Cross-Contamination Control: Facility Design

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13 October, 2014

PharmOut

Regulatory Knowledge, Practically Applied.

Cross-Contamination Definition

Draft Eudralex Vol. 4 Chapter 5: Production, 5.18

"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

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Public Health and Risk Assessment
Medicinal products – quality, safety and efficacy

Brussels, *<date>*

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.

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 authorisation 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 harmonise 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

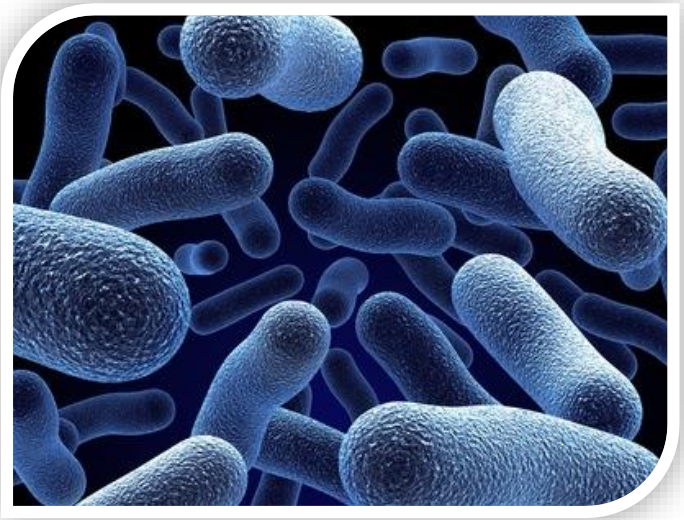
Part I

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

Cross-Contamination Regulations

Draft Eudralex Volume 4, Chapter 5 - 5.18

- 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

Draft Eudralex Volume 4, Chapter 5 - 5.19

- 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

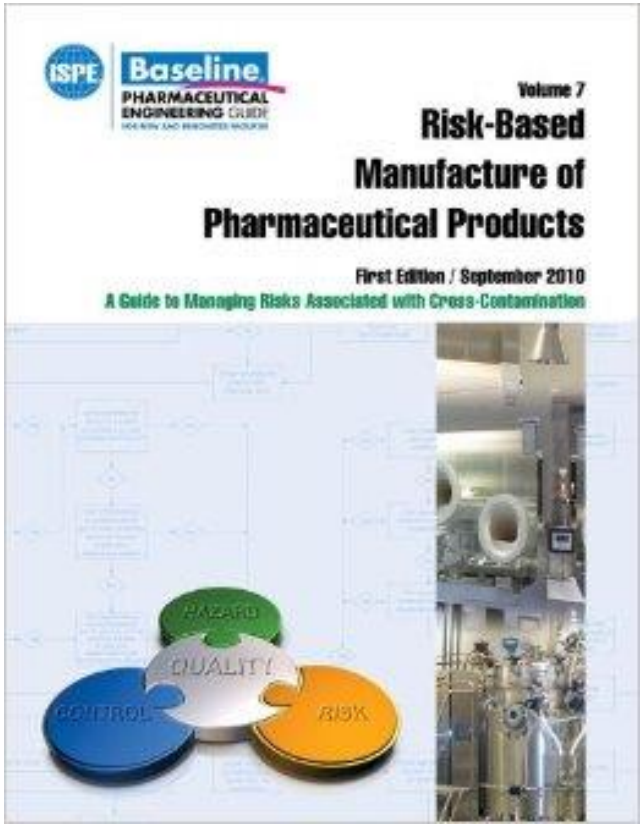
Draft Eudralex Volume 4, Chapter 5 - 5.21

