of corrective and preventative actions.

## Release for supply

For more information on release for supply (RFS), refer to:

- [Guidance on release for supply](#)

### Sponsor performing RFS

Release for supply is defined as a manufacturing step for which a TGA licence is required. For this reason, a sponsor can only perform batch certification for the purposes of release for supply (clause 1.4xv) if:

- the sponsor holds a TGA manufacturing licence

AND

- the licensed sponsor is authorised within the marketing authorisation for that step in manufacture

## Having more than one authorised person for RFS

A manufacturer is allowed to have more than one Authorised Person to perform release for supply. It is the manufacturer's responsibility to ensure that each Authorised Person is appropriately trained and experienced and that the job function relating to release is clearly documented and explained in the Pharmaceutical Quality System.

## Authorised Person needs full overview of all manufacturing steps

The Authorised Person responsible for release for supply should have a full overview of all manufacturing steps, including the ones performed by other manufacturers. Consequently, the last manufacturer in the supply chain for each batch of product is normally responsible for release for supply. However, the Authorised Person may be identified from any of the manufacturers authorised for release for supply in the marketing authorisation, as long as they have full overview of all steps performed in the manufacture of the batch involved and have full access to all details of the marketing authorisation.

## RFS includes consideration of marketing authorisation requirements

The TGA expects an Authorised Person to carry out release for supply to ensure the products meet **all** regulatory requirements. Release for supply must include assurance of compliance with the marketing authorisation, as well as meeting all relevant GMP requirements, including assessing Product Quality Reviews and the effectiveness of the on-going stability program. This applies to inspections of both Australian and overseas manufacturers.

## Senior management responsibilities for GMP and quality management

New clauses in PE009-13 (including clause 1.5) place particular emphasis on the roles and responsibilities of senior management who have ultimate control over manufacturing facilities and activities. Senior management hold the responsibility to make sure that adequate resources are available (human, financial and physical) in order to ensure that the manufacturing activity is managed appropriately.

It is expected that senior management ensure that an effective PQS is implemented and undertake an active role in the support, development and implementation of the PQS. Under the new PE009-13, senior management are ultimately responsible and accountable for the effectiveness of the PQS.

## Management reviews

Management reviews (clause 1.6) are a basic quality system element designed to collate, evaluate and communicate details of the effectiveness of the PQS to the management group. Management reviews are particularly important in escalating concerns and enabling senior management support with the aim of resolving issues and managing risks. The TGA's basic expectations, based on ICH Q10 principles are that the management review system should include:

- The results of regulatory inspections and findings, audits and other assessments, and commitments made to regulatory authorities
- Periodic quality reviews, that can include:
  - measures of customer satisfaction such as product quality complaints and recalls
  - conclusions of process performance and product quality monitoring



- the effectiveness of process and product changes including those arising from corrective action and preventive actions
- Any follow-up actions from previous management reviews

The management review system should identify appropriate actions, such as:

- improvements to manufacturing processes and products
- provision, training and/or realignment of resources
- capture and dissemination of knowledge

Management Review of the Pharmaceutical Quality System. Management should have a formal process for reviewing the PQS on a periodic basis. The review should include:

- a. Measurement of achievement of PQS objectives;
- b. Assessment of performance indicators that can be used to monitor the effectiveness of processes within the pharmaceutical quality system, such as:
  - i. complaint, deviation, corrective and preventative actions (CAPA) and change management processes
  - ii. feedback on outsourced activities
  - iii. self-assessment processes including risk assessments, trending, and audits
  - iv. external assessments such as regulatory inspections and findings and customer audits

Monitoring of internal and external factors impacting the PQS monitored by management can include:

- a. emerging regulations, guidance and quality issues that can impact the PQS
- b. innovations that might enhance the PQS
- c. changes in business environment and objectives
- d. changes in product ownership

### **Frequency of management reviews**

TGA inspectors would generally expect reviews to be conducted at least annually (clause 1.6). However, management reviews may be performed more frequently for new operations, sites that have not previously performed management reviews and sites where the initial management review identifies a number of issues that require rectification.

Also, more frequent reviews may be required for sites with larger and more diverse manufacturing operations.

## Development of a quality manual

Clause 1.7 in PE009-13 requires a Quality Manual (or equivalent document) to be written and maintained. A quality manual or equivalent should be established and should contain the description of the pharmaceutical quality system. The description should include:

- the quality policy
- the scope of the PQS
- identification of the PQS processes, as well as their sequences, linkages and interdependencies. Process maps and flow charts can be useful tools to facilitate depicting PQS processes in a visual manner
- management responsibilities within the PQS

## Product distribution expectations

Clause 1.8 (ix) states that the distribution of the products minimises any risk to their quality and takes account of 'good distribution practice'.

The TGA does not currently inspect the wholesale distribution of therapeutic goods that have been released for supply.

- The responsibility for oversight of wholesale of medicines in schedules 2, 3, 4 & 8 of the [Poisons Standard](#) currently [sits with the states and territories](#), who may issue relevant permits and licences for wholesalers.
- For medicines that are not in schedules 2, 3, 4 & 8 of the Poisons Standard and relevant biologicals, sponsors and manufacturers hold **shared responsibility** for ensuring that they are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life. These responsibilities should be clearly identified within Quality or Technical Agreements between the manufacturing site and Australian Sponsor.

TGA inspections do include an evaluation of the transport conditions for starting materials, bulk and packed medicines between sites of manufacture and clause 1.8 (ix) would apply in these circumstances.

Good distribution practices in the case of Australia would be limited to the application of transport requirements specified in Annex 15 of the PIC/S GMP guide and not necessarily any other official GDP guideline.

## Product Quality Reviews (PQRs)

Guidance regarding the documentation requirements for PQRs may be found in the [TGA Guidance for Release for Supply](#).

### PQR for Authorised products

'All authorised products' in clause 1.10 refers to all products manufactured, within the reviewed time period, under a manufacturing authorisation. This implies that domestic manufacturers are expected to conduct PQRs for all medicinal products manufactured under the manufacturing licence and overseas manufacturers are expected to conduct PQRs for all medicinal products for which a GMP clearance is granted.

## PQRs for listed medicines

Manufacturers of listed medicines are expected to generate PQRs in accordance with GMP requirements. In conjunction with industry, we have developed specific guidance for the generation of PQRs for listed complementary medicines

For more information see our guidance about [PQRs for listed complementary medicine manufacturers](#). This guidance will be revised to reflect the PIC/S Guide to GMP (PE009-13) as required and in consultation with industry.

## PQRs for export-only medicines

The PQR requirements for products that are for export only are the same as the PQR requirements for all other products, refer 'Export-only medicines' section above.

## PQRs for products with no marketing authorisation (e.g. compounded medicines)

Product Quality Reviews are performed to demonstrate the consistency of the manufacturing process. Where no marketing authorisation is available, clauses 1.10.vi and 1.10.x do not apply, but a review of the process consistency, including all other elements of clause 1.10 should be performed and documented by the manufacturer.

