PIC/S PE 009-13

Presented by Trevor Schoerie

July 2017

National GMP & Validation Forum

Hosted by PharmOut

PharmOut

Where are we?

Is Australia falling behind when it comes to global GMP regulations?

Are we doing enough to "keep up"?

Where are the US FDA going?

#omg-old-gmps

PIC/S Guide to GMP

PIC/S – Pharmaceutical Inspection Co-op Scheme

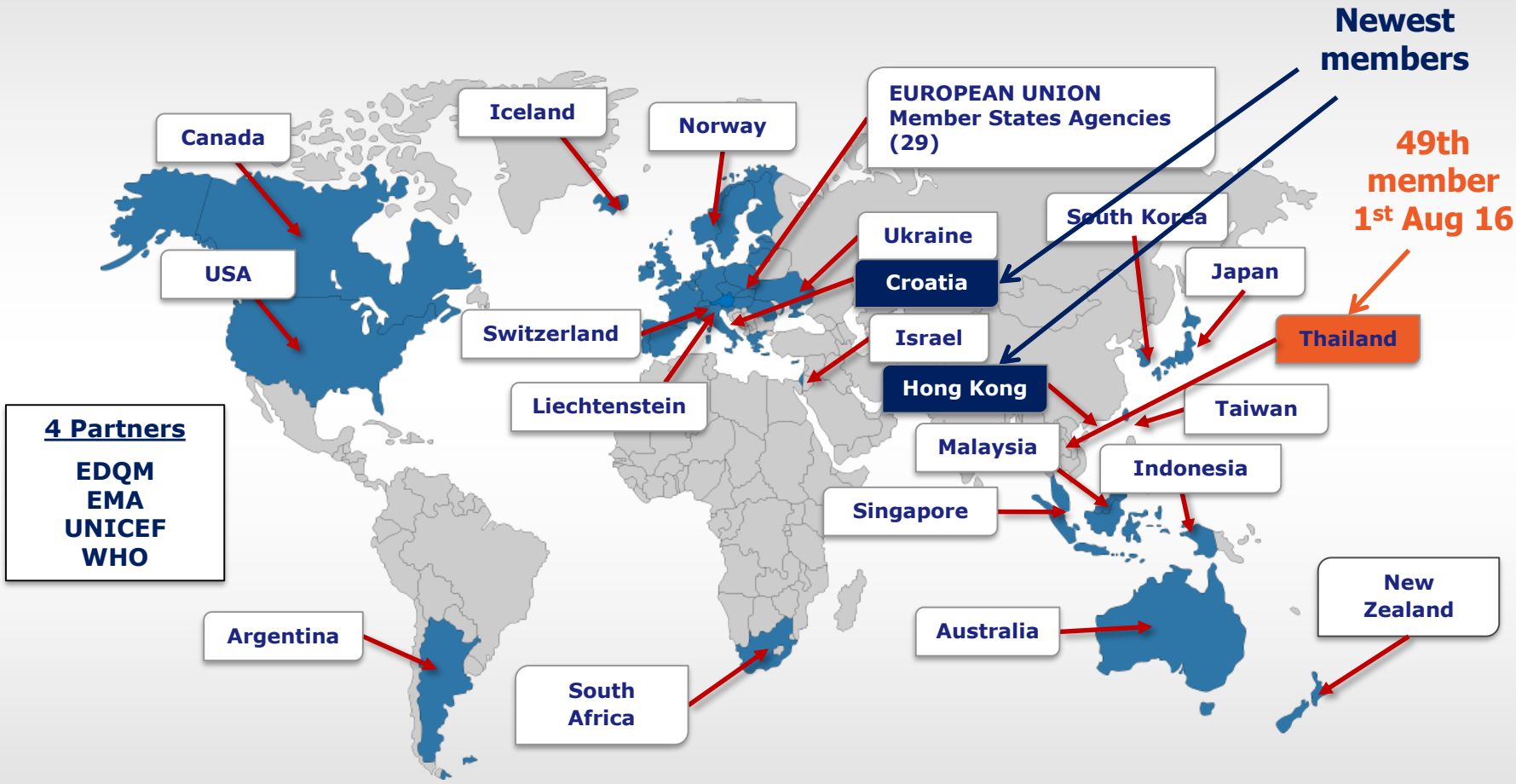
Currently **49** authorities have adopted (28 from Europe)

- GMP Guidance's used as regulatory requirements by **EU** and **Asia-Pacific** countries
- Is an informal "Cooperative Arrangement" **between GMP regulatory authorities**; i.e. not a legal treaty.

No obligation for member authorities to accept inspection reports of other members.

49 PIC/S member authorities

(August 2016)



PIC/S is involved in developing the EU GMPs

The procedure to change GMPs is continuous

- These two groups **cooperate closely** and work in parallel on the GMP Guidelines. There exists an **agreement** on the procedure used and the changes are happening **almost** simultaneously.

Current version PE 009-13 – issued 1st January 2017

- Current ANZ version v8: PIC/S Guide to Good Manufacturing Practice for Medicinal Products, PE 009-8 – issued **15th January 2009** (**9 years**)

Regulation and Red Tape Reduction

- One of the Government's **top five** priorities
- Reduction target of **$1 billion** per annum
- Regulation **should not be** the default for dealing with public policy issues

"Regulation is any rule endorsed by government where there is an expectation of compliance…
It also includes red tape burden imposed by the Commonwealth's procurement, grants and cost recovery frameworks."

http://www.health.gov.au/internet/main/publishing.nsf/Content/regulation-and-red-tape-reduction

Introduction to PIC/S GMP Guidelines

PIC/S PE 009 Guide to Good Manufacturing Practices is in 3 parts:

PIC/S PE 009-14 is on the way…

- Revision to version 14 will be due to the update of **Annex 1 for Sterile Medicinal Products**
- **Other changes?**
  - Chapters 3?
  - Chapter 5?
  - Chapter 8?
  - Annex 2? Replaced by ATMPS
  - Annex 13? Deleted in EU

PIC/S and EU on same page?

