Australian Government
Department of Health
Therapeutic Goods Administration

Cleaning and Contamination Control

A regulatory perspective

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Australian Government
Department of Health
Therapeutic Goods Administration

Cleaning and Contamination Control

- Contamination control and current GMP requirements
- Future GMP developments
- Observed practices and common inspection deficiencies
- Summary
- Questions

Contamination Control

Definitions

- **Contaminant:**

"Any adventitiously introduced materials (e.g. chemical, biochemical, or microbial species) not intended to be part of the manufacturing process of the drug substance or drug product" – ICH Q6B

- **Contamination:**

"The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto raw material, intermediate, or API during production, sampling, packaging or re-packaging, storage or transport" - EUDRALEX Volume 4 Glossary

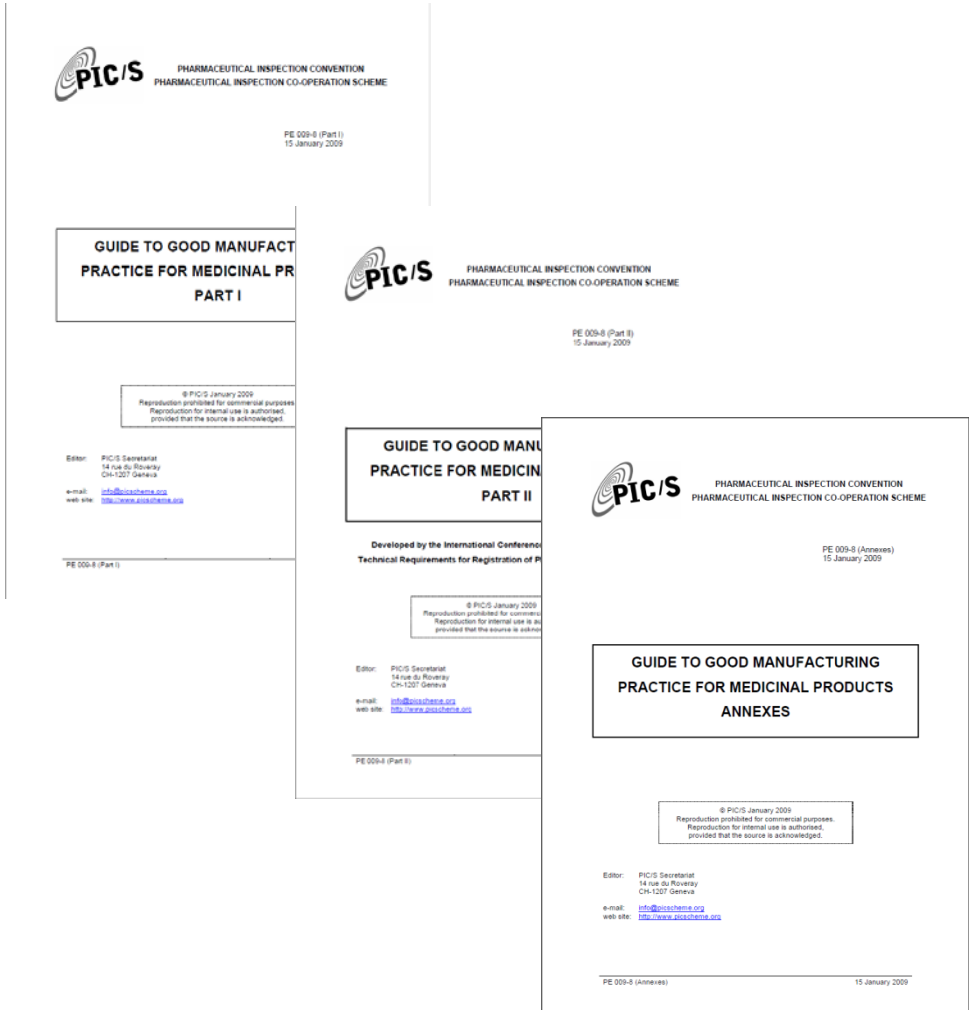
- **Cross contamination:**

"Contamination of a material or product with another material or product" – PIC/S Guide to GMP PE009-8

