Australian Government
Department of Health
Therapeutic Goods Administration

Transition to new GMP requirements for medicinal products

A notice about the implications of adopting PE009-13

Version 1.0, November 2017

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* PE009-13 (PIC/S Guide to GMP), excluding Annexes 4, 5 and 14, as the manufacturing principles for medicines and active pharmaceutical ingredients. This document is available from the PIC/S website, and will take effect on 1 January 2018 as communicated on 13 September 2017.

This will replace the manufacturing principles adopted in 2010 by the TGA for the manufacture of medicines, active pharmaceutical ingredients and sunscreens: the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products* PE009-8.

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 2018 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 Good Manufacturing Practice for Medicinal Products* PE009-13 (PIC/S Guide to GMP) applies to the manufacture of the following (unless exempt under provisions in the therapeutic goods legislation):

- Active Pharmaceutical Ingredients (APIs)
- Registered (AUST R) and Listed (AUSTL) medicines (including sunscreens)
- Medicinal gases
- Biologicals that comprise or contain live **animal** cells, tissues or organs

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 2009 version (PE009-8), which is the most recent applicable standard adopted by TGA. The *Revision history 2009 to 2017* table below details these revisions.

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

Revision history 2009 to 2017

Date	Version number	Reasons for revision
15 January 2009	PE 009-8	· Revision of Chapter 1 (Part I) · Revision of Annex 1 · New Annex 20
1 September 2009	PE 009-09	· Revision of Annex 3
1 January 2013	PE 009-10	· Revision of Chapter 4 (Part I) · Revision of Annexes 6, 7, 11 & 13
1 March 2014	PE009-11	Revision of Part II of the Guide to include: · Quality Risk Management · Revision of Annex 2 · Revision of Annex 14
30 September 2015	PE009-12	· Revision of Annex 15
1 January 2017	PE009-13	· Revision of Chapters 1, 2, 6 & 7 (Part I)

Feedback

If you have any questions or feedback regarding the adoption of the PIC/S Guide to GMP, PE009-13, 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 PE009-8 and the PIC/S Guide to GMP PE009-13. 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 PE009-13 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 1 - Pharmaceutical Quality System

New or amended requirements	Remarks
1.6 **There should be periodic management review, with the involvement of senior management, of the operation of the Pharmaceutical Quality System to identify opportunities for continual improvement of products, processes and the system itself**.	Clarification of quality management reviews. Although identified in PE009-08 (Chapter 1, Principle), this new clause better defines the requirements for a more formal and systematic approach to quality management reviews to ensure that appropriate lines of communication and escalation of issues that affect the quality system are in place to facilitate identification of quality related issues, their timely remediation and ensure adequate resourcing. ICH Q10[1] provides guidance on performing management reviews.
1.7 **The Pharmaceutical Quality System should be defined and documented. A Quality Manual or equivalent documentation should be established and should contain a description of the quality management system including management responsibilities**.	Improved guidance for documenting the quality assurance system. A quality manual or equivalent documentation should be established and should contain the description of the pharmaceutical quality system. The description should include: · the quality policy · the scope of the pharmaceutical quality system · identification of the pharmaceutical quality system processes, as well as their sequences, linkages and interdependencies. Process maps and flow charts can be useful tools to facilitate depicting pharmaceutical quality system processes in a visual manner · management responsibilities within the pharmaceutical quality system

[1] International Conference on Harmonisation of Technical Requirements of Registration of Pharmaceuticals in Human Use "Pharmaceutical Quality System Q10"

New or amended requirements	Remarks
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: … (viii) Sufficient reference samples of starting materials and products are retained **in accordance with Annex 19** to permit future examination of the product if necessary **and that the sample is retained in the final pack**	Amended wording provides clarification that retention samples should be retained in the final pack for finished products. This is to ensure that samples are truly representative of products on the market. Those manufacturers who do not currently retain retention samples in their finished pack due to pack size will now be required to ensure actual packs are retained.
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**	Additional text provides clarification that the supply chain for active ingredients should be known and verified. This is to ensure the integrity of APIs used in the manufacture of marketed products. Manufacturers will be required to have an understanding of the supply chain for APIs and include a review of the supply chain traceability in the Product Quality Review (PQR).

Part I Chapter 2 - Personnel

New or amended requirements	Remarks
2.4 **Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place to achieve the quality objectives, and, that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality and should ensure continuing suitability and effectiveness of the Pharmaceutical Quality System and GMP compliance through participation in management review**.	Further improved guidance for documenting the quality assurance system. The development of a quality policy (as defined in ICH Q10) should define the following: · senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality · the quality policy should include an expectation to comply with applicable regulatory requirements and should facilitate continual improvement of the pharmaceutical quality system · the quality policy should be communicated to and understood by personnel at all levels in the company · the quality policy should be reviewed periodically for continuing effectiveness
2.23 **Consultants should have adequate education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants**.	This new clause clarifies the responsibility of the manufacturer to ensure that consultants, when used, are determined to hold appropriate skills/knowledge in order to provide appropriate advice. This clause simply formalises the requirement to document the details of the consultant and the services that are provided.

New or amended requirements	Remarks
2.9 The heads of Production, Quality Control **and where relevant, Head of Quality Assurance or Head of Quality Unit**, generally have some shared, or jointly exercised, responsibilities relating to quality **including in particular the design, effective implementation, monitoring and maintenance of the Pharmaceutical Quality System**. These may include, subject to any national regulations: … **xii. Participation in management reviews of process performance, product quality and of the Pharmaceutical Quality System and advocating continual improvement;** **xiii. Ensuring that a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management**.	Clarified responsibilities for nominees for production, quality control and, where relevant, the head of Quality Assurance. 2.9 xii. refers to the responsibilities for management reviews; please refer to the requirements for management reviews under Chapter 1 changes above. 2.9 xiii. clarifies the responsibilities of management for the timely escalation of issues to senior management to facilitate appropriate actions and ensure appropriate resources are employed to resolve these in a timely manner. This requirement complements existing requirements in Chapter 1 Principle and basic quality system requirements.

