Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

GMP requirements for medicinal products

PIC/S Guide to GMP PE009-16

Version 1.0, June 2024

Contents

Purpose

This document is for Australian sponsors and manufacturers of medicines, active pharmaceutical ingredients (APIs) and sunscreens made or supplied in Australia. It provides a summary of the changes in GMP requirements resulting from the recent replacement of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products (PE 009-15, 1 May 2021) with PE 009-16, 1 February 2022.

The most significant change resulting from the adoption of the more recent version of the PIC/S Guide is inclusion of the new Annex 16.

Changes to the PIC/S Guide to GMP

From 3 June 2024 the PIC/S Guide to GMP version 16 applies to the manufacture of medicines, APIs and sunscreens, unless exempt under provisions in the *Therapeutic Goods Act 1989* (the Act). There is a 3-month transition period for adoption of the new Annex 16 to allow manufacturers to review and make necessary operational changes. All other changes are minor (i.e., clarifications in Annex 13) and are in force from 3 June 2024.

Annex 13 GMP requirements

The table below provides a summary of the GMP requirements for Annex 13 – Manufacture of Investigational Medicinal Products and our assessment of the impact of the changes. Annex 13 applies from 3 June 2024

Annex 13 new or amended requirements

New or amended requirement	Remarks
INTRODUCTION These guidelines lay down appropriate tools to address specific issues concerning investigational medicinal products with regard to good manufacturing practice. The tools are flexible to provide for changes as knowledge of the process increases and appropriate to the stage of development of the product. An investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form. Unless otherwise defined in national law, manufacturing is defined as total and partial manufacture, as well as the various processes of dividing up, packaging and labelling (including blinding). Investigational medicinal products shall be manufactured by applying manufacturing practices which ensure the quality of such medicinal products in order to safeguard the safety of the subject and the reliability and robustness of clinical data generated in the clinical trial ("good manufacturing practice"). The good manufacturing practice requirements for investigational medicinal products are set out in these guidelines. Various other parts of the PIC/S GMP Guide provide useful guidance also and they should be considered. Procedures need to be flexible to provide for changes as knowledge of the process increases and appropriate to the stage of development of the products. In clinical trials there may be added risk to the subjects compared to patients treated with authorised medicinal products. The application of good manufacturing	PRINCIPLE Amended clause; however, identical in intent to the existing clause. The amended clause gives further guidance to what the investigational medicinal product is and the definition of 'manufacturing', and makes reference to follow national law, if available. The Glossary section is transferred to the end of PE009-16 Annex 13.

New or amended requirement	Remarks
practice for the manufacture and import of investigational medicinal products is intended to ensure that subjects are not placed at undue risk, and that the results of clinical trials are unaffected by inadequate quality, safety or efficacy arising from unsatisfactory manufacture or import. (Note: the reference to 'Import' here and in other parts of this annex refers to importation activities into the relevant country, which should be performed in accordance with applicable national laws/requirements.) Equally, it is intended to ensure that there is consistency between batches of the same investigational medicinal product used in the same or different clinical trials and that changes during the development of an investigational medicinal product are adequately documented and justified. The production of investigational medicinal products involves added complexity in comparison with authorised medicinal products by virtue of lack of fixed routines, variety of clinical trial designs and consequent packaging designs. Randomisation and blinding add to that complexity an increased risk of product cross-contamination and mix-up. Furthermore, there may be incomplete knowledge of the potency and toxicity of the product and a lack of full process validation. Moreover, authorised products may be used which have been re-packaged or modified in some way. These challenges require personnel with a thorough understanding of and training in the application of good manufacturing practice to investigational medicinal products. The increased complexity in manufacturing operations requires a highly effective quality system. For manufacturers to be able to apply and comply with good manufacturing practice for investigational medicinal products, co-operation between manufacturers and sponsors of clinical trials is required. This co-operation should be described in a technical agreement between the sponsor and manufacturer.	
1. SCOPE These guidelines apply to manufacture or import of investigational medicinal products for human use Reconstitution of investigational medicinal products is not considered manufacturing, unless otherwise subject to national law, and therefore is not covered by this guideline. The process of reconstitution has to be undertaken as close in time as possible to administration and has to be defined in the clinical trial application dossier and document available at the clinical trial site.	The new clause provides guidance.

New or amended requirement	Remarks
While these guidelines do not apply to the activities listed below, PIC/S Participating Authorities should, in accordance with national law, make those processes subject to appropriate and proportionate requirements to ensure subject safety and reliability and robustness of the data generated in the clinical trial: Re-labelling or re-packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the country concerned to carry out such processes, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same country; The preparation of medicinal products for use as investigational medicinal products, where this process is carried out in hospitals, health centres or clinics legally authorised in the country concerned to carry out such process and where the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same country.	
2. PHARMACEUTICAL QUALITY SYSTEM The pharmaceutical quality system which is designed, set-up and verified by the manufacturer should be described in written procedures, taking into account the guidance in Chapter 1 of Part 1 of the PIC/S GMP Guide, as applicable, to investigational medicinal products.	Amended clause; however, identical in intent to the existing clause.
The product specifications and manufacturing instructions may be changed during development, but full control and traceability of the changes should be documented and maintained. Deviations from any predefined specifications and instructions should be registered, investigated and corrective and preventive action measures initiated as appropriate.	Further guidance. No change to current interpretation or expectation.
The selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, should be documented as part of the pharmaceutical quality system to ensure the integrity of the supply chain and protect against falsified products. The level of supervision should be proportionate to the risks posed by the individual materials, taking into account their source, manufacturing process, supply chain complexity and the final use to	Further guidance. No change to current interpretation or expectation

New or amended requirement	Remarks
which the material is put in the investigational medicinal product. The supporting evidence for each supplier approval and material approval should be documented and maintained.	
2.1. Product specification file **1.** The product specification file brings together and contains all of the essential reference documents to ensure that investigational medicinal products are manufactured according to good manufacturing practice for investigational medicinal products and the clinical trial authorisation. The product specification file is one of the essential elements of the pharmaceutical quality system.	Further guidance. No change to current interpretations or expectation.
2. Applicable sections of the product specification file should be available at the start of manufacturing of the first batch of the investigational medicinal product for use in a clinical trial	No change to current interpretation or expectation.
3. The product specification file should be continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions. It should include, or refer to, at least the following documents: i. specifications and analytical methods for starting materials, packaging materials, intermediate product, bulk product and finished product; ii. manufacturing methods; iii. in-process testing and methods; iv. approved label copy; v. relevant clinical trial authorisations and amendments thereof, clinical trial protocol and randomisation codes, as appropriate; vi. relevant technical agreements with contract givers and acceptors, as appropriate; vii. stability plan and reports; viii. details of plans and arrangements for reference and retention samples; ix. storage and transport conditions; and x. details of the supply chain including manufacturing, packaging, labelling and testing sites for the investigational	Additional document requirements. The information/ documents should already exist and now required to be included in the Product Specification File.

New or amended requirement	Remarks
medicinal products, preferably in the format of a comprehensive diagram.	
4. This list of documents is neither exhaustive nor exclusive. **5.** The contents of the product specification file will vary depending on the product and the stage of development. **6.** Where different manufacturing steps are carried out at different locations under the responsibility of different Authorised Persons, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations. The manufacturing site should have access to the necessary documentation of the product specification file, including changes, to enable the relevant activities to be performed.	Further guidance. No change to current interpretation or expectation.
3. PERSONNEL **1.** The guidance in Chapter 2 of Part 1 of the PIC/S GMP Guide should be taken into account, as appropriate, in relation to the manufacture of investigational medicinal products.	Further guidance. No change to current interpretation or expectation.
2. All personnel involved with the manufacture, import, storage or handling of investigational medicinal products should be appropriately trained in the requirements specific to these types of product. **3.** Even where the number of staff involved in the manufacturing or import of investigational medicinal products is small, there should be, for each batch, separate people responsible for production and quality control.	Further guidance. No change to current interpretation or expectation.
4. The Authorised Person who certifies the finished batch of investigational medicinal products for use in the clinical trial should ensure that there are systems in place that meet the requirements of good manufacturing practice and should have a broad knowledge of pharmaceutical development, clinical trial processes and supply chain of the batch concerned.	Further guidance. No change to current interpretation or expectation.

New or amended requirement	Remarks
4. PREMISES AND EQUIPMENT **1.** The toxicity, potency or sensitising potential may not be fully understood for investigational medicinal products and this reinforces the need to minimise all risks of cross-contamination. The design of equipment and premises, inspection/test methods and acceptance limits to be used after cleaning should reflect the nature of these risks and take account of the quality risk management principles detailed in Chapters 3 and 5 of Part 1 of the PIC/S GMP Guide. **2.** Consideration should be given to campaign manufacturing, where appropriate. Account should be taken of the solubility of the product in decisions about the choice of cleaning solvent.	Further guidance. No change to current interpretation or expectation.
3. A quality risk management process, which includes a potency and toxicological evaluation, should be used to assess and control the cross-contamination risks presented by the investigational medicinal products manufactured. Factors that should be taken into account include: i. facility/equipment design and use; ii. personnel and material flow; iii. microbiological controls; iv. physio-chemical characteristics of the active substance; v. process characteristics; vi. cleaning processes; vii. analytical capabilities relative to the relevant limits established from the evaluation of the investigational medicinal products.	Further guidance. No change to current interpretations or expectation.
4. Premises and equipment are expected to be qualified in accordance with Annex 15 to the PIC/S GMP Guide.	Further guidance. No change to current interpretations or expectation.

New or amended requirement	Remarks
5. DOCUMENTATION **1.** Documentation should be generated and controlled in line with the principles detailed in the PIC/S GMP Guide, Part I, Chapter 4. The retention period for instructions and records required to demonstrate compliance with good manufacturing practice should be defined according to the type of document while complying with any relevant national laws. The documentation shall be consistent with the Product Specification File. Documents which are part of the Product Specification File shall be retained for the period of at least 5 years, unless otherwise specified in relevant national laws.	Further guidance. No change to current interpretations or expectation.
2. The sponsor may have specific responsibilities for document retention of the clinical trial master file according to relevant national laws but unless otherwise specified in national laws, should retain such documentation for at least 25 years after the end of the trial. If the sponsor and the manufacturer are not the same entity, the sponsor has to make appropriate arrangements with the manufacturer to fulfil the sponsor's requirement to retain the clinical trial master file. Arrangement for retention of such documents and the type of documents to be retained should be defined in an agreement between the sponsor and manufacturer.	The new clause gives guidance to the retention period of documents that are part of the clinical trial master file.
5.1 Specification and instructions **1.** Specifications for starting materials, immediate packaging materials, intermediate products, bulk products and finished products, manufacturing formulae and processing and packing instructions should be as comprehensive as possible given the current state of knowledge. They should be re-assessed during development and updated as necessary. Each new version should take into account the latest data, current technology used, regulatory and pharmacopoeial developments and should allow traceability to the previous document. Any changes should be carried out according to a written procedure which should address any implications for product quality such as stability and bioequivalence. The approval process for instructions and	No change to current interpretations or expectation.

