Contamination & Cross-contamination best practices
New EU & PIC/S requirements
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Where and why did all this begin?

It all began in 2005, 10 years ago!
First we have to look back at some of the industry drivers that have influenced us over the last 10 years, and have had a huge impact on our GMP texts about cross-contamination risks in the last 5 years:

- Many APIs – Increasing potency & toxicity
- Reducing scale of manufacturing – personalised medicine
- Increased complexity: Products & Processes
- Increasing novelty: Products & processes
- Pressure to start facility projects as late as possible
  - Product development projects fail in late phase clinical trials.
  - Need to get into market quickly.
  - Need to be able to implement process improvement & efficiency.
- Squeezed profit margins
- Sustainability aspirations & targets
Influences of cross-contamination control guidance

From all these, the following most influenced the cross-contamination control guidance:

- Many APIs – Increasing potency & toxicity
- Reducing scale of manufacturing – personalised medicine
- Increased complexity
- Increasing novelty
- Squeezed profit margins

What firms found

- They seemed to be squeezed into more and more dedicated and separate facilities. They didn’t want these unless there was a really good reason for them.
- The language of the GMPs, bracketing attributes of products in a non-scientific way was an issue.
The problem clauses

Dedicated facilities must be available for:
- Certain
- Antibiotics
- Hormones
- Cytotoxics
- Sensitisers

Clauses 3.6, 5.18, 5.19 & 5.20 in the regulatory guidance are the problem EU & PIC/S GMP
The problem clauses

Prevention of cross-contamination in production

5.18 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays or organisms from materials and products in process, from residues on equipment, and from operators’ clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Amongst the most hazardous contaminants are highly sensitising materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time.

Clauses 3.6, 5.18, 5.19 & 5.20 in the regulatory guidance are the problem EU & PIC/S GMP
5.19 Cross-contamination should be avoided by appropriate technical or organisational measures, for example:

a) production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;

b) providing appropriate air-locks and air extraction;

c) minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

d) keeping protective clothing inside areas where products with special risk of cross-contamination are processed;

e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;

f) using “closed systems” of production;

g) testing for residues and use of cleaning status labels on equipment.

5.20 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.
Segregated and dedicated facilities
EU/PIC-S regulatory background

• Applies to:
  – GMP pilot plant.
  – Clinical scale Investigational Product manufacturing (IPs).
  – Commercial scale manufacturing.

• Increasing need to handle potent entities.
• At the same time, an increasingly risk averse culture in our industry.

Lack of clarity about degree of separation required:
  – Separate building.
  – Separate suite within common building.
  – Isolation of process within common facility.
EMA tries to fix the problem in 2005

- A concept paper was published in 2005. This announced changes to Chapter 3.6 and 5.18 intended to remove the existing ambiguity.
- Chapter 3.6 mentions, for example, "certain" products that should not be manufactured in the same production facility. This implies use of a dedicated facility, but the actual products covered are unclear.
- The text also mentions "exceptional cases" without defining either these or the "certain" products.

**Industry, including Inspectors, were confused!**
More EMA debate in 2008

- The lengthy discussion about this subject prevented the revision of the guide from being completed on schedule (2006/7).
- Due to the great interest, EMA published a progress report on 9th January 2008 on the state of the revision.
- This report says that the GMP/GDP Inspectors Working Group has reached consensus that there should be:
  - A list of substances for which a dedicated facility is mandatory.
  - Additionally a list would identify substances for which specific risk-based arguments will be necessary to allow shared facilities to be used.
  - Here, the text does not give any further details.
- So the concept of an A & B list emerges.
So, the key issues in 2008 were...

- A prescriptive list(s) or not?
- Our regulators were still open to science-based persuasion at this stage.
- What do the following mean?
  - “Dedicated…”
  - “Self-contained…”
  - “Exceptional cases”... “campaign working... can be accepted”
- Does this only relate to facilities?
- Could it also be systems serving facilities e.g. HVAC?