Chapter 1: Pharmaceutical Quality System

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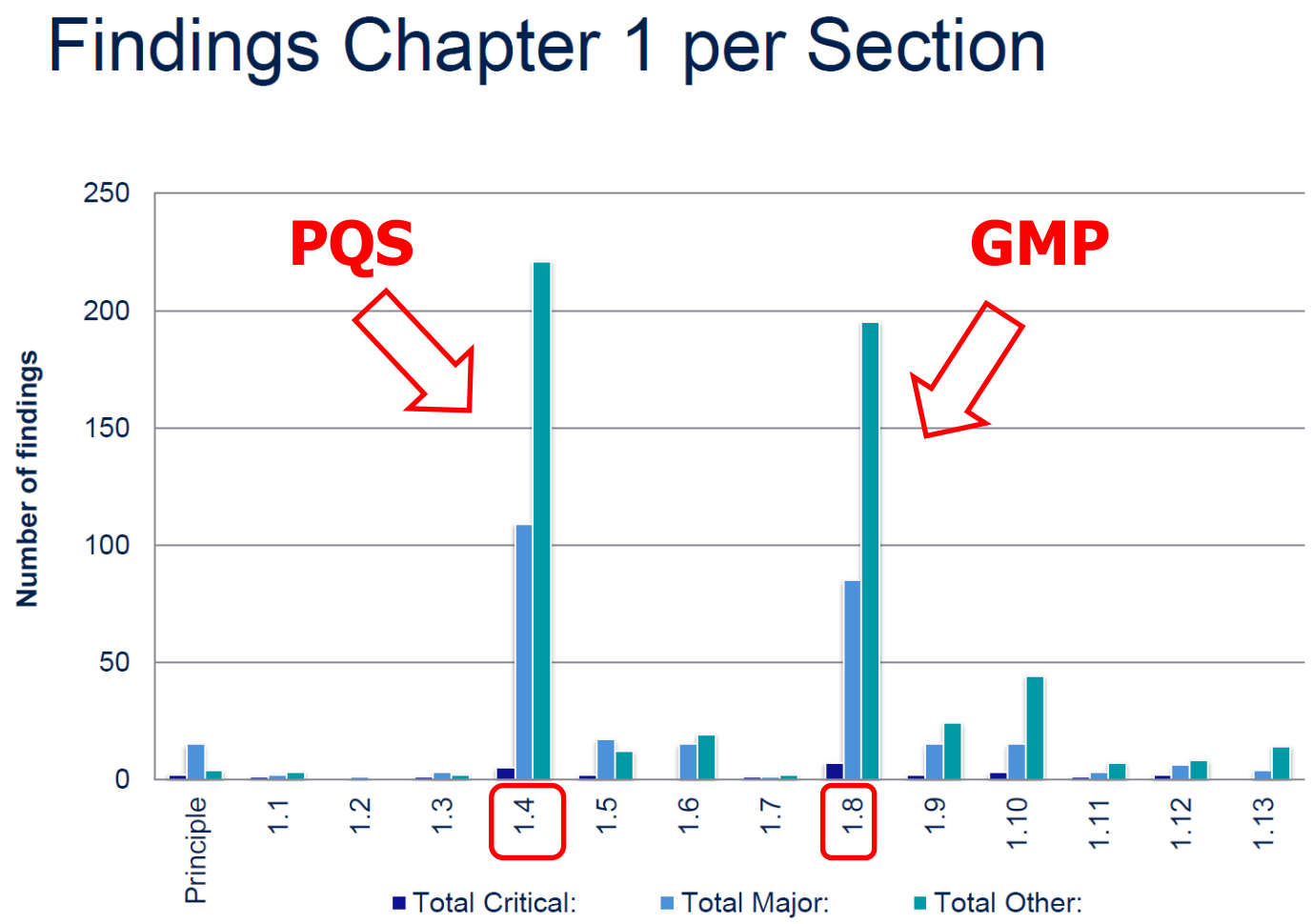
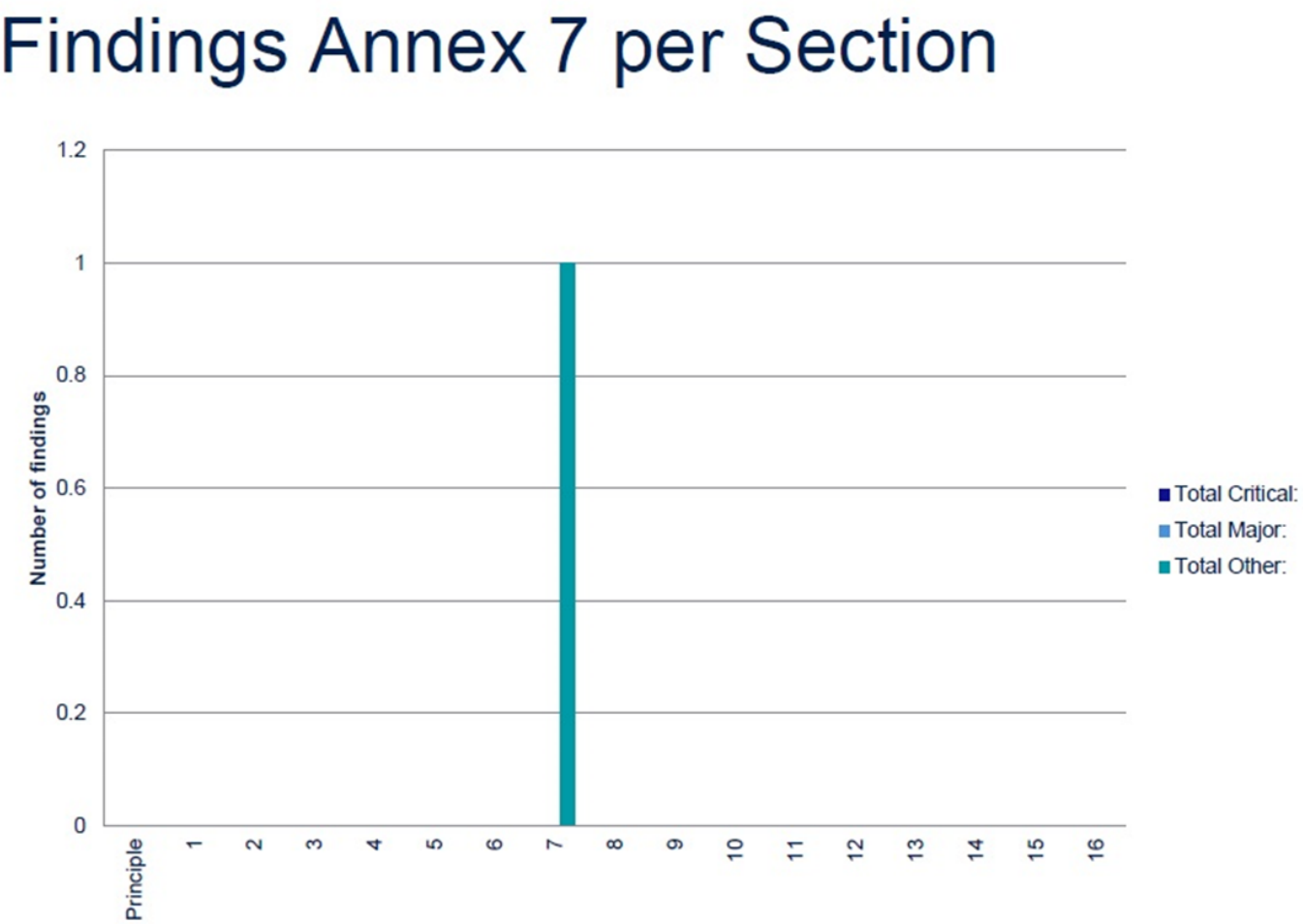
Laying the foundations

- Understanding the principles of GMP is the **foundation** of implementing quality in the workplace.
- If we understand the '**why**', the '**what**' is easier to implement.

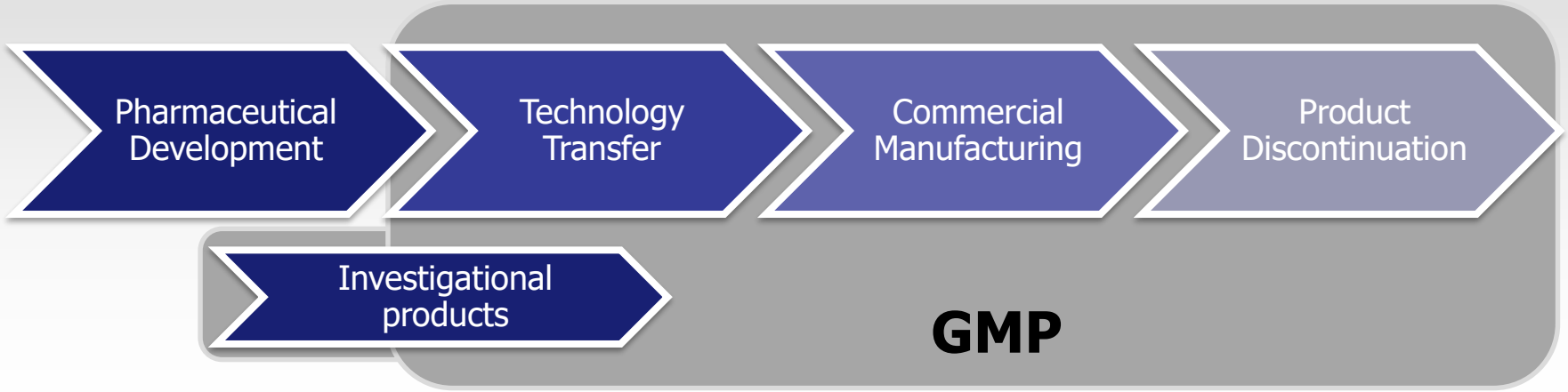
MRHA Chapter 1 deficiencies presented in December 2016