Current GMP requirements

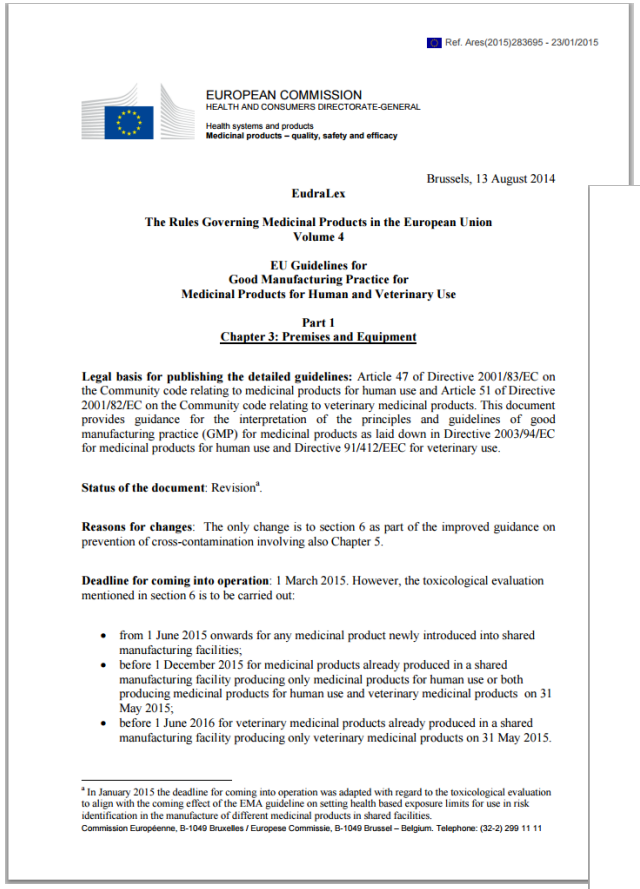
PE009-8	Section
Part I	Personnel, **Premises & Equipment**, Documentation, **Production**, Quality Control, Contract Manufacture & Analysis
Part II	Personnel, **Buildings & Facilities**, **Process equipment / cleaning**, Materials management, **Production & Process controls**, **Packaging** **Cleaning validation**, Contract manufacturers, Repackaging APIs by cell culture/fermentation
Annexes	Annex **1, 2**, 3, 6, 7, 8, 9, 10, 13, **15**, 17

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



Future GMP developments

- **Current PIC/S cGMP – PE-009-12**
  - Annex 15
  - Annexes 2&3
  - Part II – Implementation of QRM
- **Draft PE-009-13**
  - 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

Ref. Ares(2015)283689 - 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 5: Production

