Australian Government
Department of Health
Therapeutic Goods Administration

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

TGA interpretation and expectations for demonstrating compliance

Version 2.1, September 2020

TGA Health Safety Regulation

Contents

About PE009-14

The TGA has adopted version PE009-14 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

PE009-14 does **not** apply to:

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

This guidance

This guidance is for manufacturers and explains the TGA's interpretation and expectations for compliance with specific sections of the PIC/S Guide to GMP, PE009-14. 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.

PE009-14 is available from the TGA website, and takes effect on 1 July 2020. A transition period for the most significant changes has been implemented, but compliance with all other changes from 1 July 2020 is expected.

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 based on 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 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, from time to time, may 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 (GMP) requirements change over time for 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 PE009-14

PIC/S guide to GMP is mandatory

The PIC/S Guide to GMP, PE009-14 is adopted as the mandatory standard for the manufacture of medicinal products, under provisions of section 36 of *Therapeutic Goods Act 1989*, replacing PE009-13. This means that the requirements outlined in the PE009-14 will be legally enforceable following adoption.

You should note that PIC/S Guidance documents for industry (coded as PI XXX-XX) that are referenced within the PIC/S Guide to GMP provide an outline of acceptable approaches to compliance, however, are not enforceable by the TGA and compliance with these guidance documents is not mandatory. Alternative methods of demonstrating compliance with PIC/S Guide to GMP principles are acceptable where scientifically justified (refer *Therapeutic Goods (Manufacturing Principles) Determination 2020*).

Timing of adoption

PE009-14 adopted on 1 July 2020 with a transition period up to 01 July 2021, replaces PE009-13 as the manufacturing principles. TGA commences inspecting against the requirements of PE009-14 from 1 July 2020. Expectations for compliance during the transitionary period can be found in the transition plan. Compliance with all elements of the PIC/S GMP guide is mandatory from 01 July 2021.

The main changes introduced by PE009-14

The changes between the PE009-13 and PE009-14 PIC/S Guide to GMP are clarifications of existing expectations. Some of these changes may require you to revise or modify your approach to compliance.

The main differences between the PE009-13 and PE009-14 are:

1. New guidance in Chapters 3 and 5 in relation to the assessment and control of contamination and cross-contamination risks. This new guidance provides clarity regarding the operational and administrative controls that should be considered to prevent cross contamination of medicines, in line with existing GMP and international methods.
2. The addition of guidance for the oversight and management of the suppliers of raw materials, (actives and excipients) used in the production of medicines. These new guidelines have been introduced to address risks associated with the use of sub-standard raw materials and reflect the TGA's long-standing documented position and expectations regarding the level of supplier oversight required.
3. Additional guidance in relation to the management and investigation of product complaints and product recalls. This guidance has been updated to provide additional clarity for manufacturers, and aligns with the TGA's current guidance for product recalls, Uniform Recall Procedure of Therapeutic Goods(URPTG).
4. Additional guidance and requirements in relation to the application of real-time-release-testing (RTRT) and parametric release of medicinal products. The RTRT section has been added to provide the basic framework for management of technology in advanced manufacture. This guidance does not impose additional mandatory requirements, rather provides an acceptable approach to compliance should a manufacturer elect to apply RTRT.

For more information, refer to:

- Transition to new GMP requirements for medicinal products

Implications of PE009-14 adoption for current TGA guidance

TGA will be working with industry representatives and manufacturers to update all technical guidance documents, where required, to reflect any modified or clarified requirements following the adoption. These documents will be completed and available during the transition phase (i.e. prior to 1 July 2021).

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 PE009-14
- assess the required modifications to their Pharmaceutical Quality Systems
- implement changes in line with the transition plan

Application of PIC/S Guide to GMP

Sections of PE009-14 that apply

The sections of the PIC/S Guide to GMP that apply depend on 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 PE009-14, and in addition, all annexes relevant to their operations and dosage forms, including:
  - 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 PE009-14, and in addition, all annexes relevant to their operations, including:
  - Annex 1 (Manufacture of sterile medicinal products)
  - Annex 2 (Manufacture of biological medicinal substances and products for human use)
  - Annex 3 (Manufacture of radiopharmaceuticals)
  - Annex 7 (Manufacture of herbal medicinal products)
  - Annex 12 (Use of ionising radiation in the manufacture of medicinal products)
  - Annex 14 (Manufacture of medicinal products derived from human blood or plasma)

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 PIC/S Guide to GMP (Part I or II), for example:

- a manufacturer of **herbal liquid** products should meet the requirements of Part I and annexes 7, 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, (and possibly Annexes 2 & 3)

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 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

You must convey requests for inspections of veterinary medicinal products in addition to human medicinal products to the APVMA.

Veterinary medicines manufacturers who also hold a TGA licence to manufacture

For inspections of veterinary medicines manufacturers who 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 mutual-recognition-agreement (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.

The TGA have not adopted Annexes 4 and 5 of PIC/S Guide to GMP. However, if a domestic veterinary manufacturer is inspected by TGA under the European Community - Australia Mutual Recognition Agreement or the European Free Trade Association – Australia Mutual Recognition Agreement, the TGA will use the relevant parts and annexes of PIC/S Guide to GMP, including Annex 4 and Annex 5.

For more information see: Reducing technical barriers to trade.

GMP for specific medicine types

Listed and complementary medicines

The technical GMP guidance for listed and complementary medicines manufacturing provides a selection of guidance on how you can demonstrate compliance with the requirements of PIC/S Guide to GMP. Guidance is available for the following topics:

- Ongoing stability testing for listed and complementary medicines
  Technical guidance on the interpretation of the PIC/S Guide to GMP
- Process validation for listed and complementary medicines
  Technical guidance on the interpretation of the PIC/S Guide to GMP
- Product Quality Reviews (PQRs) for listed and complementary medicines
  Technical guidance on the interpretation of the PIC/S Guide to GMP
- Sampling and testing for listed and complementary medicines
  Technical guidance on the interpretation of the PIC/S Guide to GMP
- Supplier assessment, approval and qualification for listed and complementary medicines
  Technical guidance on the interpretation of the PIC/S Guide to GMP

Sunscreens

Sunscreens with a Sun Protection Factor (SPF) claim of 4 (four) or more are required to be manufactured in compliance with GMP and so are required to be compliant with PIC/S Guide to GMP. More details are in the Australian Regulatory Guidelines for Sunscreens.

The technical GMP guidance for sunscreen manufacturing provides guidance as to how you can demonstrate compliance with the requirements of PIC/S Guide to GMP.

Medicinal gases

Technical Guidance for manufacturers of medicinal gases can be found at Medicinal gases guidance. This guidance will be revised to reflect PE009-14. However, in the interim period, the TGA will accept compliance with the principles in the current TGA guidance.

