Australian Government
Department of Health
Therapeutic Goods Administration

Cleaning Validation

A regulatory perspective

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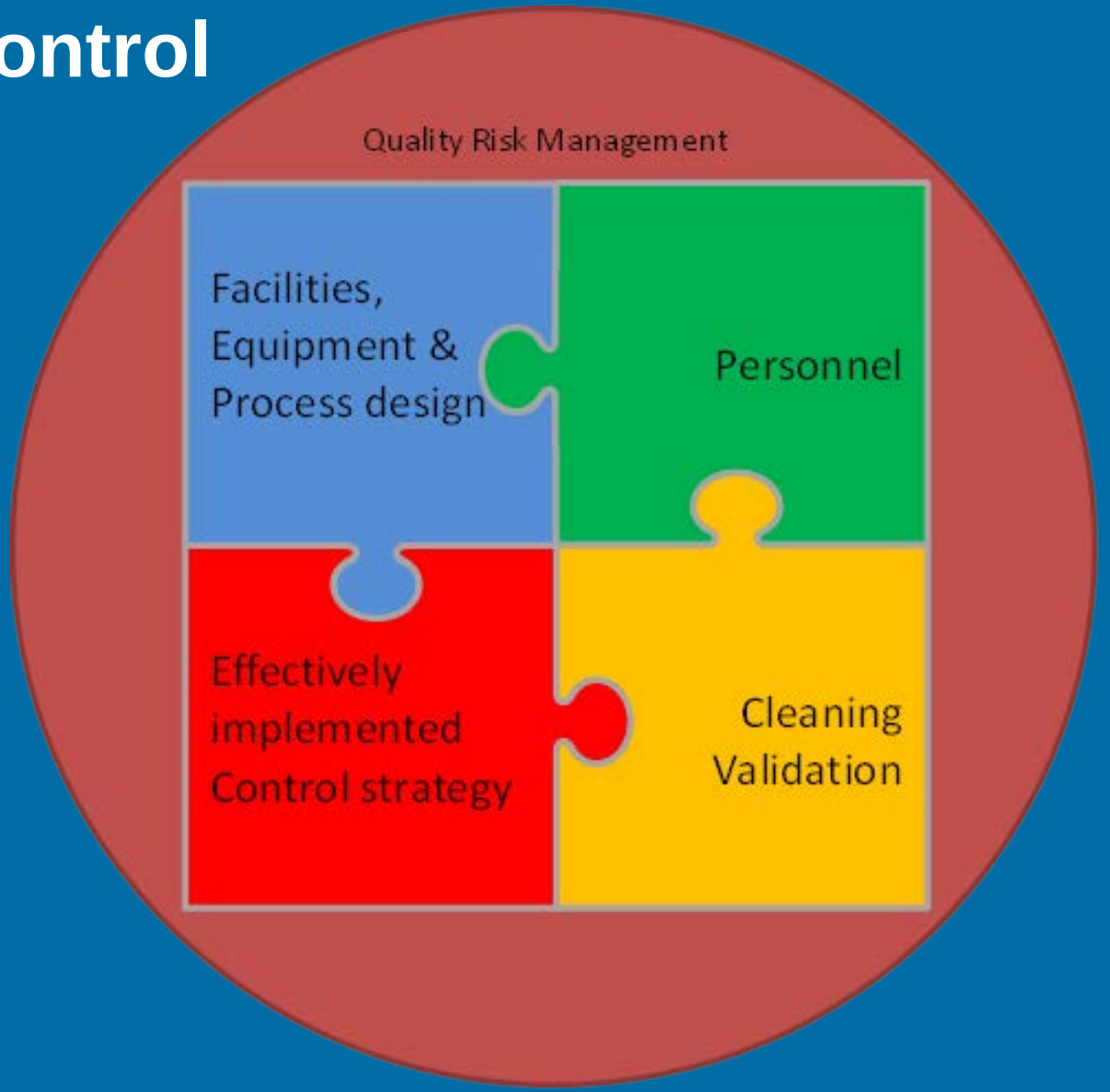
TGA Health Safety Regulation

Overview

- Cleaning Validation and GMP requirements
- Risk-based approach to cleaning validation
- Establishing Health Based Exposure Limits
- Revalidation requirements
- Observed practices and common inspection deficiencies
- Summary
- Questions