## Supply chain traceability for active substances

Manufacturers of dosage forms should have a clear understanding of the approved suppliers of active substances, and each entity and their responsibility in the supply chain between the site of manufacture and receipt (clause 1.10(i)). Supply chains should be adequately secure, integral and ensure that materials are transported under appropriate conditions. Supply chains should be mapped and any identified risks managed following the principles of quality risk management.

Guidance for the evaluation of supply chains for active materials used in non-sterile and complementary medicines may be found in our guidance about [Supplier Qualification](#). This guidance will be revised to reflect the PIC/S Guide to GMP (PE009-13) as required and in consultation with industry.

## Frequency of PQRs

It is important that manufacturers perform a review of all relevant elements of clause 1.10 on at least a yearly basis; however, where very few batches of one product are manufactured in one year, or no manufacturing takes place, it may also be acceptable to perform a full PQR on a two yearly basis providing a rationale is documented and scientifically justified.

For periods where very few batches of one product are manufactured in one year, or no manufacturing takes place, it is expected that manufacturers and sponsors maintain vigilance over elements of clause 1.10 that do not directly relate to manufacturing activities, e.g. results of ongoing stability, returns, recalls and complaints that may provide information regarding products available in the market.

## Grouping of products for PQR

Grouping (sometimes referred to as bracketing or matrixing) of products is when one PQR is prepared for a group of products. Grouping for the preparation of PQRs may be acceptable, if adequately justified. It is usually only acceptable if:

- the amount of batches manufactured annually for each product within the group is low
- the grouped products are of the same pharmaceutical form containing the same or very similar active ingredients and are manufactured using the same equipment.

Acceptability of grouping will be assessed during inspections on a case-by-case basis, and with consideration to any [applicable GMP guidance](#).

## **Batches to be included in a PQR**

All batches for which manufacture has commenced are expected to be included in a PQR. In addition, all batches for which the manufacture was terminated, delayed or has failed are also expected to be included in the PQRs. When grouping is applied, all batches of all products in each group are expected to be included in the PQR.

## **Shared responsibility for PQRs between manufacturers and the sponsor**

Preparation of PQRs is a shared responsibility between the sponsor and the manufacturer(s) of a product. Manufacturers and sponsors should design and implement effective systems to ensure that PQR reports and relevant data are supplied, compiled and reviewed. Responsibilities in relation to PQRs should be clearly defined within technical agreements between parties.

Each manufacturer in the supply chain is expected to generate and hold PQRs relevant to the specific manufacturing step they are undertaking. These are expected to be supplied to the sponsor and available for review during inspections of manufacturers.

The full PQR containing all relevant sections from all manufacturers should be held and reviewed by Authorised Persons performing the release for supply step. Sponsors are also expected to have access to the PQRs, to ensure product compliance with the marketing authorisation.

## **Quality risk management**

### **Quality risk management is mandatory**

Clauses 1.12 and 1.13 of Part I (also and clauses 2.20 and 2.21 of Part II) of PE009-13 make it a mandatory requirement for manufacturers to have an operational quality risk management system in place to ensure that the evaluation of a risk to product quality is based on a sound, scientific basis and that risk assessments are appropriately documented.

Annex 20 is voluntary and provides guidance only on Quality Risk Management tools that may be applied by a manufacturer when assessing the risk to product quality.

## Personnel (Chapter 2)

### Senior management responsibilities for personnel

New clauses in PE009-13 (including clause 2.1) place particular emphasis on the roles and responsibilities of senior management who have ultimate control over manufacturing facilities and activities. Senior management are accountable for ensuring appropriate resources are available to support the relevant manufacturing activities.

### Personnel qualifications

#### Necessary qualifications for staff

'Necessary qualifications' in clause 2.1 means having the education, training, experience and skills, or any combination of these elements, that will ensure that staff can perform assigned duties and functions at an acceptable level.

#### Qualification requirements for an Authorised Person

There are no minimum qualification requirements for Authorised Persons specified within Australian legislation. However, in accordance with Good Manufacturing Practice, senior management should ensure that person(s) undertaking the role of Authorised Person have the education, training, experience and skills or any combination of these elements to ensure that they can perform the role of the Authorised Person.

In general an Authorised Person should be able to demonstrate the following competencies:

- knowledge of the requirements of Good Manufacturing Practice applicable to the dosage forms for which they are responsible
- a comprehensive understanding of the manufacturing methods and controls for the specific dosage form(s) for which they are responsible
- knowledge of the regulatory requirements relevant to the dosage forms manufactured by their site. In particular knowledge of the marketing authorisation requirements for the specific products for which they are responsible
- working knowledge of the Pharmaceutical Quality System implemented at their manufacturing site

### Expectations for training and language

#### Training requirements

Training and assessment should be carried out by persons with relevant training, qualifications and experience in the subject matter (clauses 2.10 to 2.14).

Training should be given to all people affected by significant change in the Pharmaceutical Quality System, e.g. when SOPs or methods of manufacture change. The requirement for initial and ongoing training should be reflected in procedures, and training records should be generated and kept.

There are a number of people who have a direct bearing on quality outcomes. These include senior management, contractors, consultants and casual employees. Therefore, appropriate training and assessment should be provided and recorded.

## **Language requirements**

Manufacturers should define language requirements or standards and ensure personnel are proficient in the required language for their allocated tasks, particularly in relation to documenting and recording. Procedures employed to overcome identifiable deficiencies should also be documented.

## **Role of consultants**

### **Management of consultants**

Where consultants are engaged by a manufacturer to assist in operations, it is important that adequate records are kept and maintained, these include:

- contracts between the manufacturer and consultant outlining the scope of services;
- up-to-date copies of each consultants curriculum vitae;
- job descriptions outlining roles, responsibilities, delegations and/or authorisations;
- Training records for local PQS procedures relevant to their role.

It is the responsibility of the manufacturer to assess consultants and to ensure that they have adequate education, training, and experience, or any combination thereof, relevant to the services for which they are engaged.

### **Approval of controlled documents**

Consultants are permitted (where defined by agreements) to write, review and approve documents within the PQS; however, the licence holder ultimately remains responsible for the content of, and adherence to authorised procedures within their Pharmaceutical Quality System and cannot delegate or discharge the overall responsibility for the accuracy and content of documents signed by the consultants.

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## Premises and equipment (Chapter 3)

### Environmental controls

#### Environment for sampling non-sterile starting materials

Clause 3.9 describes the physical requirements for the area being used to sample non-sterile starting materials. In order to protect the sampled material from contamination, this sampling would be expected to be carried out in a separate room, or appropriately qualified sampling hood, that supplies air of a quality and cleanliness equivalent to that used in the manufacturing area where the material is exposed. The sampling area would also be expected to be designed with dust extraction or equivalent controls to prevent contamination of adjacent areas.