Part I Chapter 4 - Documentation

New or amended requirements	Remarks
4.10 **It should be clearly defined which record is related to each manufacturing activity and where this record is located. Secure controls must be in place to ensure the integrity of the record throughout the retention period and validated where appropriate**. 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. For investigational medicinal products, the batch documentation must be kept for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used. Other requirements for retention of documentation may be described in legislation in relation to specific types of product (e.g. Advanced Therapy Medicinal Products) and specify that longer retention periods be applied to certain documents**. 4.12 **For other types of documentation, the retention period will depend on the business activity which the documentation supports. Critical documentation, including raw data (for example relating to validation or stability), which supports information in the Marketing Authorisation should be retained whilst the authorisation remains in force. It may be considered acceptable to retire certain documentation (e.g. raw data supporting validation reports or stability reports) where the data has been superseded by a full set of new data. Justification for this should be documented and should take into account the requirements for retention of batch documentation; for example, in the case of process validation data, the accompanying raw data should be retained for a period at least as long as the records for all batches whose release has been supported on the basis of that validation exercise**.	New clauses providing improved guidance/clarification to allow for a risk-based approach to document retention.

New or amended requirements	Remarks
4.29 There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached, where appropriate, for the following examples: · Validation **and qualification of processes, equipment and systems**; · Equipment assembly and calibration; · **Technology transfer**; · Maintenance, cleaning and sanitation; · Personnel matters including **signature lists**, training in GMP and technical matters, clothing and hygiene **and verification of the effectiveness of training**; · Environmental monitoring; · Pest control; · Complaints; · Recalls; · Returns; · **Change control**; · **Investigations into deviations and non-conformances**; · **Internal quality/GMP compliance audits**; · **Summaries of records where appropriate (e.g. product quality review)**; · **Supplier audits**.	Several additions to a list of required procedures, however, all additions were already required based on other parts of PIC/S Guide to GMP PE009-08.

Part I Chapter 6 - Quality Control

New or amended requirements	Remarks
6.8 Any Quality Control documentation relating to a batch record should be retained **following the principles given in chapter 4 on retention of batch documentation**.	Application of a risk-based approach to document retention as per Chapter 4.
6.16 The results obtained should be recorded. **Results of parameters identified as critical quality attributes should be trended** and checked to make sure that they are consistent with each other. Any calculations should be critically examined.	Amended clause to provide additional clarity and guidance that is almost identical in intent to existing PE009-8 Chapter 6 clauses 6.16. The clause includes reference to the trending of critical quality attributes, which is in line with the current requirements regarding PQRs.
Technical transfer of testing methods 6.37 **Prior to transferring a test method, the transferring site should verify that the test method(s) comply with those as described in the Marketing Authorisation or the relevant technical dossier. The original validation of the test method(s) should be reviewed to ensure compliance with current ICH/VICH requirements. A gap analysis should be performed and documented to identify any supplementary validation that should be performed, prior to commencing the technical transfer process**. 6.38 **The transfer of testing methods from one laboratory (transferring laboratory) to another laboratory (receiving laboratory) should be described in a detailed protocol**.	Clauses 6.37 to 6.41 provide additional guidance as to how appropriate method transfer should be performed. These clauses are aligned to current TGA GMP expectations.

New or amended requirements	Remarks
6.39 **The transfer protocol should include, but not be limited to, the following parameters:** **i. Identification of the testing to be performed and the relevant test method(s) undergoing transfer;** **ii. Identification of the additional training requirements;** **iii. Identification of standards and samples to be tested;** **iv. Identification of any special transport and storage conditions of test items;** **v. The acceptance criteria which should be based upon the current validation study of the methodology and with respect to ICH/VICH requirements**. 6.40 - **Deviations from the protocol should be investigated prior to closure of the technical transfer process. The technical transfer report should document the comparative outcome of the process and should identify areas requiring further test method revalidation, if applicable**. 6.41 - **Where appropriate, specific requirements described in other guidelines should be addressed for the transfer of particular testing methods (e.g. Near Infrared Spectroscopy)**.	Clauses 6.37 to 6.41 provide additional guidance as to how appropriate method transfer should be defined and documented. These clauses are aligned to current TGA GMP expectations.

Part I Chapter 7 - Outsourced activities

New or amended requirements	Remarks
Principle **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.	The scope of this chapter has been amended to include oversight of all outsourced activities that may have an impact on quality operations and ultimately the quality of the medicinal product. It is expected that manufacturers manage and control those relationships in accordance with existing principles in order to manage risks, ensure compliance and ultimately ensure product quality. Examples of outsourced activities that this chapter would apply to include, (but are not limited to): · Contract manufacturing and analysis, · Maintenance and calibration services, · Providers of critical consumables, e.g. gowns, sterilised componentry · Supply of raw materials, packaging materials and printed artwork, · Provision of training and consulting services, · Validation services associated with facilities, equipment, utilities, process and product design, qualification and validation. · Provision of transport and logistical services for unreleased products. · Contract cleaning and waste management services · Contract pest control services. · Agencies that provide temporary/contract personnel · Suppliers/service providers of GMP computerised systems

Part II Section 2 - Quality Risk Management

New or amended requirements	Remarks
2.2 - **Quality Risk Management** 2.20 **Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the active substance. It can be applied both proactively and retrospectively**. 2.21 **The quality risk management system should ensure that:** · **the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient through communication with the user of the active substance.** · **the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.** **Examples of the processes and applications of quality risk management can be found, inter alia, in Annex 20**.	Clarification regarding application of quality risk management to the manufacture of Active Pharmaceutical Ingredients, which has been industry practice for many years.

Annex 2 - Manufacture of biological medicinal substances and products for human use

New or amended requirements	Remarks
SCOPE The methods employed in the manufacture of biological medicinal substances and products are a critical factor in shaping the appropriate regulatory control. Biological medicinal substances and products can be defined therefore largely by reference to their method of manufacture. **This annex provides guidance on the full range of medicinal substances and products defined as biological.** **This annex is divided into two main parts:** **a) Part A contains supplementary guidance on the manufacture of biological medicinal substances and products, from control over seed lots and cell banks or starting material through to finishing activities and testing.** **b) Part B contains further guidance on selected types of biological medicinal substances and products.** **This annex, along with several other annexes of the Guide to GMP, provides guidance which supplements that in Part I and in Part II of the Guide. There are two aspects to the scope of this annex:** **a) Stage of manufacture - for biological active substances to the point immediately prior to their being rendered sterile, the primary guidance source is Part II. Guidance for the subsequent manufacturing steps of biological products are covered in Part I. For some types of product (e.g. Advanced Therapy Medicinal Products (ATMP) cell-based products) all manufacturing steps need to be conducted aseptically.** **b) Type of product - this annex provides guidance on the full range of medicinal substances and products defined as biological.**	This Annex has undergone a major rewrite to reflect better the requirements for different biological manufacturing processes. Very little of PE 009-8 remains, and what does is included under PART A 'General guidance'. Part B is completely new and provides GMP guidance for specific biological medicinal products. Please note, Annex 2 only applies to therapeutic goods that are required to be manufactured according to the *PIC/S guide for Good Manufacturing Practice for medicinal products*.