- 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

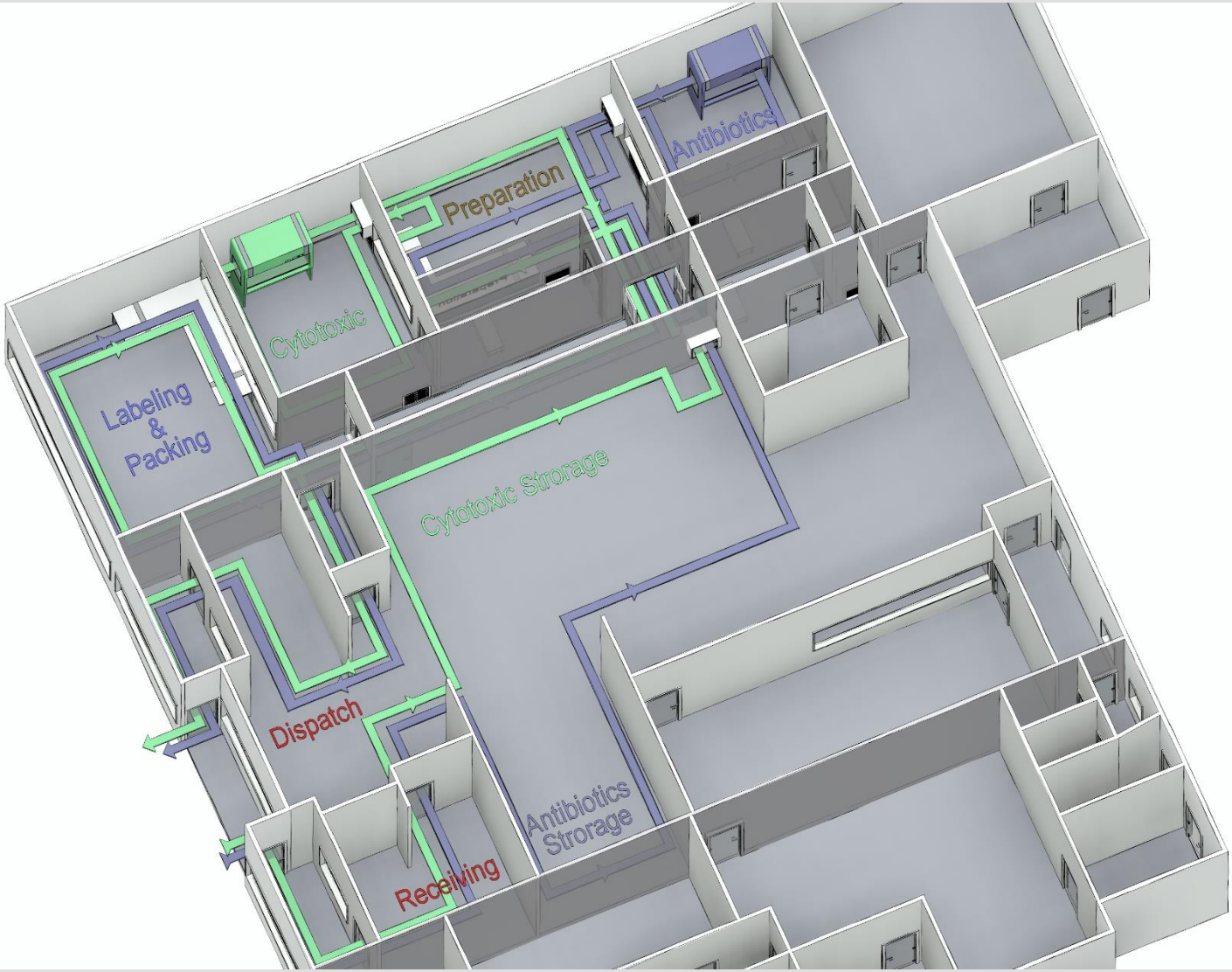
"The contamination at unsafe levels of one product with another via inadequate plant and process design or human error."

