Australian Government
Department of Health
Therapeutic Goods Administration

Transition to new GMP requirements for medicinal products

A notice about the implications of adopting the PIC/S Guide to GMP PE009-14

Version 1.0, June 2020

TGA Health Safety Regulation

Contents

A notice about adoption of a new PIC/S guide to GMP

The TGA will adopt the current version of the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products* PE009-14 (PIC/S Guide to GMP), excluding Annexes 4, 5 and 14, as the manufacturing principles for medicines and active pharmaceutical ingredients, with effect from 1 July 2020 as communicated on 4 May 2020. The PIC/S Guide to GMP is available from the PIC/S website.

This will replace the manufacturing principles adopted in 2018 by the TGA for the manufacture of medicines, active pharmaceutical ingredients and sunscreens: the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products* PE009-13.

This notice is being issued to assist with the transition period. It is a point-in-time document and we are not planning on updating this notice.

We will be updating GMP guidance during 2020 to reflect the new requirements.

Who this notice is for

This notice is intended for Australian sponsors and manufacturers of medicines and active pharmaceutical ingredients supplied in Australia.

The PIC/S Guide to GMP applies to the manufacture of the following:

- Active Pharmaceutical Ingredients (APIs)
- Registered (AUSTR) and Listed (AUSTL) medicines (including sunscreens)
- medicinal gases
- biologicals that comprise or contain live **animal** cells, tissues or organs,

unless exempt under provisions in the therapeutic goods legislation,

This notice is not applicable to medical device manufacturers or sponsors, or manufacturers, of human blood, blood components, haematopoietic progenitor cells (HPCs) or biologicals that comprise, contain or are derived from human cells and tissues.

Updates to the PIC/S guide to Good Manufacturing Practice for Medicinal Products (PE009)

There have been a number of updates to the PIC/S Guide to Good Manufacturing Practice since the publication of the January 2017 version (PE009-13), which is the most recent applicable standard adopted by TGA. The Revision history 2017 to 2018 table below details these revisions.

The majority of updates clarify existing GMP regulatory expectations. However, some manufacturers may need to implement and/or modify operational processes and procedures to maintain compliance following these updates. These changes are identified in the summary of new and amended requirements tables.

Revision history 2017 to 2018

Date	Version number	Reasons for revision
1 January 2017	PE009-13	• Revision of Chapters 1, 2, 6 & 7 (Part I)
1 July 2018	PE009-14	• Revision of Chapters 3, 5 & 8 (Part I) • Revision of Annex 17

Feedback

If you have any questions or feedback regarding the adoption of the PIC/S Guide to GMP, PE009-14, contact the Manufacturing Quality Branch (MQB).

New and amended GMP requirements

The following summary of the amended GMP requirements provides details of the more significant differences between the PIC/S Guide to GMP PE009-13 and the PIC/S Guide to GMP PE009-14. These changes may require some manufacturers to implement or modify processes to provide improved or more detailed evidence of compliance.

See the PIC/S website for the complete PIC/S Guide to GMP PE009-14 to determine the impact on your operations and to assist in formulating your approach to implementing changes necessary because of changed requirements.

New or amended text is designated in the table by the use of **bold** font.

This summary does not generally include detail of grammatical amendments, re-worded existing requirements or minor word changes.

Summary of new and amended requirements

Part I Chapter 3 - Premises and Equipment

New or amended requirements	Remarks
3.6. **Cross-contamination should be prevented for all products by appropriate design and operation of manufacturing facilities. The measures to prevent cross-contamination should be commensurate with the risks. Quality Risk Management principles should be used to assess and control the risks.** **Depending of the level of risk, it may be necessary to dedicate premises and equipment for manufacturing and/or packaging operations to control the risk presented by some medicinal products.** **Dedicated facilities are required for manufacturing when a medicinal product presents a risk because:** **i. the risk cannot be adequately controlled by operational and/ or technical measures,** **ii. scientific data from the toxicological evaluation does not support a controllable risk (e.g. allergenic potential from highly sensitising materials such as beta-lactams) or** **iii. relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a validated analytical method.** **Further guidance can be found in Chapter 5 and in Annexes 2, 3, 4, 5 & 6.**	The new text provides additional guidance to assist manufacturers in determining whether dedicated equipment and/or facilities are required for the manufacture of certain therapeutic goods that are potent, hazardous or sensitising. Rather than specifying certain molecules, the guidance provides detailed information on how molecules may be assessed and controlled, in a consistent, scientific and risk-based method. This clause provides allowance for better use of risk management for shared facilities and builds upon the existing requirements for toxicological assessments as per existing Annex 15§10.6. The new text states that cross contamination should be prevented, this is considered to be as far as practicable, with due consideration to the materials handled. The TGA appreciate and recognise that absolute exclusion of contaminants is impractical; however, prevention of contaminants at a level that may present a risk to product quality and patient safety is expected.