Sterile radiopharmaceuticals labelled with fluorine-18

The technical guidance, Manufacture of sterile radiopharmaceuticals labelled with fluorine-18, developed in conjunction with licensed manufacturers, provides additional and complementary guidance, which should be read in conjunction with this guidance.

Compounded medicines

The technical guidance Compounded medicines and good manufacturing practice (GMP) provides clarity on the interpretation of GMP requirements for compounded medicines manufacturers.

Medicinal cannabis

Guidance for the licensing and Medicinal cannabis manufacture outlines the specific interpretation of the PIC/S Guide to GMP as well as general information relating to the roles of the TGA and Office of Drug Control in the regulation of medicinal cannabis products.

Most medicinal cannabis products manufactured in Australia are currently unapproved medicines, supplied to patients through either the Special Access Scheme (SAS), Authorised Prescriber Scheme (APS), or used in clinical trials.

Manufacturers of medicinal cannabis products, including dosage forms should ensure their TGA Licence to Manufacture Therapeutic Goods includes the authorisation/s to manufacture medicinal cannabis products. Manufacturers should note that existing TGA licenses with authorisations with the Product Category of 'Registered Therapeutic Good' **do not authorise** the manufacture of medicinal cannabis products for supply as unapproved medicines, supplied under the SAS, APS & clinical trial frameworks.

Imported products

The adoption of PE009-14 has no impact on imported products cleared by GMP certificates and other evidence of GMP compliance, as outlined in the GMP Clearance Guidance.

Export-only medicines

Manufacture medicines that would require registration on the ARTG for domestic supply (that is, contain substances, quantities of substances or labels without mandatory warning statements required for supply in Australia) in accordance with the GMP applicable to registered medicines.

Manufacture medicines that can be listed in the ARTG (that is, contain substances that are included in the Therapeutic Goods (Permissible Ingredients) Determination) 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

'Pharmaceutical Quality System' (PQS) replaces the historical terminology 'Quality Management System' (QMS), 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 current terminology better reflects the specific design elements and requirements for a quality system used to manage the manufacture of medicinal products.

The PQS approach described within PIC/S Guide to GMP is applicable to the manufacture of all therapeutic goods to which the PIC/S Guide to GMP applies.

Manufacturing authorisation

The term 'manufacturing authorisation', generally refers to the:

- *Licence to Manufacture Therapeutic Goods* issued by the TGA to domestic manufacturers, or
- *Certificate of GMP Compliance* issued following an inspection to overseas manufacturers.

The manufacturing authorisation forms part of the legal basis for undertaking manufacturing operations for supply within Australia or exported from Australia, therefore it is critically important the manufacturing authorisation holders adhere to the specific conditions and authorisations specified in the licence, and only undertake steps in manufacture for which they are legally authorised.

Marketing authorisation

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

The MA includes the details of:

- the product in the ARTG
- 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.

You are responsible for ensuring your PQS 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 product sponsor is the holder of the marketing authorisation.

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. Requirements for each type of product can be found in the relevant Australian Regulatory Guidelines:

- prescription medicines (ARGPM)
- OTC medicines (ARGOM)
- complementary medicines (Australian Regulatory Guidelines for Listed Medicines and Registered Complementary Medicines)
- biologicals (ARGB)

These requirements are mandatory and are in addition to the requirements of the PIC/S Guide to GMP. The requirements within the PIC/S Guide to GMP 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), PIC/S Guide to GMP. It is an existing expectation that change control does not just apply to validation activities, but to all GMP-related activities undertaken by a manufacturer.

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

Verify effectiveness of all changes implemented.

Managing deviations

There are no changes to the expectations for managing deviations and other similar events (Clause 1.4 xiv). PIC/S Guide to GMP 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 (RFS)

Release for supply is normally the final step in the manufacture of therapeutic goods, during which an Authorised Person (AP) performs a thorough evaluation of the manufacturing data associated with a batch, and certifies the batch for release for supply, and ultimately administration to or consumption by patients.

The release for supply step is a critical step in the manufacture of therapeutic goods, and must only be undertaken by persons who are suitably trained, experienced and qualified to make appropriate decisions based on a critical review of the technical data available. For further details refer to the section on Qualification requirements for an Authorised Person below.

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. 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

You are allowed to have more than one Authorised Person to perform release for supply. It is your 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 PQS.

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.

Storage of goods prior to and following release for supply

It is a requirement of the *Therapeutic Goods Act 1989* that steps of manufacture that precede bringing the goods to their final state, for example, Release for Supply must be conducted at a premises that hold a Licence to Manufacture.

For therapeutic goods that have been fully manufactured, but not yet certified for release for supply by an Authorised Person – these goods must be held at premises that are licenced by the TGA for the storage of therapeutic goods, and included in the ARTG entry for the product.

State and Territory requirements for storage

Following certification for release for supply by an Authorised Person – the goods must be held in accordance with specific State and Territory legislation that apply to the storage of therapeutic goods. Refer to Product distribution expectations.

Individual States and Territories have adopted the Australian Code of Good Wholesaling Practice. The provisions of this Code are applied through applicable State and Territory therapeutic goods/drugs and poisons legislation, and State or Territory wholesaler licensing arrangements.

The storage of therapeutic goods that have not been certified for release for supply, at premises that do not hold a suitable licence, is not permitted and may be subject to criminal offence and civil penalty provisions under the *Therapeutic Goods Act 1989*.

Senior management responsibilities for GMP and quality management

The requirements of Chapter 1 (clause 1.5) of PIC/S Guide to GMP 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.

We expect 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 PIC/S Guide to GMP, 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 PQS - management should have a formal process for reviewing the PQS on a periodic basis. The review should include:

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

- emerging regulations, guidance and quality issues that can impact the PQS
- innovations that might enhance the PQS
- changes in business environment and objectives
- 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 PIC/S Guide to GMP requires a Quality Manual (or equivalent document) to be written and maintained. Establish a quality manual or equivalent which 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. Clearly identify these responsibilities within Quality or Technical Agreements between the manufacturing site and Australian Sponsor.

TGA inspections 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 Guide to GMP and not necessarily any other official good distribution practice guideline.

Product Quality Reviews (PQRs)

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
- 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, PE009-14 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 to 'Export-only medicines' section above.

PQRs for products with no marketing authorisation

PQRs are performed to demonstrate the consistency of the manufacturing process. Where no marketing authorisation is available (for example, compounded medicines, Dose Administration Aids, Investigational Medicinal Products), clauses 1.10.vi and 1.10.x do not apply, In this case, perform and document a review of the process consistency, including all other elements of clause 1.10.