Annex 7: Manufacture of Herbal Medicinal Products



ICH Q10: Pharmaceutical Quality System



Management Responsibilities

PQS elements

Process Performance & Product Quality Monitoring System
Corrective Action / Preventative Action System
Change Managements System
Management review

Enablers

Knowledge Management

Quality Risk Management

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Chapter 1: Pharmaceutical Quality System

Principle:

- Capitalisation of some terms: **M**arketing **A**uthorisation, **A**uthorised **P**erson(s)
- Now references **Clinical Trial Authorisation** along with Marketing Authorisation
- "Quality Assurance" now "**Quality Management**"
- Also mandates **Good Distribution Practices**
- Also **supply chain integrity**

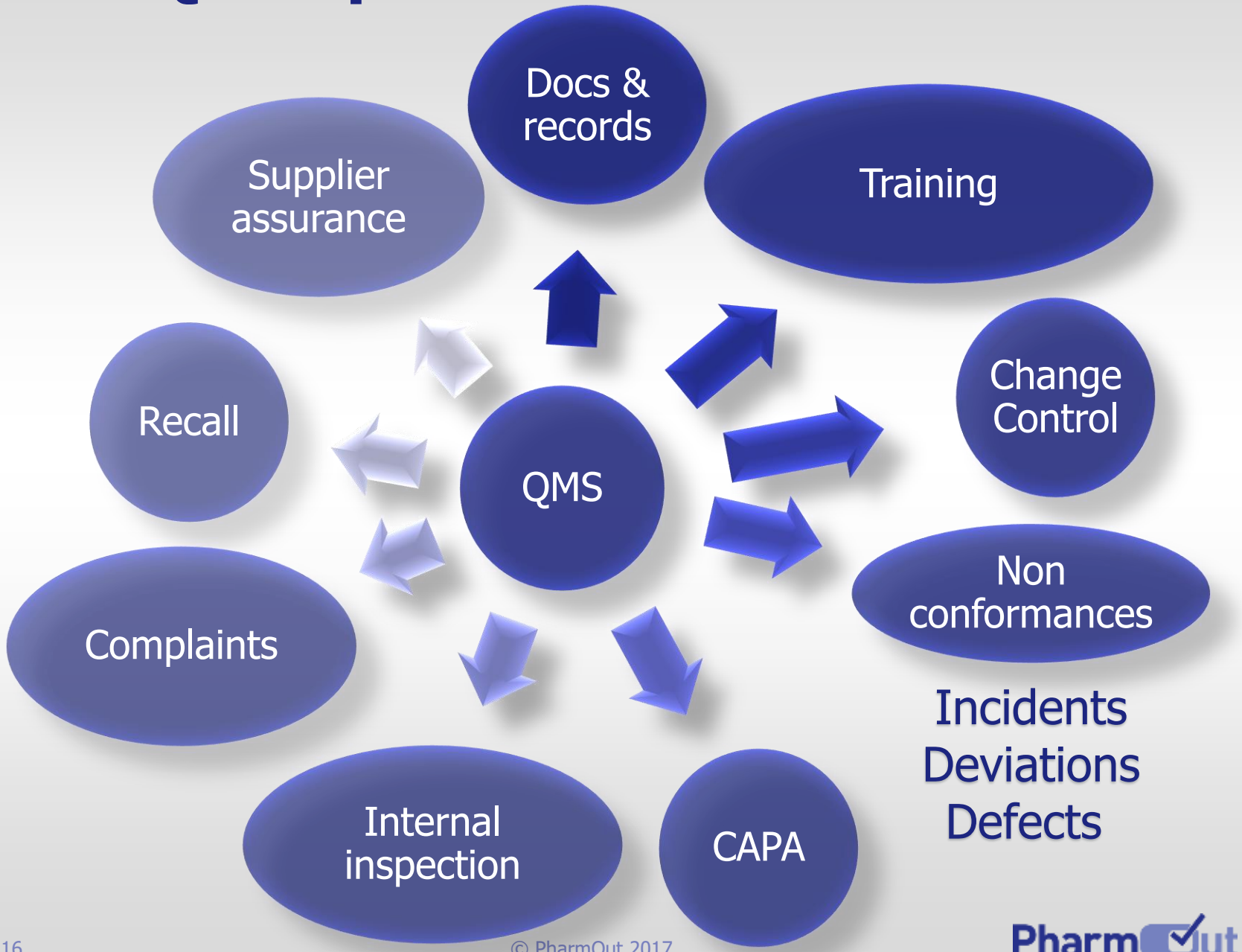
Chapter 1: Quality Management

§1.2:

GMP applies to the lifecycle stages from the **manufacture of investigational medicinal products**, **technology transfer**, **commercial manufacturing** through to **product discontinuation**.

However the Pharmaceutical Quality System can extend to the **pharmaceutical development lifecycle stage** as described in **ICH Q10**, which while optional, should **facilitate innovation and continual improvement** and strengthen the link between pharmaceutical development and manufacturing activities.

Core "QMS" processes



PQS processes

§ 1.3:

The **size and complexity** of the company's activities should be taken into consideration when developing a new Pharmaceutical Quality System or modifying an existing one.

The **design of the system** should incorporate **appropriate risk management principles** including the use of appropriate tools.

While some aspects of the system can be company-wide and others site-specific, the **effectiveness of the system is normally demonstrated at the site level**.

Senior management

§1.5 – New section:

- Senior management has **the ultimate responsibility** to ensure an effective Pharmaceutical Quality System is in place, adequately resourced and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation.
- Senior management's **leadership and active participation** in the Pharmaceutical Quality System is **essential**.
- This leadership **should ensure the support and commitment of staff** at all levels and sites within the organisation to the Pharmaceutical Quality System.

Periodic management review

§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**.

§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**.