Part I Chapter 5 - Production

New or amended requirements	Remarks
PREVENTION OF CROSS-CONTAMINATION IN PRODUCTION 5.21. **The outcome of the Quality Risk Management process should be the basis for determining the extent of technical and organisational measures required to control risks for cross-contamination. These could include, but are not limited to, the following:** **<u>Technical Measures</u>** **i. Dedicated manufacturing facility (premises and equipment);** **ii. Self-contained production areas having separate processing equipment and separate heating, ventilation and air-conditioning (HVAC) systems. It may also be desirable to isolate certain utilities from those used in other areas;** **iii. Design of manufacturing process, premises and equipment to minimize risk for cross-contamination during processing, maintenance and cleaning;** **iv. Use of "closed systems" for processing and material/product transfer between equipment;** **v. Use of physical barrier systems, including isolators, as containment measures;** **vi. Controlled removal of dust close to source of the contaminant e.g. through localised extraction** **vii. Dedication of equipment, dedication of product contact parts or dedication of selected parts which are harder to clean (e.g. filters), dedication of maintenance tools;**	Improved guidance for assessing and controlling risks of cross-contamination. This clause expands on the existing clauses 5.18 -5.19 in PE009-13 and provides greater guidance as to the technical and organisational controls that we expect you to consider when assessing/supporting the operation of a multi-product facility. Manufacturers are expected to consider these types of control measures when performing and documenting risk assessments of new and existing operations, to ensure that adequate containment and segregation of materials is maintained. Not all control measures will be required as determined by the overall risk assessment of the toxicity of materials handled.

New or amended requirements	Remarks
viii. Use of single use disposable technologies; **ix. Use of equipment designed for ease of cleaning;** **x. Appropriate use of air-locks and pressure cascade to confine potential airborne contaminant within a specified area;** **xi. Minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;** **xii. Use of automatic clean in place systems of validated effectiveness;** **xiii. For common general wash areas, separation of equipment washing, drying and storage areas.** **<u>Organisational Measures</u>** **i. Dedicating the whole manufacturing facility or a self-contained production area on a campaign basis (dedicated by separation in time) followed by a cleaning process of validated effectiveness;** **ii. Keeping specific protective clothing inside areas where products with high risk of cross-contamination are processed;** **iii. Cleaning verification after each product campaign should be considered as a detectability tool to support effectiveness of the Quality Risk Management approach for products deemed to present higher risk;** **iv. Depending on the contamination risk, verification of cleaning of non product contact surfaces and monitoring of air within the manufacturing area and/or adjoining areas in order to**	

New or amended requirements	Remarks
demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer; **v. Specific measures for waste handling, contaminated rinsing water and soiled gowning;** **vi. Recording of spills, accidental events or deviations from procedures;** **vii. Design of cleaning processes for premises and equipment such that the cleaning processes in themselves do not present a cross-contamination risk;** **viii. Design of detailed records for cleaning processes to assure completion of cleaning in accordance with approved procedures and use of cleaning status labels on equipment and manufacturing areas;** **ix. Use of common general wash areas on a campaign basis;** **x. Supervision of working behaviour to ensure training effectiveness and compliance with the relevant procedural controls.**	
STARTING MATERIALS 5.27. **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. The level of supervision should be proportionate to the risks posed by the individual materials, taking account of their source, manufacturing process, supply chain complexity and the final use to which the material is put in the medicinal product. The**	Improved guidance for the processes of supplier and material approval. This expanded clause reflects existing expectations, that the processes are documented, assessments based on risk and evidence to support the suitability of each material available.