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. Map supply chains and manage any identified risks following the principles of quality risk management.

Guidance for the evaluation of supply chains for active materials used in listed 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, PE009-14 as required and in consultation with industry.

Frequency of PQRs

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.

Maintain vigilance over elements of clause 1.10 that do not directly relate to manufacturing activities, for example, results of ongoing stability, returns, recalls and complaints that may provide information regarding products available in the market, for periods where very few batches of one product are manufactured in one year, or no manufacturing takes place.

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

Include all batches for which manufacture has commenced in a PQR. In addition, include all batches for which the manufacture was terminated, delayed or has failed in the PQRs. When grouping is applied, include all batches of all products in each group 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. Clearly define responsibilities in relation to PQRs 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.

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

Additional guidance regarding the documentation requirements for PQRs, specifically their distribution and availability to the Authorised Person, may be found in the TGA Guidance for Release for Supply.

Quality risk management

Quality risk management is mandatory

It is 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 (Clauses 1.12 and 1.13 of Part I (also and clauses 2.20 and 2.21 of Part II)).

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 PIC/S Guide to GMP (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 GMP, 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).

Give training 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, provide and record appropriate training and assessment.

Language requirements

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. Document procedures employed to overcome identifiable deficiencies.

Role of consultants

Management of consultants

Keep and maintain adequate records where consultants are engaged by you to assist in operations. Records 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 your responsibility 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.

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, carry out sampling 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. Design the sampling area 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. Design and control areas used for the sampling of non-sterile starting materials used in the manufacture of sterile products in accordance with Annex 1 requirements.

Sampling hoods may be used provided there are adequate controls in place to ensure that materials are contained. Give consideration to the use of appropriate extraction/de-dusting 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, sample primary packaging materials 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 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 your 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.

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

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

As a minimum expectation:

- Define air quality requirements (physical and microbiological) during system design and demonstrate compliance through qualification and on-going monitoring.
- Air filters used in manufacturing areas where product is exposed 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 Organization'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 contains clear requirements for cleaning and sanitisation of premises; however, there is limited detail on the actual methods required for cleaning. You are 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.

Cross-contamination and dedicated facilities

Prevent cross contamination of products for all products manufactured based on risk management principles, considering the nature and characteristics of the materials, their inherent toxicity, and measures employed to control and contain the materials during handling and processing.

The guidance provides information on how molecules may be assessed and controlled in a consistent, scientific and risk-based method and builds upon existing requirements for toxicological assessments, as per existing Annex 15 clause 10.6.

Use dedicated facilities where the risks of cross contamination cannot be managed to a safe level, for example because:

- The risks cannot be controlled by the implementation of operations or technical measures, for example, by the use of fully closed-system production, effective campaign management.
- The scientific data from the toxicological evaluation does not support a controllable risk, for example, manufacture of a highly toxic or sensitising products, the safe residue limits for which are not achievable, (e.g. allergenic potential from beta-lactams).
- The safe residue limits derived from the toxicological assessment cannot be verified by available, validated analytical methods, for example, the allowable residue limit for production surfaces is less than the limit of detection of available methods, and therefore cannot be measured.

You should ensure that a documented assessment of each active substance handled or processed in a shared facility is conducted, and the management and operation of shared facilities adequately justified.

The text states that cross contamination should be prevented, and this is considered to be as far as practical, with due consideration to the materials handled. The TGA appreciate and recognise that absolute exclusion of contaminants is not practical in all cases; however, you must implement controls to prevent avoidable contamination and manage residues of unavoidable contaminants to levels that do not present a risk to product quality and patent safety, in accordance with existing toxicological assessments.

Further guidance may be found in PIC/S PI046 '*Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities*' and PIC/S PI053 '*Questions and answers on implementation of risk based prevention of cross contamination in production' and 'Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities*'.

The degree of segregation for dedicated facilities will depend on the risk assessment and toxicological assessment, but may require for example, a combination of; fully segregated and contained facilities, segregated areas within a shared facility, closed processing equipment, dedicated product-contact parts, as necessary to adequately manage any risks of cross-contamination.

The use of dedicated and self-contained facilities is not normally required for listable complementary medicines. However, manufacturers of listable complementary medicines are required to take adequate precautions to prevent contamination between products, and note that 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

Check with the relevant state or territory authority if there are any state or territory regulatory requirements that are applicable.

Documentation (Chapter 4)

Retention of batch documents

Keep batch documents for at least one year after the expiry date or at least 5 (five) years after release for supply by the Authorised Person, whichever is the longest. Keep batch documentation for investigational products for at least 5 (five) 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.

Store documents used to record the manufacture of radiopharmaceuticals for a minimum of 3 (three) 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, implement systems 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). Recording of batch numbers in distribution records is mandatory (clause 8.13).

Signature list

You 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.

Data management and data integrity

Data management and Integrity is a critical element of GMP and you are expected to implement effective systems to assure the integrity of data generated in support of, and during manufacture.

Develop policies and procedures to manage data integrity and provide appropriate training to staff to facilitate good practices. TGA has specific guidance relating to data management and data integrity.

Production (Chapter 5)

Prevention of cross contamination

Fully evaluate and understand cross-contamination risks and the controls to prevent contamination. The TGA expects manufacturers of all types of therapeutic goods to develop and maintain risk assessments of their operations to ensure that processes are fully understood and hazards associated with cross-contamination are identified and effectively controlled.

The risk assessment should form the basis for the extent of technical and organisational measures required to control cross-contamination risks. The PIC/S Guide to GMP clause 5.21 provides a non-exhaustive list of technical and organisational measures that should be considered and assessed in your cross-contamination assessments.

You are expected to undertake periodic reviews of the effectiveness of controls for the prevention of cross-contamination, procedures outlining the process and scheduling of reviews should be documented within the QMS.

Technical measures

Technical measures are generally those that include the use of equipment specifically designed to help prevent cross contamination, and include dedicated facilities, closed-systems, dedicated equipment and environmental controls. Due to their (predominantly) physical nature, technical measures provide more robust protection from cross contamination than organisational measures, and therefore available technical measures and technologies should be considered as the preferred option.

Organisation measures

Organisation measures generally reflect behavioural or administrative measures and in some part rely on adherence to good practices. These measures may be influenced by the how the manufacturer operates and manages the manufacturing facility, and thus a high level of continued compliance is required to ensure the effectiveness of these measures.

Controls for manufacturers of listed medicines

Manufacturers of listed medicines consisting of ingredients included in the Therapeutic Goods (Permissible Ingredients) Determination, should ensure that risk assessments of their operations are conducted to ensure that appropriate measures to prevent cross-contamination are implemented. Risk assessments for listed goods should be commensurate with the risk present and give due consideration to the inherently lower toxicity profile of permitted ingredients.

