Cross-Contamination Definition

"Contamination of a starting material or of a product by another material or product ..."

A foreign starting material

Another product

Cleaning agents

Other foreign materials

Draft Eudralex Vol. 4 Chapter 5: Production, 5.18


Status of the document: Revision.

Reasons for changes: Changes have been made to sections 17 to 20 to improve the guidance on prevention of cross-contamination and to refer to toxicological assessment guidance. Changes were also introduced in sections 26 to 28 on the qualification of suppliers in order to reflect the legal obligation of manufacturing authorization holders to ensure that active substances are produced in accordance with GMP. The changes include supply chain traceability. Section (33) is inserted to clarify and harmonize expectations of manufacturers regarding the testing of starting materials while section (68) introduces guidance on notification of restrictions in supply.

Deadline for coming into operation: 6 months from publication.
## Current TGA GMP vs EU GMP

**Part I**

<table>
<thead>
<tr>
<th>Chapter</th>
<th>PIC/S Guide to GMP (v8)</th>
<th>EU GMP Guidelines</th>
<th>Degree of change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Quality management</td>
<td>Pharmaceutical Quality System (Jan 2013)</td>
<td>Major</td>
</tr>
<tr>
<td>2</td>
<td>Personnel</td>
<td>Personnel (Feb 2014)</td>
<td>Major</td>
</tr>
<tr>
<td>3</td>
<td>Premises and Equipment</td>
<td>Premise and Equipment (in draft)</td>
<td>Minor</td>
</tr>
<tr>
<td>4</td>
<td>Documentation</td>
<td>Documentation (Jan 2011)</td>
<td>Major</td>
</tr>
<tr>
<td>5</td>
<td>Production</td>
<td>Production (in draft)</td>
<td>Major</td>
</tr>
<tr>
<td>6</td>
<td>Quality control</td>
<td>Quality Control (Oct 2014)</td>
<td>Major</td>
</tr>
<tr>
<td>7</td>
<td>Contract manufacture and analysis</td>
<td>Outsourced activities (Jan 2013)</td>
<td>Minor</td>
</tr>
<tr>
<td>8</td>
<td>Complaints and product recall</td>
<td>Complaints, Quality Defects and Product Recall (in draft)</td>
<td>Major</td>
</tr>
<tr>
<td>9</td>
<td>Self Inspection</td>
<td>Self Inspection</td>
<td>Same</td>
</tr>
</tbody>
</table>
Cross-Contamination Regulations

• Describes where the risks of cross-contamination arise and includes ‘organisms’.

• The significance of this risk varies with the type of contaminant and of product being contaminated.

• Cross-contamination should be avoided by robust design of the premises, equipment and processes which take place within a manufacturing facility.
Cross-contamination Regulations

- Describes the toxicological evaluation expectations and how it relates to setting limits as part of a QRM exercise.

- Factors including; **facility/equipment design**, personnel flow, physico-chemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the threshold values for products should also be taken into account.

- Outcomes of QRM process should include the extent of facility/equipment dedication required.
Cross-contamination Regulations

*Draft Eudralex Volume 4, Chapter 5 - 5.20*

- Lists multiple technical (13) and organisational (11) measures to mitigate risks of cross-contamination
- Not exhaustive or prescriptive
- Technical measures focus on facility and equipment design
Cross-contamination Regulations

- Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.
Routes for Cross-Contamination

ISPE Baseline Guide Vol. 7 – Risk Based Manufacture of Pharmaceutical Products, Section 6.3

- Mix Up
- Retention
- Mechanical Transfer
- Airborne Transfer
Facility Design

Mix Up

"The contamination at unsafe levels of one product with another via inadequate plant and process design or human error."

- Most commonly occurs through labelling, receipting, line clearance type problems – human error

How do we prevent mix-up through facility design?

- Considerate design
  - line clearance, mental stimulation
- Physical segregation
  - even in multi-product facilities
Facility Design
Facility Design
Facility Design

Retention

“Carryover of material on product contact surfaces from one product to another in the same equipment used in a sequential or campaign manner”

How do we prevent retention through facility design?

- Dedicated facilities
- Self contained processing modules
- Disposable technologies
- Cleaning considerations
Facility Design

Mechanical Transfer

The transfer of material from contaminated non-product contact surfaces into the product

How do we prevent mechanical transfer through facility design?

› Incorporation of process related design elements
  › RABS/Isolation
  › Closed processes/automation
› Personnel and material flows
Facility Design
Facility Design
Facility Design

Containment equipment

1. undocked, unlocked & closed
2. docked, locked & closed
3. docked, locked & opened
Airborne Transfer

*The generation and subsequent movement of a stable aerosol to another area where it is deposited in unsafe quantities on another exposed product*

- Usually an OHS issue before it becomes a product quality issue
- Most relevant for highly toxic, potent or allergenic products

How do we prevent airborne transfer through facility design?

- Closed processing systems
- Dedicated/self contained facilities
- HVAC design – single pass and/or filtered exhaust
Facility Design

Standard Recirculation HVAC

Ref: WHO Supplementary Guidelines on GMP for HVAC systems for Non-sterile Pharmaceutical Dosage Forms
Facility Design

Single Pass HVAC

Ref: WHO Supplementary Guidelines on GMP for HVAC systems for Non-sterile Pharmaceutical Dosage Forms
Summary Points

Key considerations for facility design to minimise cross-contamination

a) Understand that cross-contamination is more than just one product in another

b) Understand your risks through QRM – toxicology, routes of contamination, product types, facility and process limitations

c) Mechanisms for reducing cross-contamination include both technical and organisational measures. Both can impact final facility design

d) Focus on reduced intervention and increased dedication
Thank you for your time.
Questions?

Ashley Isbel
Lead Engineer

ashley.isbel@pharmout.net
www.pharmout.net