New or amended requirement	Remarks
changes thereof shall include responsible personnel at the manufacturing site.	
2. Rationales for changes should be recorded and the consequences of a change on product quality and on any on-going clinical trials should be investigated and fully documented.	No change to current interpretations or expectation.
5.2 Order • The manufacturer should retain the order for the investigational medicinal product as part of the batch documentation. The order should request the processing and/or packaging of a certain number of units and/or their distribution and be given by or on behalf of the sponsor to the manufacturer. The order should be in writing, though it may be transmitted by electronic means, and be precise enough to avoid any ambiguity. It should be formally authorised by the sponsor or his representative and refer to the product specification file and the relevant clinical trial protocol as appropriate.	Further guidance. No change to current interpretations or expectation.
5.3 Manufacturing formulae and processing instructions **1.** For every manufacturing operation or supply there should be clear and adequate written instructions and written records which are prepared using the specific clinical study information detailed in the product specification file. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture once the marketing authorisation is granted.	Further guidance. No change to current interpretations or expectation.
2. The relevant information in the product specification file should be used to draft the detailed written instructions on processing, packaging, quality control testing, and storage, including storage conditions.	No change to current interpretations or expectation.
5.4 Packaging instructions **1.** Investigational medicinal products are normally packed in an individual way for each subject included in the clinical trial. The number of units	No change

New or amended requirement	Remarks
to be packaged should be specified prior to the start of the packaging operations, including units necessary for carrying out quality control and for any retention samples to be kept. Sufficient reconciliations should take place to ensure that the correct quantity of each product required has been accounted for at each stage of processing.	
2. Procedures should describe the specification, generation, testing, security, distribution, handling and retention of any randomisation code used for packaging investigational medicinal products as well as code-break mechanism. Appropriate records should be maintained.	Further guidance. No change to current interpretation or expectation.
5.5 Batch records **1.** Batch records should be kept in sufficient detail for the sequence of operations to be accurately determined. These records should contain any relevant remarks which justify procedures used and any changes made, enhance knowledge of the product, develop the manufacturing operations and document deviations from predefined requirements.	Amended clause, however no additional requirement. The text provides additional guidance if any deviations occur in line with how deviations should be managed in accordance with good manufacturing practice principles.
2. Batch manufacturing records should be retained by the manufacturer for at least 5 years after the completion or formal discontinuation of the last clinical trial in which the batch was used, or in accordance with the requirements of national laws.	Further guidance. No change to current interpretations or expectation.
6. PRODUCTION **6.1. Packaging materials** **1.** Specifications and quality control checks should include measures to guard against unintentional unblinding due to changes in appearance between different batches of packaging materials	No change
6.2. Manufacturing operations • During development critical parameters should be identified and in-process controls primarily used to control the process. Provisional production parameters and in-process controls may be deduced from prior experience, including that gained from earlier development work. Careful consideration by	No change

New or amended requirement	Remarks
key personnel is called for in order to formulate the necessary instructions and to adapt them continually to the experience gained in production. Parameters identified and controlled should be justifiable based on knowledge available at the time.	
• The manufacturing process is not required to be validated to the extent necessary for routine production but shall be validated in its entirety, as far as is appropriate, taking into account the stage of product development. The validation should be documented in accordance with the requirements detailed in Annex 15 of the PIC/S GMP Guide. The manufacturer shall identify the process steps that safeguard the safety of the subject and the reliability and robustness of the clinical trial data generated in the clinical study.	Further guidance. No change to current interpretation or expectation.
• To avoid cross-contamination, written cleaning procedures and analytical methods to verify the cleaning process should be available.	Further guidance. No change to current interpretation or expectation.
• For sterile products, the validation of controls and processes related to assurance of sterility should be of the same standards as for authorised medicinal products and take account of the principles for the manufacture of sterile medicinal products as detailed in Annex 1 to the PIC/S GMP Guide. Likewise, when required, virus inactivation/removal and removal of other impurities of biological origin should be demonstrated, to assure the safety of biotechnologically derived and biological products by following the scientific principles and techniques defined in the available guidance in this area	Further guidance. No change to current interpretation or expectation.
• Validation of aseptic processes presents special problems where the batch size is small; in these cases, the number of units filled may be the maximum number filled in production. If practicable, and otherwise consistent with simulating the process, a larger number of units should be filled with media to provide greater confidence in the results obtained. Filling and sealing is often a manual or semi-automated operation presenting great challenges to sterility, so enhanced attention should be given to operator training and validating the aseptic technique of individual operators.	No change

New or amended requirement	Remarks
6.3. Modification of comparator products **1.** If a product is modified, data should be available (e.g., stability, comparative dissolution or bioavailability) to demonstrate that these changes do not significantly alter the original quality characteristics of the product.	No change
2. The expiry date stated for the comparator product in its original packaging might not be applicable to the product where it has been repackaged in a different container that may not offer equivalent protection, or be compatible with the product. A suitable retest date, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the product may be subjected, should be determined by or on behalf of the sponsor. Such a date should be justified and must not be later than the expiry date of the original package. There should be compatibility of expiry dating and clinical trial duration.	No change to current interpretations or expectation.
3. A reference sample of comparator product, which has been repackaged or over encapsulated for blinding purposes, should be taken at a point representative of the additional processing and retained, as the additional processing step could have an impact on stability or be needed for identification purposes in the event of a quality defect investigation, which would not be covered by the commercial retained sample.	No change
6.4 Blinding operations **1.** Where products are blinded, systems should be in place to ensure that the blind is achieved and maintained while allowing for identification of "blinded products, when necessary, including batch numbers of the products before the blinding operation. Rapid identification of product should also be possible in an emergency. Where the manufacturer has been delegated the responsibility for generation of randomisation codes, the manufacturer should enable that unblinding information is available to the appropriate responsible investigator site personnel before investigational medicinal products are supplied.	No change

New or amended requirement	Remarks
2. Where products are blinded, the expiry date assigned to all products should be stated at the expiry of the shortest dated product so that the blinding is maintained.	No change to current expectation.
6.5 Packaging **1.** During packaging of investigational medicinal products, it may be necessary to handle different products on the same packaging line at the same time. The risk of product unintentional mixing (mix-ups) must be minimised by using appropriate procedures and/or specialised equipment as appropriate and relevant staff training. Documentation must be sufficient to demonstrate that appropriate segregation has been maintained during any packaging operations.	Amended clause, however no additional requirement. The new text gives further guidance and supports the existing clause in PE009-15 Clause 5.49 (minimising mix-ups during packaging operations)..
2. Packaging and labelling of investigational medicinal products are likely to be more complex and more liable to errors which are also harder to detect than for authorised medicinal products, particularly when blinded products with similar appearance are used. Precautions against mislabelling such as reconciliation, line clearance, in- process control checks by appropriately trained staff should accordingly be intensified.	No change to current interpretation or expectation.
3. The packaging must ensure that the investigational medicinal product remains in good condition during transport and storage at intermediate destinations. Any opening or tampering of the outer packaging during transport should be readily discernible.	No change.
4. Re-packaging operations may be performed by authorised personnel at a hospital, health centre or clinic that meet the requirements of relevant national laws or requirements (i.e., in healthcare establishments that are not otherwise subject to good manufacturing practices).	No impact on licence manufacturing sites.
6.6 Labelling **1.** The labelling of investigational medicinal products shall comply with the requirements of relevant national laws or requirements, and where	No change to current interpretation or expectation.

New or amended requirement	Remarks
no such requirements exist, it should address at least the following elements, unless their absence can be justified, e.g., use of a centralised electronic randomisation system: **i.** name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding); **ii.** the name/identifier and strength/potency, and in the case of blinded trials, all product labelling should indicate "placebo/comparator or[name/identifier] + [strength/potency]"; **iii.** pharmaceutical dosage form, route of administration, and quantity of dosage units; **iv.** the batch and/or code number to identify the contents and packaging operation; **v.** a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere; **vi.** the trial subject identification number/treatment number and where relevant, the visit number; **vii.** the name of the investigator (if not included in (i) or (v)); **viii.** directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product); **ix.** "For clinical trial use only" or similar wording; **x.** the storage conditions; **xi.** period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity; and **xii.** "keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.	
2. The information which shall appear on the labelling should comply with any relevant national laws or requirements. The labelling operation should be performed at an authorised manufacturing site in accordance with relevant national laws or requirements.	Prescriptive requirements for labelling had been removed and replaced with a generic statement. TGA will continue to allow abbreviated labelling requirements as described in in *PE009-15 Annex 13 Clause 27 – 30.*
3. If it becomes necessary to change the expiry date, an additional label should be affixed to the investigational medicinal product. This	No change to current interpretation or expectation.

New or amended requirement	Remarks
additional label should state the new expiry date and repeat the batch number and clinical trial reference number. It may be superimposed on the old expiry date, but for quality control reasons, not on the original batch number. **4.** The re-labelling operation should be performed by appropriately trained staff in accordance with good manufacturing practice principles and specific standard operating procedures and should be checked by a second person. This additional labelling should be properly documented in the batch records. To avoid mistakes the additional labelling activity should be carried out in an area which is partitioned or separated from other activities. A line clearance at the start and end of activity should be carried out and label reconciliation performed. Any discrepancies observed during reconciliation should be investigated and accounted for before release. **5.** The re-labelling operation may be performed by authorised personnel at a hospital, health centre or clinic that meet the requirements of relevant national laws or requirements (i.e., in healthcare establishments that are not subject to good manufacturing practices).	
7. QUALITY CONTROL **1.** The manufacturer should establish and maintain a quality control system placed under the authority of a person who has the requisite qualifications and is independent of production.	No change to current or expectation.
2. As processes may not be standardised or fully validated, testing takes on more importance in ensuring that each batch meets the approved specification at the time of testing.	No change to current interpretation or expectation.
3. Quality control of the investigational medicinal product, including that of the comparator product, should be performed in accordance with the information submitted in the application for the clinical trial, as authorised by the relevant country. **4.** Verification of the effectiveness of blinding should be performed and recorded.	No change to current interpretation or expectation.

New or amended requirement	Remarks
5. Retention periods for samples of investigational medicinal products should comply with the relevant national laws or other requirements. **6.** Samples are retained to fulfil two purposes: firstly, to provide a sample for future analytical testing, and secondly, to provide a specimen of the finished investigational medicinal product which may be used in the investigation of a product quality defect. **7.** Samples may therefore fall into two categories: • Reference sample: a sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analysed should the need arise. Where stability permits, reference samples from critical intermediate stages, e.g., those requiring analytical testing and release, or intermediates which are transported outside of the manufacturer's control, should be kept. • Retention sample: a sample of a fully packaged unit from a batch of finished product. It is stored for identification purposes. For example, presentation, packaging, labelling, package leaflet, batch number, expiry date should the need arise during the shelf life of the batch concerned. **8.** There may be exceptional circumstances where this requirement can be met without retention of duplicate samples, e.g., where small amounts of a batch are packaged for different markets or in the production of very expensive medicinal products.	New and amended clauses; however, no new requirements. The new clauses provide further guidance. The requirement of sample retention period of 2 years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer in PE009-15 Annex 13 Clause 36 removed. The retention period is now aligned with the requirement in PE009-15 Annex 19 Clause 3.1.
9. For retention samples it is acceptable to store information related to the final packaging as written, photographic or electronic records, if such records provide sufficient information, e.g., examples of packaging, labelling and any accompanying documentation to permit investigations associated with the use of the product. In case of electronic records, the system should comply with the requirements of Annex 11 of the PIC/S GMP Guide.	Further guidance. No change to current interpretation or expectation.

New or amended requirement	Remarks
10. Where reference samples and retention samples are presented identically, i.e., as fully packaged units, the samples may be regarded as interchangeable.	No change to current interpretation or expectation.
11. Samples are not expected of an investigational medicinal product which is an unblinded comparator in its original packaging and sourced from the authorised supply chain in the country in which the clinical trial is intended to occur or of a product which holds a marketing authorisation granted by the national competent authority of the country in which the clinical trial occurs. (Note: In the EU, it might be the European Commission that has granted the marketing authorisation.)	Further guidance. No change to current interpretation or expectation.
12. The storage location of samples should be defined in a technical agreement between the sponsor and the manufacturer(s) and should allow timely access by the competent authorities.	No change to current interpretation or expectation.
13. Reference samples of finished product should be stored under defined storage conditions in the country in which the manufacturer is located or in another country where appropriate arrangements have been made between (or on behalf of) the two countries to ensure that the manufacturer of the investigational medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the PIC/S GMP Guide. In exceptional circumstances, the reference samples of the finished product may be stored by the manufacturer in another country, in which case this should be justified and documented in a technical agreement between the sponsor, the manufacturer and the storage site.	The new clause allows storage of reference samples in another country other than where the manufacturer is located and provides guidance.
14. The reference sample should be of sufficient size to perform, on at least two occasions, all critical quality attribute tests as defined in the investigational medicinal product dossier authorised by the relevant country. Any exception to this should be justified to, and agreed with, the national competent authority.	Provide the manufacturer more flexibility.

New or amended requirement	Remarks
8. RELEASE OF BATCHES **1.** Release of investigational medicinal products should not occur until after the Authorised Person has certified that the relevant requirements have been met. The Authorised Person should take into account the elements listed below, as appropriate.	No impact
2. The scope of the certification can be limited to assuring that the products are in accordance with the authorisation of the clinical trial and any subsequent processing carried out by the manufacturer for the purpose of blinding, trial-specific packaging and labelling.	No change to current interpretation or expectation.
3. The information in the product specification file should form the basis for assessment of the suitability for certification and release of a particular batch by the Authorised Person and should therefore be accessible to him or her.	No impact
4. Assessment by the Authorised Person of each batch for certification prior to release should take account of the principles detailed in Annex 16 of the PIC/S GMP Guide and may include as appropriate; **i.** batch records, including control reports, in-process test reports and release reports demonstrating compliance with the product specification file, the order, protocol and randomisation code. These records should include all deviations or planned changes, and any consequent additional checks and tests, and should be completed and endorsed by the staff authorised to do so according to the quality system; **ii.** production conditions; **iii.** cleaning records; **iv.** the qualification status of facilities, validation status of processes and methods; **v.** examination of finished packs; **vi.** the results of any analyses or tests performed after importation, where relevant; **vii.** stability plan and reports;	Further guidance. No change to current interpretation or expectation.

