PIC/S PE009-13

Highlights of Changes & The Path Ahead

Presented by Maria Mylonas,

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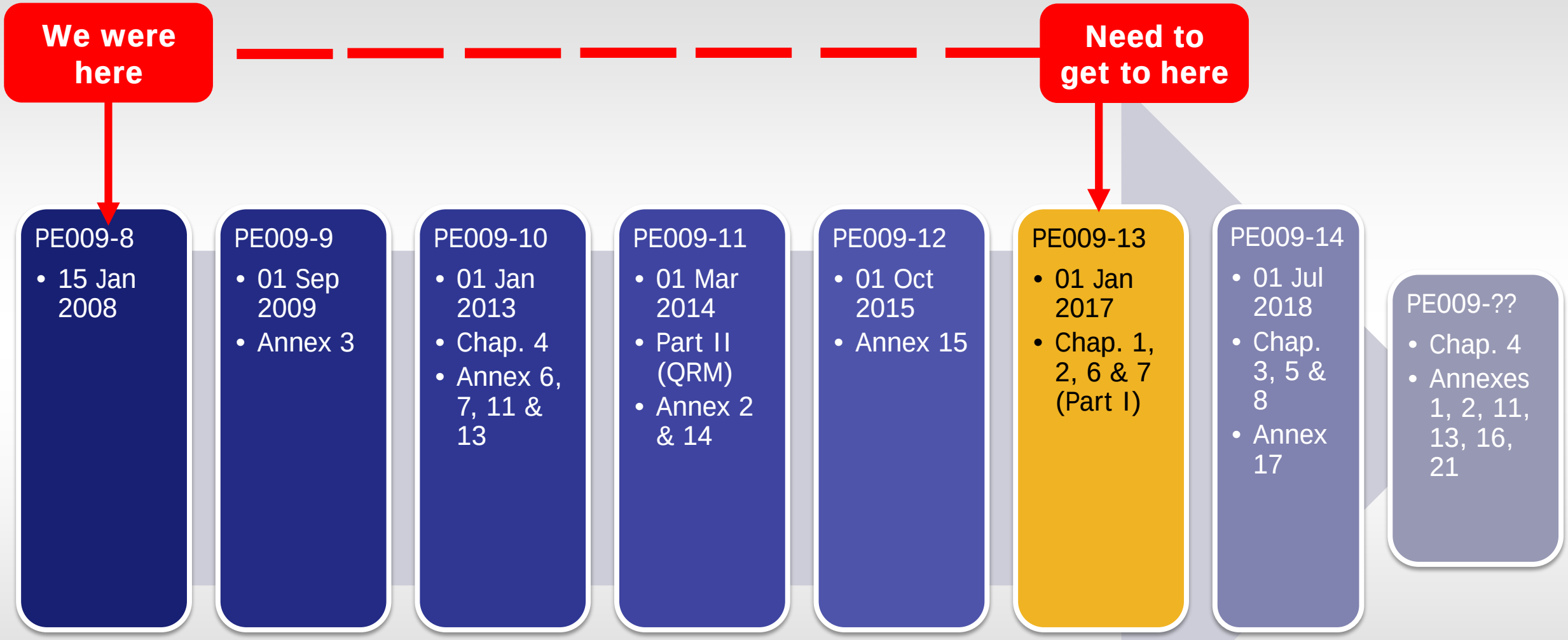
GMP, Engineering & Cannabis Forum 2018

PharmOut

Agenda

- PIC/S PE009-13 Adoption timeline
- TGA's Expectations & Deficiencies Reporting
- PICS PE009-13 Highlights Chapters 1, 2, 6 & 7
- PICS PE009-14 Highlights Chapters 3, 5, 8 Ax. 17