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: 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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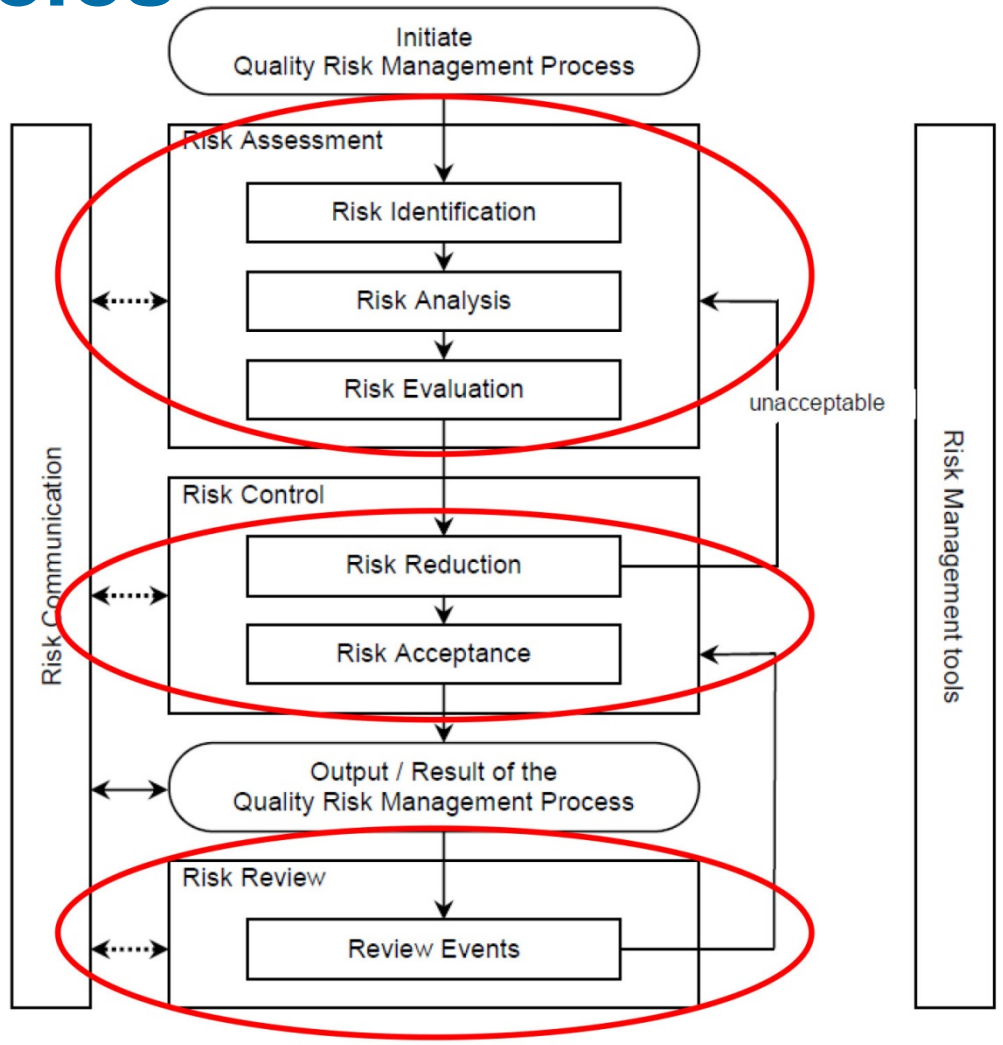
Observed practices

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)

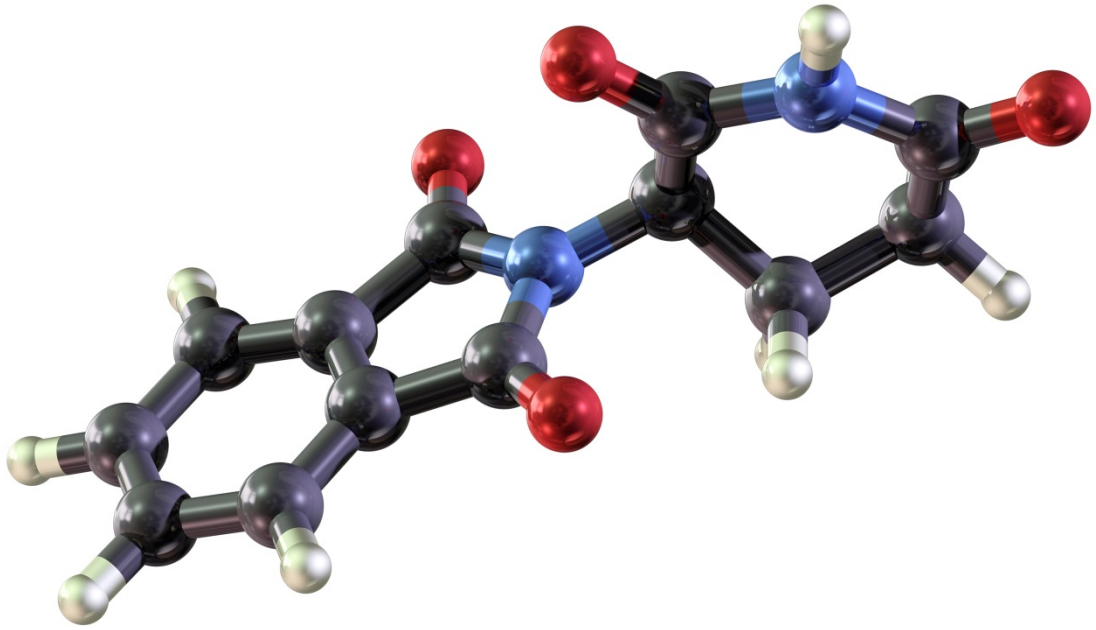
Common inspection deficiencies

- One of the most common deficiencies topics reported in 2014-2015 FY.
- 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