New or amended requirement	Remarks
viii. the source and verification of conditions of storage and shipment; **ix.** audit reports concerning the quality system of the manufacturer; **x.** documents certifying that the manufacturer is authorised to manufacture investigational medicinal product for export (as applicable under national law); by the appropriate authorities in the relevant country; **xi.** where relevant, regulatory requirements for marketing authorisation, good manufacturing practice standards applicable and any official verification of compliance with good manufacturing practice; **xii.** verification of the supply chain including manufacturing, packaging, labelling and testing sites for the investigational medicinal products; and **xiii.** all factors of which the Authorised Person is aware that are relevant to the quality of the batch. **5.** The relevance of the above elements is affected by the country of origin of the product, the manufacturer, the status of the product, i.e., with or without a marketing authorisation granted by the relevant competent authority, and the phase of development of the product.	
6. Where investigational medicinal products are produced and packaged at different sites under the supervision of different Authorised Persons, sharing of responsibilities amongst the Authorised Persons in relation to compliance of a batch must be defined in a document formally agreed by all parties.	Amended clause; no new requirements. The amended clause provides further guidance and supports the existing clause in PE009-15 Chapter 7 Principle (outsourced activities).
7. Where required to support certification, the Authorised Person has to ensure that the investigational medicinal product has been stored and transported under conditions that maintain product quality and supply chain security. Relevant situations may include short expiry date products released prior to final Authorised Person certification, or	New guidance. No change to current interpretation or expectation.

New or amended requirement	Remarks
where return of investigational medicinal products to an authorised manufacturer for re-labelling and re-packaging remains a possibility.	
8. Where the manufacturer is delegated by the sponsor to perform the regulatory release in addition to certification by the Authorised Person, the arrangements should be defined in an agreement between the sponsor and the manufacturer. Relevant clinical trial authorisation and amendment information should be available for reference in the product specification file and the manufacturer should ensure the necessary clinical trial authorisations are in place and prior to shipping product for use in the trial.	Further guidance. No change to current interpretation or expectation.
9. After certification by the Authorised Person, the investigational medicinal product should be stored and transported under conditions that maintain product quality and supply chain security.	New guidance that may require manufacturers to review their shipping policy.
10. The Authorised Person is not required to certify re-packaging (section 6.5), or re-labelling (section 6.6) performed by authorised personnel at a hospital, health centre or clinic that meet the requirements of relevant national laws or requirements.	No change to current interpretation or expectation.
9. **OUTSOURCED OPERATIONS** Activities which are outsourced should be defined, agreed and controlled by written contracts between the contract giver and the party to whom the operations are outsourced in accordance with 8the principles detailed in Part I, Chapter 7 of the PIC/S GMP Guide.	No change to current interpretation or expectation.
10. COMPLAINTS **1.** There should be written procedures describing the actions to be taken upon receipt of a complaint at the manufacturing, storage or importation site. All complaints should be documented and assessed to establish if they represent a potential quality defect or other issue. The procedures should ensure that the sponsor is able to assess the	No change to current interpretation or expectation.

New or amended requirement	Remarks
complaints to determine if they justify the reporting of a serious breach to the relevant competent authority. **2.** The investigation of quality defect should be performed in accordance with the principles detailed in Part I, Chapter 8 of the PIC/S GMP Guide.	
3. The conclusions of the investigation should be discussed between the manufacturer and the sponsor, if different, in a timely manner. This should involve the Authorised Person and those responsible for the relevant clinical trial in order to assess any potential impact on the trial, product development and on subjects.	No change to current interpretations or expectation.
11. RECALLS AND RETURNS **11.1 Recalls** **1.** Procedures for retrieving investigational medicinal products and documenting such retrievals should be in line with relevant national laws and guidelines, and be agreed by the sponsor in cooperation with the manufacturer, where different. The manufacturer, investigator and the sponsor's representative need to understand their obligations under the retrieval procedure. The procedures for retrieval of investigational medicinal products should be in accordance with the principles detailed in Chapter 8 of the PIC/S GMP Guide.	No change to current interpretation or expectation.
2. To facilitate recall, a detailed inventory of the shipments made by the manufacturer should be maintained.	No change to current interpretation or expectation.
11.2 Returns	No change to current interpretation or expectation.
Returned investigational medicinal products should be clearly identified and stored in an appropriately controlled, dedicated area. Inventory records of returned products should be kept.	No change to current interpretation or expectation

New or amended requirement	Remarks
11.3 Destruction **1.** The manufacturer or sponsor's representative should destroy investigational medicinal products only with prior written authorisation by the sponsor. The arrangements for destruction of investigational medicinal products have to be described in the protocol. Any arrangement between sponsor and manufacturer in this regard should be defined in their technical agreement.	Manufacturer may need to review their policy and procedure for destruction to include the requirements for a protocol and technical agreement.
2. Destruction of unused investigational medicinal products should be carried out only after reconciliation of delivered, used and recovered products and after investigation and satisfactory explanation of any discrepancies upon which the reconciliation has been accepted.	No change to current interpretation or expectation.
3. Records of destruction operations should be retained, including a dated certificate of destruction or a receipt for destruction to the sponsor. These documents should clearly identify or allow traceability to the batches and/or patient numbers involved and the actual quantities destroyed.	No change to current interpretation or expectation.
GLOSSARY TO ANNEX 13	No change to current interpretation or expectation.
Blinding A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s). In relation to an investigational medicinal product, blinding shall mean the deliberate disguising of the identity of the product in accordance with the instructions of the sponsor. Unblinding shall mean the disclosure of the identity of blinded products.	
Campaign manufacturing Manufacturing a series of batches of the same product in sequence in a given period of time followed by an appropriate (validated) cleaning procedure.	

New or amended requirement	Remarks
Clinical trial Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of one or more investigational medicinal product(s) with the object of ascertaining its/their safety and/or efficacy.	
Comparator product An investigational medicinal product used as a reference, including as a placebo, in a clinical trial.	
Expiry date The date placed on the container/labels of an investigational medicinal products designating the time during which the investigational medicinal products is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.	
Investigational medicinal product A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.	
Investigator A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.	

New or amended requirement	Remarks
Manufacturer/importer of Investigational Medicinal Products Any holder of the authorisation to manufacture/import. **Manufacture** All operations of purchase of materials and products, production, quality control, release, storage, distribution of investigational medicinal products and the related controls. Note that the word 'preparation' as used in this Annex should be taken as synonymous with the word ‘manufacture’.	
Order The order should request the processing and/or packaging of a certain number of units and/or their shipment and be given by or on behalf of the sponsor to the manufacturer.	
Preparation See ‘Manufacture’ above	
Product Specification File 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 investigational medicinal product.	
Randomisation The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.	

New or amended requirement	Remarks
Randomisation Code A listing in which the treatment assigned to each subject from the randomisation process is identified.	
Retest date The date when a material should be re-examined to ensure that it is still suitable for use.	
Regulatory Release The verification of batch certification and that the clinical trial site is trained, qualified and has the necessary approvals, thus is ready to receive investigational medicinal product.	
Shipping The operation of packaging for shipment and sending of ordered medicinal products for clinical trials.	
Sponsor An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.	

Annex 16 GMP requirements

The tables below provide a summary of the GMP requirements of the new Annex 16 in the PIC/S Guide to GMP version 16. These requirements may require some manufacturers to implement or modify processes to provide improved or more detailed evidence of compliance.

Our guidance for Release for Supply was based substantially on the EU GMP Annex 16 that was in effect at that time and is substantially similar to Annex 16 in the PIC/S Guide to GMP version 16.

The adoption of Annex 16 means that the expectations outlined within our Release for Supply guidance and Guidance for Releasing medicines manufactured at multiple sites will now become formal requirements for manufacturers.

Annex 16 – Scope

New or amended requirements	Remarks
SCOPE This Annex provides guidance on the certification by an Authorised Person and on batch release of medicinal products for human or veterinary use within a Pharmaceutical Inspection Co-operation Scheme (PIC/S) Participating Authority or made for export. The principles of this guidance also apply to investigational medicinal products (IMP) for human use, subject to any difference in the legal provisions and more specific guidance published by PIC/S Participating Authorities under national law.	New text providing information for users. Annex 16 would apply to all APs in the supply chain for the manufacture of dosage forms. This annex would apply to the certification of goods that are registered or listed in the ARTG, (with an MA), used as an Investigational medicinal Product (IMP) in an approved clinical trial and unapproved goods, or goods exempt under Schedules 5 or 5A of the Therapeutic Goods Regulations 1990.
Guidance in this Annex on the certification of batches by a manufacturer of a medicinal product is within the scope of the Pharmaceutical Inspection Co-operation Scheme. However, each PIC/S Participating Authority may decide whether guidance expressed in this annex should become a legally binding standard in relation to imported medicinal products.	New text providing information for users. While the Annex would apply to the process of batch certification for goods supplied to or exported from Australia, the sections of this Annex relating to the mandatory (re)testing of finished goods following importation would not necessarily apply (unless specifically required by the TGA, e.g., for the testing of certain vaccines before supply).
This Annex does not address any controls on release of medicinal products by a National Competent Authority under national law (e.g.). certain blood and immunological products); however, this Annex does apply to the Authorised Person certification and subsequent release of such batches.	New text providing information for users. This statement relates to instances where the TGA performs pre-release testing of certain goods, as required by the relevant MA, (e.g., for the testing of certain vaccines before supply)

New or amended requirements	Remarks
The basic arrangements for batch release for a medicinal product are defined by its marketing authorisation (MA) Nothing in this Annex should be taken as overriding those arrangements.	New text providing information for users. As per current expectations, the MA or CTA should be consulted in all cases for the requirements for batch certification. For goods for which there is no MA or CTA, (e.g. unapproved goods, or goods exempt under Schedules 5 or 5A of the Therapeutic Goods Regulations 1990), the principles of the Annex would apply during batch certification, noting that compliance with GMP and the specifics of any exemption must be demonstrated during certification.
The ultimate responsibility for the performance of a medicinal product over its lifetime, its safety, quality and efficacy, lies with the marketing authorisation holder (MAH). However, the Authorised Person is responsible for ensuring that each individual batch has been manufactured and checked in compliance with national requirements in accordance with the requirements of the marketing authorisation (MA) and with Good Manufacturing Practice (GMP).	New text providing information for users. This statement does not invoke any new or additional requirements; however, reiterates the responsibilities of Sponsors (MAH) and Authorised Persons (AP) at manufacturing premises.
The process of batch release comprises of: I. The checking of the manufacture and testing of the batch in accordance with defined release procedures.	New section – however, identical in intent to existing clause 4.27 in PE009-15. This new text provides an overview of the process and terminology used in the new Annex 16. 4.27 Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale of the finished product by the Authorised Person(s). All records should be available to the Authorised Person. A system should be in place to indicate special observations and any changes to critical data.
II. The certification of the finished product batch performed by an Authorised Person signifying that the batch is in compliance with GMP and the requirements of its MA. This represents the quality release of the batch.	New clause – however, identical in intent to existing clause 1.4xv and 1.9(vii) in PE009-15. This new text provides an overview of the process and terminology used in the new Annex 16. 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products;

New or amended requirements	Remarks
	1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations;
III. The transfer to saleable stock, and/or export of the finished batch of product which should take into account the certification performed by the Authorised Person. If this transfer is performed at a site other than that where certification takes place, then the arrangement should be documented in a written agreement between the sites.	New section – however, identical in intent to existing clause 1.4xiv and Annex 15§6 in PE009-15. This new text provides an overview of the process and terminology used in the new Annex 16. Existing arrangements between Manufacturers and Sponsors (as defined by Agreements/Contracts as per Chapter 7 of the GMP Guide) will continue to be the method by which compliance during transfer to saleable stock will be achieved. This new text does not invoke any new or additional expectations. 1.4(xiv) Satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life; Annex 15§6. VERIFICATION OF TRANSPORTATION 6.1 Finished medicinal products, investigational medicinal products, bulk product and samples should be transported from manufacturing sites in accordance with the conditions defined in the marketing authorisation, the approved label, product specification file or as justified by the manufacturer.
The purpose of controlling batch release is notably to ensure that: I. The batch has been manufactured and checked in accordance with the requirements of its MA. II. The batch has been manufactured and checked in accordance with the principles and guidelines of GMP. III. Any other relevant legal requirements are taken into account.	New clause – however, identical in intent to existing clause 1.4xv and 1.9(vii) in PE009-15. This new text does not invoke any new or additional expectations. 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products.