New or amended requirements	Remarks
supporting evidence for each supplier / material approval should be maintained. Staff involved in these activities should have a current knowledge of the suppliers**, the supply chain and the associated risks involved. Where possible,** starting materials should be purchased directly from the **manufacturer of the starting material**.	
5.28. **The quality requirements** established by the manufacturer for the starting materials **should** be discussed **and agreed** with the suppliers. **Appropriate** aspects of the production, **testing** and control, including handling, labelling, packaging **and distribution** requirements, complaints, **recalls** and rejection procedures **should be documented in a formal quality agreement or specification**.	Clarified guidance regarding the need for a clear understanding of quality requirements by all parties involved in the manufacture and supply of starting materials. Specific mention of the requirement for aspects of the manufacture and supply of materials to be captured within quality agreements, reflecting the existing Chapter 7 expectations.
5.29. **For the approval and maintenance of suppliers of active substances and excipients, the following is required:** **<u>Active substances</u>** **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.** **Audits should be carried out at the manufacturers and distributors of active substances to confirm that they comply with the relevant good manufacturing practice and good distribution practice requirements. The holder of the manufacturing authorisation shall**	Updated requirements outlining the expectations for the evaluation and oversight of suppliers of Active Substances (API) and Excipients. These updated requirements are designed to ensure adequate assurance of the quality of APIs is maintained, as well as address and prevent issues with starting material supply that has in some cases caused product shortages and placed patients at risk. The new clause reflects the existing requirements regarding traceability of the supply chain for active substances outlined in clause 1.10i in PE009-13 In relation to the assessment of supply chains, the current TGA guideline to the interpretation of supply chain integrity applies, i.e.: Manufacturers of dosage forms should have a clear understanding of the approved suppliers of active substances, and each entity and their responsibility in the supply chain between the site of manufacture and receipt (clause 1.10(i)). Supply chains should be adequately secure, integral and ensure that materials are transported under appropriate conditions. Supply

New or amended requirements	Remarks
verify such compliance either by himself/herself or through an entity acting on his/her behalf under a contract. For veterinary medicinal products, audits should be conducted based on risk. **Audits should be of an appropriate duration and scope to ensure that a full and clear assessment of GMP is made; consideration should be given to potential cross- contamination from other materials on site. The report should fully reflect what was done and seen on the audit with any deficiencies clearly identified. Any required corrective and preventive actions should be implemented.** **Further audits should be undertaken at intervals defined by the quality risk management process to ensure the maintenance of standards and continued use of the approved supply chain.** **<u>Excipients</u>** **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'.**	chains should be mapped and any identified risks managed following the principles of quality risk management. The supply chain assessment is a periodic function; however, verification of the use of the correct supply chain is required for each delivery and should be readily apparent from the associated delivery paperwork and shipping information. Manufacturers should ensure they hold evidence of supply chain assessments and the process for routine verification of the correct supply chain are described in local procedures. The updated clause requires the use of audits of suppliers of APIs as part of the overall evaluation. Audits may be performed by the manufacturer using the material or by an appropriate agent acting on their behalf, e.g. a sponsor, consultant, client, providing the audit is conducted by appropriately qualified individuals and ensure that the specific materials supplied are appropriately verified in the audit. Sponsors and manufacturers are encouraged to work together to identify sites and materials of common interest which may allow audit reports to be shared and used by multiple customers, however, the scope of the audit must cover the specific materials supplied. **Active substances** *Active substances used in registered medicines (or equivalent)* For active substances used in registered medicines (or equivalent), quality risk management principles should apply in determining the frequency of evaluation, and evidence of an on-site audit of the starting material manufacturer and distributor would be expected as part of the overall supplier qualification program.

