Risk-Based Manufacture of Pharmaceutical Products

Based on:

WHO TRS, No. 957, 2010-Annex 3-WHO GMP for pharmaceutical products containing hazardous substances

ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products-Risk Mapp 2010 and 2017

Eudralex-2014-Volume 4-Part 1

Q &A on implementation of risk based prevention of cross contamination in production and 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities'

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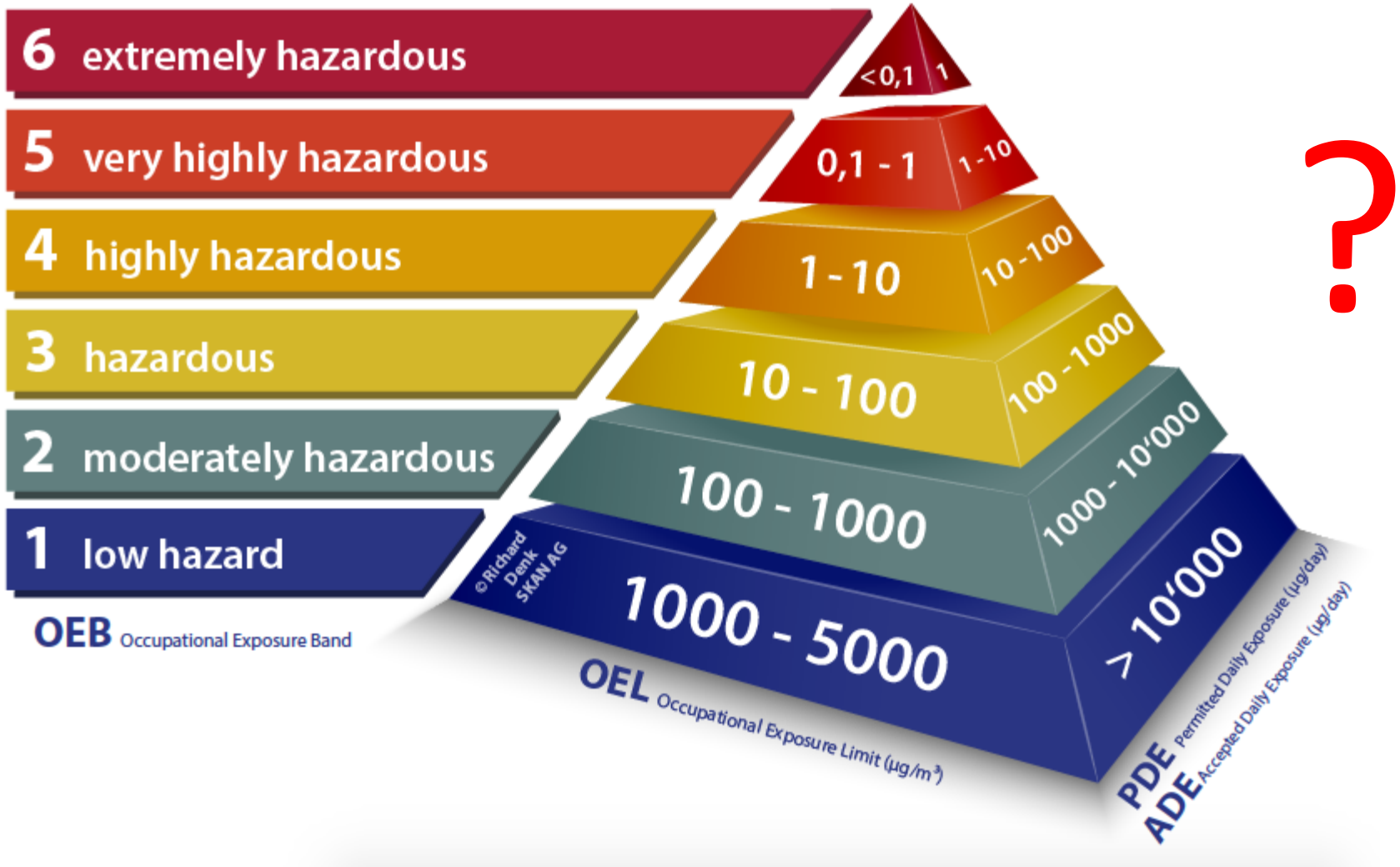
What is considered a potentially-hazardous product?



??!!

What is considered a hazardous product?

Certain substances?!

1. Introduction

1.1 These guidelines set out good practices applicable to facilities handling pharmaceutical products (including active pharmaceutical ingredients (APIs)) that contain hazardous substances such as certain hormones, steroids or cytotoxins. They do not replace national legislation for protection of the environment and personnel. Other WHO guides to good manufacturing practices (GMP) and regulations need to be observed in addition to the workers' safety criteria (*1–4*).