Allergens

Manufacturers of listed medicine products containing potentially allergenic substances should effectively manage and control these allergens, to prevent cross-contamination of products. Base the methods of control on a risk assessment, and justify the method.

Manufacturers and Sponsors should note that with the August 2020 adoption of new labelling requirements for allergens, (TGO92) manufacturers will need to declare allergens that may be in the product irrespective of concentration.

Where a label declaration for the presence of potential allergens has been made, this should be considered when determining the controls for manufacture of allergenic substances. Strict controls, such as dedicated facilities, may not be required.

Probiotics

Manufacture and packaging of listed dosage forms containing probiotics for human oral consumption is permitted in facilities that also manufactures other listed products for human oral consumption, including tablets, capsules, powders and liquids. Dedicated facilities are not expected where technical and/or organisational measures are implemented to control risks for cross-contamination.

Perform the bulk production of probiotic APIs in appropriately dedicated facilities due to the significant volumes of product and product dust liberated from the process.

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 PE009-14 version of the PIC/S Guide to GMP.

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 or maximum number of batches followed by an appropriate (validated) cleaning procedure.

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

Labelling and packaging

Label counting and verification

Count roll labels 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. You 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. 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.

Control of starting materials

Active materials for registered medicines

Requirements for the qualification, approval and maintenance of suppliers of starting materials used in registered medicines (excluding registered complementary medicines) are outlined in sections 5.27 to 5.29 of the PIC/S Guide to GMP. Additional information is located within Annex 8 - Sampling of starting and packaging material.

These requirements also apply to starting materials used by manufacturers of unapproved medicines (except complementary medicines) For example:

- Starting materials used in the production of unapproved goods supplied in accordance with Schedule 5, Item 6 or Schedule 5A, Item 5 of the *Therapeutic Goods Regulations 1990*.
- Starting materials used in the manufacture of goods where the starting materials are not included in the ARTG, for example, sterile and non-sterile compounding, radiopharmaceutical production

Starting materials cover a broad range of items that are used in the production and fabrication of therapeutic goods including:

- active pharmaceutical ingredients
- excipients
- packaging components
- labels and
- in accordance with risk management principles, extends to materials that are not necessarily persistent in the final product, but are critical to product quality, for example:
  - processing aids
  - product contact gasses
  - processing buffers, or
  - growth media.

Document the process for the selection, qualification, approval and ongoing maintenance of suppliers within the PQS. Evidence to demonstrate the suitability of the starting material manufacturer, (and where relevant supplier) and the starting material itself should be generated and collated at initial assessment and periodically during the lifecycle of the material.

Excipients for registered medicines (and equivalent)

Evaluate excipients used in registered medicines (or equivalent) in accordance with the PIC/S Guideline PI 045-1 'Guidelines on the formalised risk assessment for ascertaining the appropriate Good Manufacturing Practice for excipients of medicinal products for human use', or equivalent. Once the manufacturer has established the commensurate controls, evidence that the excipient manufacturer meets the established level of GMP would be required.

Auditing of suppliers

An on-site audit of the manufacturers and distributors of active substances used in registered medicines (excluding registered complementary medicines) is expected as part of the initial qualification and ongoing management process, to confirm that they comply with the principles of GMP and where relevant good distribution practice. Use quality risk management principles in determining the frequency of evaluation, and evidence of an on-site audit of the starting material manufacturer and distributor would be expected as part of the overall supplier qualification program.

The audit of manufacturers and distributors of active substances can to be performed either by the manufacturing authorisation holder or by persons acting on their behalf, for example, Sponsor or independent auditors. Where independent auditing entities are utilised, document and retain evidence of the suitability of the auditors regarding their qualifications and independence from the auditee, within the manufacturer's PQS.

Sponsors of registered medicines are required to ensure that suppliers of APIs maintain compliance with the requirements of GMP, and thus agreements between Sponsors and Contracted Manufacturers should outline the responsibilities for the conduct of supplier audits and their resourcing.

Inspection reports from MRA partners or recognised authorities

When inspection reports or GMP certificates issued by mutual-recognition-agreement (MRA) partners or other recognised authorities are available, these can provide useful information to manufacturing authorisation holders. However, these alone cannot fulfil the statutory obligations of the manufacturing authorisation holder or the requirements of section 5.29 of the PIC/S Guide to GMP. You may use the results of inspections together with other supporting information in a risk-based approach in establishing priorities for your own audit programme of active-substance suppliers.

Independent auditors

Independent auditors should have sufficient scientific, technical and other experience to enable them to perform an adequate and thorough audit of the active substance manufacturer, as related to the planned scope of the audit. Where a proposed auditor lacks an appropriate level of direct experience in the field of active substance manufacture, he or she should undergo a documented training and assessment programme in the areas that are relevant to the audit, taking into account the auditor's anticipated role in the audit and the technologies that are likely to be encountered during the audit. Auditors must also be trained and assessed in their knowledge and understanding of PIC/S Guide to GMP part II and in auditing techniques in general. Fully document the training and assessment.

The qualification and experience of contracted auditors are the same as the requirements for the manufacturing authorisation holder's own auditors.

OTC medicines

In accordance with the ARGOM, it is the responsibility of the sponsor to ensure that the active substance is manufactured to a standard consistent with the principles of the PIC/S Guide to GMP. In the case where the active substance is manufactured overseas the standard of GMP must be comparable to that required for Australian manufacturers. Evidence of licensing or approval of the manufacturer of the active substance does not need to be submitted to the TGA, except where it is an intermediate product (for example, premixes).

Active materials and excipients for listed and complementary medicines

Technical guidance documents are available for Supplier assessment, approval and qualification for listed and complementary medicines and sampling and testing for listed and complementary medicines.

An audit of a starting material manufacturer and distributor of APIs used in listed medicines would not be expected, and compliance would be satisfied, providing the manufacturer follows the TGA's technical guidance for Supplier assessment, approval and qualification for listed and complementary medicines, or equivalent.

Although the principles in these guidance documents are still applicable, they will be revised where necessary, in consultation with industry, to clarify requirements in the PE009-14 version of the PIC/S Guide to GMP.