New or amended requirements	Remarks
	Note: Where evidence of inspection for an active substance manufacturer is available from a recognised comparable regulator, this may be used in determining the audit frequency or scope, but cannot be used as a basis for not conducting an independent audit of the manufacturer/distributor. *Active substances used in listed medicines (or equivalent)* For active substances used in listed medicines, an audit of the starting material manufacturer and distributor would not be expected and compliance with this clause would be satisfied providing the manufacturer follows the TGA's guidance for supplier approval for listed medicines or equivalent. However, should the manufacturer of a listed medicine elect to perform an audit of a manufacturer and supplier of a starting material, upon successful completion of the supplier evaluation, reduced testing (as outlined by clause 5.35) would be permitted. **Note:** Where the desk-top assessment of the manufacturer or supplier fails to result in an acceptable outcome, manufacturers of listed medicines would be expected to perform full sampling and testing of starting materials in accordance with the TGA's guidance on sampling and testing for listed and complementary medicines. **Excipients** TGA licensing or certification of excipient suppliers will not be conducted. For excipients used in *registered medicines* (or equivalent), an evaluation in accordance with the PIC/S Guideline PI 045-1 'Guidelines on the formalised risk assessment for ascertaining the appropriate Good Manufacturing Practice for excipients of medicinal products for human use' or equivalent would be expected. Once the manufacturer has

New or amended requirements	Remarks
	established the commensurate controls, evidence that the excipient manufacturer meets the established level of GMP would be required. **Note:** Manufacturers should note that PIC/S Guidance documents for industry (coded as PI XXX-XX) provide an outline of acceptable approaches to compliance; however, are not enforceable by the TGA and compliance with the guidance documents is not mandatory. Alternative methods of demonstrating compliance with PE009 principles are acceptable where scientifically justified, (refer Therapeutic Goods (Manufacturing Principles) Determination 2018). For excipients used in *listed medicines*, compliance with this clause would be satisfied providing the manufacturer follows the TGA's guidance for supplier approval for listed medicines.
5.35. **Manufacturers of finished products are responsible for any testing of starting materials[3] as described in the marketing authorisation dossier. They can utilise partial or full test results from the approved starting material manufacturer but must, as a minimum, perform identification testing[4] of each batch according to Annex 8.** **[3]A similar approach should apply to packaging materials as stated in section 5.45.** **[4]Identity testing of starting materials should be performed according to the methods and the specifications of the relevant marketing authorisation dossier.**	New clause which includes a provision permitting acceptance of a delivery of raw material based on ID testing only (as per Annex 8). Existing TGA expectations would remain that the release of a material based on an ID test only would only be applicable for those materials supplied from a fully qualified manufacturer and supplier, assessed in full accordance with Annex 8 and clause 5.29, i.e. where evidence of an on-site audit is available to the end-user.
5.36. **The rationale for the outsourcing of this testing should be justified and documented and the following requirements should be fulfilled:**	This new clause links to the previous clause (5.35) and provides additional guidance for organisations in the management of outsourced

New or amended requirements	Remarks
i. Special attention should be paid to the distribution controls (transport, wholesaling, storage and delivery) in order to maintain the quality characteristics of the starting materials and to ensure that test results remain applicable to the delivered material; **ii. The medicinal product manufacturer should perform audits, either itself or via third parties, at appropriate intervals based on risk at the site(s) carrying out the testing (including sampling) of the starting materials in order to assure compliance with Good Manufacturing Practice and with the specifications and testing methods described in the marketing authorisation dossier;** **iii. The certificate of analysis provided by the starting material manufacturer/supplier should be signed by a designated person with appropriate qualifications and experience. The signature assures that each batch has been checked for compliance with the agreed product specification unless this assurance is provided separately;** **iv. The medicinal product manufacturer should have appropriate experience in dealing with the starting material manufacturer (including experience via a supplier) including assessment of batches previously received and the history of compliance before reducing in-house testing. Any significant change in the manufacturing or testing processes should be considered;** **v. The medicinal product manufacturer should also perform (or via a separately approved contract laboratory) a full analysis at appropriate intervals based on risk and compare the results with the material manufacturer's or supplier's**	testing facilities and includes a direct link to chapter 7 provisions for the requirements of outsourcing of testing of materials. This specific clause applies to circumstances where the user proposes to rely on starting material testing conducted by either the manufacturer of the substance or conducted by a contract laboratory that is not under the control of the user. This clause outlines the assessment of testing conducted by the substance manufacturer or contract laboratories required in order to permit reliance on these test results. Following this approach could result in reduced testing of the substance by the end-user, noting that the reliance on such testing is not mandatory and users may elect to test materials themselves. TGA would expect manufacturers to take a risk-based approach to the audit of laboratories performing starting material testing on their behalf. The expectations are in principle: • the basic expectation is that audits are performed. Base the method of auditing (on-site or desk-based) on a risk assessment of the tests performed and the criticality of the results. • consider on-site audits where the testing performed by the lab is complex or consists of non-standard test methods, for example. characterisation and testing of complex chemical or biological starting materials, or the use of novel equipment and methodologies requiring specialised expertise. • desk-based assessment evidence may be suitable for lower risk and standard phamacopoeial testing. For example. testing of starting materials in accordance with a pharmacopoeial monograph, wet-chemistry and basic chromatographic testing. • where the manufacturer holds evidence of the following, reliance on official TGA inspections may be acceptable for the testing of low risk

