Adoption of Future PIC/S Revisions Implementation of PIC/S Guide to GMP PE009-16

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Overview

- Why adopt the latest PIC/S version
- Implementation strategy
- What are the changes?
- Upcoming revisions

Why adopt the latest version of PIC/S

- Provide guidance for the management of new technologies
- Address gaps in existing compliance requirements
- Facilitate continuous improvement
- In response to identified risks to patients' health:
- Relevant to our Mutual Recognition Agreements
- Provides assurance of equivalence to international markets

Adoption Process

The TGA doesn't automatically adopt new versions of PIC/S GMP Guide.

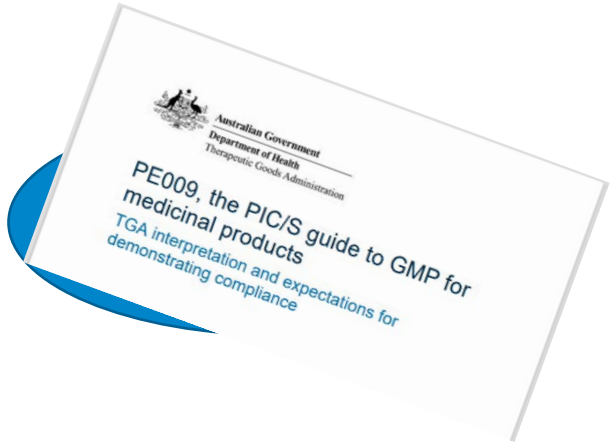
Gap analysis (technical requirements)

Regulatory burden

Consultation with stakeholders (e.g. TIWGG)