Contamination control



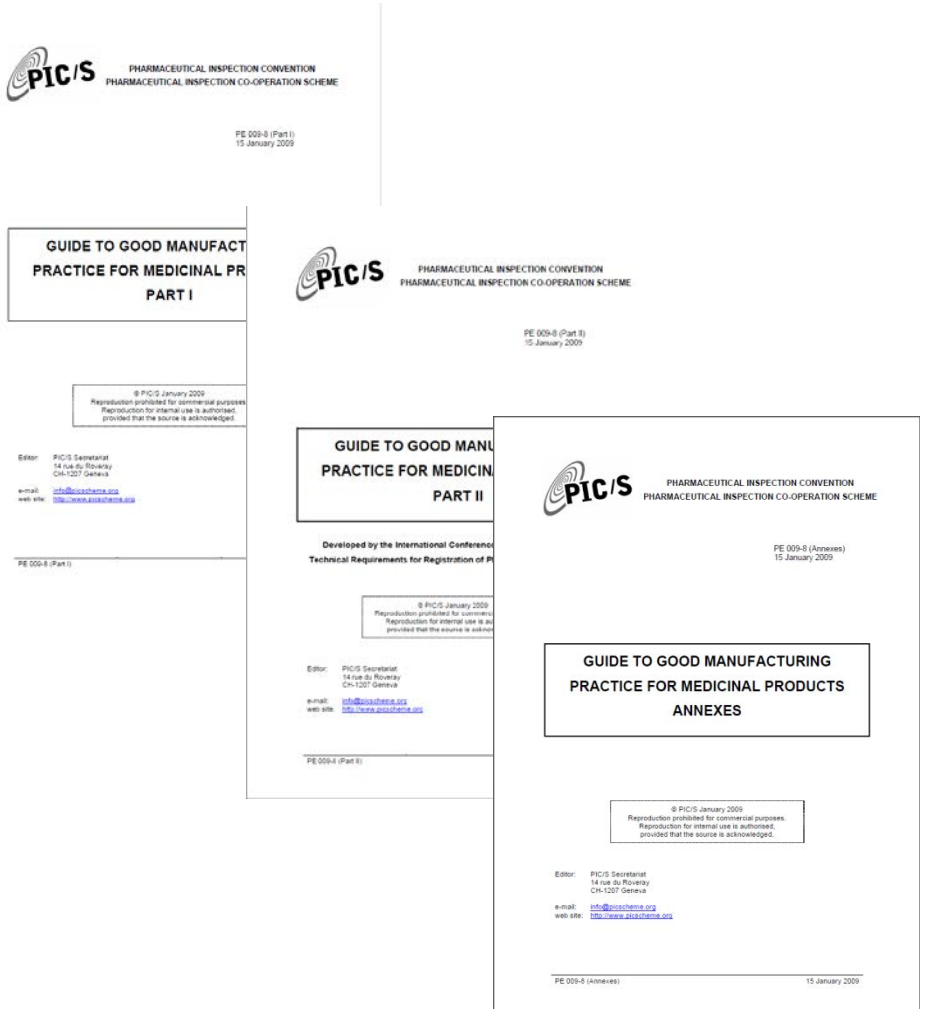
Cleaning validation

*"Cleaning validation is **documented** evidence that an approved cleaning procedure will **reproducibly** remove the previous **product** or **cleaning agents** used in the equipment below the **scientifically** set maximum allowable carryover level"*

PIC/S Guide to GMP for Medicinal Products; Annex 15 Qualification & Validation

Current GMP requirements

PE009-8	Section
Part I	Personnel, **Premises & Equipment**, Documentation, **Production**, Quality Control, Contract Manufacture & Analysis
Part II	Personnel, **Buildings & Facilities**, **Process equipment / cleaning**, Materials management, **Production & Process controls**, **Packaging Cleaning validation**, Contract manufacturers, Repackaging APIs by cell culture/fermentation
Annexes	**1, 2**, 3, 6, 7, 8, 9, 10, 13, **15**

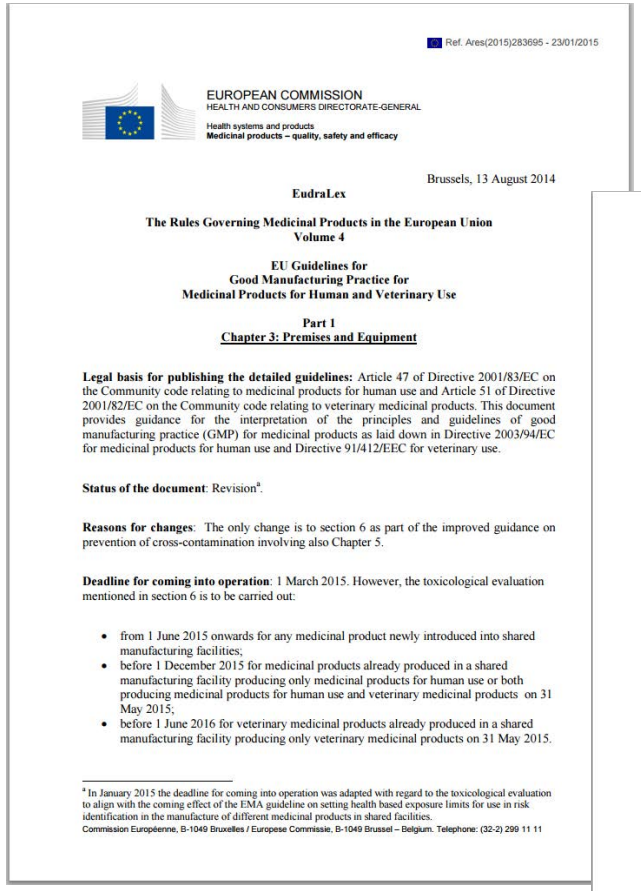


– GMPs not prescriptive - allowing flexibility and adoption of new technologies/science.