New or amended requirements	Remarks
Table 1. Illustrative guide to manufacturing activities within the scope of Annex 2 See the PIC/S website for the new table.	The scope of the annex provides clarification to requirements for some early stages of manufacture the control of which directly affects the quality of medicinal products, e.g. collection of plant, organ, tissue or fluid. The TGA expects each biological medicine manufacturer in the supply chain to have adequate oversight of their suppliers in the supply chain, and to hold appropriate supplier (or vendor) qualification documentation for each supplier that includes, among other things an assessment of whether the supplier operates in accordance with the general principles of GMP as outlined in this Annex. e.g. A manufacturer utilising porcine intestinal mucosa as a starting material for an API extraction process would be expected to hold adequate documentation to demonstrate that the abattoir utilised operates to an appropriate level of GMP. Annex 2 only applies to therapeutic goods that are required to be manufactured according to the *PIC/S guide for Good Manufacturing Practice for medicinal products*.

New or amended requirements	Remarks
20. **In addition to compliance with TSE regulations, other adventitious agents that are of concern (zoonotic diseases, diseases of source animals) should be monitored by an ongoing health programme and recorded. Specialist advice should be obtained in establishing such programmes. Instances of ill-health occurring in the source animals should be investigated with respect to their suitability and the suitability of in-contact animals for continued use (in manufacture, as sources of starting materials, in quality control and safety testing), the decisions must be documented. A look-back procedure should be in place which informs the decision making process on the continued suitability of the medicinal substance(s) or product(s) in which the materials have been used or incorporated. This decision-making process may include the re-testing of retained samples from previous collections from the same donor (where applicable) to establish the last negative donation. The withdrawal period of therapeutic agents used to treat source animals must be documented and used to determine the removal of those animals from the programme for defined periods**.	Clarified requirement for establishing health programme for animals and actions to be taken when ill-health detected.
24. **For different animal species, key criteria should be defined, monitored, and recorded. These may include age, weight and health status of the animals**.	Improved guidance for requirements to maintain specific data in relation to each animal used in production.
29. **Given the variability inherent in many biological substances and products, steps to increase process robustness thereby reducing process variability and enhancing reproducibility at the different stages of the product lifecycle such as process design should be reassessed during Product Quality Reviews**.	Improved guidance to ensure the robustness of manufacturing and quality control processes, e.g. process design, as part of PQR processes.

New or amended requirements	Remarks
32. **The risk of contamination of starting materials during their passage along the supply chain must be assessed, with particular emphasis on TSE. Materials that come into direct contact with manufacturing equipment or the product (such as media used in media fill experiments and lubricants that may contact the product) must also be taken into account**.	Addition of a specific reference to TSEs for starting materials. This clause aligns with the prevailing TGA requirements for minimising the risk of transmitting transmissible spongiform encephalopathies: 'Transmissible Spongiform Encephalopathies (TSE): TGA approach to minimising the risk of exposure'
65. **The compatibility of labels with ultra-low storage temperatures, where such temperatures are used, should be verified**.	Improved guidance for the requirement to validate the compatibility of labels used on containers maintained in ultra-low storage conditions.
68. **Where intermediates can be stored for extended periods of time (days, weeks or longer), consideration should be given to the inclusion of final product batches made from materials held for their maximum in-process periods in the on-going stability programme**.	Improved clarification of requirements for ongoing-stability program. The principles outlined by this clause align with existing TGA expectations.

New or amended requirements	Remarks
71. For products with a short shelf life, which need batch certification before completion of all end product quality control tests (e.g. sterility tests) a suitable control strategy must be in place. Such controls need to be built on enhanced understanding of product and process performance and take into account the controls and attributes of input materials. The exact and detailed description of the entire release procedure, including the responsibilities of the different personnel involved in assessment of production and analytical data is essential. A continuous assessment of the effectiveness of the quality assurance system must be in place including records kept in a manner which permit trend evaluation. Where end product tests are not possible due to their short shelf life, alternative methods of obtaining equivalent data to permit batch certification should be considered (e.g. rapid microbiological methods). The procedure for batch certification and release may be carried out in two or more stages - before and after full end process analytical test results are available: **a) Assessment by designated person(s) of batch processing records and results from environmental monitoring (where available) which should cover production conditions, all deviations from normal procedures and the available analytical results for review and conditional certification by the Responsible Person.** **b) Assessment of the final analytical tests and other information available before end product dispatch for final product certification by the Responsible Person.** **c) A procedure should be in place to describe the measures to be taken (including liaison with clinical staff) where out of specification test results are obtained after product dispatch. Such events should be fully investigated and the relevant corrective and preventative actions taken to prevent recurrence documented.** **A procedure should describe those measures which will be taken by the Responsible Person if unsatisfactory test results are obtained after dispatch.**	Additional clause to provide improved guidance to facilitate the timely release for short-shelf-life products and where products are not able to be tested prior to release because of their short shelf life. This clause includes the principles of a 'control strategy' and expected knowledge of the entire manufacturing process, as well as aspects relating to: · Release procedure · Record keeping · Roles and responsibilities

New or amended requirements	Remarks
B1. **ANIMAL SOURCED PRODUCTS**	New section providing GMP guidance for the manufacturers of animal sourced products. This section contains seven clauses providing requirements for supplier approval and management, supply chain integrity, material traceability, and the control and health monitoring of livestock.
B2. **ALLERGEN PRODUCTS**	New section providing GMP guidance for the manufacturers of allergen products. This section contains four clauses providing requirements for supplier approval and management and processing controls.