1.8 GMP for Medicinal Products

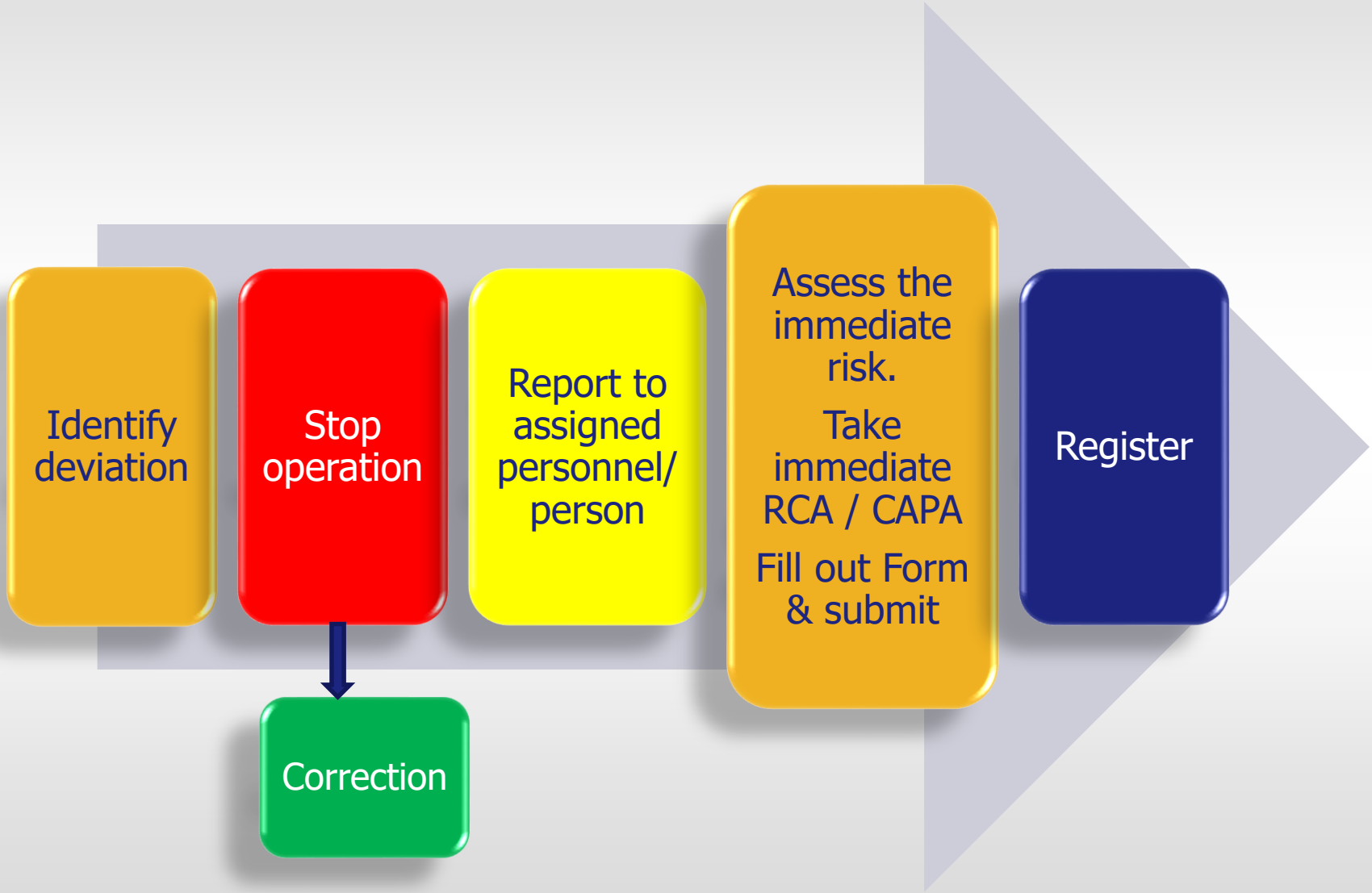
(vii) Any **significant deviations** are fully recorded, investigated with the **objective of determining the root cause** and **appropriate corrective and preventive action** implemented;

(viii) Records of manufacture **including distribution** which enable the complete history of a batch to be traced are retained in a comprehensible and accessible form;

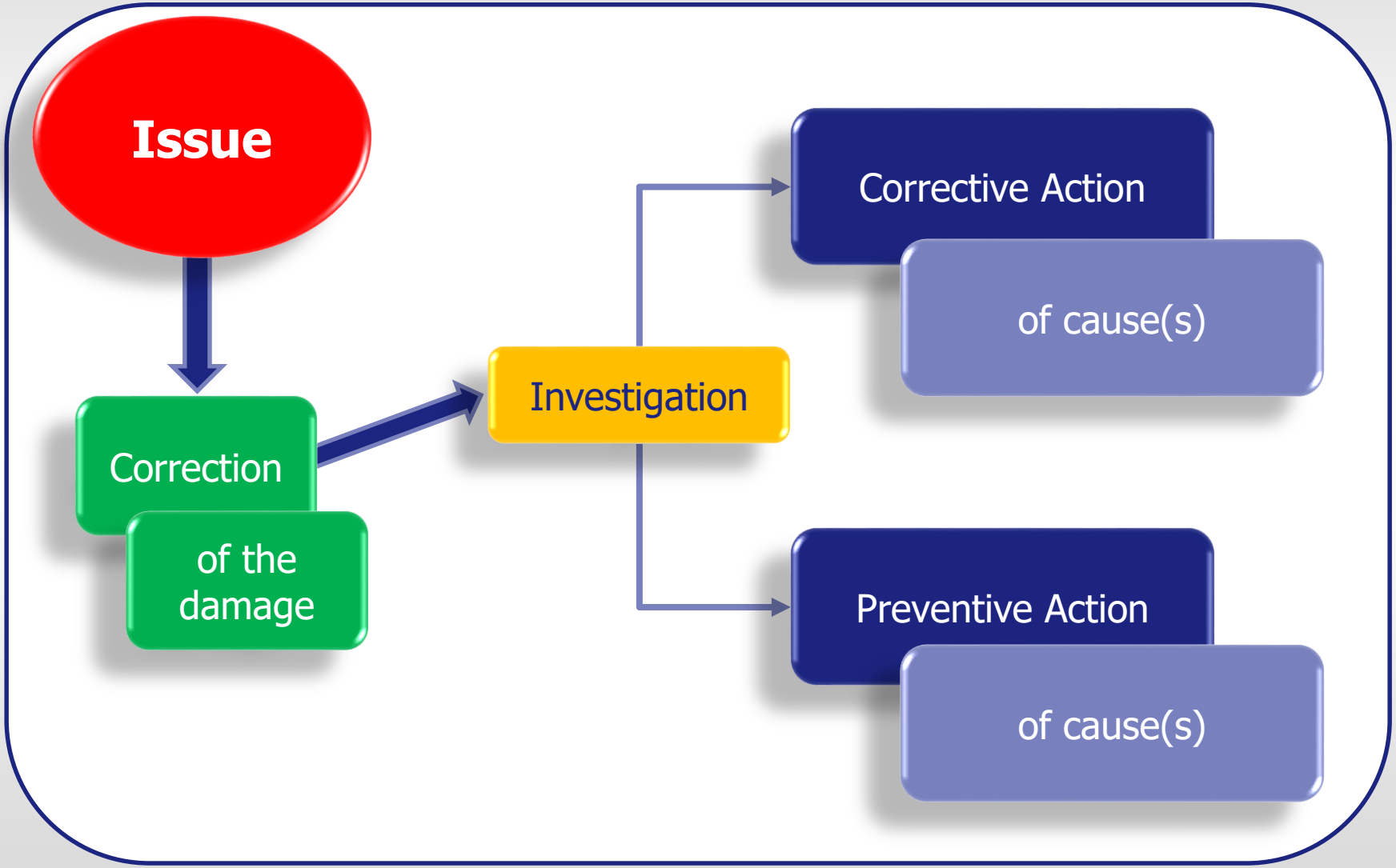
(ix) The distribution of the products minimises any risk to their quality and takes account of **good distribution practice**;

What is a "significant deviation"?
How do you determine this?