- No or limited 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
- No or limited assessment of processes
  - No risk assessment for new processes
  - Campaign practices implemented without due assessment



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

There was no consolidated document, or set of documents, detailing the manufacturer's (risk based and systematic) control strategy and methodology:

- For the handling of potent materials,
- For the introduction of new molecules, including their categorisation, and then as applicable (1) rejection, (2) integration, and/or (3) process changes and then integration,
- For managing the risk(s) of cross-contamination, particularly in the context of the aforementioned facilities limitations,
- For the absence of a residue monitoring program.

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.
- The analytical validation of the recovery of Product X from equipment surfaces considered **recovery from stainless steel surfaces only**. This was not truly representative of all product contact parts used in the manufacture of all products.

Assessment of intrinsic hazards - issues

While acknowledging the line specific completed cleaning validation studies, there was no evidence to support a systematic review of:

- All products and their characterisation in terms of their solubility, LD 50, and concentration.
- All items of (contact) equipment, including the complete equipment trains and their permutations and combinations, and the difficult to clean points, e.g. there was no evidence of the mapping of all manufacturing lines for the identification of all permutations and combinations, for the determination and substantiation of worst case, including surface area and hard to clean items/points.
- All cleaning methods (i.e. manual and CIP).

for the determination of, and to support that completed studies were representative of the worst case.

Design of Facility / Processes - issues

Within the General Manufacturing area the following aspects of the design, operation and maintenance of the facilities and equipment were deficient:

- Mixing room #1 and #2 operated at **positive pressure** and airflow to the main access corridor and contrary to the principle of containment; while mixing room #3 (M06), in contrast, operated at **negative pressure** and airflow to the main access corridor.
- The risks associated with inconsistencies in pressure differentials and the directions of airflow were compounded by the presence and operation of the **interconnecting doors between mixing rooms #1, #2 and #3**, in that these doors allowed the unrestricted movement of equipment, materials, personnel and (intermediate) product between these rooms during formulation.
- The wash room, packing room #2, the dispensary and mixing room #3 operated at negative pressure to the main access corridor, and consequentially were **“sinks”** to mixing rooms #1 & #2, and Packaging rooms #1 & #3.
- The equipment **washroom** was congested and used for **storage of ‘cleaned’ equipment** .

Design of Facility / Processes - issues

There was no study available to demonstrate the **effectiveness of the decontamination and transfer process** for box, (grade C to B transfer). Items transferred included materials transferred to the aseptic processing area via the UV transfer agar plates, air samplers, product filters, gloves, masks, particle counters, UV meters and trolleys.

Design of Facility / 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**.
- There was no cleaning validation for **the manual cleaning process for the lyophiliser on line 1**. There was no justification or risk assessment for the omission of this study.
- 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**. The vessel was cleaned using a combination of a spray-ball and manual cleaning and the sample locations selected were on the inner vertical surfaces of the vessel, at a midpoint between the base and top of the vessel which would be easily reached by the spray and operator. 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 studies had not been performed for the **dispensing cRABS** used for dispensing multiple active materials and for the **preparation of active slurry**
- 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 Facility / 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 **“XXX”** the manufacturer now uses **“YYY”** it was not clear as to whether these solutions were equivalent.

Design of Facility / Processes - issues

In relation to the existing cleaning validation study of ZZZ:

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

Design of Facility / Processes - issues

In relation to the proposed cleaning validation study NNNNNN:

- 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 cleaning record for the paclitaxel compounding area indicated that the room was clean; however:

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

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

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 caplets. 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 Health Based limits approach to cleaning validation
- Health based limits are likely to be mandated in the future
- Knowledge management and transfer of information is key
- Will need expert advice in establishing ADE/PDE limits – sponsors play key role
- This change is important to maintaining patient safety
- ***Manufacturers and sponsors need to remain vigilant regarding contamination control***

Questions

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