Annex 3 - Radiopharmaceuticals

New or amended requirements	Remarks
18. **Access to the manufacturing areas should be via a gowning area and should be restricted to authorised personnel**.	New clause providing improved guidance on the requirements for the use of separate gowning areas for access to manufacturing areas. Manufacturers of sterile radiopharmaceuticals already have more stringent requirements based on Annex 1; manufacturers of non-sterile radiopharmaceuticals only are already required to have gowning facilities based on the general requirements of GMP.
27. **In case of use of closed and automated systems (chemical synthesis, purification, on-line sterile filtration) a grade C environment (usually "Hot-cell") will be suitable. Hot-cells should meet a high degree of air cleanliness, with filtered feed air, when closed. Aseptic activities must be carried out in a grade A area**.	New clause for sterile radiopharmaceutical products providing clarification for the minimum environmental requirements for fully closed and automated systems in that these activities may be performed in a grade C hot-cell. Operations not defined as fully closed and automated should be performed in environments conforming to Annex 1 grading principles.
33. **Records should be retained for at least 3 years unless another timeframe is specified in national requirements**.	Improved clarification for the retention period for records.

Annex 6 - Medicinal gases

New or amended requirements	Remarks
PERSONNEL 5. **All personnel involved in the manufacture and distribution of medicinal gases should receive an appropriate GMP training applying to this type of products. They should be aware of the critically important aspects and potential hazards for patients from these products**. 6. **Personnel of subcontractors that could influence the quality of medicinal gases (such as personnel in charge of maintenance of cylinders or valves) should be appropriately trained**.	Clearer requirements relating to training, now including expectations for staff to be trained on hazards to patients and for subcontractor staff to be appropriately trained.
17. Data included in the records for each batch of cylinders / mobile cryogenic vessels must ensure that each filled cylinder is traceable to significant aspects of the relevant filling operations. As appropriate, the following should be entered: b) **batch number**; g) quantity of cylinders/mobile cryogenic vessels before filling, **including individual identification references and water capacity(ies)**; m) **quantity of rejected cylinders/mobile cryogenic vessels, with individual identification references and reasons for rejections**; o) **certification statement by the Authorised Person, date and signature**.	Improved clarification of requirements for items recorded during batch manufacture.

New or amended requirements	Remarks
18. **Records should be maintained for each batch of gas intended to be delivered into hospital tanks. These records should, as appropriate, include the following (items to be recorded may vary depending on local legislation):** **a) name of the product;** **b) batch number;** **c) identification reference for the tank (tanker) in which the batch is certified;** **d) date and time of the filling operation;** **e) identification of the person(s) carrying out the filling of the tank (tanker);** **f) reference to the supplying tanker (tank), reference to the source gas as applicable;** **g) relevant details concerning the filling operation;** **h) specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment);** **i) details of any problems or unusual events, and signed authorisation for any deviation from filling instructions; and** **j) certification statement by the Authorised Person, date and signature**.	Additional guidance for the control of bulk deliveries to hospitals. These clauses would only apply in situations where the gas is not exempt under Schedule 7 item 17 of the Therapeutic Goods Regulations 1990.

Annex 7 - Herbal medicinal products

New or amended requirements	Remarks
Principle **The "starting material" in the manufacture of an herbal medicinal product[2] can be a medicinal plant, an herbal substance[3] or an herbal preparation[2]. The herbal substance should be of suitable quality and supporting data should be provided to the manufacturer of the herbal preparation/herbal medicinal product. Ensuring consistent quality of the herbal substance may require more detailed information on its agricultural production. The selection of seeds, cultivation and harvesting conditions represent important aspects of the quality of the herbal substance and can influence the consistency of the finished product. Recommendations on an appropriate quality assurance system for good agricultural and collection practice are provided in national or international guidance documents on Good Agricultural and Collection Practice for starting materials of herbal origin[4].** **This Annex applies to all herbal starting materials: medicinal plants, herbal substances or herbal preparations**.	Additional guidance regarding the control of starting materials, which aligns to current practices and expectations. Note that the statements within this annex relating to Good Agricultural and Collection Practice (GACP) are not mandatory. Alternative methods of assuring the suitability and quality of herbal starting materials are permissible. It is recommended that GACP practices are considered during supplier qualification, as GACP may assist in influencing routine sampling and testing programs for herbal starting materials. The recommendations herein regarding GACP apply to manufacturers involved in the cultivation of herbal starting materials (herbs) only, and do not apply to local manufacturers using herbal extracts in the manufacture of therapeutic goods. GMP exemptions provided under Schedule 7 of the Therapeutic Goods Regulations 1990 are not affected by the wording of the new annex 7.

2 Throughout the annex and unless otherwise specified, the term "herbal medicinal product / preparation" includes "traditional herbal medicinal product / preparation".

3 The terms herbal substance and herbal preparation are considered to be equivalent to the terms herbal drug and herbal drug preparation respectively.

4 European Medicines Agency (EMA), World Health Organization (WHO) or equivalent.

New or amended requirements	Remarks
9. The processing instructions should describe the different operations carried out upon the herbal substance such as **cleaning**, drying, crushing and sifting, and include drying time and temperatures, and methods used to control cut size or particle size. 10. **In particular, there should be written instructions and records, which ensure that each container of herbal substance is carefully examined to detect any adulteration/substitution or presence of foreign matter, such as metal or glass pieces, animal parts or excrement, stones, sand, etc., or rot and signs of decay**. 11. **The processing instructions should also describe security sieving or other methods of removing foreign materials and appropriate procedures for cleaning/selection of plant material before the storage of the approved herbal substance or before the start of manufacturing**.	Additional guidance regarding the requirements for the cleaning of herbal materials, removal of foreign matter and checking for adulteration prior to use.

Annex 11 - Computerised systems

New or amended requirements	Remarks
-	This annex has been re-written to align with current standards developed by industry, to increase clarity and to reduce prescriptive characteristics of the Annex where possible. All amendments in the annex provide clarification of existing expectations for both stand-alone and networked systems and no additional regulatory burden is anticipated.