GMP developments

- **PIC/S cGMP – PE009-13**
  - Annex **15**
  - Annexes 2 & 3
  - Part II - Implementation of QRM
  - Part I Chapter 3
  - Part I Chapter 5
  - Annex 1

- **PIC/S adoption of setting health based exposure limit guidelines (EMA)**



Ref. Ares(2015)283695 - 23/01/2015

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL
Health systems and products
Medicinal products – quality, safety and efficacy

Brussels, 13 August 2014

EudraLex

The Rules Governing Medicinal Products in the European Union
Volume 4

EU Guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use

Part 1
Chapter 3: Premises and Equipment

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

Status of the document: Revision[a].

Reasons for changes: The only change is to section 6 as part of the improved guidance on prevention of cross-contamination involving also Chapter 5.

Deadline for coming into operation: 1 March 2015. However, the toxicological evaluation mentioned in section 6 is to be carried out:

- from 1 June 2015 onwards for any medicinal product newly introduced into shared manufacturing facilities;
- before 1 December 2015 for medicinal products already produced in a shared manufacturing facility producing only medicinal products for human use or both producing medicinal products for human use and veterinary medicinal products on 31 May 2015;
- before 1 June 2016 for veterinary medicinal products already produced in a shared manufacturing facility producing only veterinary medicinal products on 31 May 2015.

[a] In January 2015 the deadline for coming into operation was adapted with regard to the toxicological evaluation to align with the coming effect of the EMA guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities.
Commission Européenne, B-1049 Bruxelles / Europese Commissie, B-1049 Brussel – Belgium. Telephone: (32-2) 299 11 11

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EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL
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The Rules Governing Medicinal Products in the European Union

Volume 4
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Part 1
Chapter 5: Production

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Status of the document: Revision[a].

Reasons for changes: Changes have been made to sections 17 to 21, including adding a new section, to improve the guidance on prevention of cross-contamination and to refer to toxicological assessment. Changes were also introduced in sections 27 to 30, including adding a new section, on the qualification of suppliers in order to reflect the legal obligation of manufacturing authorisation holders to ensure that active substances are produced in accordance with GMP. The changes include supply chain traceability. Sections 35 and 36 are inserted to clarify and harmonise expectations of manufacturers regarding the testing of starting materials while section 71 introduces guidance on notification of restrictions in supply.

Deadline for coming into operation: 1 March 2015. However, the toxicological evaluation mentioned in section 20 has to be carried out:

[a] In January 2015 the deadline for coming into operation was adapted with regard to the toxicological evaluation to align with the coming effect of the EMA guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities. Furthermore, correction of the reference in footnote 2 took place.
Commission Européenne, B-1049 Bruxelles / Europese Commissie, B-1049 Brussel – Belgium. Telephone: (32-2) 299 11 11
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Key concepts

Health Based Exposure Limits (HBELs)

- A daily dose of a substance below which no adverse effects are anticipated, by any route, even if exposure occurs for a lifetime.
- Required for cleaning validation of hazardous products in shared facilities.
- Derived from a structured scientific evaluation of relevant data.

EMA/CHMP/CVMP/SWP/169430/2012

No Observable Adverse Effect Level (NOAEL)

- NOAEL must be established for all critical effects identified
- The NOAEL is the highest tested dose at which no adverse effect is observed
- If NOAEL is not calculable, the lowest-observed-effect level (LOEL) may be used
- Determined by toxicological expert

PDE or ADE?

- **Permitted Daily Exposure** (PDE) represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime

- **Acceptable Daily Exposure** (ADE) represents a dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every

PDE and ADE are effectively synonymous

MACO - Maximum Allowable Carryover

Mathematically calculated quantity of residue from a previous product when carried over into a different product that CAN represent potential harm to the patient.