New or amended requirements	Remarks
IV: In the event that a quality defect as referred to in Chapter 8 of PIC/S GMP Guide, Part I, needs to be investigated or a batch recalled, to ensure that any Authorised Persons involved in the certification or confirmation[1] and any relevant records are readily identifiable. 1 Information required for the confirmation, where Authorised Person responsibilities for the batch are being transferred between sites, is recommended in Appendix I to this Annex.	1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations. New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Duties of an authorised person performing RFS". Annex 16 introduces a new term "Confirmation" which is essentially synonymous with the TGA term "Release for Further Processing" as described in our Guidance for Releasing medicines manufactured at multiple sites. Batch 'Confirmation' is performed by each manufacturer in the supply chain to confirm that the steps performed by each discrete manufacturer has been performed in accordance with Good Manufacturing Practice, the Marketing Authorisation, (or CTA) the terms of the Technical quality agreement and any other regulations relevant to the goods. These 'confirmations' are passed to the AP performing final "Batch Certification" (Release for Supply)

Annex 16 – 1. The process of certification

New or amended requirements	Remarks
1. THE PROCESS OF CERTIFICATION 1.1 Each batch of finished product must be certified[2] by an Authorised Person before being released for sale, supply or export. Certification can only be performed by an Authorised Person of the manufacturer and/or importer which are described in the MA.	New clause – however, identical in intent to existing clause 1.4xv and 1.9(vii) in PE009-15. This new text does not invoke any new or additional expectations. 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing

New or amended requirements	Remarks
2. The contents of a batch certificate for medicinal products are recommended in Appendix II to this Annex. The content of a batch certificate may differ from Appendix II as required under national law or as required to facilitate arrangements between National Competent Authorities.	Authorisation and any other regulations relevant to the production, control and release of medicinal products. 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations. Annex 16 uses the existing term “Certification” which is essentially synonymous with the TGA term “Release for Supply” as described in our existing Guidance for Release for Supply. Batch ‘Certification’ is usually performed by the last Authorised Person in the process of manufacturing the goods. The process ensures that each preceding step in the manufacture of the goods have has been performed in accordance with Good Manufacturing Practice, the Marketing Authorisation, (or CTA) the terms of the Technical quality agreement and any other regulations relevant to the goods. Appendix II of the Annex includes a letter template that may be used to assist Authorised Persons performing batch certification (release for supply). This format is not mandatory; however, certification letters/notices should include at least this information.
1.2. Any Authorised Person involved in the certification or confirmation of a batch must have detailed knowledge of the steps for which they are taking responsibility. The Authorised Persons should be able to prove their continuous training regarding the product type, production processes, technical advances and changes to GMP.	New clause – however, identical in intent to existing clause 1.4(ii), 1.4(xv), 1.9(vii) and 2.11 in PE009-15. This new text does not invoke any new or additional expectations. 1.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that: (ii) Product and process knowledge is managed throughout all lifecycle stages; (xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products.

New or amended requirements	Remarks
	1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations. 2.11 Besides the basic training on the theory and practice of the Pharmaceutical Quality System and Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. – e.g. refer to "Authorised person responsibilities" and the Guidance for Releasing medicines manufactured at multiple sites – e.g. refer to "RFS authorised person responsibilities" Annex 16 introduces a new term "Confirmation" which is essentially synonymous with the TGA term "Release for Further Processing". Batch 'Confirmation' is performed by each manufacturer in the supply chain to confirm that the steps performed by each discrete manufacturer has been performed in accordance with Good Manufacturing Practice, the Marketing Authorisation, (or CTA) the terms of the Technical quality agreement and any other regulations relevant to the goods. The requirements for batch confirmation are essentially identical to text included in the TGA's existing Guidance for Releasing medicines manufactured at multiple sites – e.g. refer to "RFS authorised person responsibilities"
1.3 There may be several sites involved in the various stages of manufacture, importation, testing and storage of a batch before it undergoes certification. Regardless of how many sites are involved, the Authorised Person performing certification of the finished product must ensure that all necessary steps have been completed under accepted pharmaceutical quality systems to assure compliance of the batch with GMP, the MA and any other national requirements where certification is taking place.	New clause – however, identical in intent to existing clause 1.4(ii), 1.4(xv), 1.9(vii) in PE009-15. This new text does not invoke any new or additional expectations. 1.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that: (ii) Product and process knowledge is managed throughout all lifecycle stages;

New or amended requirements	Remarks
	(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products; 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations; New text is essentially identical to text included in the TGA's existing Guidance for Releasing medicines manufactured at multiple sites – e.g. refer to "RFS authorised person responsibilities", "Relying on decisions of other authorised persons" and "RFFP authorised person responsibilities".
1.4. Each manufacturing site must have at least one Authorised Person.	New clause – however, identical in intent to clauses 2.5 & 2.6 of PE009-15 and reflects existing regulatory framework for GMP licenses and overseas GMP certification, in that a nominated person for Quality Control (normally the AP) must accompany the application and be included as a nominee on a domestic licence. This new text does not invoke any new or additional expectations. 2.5 Senior Management should appoint Key Management Personnel including the head of Production, the head of Quality Control, and if at least one of these persons is not responsible for the release of products the Authorised Person(s) designated for the purpose. 2.6 The duties of the Authorised Person(s) are described in the national requirements and can be summarised as follows: a) An Authorised Person must ensure that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that country and in accordance with the requirements of the Marketing Authorisation. b) The Authorised Person(s) must meet the qualification requirements laid down in the national legislation, they shall be permanently and continuously at the disposal of the holder of the Manufacturing Authorisation to carry out their responsibilities.

New or amended requirements	Remarks
	c) The responsibilities of an Authorised Person may be delegated, but only to other Authorised Person(s).
1.4.1 Where the site only undertakes partial manufacturing operations in relation to a batch, then an Authorised Person at that site must at least confirm that the operations undertaken by the site have been performed in accordance with GMP and the terms of the written agreement detailing the operations for which the site is responsible. If the Authorised Person is responsible for providing confirmation of compliance for those operations with the relevant MA, then the Authorised Person should have access to the necessary details of the MA	New clause – however, identical in intent to clauses 2.5 & 2.6 of PE009-15 and reflects existing regulatory framework for GMP licenses and overseas GMP certification, in that a nominated person for Quality Control (normally the AP) must accompany the application and be included as a nominee on a domestic licence. This new text does not invoke any new or additional expectations. 2.5 Senior Management should appoint Key Management Personnel including the head of Production, the head of Quality Control, and if at least one of these persons is not responsible for the release of products the Authorised Person(s) designated for the purpose. 2.6 The duties of the Authorised Person(s) are described in the national requirements and can be summarised as follows: a) An Authorised Person must ensure that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that country and in accordance with the requirements of the Marketing Authorisation. b) The Authorised Person(s) must meet the qualification requirements laid down in the national legislation, they shall be permanently and continuously at the disposal of the holder of the Manufacturing Authorisation to carry out their responsibilities. c) The responsibilities of an Authorised Person may be delegated, but only to other Authorised Person(s). Annex 16 introduces a new term “Confirmation” which is essentially synonymous with the TGA term “Release for Further Processing” as described in our Guidance for Releasing medicines manufactured at multiple sites. New text is essentially identical to text included in the TGA’s existing Guidance for Releasing medicines manufactured at multiple sites – e.g. refer to “RFS authorised person responsibilities”, “Relying on decisions

New or amended requirements	Remarks
	of other authorised persons" and "RFFP authorised person responsibilities".
1.4.2 The Authorised Person who performs certification of the finished product batch should assume full responsibility for all stages of manufacture of the batch or this responsibility may be shared with other Authorised Persons who have provided confirmation for specified steps in the manufacture and control of a batch. These could be other Authorised Persons who are operating under the same manufacturing authorisation holder or operating under different manufacturing authorisation holders.	New clause – however, identical in intent to existing clause 1.4xv and 1.9(vii) in PE009-15. This new text does not invoke any new or additional expectations. 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products. 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations. Annex 16 uses the existing term "Certification" which is essentially synonymous with the TGA term "Release for Supply" as described in our existing Guidance for Release for Supply. Batch 'Certification' is usually performed by the last Authorised Person in the process of manufacturing the goods. The process ensures that each preceding step in the manufacture of the goods have has been performed in accordance with Good Manufacturing Practice, the Marketing Authorisation, (or CTA) the terms of the Technical quality agreement and any other regulations relevant to the goods. New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. – e.g. refer to "Authorised person responsibilities" and the Guidance for Releasing medicines manufactured at multiple sites – e.g. refer to "RFS authorised person responsibilities"

New or amended requirements	Remarks
1.4.3 Any sharing of responsibilities amongst Authorised Persons in relation to compliance of a batch must be defined in a written agreement. This document should detail responsibility for assessment of the impact any deviation(s) has/have on compliance of the batch with GMP and the MA	New clause – however, identical in intent to existing clause 4.27 and Chapter 7 (e.g., 7.11-7.12) in PE009-15. This new text does not invoke any new or additional expectations. 4.27 Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale of the finished product by the Authorised Person(s). All records should be available to the Authorised Person. A system should be in place to indicate special observations and any changes to critical data. 7.11 A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities and communication processes relating to the outsourced activities. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in related outsourced activities and Good Manufacturing Practice. All arrangements for outsourced activities must be in accordance with regulations in force and the Marketing Authorisation for the product concerned and agreed by both parties. 7.12 The contract should describe clearly which party to the contract has responsibility for conducting each step of the outsourced activity, e.g., knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials, undertaking production and quality controls (including in-process controls, sampling and analysis). New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. – e.g. refer to "Authorised person responsibilities" and the Guidance for Releasing medicines manufactured at multiple sites – e.g. refer to "RFS authorised person responsibilities", "Relying on decisions of other authorised person(s)" and "GMP Agreements" **GMP agreements** Sponsors and manufacturers are required to establish valid GMP agreements to cover all partial manufacturers in the supply chain, in accordance with the PIC/S Guide to GMP. **Valid GMP agreements**

New or amended requirements	Remarks
	Valid GMP agreements are to: • clearly define the RFFP to the next manufacturer in the supply chain, as applicable • clearly establish responsibilities for all GMP related activities at each licenced or certified site. • specify how the RFS authorised person ensures that each batch has been manufactured and checked for compliance with the marketing authorisation, where applicable • include an obligation on all providers of bulk or intermediate product to notify the recipient(s) of any: – significant deviations from the agreed production process – out-of-specification results – non-compliance with GMP – investigations – complaints other matters that should be taken into account by the RFS authorised person.
1.5 For medicinal products manufactured outside the jurisdiction of a National Competent Authority, physical importation and certification are the final stages of manufacturing which precede the transfer to saleable stock of the batch, depending on national law	New section – no direct equivalent in PE009-15. This clause reflects the existing EU model for the importation and batch certification of goods, whereby goods are imported, subjected to further analysis (QC release testing) within the EU, before final certification by a QP. The TGA do not intend to adopt a similar model, and as such this clause would not be applicable in the Australian context, and existing legal framework. As per existing practices, product testing requirements would continue to be dictated by the Marketing Authorisation, Clinical trial Authorisation or equivalent. Batch testing and certification would continue to be performed in accordance with the Marketing Authorisation which may permit testing and Certification (release for supply) by an approved overseas manufacturer.

New or amended requirements	Remarks
	The sections of this Annex relating to the mandatory (re)testing of finished goods following importation would not necessarily apply (unless specifically required by the TGA, e.g., for the testing of certain vaccines before supply). This position would be reflected in official guidance published by the TGA.
1.5.1 The process of certification as described in Section 1 of this Annex, applies to all medicinal products intended to be released within domestic markets, or for export, irrespective of the complexity of the supply chain and the global locations of manufacturing sites involved.	New clause – however, identical in intent to existing clause 1.4xv and 1.9(vii) in PE009-15. This new text does not invoke any new or additional expectations. 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products. 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations. Annex 16 uses the existing term “Certification” which is essentially synonymous with the TGA term “Release for Supply” as described in our existing Guidance for Release for Supply.
1.5.2 In accordance with the principles described in Section 1.4 of this Annex and the law in each jurisdiction, the Authorised Person certifying the finished medicinal product batch may take account of the confirmation by, and share defined responsibilities with, other Authorised Persons in relation to any manufacturing or importation operations taking place at other sites in the same jurisdiction and other manufacturing authorisation holders defined in the relevant MA.	New clause – however, identical in intent to existing clause 4.27 and Chapter 7 (e.g., 7.11-7.12) in PE009-15. This new text does not invoke any new or additional expectations. 4.27 Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale of the finished product by the Authorised Person(s). All records should be available to the Authorised Person. A system should be in place to indicate special observations and any changes to critical data.