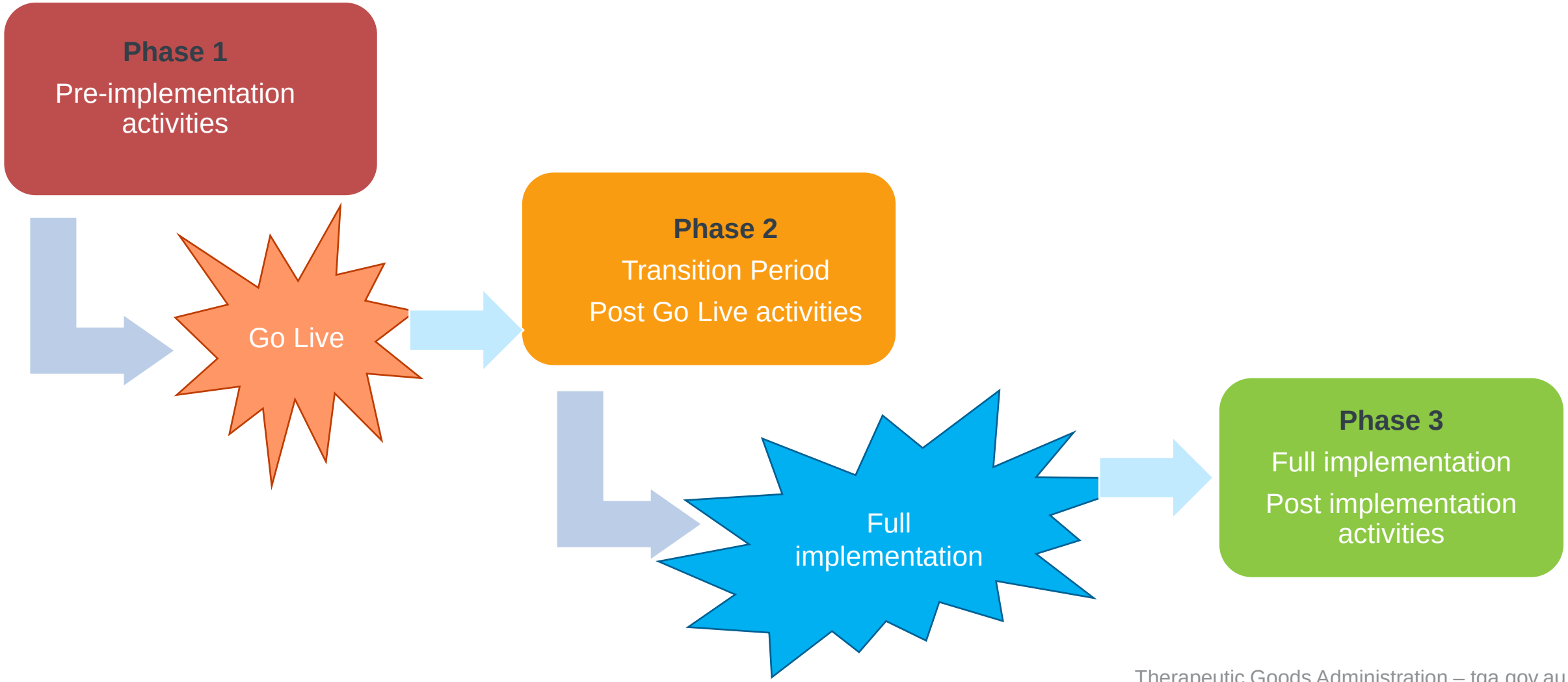
Feedback assessed

Areas of concerns



Provides other guidance documents

Implementation Strategy



What are the changes in PE009-16?

ANNEX 13

MANUFACTURE OF INVESTIGATIONAL MEDICINAL PRODUCTS

INTRODUCTION

These guidelines lay down appropr… to address specific issues concerning investigational medi… gard to good manufacturing practice. The tools are fl… anges as knowledge of the process increases and a… of development of the product.

An investigational medic… uct is a pharmaceutical form of an active substance or placebo bein… sted or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

Unless otherwise defined in national law, manufacturing is defined as total and partial manufacture, as well as the various processes of dividing up, packaging and labelling (including blinding).

Revision

ANNEX 16

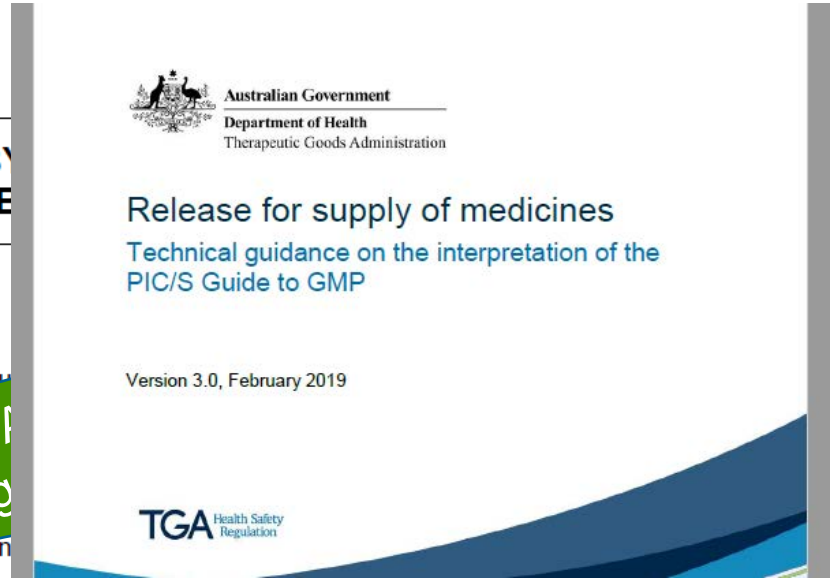
CERTIFICATION BY E…

SCOPE

This Annex provides gu… on batch rele… Pharmac… or made … medicinal … provisions … Authorities u… ation…

Guidance in this Annex on the certification of batches by a manufacturer of a medicinal product is within the scope of the Pharmaceutical Inspection Co-operation Scheme. However, each PIC/S Participating Authority may decide whether guidance expressed in this annex should become a legally-binding standard in relation to imported medicinal products.