Acceptance of a starting material delivery based on ID testing only

The PIC/S Guide to GMP includes provisions that allow manufacturers to significantly reduce the testing of starting materials upon receipt, providing a full evaluation of the supplier, in accordance with clauses 5.27 – 5.29 and including an on-site audit has been successfully conducted. In these circumstances, you can utilise partial or full test results from the approved starting material manufacturer for each delivery received. However, this practice is conditional to fulfilling specific requirements:

- The material is supplied from a fully qualified manufacturer, and distributed via a qualified supply chain. This qualification must include evidence of an on-site audit that demonstrates an acceptable level of control of the starting material. The evidence of the on-site audit should be available to the end-user.
- Perform as a minimum, identification testing on every delivery as per Annex 8 expectations.
- Perform identity testing of starting materials according to the methods and the specifications of the relevant marketing authorisation dossier.
- The medicinal product manufacturer should perform (either themselves or or via a separately approved contract laboratory) a full analysis of the material at appropriate intervals based on risk and compare the results with the material manufacturer's, or supplier's, certificate of analysis in order to check the reliability of the latter.

Supply chain verification

Supply chain assessment and verification for active starting materials is an important step in ensuring that APIs are shipped via approved and secure methods, and in accordance with any specific requirements, for example, temperature control. Supply chain integrity is critical in ensuring that APIs are not subjected to adverse conditions or activities, for example, substitution or subversion that may lead to material quality and patient safety risks. Verification is a periodic function, and the use of the correct supply chain can be verified for each delivery from the associated delivery paperwork and shipping information.

Product shortages

The concept of mandatory reporting of real or potential shortages due to manufacturing constraints is introduced in Clause 5.71 of the PIC/S Guide to GMP. Any manufacturer experiencing or anticipating any constraints in manufacturing operations, which may result in abnormal restriction in supply, should report this to the relevant marketing authorisation holder. Report this in a timely manner to facilitate reporting of the restriction in supply by the marketing authorisation holder, to the relevant competent authorities, in accordance with the existing mandatory shortages reporting mechanisms.

Quality control (Chapter 6)

Sampling and testing of listed and complementary medicines

A separate guidance document is available for the sampling and testing for listed and 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 PE009-14 version of the PIC/S Guide to GMP.

Testing of probiotics

Probiotic therapeutic goods and their active ingredients are expected to be manufactured and controlled in compliance with all Default Standard monographs relevant to the goods, including general and specific monographs including. “Live Biotherapeutic Products for Human Use” (Ph. Eur. 3053), BP Appendix XVI H. Microbiological Examination of Live Biotherapeutic Products, (Ph. Eur. 2.6.36 & 2.6.38).

Perform an identification test on every container of probiotic raw material received by a medicinal product manufacturer.

Identification testing

Select a discriminatory identification test to allow correct identification of the strain or strains of organisms claimed on the product label. Biochemical identification methods may not be reliable for this purpose and genotypic identification methods should be employed for example, 16S rRNA sequencing, PCR etc.

Where the product label claim is for a particular genus or organism only, traditional biochemical methods may be suitable for identification purposes.

Reduced sampling of probiotics

Reduced sampling of probiotics may be performed, following vendor qualification that considers the:

- quality system and compliance of the API manufacturer
- controls in place to segregate manufacturing operations from cross contamination, verified by audit
- number and nature of microorganisms produced by the vendor. (Where there is a risk of cross contamination with pathogenic organisms or alternate strains during manufacture, reduced sampling may not be possible).

Control of external contract laboratories performing starting material testing

Laboratories conducting testing of starting materials on behalf of the API manufacturer

The manufacturer of the dosage form is responsible for any testing performed of starting materials used to ensure that materials meet the relevant requirements of the Default Standards and Marketing Authorisation. However, the PIC/S Guide to GMP recognises that a risk-based approach may be used, to permit reliance in full or part, upon testing performed by a fully approved starting material manufacturer.

Using this risk based approach, where a full evaluation of the starting material manufacturer (including on-site audit) has been successfully performed it may be possible for manufacturers of dosage forms to perform identity testing of each lot received (in accordance with Annex 8 requirements).

For laboratories conducting testing of starting materials on behalf of the API manufacturer:

- The basic expectation is that audits are performed by the manufacturer of the dosage form, before full or partial reliance on these results is permitted.
- reliance on official TGA inspections may be acceptable for the testing of low risk starting materials, for example, those subject to a pharmacopoeia monograph, where the manufacturer of the dosage form holds evidence of the following:
  - The contract laboratory is suitably licensed to perform the testing requested.
  - The test methodology used by the laboratory is in full accordance with the marketing authorisation testing requirements, or
  - Where alternative methods are utilised, these are appropriately validated, and
  - The methods used have been suitably verified (where required)

Laboratories contracted on behalf of the dosage form manufacturer, e.g. a domestic testing laboratory

The TGA expect manufacturers to take a risk based approach to the audit of laboratories performing starting material testing on their behalf. In principle, this includes the following:

- The method of auditing (on-site or desk-based) should be based on a risk assessment of the tests performed and the criticality of the results.
- On-site audits should be considered where the testing performed by the lab is complex or consists of non-standard test methods, for example, characterisation and testing of complex chemical or biological starting materials, or the use of novel equipment and methodologies requiring specialised expertise.
- Desk-based assessment evidence may be suitable for lower risk and standard pharmacopoeia testing, for example. testing of starting materials in accordance with a pharmacopoeia monograph, wet-chemistry and basic chromatographic testing.

- Reliance on official TGA inspections may be acceptable for the testing of low risk starting materials, for example, those subject to a pharmacopoeia monograph, where the manufacturer holds evidence of the following:
  - The contract laboratory is suitably licensed to perform the testing requested.
  - The test methodology used by the laboratory is in full accordance with the marketing authorisation testing requirements, or
  - Where alternative methods are utilised, these are appropriately validated, and
  - The methods used have been suitably verified (where required)

Conducting on-going stability studies

Principles for conducting on-going stability studies

In general, base on-going stability studies on the principles of ICH Q1.

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

Make available the results of the on-going stability program 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 PE009-14 version of the PIC/S Guide to GMP.

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

Ongoing stability testing does not need to be conducted in a GMP certified laboratory, because ongoing stability testing is not considered 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.

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.

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.

Perform required on-going stability 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.

Authorised Person's review of on-going stability data

The Authorised Person responsible for product certification for release for supply should ensure that the on-going stability programme is on track and that up-to-date results for stability studies are available and are compliant.

Where stability testing are not performed by the manufacturer performing release for supply, the arrangements for testing and provision of ongoing stability reports should be specified within GMP agreements.

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, you must notify the area of the TGA responsible for regulating the product ARTG entry of all statistically significant departures from established stability profiles. 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.

GMP agreements between sponsors and manufacturers should specify the responsibilities for the review of stability data and reporting of any issues identified.