New or amended requirements	Remarks
certificate of analysis in order to check the reliability of the latter. Should this testing identify any discrepancy then an investigation should be performed and appropriate measures taken. The acceptance of certificates of analysis from the material manufacturer or supplier should be discontinued until these measures are completed.	starting materials, for example. those subject to a pharmacopoeial monograph: – the contract laboratory is suitably licensed to perform the testing requested. – the test methodology used by the lab is in full accordance with the marketing authorisation pharmacopoeial testing requirements, or – where alternative methods are utilised, these are appropriately validated, and – the methods used have been suitably verified (where required)
PRODUCT SHORTAGE DUE TO MANUFACTURING CONSTRAINTS **5.71. The manufacturer should report to the marketing authorisation holder (MAH) any constraints in manufacturing operations which may result in abnormal restriction in the supply. This should be done in a timely manner to facilitate reporting of the restriction in supply by the MAH, to the relevant competent authorities, in accordance with its legal obligations.**	Inclusion of this clause aligns with TGA expectations regarding mandatory reporting of medicines shortages commencing 1 January 2019. Manufacturers are expected to have procedures in place to ensure mandatory reporting of potential shortages occurs as necessary. Further information regarding the reporting of medicine shortages can be found on the TGA website.

Part I Chapter 8 - Complaints and Product Recall

New or amended requirements	Remarks
PRINCIPLE **In order to protect public and animal health, a system and appropriate procedures should be in place to record, assess, investigate and review complaints including potential quality defects, and if necessary, to effectively and promptly recall medicinal products for human or veterinary use and investigational medicinal products from the distribution network. Quality Risk Management principles should be applied to the investigation and assessment of quality defects and to the decision-making process in relation to product recalls corrective and preventative actions and other risk-reducing actions. Guidance in relation to these principles is provided in Chapter 1.** **All concerned Competent Authorities should be informed in a timely manner in case of a confirmed quality defect (faulty manufacture, product deterioration, detection of falsification, non-compliance with the marketing authorisation or product specification file, or any other serious quality problems) with a medicinal or investigational medicinal product which may result in the recall of the product or an abnormal restriction in the supply. In situations where product on the market is found to be non-compliant with the marketing authorisation, there may be a requirement to notify concerned Competent Authorities. Reference should be made to relevant legislative requirements.** **In case of outsourced activities, a contract should describe the role and responsibilities of the manufacturer, the marketing authorisation holder and/or sponsor and any other relevant third parties in relation to assessment, decision-making, and dissemination of information and implementation of risk-reducing**	This chapter has been largely re-written to provide greater clarity for expectations regarding the management of complaints and recall actions, and further outlines the application of QRM in the investigation and management of issues. The section includes additional guidance for complaints, quality defects and recall activities and outlines other 'risk reducing activities' (other than recall) that may be considered. The content of this chapter now includes specific instructions that largely reflect the requirements of the URPTG and historic TGA practices.

New or amended requirements	Remarks
actions relating to a defective product. Guidance in relation to contracts is provided in Chapter 7. Such contracts should also address how to contact those responsible at each party for the management of quality defect and recall issues.	
8.6. Special attention should be given to establishing whether a complaint or suspected quality defect relates to falsification.	Updated clause includes the use of the term 'falsification' which represents a more broader range of questionable products than the term 'counterfeiting'. Falsification includes any medicinal product "which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient (inadequate quantities of) active ingredient(s) or with fake packaging." Source: WHO Technical Report Series, No. 957, 2010
8.9. When a quality defect investigation is initiated, procedures should be in place to address at least the following: **i. The description of the reported quality defect.** **ii. The determination of the extent of the quality defect. The checking or testing of reference and/or retention samples should be considered as part of this, and in certain cases, a review of the batch production record, the batch certification record and the batch distribution records (especially for temperature-sensitive products) should be performed.** **iii. The need to request a sample, or the return, of the defective product from the complainant and, where a sample is**	Amended clause providing greater clarity as to the scope and detail of an investigation into quality defects, the instructions for which are in accordance with current TGA expectations and reflect existing Chapter 1 requirements for the investigation of issues. Manufacturers should ensure that existing procedures reflect these requirements.