- toxicity/pharmacology
- mode of administration
- batch size
- shared equipment surface area plus a safety factor

Risk-based approach

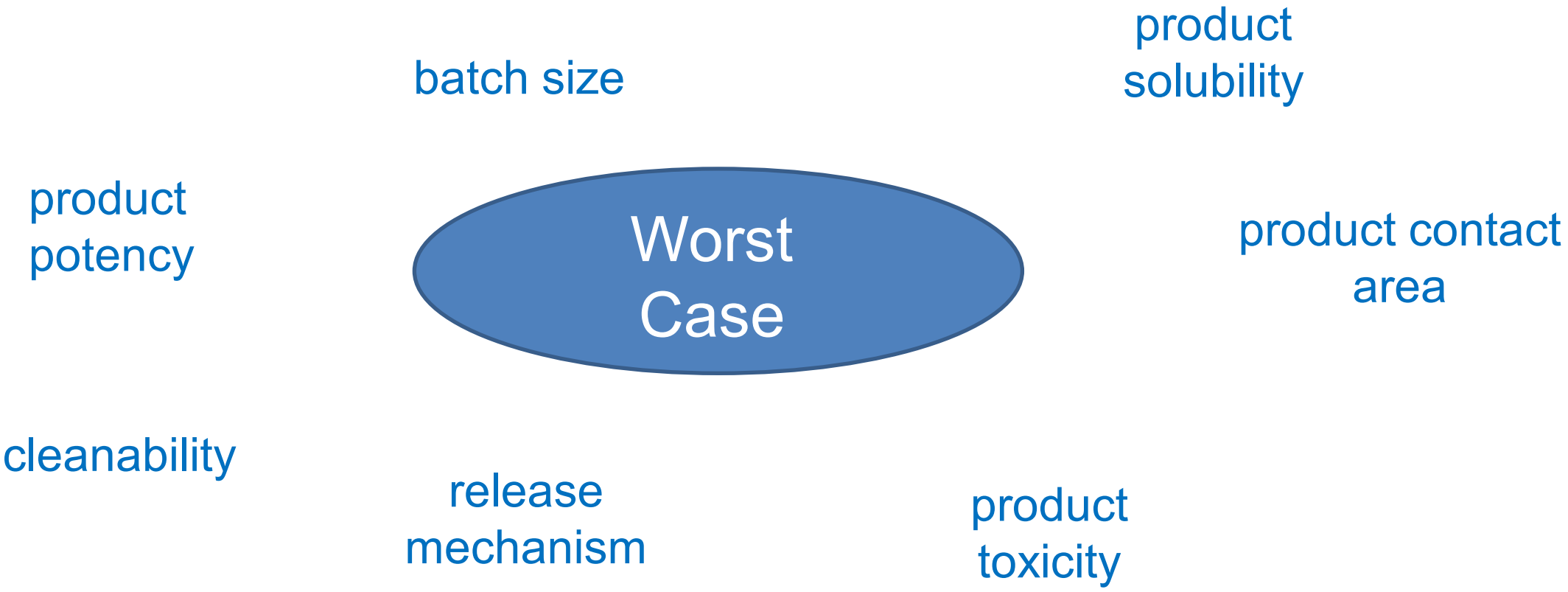
- Health Based Exposure Limits
- Good knowledge management (ICH Q10)
- Risk based approach (ICH Q9)
  - Risk assessments for operations
  - Cross contamination strategy links to protection of patient
  - Shared facilities - scientific approach to ensure contamination risks are managed appropriately

Bracketing for cleaning validation

- Groups typically based on:
  - Equipment train
  - Cleaning procedure
  - Dosage Form
- Rationale explained in SOP or Cleaning Validation document
- Groupings from which ‘worst-case’ will be selected
- Any product that does not conform to ‘bracket’ must be validated individually

Worst-case determination

- Crucial step in defining contamination limits.