Areas for the sampling of starting materials used in non-sterile products should be filtered using air filters of at least EU7 grade or equivalent. Areas used for the sampling of non-sterile starting materials used in the manufacture of sterile products should be designed and controlled in accordance with Annex 1 requirements.

Sampling hoods may be used provided there are adequate controls in place to ensure that materials are contained. Consideration should be given to the use of appropriate extraction/dedusting facilities, the qualification of the hood, the possibility of contaminating the sampled material and adjacent storage area and whether materials sampled are hazardous.

#### Sampling primary packaging materials for non-sterile products

Clause 3.9 also describes the physical requirements for the area being used to sample primary packaging material for non-sterile products. As product-contact components, primary packaging materials should be sampled within an environment that adequately protects the packaging from contamination. However, sampling of primary packaging materials in an open warehouse would **not** be allowed.

#### Air quality for non-sterile medicine manufacture

The PIC/S Guide to GMP (PE009-13) does not reference a specific standard for air quality for non-sterile manufacturing areas. There are also no Australian or ISO standards for air quality specific to non-sterile medicine manufacture.

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

Manufacturers 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



As a minimum expectation:

- Air quality requirements (physical and microbiological) should be defined during system design and compliance demonstrated through qualification and on-going monitoring.
- Air filters used in manufacturing areas where product is exposed should be at least EU7 grade or equivalent
  - Higher efficiency air filters may be required for products or processes that present a contamination risk
- Pressure differentials and air flows must be defined and appropriate

For additional guidance in relation to recommended levels of air filtration, consult the World Health Organisation's [Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms](#).

## Cleaning and sanitisation

The PIC/S Guide to GMP (PE009-13) contains limited detail on requirements for cleaning and sanitisation. This is because the manufacturer is responsible for demonstrating that the applied cleaning and sanitisation procedures are suitable for its intended purpose. This can be demonstrated by qualification, validation and monitoring studies. The extent of these studies will depend on the nature and types of products manufactured and the associated risks of contamination.

## Premises and equipment definitions

### Campaign manufacture

Clause 5.19 defines campaign manufacture as being a separation in time of production. That is, manufacturing a series of batches of the same product in sequence in a given period of time and/or maximum number of batches followed by an appropriate (validated) cleaning procedure.

Campaign manufacturing operations may be performed where the manufacturer has undertaken an appropriate risk assessment of the proposed operations, considering all potential risks to product quality, and detailed instructions regarding the management of operations and associated control measures are in place.

### Clause 3.6 – meaning of 'Certain'

In clause 3.6 of PE009-13, the word 'certain' (as per certain additional products, certain antibiotics, certain hormones etc.) refers to materials known to cause specific (side) effects in low doses. For example:

- 'certain antibiotics' refers to antibiotics, usually of the beta lactam group, which are known to cause allergic reactions
- 'certain hormones' refers to hormones that can have pharmacological effects if trace amounts cross-contaminate other products e.g. oestrogens and some progesterone-like hormones.



Manufacturers should evaluate materials that are processed and ensure that adequate control measures are in place. Dedicated facilities are normally required where the risk associated with the material cannot be adequately controlled by operational and technical measures, or the available scientific toxicological data does not support a controllable risk.

Further guidance may be found in [EMA/CHMP/CVMP/SWP/463311/2016](#), *Questions and answers on implementation of risk based prevention of cross contamination in production*.

The use of dedicated and self-contained facilities is not normally required for listable complementary medicines. However, dedicated equipment may be required for potentially allergenic or sensitizing products.

## Warehouses and distribution centres

By definition, 'manufacture' includes all steps in bringing the product to its final form and 'release for supply' is considered to be the last step in this process.

From a GMP point of view, warehousing and distribution after release for supply and after the product has left the manufacturer's control, is not currently regulated by the TGA. Hence, a facility that is used only for warehousing and distribution of **fully finished and released** products does not require a TGA manufacturing licence and is not required to comply with the *PIC/S guide to GMP for medicinal products*.

However, for an effective recall, cooperation from wholesalers and distributors is often essential. As a wholesaler, you should have a procedure for conducting a recall at a sponsor's request. For more information, refer to:

- [Uniform recall procedure for therapeutic goods](#)

There may be state or territory regulatory requirements that are applicable, which should be checked with the relevant state or territory authority.

## Documentation (Chapter 4)

### Retention of batch documents

Batch documents must be kept for at least one year after the expiry date or at least 5 years after release for supply by the Authorised Person, whichever is the longest. The batch documentation for investigational products must be kept for at least 5 years following completion or formal discontinuation of the last clinical trial. Other times of retention of batch documents may be required based on specific legislative requirements.

Documents used to record the manufacture of radiopharmaceuticals should be stored for a minimum of 3 years.

### Authorised Person access to records

As the Authorised Person for release for supply takes responsibility for releasing and placing batches of product on the market, it is important that they have appropriate access to any documents that facilitate or influence their decisions. Accordingly, systems should be implemented to facilitate an Authorised Person's access to all documentation relevant to a specific batch, including, but not limited to, validation documents, stability data, test results, batch records, etc.

Guidance as to the minimum documentation requirements required to be held by Authorised Persons performing release for supply of products manufactured under contract may be found in the [Guidance on Release for Supply](#).

### Batch numbers in distribution records

Distribution records require batch numbers (clause 4.28). According to Clause 8.13 the recording of batch numbers in distribution records is mandatory.

### Signature list

Manufacturers need to maintain a signature list. These should include the names, signatures and initials used by individuals who complete GMP documentation. The signature list is the key reference when providing traceability between manual signatures used on documents and the individuals who completed them.

# Production (Chapter 5)

## Listed medicine production

### Process validation for listed medicine manufacturers

A separate guidance document is available for [process validation for listed complementary medicines](#)

The technical GMP guidance for listed complementary medicines are baseline documents, elements of which can also be applied to other listed medicines if justified.

Although the principles in this guidance are still applicable, it will be revised where necessary, in consultation with industry, to clarify requirements in the PE009-13 version of the *PIC/S Guide to GMP*.

### Supplier qualification for non-sterile and complementary medicines

A separate guidance document is available for [Supplier qualification for non-sterile and complementary medicine manufacturers](#).

Although the principles in this guidance are still applicable, it will be revised where necessary, in consultation with industry, to clarify requirements in the PE009-13 version of the *PIC/S Guide to GMP*.

## Labelling and packaging

### Label counting and verification

Roll labels must be counted either on receipt or at issue. Supplier counts are not acceptable unless the supplier is specifically qualified and supplier certifies the exact count for each roll. Supplier sequential numbering on the backing web of labels is an acceptable alternative.

Cut labels must be counted and effectively verified by the manufacturer because of risks of mix-ups.