Outsourced activities (Chapter 7)

Scope of outsourced activities

There are a number of activities that manufacturers can outsource under contract, many of which have a direct or indirect effect on the quality of medicinal product manufactured by a site. It is a requirement that manufacturers have effective systems in place to manage the selection, evaluation, approval and monitoring of all outsourced activities throughout their lifecycle. Records of these activities must be maintained, and contracts are required to be in place to manage all outsourced activities and outline the responsibilities for each party.

Examples of outsourced activities that this chapter applies to include, but are not limited to:

- contract manufacturing and analysis
- outsourced maintenance, construction 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 and Sponsors (normally 'contract givers') to manage all relationships with contract acceptors in accordance with principles of chapter 7. All outsourced GMP-related activities that may impact product quality, (including, but not limited to the examples listed above), should be assessed, defined and covered by a written contract agreement. Contract agreements should identify the organisation providing the services, and detail the services supplied and any relevant arrangements associated with the activity as relevant. Agreements should be maintained in accordance with the PQS throughout the lifecycle of the outsourced activity.

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, electrical contractor permit, 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. Monitoring of contract acceptors should be performed periodically, and include confirmation of compliance with GMP, adherence to the quality agreement and delivery of agreed quality metrics. Where quality related issues are identified, it is expected that appropriate actions are taken to address and remediate the concerns. Record records of actions taken in the PQS.

Responsibility for review of records and results

The contract giver should be responsible for reviewing and assessing the records and the results related to the outsourced activities (Clause 7.5).

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

- 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)

Reporting of recalls to TGA

The reporting of real and potential recall actions to the TGA is both a mandatory requirement and an important element in maintaining vigilance of manufacturing and supply issues. Recall actions, including notifications should follow the guidance given in the Uniform Recall Procedure for Therapeutic Goods (URPTG).

It is expected that all suspected or serious adverse reactions related to therapeutic goods will be reported to the TGA.

In any circumstances where the manufacturer or sponsor is made aware of any quality issue that would have prevented release of the goods or resulted in recall of products that have been released for supply, these events are reported to the TGA recalls coordinator, irrespective of where the product resides in the supply chain.

Recall notifications are also required in circumstances where the manufacturer or sponsor is made aware of any quality issue that would have prevented release of the goods or resulted in recall of products irrespective of whether any units are recoverable from the market, e.g. following identification of out-of-specification stability data, retrospective testing failures or significant environmental monitoring excursions that indicate an unacceptable risk to process integrity or product quality.

Quality agreements should outline the responsibilities for Authorised Persons, Manufacturers and Sponsors in relation to the management, communication and investigation of recall notifications and recalls.

Section 40(4)(ab) of the *Therapeutic Goods Act 1989*, imposes statutory conditions on all manufacturing licenses that require the manufacturer to notify the TGA as soon as they become aware of any potential harm, quality, safety, or efficacy issues associated with products manufactured.

This mandatory reporting requirement applies to any goods that have been released for supply, irrespective of where the goods may be physically located.

Falsified products

The procedures on complaints handling is required to include an assessment for whether the complaint or suspected quality defect relate to falsification (Clause 8.6). This is an amended clause that is similar in intent to existing PE009-13 Chapter 8 clause 8.7; however, the use of the term ‘falsification’ is largely interchangeable with the TGA definition of Counterfeit Goods contained in the Act.

Falsified medicines as defined by PIC/S include any medicinal product with a false representation of:

- its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients
- its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder, or
- its history, including the records and documents relating to the distribution channels used.

Counterfeit goods are defined under section 42E(2) of the *Therapeutic Goods Act 1989*:

(2) Goods are ***counterfeit*** if any of the following contain a false representation of a matter listed in subsection (3):

(a) the label or presentation of the goods;

(b) any document or record relating to the goods or their manufacture;

(c) any advertisement for the goods.

(3) The matters are as follows:

(a) the identity or name of the goods;

(b) the formulation, composition or design specification of the goods or of any ingredient or component of them;

(c) the presence or absence of any ingredient or component of the goods;

(d) the strength or size of the goods (other than the size of any pack in which the goods are contained);

(e) the strength or size of any ingredient or component of the goods;

(f) the sponsor, source, manufacturer or place of manufacture of the goods.

If falsified or counterfeit goods are detected, you must notify the TGA immediately in accordance with the Uniform Recall Procedure for Therapeutic Goods.

Investigating adverse events

You are required to implement procedures and processes to investigate the quality of products in the event of a reported suspected adverse events (Clause 8.8).

Effectiveness of recalls

The requirement to periodically verify the arrangements for product recall has been a long standing requirement of the PIC/S Guide to GMP; however, the latest iteration of the guide requires you to challenge the arrangements both within office hour situations and out-of-office hour situations. Accordingly, the design of any mock-recall should address these situations.

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 materials

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, and so on, 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 PIC/S PI046 '*Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities*' and PIC/S PI053 '*Questions and answers on implementation of risk based prevention of cross contamination in production' and 'Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities*'.

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)

Starting material and API supplier management

Implement robust systems for 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 PIC/S Guide to GMP is applicable to the manufacture of APIs for biological medicinal products.

Guidance relating to the application of Annex 2 and Part II of the PIC/S guide to GMP 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 Therapeutic Goods (Permissible Ingredients) Determination could be considered biological medicinal products, the additional requirements of Annex 2 will **not** be applied to raw materials included in the determination intended for use in the manufacture of listed medicines, for example:

- beta-carotene
- shark cartilag
- 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)

Exemptions

Irradiation of targets in a reactor or cyclotron

Annex 3 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 PIC/S Guide to GMP. 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 Guide to GMP, and equipment and processes should be located within environments conforming to the required grade, (A, B, C or D). The current 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

Store documents used to record the manufacture of radiopharmaceuticals 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 Guide to 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, obtain a suitably controlled and characterised reference material of that compound from external sources.

Quantified by input

Please refer to the Quality for listed 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 GACP are not mandatory. Alternative methods of assuring the suitability and quality of herbal starting materials are permissible. Consider GACP practices during supplier qualification, as GACP may assist in influencing routine sampling and testing programs for herbal starting materials.

The recommendations regarding GACP apply to manufacturers involved in the cultivation of herbal starting materials (herbs) only.

Adulteration or substitution of herbal substances

You 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

Only purchase starting materials from suppliers that have been appropriately qualified, as per Chapter 5 of the PIC/S Guide to GMP.

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.
- For listed medicines there are specific provisions for the sampling of materials used in the manufacture of listed and complementary medicines as described in the technical guidance on sampling and testing for listed and complementary medicines.
- The validation of a supplier cannot be accepted without a regular and adequate assessment. Such validation should comprise a number of actions, including, but not limited to:
  - The use of a questionnaire prepared by the potential customer and completed by the potential supplier, concerning the supplier's operating Quality System.
  - 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, a sponsor, consultant or client, providing the audit is conducted by appropriately qualified individuals in an objective manner. Sponsors and manufacturers are encouraged to work together to identify sites and materials of common interest that may allow audit reports to be shared and used by multiple customers.