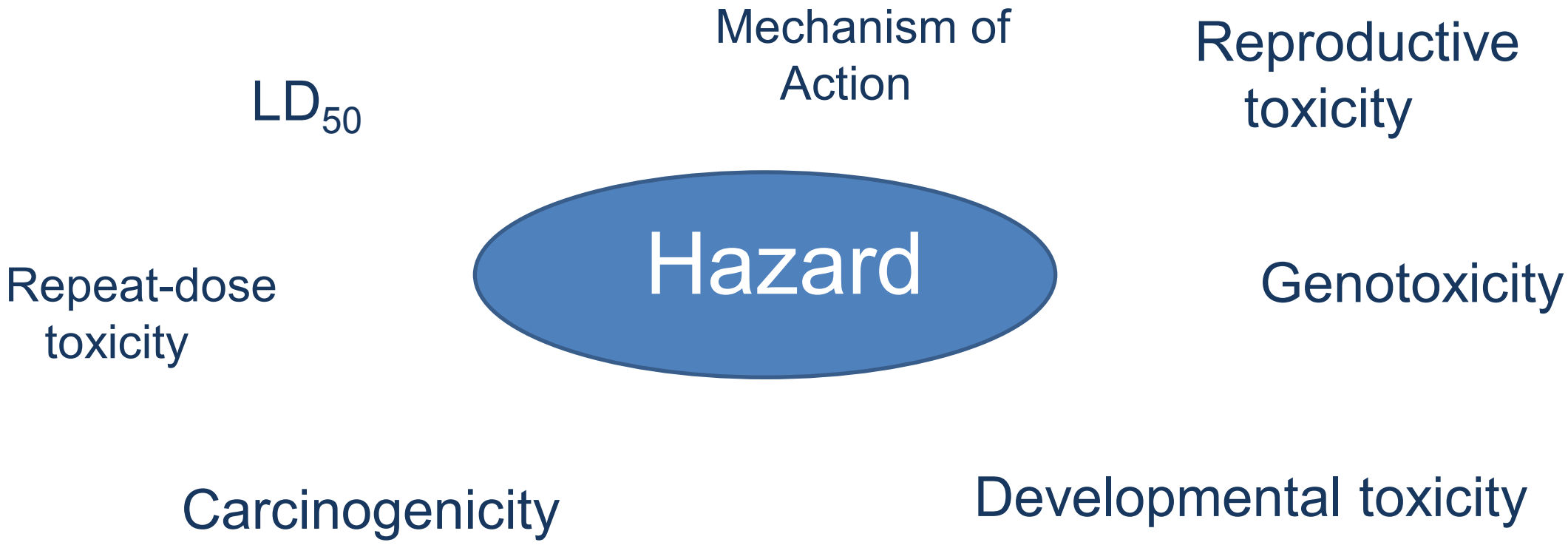


Worst-case process conditions

- Campaign length (no. of batches or time elapsed)
- Dirty Hold Time
- Minimum limits for manual cleaning:
  - Time for Cleaning Steps
  - Temperature
- CIP programs

Establishing health based exposure limits

Step 1: Hazard Identification



Establishing health based exposure limits

Step 2: “Critical Effects”

- Clinical & non-clinical studies
- Therapeutic effects
- Adverse effects

Step 3: Determine NOAEL

- Based on Step 1 and 2 evaluation
- Requires toxicological expertise
- Defined as mg/kg/day

Establishing health based exposure limits

Step 4: Calculate PDE

$$\textbf{PDE}\ (\text{mg/day}) = \frac{\text{NOAEL} \times \text{Weight Adjustment}}{\text{F1} \times \text{F2} \times \text{F3} \times \text{F4} \times \text{F5}}$$

NOAEL: Expressed as mg/kg/day

Weight Adjustment: 50 kg

F1: A factor (values between 2 and 12) to account for extrapolation between species

F2: A factor of 10 to account for variability between individuals

F3: A factor 10 to account for repeat-dose toxicity studies of short duration

F4: A factor (1-10) that may be applied in cases of severe toxicity

F5: A variable factor that may be applied if the no-effect level was not established.

ADE approach

$$\textbf{ADE}\ (\text{mg/day}) = \frac{\text{NOAEL x Weight Adjustment}}{\text{UFc x MF x PK}}$$

NOAEL: Expressed as mg/kg/day

Weight Adjustment: 50 kg - 60 kg

UFc: Composite Uncertainty Factor similar to F1-F5 in PDE formula

MF: Modifying Factor

PK: Pharmacokinetic Adjustments

MACO determination

$$\textbf{MACO}\ (\text{mg}) = \frac{\text{PDE} \times \text{MBS}_{\text{next}}}{\text{SF} \times \text{TDD}_{\text{next}}}$$

PDE: Obtained in Step 4

MBS_{next}: Min. Batch Size

SF: Safety Factor

TDD_{next}: Standard Therapeutic Daily Dose (mg/day)

Safety factors:
Topicals 10 - 100
Oral products 100 - 1000
Parenterals 1000 - 10000

Assessment report

Annex

PDE Determination Strategy

EMA/CHMP/CVMP/SWP/169430/2012

Expert

Company Name

Company Address

Expert Name and Signature **Date**

Assessment Review Date

Chemical Name/s

Hazards

Hazards Identified

	YES	NO	UNKNOWN
Genotoxicant			
Reproductive developmental toxicant			
Carcinogen			
Highly sensitizing potential			

PDE

Basis for the PDE
Justification for selection of "lead" critical effect used for final PDE calculation
NOAEL and applied adjustment factors upon which the PDE is based