### Unique batch numbering

The system that a manufacturer adopts for batch numbering may include numerals, letters or symbols (or any combination of these) and must effectively serve to identify uniquely a batch of product, and from which it is possible to trace that batch through all stages of manufacture and distribution. The manufacturer should be able to demonstrate that the system for batch numbering meets these requirements and is effective.

Unpacked bulk products, should have a batch number that is unique to both product and batch, to minimise the potential for mix-ups during manufacturing. For finished products which are easily distinguished, a batch numbering system that only designates batches from that product may be acceptable.

The topic of batch numbering is dealt with in:

- [Medicines labels: Guidance on TGO 91 and 92](#)

## TSE status of materials

The TGA has published guidance relating to the [management of materials susceptible to TSEs](#) (transmissible spongiform encephalopathies) used in the manufacture of therapeutic goods. Manufacturers should undertake an assessment of materials used in the production of medicinal products and ensure that current evidence to demonstrate the TSE status of materials is held and available for inspection.

## Quality control (Chapter 6)

### Sampling and testing complementary medicines

A separate guidance document is available for the [sampling and testing of complementary medicines](#).

The technical GMP guidance for listed complementary medicines are baseline documents, elements of which can also be applied to other listed medicines if justified.

Although the principles in this guidance are still applicable, this guidance will be revised where necessary, in consultation with industry, to clarify the requirements in the PE009-13 version of the *PIC/S Guide to GMP*.

### Conducting on-going stability studies

#### Principles for conducting on-going stability studies

In general, on-going stability studies should be based on the principles of [ICH Q1](#).

#### Use of on-going stability program results in release for supply

The results of the on-going stability program are expected to be available to the Authorised Person who should consider the results before releasing a batch for supply.

#### On-going stability studies for listed complementary medicines

The TGA's expectations for on-going stability studies for listed complementary medicines are similar to those for other medicines. A separate guidance document is available for the [on-going stability testing for listed complementary medicines](#).

The technical GMP guidance for listed complementary medicines are baseline documents, elements of which can also be applied to other listed medicines if justified.

Although the principles in this guidance are still applicable, this guidance will be revised where necessary, in consultation with industry, to clarify the requirements in the PE009-13 version of the *PIC/S Guide to GMP*.

#### On-going stability studies in a GMP certified laboratory

Ongoing stability testing does not need to be conducted in a GMP certified laboratory, because ongoing stability testing is not considered to be a step in manufacture, as defined by the *Therapeutic Goods Act 1989*.

However, the results from these studies are required to be reliable and meaningful. It is the responsibility of the contract giver to ensure that any laboratories used for ongoing stability testing is appropriate. For that reason, other certification may be used in lieu of a GMP certification, such as a licence issued by a regulatory authority acceptable to the TGA or a current ISO 17025 accreditation certificate. Stability test methods used by the laboratory should be appropriately validated and documented according to the requirements of the *PIC/S Guide to GMP* (PE009-13).

The results from the on-going stability monitoring studies must be considered as part of release for supply, which is the final step in manufacturing.

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## Responsibility for ongoing stability studies of imported medicines

In the case of imported medicines, the responsibility to conduct an on-going stability monitoring program is with both the manufacturer and the sponsor.

- The manufacturer who carries out release for supply needs to ensure that the batch meets its marketing authorisation, and that an on-going stability monitoring program is conducted and data is available to support the expiry date.
- The sponsor is responsible for the marketing authorisation, ensures an on-going stability testing program is performed and has access to the stability results.

In the contract manufacturing agreement, the responsibility for on-going stability may be contracted out to the manufacturer or other parties.

## Bulk medicine on-going stability studies

Where bulk medicines are imported into Australia to be packaged by a domestic manufacturer, the domestic manufacturer cannot use the on-going stability program of the bulk manufacturer to support the packed product stability.

On-going stability is required to be performed in the packaging material in which the product is marketed in Australia. The overseas bulk manufacturer will use different packaging equipment and processes although the packaging materials might be the same.

## Grouping for the purposes of stability testing

Grouping (also known as bracketing or matrixing) could be acceptable, if scientifically justified. This will be assessed during inspections on a case-by-case basis.

## Review of on-going stability data during inspections

During inspections, the operation of an appropriate on-going stability program is normally reviewed, including the results of on-going stability studies, where appropriate. If there are any concerns, the inspector can refer the evaluation to the area of the TGA responsible for regulating the product ARTG entry.

## Notifying TGA of on-going stability issues

Although it is acknowledged that some normal variability in the results of on-going stability studies can be expected, all statistically significant departures from established stability profiles must be notified to the area of the TGA responsible for regulating the product ARTG entry. In general, 'significant change' for a medicinal product is defined as:

- a 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures
- any degradation products exceeding its acceptance criterion
- failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g. colour, phase separation, re-suspendibility, caking, hardness, dose delivery per actuation); however, some changes in physical attributes (e.g. softening of suppositories, melting of creams) may be expected under accelerated conditions
- OR, as appropriate for the dosage form:
  - failure to meet the acceptance criterion for pH
  - OR
  - failure to meet the acceptance criteria for dissolution for 12 dosage units

# Outsourced activities (Chapter 7)

## Change in scope of chapter 7

The title of chapter 7 has changed from 'Contract manufacturer and analysis' to 'Outsourced activities' in recognition of the fact that there are a number of outsourced (contracted) activities that may have a direct effect on the quality of medicinal product manufactured by a site. The previous title of the chapter restricted the extent of GMP controls to only outsourced manufacturing and testing services and thus did not appropriately manage the risk associated with other outsourced activities.

Examples of outsourced activities that this chapter would now apply to 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

## Managing outsourced activities

TGA expect manufacturers (normally 'contract givers') to manage all relationships with contract acceptors in accordance with existing principles of chapter 7. All outsourced GMP-related activities that may impact on product quality should be assessed, defined and covered by a written contract. Agreements should be maintained in accordance with the Pharmaceutical Quality System.

## Legality of outsourced activities

The term 'legality' in clause 7.4.1 means that contract givers are responsible for making sure that the entity undertaking the outsourced activities is appropriately authorised to undertake the activity. This may be achieved by many means including ensuring that the contract acceptor:

- holds the appropriate manufacturing authorisation (licence) to undertake the specific steps in manufacture;
- is nominated as being authorised to undertake the specific activity in the specific marketing authorisation of the products;
- holds any necessary licenses or permits applicable to the outsourced activities, e.g. wholesale authorisations, Schedule 8 drugs permits etc.

- holds the necessary accreditation related to the activities undertaken, e.g. a contract calibration company may hold NATA or ISO 17025 certification

## **Monitoring the contract acceptor**

The contract giver should have a system in place to measure and monitor the quality of products (or service) provided by the contract acceptor, in accordance with risk management principles. Where quality related issues are identified, it is expected that appropriate actions are taken to address and remediate the concerns. Records of actions taken should be recorded within the PQS.