New or amended requirements	Remarks
	7.11 A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities and communication processes relating to the outsourced activities. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in related outsourced activities and Good Manufacturing Practice. All arrangements for outsourced activities must be in accordance with regulations in force and the Marketing Authorisation for the product concerned and agreed by both parties. 7.12 The contract should describe clearly which party to the contract has responsibility for conducting each step of the outsourced activity, e.g., knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials, undertaking production and quality controls (including in-process controls, sampling and analysis). New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. – e.g. refer to "Authorised person responsibilities" and the Guidance for Releasing medicines manufactured at multiple sites – e.g. refer to "RFS authorised person responsibilities", "Relying on decisions of other authorised person(s)", "GMP Agreements" and "Delegated Authorised Persons"
1.5.3 Conditions of storage and transport for the batch and the sample, if sent separately, should be taken into account by the Authorised Person before certification of a batch.	New clause – however, identical in intent to existing clauses 1.4(xiv), 4.27 and Chapter 7 (e.g., 7.11-7.12) and Annex 15§6 in PE009-15. This new text does not invoke any new or additional expectations and reflects current expectations regarding Transport Verification. APs performing batch Certification (RFS) or Confirmation (RFFP) are already required to review all data critical to the quality of goods including transportation data. Where Certification is performed domestically following shipment and importation, the AP should review transportation data to ensure that the goods have been shipped and stored in accordance with label requirements. In the case of goods that are certified overseas prior to shipment and importation to Australia, the existing requirements of Chapter 7 and Annex 15§6 require transportation methods to be validated and controlled to ensure goods are shipped and stored in accordance with the label requirements. In these cases the overseas AP may rely on the

New or amended requirements	Remarks
	robustness of the transportation validation to give assurance that goods will be shipped to and stored in Australia under appropriate storage conditions, obviating the requirement to check transportation data for each shipment prior to Certification. References within this clause to 'samples' is restricted to samples for quality control (release testing) purposes that are shipped with an (as yet) unreleased) batch, for the purposes of domestic testing, prior to certification, when required by the MA. 1.4(xiv) Satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life; 4.27 Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale of the finished product by the Authorised Person(s). All records should be available to the Authorised Person. A system should be in place to indicate special observations and any changes to critical data. 7.11 A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities and communication processes relating to the outsourced activities. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in related outsourced activities and Good Manufacturing Practice. All arrangements for outsourced activities must be in accordance with regulations in force and the Marketing Authorisation for the product concerned and agreed by both parties. 7.12 The contract should describe clearly which party to the contract has responsibility for conducting each step of the outsourced activity, e.g., knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials, undertaking production and quality controls (including in-process controls, sampling and analysis). Annex 15§6. VERIFICATION OF TRANSPORTATION 6.1 Finished medicinal products, investigational medicinal products, bulk product and samples should be transported from manufacturing sites in accordance with the conditions defined in the marketing authorisation,

New or amended requirements	Remarks
	the approved label, product specification file or as justified by the manufacturer. New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. – e.g. refer to "Provide authorised person(s) access to information". **Provide authorised person(s) access to information** The manufacturer and, where different, sponsor, are responsible for ensuring the authorised person(s) responsible for RFS have full access to: Transport arrangements and any transport data that is available
1.5.4 The Authorised Person certifying the finished product is responsible for ensuring that each finished medicinal product batch has been manufactured in accordance with GMP and the MA. The Authorised Person is also responsible for ensuring that the finished medicinal product batch has undergone testing required upon importation in accordance with national law.	New clause – however, identical in intent to existing clause 1.4xv and 1.9(vii) in PE009-15. This clause reflects the existing EU model for the importation and batch certification of goods, whereby goods are imported, subjected to further analysis (QC release testing) within the EU, before final certification by a QP. **The TGA do not intend to adopt a similar model, and as such the second sentence in this clause would not be applicable in the Australian context, and existing legal framework. As per existing practices, product testing requirements would continue to be dictated by the Marketing Authorisation, Clinical trial Authorisation or equivalent.** Batch testing and certification would continue to be performed in accordance with the Marketing Authorisation which may permit testing and Certification (release for supply) by an approved overseas manufacturer. The sections of this Annex relating to the mandatory (re)testing of finished goods following importation would not necessarily apply (unless specifically required by the TGA, e.g., for the testing of certain vaccines before supply). This position would be reflected in official guidance published by the TGA.

New or amended requirements	Remarks
	1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products. 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations
1.5.5 If sampling of imported product is necessary, it should be fully representative of the batch. Samples may either be taken after arrival in the jurisdiction of the National Competent Authority, or be taken at the manufacturing site located in another jurisdiction in accordance with national law and a technically justified approach which is documented within the company's quality system. Responsibilities in relation to the sampling should be defined in a written agreement between the sites. Any samples taken outside the National Competent Authority jurisdiction should be shipped under equivalent transport conditions as the batch that they represent.	New clause – however, similar in intent to existing clause 1.4xv and 1.9(vii) in PE009-15. The clause reflects the existing EU model for the importation and batch certification of goods, whereby goods are imported, subjected to further analysis (QC release testing) within the EU, before final certification by a QP. **The TGA do not intend to adopt a similar model (i.e., mandatory testing following importation), and as such this clause would only be applicable in the circumstances where testing following importation is a requirement of the MA, CTA or other regulatory requirement. Where sampling for analysis following importation is required, manufacturers should hold an appropriate justification for the sampling plan, noting that this is an existing requirement of PE009-15 clause 6.12.** Batch testing and certification would continue to be performed in accordance with the Marketing Authorisation which may permit testing and Certification (release for supply) by an approved overseas manufacturer. The sections of this Annex relating to the mandatory (re)testing of finished goods following importation would not necessarily apply (unless specifically required by the TGA, e.g., for the testing of certain vaccines before supply). This position would be reflected in official guidance published by the TGA.

New or amended requirements	Remarks
	1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products. 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations. 6.12 Samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g., beginning or end of a process). The sampling plan used should be appropriately justified and based on a risk management approach.
1.5.6 Where sampling is performed at a manufacturing site located in another jurisdiction, the technical justification should include a formal Quality Risk Management process to identify and manage any risks associated with this approach. This should be fully documented and include at least the following elements: I. Audit of the manufacturing activity including any sampling activity in the other jurisdiction and evaluation of subsequent transportation steps of both the batch and samples to ensure that the samples are representative of the imported batch. II. A comprehensive scientific study, including data to support any conclusions that samples taken in the other jurisdiction are representative of the batch after importation. This study should at least include: • description of the sampling process in the other jurisdiction;	New clause – however, similar in intent to existing clause PE009-15 clause 6.12. The clause reflects the existing EU model for the importation and batch certification of goods, whereby goods are imported, subjected to further analysis (QC release testing) within the EU, before final certification by a QP. **The TGA do not intend to adopt a similar model (i.e., Mandatory testing following importation), and as such this clause would only be applicable in the circumstances where testing following importation is a requirement of the MA, CTA or other regulatory requirement. Where sampling for analysis following importation is required, manufacturers should hold an appropriate justification for the sampling plan.** Batch testing and certification would continue to be performed in accordance with the Marketing Authorisation which may permit testing and Certification (release for supply) by an approved overseas manufacturer.

New or amended requirements	Remarks
• description of the transported conditions of the sample and the imported batch. Any differences should be justified; • comparative analysis of samples taken in the other jurisdiction and samples taken after importation; and • consideration of the time interval between sampling and importation of the batch and generation of data to support appropriate defined limits. III. Provision for random periodic analysis of samples taken after importation to justify ongoing reliance on samples taken in another jurisdiction. IV. A review of any unexpected result or confirmed out of specification result. These may have implications for reliance on sampling performed at a manufacturing site located in another jurisdiction and should be notified to the National Competent Authority for the site where certification is performed. Such an occurrence should be regarded as a potential quality defect and investigated in line with the guidance in Chapter 8 of the PIC/S GMP Guide, Part I.	The sections of this Annex relating to the mandatory (re)testing of finished goods following importation would not necessarily apply (unless specifically required by the TGA, e.g., for the testing of certain vaccines before supply). This position would be reflected in official guidance published by the TGA. 6.12 Samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g., beginning or end of a process). The sampling plan used should be appropriately justified and based on a risk management approach.
1.5.7 Different imported finished product batches may originate from the same bulk product batch. If testing upon importation is required (see 1.5.4), the Authorised Person(s) certifying the different finished product batches may base their decision on the quality control testing of the first imported finished batch provided that a justification has been documented based on Quality Risk Management principles. This should take into account the provisions of paragraph 1.5.6 in relation to reliance on any samples taken in another jurisdiction. Evidence should be available to ensure that the integrity and identity of the imported finished product batch has been established through documented verification of at least the following: I. relevant requirements for storage of the bulk product prior to packaging have been satisfied; II. the finished product batch has been stored and transported under the required conditions;	New clause – no equivalent clause in PE009-15. This clause provides new guidance; however, no additional mandatory expectations apply. The clause reflects the existing EU model for the importation and batch certification of goods, whereby goods are imported, subjected to further analysis (QC release testing) within the EU, before final certification by a QP. **The TGA do not intend to adopt a similar model (i.e., mandatory testing following importation), and as such this clause would only be applicable in the circumstances where testing following importation is a requirement of the MA, CTA or other regulatory requirement. Where sampling for analysis following importation is required, manufacturers should hold an appropriate justification for the sampling plan.** Batch testing and certification would continue to be performed in accordance with the Marketing Authorisation which may permit testing

New or amended requirements	Remarks
III. the consignment has remained secure and there is no evidence of tampering during storage or transportation; IV. correct identification of the product has been established; and V. the sample(s) tested are representative of all finished product batches derived from the bulk batch.	and Certification (release for supply) by an approved overseas manufacturer. This specific clause would allow greater flexibility to APs performing certification (RFS) in that the certification of multiple sub-lots of the same bulk batch may be performed based on evidence from one representative lot, (e.g., QC analysis reports, batch records, deviations reports etc.) This position would be reflected in official guidance published by the TGA.
1.6 The Authorised Person must ensure that the following operational responsibilities are fulfilled prior to certification of a batch: I. Certification is permitted under the terms of any authorisation by the national competent authority. II. Any additional duties and requirements of national law are complied with. III. Certification is recorded in accordance with this Annex and in accordance to national law	New clause – however, identical in intent to existing clause 1.4xv and 1.9(vii) in PE009-15. 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products. 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations. 6.12 Samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g., beginning or end of a process). The sampling plan used should be appropriately justified and based on a risk management approach. New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Duties of an authorised person performing RFS".

New or amended requirements	Remarks
1.7 In addition, the Authorised Person has responsibility for ensuring points 1.7.1 to 1.7.21 are secured. These tasks may be delegated to appropriately trained personnel or third parties. It is recognised that the Authorised Person will need to rely on the pharmaceutical quality system and the Authorised Person should have on-going assurance that this reliance is well founded.	New clause – however, identical in intent to existing clause 2.6, 2.11 and Chapter 7 in PE009-15. 2.6 The duties of the Authorised Person(s) are described in the national requirements and can be summarised as follows: a) An Authorised Person must ensure that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that country and in accordance with the requirements of the Marketing Authorisation; b) The Authorised Person(s) must meet the qualification requirements laid down in the national legislation, they shall be permanently and continuously at the disposal of the holder of the Manufacturing Authorisation to carry out their responsibilities; c) The responsibilities of an Authorised Person may be delegated, but only to other Authorised Person(s). 2.11 Besides the basic training on the theory and practice of the Pharmaceutical Quality System and Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programmes should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept. **PRINCIPLE – Chapter 7 -0 Outsourced Activities** Any activity covered by the GMP Guide that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the roles and responsibilities of each party. The Pharmaceutical Quality System of the Contract Giver must clearly state the way that the Authorised Person certifying each batch of product for release exercises his/her full responsibility.

New or amended requirements	Remarks
	New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Duties of an authorised person performing RFS".
1.7.1. All activities associated with manufacture and testing of the medicinal product have been conducted in accordance with the principles and guidelines of GMP.	New clause – however, identical in intent to existing clause 1.4xv and 1.9(vii) in PE009-15. 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products; 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations; 6.12 Samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g., beginning or end of a process). The sampling plan used should be appropriately justified and based on a risk management approach. New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Duties of an authorised person performing RFS".
1.7.2 The entire supply chain of the active substance and medicinal product up to the stage of certification is documented and available for the Authorised Person. This should include the manufacturing sites of the starting materials and packaging materials for the medicinal product and any other materials deemed critical through a risk assessment of the manufacturing process. The document should preferably be in the format of a comprehensive diagram, where each party, including subcontractors of	New clause – however, identical in intent to existing clause 1.10, 4.27 and 5.29 in PE009-15. These existing clauses require all records to be made available to the AP, (4.27) the supply chain to be defined, qualified and monitored (5.29). Clause 1.10 requires this information to be provided to the AP via the Product Quality Review processes.