NOAEL

Reference(s)
Publication(s) used to identify the critical effect and dose

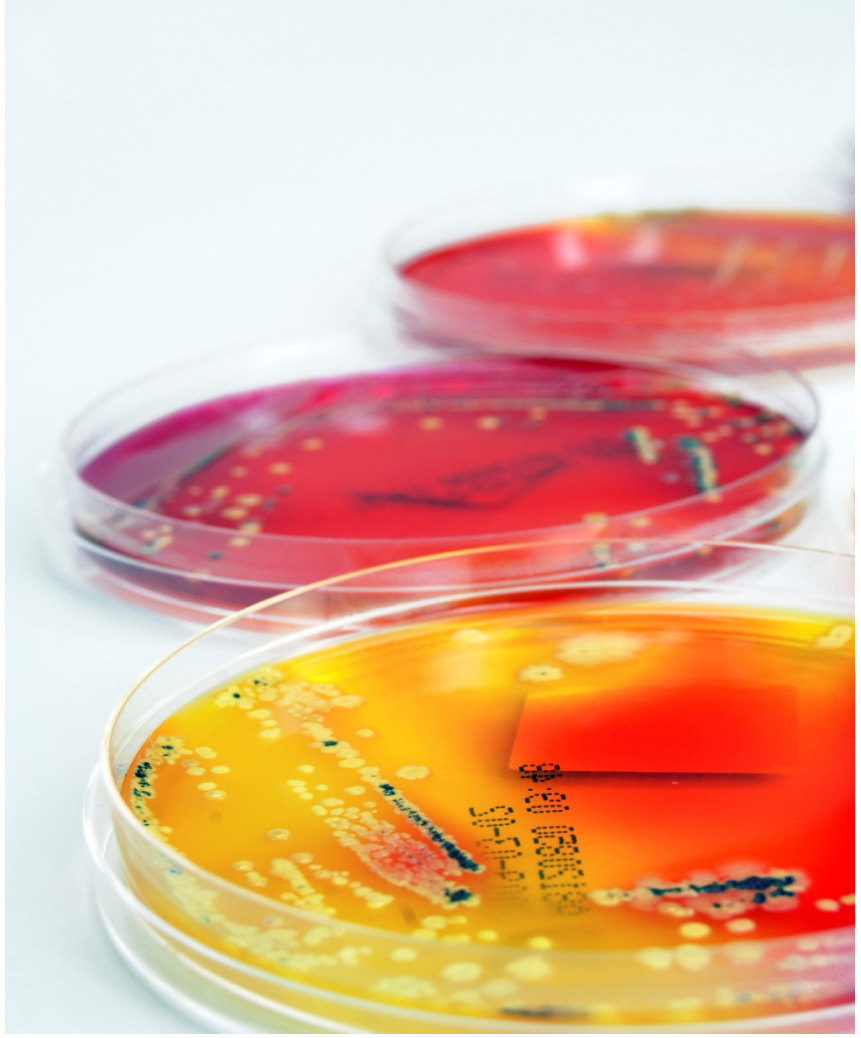
Summary of the Expert CV

Revalidation requirements

- Introduction of new “worst-case” product
- Change in “product contact” equipment
- Change in bracketing approach
  - Validation should be assessed for impact
- Annex 15 (PE009-13)
  - Continuous process verification
  - Effectiveness of manual cleaning should be confirmed at a justified frequency

Microbiological risks

- Annex 15 (PE009-13)
  - More prescriptive clauses for cleaning validation
  - Microbial and endotoxin contamination risks
- Appropriate sampling method
  - Represents “worst-case” locations
  - Trained personnel
  - Sample handling before testing
- Validated Test Methods
  - Acceptable recovery
  - Objectionable organisms