Deviations – typical process

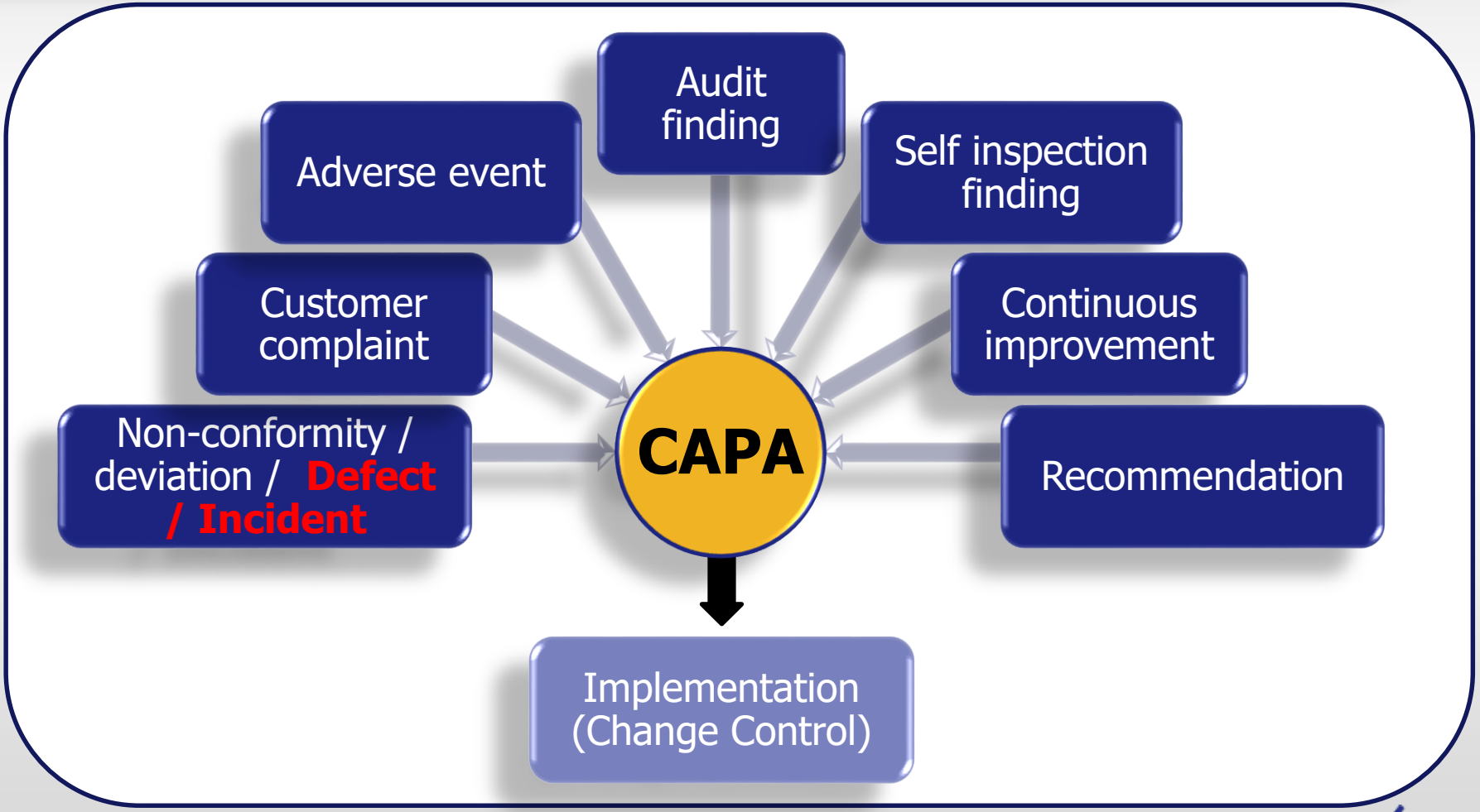


Correction, Corrective Action and Preventative Action



What initiates a CAPA?

CAPA is the centrepiece of Issue Management and Continuous Improvement (CI)



Key CAPA Definitions

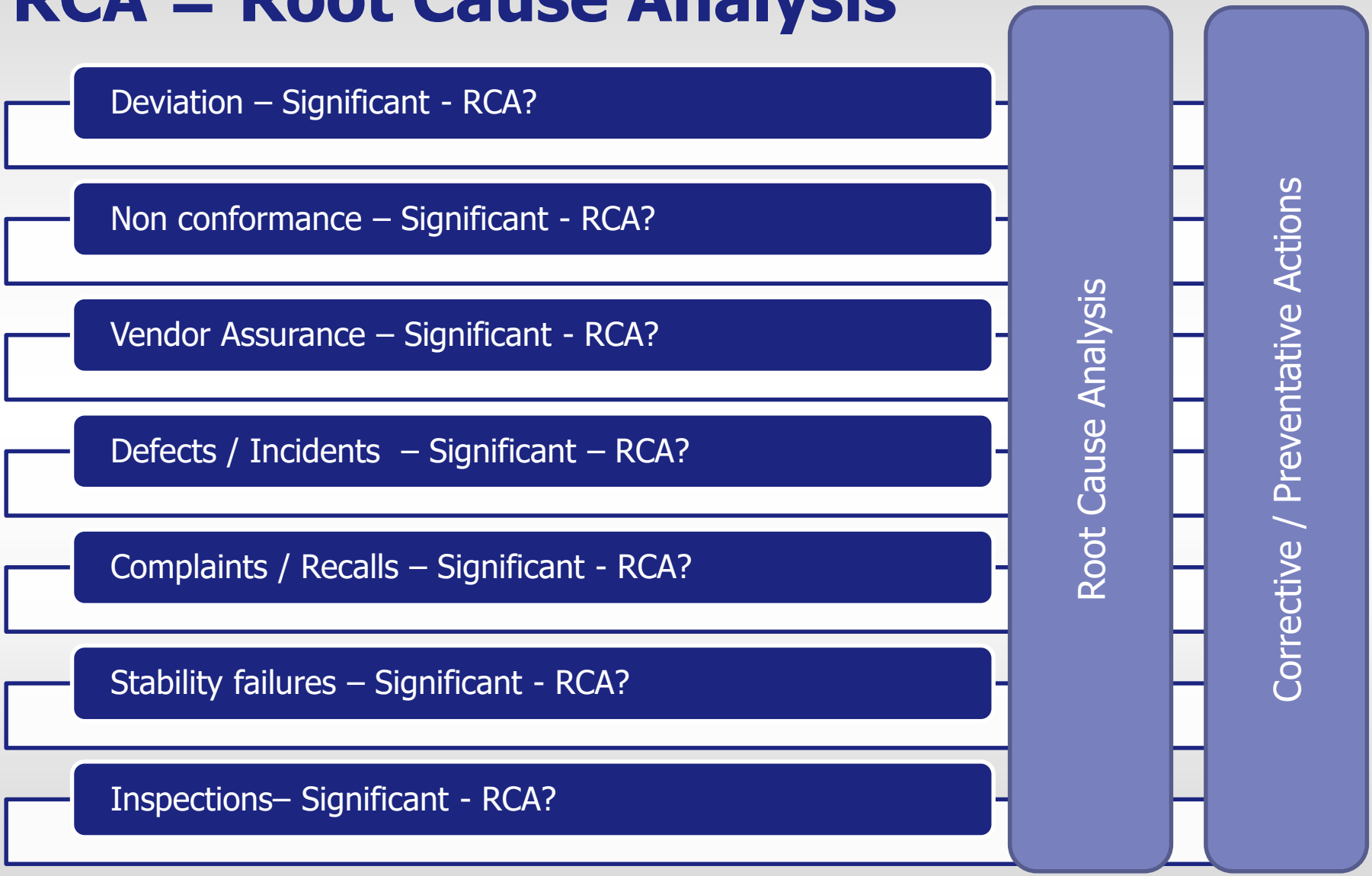
Corrective Action

Action to eliminate the **causes** of a **detected** nonconformity or other undesirable situation. The corrective action should eliminate the recurrence of the issue.

Preventive Action

Action to eliminate the **causes** of a **potential** nonconformity or other undesirable potential situation. Preventive action should prevent the occurrence of the potential issue.

Sources of CAPA
RCA = Root Cause Analysis



Example Root Cause Categories

Personal Performance

- Lack of attention
- Attitude problems
- Fatigue
- Lack of capability
- Personal problems

Training

- Lack of training
- Training not effective
- Instructor not adequate
- Insufficient hands on experience

Equipment

- Design and/or installation
- Equipment reliability
- Equipment maintenance
- Calibration issues

Example Root Cause Categories

Human Reliability Factors

- Work area cluttered
- Inadequate housekeeping
- Stressed conditions
- Excessive work load

Procedures and Instruction

- Not used
- Misleading or confusing
- Wrong or incomplete
- Obsolete

Materials

- Inadequate sampling or controls
- Specification not appropriate
- Supplier not approved

Finally…don't forget about QRM…

PIC/S 1.12 & 1.13 Quality Risk Management

Systematic process for the assessment, control communication and review of risks

- Risk must be assessed based on scientific knowledge and patient safety.
- Level of effort of risk management needs to be commensurate with the level of risk.

