Understanding Cross-contamination

Source, target & vectors

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Regulatory Knowledge, Practically Applied.

Agenda

Cross-contamination from a PIC/S perspective

- What is cross-contamination?
- Just the possibility of an event is a problem.
- The ADE ADI principles

Understanding Cross-contamination mechanisms

- Source – Vector – Target
- Most common vectors

Classic Risk Assessment

- QRM basis
- RM tools

Preventative measures

- Product
- Process
- Facility
- Management

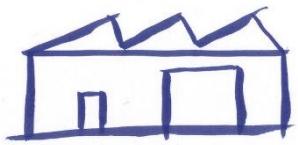
What is cross-contamination ?

- Cross-contamination (in the context of pharmaceutical manufacturing) is when:
  - Material from one product or process is transferred to an adjacent or subsequent product or process.
  - Cross-contamination can be tolerated if the quantity can be proven to be harmless.
  - Cross-contamination is deemed unacceptable if the quantity is deemed to be harmful.
- From a GMP perspective, the possibility of cross-contamination is sufficient to raise an observation – it isn't necessary to actually measure a quantity of cross-contamination event.

Cross-contamination – A PIC/S perspective

PIC/s Expectation – Based on EU GMP Today – new Part 1 Ch 3 & 5

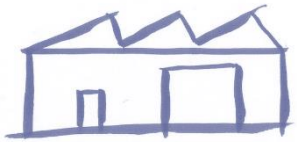
- In a multi-product plant ZERO cross contamination is impossible to achieve or prove.
- Separate dedicated facilities are required for products deemed to be sensitising agents, where cross-contamination levels below detectable limits could cause severe adverse reaction in patients.
- Then there is difficult and confusing language that tries to (bracket) families of toxic, sensitising, or products with similar characteristics together.
- The judgements are subjective, and not really science based; leading to variable opinions.



PIC/s Expectation – Based on EU GMP Future

In a multi-product plant, very low levels of cross-contamination can be accepted provided that:

- There is toxicological data that supports the definition of an ADE or ADI (allowable daily exposure OR allowable daily intake).
- The amount is less that the ADE or ADI.
- All reasonable measures are taken to avoid cross-contamination.



Cross-contamination mechanisms

Cross-contamination mechanisms

- Presence of API
- Concentration
- Strength
- Frequency

Airborne – room to room
Mechanical transfer on operator garments
Mechanical transfer on materials moved
Airborne – via a recirculation HVAC system
Mechanical transfer – on contact surfaces
Airborne – adjacent processes in same room

Cross-contamination control

- Presence of API
- Concentration
- Strength
- Frequency

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Restrict the source:

- Remove the API – use something else.
- Contain the process or activity.
- Capture at point of generation.
- Dilute source strength in room by ventilation.

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Block the vectors:

- Air filtration
- Dedicated equipment
- Effective cleaning
- Gowning control.
- Pressure regimes.
- Air locks.

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Harden the target:

- Close the process.
- Separate by time.

Cross-contamination control-
putting it all together

- Presence of API
- Concentration
- Strength
- Frequency

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- Available target
- Multi-use equipment

Our control objective:

- To use all the appropriate achievable measures to control and limit the extent of cross-contamination.
- There is unlikely to be a single magic bullet.
- Performance of measures should be monitored.

Cross-contamination control-
greatest risk

- Presence of API
- Concentration
- Strength
- Frequency

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Risk based thinking:

- The most likely cross-contamination pathway is via dirty equipment contact surfaces.
- Effective cleaning of equipment is also one of the easiest to achieve with automated CIP, and to prove through cleaning validation trials.

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Thinking about the reality of the cross-contamination potential

As well as thinking about the greatest risk of cross-contamination in terms of source, vector, & target; we should also evaluate the following:

- How much cross-contamination would be need to cause a problem? Based on toxicological information.
- Decide if it is practical for this to happen.

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Thank you for your time.
Questions?

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