Observed practices

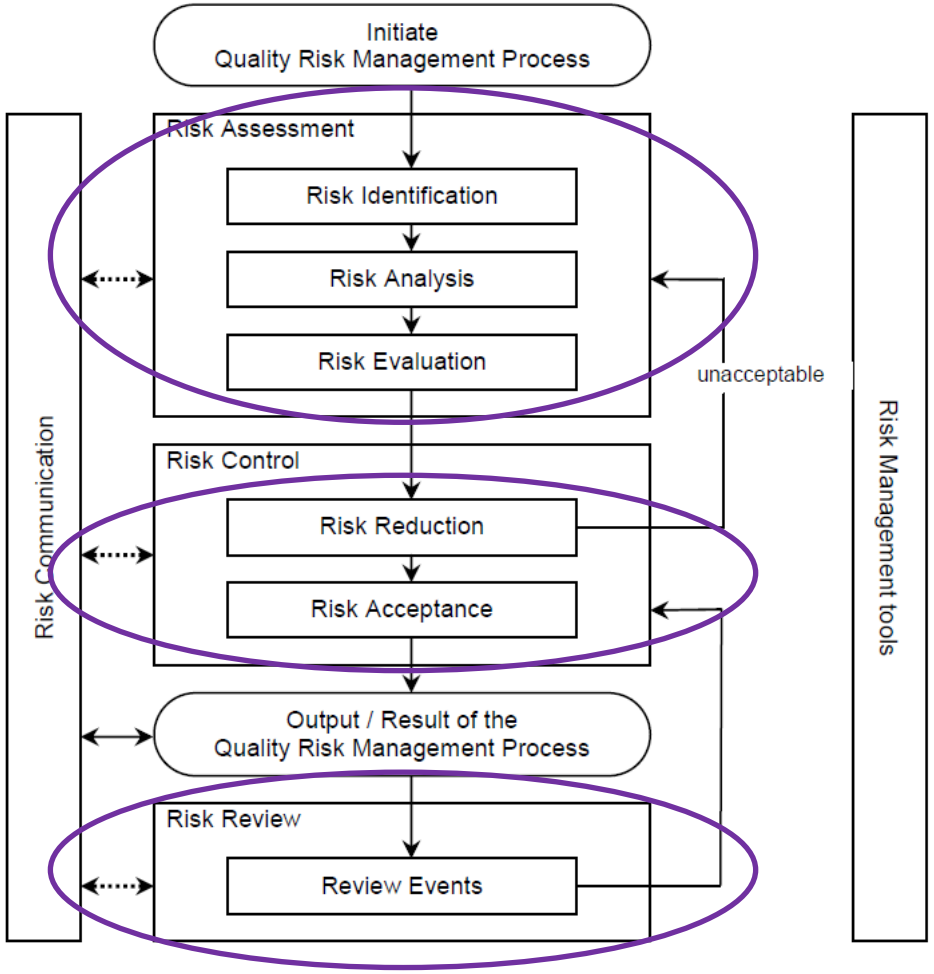
Good Contamination Control Practices

- Documented Contamination Control Strategy
- Relies on good knowledge management (ICH Q10)
- Risk based approach (ICH Q9)
  - Risk assessments for operations
  - Cross contamination strategy links to protection of patient
  - Shared facilities - methods follow scientific approach to ensure contaminants and contamination risks are understood and managed appropriately.
- Guidance documents:
  - APIC “Guidance on Aspects of Cleaning Validation in API Plants” (2014)
  - ISPE Baseline® Guide - Risk MaPP
  - PDA TR 29 “Points to Consider for Cleaning Validation” (2009)

Common inspection deficiencies

Deficiency categorisation:

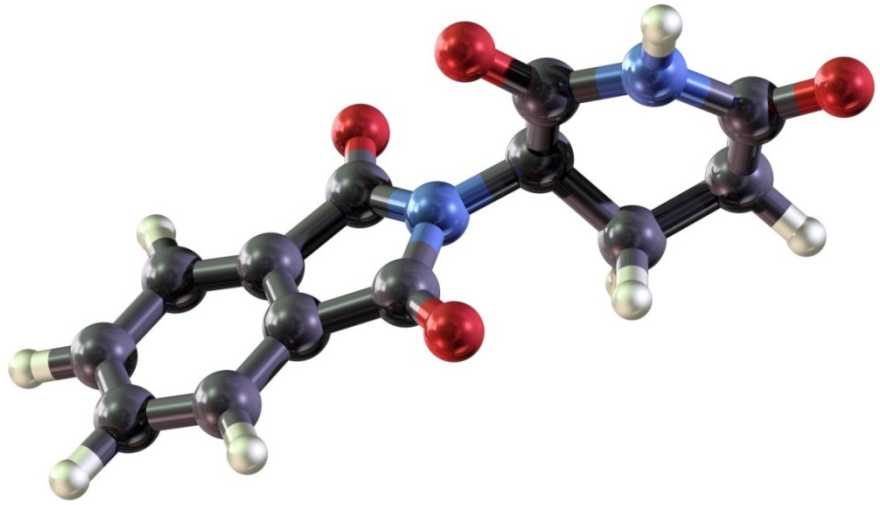
- Assessment of intrinsic hazards presented by the products/processes
- Design of facilities, utilities, equipment and processes
- Controls to address hazards
  - Technical and organisational controls
- Periodic review



Assessment of intrinsic hazards - issues

Poor assessment of molecules handled by the facility:

- Limited or no data from product sponsor
- No clear policies on what products are manufactured in which areas
- Generic evaluation of risks presented by substances



Deficient assessment of processes:

- No risk assessment for new processes
- Campaign practices implemented without due validation

Assessment of intrinsic hazards - issues

*There was **no completed risk assessment** in place to justify the current operation of the facility as a **shared use, multi-product facility.** It was noted that the lines and rooms used for the production of XXXXX were also used for the production of other **cytotoxics, steroids, analgesics and non-β-lactam antibiotics** in injectable forms. In addition, the site product range included **hormonal** products, e.g. methyl progesterone.*

Assessment of intrinsic hazards - issues

The validation of **all cleaning processes for all products and equipment trains** used by the manufacturer was based on the cleaning validation of a **single liquid product only,** ("Product X") Product X is a flammable liquid product, and the applicability of this specific cleaning validation exercise to the cleaning of powder, granule, tablet, cream, ointment and other liquid processes had not been scientifically established, justified and documented by the manufacturer.

- The written instructions for the cleaning of equipment used in the liquids manufacturing areas, differed to that in the solids manufacturing areas; the methods were **not equivalent**.
- The limits for allowable residues of Product X were based on a 10ppm carry over into the smallest flammable liquids batch size. It was **not possible to extrapolate** this calculated limit to other product types or equipment trains.
- Product X was a topical product, and the assessment of allowable carry over did **not consider the route of administration** for other dosage forms or product types.

Design of processes - issues

In relation to cleaning validation:

- There was **no risk assessment or justification** available to outline the manufacturer's current **approach to cleaning validation.**

- The cleaning validation of the line 2 lyophiliser had been conducted based on the removal of **sodium chloride only**; multiple **active cytotoxic materials** were processed in the common lyophilisers.