New or amended requirements	Remarks
provided, the need for an appropriate evaluation to be carried out. **iv. The assessment of the risk(s) posed by the quality defect, based on the severity and extent of the quality defect.** **v. The decision-making process that is to be used concerning the potential need for risk-reducing actions to be taken in the distribution network, such as batch or product recalls, or other actions.** **vi. The assessment of the impact that any recall action may have on the availability of the medicinal product to patients/animals in any affected market, and the need to notify the relevant authorities of such impact.** **vii. The internal and external communications that should be made in relation to a quality defect and its investigation.** **viii. The identification of the potential root cause(s) of the quality defect.** **ix. The need for appropriate Corrective and Preventive Actions (CAPAs) to be identified and implemented for the issue, and for the assessment of the effectiveness of those CAPAs.**	
8.15. Quality defects should be reported in a timely manner by the manufacturer to the marketing authorisation holder/sponsor and all concerned Competent Authorities in cases where the quality defect may result in the recall of the product or in an abnormal restriction in the supply of the product.	New clause reflecting the existing responsibilities of both sponsors and manufacturers in relation to recalls, as specified in the current URPTG. The additional wording of this clause places emphasis on notifying the product sponsor and considering any restrictions in supply, in line with the TGA's existing Medicine Shortages Information Initiative.

New or amended requirements	Remarks
ROOT CAUSE ANALYSIS AND CORRECTIVE AND PREVENTATIVE ACTIONS **8.16. An appropriate level of root cause analysis work should be applied during the investigation of quality defects. In cases where the true root cause(s) of the quality defect cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those.** **8.17. Where human error is suspected or identified as the cause of a quality defect, this should be formally justified and care should be exercised so as to ensure that process, procedural or system-based errors or problems are not overlooked, if present.** **8.18. Appropriate CAPAs should be identified and taken in response to a quality defect. The effectiveness of such actions should be monitored and assessed.**	New clauses providing additional clarity regarding the specific need for determining the root cause of quality defects. These clauses align with existing Chapter 1 requirements.
8.25. Consideration should be given following consultation with the concerned Competent Authorities, as to how far into the distribution network a recall action should extend, taking into account the potential risk to public or animal health and any impact that the proposed recall action may have. The Competent Authorities should also be informed in situations in which no recall action is being proposed for a defective batch because the batch has expired (such as with short shelf-life products.)	New clause that specifies the need to consider the extent of any recall actions. This aligns with existing URPTG and TGA recall processes. The last sentence outlines that TGA should be notified, even in the event that a physical recall of products is not performed as the product has expired. This reflects existing requirements for short-shelf-life products, for example. radiopharmaceuticals or compounded medicines.
8.30. The effectiveness of the arrangements **in place** for recalls should be **periodically** evaluated **to confirm that they remain robust and fit for use. Such evaluations should extend to both within office-hour situations as well as out-of-office hour situations and, when performing such evaluations, consideration should be given as to whether mock-recall actions should be performed. This evaluation should be documented and justified.**	Updated clause to include the new requirement of ensuring the ability to perform a recall at any time, including out of normal operating hours. Manufacturers should ensure that persons responsible for recall actions can be readily contacted outside normal office hours.