Exciting Times Ahead



Adoption Timeline for PE009-13

Sep 2017
- 1st notification for industry
- APVMA notification

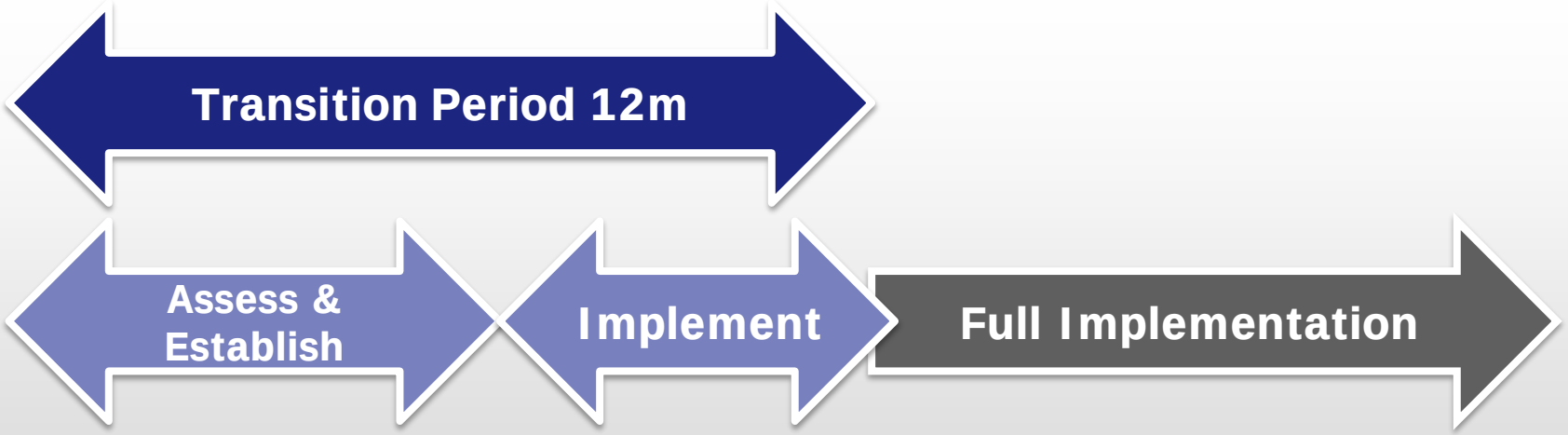
Nov 2017
- 2nd notification for industry
- Adoption strategy