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

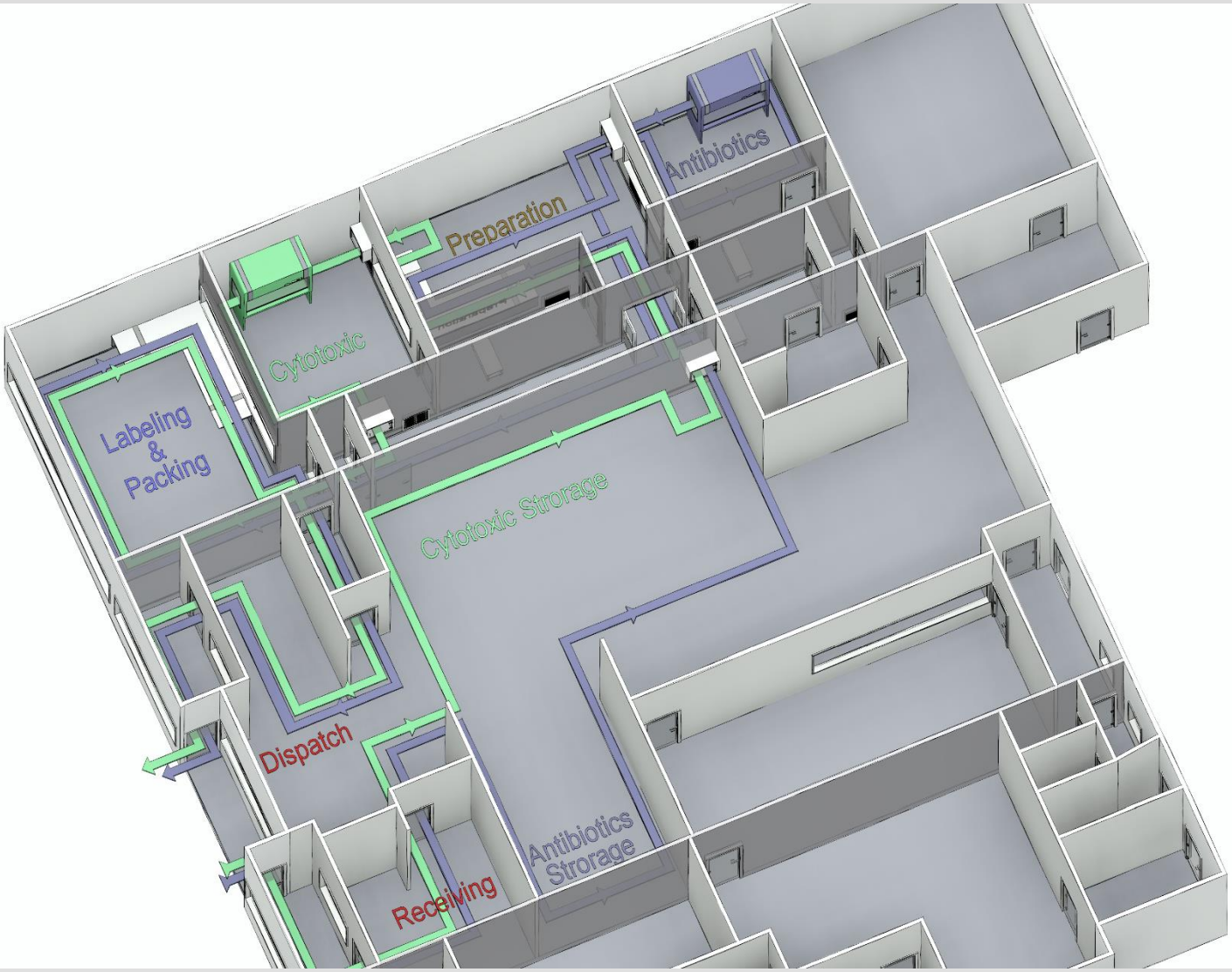
How do we prevent mix-up through facility design?