## **Responsibility for review of records and results**

Clause 7.5 states that the contract giver should be responsible for reviewing and assessing the records and the results related to the outsourced activities.

It is expected that the responsibility for review of the records and results to be specified by contract and should be based on the risk and nature of the service provided e.g.:

- For contract manufacture and analysis it may be appropriate for the contract giver to rely fully on the contract acceptor where an authorised representative of the contract acceptor, e.g. quality manager, has authorised the data and records.
- For contract service providers (e.g. contract calibration services) it would be appropriate for the contract giver to review the available records and data to ensure that the results or work provided meet the requirements of the contract giver's quality system and procedures.



## Complaints and product recall (Chapter 8)

### Counterfeit products

Clauses 8.7 and 8.8 of PE009-13 require that the procedures on complaints handling should include an assessment for counterfeit products. If counterfeiting is detected the TGA must be notified in accordance with the [Uniform Recall Procedure for Therapeutic Goods](#).

# Sterile medicinal products (Annex 1)

## Technical interpretation of Annex 1

The TGA has endorsed a PIC/S interpretative guidance on Annex 1, which is called [Technical interpretation of revised Annex 1 to PIC/S GMP Guide](#) (PI 032-2). This document gives a technical interpretation of Annex 1.

## Classification of clean-rooms

Guidance on the TGA's expectations for the classification of cleanrooms is available in our notice on [Implementation of updates to ISO 14644 Parts 1 & 2 \(2015\)](#).

## Highly potent or sensitising material

Generally, dedicated buildings, facilities and equipment are required for potent or highly-sensitising material manufacture. An isolator operating at negative pressure would be regarded as a 'micro-environment' and could be accepted for manufacture of a potent or highly-sensitising material provided that factors such as cleaning, sanitation (noting that if the isolator is opened during cleaning this could present specific concerns), preventative maintenance, environmental monitoring (residues), spillage, etc. are adequately addressed with respect to cross contamination. However, the manufacture of 'other drugs' in the same isolator would not be permitted.

Further guidance may be found in the EMA's [Questions and Answers document](#) for risk based prevention of cross contamination.

## Cleanroom clothing

Cleanroom clothing is not a therapeutic good and manufacturers of such clothing are not subject to inspection and licensing under the *Therapeutic Goods Act 1989*. However, licensed manufacturers of sterile medicinal products should qualify their vendors of critical goods used in the cleanrooms, such as cleanroom apparel and these relationships should be defined and managed in accordance with Chapter 7 principles.

# Biological medicinal substances and products for human use (Annex 2)

## Implications of changes in Annex 2

Annex 2 of PE009-13 contains greater guidance for the management of biological medicinal substances and products. The main changes are:

- Application of GMP principles to all critical stages in the production of biological medicines, following a risk-based approach and in alignment with international regulations
- Greater emphasis has been placed on the control of initial components used, e.g. management of animals, materials sourced from animal or plant sources, establishment and maintenance of master cell banks and/or seed lots. Specific guidance has been included that emphasises the importance of managing risks associated with the starting materials used
- Clarification of existing requirements and the application of quality risk management
- Re-write of the annex to provide clarity on the GMP requirements for novel technologies used in biotechnology, including transgenic animal and plant products

Most of the changes in Annex 2 relate to a clarification of existing requirements, and as such it is anticipated that most manufacturers involved with the manufacture of biotechnology products should already be compliant with the updated requirements.

The main emphasis of the changes relate to the management and oversight of manufacturers in the supply chain undertaking critical early steps in the manufacturing process. These entities include, but are not limited to, those involved in:

- collection of organs, tissues or fluids
- establishment and maintenance of master and working cell banks or seed lots

It is expected that manufacturers using these suppliers undertake appropriate evaluation and oversight of these critical suppliers to ensure appropriate GMP principles are met.

For more information, see guidance on the [GMP evidence requirements](#) for these manufacturing activities.

## Annex 2 applies to APIs for biological medicines

The manufacture of APIs for biological medicines is usually performed in immediate conjunction with the manufacture of the biological medicinal product itself. For that reason, Annex 2 is written to cover both the API and the finished product manufacturing steps of biological medicines. Additionally, Part II of PE009-13 is applicable to the manufacture of APIs for biological medicinal products.

Guidance relating to the application of Annex 2 and Part II of the GMP guide to the manufacture of biological APIs may be found in the tables published in the respective documents.

## Human blood, blood components, tissues and cellular therapies are not covered by Annex 2

Annex 2 has **not** been adopted by the TGA for the regulation of human blood, blood components, human tissues and human cellular therapies. These products will continue to be inspected in

accordance with the [Australian Code of Good Manufacturing Practice for human blood and blood components, human tissues and human cellular therapy products](#).

## Biological substances covered by Annex 2

As a general guide, the following are considered biological medicinal products under the requirements of Annex 2:

- animal derived fractionation products
- antibiotics produced by fermentation
- antigens
- antitoxins, antivenenes, enzymes and venoms
- products used for allergy testing
- biological medicinal products
- cytokines
- hormones
- human derived fractionation products
- immunosera
- monoclonal antibodies
- somatic cellular products
- therapeutic recombinant products
- toxoids/toxins

## Raw materials intended for listed medicines are not covered by Annex 2

Also, as a general guide, although certain starting materials listed in the [Catalogue of permitted ingredients for use in listed medicines](#) could be considered biological medicinal products, the additional requirements of Annex 2 will **not** be applied to raw materials included in the catalogue intended for use in the manufacture of listed medicines, e.g.:

- beta-carotene
- shark cartilage
- bee propolis
- green lipped mussel
- deer antler
- royal jelly

## Biological medicinal products with a short shelf-life

Biological medicinal products with a short shelf-life can be released for supply before all quality control results are finalised, provided an adequate control strategy is in place. The requirements for this control strategy are provided in clause 71 of Annex 2, and should reflect any conditions of the marketing authorisation (where relevant).

# Radiopharmaceuticals (Annex 3)

## Implications of changes to Annex 3

Annex 3 of PE009-13 contains some minor changes from PE009-8. The main additions are:

- clarification of the application of the Annex to steps in the production of radiopharmaceuticals and radiochemical (APIs)
- a new explicit requirement to have separate gowning facilities at the entry to the production areas
- a greater emphasis on radiation monitoring as a contamination control measure
- changes to the environmental requirements for the location of closed systems used for sterile products

## Exemptions

### Irradiation of targets in a reactor or cyclotron

Annex 3 now clarifies that activities relating to the irradiation of targets in a reactor or cyclotron are outside the scope of GMP. This means that the reactor and cyclotron equipment are not generally subject to inspection for compliance to PE009-13. However, GMP requirements apply to the supply and preparation of target materials prior to irradiation, as well as any subsequent post-irradiation processing of the irradiated targets. GMP requirements also apply to the target and transfer system from cyclotron to synthesis equipment.