Annex 13 - Investigational medicinal products

New or amended requirements	Remarks
36. **Samples are retained to fulfil two purposes; firstly to provide a sample for analytical testing and secondly to provide a specimen of the finished product...** **Reference and retention samples of investigational medicinal product, including blinded product should be kept for at least two years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer**. Consideration should be given to keeping retention samples until the clinical report has been prepared to enable confirmation of product identity in the event of, and as part of an investigation into inconsistent trial results.	Additional clause bringing requirements relating to retention samples in line with existing Annex 19.
37. **The storage location of Reference and Retention samples should be defined in a Technical Agreement between the sponsor and manufacturer(s) and should allow timely access by the competent authorities.** **The reference sample should be of sufficient size to permit the carrying out, on, at least, two occasions, of the full analytical controls on the batch in accordance with the IMP dossier submitted for authorisation to conduct the clinical trial.** **In the case of retention samples, it is acceptable to store information related to the final packaging as written or electronic records if such records provide sufficient information. In the case of the latter, the system should comply with the requirements of Annex 11**.	Additional clause bringing requirements relating to retention samples in line with existing Annex 19.

Annex 15 - Qualification and validation

New or amended requirements	Remarks
PRINCIPLE This Annex describes the principles of qualification and validation which are applicable to the **facilities, equipment, utilities and processes used for** the manufacture of medicinal products **and may also be used as supplementary optional guidance for active substances without introduction of additional requirements to Part II. It is a GMP requirement that manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process. Any planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, should be formally documented and the impact on the validated status or control strategy assessed. Computerised systems used for the manufacture of medicinal products should also be validated according to the requirements of Annex 11. The relevant concepts and guidance presented in ICH Q8, Q9, Q10 and Q11 should also be taken into account**.	The new principle includes clarification to the scope of Annex 15; however, no new or additional requirements are implicated as a result of the change to this section. Introduces the concept of the 'validation life-cycle'. This is a concept alluded to in the existing Annex 15, (and Chapter 5 clauses 5.21-5.24). The principle outlines a link between Annex 15 and Part II of the GMP guide; in that Annex 15 can provide guidance but does not invoke additional requirements for validation for APIs under Part II. i.e. Annex 15 does not apply to the validation of APIs as Part II section 12 specifies the validation requirements for manufacturers of APIs. The ICH Q8-Q11 documents are and remain as guidance for industry – the use of the word 'should' in the last sentence should be taken in its literal sense and should not be interpreted as a mandatory requirement.
GENERAL **... Retrospective validation is no longer considered an acceptable approach**.	The concept of process validation has been in place for over 14 years, it is now expected that existing processes are validated, and that any new or modified processes from this point on should be validated prior or concurrently with the supply of medicinal products. All medicines supplied in Australia must have appropriate and documented process validation. The manufacturing process should be validated before the product is placed on the market. Therefore it is expected that validation should be performed prospectively, or (where justified and under exceptional circumstances only) concurrently for all medicines newly introduced to manufacturing sites post implementation.

New or amended requirements	Remarks
User requirements specification (URS) 3.2 **The specification for equipment, facilities, utilities or systems should be defined in a URS and/or a functional specification. The essential elements of quality need to be built in at this stage and any GMP risks mitigated to an acceptable level. The URS should be a point of reference throughout the validation life cycle**.	Improved guidance on the requirement to develop and verify URS documentation to support validation activities. (where warranted e.g. for qualification of new systems).
5.10 **For all products irrespective of the approach used, process knowledge from development studies or other sources should be accessible to the manufacturing site, unless otherwise justified, and be the basis for validation activities**.	Clarifies that data and information from drug development/process development stages should be available to the manufacturing facility and considered when undertaking process validation. This concept is a continuation to the lifecycle approach to validation. A risk based compliance approach would be expected based on whether the process is new, has been transferred or subject to prior development.

New or amended requirements	Remarks
5.12 **The suppliers of critical starting and packaging materials should be qualified prior to the manufacture of validation batches; otherwise a justification based on the application of quality risk management principles should be documented**.	Provides improved clarification regarding the documented justification for the use of unapproved materials to be used in validation activities. This is in line with current expectations. It is expected that this clause would only apply where concurrent vendor approval is underway, i.e. the material is under evaluation (pending approval) as part of the validation exercise. The justification for using unapproved suppliers should consider: · Risks to the manufacturing process, plant and other existing products as a result of using unapproved materials · Assurance that the materials are from the correct vendor and meet the required specification · Controls regarding the approval, analysis and release of unapproved materials are in place · Controls regarding issuance and reconciliation of starting materials are in place · Systems in place to prevent release of validation batches prior to the material supplier being fully qualified
5.16 In exceptional circumstances, **where there is a strong benefit-risk ratio for the patient**, it may be acceptable not to complete a validation programme before routine production starts and **concurrent validation could be used. However**, the decision to carry out concurrent validation must be justified, documented **in the VMP for visibility** and approved by authorised personnel. 5.17 **Where a concurrent validation approach has been adopted, there should be sufficient data to support a conclusion that any given batch of product is uniform and meets the defined acceptance criteria. The results and conclusion should be formally documented and available to the Authorised Person prior to certification of the batch**.	Improved clarity for the requirement that concurrent process validation is only performed where there is an established and justified benefit for the patient. Where concurrent process validation has been performed, the details of the validation should be reported and finalised, and made available to the authorised person performing batch certification (release for supply).

New or amended requirements	Remarks
5.19 **The number of batches manufactured and the number of samples taken should be based on quality risk management principles, allow the normal range of variation and trends to be established and provide sufficient data for evaluation. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product**. 5.20 **Without prejudice to 5.19, it is generally considered acceptable that a minimum of three consecutive batches manufactured under routine conditions could constitute a validation of the process. An alternative number of batches may be justified taking into account whether standard methods of manufacture are used and whether similar products or processes are already used at the site. An initial validation exercise with three batches may need to be supplemented with further data obtained from subsequent batches as part of an on-going process verification exercise**.	Improved clause allows the manufacturer to justify the number of batches manufactured for process validations, rather than mandate a minimum of 3. The number of batches should be justified using Quality Risk Management (QRM) principles (See ICH Q9 for guidance). TGA's basic expectation is that: · For a new process/product, a minimum of 3 batches to be conducted for process validation purposes · For a process subject to technology transfer from one site to another an extensive evaluation and risk assessment would be required (with supporting data) regarding the similarities and differences in manufacturing processes, equipment, methods and materials should be in place to justify performing less than three batches · For changes to existing (validated) processes, e.g. batch size increase, an extensive evaluation and risk assessment would be required (with supporting data) regarding the similarities and differences in manufacturing processes, equipment, methods and materials should be in place to justify the number of batches selected
5.21 **A process validation protocol should be prepared which defines the critical process parameters (CPP), critical quality attributes (CQA) and the associated acceptance criteria which should be based on development data or documented process knowledge**.	This clause introduces the terms CPP and CQA in line with ICH Q11 terminology. While the terminology has been adopted, the process of identifying critical steps (that directly influence the critical attributes of the product) and acceptance criteria remain very similar to existing methods and expectations. (Note that these concepts already exist for API manufacturers.)