New or amended requirements	Remarks
critical steps such as the sterilisation of components and equipment for aseptic processing, are included.	All of this information should already be available to the Authorised Person(s). 1.10 Regular periodic or rolling quality reviews of all authorised medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, considering previous reviews, and should include at least: (i) A review of starting materials including packaging materials used in the product, especially those from new sources and in particular the review of supply chain traceability of active substances. 4.27 Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale of the finished product by the Authorised Person(s). All records should be available to the Authorised Person. A system should be in place to indicate special observations and any changes to critical data. 5.29 For the approval and maintenance of suppliers of active substances and excipients, the following is required: **Active substances** Supply chain traceability should be established and the associated risks, from active substance starting materials to the finished medicinal product, should be formally assessed and periodically verified. Appropriate measures should be put in place to reduce risks to the quality of the active substance. The supply chain and traceability records for each active substance (including active substance starting materials) should be available and be retained by the manufacturer of the medicinal product. **Excipients** Excipients and excipient suppliers should be controlled appropriately based on the results of a formalised quality risk assessment in accordance with the PIC/S Guideline PI 045-1 ‘Guidelines on the

New or amended requirements	Remarks
	formalised risk assessment for ascertaining the appropriate Good Manufacturing Practice for excipients of medicinal products for human use'. New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Provide authorised person(s) access to information". **Provide authorised person(s) access to information** The manufacturer and, where different, sponsor, are responsible for ensuring the authorised person(s) responsible for RFS have full access to: • all aspects of the marketing authorisation, including details in the ARTG and other matters agreed on in writing between TGA and the Australian sponsor • all relevant aspects of the manufacturers and manufacturing steps: – for TGA-licensed manufacturers: ▪ the licence to manufacture therapeutic goods ▪ all authorisations and conditions under the licence ▪ the steps in manufacture granted under section 38, Therapeutic Goods Act 1989 and conditions of licences as imposed under section 40, Therapeutic Goods Act 1989 – for overseas manufacturers: ▪ the TGA GMP certificate and GMP clearances ▪ all authorisations and conditions, as imposed under sections 25(1)(g), 26(1)(g) and 26A(3), Therapeutic Goods Act 1989 – the PIC/S Guide to GMP as specified in the current manufacturing principles – default standards under section 10 of the Therapeutic Goods Act 1989 – all applicable Therapeutic Goods Orders

New or amended requirements	Remarks
	• relevant batch certificate of analysis • complete and reviewed PQRs • ongoing stability data and updates • significant batch deviations • approved artwork specifications • significant changes to manufacturing processes and ongoing validation: – product release and expiry specifications – marketplace feedback or signals – complaints, recalls, adverse events – supply chain details and approved manufacturers and suppliers (all contracts) • Transport arrangements and any transport data that is available Responsibilities for providing authorised person(s) access to information when performing confirmation (RFFP) are covered in the Guidance for Releasing medicines manufactured at multiple sites
1.7.3 All audits of sites involved in the manufacture and the testing of the medicinal products and in the manufacture of the active substance have been carried out and that the audit reports are available to the Authorised Person performing the certification.	New clause – no direct equivalent clause in PE009-15. This new clause requires the AP performing Certification (RFS) to have access to the audit reports for all manufacturers within the supply chain. New text is similar in intent to text included in the TGA's existing Guidance for Release for Supply. Refer to "Duties of an authorised person performing RFS". However, Annex 16 specifically requires audit reports to be made available to the AP. **For registered medicines:** Audit reports for the API manufacturer are already a mandatory requirement as per Chapter 5 – Qualification of supplier of Starting Materials (5.29) and should be available and supplied to the AP. Audits conducted by the Contract Giver (and audit reports) for manufacturers in the supply chain are already expected as per Chapter

New or amended requirements	Remarks
	7 clauses 7.4.1 and 7.14. These are in addition to verification of Certification by a National Competent Authority. This clause now requires these reports to be made available to the AP. **For listed medicines:** Current guidance regarding Supplier assessment, approval and qualification for listed and complementary medicines would continue to apply for the control of starting materials used in the manufacture of listed and complementary medicines. The current supplier approval processes (questionnaires, testing of deliveries etc) would be considered sufficient 'audit' for listed medicines API manufacturer There is currently no expectation that additional audits will be conducted of listed medicine contract manufacturers in the supply chain, in addition to those inspections conducted by TGA or other approved regulator. It is deemed acceptable evidence for clause 7.4.1 that the contract manufacturer holds a TGA licence or certificate **for the relevant steps in manufacture**. Clause 7.14 states that an audit should be permitted. It doesn't mandate that it must occur. Prior to outsourcing activities, the Contract Giver is responsible for assessing the legality, suitability and the competence of the Contract Acceptor to carry out successfully the outsourced activities. The Contract Giver is also responsible for ensuring by means of the contract that the principles and guidelines of GMP as interpreted in this Guide are followed. The contract should permit the Contract Giver to audit outsourced activities, performed by the Contract Acceptor or their mutually agreed subcontractors. **Duties of an authorised person performing RFS** Before release of a production batch for supply, the authorised person is responsible for ensuring:

New or amended requirements	Remarks
	• all necessary steps have been completed in accordance with the pharmaceutical quality system (PQS), regardless of how many sites are involved GMP internal audits and supplier audit systems are operational **GMP Release for supply guidance is also being prepared for medicines that are not registered medicines to meet this clause.**
1.7.4 All sites of manufacture, analysis and certification are compliant with the terms of the MA for the intended jurisdiction.	New clause – however, identical in intent to existing clause 1.4xv and 1.9(vii) in PE009-15. 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products. 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations. New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Duties of an authorised person performing RFS" and "Relevant Authorisations and Standards"
1.7.5 All manufacturing activities and testing activities are consistent with those described in the MA.	New clause – however, identical in intent to existing clause 1.4xv and 1.9(vii) in PE009-15. This clause reflects current requirements that the APs performing Certification (RFS) or Confirmation (RFFP) have access to the relevant sections of the Marketing Authorisation, (refer also Clause 7.2.4). 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing

New or amended requirements	Remarks
	Authorisation and any other regulations relevant to the production, control and release of medicinal products. 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations; 7.4.2 The Contract Giver should provide the Contract Acceptor with all the information and knowledge necessary to carry out the contracted operations correctly in accordance with regulations in force, and the Marketing Authorisation for the product concerned. New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Duties of an authorised person performing RFS" and "Relevant Authorisations and Standards"
1.7.6 The source and specifications of starting materials and packaging materials used in the batch are compliant with the MA. Supplier quality management systems are in place that ensures only materials of the required quality have been supplied.	New clause – however, identical in intent to existing clause 1.4xv and 1.9(vii) in PE009-15. This clause reflects current requirements that the APs performing Certification (RFS) or Confirmation (RFFP) have access to the relevant sections of the Marketing Authorisation, (refer also Clause 7.2.4). 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products. 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations. 7.4.2 The Contract Giver should provide the Contract Acceptor with all the information and knowledge necessary to carry out the contracted operations correctly in accordance with regulations in force, and the Marketing Authorisation for the product concerned. New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Duties of an authorised person performing RFS" and "Relevant Authorisations and Standards"

New or amended requirements	Remarks
1.7.7 For medicinal products, the active substances have been manufactured in accordance with GMP and, where required, distributed in accordance with Good Distribution Practice (GDP) for Active Substances.	New clause – however, identical in intent to existing clause 1.10, 4.27 and 5.29 in PE009-15. These existing clauses require all records to be made available to the AP, (4.27) the supply chain to be defined, qualified and monitored (5.29). Clause 1.10 requires this information to be provided to the AP via the Product Quality Review processes. The expected extent of GDP for Active substances in the case of Australia would be limited to the application of the above clauses and not necessarily any other official good distribution practice guideline. All of this information should already be available to the Authorised Person(s). 1.10 Regular periodic or rolling quality reviews of all authorised medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, considering previous reviews, and should include at least: (i) A review of starting materials including packaging materials used in the product, especially those from new sources and in particular the review of supply chain traceability of active substances. 4.27 Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale of the finished product by the Authorised Person(s). <u>All records should be available to the Authorised Person.</u> A system should be in place to indicate special observations and any changes to critical data. 5.29 For the approval and maintenance of suppliers of active substances and excipients, the following is required: **Active substances** Supply chain traceability should be established and the associated risks, from active substance starting materials to the finished medicinal product, should be formally assessed and periodically verified.

New or amended requirements	Remarks
	Appropriate measures should be put in place to reduce risks to the quality of the active substance. The supply chain and traceability records for each active substance (including active substance starting materials) should be available and be retained by the manufacturer of the medicinal product. **Excipients** Excipients and excipient suppliers should be controlled appropriately based on the results of a formalised quality risk assessment 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'. New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Provide authorised person(s) access to information".
1.7.8 Active substances used in the manufacture of medicinal products for human use shall only be imported if the active substances comply with the following requirements: i. the active substances have been manufactured in accordance with standards of GMP and, where applicable, distributed in accordance with Good Distribution Practice according to national law; and **ii**. there is evidence of GMP compliance of the manufacturer of the active substance in accordance to national law.	New clause – however, identical in intent to existing clause 1.10, 4.27 and 5.29 in PE009-15. These existing clauses require all APIs to be provided by suitably certified/authorised suppliers, records to be made available to the AP, (4.27) the supply chain to be defined, qualified and monitored (5.29). Clause 1.10 requires this information to be provided to the AP via the Product Quality Review processes. The expected extent of GDP for Active substances in the case of Australia would be limited to the application of the above clauses and not necessarily any other official good distribution practice guideline. All of this information should already be available to the Authorised Person(s). **For listed medicines:** Current guidance regarding Supplier assessment, approval and qualification for listed and complementary medicines would continue to apply for the control of starting materials used in the manufacture of listed and complementary medicines. Confirmation of the suitability of active substances and suppliers may be provided by APs within the supply chain during batch Confirmation (RFFP).

New or amended requirements	Remarks
	1.10 Regular periodic or rolling quality reviews of all authorised medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, considering previous reviews, and should include at least: (i) A review of starting materials including packaging materials used in the product, especially those from new sources and in particular the review of supply chain traceability of active substances 4.27 Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale of the finished product by the Authorised Person(s). All records should be available to the Authorised Person. A system should be in place to indicate special observations and any changes to critical data. 5.29 For the approval and maintenance of suppliers of active substances and excipients, the following is required: **Active substances** Supply chain traceability should be established and the associated risks, from active substance starting materials to the finished medicinal product, should be formally assessed and periodically verified. Appropriate measures should be put in place to reduce risks to the quality of the active substance. The supply chain and traceability records for each active substance (including active substance starting materials) should be available and be retained by the manufacturer of the medicinal product. New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Provide authorised person(s) access to information" and "Overseas Manufacturers" **Overseas manufacturers** We recognise release for supply by an authorised person located at an overseas manufacturer, provided all of the following conditions are met:

New or amended requirements	Remarks
	• the manufacturing steps performed are covered by a current TGA GMP certificate and/or GMP clearance(s), specifically their authorisations and conditions, as imposed under sections 25(1)(g), 26(1)(g) and 26A(3) of the Therapeutic Goods Act 1989 • responsibilities for RFS are clearly defined in either: – a GMP agreement between the contract giver (which can be the sponsor or a manufacturer) and the contract acceptor (RFS manufacturer) OR, if both are part of one multinational organisation and are covered by the same corporate quality system: – an arrangement within the corporate quality system – nominated in the ARTG entry that RFS is being performed by the overseas manufacturer **The position would be reflected in official guidance published by the TGA.**
1.7.9 The excipients used to manufacture a medicinal product have been manufactured with an appropriate good manufacturing practice. Where applicable, this shall be in accordance with PI 045-1: Guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use.	New clause – however, identical in intent to existing clause 1.10, 4.27 and 5.29 in PE009-15. These existing clauses require all APIs to be provided by suitably certified/authorised suppliers, records to be made available to the AP, (4.27) the supply chain to be defined, qualified and monitored (5.29). Clause 1.10 requires this information to be provided to the AP via the Product Quality Review processes. All of this information should already be available to the Authorised Person(s). **For listed medicines:** Current guidance regarding Supplier assessment, approval and qualification for listed and complementary medicines would continue to apply for the control of starting materials used in the manufacture of listed and complementary medicines. Confirmation of the suitability of excipient and suppliers may be provided by APs within the supply chain during batch Confirmation (RFFP).