New A… g…



Annex 13

Manufacture of Investigational Medicinal Products

ANNEX 13 MANUFACTURE OF INVESTIGATIONAL MEDICINAL PRODUCTS

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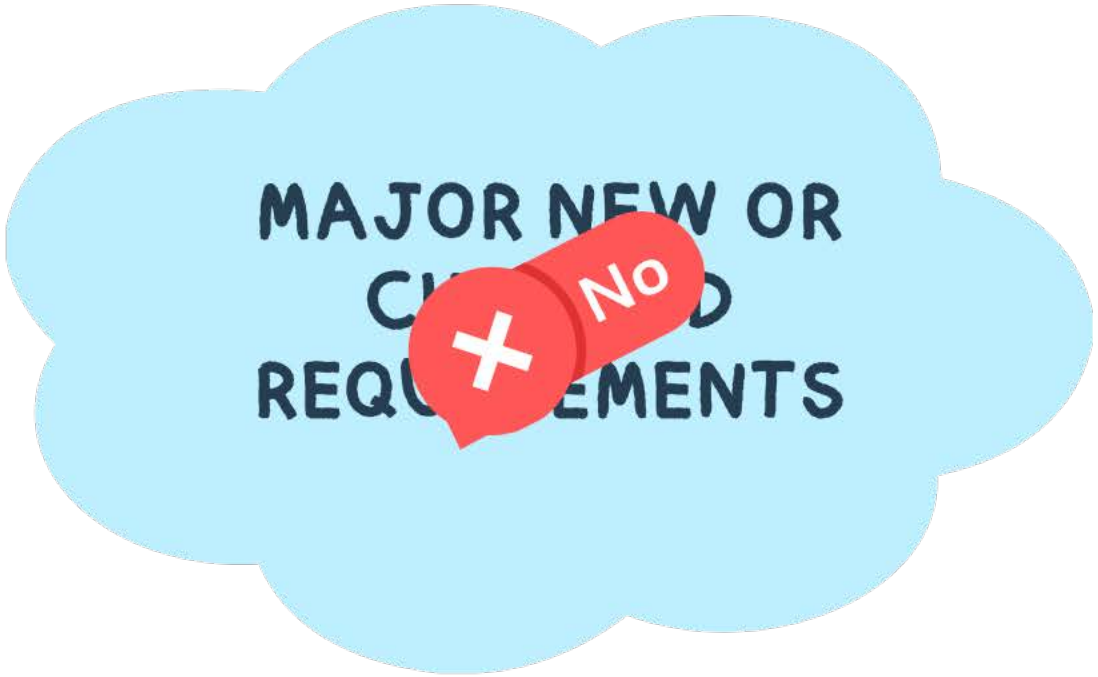


ANNEX 13 MANUFACTURE OF INVESTIGATIONAL MEDICINAL PRODUCTS

SIGNIFICANT MODIFICATIONS TO CLARIFY REQUIREMENTS

Changes in Annex 13 – Section 2 Pharmaceutical Quality System

Section 2 - *The* ***selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance****, should be documented as part of the pharmaceutical quality system to ensure the* ***integrity of the supply chain*** *and protect against falsified products…….*

- No equivalent clause but not a new requirement.
- Support PE009-15 Clause 5.27 (selection and approval of suppliers) and 1.4vi (integrity of the supply chain).
- Support PE009-15 Annex 13 Clause 38 (certification of manufacture)

Section 2.1(3) – ***Product Specification File*** *to also include clinical trial authorisations, randomisation codes, reference and retention sample details, details of supply chain including manufacturing, packaging, labelling and testing sites for the investigational medicinal products, preferably in the format of a comprehensive diagram.*

- Existing information/documents
- Now required to be included in the Product Specification File.

Changes in Annex 13 – Section 5 Documentation

Section 5(1) - *……Documents which are part of the **Product Specification File** shall be retained for the period of **at least 5 years**, unless otherwise specified in relevant national laws*

- No equivalent clause but not a new requirement.
- The requirement is already in PE009-15 Clause 4.11

Section 5(2) - *The sponsor may have specific responsibilities for document retention of the **clinical trial master file**……. should retain such documentation for **at least 25 years** after the end of the trial.*

- New requirement
- Manufacturer may need to review their document retention policy.

Section 5.2 - *The manufacturer should retain the **order** for the investigational medicinal product as part of the batch documentation*

- Amended clause but no change to expectation.

Changes in Annex 13 – Section 6 Production

Section 6.2(3) - *To avoid cross-contamination, written **cleaning procedures** and **analytical methods** to verify the cleaning process should be available.*

- New clause but no new requirements.
- Gives further guidance and supports the existing clause in PE009-15 Annex 15 Clause 10.3 (cleaning verification)

Section 6.4(2) - *Where products are blinded, the expiry date assigned to all products should be stated at the **expiry of the shortest dated product** so that the blinding is maintained.*

- No equivalent clause but not a new requirement.
- Clarifies the existing expectation.