### Hospitals supplying radiopharmaceuticals to other hospitals

Hospitals supplying radiopharmaceuticals to other hospitals require a TGA licence, with one exemption. Public hospitals supplying radiopharmaceuticals to other hospitals or public institutions in the same state or territory do not require a TGA licence. In that case, the biomedical engineers, radiochemists and pharmacists employed by those public hospitals are exempt from the requirement to obtain a TGA licence to manufacture radiopharmaceuticals. Further information may be found in Schedule 8 of the [Therapeutic Goods Regulations 1990](#).

### Room classification for sterile radiopharmaceuticals

Manufacturing environments for sterile products must follow the general principles outlined within Annex 1 of the PIC/S GMP Guide, and equipment and processes should be located within environments conforming to the required grade, (A, B, C or D). The new version of Annex 3 (clause 27) permits fully closed and automated systems used in the manufacture of sterile goods to be located in a Grade C environment. 'Fully closed and automated systems' are interpreted to be those where the product sterile fluid pathway is at no point open to the external environment, and where manual intervention for operation is not required, e.g. a closed sterile holding vessel.

### Minimum background grade for hot-cells used for sterile products

Hot-cells should be located in a suitable background environment in accordance with Annex 1 requirements. Fully closed hot cells used for sterile products, should be located in an

environment that meets at least Grade D requirements. Higher background grade environments may be required for open processes performed in hot-cells.

A closed process is not opened to the environment at any point after sterilisation, and is normally verified by pressure testing. For this reason, operations involving the piercing of stoppers or septa with needles are not closed systems.

## **Record retention requirements**

Documents used to record the manufacture of radiopharmaceuticals should be stored for a minimum of 3 years.

## **Retention samples for radiopharmaceuticals**

The retention period for radiopharmaceuticals is at least 6 months following product expiry unless justified by sound risk assessment.

## Medicinal gases (Annex 6)

### Bulk, liquefied medical gas manufacturer exemption

All entities involved in the manufacture of medicinal gases are required to hold a TGA licence and meet PIC/S GMP requirements (including Annex 6), except those entities responsible for the manufacture of bulk, liquefied medical gases, as they are exempt from GMP licensing requirements under item 17 of Schedule 7 of the [Therapeutic Goods Regulations 1990](#). Any step of manufacture, prior to receipt of the bulk gas is not subject to GMP requirements, including where bulk liquefied gases are produced on site.

For more information, refer to:

- [Medicinal gases and good manufacturing practice \(GMP\)](#)

# Herbal medicinal products (Annex 7)

## Reference standards

If an active or marker compound is identified and no commercially available primary standard is available, a suitably controlled and characterised reference material of that compound should be obtained from external sources.

## Quantified by input

Please refer to the [ARGCM Part B: Listed complementary medicines](#) for guidance on use of the term 'quantified by input' for listed complementary medicines.

## Good Agricultural and Collection Practices (GACP)

Statements within this annex relating to Good Agricultural and Collection Practice are not mandatory. Alternative methods of assuring the suitability and quality of herbal starting materials are permissible. It is recommended that GACP practices are considered during supplier qualification, as GACP may assist in influencing routine sampling and testing programs for herbal starting materials.

The recommendations regarding Good Agricultural and Collection Practice apply to manufacturers involved in the cultivation of herbal starting materials (herbs) only.

## Adulteration or substitution of herbal substances

Manufacturers should assess the range of herbal substances used in order to determine whether specific herbal substance is at risk of adulteration or substitution. Potential risk factors include:

- materials with high intrinsic value that may be substituted or 'bulked-out' with other materials, i.e. cheap plant material, fillers
- highly active compounds including Schedule 8 medicines
- ingredients for use in listed medicines that may be adulterated with medicinal substances included in schedules 3, 4 and 8 of the Poisons Standard, e.g. steroids, diuretics, stimulants or medicines used in the treatment of erectile dysfunction
- herbal materials that are difficult to distinguish microscopically, e.g. milled or powdered materials and plant parts that have very similar microscopic appearance
- materials from new sources especially in circumstances where the reputation of reliability of the supplier is not known
- large offers of herbal materials that are generally only available in limited quantities
- out-of-range prices for materials

The justification and application of additional testing should follow basic risk management principles.

## Identification of herbal materials

The TGA has published guidance regarding the [requirements for identification of herbal materials](#).



## **Samples of unmilled plants**

Manufacturers performing the identity testing of herbal materials are required to hold appropriate certified reference samples for the herbal materials used. Reference samples should be traceable back to a suitable primary reference material. Where powdered materials are used in the manufacture of an API or product, the manufacturer performing the testing is expected to hold an appropriate certified reference material of unmilled plant. This is due to the inherent difficulties and risks associated with the identification of powdered plants.

# Sampling of starting and packaging material (Annex 8)

## Reduced sampling of starting materials



It is improbable that reduced sampling and testing would be accepted for:

- starting materials supplied by intermediaries such as brokers where the source of manufacture is unknown or not audited;
- starting materials for use in parenteral products.

A validated procedure that would permit less than all containers to be sampled and tested for identification purposes should consider the following:

- Every container of starting material must be sampled and tested for identity if the supplier is not classified as reliable and is not validated according to Annex 8.
- For registered medicines, the requirements for sampling active materials do not differ from those for excipients. However, [TGA guidance](#) should be consulted for manufacturers of listed medicines.
- The validation of a supplier cannot be accepted without a regular and adequate assessment. Such validation should comprise a number of actions, which may include all or most of the following:
  - a. The use of a questionnaire prepared by the potential customer and completed by the potential supplier, concerning the supplier's operating Quality System
  - b. Approval inspection of the potential supplier's operation by the potential customer, or by a third party on their behalf. For example, a sister company located in the same country as the supplier. Reliance on inspection reports of other regulatory authorities by the potential customer is normally not sufficient, unless it can be demonstrated that the inspection covered the specific operations to be used in the processing of materials for the potential customer
  - c. A program to evaluate the quality of each shipment of materials on receipt by the customer. In this regard, sampling of powders should be representative of the container contents. For example, sampling from the top, middle and bottom of drums, in the absence of validated sampling positions. Reduced testing programs should be evaluated by the inspector. Sampling by the suppliers should be validated
  - d. A program for regular re-inspection of the supplier's operation and for ongoing monitoring of the quality of material supplied, for example, through trend analysis of analytical results, periodic full testing
  - e. In the case of active ingredients, the use of brokers as sources should be carefully evaluated. The quality of each batch of material should be confirmed through testing of representative samples



Note: Certification such as a Certificate of Suitability for compliance with Monographs of the European Pharmacopoeia, **does not** replace an inspection.

## Application of $\sqrt{n+1}$ sampling

Where a validated procedure is established to justify reduced sampling, and scientific and statistical evidence is presented,  $\sqrt{n+1}$  sampling may be justified as applicable.