- 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

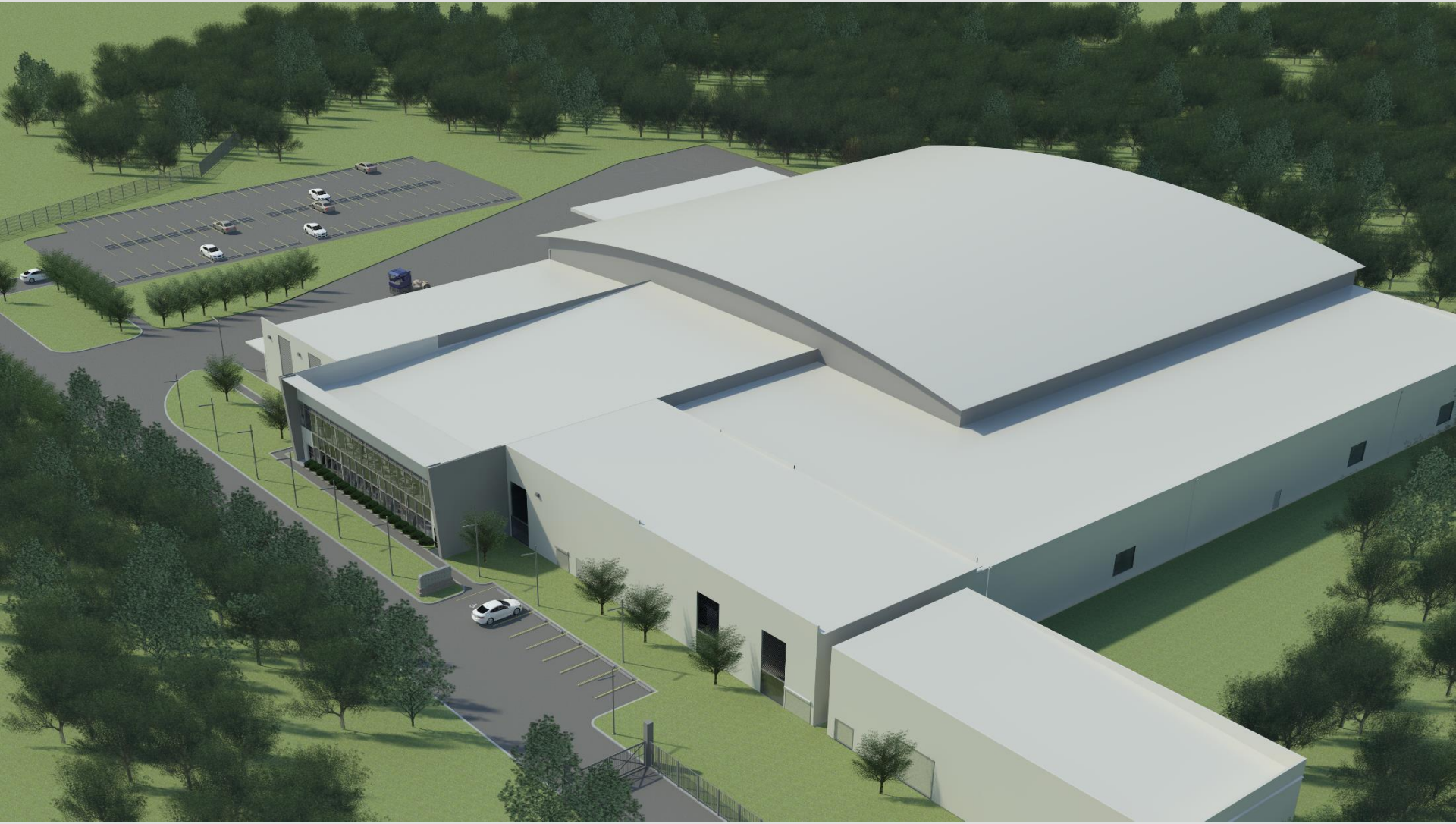
Mechanical Transfer

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