New or amended requirements	Remarks
5.22 **Process validation protocols should include, but are not limited to the following**: i. A short description of the process **and a reference to the respective Master Batch Record**; ii. Functions and responsibilities; iii. **Summary of the CQAs to be investigated**; iv. **Summary of CPPs and their associated limits**; v. **Summary of other (non-critical) attributes and parameters which will be investigated or monitored during the validation activity, and the reasons for their inclusion**; vi. List of the equipment/facilities to be used (including measuring/monitoring/recording equipment) together with the calibration status; vii. List of analytical methods **and method validation**, as appropriate; viii. Proposed in-process controls with acceptance criteria **and the reason(s) why each in-process control is selected**; ix. Additional testing to be carried out, with acceptance criteria; x. Sampling plan **and the rationale behind it**; xi. Methods for recording and evaluating results; xii. **Process for release and certification of batches (if applicable)**.	This new clause provides clarity of some existing expectations by outlining requirements for all process validation documentation. Items iii and iv use the newly introduced terminology of CPP and CQA. The actual output of these requirements would align with the current requirements for risk based validation, but would standardise terminology.

New or amended requirements	Remarks
Continuous process verification 5.23 **For products developed by a quality by design approach, where it has been scientifically established during development that the established control strategy provides a high degree of assurance of product quality, then continuous process verification can be used as an alternative to traditional process validation.** 5.24 **The method by which the process will be verified should be defined. There should be a science based control strategy for the required attributes for incoming materials, critical quality attributes and critical process parameters to confirm product realisation. This should also include regular evaluation of the control strategy. Process Analytical Technology and multivariate statistical process control may be used as tools. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product.** 5.25 **The general principles laid down in 5.1 – 5.14 above still apply**.	This clause relates to those products using a Quality by Design (QbD) approach to development and process control. This concept is only applicable to these products and reflects contemporary approaches to process validation.
Hybrid approach 5.26 **A hybrid of the traditional approach and continuous process verification (CPV) could be used where there is a substantial amount of product and process knowledge and understanding which has been gained from manufacturing experience and historical batch data.** 5.27 **This approach may also be used for any validation activities after changes or during ongoing process verification even though the product was initially validated using a traditional approach**.	This clause applies to products that have undergone traditional validation, and where the manufacturer has significant data regarding the process control parameters. A CPV approach may be adopted for continuous verification of the process to ensure it is under control.

New or amended requirements	Remarks
Ongoing Process Verification during Lifecycle 5.28 **Paragraphs 5.28-5.32 are applicable to all three approaches to process validation mentioned above, i.e. traditional, continuous and hybrid.** 5.29 **Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated.** 5.30 **The extent and frequency of ongoing process verification should be reviewed periodically. At any point throughout the product lifecycle, it may be appropriate to modify the requirements taking into account the current level of process understanding and process performance.** 5.31 **Ongoing process verification should be conducted under an approved protocol or equivalent documents and a corresponding report should be prepared to document the results obtained. Statistical tools should be used, where appropriate, to support any conclusions with regard to the variability and capability of a given process and ensure a state of control.** 5.32 **Ongoing process verification should be used throughout the product lifecycle to support the validated status of the product as documented in the Product Quality Review. Incremental changes over time should also be considered and the need for any additional actions, e.g. enhanced sampling, should be assessed**.	Improved clarity of requirements for monitoring process performance. Manufacturers are expected to perform ongoing process verification for validated processes to ensure that they continue to operate in a state of control. The frequency for this review should be based on risk, and should be linked to process knowledge – more frequent for less well understood processes and vice versa.

New or amended requirements	Remarks
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.** 6.2 **It is recognised that verification of transportation may be challenging due to the variable factors involved however, transportation routes should be clearly defined. Seasonal and other variations should also be considered during verification of transport** 6.3 **A risk assessment should be performed to consider the impact of variables in the transportation process other than those conditions which are continuously controlled or monitored, e.g. delays during transportation, failure of monitoring devices, topping up liquid nitrogen, product susceptibility and any other relevant factors.** 6.4 **Due to the variable conditions expected during transportation, continuous monitoring and recording of any critical environmental conditions to which the product may be subjected should be performed, unless otherwise justified**.	Improved guidance on the requirements relating to the validation of transportation of medicines. Controls must be in place for the transport processes for starting materials, bulk and packed medicines between sites of manufacture, including to overseas destinations, and these clauses would apply in those circumstances. Products should be transported in accordance with their labelled and authorised conditions only, and the transport conditions should have been formally evaluated and confirmed as effective. While the TGA does not have regulatory oversight of wholesaling and distribution activities regulated by state and territory governments, quality agreements (as per Chapter 7) should clearly specify which party is responsible for the management of transportation.
10.5 **For all cleaning processes an assessment should be performed to determine the variable factors which influence cleaning effectiveness and performance, e.g. operators, the level of detail in procedures such as rinsing times etc. If variable factors have been identified, the worst case situations should be used as the basis for cleaning validation studies**.	Improved clarity on the requirement for the assessment of cleaning practices.

New or amended requirements	Remarks
10.6 **Limits for the carryover of product residues should be based on a toxicological evaluation[2]. The justification for the selected limits should be documented in a risk assessment which includes all the supporting references. Limits should be established for the removal of any cleaning agents used. Acceptance criteria should consider the potential cumulative effect of multiple items of equipment in the process equipment train.** 10.6.1 **Therapeutic macromolecules and peptides are known to degrade and denature when exposed to pH extremes and/or heat, and may become pharmacologically inactive. A toxicological evaluation may therefore not be applicable in these circumstances.** 10.6.2 **If it is not feasible to test for specific product residues, other representative parameters may be selected, e.g. total organic carbon (TOC) and conductivity.** **[2] In the EU/EEA, this is the EMA Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities**	This clause provides clarification of setting of cleaning limits based on toxicological data. This clause would not normally apply to the manufacture of listed complementary medicines. The guideline referenced is also referenced in the proposed updates to Chapters 3 and 5; it is expected that this EMA Guideline (or PIC/S equivalent) will be considered for adoption in Australia.