There are specific provisions for the sampling of materials used in the manufacture of listed complementary medicines as described in the technical guidance on [sampling and testing of complementary medicines](#). Although the principles in this guidance are still applicable, it will be revised where necessary, in consultation with industry, to clarify requirements in the PE009-13 version of the *PIC/S Guide to GMP*.

The technical GMP guidance for listed complementary medicines are baseline documents, elements of which can also be applied to other listed medicines if justified.

# Computerised systems (Annex 11)

## Implications of changes to Annex 11

Annex 11 has been updated to provide clarification of existing requirements to ensure that computerised systems are managed appropriately, particularly in relation to data management and integrity. In some cases, the wording of the clauses has become less prescriptive to allow better use of quality risk management principles in the validation and control of computerised systems.

## Validation and control of computerised systems

All computerised systems (including commercial off the shelf systems) used by licensed manufacturers in the manufacture of medicines should be validated and controlled in accordance with Annex 11 requirements (i.e. GMP computerised systems).

The level, extent and formality of system control should be commensurate with the criticality of the system. Manufacturers should have a good understanding of all the systems used, and the impact and criticality of each system.

In general, the following systems (list is not exhaustive) should be fully validated and controlled, such as those used:

- for the electronic acquisition of quality control data
- to control and monitor the operation of critical utilities, facilities and equipment
- to generate, store or access electronic GMP records
- to generate, process, calculate or monitor data that forms part of the batch processing record, or batch control testing records
- in the place of physical (hard-copy) records, e.g. electronic spreadsheets used to track records or perform calculations, electronic documents used to record data
- to control the status of materials, products, equipment or processes, e.g. Enterprise Resource Planning systems
- to perform the release of materials and release for supply of finished goods
- to track the distribution of products and/or control the reconciliation of products and materials in the case of quality defects or recalls

## ‘Regulated users’ definition

The TGA regards ‘regulated users’ to be the licence or GMP certificate holder responsible for the application of Good Manufacturing Practice.

## ‘Life-cycle’ of a computerised system

The ‘life-cycle’ of a computerised system includes all stages from the initial concept, design, qualification, validation, and use through to the eventual retirement of the system and archival of all data.

Manufacturers need to manage computerised systems effectively at all stages in the life-cycle to ensure that they function correctly. Therefore, validation not only applies at the initial introduction of the system, but throughout all stages of use. Further guidance regarding the life-cycle management of computerised systems may be found within the [PIC/S Good Practices for Computerised Systems in Regulated GXP Environments](#).

## Investigational medicinal products (Annex 13)

The *Australian clinical trials handbook* version 2.0 (to be published early 2018) contains guidance on manufacturing products for clinical trials.

### Manufacture in Australia

The manufacture of medicines for initial experimental studies in human volunteers (which generally means first-in-human trials, which are generally, but not always, Phase I trials) is not subject to inspection and licensing by the TGA (specified in item 1, Schedule 7, *Therapeutic Goods Regulations 1990*). However, the domestic manufacture of **all other** clinical trial medicines is subject to inspection (including Annex 13) and licensing by the TGA.

Manufacturers in Australia of investigational medicinal products (IMPs) for clinical trials in phase 3 and phase 2 that are not initial experimental studies in human volunteers must hold a valid TGA licence that **specifically authorises** that site for the manufacture of clinical trial products.

- Even if a pilot facility is dedicated for the development of dosage forms and new products, and is not used for the manufacture of saleable product, it is still subject to TGA inspecting and licencing if it is used to manufacture investigational medicinal products for clinical trials that are not initial experimental studies in human volunteers.

### Labelling investigational medicines

#### 'Certain characteristics' in clause 32 of Annex 13

The 'certain characteristics' in clause 32 of Annex 13 of the *PIC/S Guide to Good Manufacturing Practice for medicinal products* refers to non-commercial clinical trials performed by researchers without the participation of the pharmaceutical industry. These trials are usually performed with registered (or listed) products that are obtained from the market for use in a clinical trial. The requirements in this clause relate to the way these products are to be labelled.

## Qualification and validation (Annex 15)

For qualification and validation guidance, TGA encourage the use of [PIC/S recommendation publications](#), as expand on various clauses within Annexes 1 and 15 of the *PIC/S Guide to GMP* (PE009-13). However, these are for guidance only and may not fully reflect the current requirements of PIC/S PE009-13. For example:

- PI-006-3 Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation (recommendations)
- PI-007-6 Validation of Aseptic Processes (recommendations)

All equipment used in the manufacture of medicinal products must be appropriately qualified following the principles outlined in Annex15 section 3. Acceptability of the approach taken will be assessed during inspections on a case-by-case basis.

The nature and extent of qualification should be determined based on risk management principles. Depending on the use, stage in the equipment lifecycle and nature of the equipment, some of the stages outlined in Annex 15 section 3 may be omitted where appropriately justified, based on risk. It is generally expected that all stages would be addressed in the qualification of new and/or complex equipment.

### Retrospective process validation no longer permitted

Process validation is a critical step in assuring the quality of medicinal products. When Annex 15 was originally published in 2001 the provision for retrospective validation was given to provide a means by which existing products could be validated. As the process validation requirements of Annex 15 have been in place for over 15 years, it is now expected that all products currently manufactured are validated, and that new products undergo validation prior to release to the market.

Unfortunately the previous provisions for retrospective validation could be incorrectly interpreted by manufacturers to suggest that products may be released to market prior to process validation being completed. The changes to Annex 15 rectify this issue. There should be no existing medicines supplied for which appropriate and documented validation is not currently in place. The manufacturing process should be validated before the product is placed on the market.

Any existing validations based on retrospective validation will be accepted; however, any new products, processes, updates or changes to existing processes should undergo full prospective process validation.

### Application of concurrent process validation

For registered therapeutic goods or equivalent, concurrent process validation may only be conducted where there is a strong benefit-risk ratio for the patient, i.e. to permit timely access to a critical medicine.

For listed therapeutic goods, concurrent process validation is permitted.

Concurrent process validations should be approved under the sites PQS and where used, the results and conclusion of any supporting data should be made available to the Authorised Person performing release for supply of the product.

## Number of batches used in process validation

The number of batches used for process validation should be determined and justified by the manufacturer based on risk management principles. Our general expectations are that:

- For a new process or product, a minimum of 3 batches are to be conducted for validation purposes
- For a process subject to technology transfer from one site to another, an extensive evaluation and risk assessment (with supporting data) are to be conducted regarding the similarities and differences in manufacturing processes, equipment, methods and materials should be in place to justify performing less than three batches
- For changes to existing (validated) processes (e.g. batch size increase), an extensive evaluation and risk assessment (with supporting data) are to be conducted regarding the similarities and differences in manufacturing processes, equipment, methods and materials should be in place to justify the number of batches selected

Any variations from this approach should be clearly documented and justified by the manufacturer using sound QRM principles.