Annex 17 - Real Time Release Testing and Parametric Release

New or amended requirements	Remarks
General	This annex has been subject to a general revision and the order of sections as well as content, has been amended from the existing Annex 17. The new annex text expands the scope and provides additional guidance for the application of Real Time Release Testing (RTRT) (for example. in-line PAT testing) which may replace the conduct of finished product testing where justified and authorised by the regulator. The sections relating to parametric release (i.e. release of terminally sterilized products without performing a final test for sterility) have been amended to clarify requirements.
3.Real time release testing (RTRT) **3.1. Under RTRT, a combination of in-process monitoring and controls may provide, when authorised, a substitute for end-product testing as part of the batch release decision. Interaction with all relevant regulatory authorities prior and during the assessment process preceding regulatory approval is required. The level of interaction will depend on the level of complexity of the RTRT control procedure applied on site.** **3.2. When designing the RTRT strategy, the following minimum criteria are expected to be established and met:** **i. Real time measurement and control of relevant in-process material attributes and process parameters should be accurate predictors of the corresponding finished product attributes.**	New clauses, which outline the expectations for the application of RTRT. The application of RTRT is not mandatory. RTRT relies on the concept that in-process monitoring and effective production controls may provide greater assurance than end-product testing, and therefore in-process and control data may be used to support product acceptance/release as an alternative to routine end-product testing of active substances and/or finished products. RTRT relies on the manufacturers thorough understanding of the manufacturing process, real-time measurement of critical process parameters (CPP), a thorough understanding of critical material attributes and a fully defined control strategy incorporating Quality Risk Management, validation and training of staff etc. Where authorised, RTRT may apply to any stage in the manufacturing process and to any type of finished products or active substances, including their intermediates.

New or amended requirements	Remarks
ii. The valid combination of relevant assessed material attributes and process controls to replace finished product attributes should be established with scientific evidence based on material, product and process knowledge. **iii. The combined process measurements (process parameters and material attributes) and any other test data generated during the manufacturing process should provide a robust foundation for RTRT and the batch release decision.** **3.4. In accordance with the principles described in the PIC/S Guide to Good Manufacturing Practice for Medicinal Products, Part I Chapter 1, Part II Chapter 13 and Annex 15, the change control program is an important part of the real time release testing approach. Any change that could potentially impact product manufacturing and testing, or the validated status of facilities, systems, equipment, analytical methods or processes, should be assessed for risk to product quality and impact on reproducibility of the manufacturing process. Any change should be justified by the sound application of quality risk management principles, and fully documented. After change implementation, an evaluation should be undertaken to demonstrate that there are no unintended or deleterious impact on product quality.**	Manufacturers who wish to apply RTRT should discuss their approach with the relevant product evaluation section of the TGA, and where required seek Marketing Authorisation approval before an inspection against these requirements can be conducted.
4. Parametric release and sterilisation **4.1. This section provides guidance on parametric release which is defined as the release of a batch of terminally sterilised product based on a review of critical process control parameters rather than requiring an end-product testing for sterility.** **4.5. The sterility assurance program should be documented and include, at least, the identification and monitoring of the critical**	Updated guidance to clarify existing requirements. This section now provides greater clarity about: • what information and controls should be included in the sterility assurance program • application of Quality Risk Management • bioburden monitoring and controls

New or amended requirements	Remarks
process parameters, steriliser cycle development and validation, container/packaging integrity validation, bioburden control, environmental monitoring program, product segregation plan, equipment, services and facility design and qualification program, maintenance and calibration program, change control program, personnel training, and incorporate a quality risk management approach.	• implementation of an overarching control strategy to manage parametrically released sterile medicines. Manufacturers who currently hold a Manufacturing Authorisation, (Licence) that permits parametric release should read and understand the revised text and update quality systems as required.

Transition plan

The transition period from 1 July 2020 to 1 July 2021 serves to allow manufacturers to assess and plan for these changes and permit time for implementation.

For the most significant changes, we have produced transition plan tables, which summarise the minimum requirements to demonstrate compliance

The approach that will be taken where these have not been met is outlined below.

Compliance with all other changes is expected from 1 July 2020 and transition arrangements do not apply.

Our expectation is that by 1 January 2021, manufacturers will have:

- completed their assessment of the impact of the new manufacturing principles on their operations
- completed, or be well advanced, towards updating quality systems documentation and implementing revised practices

We recognise the complexity associated with these changes and have therefore provided appropriate timeframes for implementation, which reflect the complexity and significance of each change. Where the impact is minimal to the manufacturer, we would expect that adoption would be well progressed or implemented by January 2021, unless justified.

The TGA is closely monitoring the impact of the COVID-19 pandemic on manufacturers and the timelines may be extended as a result.

Any extension to the timelines for compliance will be communicated via the TGA website.