Transition plan

The transition period from 1 January 2018 to 1 January 2019 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.

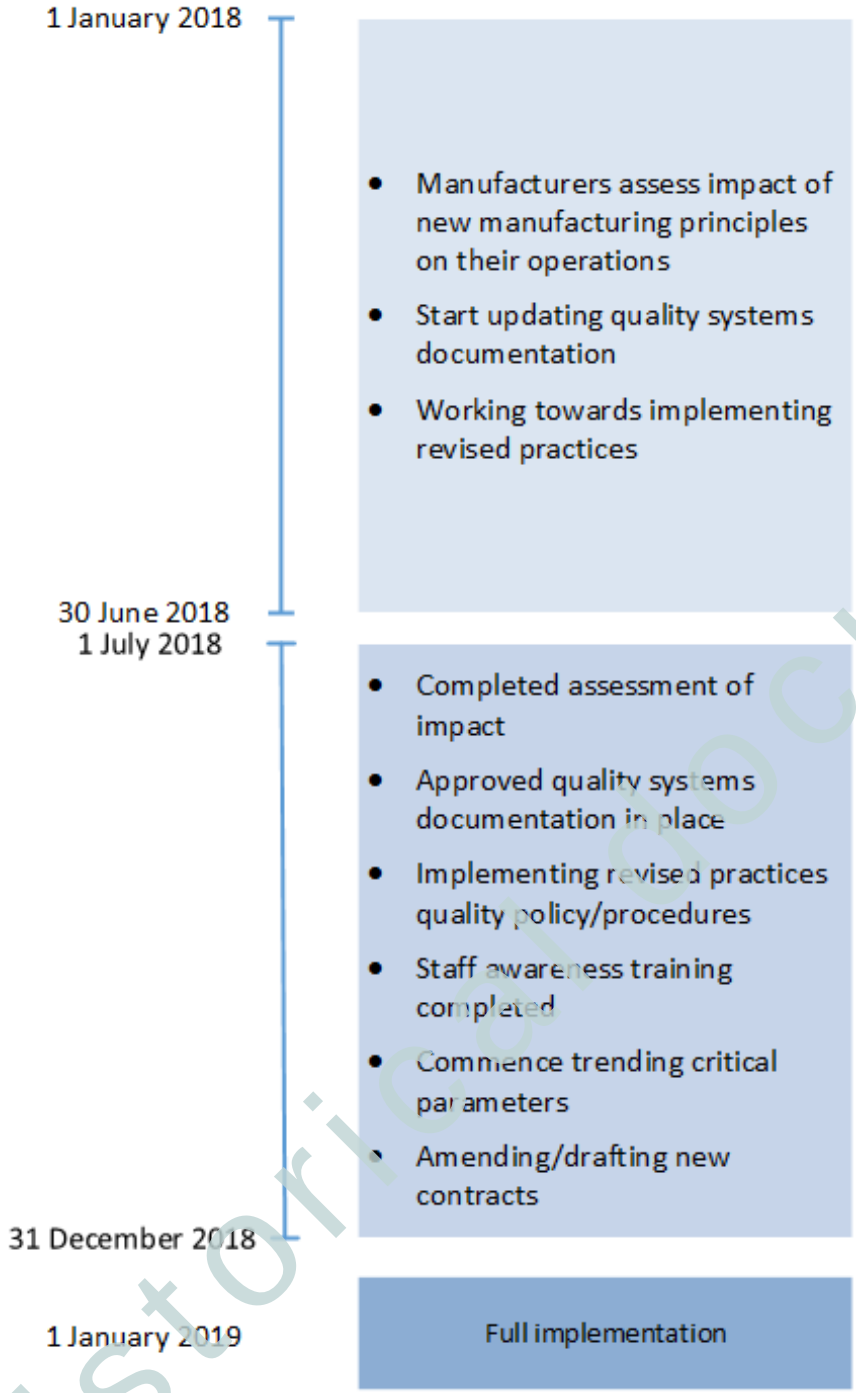
Compliance with all other changes is expected from 1 January 2018 and transition arrangements do not apply.

Our expectation is that by 1 July 2018, 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 July 2018, unless justified.

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 only be cited 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 1

PIC/S GMP Requirement	Between 1 January and 30 June 2018	Between 1 July 2018 and 31 December 2018	From 1 January 2019
Clause 1.6: Management Reviews	· Approved policy · Documented assessment of which data will be collated and reported · Commenced amending and drafting procedures · Commenced training staff in Management Reviews	· Initial management review meetings held · Mechanisms for resolving issues formalised and implemented · Schedule for management reviews finalised	Full implementation
Clause 1.7: Quality Manual	· Commence drafting of Quality Manual (ICH Q10)	· Approved Quality Manual in place	Full implementation
Clause 1.10(i): Review of supply chain traceability for APIs	· Documented assessment of APIs utilised by the manufacturer · Commenced drafting procedures for the evaluation of API supply chains and schedule for completion · Drafting updates to existing Product Quality Review (PQR) procedures to incorporate new requirements	· Commence evaluation of supply chains for APIs used by the site	Full implementation

Part I, Chapter 2

PIC/S GMP Requirement	Between 1 January and 30 June 2018	Between 1 July 2018 and 31 December 2018	From 1 January 2019
Clause 2.4: Quality Policy	· Senior management commence drafting of Quality Policy (ICH Q10) · Mechanism for continuous improvement defined and documented	· Approved Quality Policy in place · Staff awareness training completed · Periodic reviews of Quality Policy scheduled · Full implementation	Full implementation