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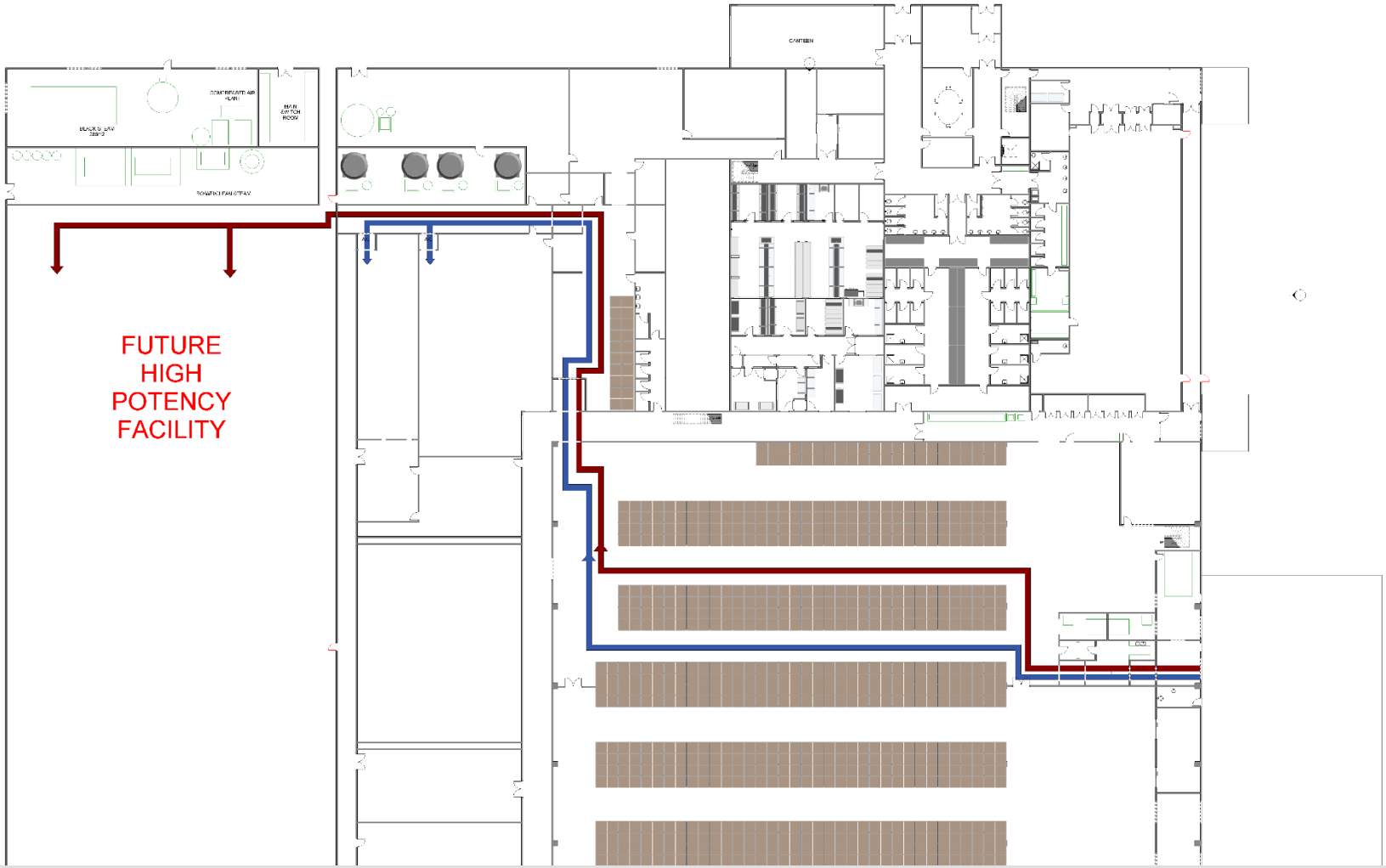
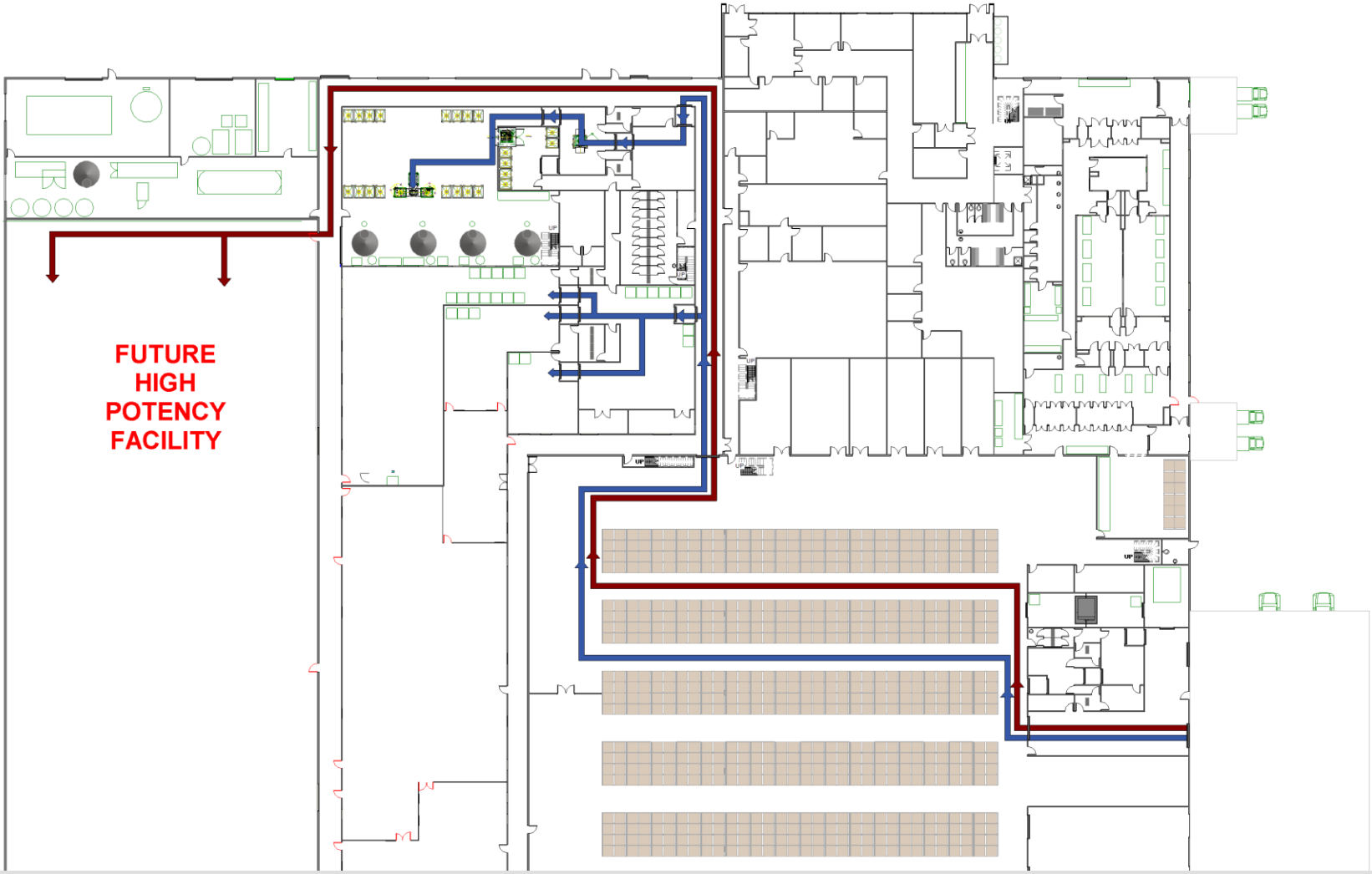
Facility Design