Inspection reports or GMP certificates issued by mutual-recognition-agreement (MRA) partners or other recognised authorities may be used together with other supporting information in a risk-based approach by the manufacturer in establishing priorities for its own audit programme of active-substance suppliers.

However, these alone cannot fulfil the statutory obligations of the manufacturing-authorisation holder or the requirements of section 5.29 of the PIC/S Guide to GMP

- 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 auditor. Sampling conducted by the suppliers should be validated.
- A program for regular re-assessment of the supplier's operation is expected. Quality risk management principles should apply in determining the frequency of evaluation. Where evidence of audit for an active substance manufacturer is available from a recognised comparable regulator, this may be used in determining the audit frequency, scope and depth required.
- Ongoing monitoring of the quality of material supplied through trend analysis of analytical results, and/or periodic full testing.
- 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.

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

Application of √n+1 sampling

Where a validated procedure is established to justify reduced sampling, and scientific and statistical evidence is presented, √n+1 sampling may be justified as applicable for materials received from fully qualified and validated suppliers.

Computerised systems (Annex 11)

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 (that is, GMP computerised systems).

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

In general, systems should be fully validated and controlled, such as systems used for:

- 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 GMP.

‘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.

You 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 computerises systems may be found within the PIC/S Good Practices for Computerised Systems in Regulated GXP Environments.

Investigational medicinal products (Annex 13)

The manufacture of IMPs differs from the manufacture of commercial products in various aspects, requiring additional consideration and oversight to manage the risks associated with IMP manufacture. It is critical that manufacturers of IMPs have a clear and documented understanding of the nature of the products, so that the PQS can be developed to manage ongoing communication with the sponsor and effectively manage the nuances of IMP manufacturing. Some of the challenges associated with IMP manufacture are:

- Regular and sometimes frequent changes requiring robust and responsive change management processes:
  - Regular process developments & changes
  - Updates to processes, specifications, test methods and other changes throughout the IMP lifecycle.
  - Ongoing, (sometimes concurrent) stability data/updates, and potential relabelling to extend expiry dates
  - Continuous updates to the Product Specification File to ensure that it is accurate for its intended use as the basis for production and release by the Authorised Person.
- Specific labelling requirements of Annex 13
- Risk of product mix-ups
  - Manufacturing, and packaging multiple products, that may appear identical, e.g. active and placebo products.
  - Managing blinding processes, ensuring that appropriate traceability of which units contain active or placebo during packaging and labelling and keeping records and implementing systems to un-blind product as required.
  - Managing the control and labelling of any randomisation processes, e.g. labelling containers of products that allow units to be dispensed to a specific patient based on the label randomisation code.
- Cross contamination risks, as many IMPs are in the early stages of their lifecycle, a full understanding of their toxicity profile may not be determined. A conservative approach to production, i.e. dedicated equipment and facilities and the development of adequately validated test methods for cleaning validation studies may therefore take on more importance.
- Challenges with vendor qualification may exist for the IMP manufacturer, as starting materials for IMPs may be provided by the sponsor or be sourced from unique suppliers not yet qualified or certified in accordance with GMP. The level and formality of the assessment of the suitability of these suppliers should be performed based on risk management principles.
- Reduced process validation, IMPs in early production phases may be made in small quantities or infrequently which affect the manufacturers ability to complete full process validation.
- The manufacturers understanding of the use of the product(s). You must have a good understanding of the nature and use of the product, so that risks associated with manufacturing, e.g., deviations, can be assessed appropriately.

The Australian clinical trials handbook contains additional 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.

Product specification files

Manufacturers involved in any steps in the manufacture of investigational medicinal products (IMPs) must generate and maintain a product specification file (PSF) for each individual IMP manufactured by the site. A PSF is a reference file containing, or referring to files containing, all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an IMP.

The PSF requires continual updates as product knowledge develops and should contain a full reference to all retained copies of previous versions of contents.

The PSF should contain:

- specifications and analytical methods for starting materials, packaging materials, intermediate, bulk and finished product
- manufacturing methods
- in-process testing and methods
- approved label copy
- relevant clinical trial protocols and randomisation codes, as appropriate
- relevant technical agreements with contract givers, as appropriate
- stability data
- storage and shipment conditions.

Manufacturing processing instructions and batch certification for release for supply relies in part on verification of compliance with the PSF, therefore the maintenance of a PSF is critical to operations. The Trial Sponsor should provide any information required by the Authorised Person in determining the suitability of an IMP for release.

Extent of validation required for IMPs

Process validation

Due to the nature of IMPs, it is not expected that products in early phases of production are validated to the same extent expected for commercial products. However, the level and extent of validation should be based on sound risk management principles and as process knowledge increases and production processes become better defined, increasing validation is expected. For example, for IMPs that have or are likely to be produced over a series of batches and/or for an extended period of time where process control and validation data may be captured and evaluated.

Premises and equipment qualification

Manufacturers for IMPs should ensure that all premises and equipment (including computerised systems) used in the production of IMPs are fully qualified in accordance with Annex 15 requirements.

Sterile and biological medicines

For sterile medicines, all processes associated with the assurance of product sterility should be fully validated to the extent outlines in Annex 1. This includes, (but is not limited to):

- All sterilisation methods, (filtration, terminal sterilisation, and so on), for the product and equipment used in the manufacture of IMPs must be validated in accordance with Annex 1 requirements.
- Aseptic process simulations (media fills) should be conducted for any aseptically processed IMPs in full accordance with Annex 1 requirements.
- Processes used for the viral removal, viral inactivation or removal of other infectious extraneous agents in biological medicines must be fully validated in accordance with Annex 2 and any relevant Monograph of a Default Standard, e.g. pharmacopoeia.
- Processes designed to prevent the contamination of sterile products or aseptic areas, e.g. disinfectant validation for surfaces and non-sterilisable items, should be validated.

Labelling investigational medicines

Basic label content

The labelling therapeutic goods orders TGO 69, TGO 91 and TGO 92 do not apply to investigational medicinal products. Instead, labelling requirements are specified in Annex 13 of the PIC/S Guide to GMP. This document outlines the information to be included on labels, unless its absence can be justified, for example, use of a centralised electronic randomisation system.

Complete details on primary and secondary packaging and labelling requirements can be found in Annex 13 of the PIC/S Guide to GMP. However, some items have been discussed further below.