- For the cleaning validation of XXXX, the **locations for residue swabbing** in the mixing vessel were not regarded as **worst case or hard to clean surfaces**. Other areas of the vessel, that were regarded by the inspector as being more difficult to clean, such as inlet ports, sample valves and under the impellor were not tested.

- Cleaning validation had not been performed on the **glass "Schott" bottles** used for API slurry formulation; these bottles were **not labelled as dedicated** to a specific active.

Design of Processes - issues

In relation to the existing cleaning validation studies XX & YY:

- The existing cleaning validation for the facility was **limited to the AAA and BBB machines only;** it was not apparent as to how the cleaning studies were applicable to other equipment trains
- There was **no cleaning validation study** available for **liquids/creams**
- There was **no clearly defined** cleaning method for the study; the cleaning SOP used at the **time of the validation** (Version 1) did not contain sufficient details regarding the specific cleaning methods used.
  (Also Clause 4.4)
- The cleaning agent used at the time of the validation was “XXXX” but the manufacturer now uses “YYYY” it was **not clear** as to whether these solutions were **equivalent**.

Design of processes - issues

In relation to the existing cleaning validation study:

- The surface area calculation was limited to the **filling line equipment only**, and did not include the upstream of filling process (i.e. formulation) equipment train
- The study for the effective removal of detergent residues did not reflect the current practices used in manufacturing as the **concentration of the detergent was not defined** in the cleaning process

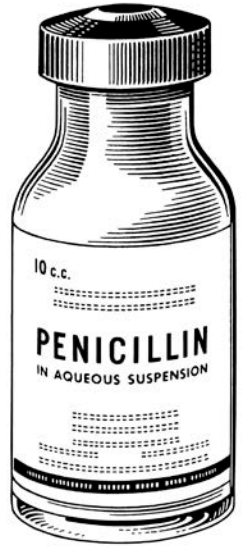
Design of facility / processes - issues

In relation to the proposed cleaning validation study:

- The protocol **did not include consideration of product contact parts** used in the manufacture of dosage forms, e.g. plastic jugs, bowls and sieves used in the manufacturing area
- The **cleaning method** described in the procedure **did not provide detail** regarding the soak times or method of mechanical removal of residues
- Specific **swabbing locations** (worst case) within equipment trains **were not clearly defined and justified**; e.g. locations were identified as “hopper” or “perforated plate”

Lack of appropriate controls - issues

- *The procedure for label issue (SOP 123) stated that **labels for the powders batches (penicillins)** were to be placed in a **grey box** and secured. The majority of the **boxes used for label issue to the non-penicillin area were grey**, and the mechanism to ensure that boxes that had accessed the penicillin building were not used in the general facility was not apparent*



Lack of Appropriate Controls - issues

The cleaning record for the paclitaxel compounding area indicated that the room was clean; however the inspector observed:

- A large **pool of standing water** was observed on the floor
- **White powder residue** was observed around the balances
- **White residue** was observed on the floor in the area

Lack of appropriate controls - issues

Re-usable equipment for CYTOTOXIC was stated to be dedicated, however the inspector observed that:

- Although the filling needles and carboy siphon tubes were marked, these filling needles and carboy siphon tubes were **stored mixed up with needles and siphon tubes for other products**
- Although the Equipment Preparation List for CYTOTOXIC stated “use CYTOTOXIC dedicated equipment” the records available **did not demonstrate that CYTOTOXIC dedicated equipment was used**, and the system in place did not clearly demonstrate that CYTOTOXIC dedicated equipment was controlled in a manner to ensure that the dedicated equipment was not used for the manufacture of other products
- The flasks used for the collection of CYTOTOXIC flush and priming solutions **were not dedicated** to CYTOTOXIC

Ineffective periodic reviews - issues

The (cleaning) studies were last performed in 2007 and were based on the cleaning and carry-over from PROD A capsules. The cleaning validation had not been modified or reconsidered in light of new products or equipment introduced to the site since the completion of the study in 2007.

There was no available risk assessment of the current cleaning practices in light of the changes to the product range manufactured on site, i.e. the process ability to effectively clean residues from those additional products introduced into manufacturing since the 2007 study. (Also clauses 1.5 & 1.6)

A 2009 review of the cleaning validation study identified several issues with the 2007 study; issues were noted regarding the swabbing methods used, as well as the spiking of samples. However, those recommendations had not yet been actioned.

Summary

- International GMPs have incorporated HBELs approach to cleaning validation
- Knowledge management and transfer of information is key
- Will need expert advice in establishing PDE limits - sponsors play key role
- This change is important to maintaining patient safety
- **Manufacturers and Sponsors need to remain vigilant regarding cleaning validation**

Questions

Australian Government

Department of Health

Therapeutic Goods Administration