What is the criteria that your company uses for quality risk management?

Quality Risk Management not going away?

Year	GMP reference	x times risk mentioned
1971	First TGA code of GMP	3
1990	TGA GMP code (Blue Book)	20
2002	First PIC/S code adopted in Australia	57
2008	Current – 2009 version of the PIC/S GMP code	30+10+379=**419**
2017	Latest PIC/S Version 13	38+20+454=**512**

ICH	ICH Title	x times risk mentioned
Q8	Pharmaceutical Development (2006)	10
Q9	Quality Risk Management (June 2006)	279
Q10	Pharmaceutical Quality System (April 2009)	34
Q11	Development & Manufacture of Drug Substances (4/2011)	51

Chapter 2: Personnel

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Some major differences between PE 009-8 and PE 009-13

- Major changes to the **General, Key Personnel** and **Consultants** Subchapters.
- **Clause 2.1 and 2.2** was expanded with more information regarding **senior management**
- **Clause 2.1** refers to "…adequate and appropriate…**financial resources**" to maintain the PQS.
- Clause 2.2 points to the **Authorised Person**:

The manufacturer must have an organisation chart in which the relationships between the heads of Production, Quality Control and where applicable Head of Quality Assurance or Quality Unit referred to in point 2.5 and the position of the **Authorised Person(s)** are clearly shown in the managerial hierarchy.

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 3: Premises & Equipment

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PIC/S PE 009-13 vs Eudralex Vol. 4

Section 3.6 updated on 01 March 2015

Removal of specific reference to "**certain**" product types

Inclusion of QRM to **cross-contamination prevention**

Use of **toxicological evaluations**

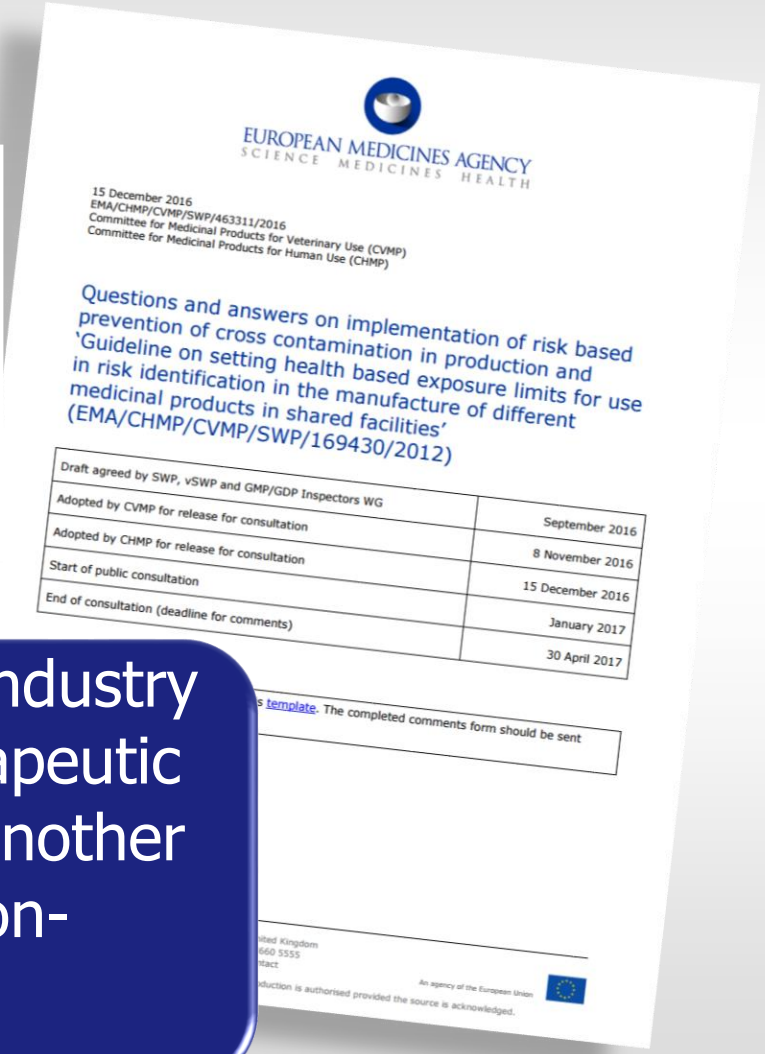
but only for **highly toxic compounds <10mg/day**

Draft Q&A on implementation of risk based prevention of cross contamination

Q6. How can limits for cleaning purposes be established?

A: Although the EMA guideline (EMA/CHMP/CVMP/SWP/169430/2012) may be used to justify cleaning limits (as per Introduction paragraph 3), it is not intended to be used to set cleaning limits at the level of the calculated HBEL (using the guideline methodology). The cleaning limits should continue to be based via risk assessment and additional safety margins to help account for uncertainty in the cleaning processes and analytical variability. Traditional cleaning limits used by industry such as 1/1000th of minimum therapeutic dose or 10 ppm of one product in another product, may accomplish this for non-highly hazardous products.

For products classed as highly hazardous, where a thorough risk assessment can justify manufacture in shared facilities, cleaning limits should include safety factors beyond the HBEL and should not be higher than the traditional cleaning limits approach.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 December 2016
EMA/CHMP/CVMP/SWP/463311/2016
Committee for Medicinal Products for Veterinary Use (CVMP)
Committee for Medicinal Products for Human Use (CHMP)

Questions and answers on implementation of risk based prevention of cross contamination in production and 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities' (EMA/CHMP/CVMP/SWP/169430/2012)

Draft agreed by SWP, vSWP and GMP/GDP Inspectors WG	September 2016
Adopted by CVMP for release for consultation	8 November 2016
Adopted by CHMP for release for consultation	15 December 2016
Start of public consultation	January 2017
End of consultation (deadline for comments)	30 April 2017

s template. The completed comments form should be sent

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An agency of the European Union

duction is authorised provided the source is acknowledged.

Traditional cleaning limits used by industry such as 1/1000th of minimum therapeutic dose or 10 ppm of one product in another product, may accomplish this for non-highly hazardous products.

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Chapter 4: Documentation

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Major differences between PE 009-8 and PE 009-13

Major changes to all the clauses.

Except clauses 4.13, 4.15, 4.16, 4.17, 4.23, 4.24, 4.25, 4.26 and 4.28 which had only minor/no changes.

Plus Data Management and Data Integrity (DMDI) guidance April '17

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Chapter 4: Documentation

Sections:

- Principles
- Required GMP Documentation (by type)
- Generation and Control of Documentation
- Good Documentation practices
- Retention of documents
- Specifications
- Manufacturing Formula and Processing Instructions
- Procedures and records
- Testing
- Other

Data Integrity

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World's biggest medicines recall

28th April 2003

The suspension follows audits of the company's manufacturing premises, which revealed widespread and serious deficiencies and failures in the company's manufacturing and quality control procedures, including the **systematic and deliberate manipulation** of quality control test **data**.

- 219 products **immediately** recalled
- 1650 export products **cancelled**

'The **Australian** public should not forget how bad the manufacturing practices were at **<the company>** which prompted what may be the world's biggest medicines recall.'