1 Jan 2018
- Adopt version 13

31 Jun 2018

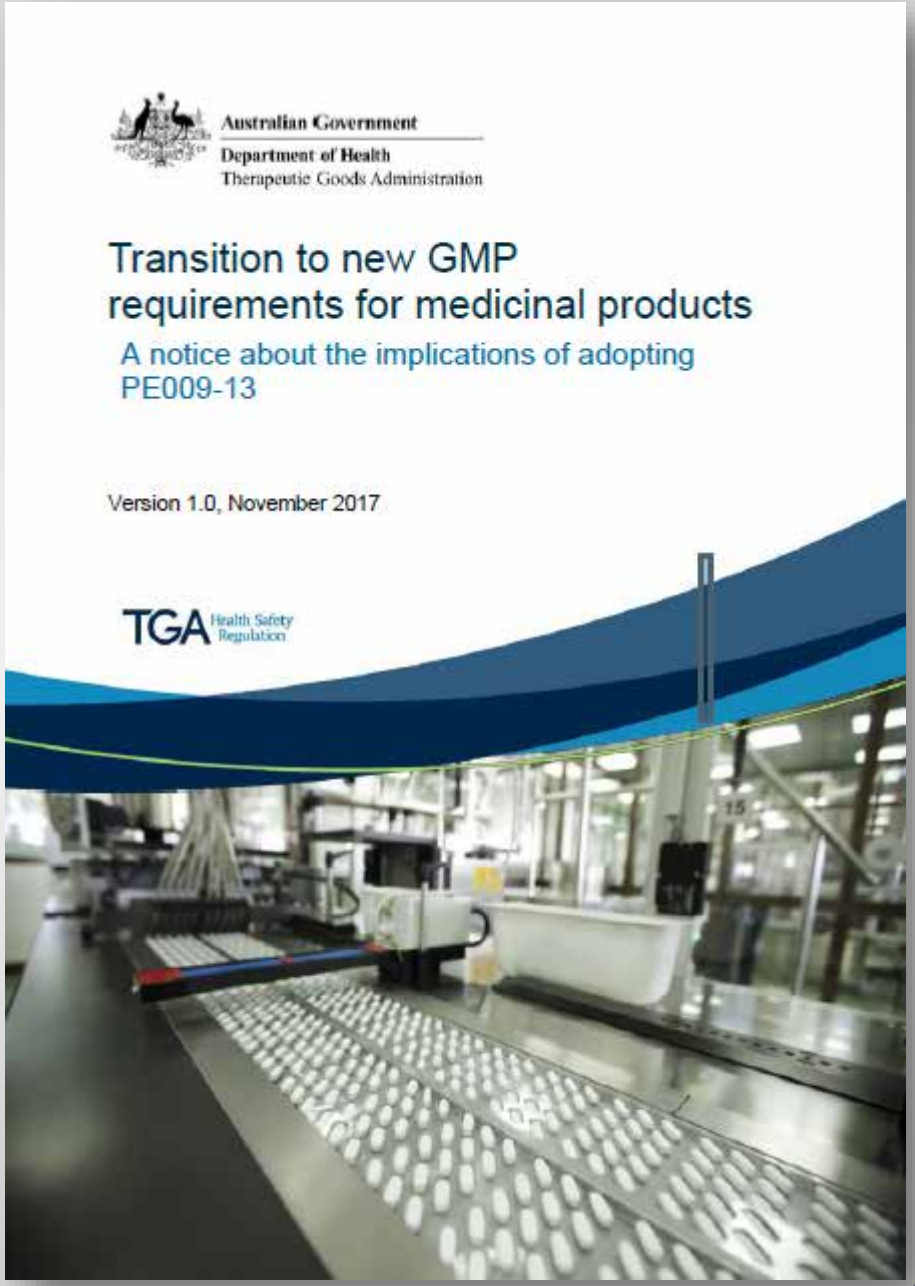
1 Jan 2019

Ongoing



Need more detail?

- 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.



How will TGA report deficiencies during this period?

- TGA will aim to assist and encourage implementation of the new requirements.
- Can you demonstrate you're meeting the minimum expectations?
- The TGA 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.

How will TGA report deficiencies during this period?

- 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.

Highlights of new and amended requirements

Chapter 1: Pharmaceutical Quality System

1.5 **Senior management** is ultimately responsible for the PQS including resources, leadership and active participation and ensuring the support and commitment of all staff.

1.6 Clarification of **periodic management reviews** of the PQS including involvement of **senior management** and the identification of **continual improvement** opportunities

1.7 Defined and **documented PQS** with a new requirement for a **quality manual** or equivalent.

Chapter 1: Pharmaceutical Quality System

1.9 (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**

1.10 Periodic quality reviews of all authorised medicinal products.

(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**

Chapter 2: Personnel

2.4 Development of a **Quality Policy** by **senior management,** describing the intentions and direction of the company related to quality.

Expectation to comply with applicable regulatory requirements and should facilitate **continual improvement** of the PQS