New or amended requirements	Remarks
	1.10 Regular periodic or rolling quality reviews of all authorised medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least: (i) A review of starting materials including packaging materials used in the product, especially those from new sources and in particular the review of supply chain traceability of active substances; 4.27 Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale of the finished product by the Authorised Person(s). All records should be available to the Authorised Person. A system should be in place to indicate special observations and any changes to critical data. 5.29 For the approval and maintenance of suppliers of active substances and excipients, the following is required: **Excipients** Excipients and excipient suppliers should be controlled appropriately based on the results of a formalised quality risk assessment 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'. New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Provide authorised person(s) access to information"
1.7.10 When relevant, the TSE (Transmissible Spongiform Encephalopathy) status of all materials used in batch manufacture is compliant with the terms of the MA	New clause – however, reflects existing TGA guidelines regarding TSEs. Manufacturers are already required to 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

New or amended requirements	Remarks
	available for inspection. This information now needs to be provided to the AP performing Confirmation (RFFP) or Certification (RFS).
1.7.11 All records are complete and endorsed by appropriate personnel. All required in-process controls and checks have been made.	New clause – however, identical in intent to existing Principle of Chapter 4, clauses 4.20, 4.21 and 6.3 (and others) in PE009-15. Principle – Chapter 4 - Documentation The main objective of the system of documentation utilised must be to establish, control, monitor and record all activities which directly or indirectly impact on all aspects of the quality of medicinal products. 4.20 A Batch Processing Record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions, and should contain the following information: i) Approval by the person responsible for the processing operations. 4.21 A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions. i) Approval by the person responsible for the packaging operations. 6.3 Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack. New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Batch records"
1.7.12 All manufacturing and testing processes remain in the validated state. Personnel are trained and qualified as appropriate.	New clause – however, identical in intent to existing clause 1.4xv, 1.9(vii) and 1.10 in PE009-15. This clause reflects current requirements that the APs performing Certification (RFS) or Confirmation (RFFP) have knowledge of the validation status of the manufacturing and testing processes, and training of personnel. The PQR should provide this information to the APs allowing them to verify the validation status of processes and methods. In addition, clause 7.4.2 requires the Contract Giver to make all relevant information available to the Contract

New or amended requirements	Remarks
	Acceptor, therefore the validation status of methods and processes should be available and understood by the APs. 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products; 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations; 1.10 Regular periodic or rolling quality reviews of all authorised medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least: (ii) A review of critical in-process controls and finished product results; (iv) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken; (v) A review of all changes carried out to the processes or analytical methods; (xi) The qualification status of relevant equipment and utilities, e.g., HVAC, water, compressed gases, etc; 7.4.2 The Contract Giver should provide the Contract Acceptor with all the information and knowledge necessary to carry out the contracted operations correctly in accordance with regulations in force, and the Marketing Authorisation for the product concerned. New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Validating Processes"

New or amended requirements	Remarks
1.7.13 Finished product quality control (QC) test data complies with the Finished Product Specification described in the MA, or where authorised, the Real Time Release Testing programme.	New clause – however, identical in intent to existing clause 1.4xv, 1.9(vii) in PE009-15. 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products; 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations; New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Batch records"
1.7.14 Any regulatory post-marketing commitments relating to manufacture or testing of the product have been addressed. On-going stability data continues to support certification.	New clause – however, identical in intent to existing clause 1.4xv, 1.9(vii) and 1.10 in PE009-15. This new clause reflects the existing expectation that the APs have appropriate visibility of the MA, PQR and ongoing stability in order to support the continued Certification (RFS) of the goods. 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products; 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations; 1.10 Regular periodic or rolling quality reviews of all authorised medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:

New or amended requirements	Remarks
	(vii) A review of the results of the stability monitoring programme and any adverse trends; (x) For new Marketing Authorisations and variations to Marketing Authorisations, a review of post-marketing commitments;
1.7.15 The impact of any change to product manufacturing or testing has been evaluated and any additional checks and tests are complete.	New clause – however, identical in intent to existing clause 1.4xv, 1.9(vii) and 1.10 in PE009-15. This new clause reflects the existing expectation that the APs have appropriate visibility of the MA, PQR and ongoing stability in order to support the continued Certification (RFS) of the goods. 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products; 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations; 1.10 Regular periodic or rolling quality reviews of all authorised medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least: (iv) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken; (v) A review of all changes carried out to the processes or analytical methods; (vi) A review of Marketing Authorisation variations submitted, granted or refused, including those for third country (export only) dossiers;

New or amended requirements	Remarks
	New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Deviations and Changes" **Deviations and changes** For all medicines: • Check that any significant deviations or planned changes in production or quality control have been authorised by the persons responsible in accordance with a defined system. • Check that the TGA has authorised any changes requiring variation to the: – marketing authorisation, for medicines in the ARTG – manufacturing licence, for TGA-licensed manufacturers GMP clearance, for overseas manufacturers
1.7.16 All investigations pertaining to the batch being certified (including out of specification and out of trend investigations) have been completed to a sufficient level to support certification.	New clause – however, identical in intent to existing clause 1.4(ix), (xiv), Clause 1.9(vi). No change to interpretation. 1.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that: (ix) The results of product and processes monitoring are taken into account in batch release, in the investigation of deviations, and, with a view to taking preventive action to avoid potential deviations occurring in the future; (xiv) An appropriate level of root cause analysis should be applied during the investigation of deviations, suspected product defects and other problems. 1.9 Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. The basic requirements of Quality Control are that:

New or amended requirements	Remarks
	(vi) Records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures; New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Deviations and Changes"
1.7.17 A batch should not be certified if there are any on-going complaints, investigations or recalls that may have impact on the batch.	New clause – however, identical in intent to existing clause 1.9(vii) in PE009-15. This clause explicitly states that batch certification cannot be performed where quality issues exist. 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations;
1.7.18 The required technical agreements are in place.	New clause however identical in requirements as per Part 1 Chapter 7
1.7.19 The self-inspection programme is active and current.	New clause – however, identical in intent to existing clause 1.4(xvii), and clause 9.1 of PE009-15.). No change to interpretation. 1.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that: (xvii) There is a process for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Pharmaceutical Quality System. 9.1. Personnel matters, premises, equipment, documentation, production, quality control, distribution of the medicinal products, arrangements for dealing with complaints and recalls, and self inspection, should be examined at intervals following a pre-arranged programme to verify their conformity with the principles of Quality Assurance. New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Acceptability of PQS".
1.7.20 The appropriate arrangements for distribution and shipment are in place	New section – however, identical in intent to existing clause 1.4xiv and Annex 15§6 in PE009-15. Existing arrangements between Manufacturers and Sponsors (as defined by Agreements/Contracts as

New or amended requirements	Remarks
	per Chapter 7 of the GMP Guide) will continue to be the method by which compliance transportation will be demonstrated. This new text does not invoke any new or additional expectations. 1.4(xiv) Satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life; Annex 15§6. VERIFICATION OF TRANSPORTATION 6.1 Finished medicinal products, investigational medicinal products, bulk product and samples should be transported from manufacturing sites in accordance with the conditions defined in the marketing authorisation, the approved label, product specification file or as justified by the manufacturer. New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Batch records"
1.7.21 Where required in national law, safety features have been affixed to the packaging enabling wholesale distributors and persons authorised or entitled to supply medicinal products to the public to: i. verify the authenticity of the medicinal product; ii. identify individual packs; and iii. verify, via a device, of whether the outer packaging has been tampered with.	New clause – however, identical in intent to existing clause 1.4xv, 1.9(vii) of PE009-15. These existing requirements already require the AP to ensure that any regulations or standards applicable to the Goods. The MA for goods included in the ARTG will already include the need to apply appropriate safety features. Safety features for exported goods will be dictated by the relevant MA. In accordance with Section 10 of the Therapeutic Goods Act 1989, TGO 106 – Standard for the Serialisation and data matrix codes on medicines may be applicable to the goods. In addition, the TGA's Code of practice for tamper-evident packaging of therapeutic goods may also apply. In the case where safety features are required, the APs should verify that these have been appropriately applied to the goods prior to Confirmation (RFFP) or Certification (RFS). 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products;

New or amended requirements	Remarks
	1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations;
1.8 For certain products, special guidance may apply, such as PIC/S GMP Guide Annex 2: Manufacture of Biological active substances and Medicinal Products for Human Use, and Annex 3: Manufacture of Radiopharmaceuticals	New clause – no direct equivalent clause PE009-15. Non-instructive clause providing guidance only.
1.9 In the case of parallel importation and parallel distribution, any repackaging operation carried out on a batch which has already been released must be approved by the competent authority of the intended market, as applicable under national law.	New clause – no direct equivalent clause PE009-15. **The parallel importation of goods is not permitted under the Australian regulatory framework. Therefore this clause is not applicable and will not apply in the Australian context.** This position would be reflected in official guidance published by the TGA.
1.9.1 Prior to certification of a repacked batch the Authorised Person should confirm compliance with national requirements for parallel importation and rules for parallel distribution.	New clause – no direct equivalent clause PE009-15. **The parallel importation of goods is not permitted under the Australian regulatory framework. Therefore this clause is not applicable and will not apply in the Australian context.** This position would be reflected in official guidance published by the TGA.
1.9.2 The Authorised Person, who is responsible for the certification of the batch in the MA of the repackaged finished product, certifies that the repackaging has been performed in accordance with the relevant authorisation pertaining to the repackaged product and GMP.	New clause – no direct equivalent clause PE009-15. **The parallel importation of goods is not permitted under the Australian regulatory framework. Therefore this clause is not applicable and will not apply in the Australian context**. This position would be reflected in official guidance published by the TGA.
1.10 Recording of Authorised Person certification: 1.10.1 The certification of a medicinal product is recorded by the Authorised Person in the document provided for that purpose. The record should show that each production batch satisfies the following provisions:	New clause – however, identical in intent to existing clause 1.4xv, 1.9(vii) of PE009-15. This new clause provides specific instructions of how certification should be recorded and is limited to minor administrative tasks only.

New or amended requirements	Remarks
i. Each batch of medicinal products has been manufactured and checked in compliance with national law and in accordance with the requirements of the marketing authorisation.	
ii. In the case of medicinal products coming from another jurisdiction each production batch has a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation. Such testing is also performed in the importing country where required in national law.	New clause – however, identical in intent to existing clause 1.4xv and 1.9(vii) in PE009-15. This clause reflects the existing EU model for the importation and batch certification of goods, whereby goods are imported, subjected to further analysis (QC release testing) within the EU, before final certification by a QP. **The TGA do not intend to adopt a similar model, and as such the second sentence in this clause would not be applicable in the Australian context, and existing legal framework. As per existing practices, product testing requirements would continue to be dictated by the Marketing Authorisation, Clinical trial Authorisation or equivalent.** Batch testing and certification would continue to be performed in accordance with the Marketing Authorisation which may permit testing and Certification (release for supply) by an approved overseas manufacturer. The sections of this Annex relating to the mandatory (re)testing of finished goods following importation would not necessarily apply (unless specifically required by the TGA, e.g., for the testing of certain vaccines before supply). This position would be reflected in official guidance published by the TGA. 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products; 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations;
iii. In the case of medicinal products imported from another jurisdiction, where appropriate arrangements have been made with the exporting jurisdiction to ensure that	New clause – however, identical in intent to existing clause 1.4xv and 1.9(vii) in PE009-15. This clause reflects the existing EU model for the

New or amended requirements	Remarks
the manufacturer of the medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the national competent authority, and to ensure that the controls referred to under point (ii) have been carried out in the exporting country, the authorised person may be relieved of responsibility for carrying out those controls.	importation and batch certification of goods, whereby goods are imported, subjected to further analysis (QC release testing) within the EU, before final certification by a QP. **The TGA do not intend to adopt a similar model, and as such the second sentence in this clause would not be applicable in the Australian context, and existing legal framework. As per existing practices, product testing requirements would continue to be dictated by the Marketing Authorisation, Clinical trial Authorisation or equivalent.** Batch testing and certification would continue to be performed in accordance with the Marketing Authorisation which may permit testing and Certification (release for supply) by an approved overseas manufacturer. The sections of this Annex relating to the mandatory (re)testing of finished goods following importation would not necessarily apply (unless specifically required by the TGA, e.g., for the testing of certain vaccines before supply). This position would be reflected in official guidance published by the TGA. 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products; 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations; New text relating to the verification of test reports is essentially identical to text included in the TGA's existing Guidance for Release for Supply. Refer to "Duties of an authorised person performing RFS".
iv. The record must be kept up to date as operations are carried out and must remain at the disposal of the agents of the National Competent Authority the longer of	New clause – however, identical in intent to existing clause 4.11 in PE009-15.

New or amended requirements	Remarks
one year after expiry of the batch or five years unless otherwise specified in national law.	4.11 Specific requirements apply to batch documentation which must be kept for one year after expiry of the batch to which it relates or at least five years after certification of the batch by the Authorised Person, whichever is the longer.
1.10.2 The control report referred to in 1.10.1 or another proof for release for sale, supply, or export, based on an equivalent system, should be made available for the batch in order to be exempted from further controls when entering another National Competent Authority jurisdiction.	New clause – no equivalent clause in PE009-15. This clause requires the AP to provide the record of certification (Control Report, or equivalent) to be provided with the batch, which is common practice, in order to avoid additional controls upon importation. While there are no anticipated issues for goods imported into Australia, this clause may apply to goods exported from Australia, and the reliance on control reports by other countries would be at the discretion of the importing jurisdiction. MAHs should already be aware of these requirements to permit export.