Source

https://www.tga.gov.au/product-recall/pan-pharmaceuticals-limited-regulatory-action-product-recall-information
https://www.tga.gov.au/media-release/tga-reminds-australians-potential-danger-pan-pharmaceuticals

Data Integrity – the "hot" topic…

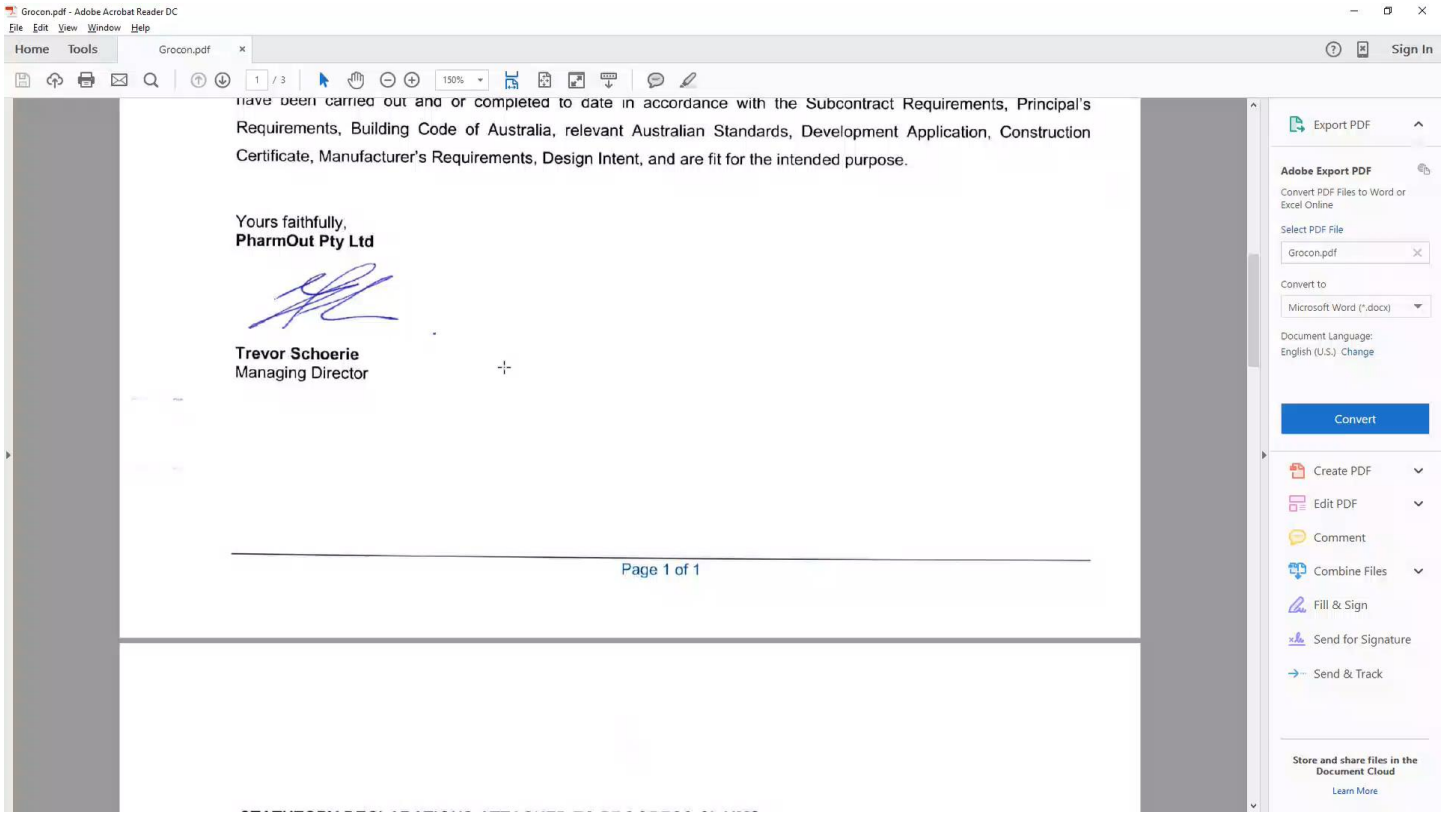
The word "integrity" **is not** in Chapter 4 of PE 009-8.

The word "integrity" is in Chapter 4 of PE 009-13:

- PRINCIPLE: "Suitable controls should be implemented to ensure the accuracy, **integrity**, availability and legibility of documents. Instruction documents should be free from errors and available in writing."
- 4.1: "…**Appropriate controls** should be in place to ensure the **integrity of the record** throughout the retention period."
- 4.10: "**Secure controls** must be in place to ensure the **integrity of the record** throughout the retention period and validated where appropriate."

Data Integrity – Why Bother?

- What's all the fuss about?
- What could really go wrong?



Motive, Opportunity and Means (MOM)

- **MOM** – how do we control these three key factors?
- **Means** by better system design.
- **Opportunity** and means can be controlled to a certain extent.
- **Motive** is a factor controlled by leadership and culture.
  - People still need access and trust to do their work.

Designing DI into systems (ALCOA)

Paper-based

Attributable	Legible/ Permanent	Contemporaneous	Original	Accurate
Initials & Signature registers	Control of blank forms, pen policy/white out	Documents available in right place at right time, +/- time limits	Verified 'true copy', scans	Reflective of the observation data checking

Electronic

Attributable	Legible/ Permanent	Contemporaneous	Original	Accurate
Active directory, e-sig, audit trails, metadata	Data annotation tools, audit trail	System clock, sync., transaction window	Metadata, data about the data that permits reconstruction	Data capture, manual data entry

ALCOA +

- The US FDA introduced the acronym "ALCOA" to provide **attributes of integrity**; the term "**ALCOA+**" adds four additional attributes – **complete**, **consistent**, **enduring** and **available**.

- The WHO Draft Guidance on **Good Data and Record Management Practices**, Sept 2015 refers to ALCOA and adds additional terms to each stage of the acronym.

- **ALCOA is a good start, but doesn't cover everything**

The signature register- traceability

4.29 There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached, where appropriate, for the

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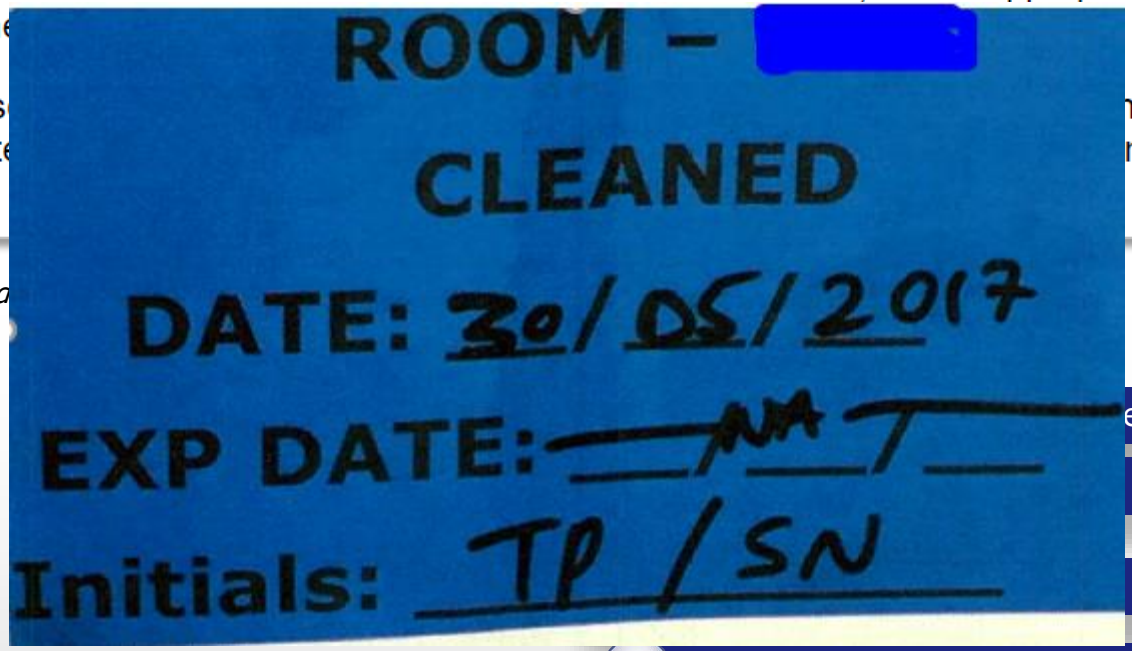

erating the data

O – Original record (or "true copy")

c) Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;