All very unclear and messy!!!!!!
ISPE gets in on the act in 2008 – with proper risk based thinking

Risk based thinking


So called RiskMaPP.

**Note:** A 2nd Edition is in preparation currently.

- Gets away from lists.
- Requires application of scientific knowledge of ADI (allowable daily intake), and assessment of the risk that cross-contamination $\geq$ ADI could occur, and application of mitigation measures to keep below this threshold.
So, the key issues are...

- Dedicated
  - e.g. non-penicillin

- Dedicated
  - e.g. penicillin

- Segregated
  - e.g. hormone cytotoxic

- Isolated
  - Low dose high-potency

"Dedicated......"
"Self-contained......."
"Exceptional cases" "....campaign working...can be accepted"
Acknowledgement

• Many of the images and explanations included in this presentation has been prepared by member of ISPE’s Risk-MaPP Task Team. They have been utilised to ensure consistent expression of the Risk-MaPP objectives.

• Other slides expressing industry practice and regulatory experience are taken from the authors international experience.
**ISPE RiskMaPP**

Decision tree to assist with Manufacturing and Sourcing decisions Compound X - cGMP/Regulatory focus

- **Is there a specific requirement to handle in a dedicated facility?**
  - **N**
    - Obtain cleaning val criteria
    - Can cleaning be demonstrably carried out to meet criteria? feasibility cost practicability
  - **Y**
    - Are there any other factors that Could prevent the use of a Multi-product plant? facility standards operational business confidentiality

- **N**
  - Can the cleaning criteria be met by some of the stages?
  - **Y**
    - Can the contaminated equipment be isolated to prevent facility contamination?
    - **Y**
      - Can these issues be resolved?
      - **Y**
        - Can only be in multi-product facility with dedicated equipment or units.
        - **OPTIONS**
          - Disposable equipment for given step
          - Dedicated equipment for given step
          - Dedicated unit
      - **N**
    - **N**
  - **N**
    - Can only be in single product facility
Now in 2015, we have the new EU GMP requirements

Production Area

3.6 Cross-contamination should be prevented for all products by appropriate design and operation of manufacturing facilities. The measures to prevent cross-contamination should be commensurate with the risks. Quality Risk Management principles should be used to assess and control the risks. Depending on the level of risk, it may be necessary to dedicate premises and equipment for manufacturing and/or packaging operations to control the risk presented by some medicinal products.

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

i. the risk cannot be adequately controlled by operational and/or technical measures,
ii. scientific data from the toxicological evaluation does not support a controllable risk (e.g. allergenic potential from highly sensitising materials such as β-lactams) or
iii. relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a validated analytical method.

1. The basic requirement demands understanding the X-contam risk, severity, and applying appropriate control measures for all multi-product facilities.

2. Default requirement. Dedicated facilities are required when:
   - Operational or technical measures are inadequate.
   - Toxicological evaluation does not support controllable risk.
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Prevention of cross-contamination in production

5.17 Normally, the production of non-medicinal products should be avoided in areas and with equipment destined for the production of medicinal products but, where justified, could be allowed where the measures to prevent cross-contamination with medicinal products described below and in Chapter 3 can be applied. The production and/or storage of technical poisons, such as pesticides (except where these are used for manufacture of medicinal products) and herbicides, should not be allowed in areas used for the manufacture and/or storage of medicinal products.