Facility Design



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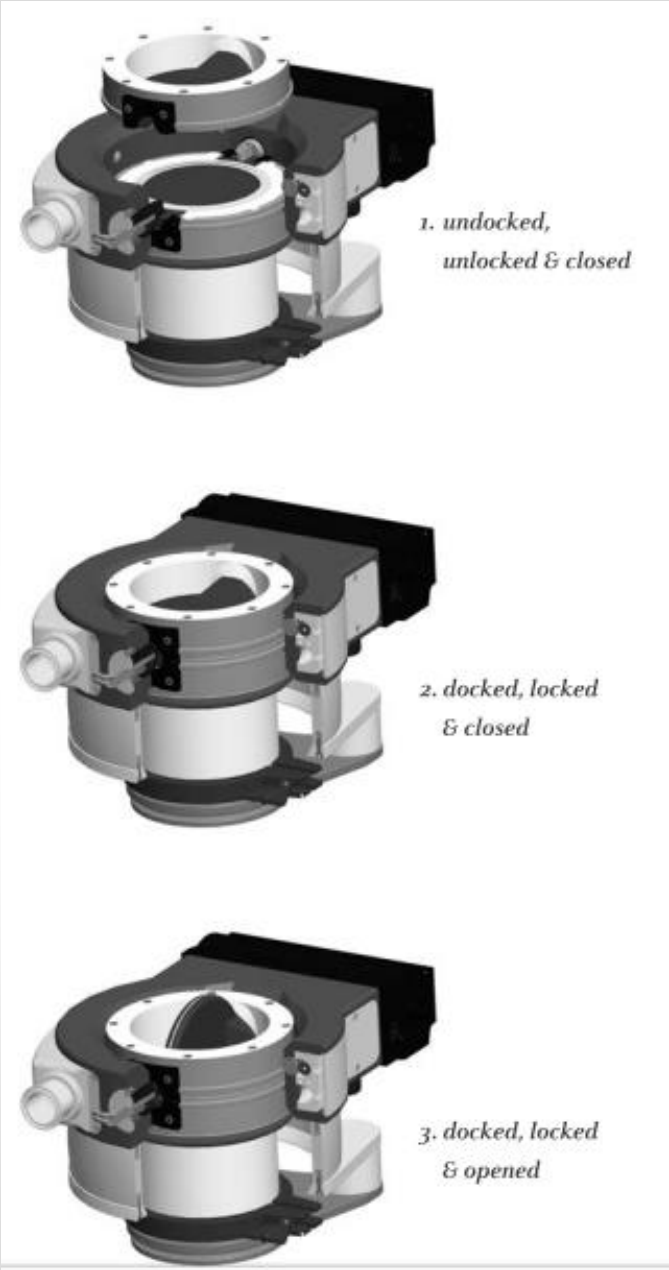
Containment equipment