Section 6.3(3) - *A reference sample of comparator product, which has been **repackaged or over encapsulated for blinding purposes**, should be taken at a point representative of the additional processing and retained, as the additional processing step could have an impact on stability or be needed for identification purposes in the event of a quality defect investigation, which would not be covered by the commercial retained sample.*

- No equivalent clause but not a new requirement.
- Supports the existing clause in PE009-15 Annex 13 Clause 36 (reference and retention samples).

Changes in Annex 13 – Section 6 Production

Section 6.5(1) - *Documentation must be sufficient to demonstrate that **appropriate segregation** has been maintained during any packaging operations.*

- No equivalent clause but not a new requirement.
- Clarify the existing expectation.

Section 6.6(2) - *The information which shall appear on the labelling should comply with any relevant national laws or requirements.*

Clauses 27 – 32 and Table 1 which contained very prescriptive labelling requirements (in addition to clause 26) have been removed, and replaced with a general statement in Section 6.6(2).

However, the TGA's expectation is that the requirements in Clauses 27-32 still apply. These requirements will be included in the Interpretation guidance.

PE009-15 Annex 13 Clauses 27-32 and Table 1

product);

h) "For clinical trial use only" or similar wording;

i) the storage conditions;

j) period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity.

k) "keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.

27. The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times.

28. Particulars should appear in the official language(s) of the country in which the investigational medicinal product is to be used. The particulars listed in Article 26 should appear on the primary packaging and on the secondary packaging (except for the cases described in Articles 29 and 30). The requirements with respect to the contents of the label on the primary and secondary packaging are summarised in table 1. Other languages may be included.

29. When the product is to be provided to the trial subject or the person administering the medication within aprimary packaging together with secondary packaging that is intended to remain together, and the secondary packaging carries the particulars listed in paragraph 26, the following information should be included on the label of the primary package (or any sealed dosing device that contains theprimary packaging):

a) name of sponsor, contract research organisation or investigator;

b) pharmaceutical dosage form, route of administration (may be excluded for oral solid dose forms), quantity of dosage units and in the case of open label trials, the name/identifier and strength/potency;

c) batch and/or code number to identify the contents and packaging operation;

d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

e) the trial subject identification number/treatment number and where relevant, the visit number.

30. If the primary packaging takes the form of blister packs or small units such as ampoules on which the particulars required in paragraph 26 cannot be displayed, outer packaging should be provided bearing a label with those particulars. The immediate container should nevertheless contain the following:

a) name of sponsor, contract research organisation or investigator;

b) route of administration (may be excluded for oral solid dose forms) and in the case of open label trials, the name/identifier and strength/potency;

c) batch and/or code number to identify the contents and packaging operation;

d) a trial reference code allowing identification of the trial, site, investigator

TABLE 1. SUMMARY OF LABELLING DETAILS (§26 TO 30)

a) name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding);

b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials[3], the name/identifier and strength/potency;

c) the batch and/or code number to identify the contents and packaging operation;

d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

e) the trial subject identification number / treatment number and where relevant, the visit number;

f) the name of the investigator (if not included in (a) or (d);

g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product

h) "for clinical trial use only" or similar wording;

i) the storage conditions;

j) period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity.

k) "keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.

GENERAL CASE

For both the primary and secondary packaging (§26)

Particulars
a[4] to k

PRIMARY PACKAGE
Where primary and secondary packaging remain together throughout (§29)[5]

a[5] b[7] c d e

PRIMARY PACKAGE
Blisters or small packaging units (§30)[5]

a[5] b[7,8] c d e

[3] For closed blinded trials, the labelling should include a statement indicating "placebo or [name/identifier] + [strength/potency]".

[4] The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times (§ 27).

[5] When the outer packaging carries the particulars listed in Article 26.

[6] The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not be included.

[7] Route of administration may be excluded for oral solid dose forms.

[8] The pharmaceutical dosage form and quantity of dosage units may be omitted.

Changes in Annex 13 – Section 6 Production

Section 6.5(1) - *Documentation must be sufficient to demonstrate that **appropriate segregation** has been maintained during any packaging operations.*

- No equivalent clause but not a new requirement.
- Clarify the existing expectation.

Section 6.6(2) - *The information which shall appear on the labelling should comply with any relevant national laws or requirements.*

Clauses 27 – 32 and Table 1 which contained very prescriptive labelling requirements (in addition to clause 26) have been removed, and replaced with a general statement in Section 6.6(2).