Part I, Chapter 6

PIC/S GMP Requirement	Between 1 January and 30 June 2018	Between 1 July 2018 and 31 December 2018	From 1 January 2019
Clause 6.16: Trending of critical parameters	· Documented assessment of which data will be collated and reported, including assessment of the extent of any retrospective trending · Commenced amending and drafting procedures · Commenced training staff in trending of critical parameters	· Commence trending of critical parameters	Full implementation
Clauses 6.37-6.41: Guidelines for method transfer	· Documented assessment of existing procedures against new guidance · Defined timeline for any amendments required for existing procedures	· Approved procedures in place for method transfer · Method transfer activities performed in accordance with new requirements	Full implementation

Part I, Chapter 7

PIC/S GMP Requirement	Between 1 January and 30 June 2018	Between 1 July 2018 and 31 December 2018	From 1 January 2019
Outsourced activities	· Approved policy · Commenced drafting procedures · Risk assess/Determine list of all service providers implicated · Develop priority list for evaluation and approval of providers	· Approved procedures · Commenced amending/drafting new contracts	Full implementation All outsourced activities approved and covered by an appropriate contract

Part II, Chapter 2

PIC/S GMP Requirement	Between 1 January and 30 June 2018	Between 1 July 2018 and 31 December 2018	From 1 January 2019
Clause 2.2: Application of Quality Risk Management (QRM) to the manufacture of Active Pharmaceutical Ingredients	· Approved policy · Documented assessment where QRM will apply · Commenced amending and drafting procedures · Commenced training staff in QRM	· QRM is built into the Quality System · Commenced using QRM in changes, investigations etc	Full implementation

Annex 2 Manufacture of biological medicinal substances and products for human use

PIC/S GMP Requirement	Between 1 January and 30 June 2018	Between 1 July 2018 and 31 December 2018	From 1 January 2019
Annex 2: Manufacture of biological medicinal substances and products for human use	· Documented assessment of Annex 2 changes and impact upon existing operations · Change controls initiated within Quality Management System (QMS) · Commence updates to Marketing Authorisations for affected products	· Commence implementing changes	Full implementation
Application of Good Manufacturing Practice to additional elements of the supply chain, e.g. collection sites for animal/plant tissues	· Documented assessment of Annex 2 changes and impact upon existing operations · Change controls initiated within QMS · Collate list of impacted manufacturing sites	· Commence evaluation and supplier approval of additional manufacturing sites within the scope of Annex 2	Full implementation

Annex 3 Manufacture of Radiopharmaceuticals

PIC/S GMP Requirement	Between 1 January and 30 June 2018	Between 1 July 2018 and 31 December 2018	From 1 January 2019
Clause 18: Requirement to have separate gowning facilities at entry of production area	· Documented assessment of impact of change · Change controls and implementation plans initiated within QMS for any modifications identified	· Commence any modification of facilities required	Full implementation

PIC/S GMP Requirement	Between 1 January and 30 June 2018	Between 1 July 2018 and 31 December 2018	From 1 January 2019
Clause 27: Positioning of closed and automated systems	· Documented assessment of impact of change · Change controls and implementation plans initiated within QMS for any modifications identified	· Commence any modification of facilities where required	Full implementation
Clause 33: Introduction of a fixed retention period for batch records	· Documented assessment of impact of change · Commence drafting of procedures for document retention	· Approved procedures in place for batch record retention	Full implementation

Annex 6 Manufacture of Medicinal Gases

PIC/S GMP Requirement	Between 1 January and 30 June 2018	Between 1 July 2018 and 31 December 2018	From 1 January 2019
General	· Documented assessment of Annex 6 changes and impact upon existing operations · Change controls initiated within QMS	· Commence implementing changes	Full implementation

Annex 7 Manufacture of Herbal medicinal products

PIC/S GMP Requirement	Between 1 January and 30 June 2018	Between 1 July 2018 and 31 December 2018	From 1 January 2019
General	· Documented assessment of Annex 7 changes and impact upon existing operations · Change controls initiated within QMS	· Commence implementing changes	Full implementation

Annex 11 Computerised Systems

PIC/S GMP Requirement	Between 1 January and 30 June 2018	Between 1 July 2018 and 31 December 2018	From 1 January 2019
General	· Documented assessment of Annex 11 changes and impact upon existing operations · Change controls initiated within QMS	· Commence implementing changes	Full implementation

Annex 13 Manufacture of Investigational Medicinal Products

PIC/S GMP Requirement	Between 1 January and 30 June 2018	Between 1 July 2018 and 31 December 2018	From 1 January 2019
Clauses 36 & 37: Management of retention/reference samples	· Documented assessment of Annex 13 changes and impact upon existing operations · Change controls initiated within QMS to address reference/retention sample requirements	· Commence implementing changes	Full implementation

Annex 15 Qualification and Validation

PIC/S GMP Requirement	Between 1 January and 30 June 2018	Between 1 July 2018 and 31 December 2018	From 1 January 2019
General	· Documented assessment of Annex 15 changes and impact upon existing operations · Change controls initiated within QMS to address new requirements	· Commence implementing changes	Full implementation
Removal of provision to perform retrospective process validation	· Assessment of current products undergoing retrospective validation · Record plan for completion of process validation based on retrospective data · Update internal procedures to remove provisions for retrospective process validation · Prospective validation required prior to release for all new products	· Full implementation from 1 July 2018 · Only prospective or (in justified cases) concurrent process validation permitted from this date onwards	Full implementation
Clauses 5.8-5.32: Introduction of ongoing process verification	· Documented assessment of the impact of the new requirement · Commenced amending and drafting procedures · Commenced training staff	· Commence collation of data for ongoing verification process · Commence reporting of outcomes from ongoing verification process	Full implementation

PIC/S GMP Requirement	Between 1 January and 30 June 2018	Between 1 July 2018 and 31 December 2018	From 1 January 2019
Clauses 6.1-6.4: Verification of transportation	· Approved policy · Commenced amending and drafting procedures including system for assessing transport routes · Identify key transportation methods and routes and define plan for assessment · Commenced training staff	· Commence risk assessments for transportation methods and routes · Commence monitoring of transported products	Full implementation
Clause 10.6: Cleaning validation – toxicological assessments	· Approved policy · Commenced amending and drafting procedures for toxicological assessments · Identify actives and materials that require toxicological assessment and devise risk-based plan for systematic assessment · Commenced training staff	· Commence performing and documenting toxicological assessment of actives and excipients used by the manufacturing facility	Full implementation

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Manufacturing Quality Branch	November 2017

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