Communicated to and understood by all staff

Reviewed periodically for continuing effectiveness

Chapter 2: Personnel
Consultants

2.23

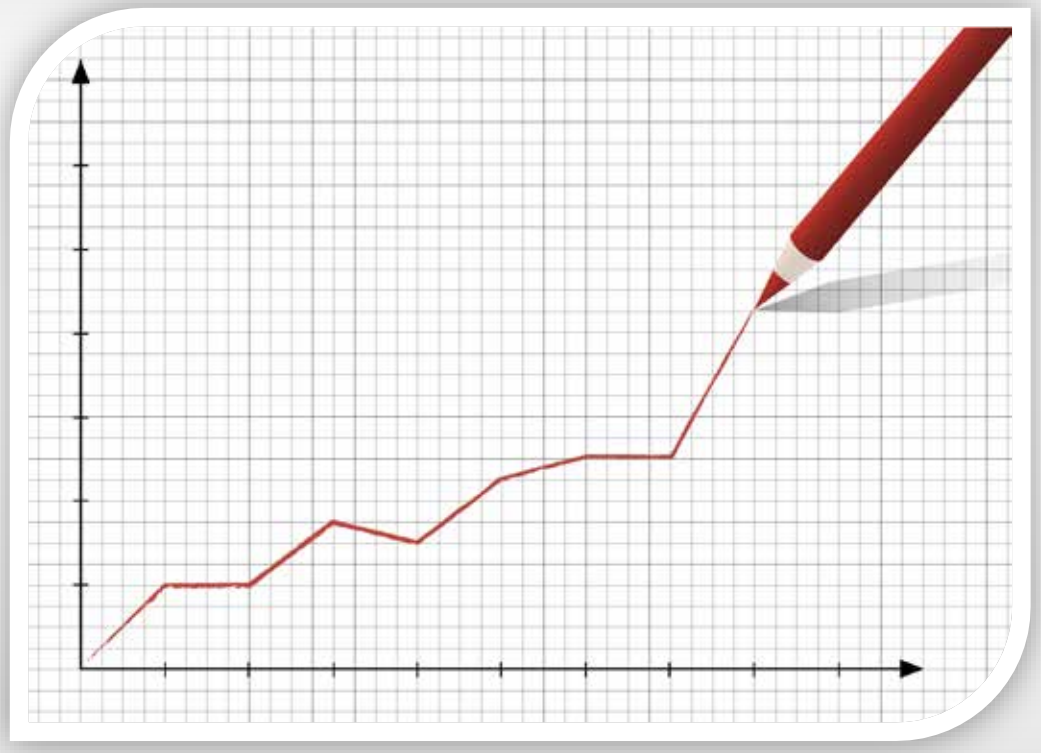
Consultants should have adequate education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

Chapter 6: Quality control

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**.

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.



Chapter 6: Quality control
Technical Transfers

Clauses 6.37 to 6.41 provide additional guidance as to how appropriate method transfer should be performed.

Transfer of Testing between:

- R&D to QC
- QC lab to other internal QC lab
- To contract manufacturer
- To contract test laboratory

All require a detailed, documented technical transfer protocol and a completed report before test use in manufacturing