## Batch sizes for process validation

The process must be validated for the smallest and the largest batch sizes intended to be manufactured at industrial scale. Process validation may not be required for intermediate batch sizes if it can be demonstrated, based on risk assessment, that process consistency can be achieved for any intermediate batch size.

## Scope and extent of validation and risk

The scope and extent of validation should be based on risk according to the manufacturer's quality risk management procedures. Qualification and validation work is required to control the critical aspects of the particular operation and a common sense approach should be applied.

## Performance qualification (PQ) and process validation

For significant changes to equipment (e.g. for new or modified items of equipment), the performance qualification is separate from and precedes process validation.

For minor changes not impacting on already qualified equipment (e.g. to processing parameters only):

- performance qualification may be performed in conjunction with operational qualification and process validation
- separate installation qualification and operational qualification are not necessary

## Complementary medicines and process validation

A separate guidance document is available for [process validation for listed complementary medicines](#).

The technical GMP guidance for listed complementary medicines are baseline documents, elements of which can also be applied to other listed medicines if justified.

Although the principles in this guidance are still applicable, it will be revised where necessary, in consultation with industry, to clarify requirements in the PE009-13 version of the *PIC/S Guide to GMP*.

## **Critical Quality Attributes (CQA) and Critical Control Parameters (CPP)**

A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are used to guide process development and control strategies. The list of potential CQAs can be modified as product knowledge and process understanding increase.

A CPP is a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

CQAs and CPPs are important elements of product and process knowledge and should be utilised in the design, validation and control of manufacturing processes.

## **Ongoing process verification (Annex 15 clauses 5.28-5.32)**

Ongoing process verification is used periodically to evaluate process parameters and trends and ensure that processes are consistent, and remain in a validated state. The outcomes from the OPV exercise should be used to look at any correlation between process capability and trends identified in the PQR. The frequency of the verification should be based on risk management principles.

Ongoing process verification should normally occur for all therapeutic goods (or equivalent), irrespective of the method used for process validation.

## **Use of materials from approved suppliers for validation**

When conducting validation exercises, it would be expected that raw materials from approved suppliers are used. However, in exceptional circumstances, materials from unqualified suppliers may be used where supported by a comprehensive risk assessment. It is expected that this would only apply when concurrent vendor approval is underway, such that the material under evaluation is part of the validation exercise. There must however be an appropriate justification to use the unapproved material based on all of the following:

- The risk to the following manufacturing process, plant and other products
- Assurance that the vendor has met the specifications required
- Suitable controls regarding approval, analysis and release of the material
- Adequate control regarding the starting material issuance and reconciliation
- Relevant systems in place to prevent release of the validation batches prior to full qualification of the material

## **Validation of legacy products**

Legacy products are normally older products that may have been manufactured for a long period of time using well established processes and technologies. Where these products are transferred from one site to another, it is expected that the product is re-validated in accordance with the MA and that, where identified, manufacturing processes should be updated to meet current standards and the necessary modifications to the MA made.



The validation requirements for legacy products must meet the current marketing authorisation standards and if required should result in incorporating current validation requirements.

Clear processes should be in place to facilitate the transfer of process knowledge from the originating site. Manufacturers of transferred products should be in possession of appropriate validation and quality documentation from the original site of manufacture, in support of current validated processing parameters.

## Transport verification

The basic expectation is that all products (including bulk products, finished products, samples and IMP's) are transported in full accordance with their labelled, authorised and appropriate storage conditions, and that the supply chain has been formally evaluated and confirmed as effective. This assessment should be conducted using sound QRM principles. It is not acceptable to store or transport medicines outside their labelled and approved storage conditions.

Consideration should be given to the supply chain used for each medicinal product, and the inherent hazards to product quality, e.g. temperature excursions, potential security breaches, and their respective risks.

Appropriate arrangements should be in place to monitor storage conditions in order to demonstrate continued compliance. The responsibilities for the transportation (including validation), monitoring and storage of medicinal products should be clearly specified within Quality or Technical Agreements.

TGA does not currently inspect the wholesale distribution of therapeutic goods that have been released for supply.

- The responsibility for oversight of wholesale of medicines in schedules 2, 3, 4 & 8 of the [Poisons Standard](#) currently [sits with the states and territories](#), who may issue relevant permits and licences for wholesalers
- For medicines that are not in schedules 2, 3, 4 & 8 of the Poisons Standard and relevant biologicals, sponsors and manufacturers hold **shared responsibility** for ensuring that they are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life. These responsibilities should be clearly identified within Quality or Technical Agreements between the manufacturing site and Australian Sponsor

TGA inspections do include an evaluation of the transport conditions for starting materials, bulk and packed medicines between sites of manufacture and clause 1.8 (ix) would apply in these circumstances.

## Validation of cleaning processes

### Limits for the carryover of product residues

Limits for residue carryover should be based on a toxicological evaluation of the active materials. These evaluations should be verified by a toxicologist (or equivalent) and performed in accordance with current guidance. (Guidance may be found in [EMA/CHMP/ CVMP/ SWP/169430/2012 Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities](#)).

## **Cleaning validation for listed complementary medicines**

TGA generally expects cleaning processes for listed complementary medicines to be validated and appropriately documented. However, due to the low toxicity of permissible ingredients used in the manufacture of listed complementary medicines cleaning validations can be grouped looking at worse case situations. The acceptance criteria of 'visibly clean' will normally be accepted for most listed complementary medicines.

In addition to the acceptance criteria of 'visibly clean', cleaning validation studies should give consideration to:

- The microbiological bioburden of processed materials and cleaned equipment and their acceptable limits
- Residue limits for chemical cleaning agents where used. In these cases, additional testing e.g. pH or total organic carbon (TOC) may be used where justified to demonstrate adequate cleanliness

Additional consideration of more stringent acceptance criteria should be given to products containing potentially allergenic materials, such as:

- milk
- eggs
- fish
- crustacean shellfish
- tree nuts
- peanuts
- wheat
- soybeans
- bee products, e.g. propolis, royal jelly and honey

## **Reference and retention samples (Annex 19)**

A reference sample is a sample for the purpose of future analysis, which could refer to starting materials, packaging materials or finished products.

A retention sample is a sample representing the batch of finished product as distributed.

Samples from a stability trial program cannot be used as retention samples.

## **Multipack products and retention samples**

Complete multipacks for products packaged this way do not necessarily need to be kept as retention samples. The requirement is that the amount of retention samples is sufficient to carry out analytical work during the entire shelf life of the product.

## Compounded medicines and dose administration aids (DAA)

For specific guidance on the GMP and regulatory requirements for the manufacture of compounded medicines and DAAs refer to our guidance on [GMP information for manufacturers of compounded medicines and DAAs](#).

## Version history

Version	Description of change	Author	Effective date
V1.0	Original publication  <i>Replaces Questions and answers on the code of good manufacturing practice for medicinal products</i>	Manufacturing Quality Branch	December 2017

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