WHO Technical Report Series, No. 957, 2010

Annex 3

WHO good manufacturing practices for pharmaceutical products containing hazardous substances

What is considered a hazardous product?

Certain substances?!

Production areas

12.24 In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g. penicillins) or biological preparations (e.g. live microorganisms). The production of certain other highly active products, such as some antibiotics, hormones, cytotoxic substances and certain non-pharmaceutical products, should not be conducted in the same facilities. In exceptional cases,

WHO Technical Report Series, No. 908, 2003

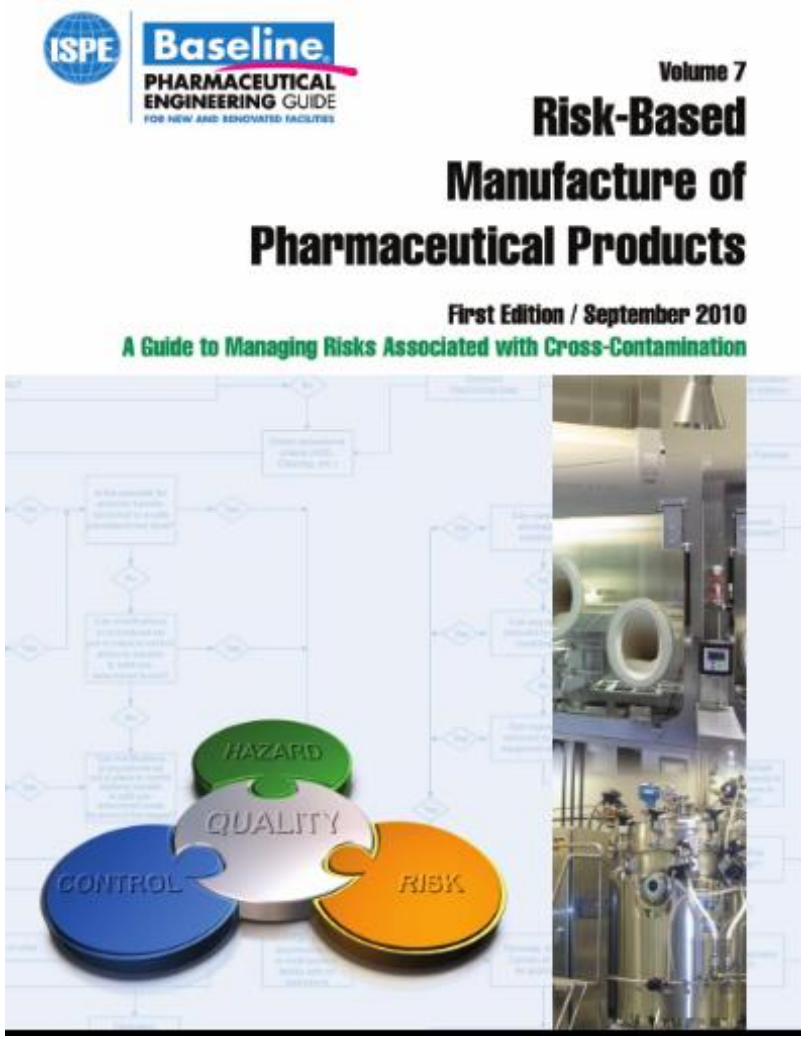
Annex 4

Good Manufacturing Practices for pharmaceutical products: main principles

What is considered a hazardous product?

- Terms such as **potent, cytotoxic, cytostatic, and steroid are not precise** when categorizing specific API hazard potential, and **conclusions based on a reactive response, rather than specific scientific data, should be avoided.**

- These general terms induce an emotional response that may imply that without exception these compounds are always difficult to handle and require the highest level of control.