Chapter 7: Outsourced activities

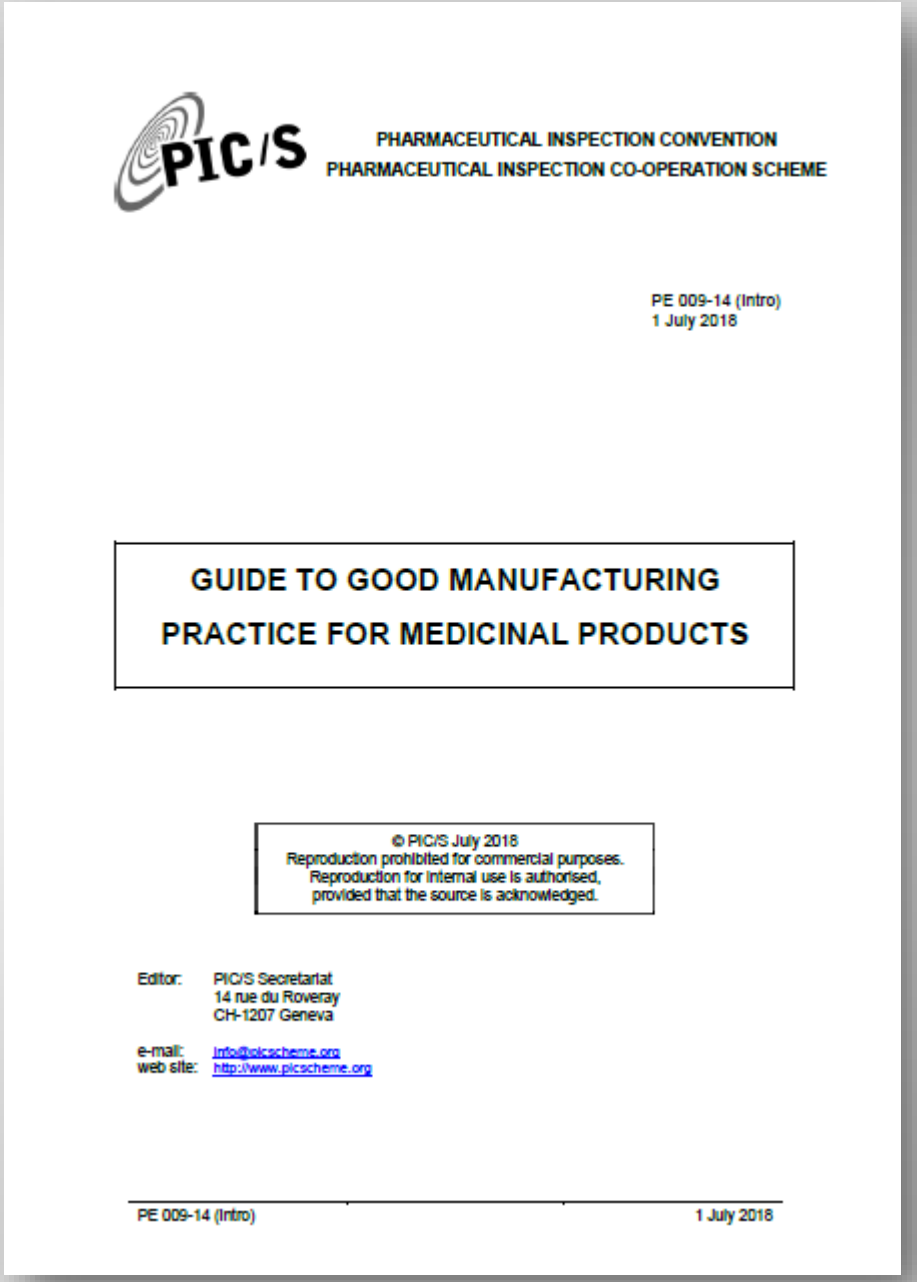
Principle

“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**.

What about PIC/S PE009-14?



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PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PE 009-14 (Intro)
1 July 2018

GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS

Editor: PIC/S Secretariat
14 rue du Roveray
CH-1207 Geneva

e-mail: info@picscheme.org
web site: http://www.picscheme.org

PIC/S PE009-14 - Chapter 3: Premises & Equipment

Cross-contamination prevention a major focus

Quality Risk Management principles should be used to assess and control risks

PIC/S PE009-14 - Chapter 3: Premises & Equipment
Dedicated facilities

Dedicated facilities are required for manufacturing when a medicinal product presents a **risk** because:

a) The risk cannot be adequately controlled by **operational** and/ or **technical** measures or

b) **Scientific data** does not support **threshold values** (e.g. allergenic potential from highly sensitising materials such as beta lactams) or

c) Relevant residue limits, derived from the **toxicological evaluation**, cannot satisfactorily determined by a validated analytical method

PIC/S PE009-14 - Chapter 5: Production Cross-Contamination

- Cross-contamination should be prevented by **attention to design** of the premises and equipment as described in Chapter 3.

- This should be supported by attention to process design and implementation of any relevant **technical or organizational measures**, including effective and reproducible **cleaning processes** to control risk of cross-contamination.

PIC/S PE009-14 - Chapter 5: Production Technical Measures

- Dedicated processes, equipment and facilities
- Use of “closed systems”, physical barrier systems including isolators and single-use disposable technologies
- Controlled removal of dust through localised extraction, use of airlocks and pressure cascades to confine potential airborne contaminants
- Use of equipment designed for ease of cleaning and use of automatic clean in place systems

PIC/S PE009-14 - Chapter 5: Production Organisational Measures

- Campaign manufacture, followed by validated cleaning process
- Cleaning verification after each product campaign should be considered as a detectability tool – high risk products
- Management of protective clothing – high risk products
- Design of cleaning processes and records

PIC/S PE009-14 - Chapter 5: Production Starting Materials

Introduction of key stages of **supplier management** i.e. supplier selection, qualification, approval and ongoing monitoring

Level of **supplier oversight** should be based on **risk**

Evidence of supplier assessment and monitoring should be **recorded**

PIC/S PE009-14 - Chapter 5: Production Starting Materials

Recognition that the **supply chain** needs to also be considered as part of the risks to materials