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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

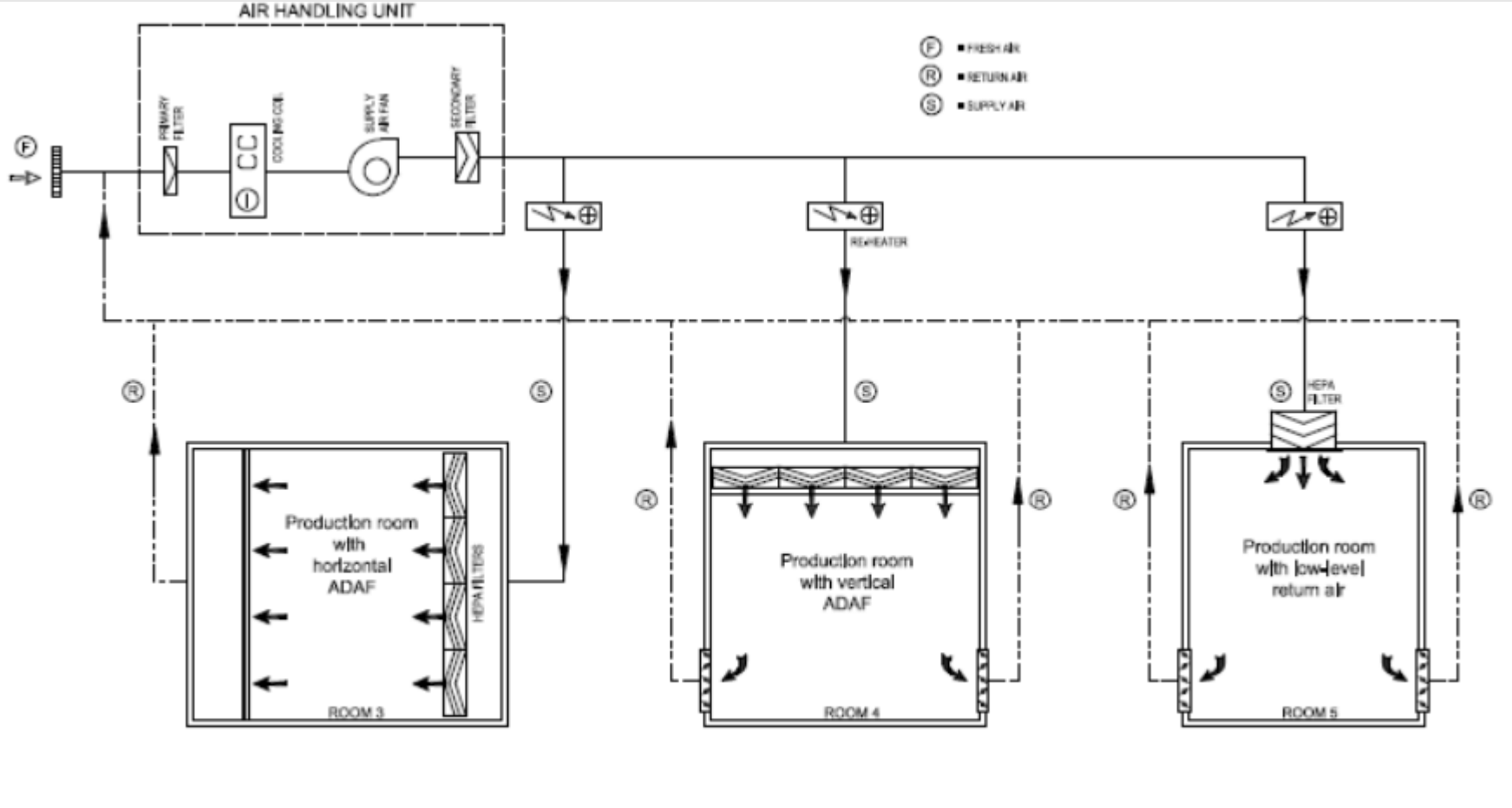
- Usually an OHS issue before it becomes a product quality issue
- Most relevant for highly toxic, potent or allergenic products