However, the TGA's expectation is that the requirements in Clauses 27-32 still apply. These requirements will be included in the Interpretation guidance.

Changes in Annex 13 – Section 7 Quality Control

Section 7 – Retention and reference sample retention period

- The requirement of to retain retention and reference sample 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 was ***deleted***.
- Align with the requirements with Annex 19 clause 3.1 (duration of storage)

Section 7(11-14) – Retention and reference samples

- No equivalent clause but not a new requirement. Clarify the existing expectation.

Changes in Annex 13 – Section 8 Release of Batches

Section 8(4) – *The assessment by the Authorised Person of each batch for certification prior to release ……*

- Make reference to Annex 16, and include ***verification of the supply chain including manufacturing, packaging, labelling and testing sites for the investigational medicinal products.***
- Not a new requirement, support PE009-15 Clause 1.4vi (integrity of the supply chain).

Section 8.7 – Where required to support certification, the Authorised Person has to ensure that the investigational medicinal product has been ***stored and transported under conditions that maintain product quality and supply chain security.***

- No equivalent clause but not a new requirement. Clarify the existing expectation.

Section 8(6) – Where investigational medicinal products are produced and packaged at different sites under the supervision of different Authorised Persons, sharing of responsibilities amongst the Authorised Persons in relation to compliance of a batch must be ***defined in a document formally agreed by all parties****.*

- New requirement.

Annex 16

Certification by the Authorised Person and Batch Release

Annex 16

Provide guidance to support:

PIC/S Part I Chapter 1, Clause1.4 (xv) – *Medicinal products are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products.*