Preference to **purchase direct** from manufacturers of materials

Detailed quality agreement should be **documented** with suppliers

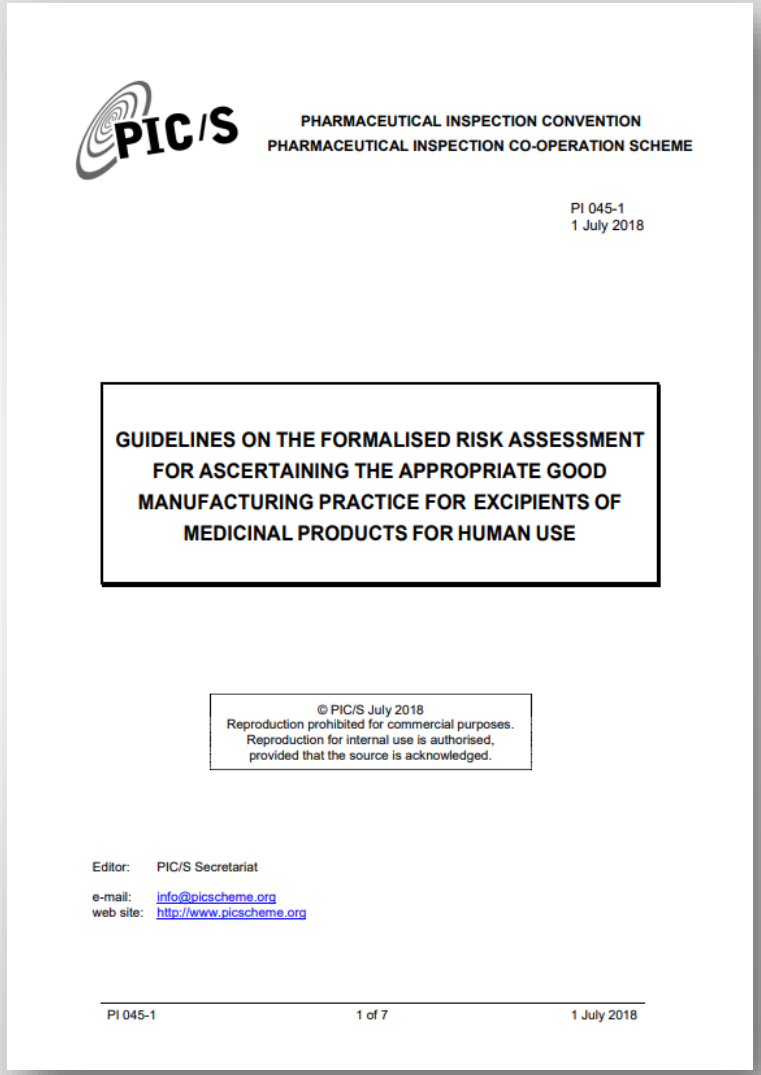
PIC/S PE009-14 - Chapter 5: Production Active Substances

- **Supply chain traceability** should be established and the associated risks should be formally assessed and periodically verified.

- **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.

PIC/S PE009-14 - Chapter 5: Production Excipients

Excipients and excipient suppliers should be controlled appropriately based on the results of a formalised **quality risk assessment** in accordance with the PIC/S Guideline PI 045-1



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PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 045-1
1 July 2018

GUIDELINES ON THE FORMALISED RISK ASSESSMENT FOR ASCERTAINING THE APPROPRIATE GOOD MANUFACTURING PRACTICE FOR EXCIPIENTS OF MEDICINAL PRODUCTS FOR HUMAN USE