Chapter 5: Production

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PE 009-8 vs PE 009-13

No content changes to Chapter 5

EU Chapter 5: Production Cross-contamination

- Reference to those "**certain**" products removed
- "Cross contamination should be avoided by **robust design** of the premises, equipment and processes which take place within a manufacturing facility. This should be supported by **appropriate procedures** and **technical or organizational measures**, including **reproducible** cleaning and decontamination processes of **validated effectiveness**."
- Section contains reworded & additional technical and organizational measures that can mitigate the risks of cross-contamination in greater detail

Suppliers

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 **technical agreement** should be **documented** with suppliers

Chapter 6: Quality Control

Chapter 6: Quality Control

- 6.5 includes cross contamination measures for lab equipment and micro labs
- 6.7 & 6.9 include a requirement for procedures for OOS/OOT
- 6.8 general reference to Ch. 4 Documentation for batch record retention
- Sections are generally aligned
- Sec 6.8 states QC documents relating to a batch record should be retained following the principles given in Chapter 4 on retention of batch documentation

PIC/S PE 009-13 vs Eudralex Vol. 4

- 6.12 includes using QRM for the sampling plan
- 6.14 diverts to Annex 19 and requires reference sample size for minimum 2 full retests
- 6.15 distinguishes between validation and verification of methods
- Sec 6.20 is new for reference standard suitability
- Sec 6.21-6.24 new sections on receipt of reagents, culture media use and prevention of cross contamination of micro media
- Sec 6.34 refers to Authorised Person

Technical Transfer

Specific requirements for Tech Transfer Protocol, including **training** requirements & **transport** requirements

Acceptance criteria defined and based on **current** validation study

EU Ch 6 has says that Requirements of other European Guidelines should be addressed if appropriate (e.g. NIR)

Protocol deviations should be investigated as per validation deviation methods and technical transfer **not closed** until complete

Chapter 7: Outsourced Activities

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PE 009-8 vs PE 009-13

- Now titled as "Outsourced Activities"
- Large amount of changes to the Chapter.
- No major changes, general clarification in language and reference to the PQS of the contract acceptor.
- Clauses 7.7-7.8 having only minor text changes

Written Contracts and/or Agreements?

PE 009-8:

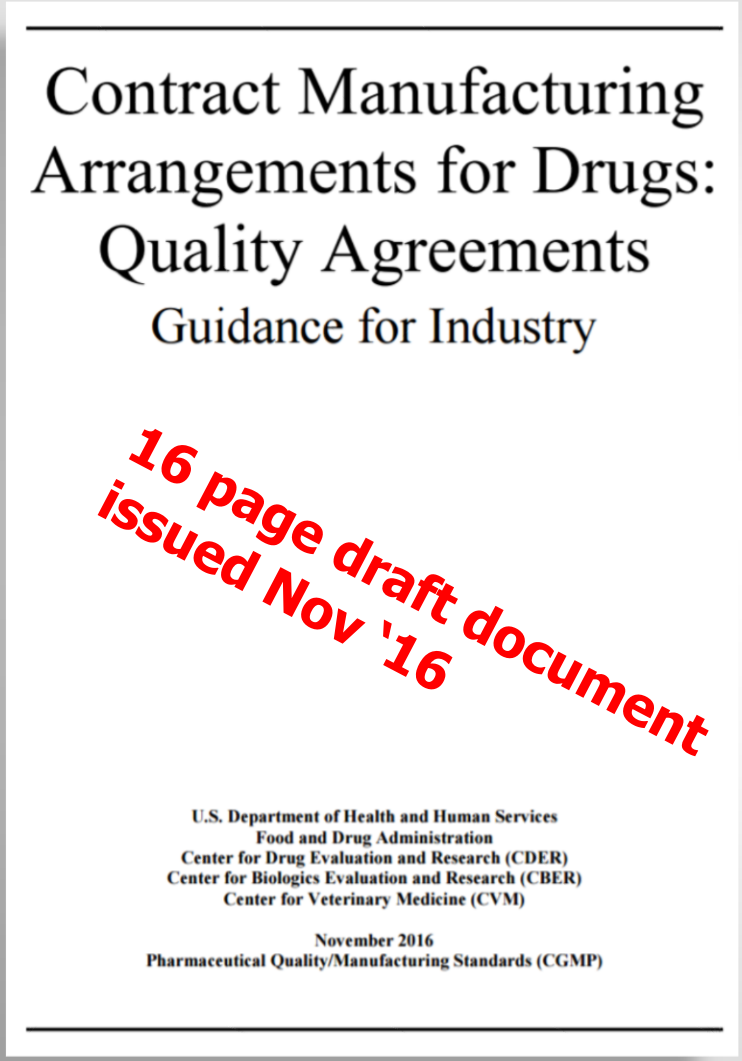
- **Chapter 1: Quality Management Systems** uses the term "technical agreement" (Clause 1.4 last section)
- **Chapter 6: Quality Control** uses the term "written agreement" (Clause 6.31)

PE 009-13:

- **Chapter 1: Pharmaceutical Quality Systems** uses the term "technical agreement" (Clause 1.11)
- **Chapter 4: Documentation** defines the term "**Technical Agreement**"
- **Chapter 6: Quality Control** uses the term "written agreement" (Clause 6.34)

Its a Quality Agreement in the US?

- A quality agreement is a comprehensive written agreement between parties involved in the contract manufacturing of drugs that defines and establishes each party's manufacturing activities in terms of how each will comply with CGMP
- **Global harmonisation?!**


Contract Manufacturing Arrangements for Drugs: Quality Agreements

Guidance for Industry

16 page draft document issued Nov '16

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

November 2016
Pharmaceutical Quality/Manufacturing Standards (CGMP)

March 7 to 18, 2016

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm538105.htm

Chapter 8: Complaints & Product Recall

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PE 009-8 vs PE 009-13

- **No changes to Chapter 8**

PRINCIPLE

- All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures. In order to provide for all contingencies, a system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.

PIC/S PE 009-13 vs Eudralex Vol. 4

- **Ch. 8 Complaints, Quality Defects and Product Recall:**
- EU Vol. 4 Principle refers directly to Article 117 of Directive 2001/83/EC and Article 84 of Directive 2001/82/EC
- All sections the same (currently all 16 sections)
- Updated 01 March 2015 (31 sections)
- Extensive revision to include **QRM for investigations**
- Emphasise **better RCA and CAPA processes**
- Clarify reporting requirements to the market authorities

EU Ch. 8: Complaints, Quality Defects and Product Recall

8.9 When a quality defect investigation is initiated, procedures should be in place to address at least the following:

- viii. The identification of the potential root cause(s) of the quality defect.
- ix. The need for appropriate Corrective and Preventative Actions (CAPAs) to be identified and implemented for the issue, and for the assessment of the effectiveness of those CAPAs.

EU Ch 8: Complaints, Quality Defects and Product Recalls

The reasons for changes to EU Chapter in March 2015:

"Extensive changes…now reflect that **Quality Risk Management** principles should be applied…the need for the **cause(s)** of **quality defects** or complaints to be investigated and determined…appropriate **preventative actions**…clarifies expectations and responsibilities in relation to the **reporting of quality defects** to the Competent Authorities."

Chapter 9: Self Inspection

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Chapter 9: Self-Inspection

CHAPTER 9

SELF INSPECTION

PRINCIPLE

No changes to Chapter 9…not even for typos!

Self inspections should be conducted in order to monitor the implementation and compliance wit Good Manufacturing Practice principles and to propose necessary corrective measures.

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Thank you for your time.
Questions?

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