Annex 16

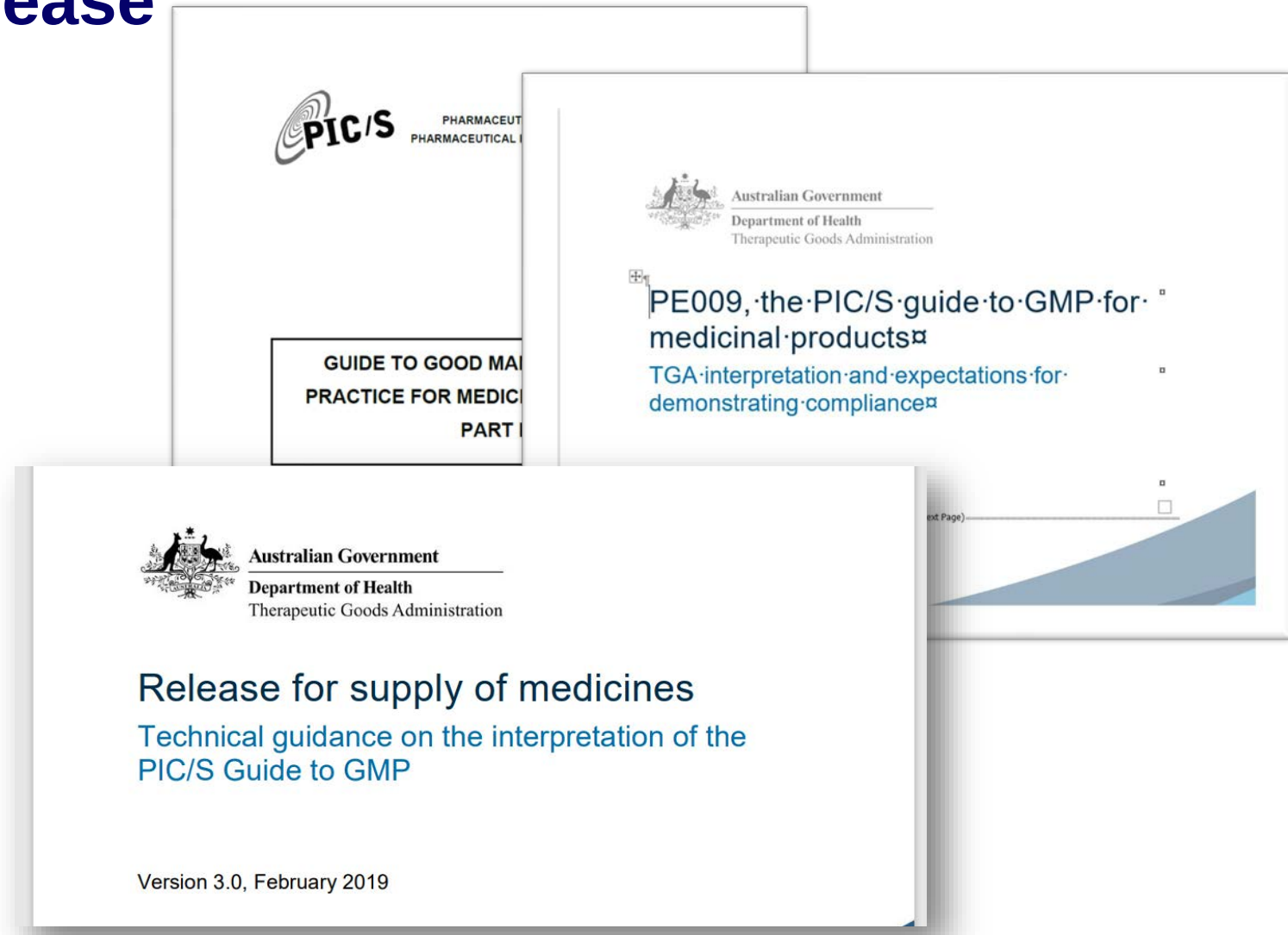
- New Annex to PIC/S Guide to GMP

- Based on Annex 16 of European cGMP, Eudralex Volume 4 (effective since April 2016
  - Almost identical (reference to European ‘Directives’ removed and replaced with more generic terms)
  - Authorised Person (AP) in PIC/S vs Qualified Person (QP) in Eudralex

- Scope:
  - Applicable to medicines for ***human or veterinary use***
  - Also applies to ***investigational medicinal products*** (IMP) for human use
  - Applicable to locally manufactured and imported products

Annex 16 Certification by the Authorised Person and Batch Release

New Annex



Annex 16

The purpose of controlling batch release

- Meet MA requirements
- Meet GMP requirements
- Meet other legal requirements

AP must have

- Detailed knowledge
- Continuous training - product type, product processes, technical advances, changes to GMP

Confirmation vs Certification

- **Confirmation** = Release for further processing (RFFP) – template in Appendix 1
- **Certification** = Release for supply (RfS) – template in Appendix 2

Annex 16

Section 1: The Process of Certification

- Section 1.3 – Multi sites

- Section 1.4 – AP
  - 1.4.1 AP should have access to the necessary details of MA
  - 1.4.3 written agreement showing shared release responsibilities

- Section 1.5 – Medicinal products manufactured outside the jurisdiction of a National Competent Authority
  - Not applicable unless specifically required in the MA

Annex 16

Section 1: The Process of Certification (continued)

- Section 1.7 – List of AP's responsibilities when performing RfS
  - More explicit – TGA is determining the expectations based on risk.

- Section 1.9 – Parallel importation and distribution
  - Not applicable as Australia does not permit 'parallel importation'

- Section 1.10 – Records
  - TGA is working through our expectations

Annex 16

- Section 2: Relying on GMP assessment by 3rd party
  - clarification of existing requirement
  - more explicit
  - TGA is determining the expectations based on risk

- Section 3: Handling of unexpected deviations
  - Permit batch with unexpected deviations to be released if registered specifications are met (if appropriate after investigation and risk assessment).
  - In Australia, TG Act includes penalties for supply of products not conforming to standards. Consent to supply must be obtained from the TGA.

- Section 4: The release of a batch
  - 4.1 and 4.2 – Shipping under quarantine

    '*shipped under quarantine to another site which has been approved for that purpose by the relevant National Competent Authority*' **(= have the relevant licence step**), and the receiving site have adequate safeguards against inadvertent transfer to released stock …….

Future Revisions

Future Revisions

- PIC/S PE009-17 including Annex 1 Manufacture of sterile medicinal products
- Annex 14 Manufacture of medicinal products derived from human blood and plasma
- Chapter 4 (Documentation), Annex 11 (Computerised Systems) and Annex 15 (Qualification and Validation)

Participate in the Q&A

Verbal questions:

Raise your hand to ask a verbal question. A member of the GMP Forum staff will provide a roaming microphone.

Written questions:

Scan the QR code below or click the link in your calendar to access Slido via your mobile device. You can submit your question, and vote on other questions submitted.

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Coming up next in this room

Jenny Burnett

GMP Forum 2023 Concluding remarks