Editor: PIC/S Secretariat

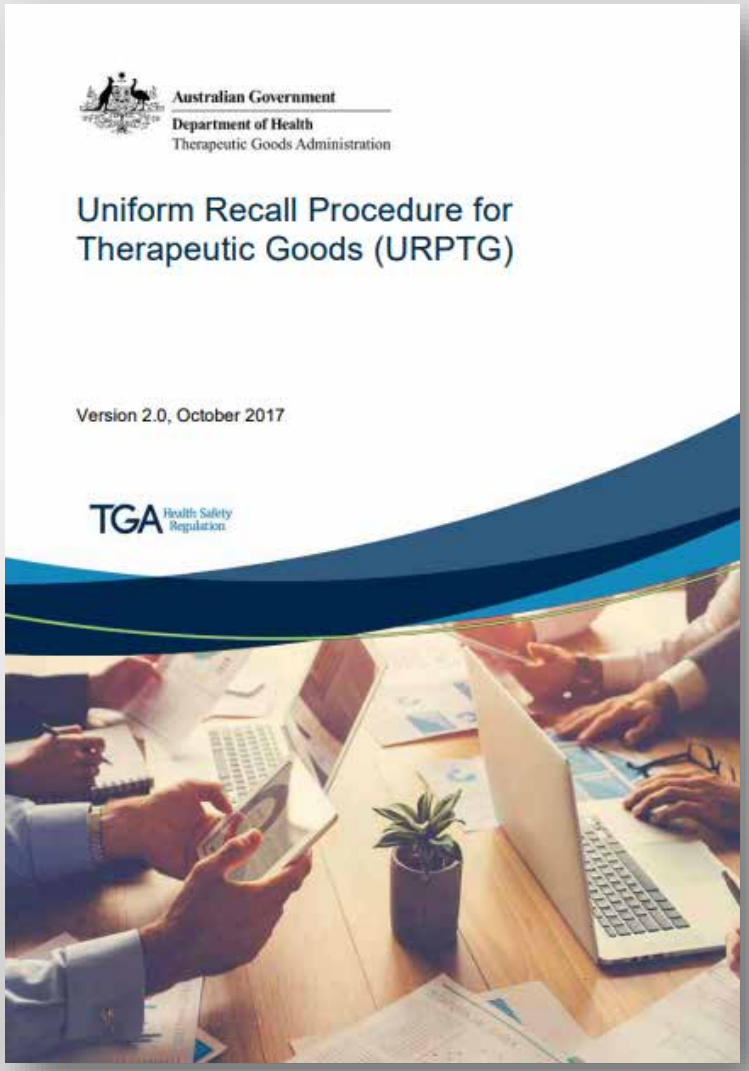
e-mail: info@picscheme.org
web site: http://www.picscheme.org

PIC/S PE009-14
Chapter 8: Complaints & Product Recall

- Extensive revision from 16 – 31 clauses
- Section changes with the introduction of:
  - Personnel and Organisation
  - Procedures for handling and investigating complaints including possible quality defects
  - Investigation and decision making
  - Root Cause Analysis and CAPA
  - Product recalls and risk-reducing actions

PIC/S PE009-14
Chapter 8: Complaints & Product Recall

- Revision to include **QRM for investigations**
- Emphasise improved **RCA and CAPA** processes
- Clarify reporting requirements to concerned Competent Authorities of confirmed quality defects
- Reflects URPTG requirements



PIC/S PE009-14
Annex 17: RTRT & Parametric Release

Outlines the requirements for application of Real Time Release Testing (RTRT) and parametric release, where the **control of critical parameters** and relevant **material attributes** are **authorised as an alternative** to routine end-product testing of active substances and/or finished products.

PIC/S PE009-14
Annex 17: RTRT & Parametric Release

Real time **measurement** and **control** of relevant in-process material attributes and process parameters should be accurate predictors of the corresponding finished product attributes.

A well defined a strategy should be integrated and controlled through the PQS and include or reference information from:

- QRM
- Change control
- Training
- Qualification and Validation
- Deviation/CAPA system
- Etc.

PIC/S PE009-14
Annex 17: Parametric Release & Sterilisation

- Release of terminally sterilised product based on a review of critical process control parameters rather than requiring end-product testing for sterility.
- Detailed guidance regarding the scope of the sterility assurance program.
- Quality Risk Management is an essential requirement and should focus on mitigating the factors which increase the risk of failure to achieve and maintain sterility in each unit of every batch.
- A pre-sterilisation bio-burden monitoring program for the product and components should be developed to support parametric release.
- Product bio-burden should be minimised by appropriate design of the manufacturing environment and the process.

Recap?

- <5 months to go until full implementation – Live 1st January 2019
- Refer to TGA website for all updates (Ax 2, 3, 6, 7, 11, 13, 15)
- Have you started thinking about 14 and beyond?

Thank you for your time.
Questions?

Maria Mylonas

Training Services Manager / Lead Consultant

maria.mylonas@pharmout.net

www.pharmout.net