Annex 16 – 2. Relying on GMP assessments by third parties e.g., audits

New or amended requirements	Remarks
2. RELYING ON GMP ASSESSMENTS BY THIRD PARTIES, E.G. AUDITS In some cases the Authorised Person will rely on the correct functioning of the pharmaceutical quality system of sites involved in the manufacture of the product and this may be derived from audits conducted by third parties.	New clause – no direct equivalent clause in PE009-15. This new clause requires the AP performing Certification (RFS) to have access to the audit reports for all manufacturers within the supply chain. This section outlines the principles that may be applied in relying upon audits conducted by third parties. Reliance upon third party audits is not mandatory, but these sections would apply where this practice occurs. New text is similar in intent to text included in the TGA's existing Guidance for Release for Supply. Refer to "Duties of an authorised person performing RFS". However, Annex 16 specifically requires audit reports to be made available to the AP. **Duties of an authorised person performing RFS** Before release of a production batch for supply, the authorised person is responsible for ensuring: • all necessary steps have been completed in accordance with the pharmaceutical quality system (PQS), regardless of how many sites are involved

New or amended requirements	Remarks
	GMP internal audits and supplier audit systems are operational
2.1 Relying on assessment by third parties, e.g., audits should be in accordance with Chapter 7 of the PIC/S GMP Guide in order to appropriately define, agree and control any outsourced activity	New clause – no direct equivalent in PE009-15; however, the principles of Chapter 7 are identical. Principle – Chapter 7 – Outsourced Activities Any activity covered by the GMP Guide that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality.
2.2 Special focus should be given to the approval of audit reports: **i.** The audit report should address general GMP requirements, as for example the quality management system, all relevant production and quality control procedures related to the supplied product, e.g., active substance manufacturing, quality control testing, primary packaging, etc. All audited areas should be accurately described resulting in a detailed report of the audit. **ii.** It should be determined whether the manufacture and quality control of the active substance and medicinal product complies with GMP or in case of manufacture in another jurisdiction, GMP at least equivalent to that of each National Competent Authority. **iii.** In case of outsourced activities compliance with the MA should be verified. **iv.** The Authorised Person should ensure that a written final assessment and approval of third party audit reports have been made. The Authorised Person should have access to all documentation which facilitates review of the audit outcome and continued reliance on the outsourced activity. **v.** Outsourced activities with critical impact on product quality should be defined in accordance with the principles of Quality Risk Management as described in Annex 20 of the PIC/S GMP Guide. According to this, the Authorised Person should be aware of the outcome of an audit with critical impact on the product quality before certifying the relevant batches. **vi.** Repeated audits should be performed in accordance with the principles of Quality Risk Management.	New clause – no direct equivalent in PE009-15. This section outlines the principles that may be applied in relying upon audits conducted by third parties. Reliance upon third party audits is not mandatory, but these sections would apply where this practice occurs. These clauses provide additional guidance as to the conduct and management of third party external audits, incorporating existing principles from the PIC/S Guide to GMP PE009-15, including: - Reporting of audits (similar in intent to clause 9.3) - Verification of appropriate compliance with GMP (identical in intent to clause 5.27 & 7.4) - Management of outsourced activities and assessment of the suitability and compliance of service providers (identical in intent to clause 5.27 & 7.4) - Application of Quality Risk Management to outsourced activities (identical in intent to clause 1.12/1.13 & 7.4) **For listed medicines:** The AP must hold evidence that each contract manufacturer used in the manufacture of a particular batch holds a TGA licence or certificate **for the relevant steps in manufacture** undertaken. **The position would be reflected in official guidance published by the TGA.**

Table 1 Annex 16 – 3. Handling of deviations

New or amended requirements	Remarks
3 HANDLING OF UNEXPECTED DEVIATIONS Provided registered specifications for active substances, excipients, packaging materials and medicinal products are met, an Authorised Person may consider confirming compliance or certifying a batch where an unexpected deviation concerning the manufacturing process and/or the analytical control methods from details contained within the MA and/or GMP has occurred. The deviation should be thoroughly investigated and the root cause corrected. This may require the submission of a variation to the MA for the continued manufacture of the product.	New clause – however, identical in intent to existing clause 1.4(ix), (xiv), Clause 1.9(vi). In addition to these existing requirements, this new clause refers to the potential need to submit a variation to the MA to the TGA or seek authorisation to supply goods that may not meet a Default Standard, (e.g. application for consent to import, supply or export therapeutic goods that do not comply with standards under Section 14 of the Therapeutic Goods Act 1989). 1.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that: (ix) The results of product and processes monitoring are taken into account in batch release, in the investigation of deviations, and, with a view to taking preventive action to avoid potential deviations occurring in the future. (xiv) An appropriate level of root cause analysis should be applied during the investigation of deviations, suspected product defects and other problems. 1.9 Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. The basic requirements of Quality Control are that: (vi) Records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;
3.1 The impact of the deviation should be assessed in accordance with a quality risk management process using an appropriate approach such as described in Annex 20 of the PIC/S GMP Guide. The quality risk management process should include the following;	New clause – however, identical in intent to existing clause 1.4(ix), (xiv), Clause 1.9(vi). 1.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that:

New or amended requirements	Remarks
i. Evaluation of the potential impact of the deviation on quality, safety or efficacy of the batch(es) concerned and conclusion that the impact is negligible. ii. Consideration of the need to include the affected batch(es) in the ongoing stability programme. iii. In the case of biological medicinal products, consideration that any deviations from the approved process can have an unexpected impact on safety and efficacy. Taking account that responsibilities may be shared between more than one Authorised Person involved in the manufacture and control of a batch, the Authorised Person performing certification of a batch of medicinal product should be aware of and take into consideration any deviations which have the potential to impact compliance with GMP and/or compliance with the MA.	(ix) The results of product and processes monitoring are taken into account in batch release, in the investigation of deviations, and, with a view to taking preventive action to avoid potential deviations occurring in the future. (xiv) An appropriate level of root cause analysis should be applied during the investigation of deviations, suspected product defects and other problems. This can be determined using Quality Risk Management principles. In cases where the true root cause(s) of the issue cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those. Where human error is suspected or identified as the cause, this should be justified having taken care to ensure that process, procedural or system-based errors or problems have not been overlooked, if present. Appropriate corrective actions and/or preventive actions (CAPAs) should be identified and taken in response to investigations. The effectiveness of such actions should be monitored and assessed, in line with Quality Risk Management principles. 1.9 Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. The basic requirements of Quality Control are that: (vi) Records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;

Annex 16 – 4. The release of batch

New or amended requirements	Remarks
4 THE RELEASE OF A BATCH	New clause – however, identical in intent to existing clause 1.4xv and 1.9(vii) in PE009-15. This clause also reflects the existing Australian regulatory framework, whereby the storage of unreleased medicinal products is a step-in manufacture and can only be performed by sites

New or amended requirements	Remarks
4.1 Batches of medicinal products should only be released for sale or supply to the market after certification by an Authorised Person as described above. Until a batch is certified, it should remain at the site of manufacture or be shipped under quarantine to another site which has been approved for that purpose by the relevant National Competent Authority.	that hold an appropriate Manufacturing Authorisation (licence) and are approved in the product's Marketing Authorisation for storage of the goods. 1.4(xv) Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products. 1.9(vii) No batch of product is released for sale or supply prior to certification by an Authorised Person that it is in accordance with the requirements of the relevant authorisations;
4.2 Safeguards to ensure that uncertified batches are not transferred to saleable stock should be in place and may be physical in nature, e.g., the use of segregation and labelling or electronic in nature, e.g., the use of validated computerised systems. When uncertified batches are moved from one authorised site to another, the safeguards to prevent premature release should remain	New clause – however, identical in intent to existing clause 5.63 in PE009-15 5.63 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.
4.3 The steps necessary to notify Authorised Person certification to the site where the transfer to saleable stock is to take place should be defined within a technical agreement. Such notification by an Authorised Person to the site should be formal and unambiguous and should be subject to the requirements of Chapter 4 of the PIC/S GMP Guide, Part I	New clause – however, identical in intent to existing clause 4.27 and Chapter 7 (e.g., Principle, 7.11-7.12) in PE009-15. This new text does not invoke any new or additional expectations. 4.27 Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale of the finished product by the Authorised Person(s). All records should be available to the Authorised Person. A system should be in place to indicate special observations and any changes to critical data. <u>Principle – Chapter 7 – Outsourced Activities</u> The Pharmaceutical Quality System of the Contract Giver must clearly state the way that the Authorised Person certifying each batch of product for release exercises his/her full responsibility. 7.11 A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities and communication processes relating to the outsourced activities. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in related outsourced activities and Good Manufacturing Practice. All arrangements for outsourced activities must

New or amended requirements	Remarks
	be in accordance with regulations in force and the Marketing Authorisation for the product concerned and agreed by both parties. 7.12 The contract should describe clearly which party to the contract has responsibility for conducting each step of the outsourced activity, e.g., knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials, undertaking production and quality controls (including in-process controls, sampling and analysis). New text is essentially identical to text included in the TGA's existing Guidance for Release for Supply. – e.g. refer to "Authorised person responsibilities" and the Guidance for Releasing medicines manufactured at multiple sites – e.g. refer to "RFS authorised person responsibilities", "Relying on decisions of other authorised person(s)", "GMP Agreements" and "Delegated Authorised Persons"
4.4 National law may require a specific release for the local market (market release) by the MAH which takes into consideration the certification of the finished product by the manufacturer**.**	New clause – No equivalent in PE009-15. The clause reflects the existing EU model for the importation and batch certification of goods, whereby goods are imported, subjected to further analysis (QC release testing) within the EU, before final certification by a QP. **The TGA do not intend to adopt a similar model (i.e., mandatory testing following importation), and as such this clause would only be applicable in the circumstances where testing following importation is a requirement of the MA, CTA or other regulatory requirement. Where sampling for analysis following importation is required, manufacturers should hold an appropriate justification for the sampling plan.** Batch testing and certification would continue to be performed in accordance with the Marketing Authorisation which may permit testing and Certification (release for supply) by an approved overseas manufacturer. The sections of this Annex relating to the mandatory (re)testing of finished goods following importation would not necessarily apply (unless specifically required by the TGA, e.g., for the testing of certain vaccines before supply).

New or amended requirements	Remarks
	This position would be reflected in official guidance published by the TGA.

Table 2 Annex 16 – Glossary

New or amended requirements	Remarks
GLOSSARY TO ANNEX 16 Certain words and phrases in this annex are used with the particular meanings defined below. Reference should also be made to the Glossary in the main part of the PIC/S GMP Guide.	Use of slightly different terminology, which will be adopted and incorporated into relevant TGA guidelines as necessary. However, these new definitions do not invoke any changes to interpretation of GMP requirements.
Certification of the finished product batch The certification in a document by an Authorised Person, as defined in this annex, and represents the quality release of the batch before the batch is released for sale or distribution.	The term “Certification” is synonymous with the TGA term “Release for Supply”
Confirmation (Confirm and confirmed have equivalent meanings) A signed statement by an Authorised Person that a process or test has been conducted in accordance with GMP and the relevant marketing authorisation or clinical trial authorisation, product specification file and/or technical agreement, as applicable, as agreed in writing with the Authorised Person responsible for certifying the finished product batch before release. The Authorised Person providing a confirmation takes responsibility for those activities being confirmed.	The term “Confirmation” is synonymous with the TGA term “Release for Further Processing”
Finished product batch With reference to the control or test of the finished product, a finished medicinal product batch is an entity which comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time. In the context of this annex the term in particular denotes the batch of product in its final pack for release to the market.	No change

New or amended requirements	Remarks
Importer Any holder of the authorisation to import as required by national law.	The term “Importer” is synonymous with the TGA term “Sponsor” or “Marketing Authorisation Holder”
Jurisdiction A jurisdiction is a territory within which a court or government agency is exercising its power. A jurisdiction can be e.g., a State (whether internationally recognised or not) or a region.	No change

Annex 16 – Appendices

New or amended requirements	Remarks
APPENDIX I Recommended content of the confirmation of the partial manufacturing of a medicinal product [LETTER HEAD OF MANUFACTURER WHO CARRIED OUT THE MANUFACTURING ACTIVITY] 1. Name of the product and description of the manufacturing stage (e.g., paracetamol 500 mg tablets, primary packaging into blister packs). 2. Batch number. 3. Name and address of the site carrying out the partial manufacturing. 4. Reference to the Technical Quality Agreement (in accordance with Chapter 7 of the PIC/S GMP Guide). 5. Confirmation statement. I hereby confirm that the manufacturing stages referred to in the Technical Quality Agreement have been carried out in full compliance with the GMP requirements of the [insert jurisdiction] and the terms described in the Agreement for ensuring compliance with the requirements of the Marketing Authorisation(s) as provided by [Contract Giver/manufacturer certifying and releasing the batch]. 6. Name of the Authorised Person confirming the partial manufacturing.	Recommended minimal content for partial manufacturing. Further information may be requested by the Authorised person to satisfy the requirements of Annex 16

New or amended requirements	Remarks
7. Signature of Authorised Person confirming the partial manufacturing. 8. Date of signature.	
APPENDIX II Recommended content of the Batch Certificate for Medicinal Products [LETTER HEAD OF THE BATCH CERTIFYING AND RELEASING MANUFACTURER] 1. Name, strength/potency, dosage form and package size (identical to the text on the finished product package). 2. Batch number of the finished product. 3. Name of the destination country/countries of the batch. 4. Certification statement. I hereby certify that all the manufacturing stages of this batch of finished product have been carried out in full compliance with the GMP requirements of the [insert jurisdiction] and [as applicable] with the requirements of the Marketing Authorisation(s) of the destination country/countries. 5. Name of the Authorised Person certifying the batch. 6. Signature of the Authorised Person certifying the batch. 7. Date of signature.	Recommended minimal content for batch certification. Further information may be requested by the Authorised person to satisfy the requirements of Annex 16

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