5.18 Contamination of a starting material or of a product by another material or product should be prevented. This risk of accidental cross-contamination resulting from the uncontrolled release of dust, gases, vapours, aerosols, genetic material or organisms from active substances, other starting materials, and products in process, from residues on equipment, and from operators’ clothing should be assessed. The significance of this risk varies with the nature of the contaminant and that of the product being contaminated. Products in which cross-contamination is likely to be most significant are those administered by injection and those given over a long time. However, contamination of all products poses a risk to patient safety dependent on the nature and extent of contamination.
5.20 A Quality Risk Management process, which includes a potency and toxicological evaluation, should be used to assess and control the cross-contamination risks presented by the products manufactured. Factors including; facility/equipment design and use, personnel and material flow, microbiological controls, physico-chemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the relevant limits established from the evaluation of the products should also be taken into account. The outcome of the Quality Risk Management process should be the basis for determining the necessity for and extent to which premises and equipment should be dedicated to a particular product or product family. This may include dedicating specific product contact parts or dedication of the entire manufacturing facility. It may be acceptable to confine manufacturing activities to a segregated, self contained production area within a multiproduct facility, where justified.

5. Identifies the QRM role, and lists some aspects to consider

6. Broadens the concept of dedication and segregation to contact parts, and specific zones within a general facility.
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5.21 The outcome of the Quality Risk Management process should be the basis for determining the extent of technical and organisational measures required to control risks for cross-contamination. These could include, but are not limited to, the following:

Technical Measures

i. Dedicated manufacturing facility (premises and equipment);

ii. Self-contained production areas having separate processing equipment and separate heating, ventilation and air-conditioning (HVAC) systems. It may also be desirable to isolate certain utilities from those used in other areas;

iii. Design of manufacturing process, premises and equipment to minimize opportunities for cross-contamination during processing, maintenance and cleaning;

iv. Use of “closed systems” for processing and material/product transfer between equipment;

v. Use of physical barrier systems, including isolators, as containment measures;

vi. Controlled removal of dust close to source of the contaminant e.g. through localised extraction;

vii. Dedication of equipment, dedication of product contact parts or dedication of selected parts which are harder to clean (e.g. filters), dedication of maintenance tools;

viii. Use of single use disposable technologies;

ix. Use of equipment designed for ease of cleaning;

x. Appropriate use of air-locks and pressure cascade to confine potential airborne contaminant within a specified area;

xi. Minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

xii. Use of automatic clean in place systems of validated effectiveness;

xiii. For common general wash areas, separation of equipment washing, drying and storage areas.
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Organisational Measures

i. Dedicating the whole manufacturing facility or a self contained production area on a campaign basis (dedicated by separation in time) followed by a cleaning process of validated effectiveness;

ii. Keeping specific protective clothing inside areas where products with high risk of cross-contamination are processed;

iii. Cleaning verification after each product campaign should be considered as a detectability tool to support effectiveness of the Quality Risk Management approach for products deemed to present higher risk;

iv. Depending on the contamination risk, verification of cleaning of non product contact surfaces and monitoring of air within the manufacturing area and/or adjoining areas in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer;

v. Specific measures for waste handling, contaminated rinsing water and soiled gowning;

vi. Recording of spills, accidental events or deviations from procedures;

vii. Design of cleaning processes for premises and equipment such that the cleaning processes in themselves do not present a cross-contamination risk;

viii. Design of detailed records for cleaning processes to assure completion of cleaning in accordance with approved procedures and use of cleaning status labels on equipment and manufacturing areas;

ix. Use of common general wash areas on a campaign basis;

x. Supervision of working behaviour to ensure training effectiveness and compliance with the relevant procedural controls.

8. Useful guidance section on the Organisational measures you might consider to manage the X-contam risk to an acceptable level.
Now in 2015, we have the new EU GMP requirements - Finally

9. A periodic review of the effectiveness of the procedures is required.

5.22 Measures to prevent cross-contamination and their effectiveness should be reviewed periodically according to set procedures.
Summary – separated and dedicated facilities – the new GMP requirements

• Strong new focus on Multi-product facilities.
• Separated and dedicated is the DEFAULT requirement unless a proper risk assessment can determine alternative measures to manage the risk can be deployed.
• The science & technical based approach is:
  – Knowledge of the toxicological risks from cross-contamination agents.
  – Understanding the cross-contamination vectors.
  – Controlling the risk to an acceptable level.
• Periodic review of the effectiveness of the measures deployed.
Thank you for your time. Questions?

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