Notes on clauses in Annex 13

Clause	Notes
26(a)	The main contact details for information on the product, clinical trial and emergency unblinding, must be an Australian contact.
26(b)	For closed blinded trials, the labelling should include a statement indicating "placebo or [name/identifier] + [strength/potency]".
26(d)	The trial reference code used should identify the particular trial site, unless provided elsewhere or its absence can be justified. This is the case even for trials involving multiple sites.
26(d)	The trial reference code used should identify the Australian trial sponsor, unless provided as the main contact (clause 26(a)) or its absence can be justified. It is not sufficient to identify only an overseas trial sponsor in the case of a multinational trial.
26(f)	The name of the principal investigator should appear on the label unless already included in a trial reference code or unless its absence can be justified.
27	Allows for a participant to be provided a leaflet or card that contains the address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding. The participant must be instructed to keep this in their possession at all times.
32	'Certain characteristics' refers to non-commercial clinical trials performed by researchers without the participation of the pharmaceutical industry. These trials are often 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.
33	We do not allow labels to omit an expiry, use-by or re-test date. Trial sponsors must comply with the requirements of this clause.

Departures from labelling requirements

In exceptional circumstances it may not be possible to meet the requirements of Annex 13 of the PIC/S Guide to GMP for labelling investigational products. In this case, the trial sponsor must contact us if they wish to request a departure from the requirements of Annex 13. Subclause 3 of the Therapeutic Goods (Manufacturing Principles) Determination 2020 provides the criteria that we must be satisfied with if an alternative procedure to the procedure or requirement set out in the PIC/S Guide to GMP is adopted.

'Certain characteristics' in clause 32 of Annex 13

The 'certain characteristics' in clause 32 of Annex 13 of the PIC/S Guide to GMP 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.

Importance of robust sampling and QC testing

As processes for the manufacture of IMPs may not be validated to the extent required for a commercial product, there is an increased emphasis on the importance of sampling and testing of IMPs. As such, you should implement robust sampling and testing procedures in order to generate and collate data that supports the suitability of the manufacturing process and the products manufactured. The sampling and testing system should consider:

- Increased sampling plans and test plans for starting materials, in-process materials, intermediates and finished goods.
- Comprehensive test method validation for all methods used in the analysis of materials and products.
- Robust laboratory controls for data integrity required - particularly when data annotation tools are needed, which may be common for products in development, e.g. where quantification of related substances/impurities requires manual integration.
- Product specification file outlines agreed testing program and specifications.

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. However, these are for guidance only and may not fully reflect the current requirements of PIC/S Guide to GMP. 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)

Appropriately qualify all equipment used in the manufacture of medicinal products 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.

The previous provisions for retrospective validation could be incorrectly interpreted to suggest that products may be released to market prior to process validation being completed. The current wording of Annex 15 rectifies 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 products, processes, updates or changes to existing processes that have taken place since January 2019 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, that is, 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

You should determine and justify the number of batches used for process validation 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.

Clearly document and justify any variations from this approach 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 (for example, 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 (for example, 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 PE009-14 version of the PIC/S Guide to GMP.

Critical Quality Attributes (CQA) and Critical Process 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

Ongoing process verification (OPV) 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 (Annex 15 clauses 5.28-5.32).

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, for example, 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. Clearly specify the responsibilities for the transportation (including validation), monitoring and storage of medicinal products 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. Clearly identify these responsibilities 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

Base limits for residue carryover 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 PIC/S PI046 '*Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities*' and PIC/S PI053 '*Questions and answers on implementation of risk based prevention of cross contamination in production' and '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 medicines

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

Give additional consideration of more stringent acceptance criteria 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.

Real Time Release Testing and Parametric Release (Annex 17)

Implications of changes in Annex 17

Annex 17 of PIC/S Guide to GMP has been largely re-written from the previous version of the PIC/S Guide to GMP and contains additional guidance for the application and management of real-time-release testing (RTRT) and parametrically released sterile products. The main changes are:

- Additional guidance for the application of real time release testing (e.g. in-line PAT testing) which may replace the conduct of finished product testing where justified and authorised by the regulator (TGA).
- The sections relating to parametric release (i.e. release of terminally sterilized products without performing a final test for sterility) have been amended to clarify existing requirements.

Real time release testing (RTRT)

in-process or final product based on process data, which typically include a valid combination of measured material attributes and process controls[1]. It is based on the principle that the continuous control of well understood critical process parameters (CPP) and relevant starting material attributes may provide greater process control and under defined conditions, act as an alternative to routine end-product testing of active substances and/or finished products.

RTRT relies on the real time measurement of CPP(s) as a predictor of compliance with CQA, and thus requires extensive knowledge of the relationship between variations in CPPs and material attributes and their influences in varying the quality attributes of process outputs. This advanced process knowledge is typically derived from detailed process and material challenge tests combined with multivariate statistical modelling and analysis to determine the outcome and significance that each variable parameter (CPP) has on each quality attribute.

RTRT may apply to any stage in the manufacturing process and to any type of finished products or active substances, including their intermediates.

Regulatory approval

Due to the complexity of an RTRT approach, prior regulatory approval is normally required, and any proposals to apply RTRT should be discussed with the relevant evaluation section of the TGA and with consideration to the relevant Australian Regulatory Guidelines.

Manufacturers wishing to be authorised to apply RTRT should seek specific authorisation for RTRT to be added to their Licence to manufacture Therapeutic Goods.

[1] ICH HARMONISED TRIPARTITE GUIDELINE PHARMACEUTICAL DEVELOPMENT Q8(R2) Current Step 4 version dated August 2009

Control strategy

The correct application of RTRT requires a well defined control strategy that addresses the key elements of maintaining control and compliance over the process. The control strategy should be documented and address:

- quality risk management, including a full process related risk assessment, in accordance with the principles described in the PIC/S Guide to GMP, Part I Chapter 1 and Part II Chapter 2
- change control program
- control strategy
- specific personnel training program
- qualification and validation policy
- deviation/CAPA system
- contingency procedure in case of a process sensor/equipment failure
- periodic review/assessment program to measure the effectiveness of the RTRT plan for continued assurance of product quality.

Product testing if RTRT fails

Once approved, use the RTRT approach for the routine control and batch release. However, if the data from the RTRT process indicates product failure, or trending towards failure, the approved RTRT process cannot be substituted by end product testing.

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.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication Replaces *Questions and answers on the code of good manufacturing practice for medicinal products*	Manufacturing Quality Branch	December 2017
V2.0	Updated following adoption of *PIC/S Guide to Good Manufacturing Practice for Medicinal Products PE009-14*	Manufacturing Quality Branch	July 2020
V2.1	Updated to incorporate minor editorial changes	Manufacturing Quality Branch	September 2020

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