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

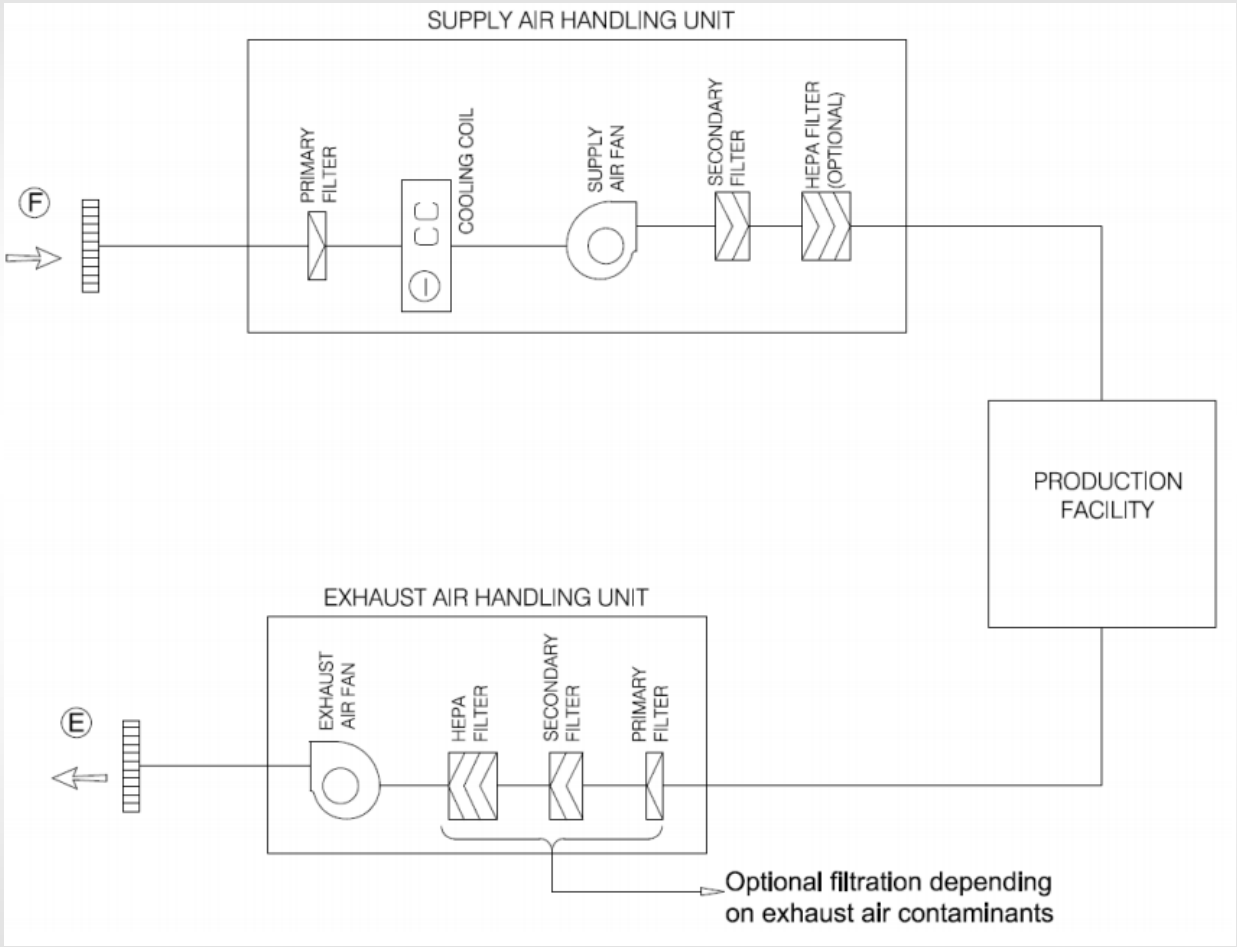
Standard Recirculation HVAC



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

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Thank you for your time.
Questions?

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