Transition plan diagram

Reporting deficiencies in Post Inspection Letters (PIL)

We issue a PIL at the conclusion of an on-site inspection to communicate departures from GMP, with the purpose of assisting companies to restore compliance through root cause assessment and corrective actions.

During the transitional implementation period, we will be aiming to assist and encourage implementation of the new requirements. As a result, we will not cite a deficiency when companies demonstrate they are meeting the minimum expectations summarised below.

We will report a deficiency if the company has not undertaken an appropriate approach to implementing the new requirements or may not achieve compliance in a timely manner. This will usually be cited as an 'other' deficiency against the relevant part of the PIC/S Guide to GMP.

Major deficiencies will generally be cited only where a manufacturer has not commenced, or significantly progressed, action to implement the new PIC/S Guide to GMP requirements. A major deficiency may also be cited where a manufacturer's implemented procedures and systems do not meet the requirements of the PIC/S Guide to GMP.

Transition plan tables

Part I, Chapter 3 Premises and Equipment

PIC/S GMP Requirement	Between 1 July 2020 and 1 January 2021	Between 1 January 2021 and 30 June 2021	From 1 July 2021
Clause 3.6: Cross-contamination	• Review updated clause • Evaluate impact to existing risk assessments/controls • Commenced amending and drafting procedures • Commenced training staff in updated procedures	• Complete cross-contamination risk assessments • Finalise implementation of any additional controls identified	Full implementation

Part I, Chapter 5 Production

PIC/S GMP Requirement	Between 1 July 2020 and 1 January 2021	Between 1 January 2021 and 30 June 2021	From 1 July 2021
Clause 5.21: Cross-contamination	• Review updated clause • Evaluate impact to existing risk assessments/controls • Commenced amending and drafting procedures • Commenced training staff in updated procedures	• Complete cross-contamination risk assessments • Finalise implementation of any additional controls identified	Full implementation

PIC/S GMP Requirement	Between 1 July 2020 and 1 January 2021	Between 1 January 2021 and 30 June 2021	From 1 July 2021
Clause 5.29: Starting material controls	• Review updated clause • Documented assessment of all starting material providers implicated • Commenced drafting procedures including approach for on-site audits • Develop priority list for evaluation and approval of starting material providers	• Updated procedures in place • Staff training completed • Commenced collation of evidence for on-site audits of API suppliers • Commenced assessment of excipient suppliers	Full implementation
Clause 5.35-5.36: Outsourced testing of starting materials	• Review updated clauses • Documented assessment of all starting material providers and testing laboratories implicated • Commenced drafting procedures including approach for audits (on-site and desk-top as relevant) • Develop priority list for evaluation and approval of providers and testing laboratories	• Updated procedures in place • Staff training completed • Commenced collation of evidence for audits of starting material providers/test laboratories	Full implementation
Clause 5.71: Medicines shortages	• Review updated clause • Draft procedures to manage and communicate potential medicines shortages	• Updated procedures in place • Update contracts as required • Staff training completed	Full implementation

Part I, Chapter 8 Complaints and Product Recall

PIC/S GMP Requirement	Between 1 July 2020 and 1 January 2021	Between 1 January 2021 and 30 June 2021	From 1 July 2021
Whole chapter	• Review updated clauses • Assess any gaps or changes in terminology and update local procedures.	• Updated procedures in place • Conduct "mock recall" to verify the effectiveness of the procedure against updated requirements.	Full implementation

Annex 17 Real Time Release Testing and Parametric Release

PIC/S GMP Requirement	Between 1 July 2020 and 1 January 2021	Between 1 January 2021 and 30 June 2021	From 1 July 2021
Real Time Release Testing (RTRT)	Where a manufacturer elects to apply RTRT: • Review updated clauses • Commenced drafting procedures • Risk assess/Determine list of all products and processes implicated • Notify relevant TGA evaluation section of intent to apply RTRT	• Updated procedures in place • Commenced validation and documentation of control strategy.	Full implementation
Parametric Release	• Review updated clauses • Assess any gaps or changes in terminology and update local procedures.	• Updated procedures in place • Complete documentation of control strategy.	Full implementation

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Manufacturing Quality Branch	June 2020

Therapeutic Goods Administration

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

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