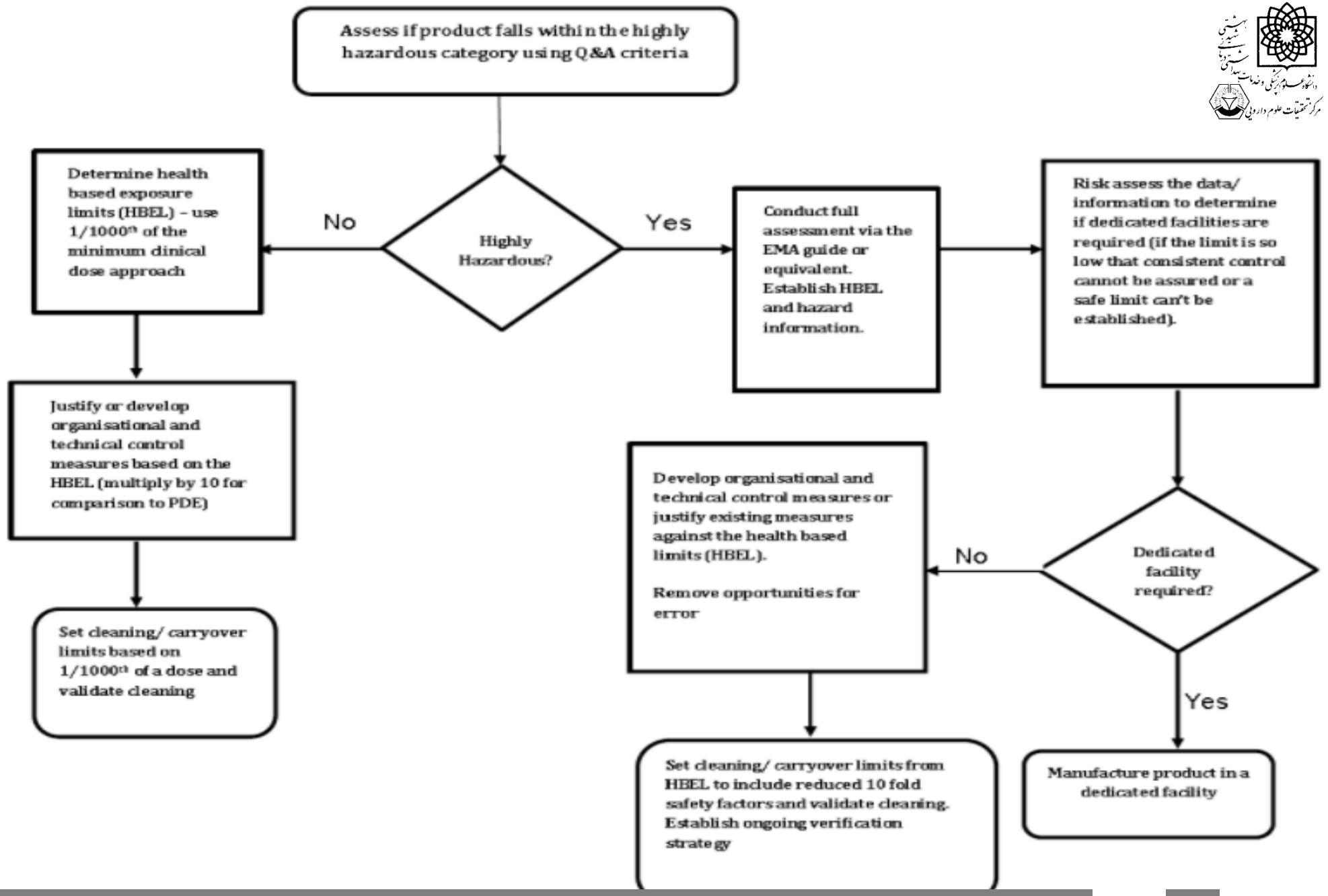
What is considered a hazardous product?

- The original intention of ISPE Risk Mapp was to provide a method to identify highly hazardous compounds.
- However, during development, it became apparent that an approach **to identify acceptable risk in the manufacture of pharmaceutical products was more appropriate.**

In order to identify acceptable risk, it is necessary to first assess and categorize a compound.

Risk Management
in Hazardous Products Identification and Handling

How risk management concepts are employed in GMP of hazardous products and material?



How risk management concepts are employed in GMP of hazardous products and material?

The acceptable limits for Cross contamination, Cleaning validation, Worker safety and Environmental safety are derived from these data,

but the application of Uncertainty Factors to these data might be different for Quality versus Workplace Health and Hygiene, primarily due to differences In the subpopulations at risk and potential route(s) of exposure.

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 detail
the Community code relating to medici
2001/82/EC on the Community code re
provides guidance for the interpret
manufacturing practice (GMP) for med
for medicinal products for human use a

Status of the document: Revision[a].

Reasons for changes: The only chang
prevention of cross-contamination invo

Deadline for coming into operation:
mentioned in section 6 is to be carried

- from 1 June 2015 onwards for a
manufacturing facilities;
- before 1 December 2015 for me
manufacturing facility producing
producing medicinal products fo
May 2015;
- before 1 June 2016 for veterinar
manufacturing facility producing

[a] In January 2015 the deadline for coming into
to align with the coming effect of the EMA gui
identification in the manufacture of different m
Commission Européenne, B-1049 Bruxelles / Europes

ISPE Baseline PHARMACEUTICAL ENGINEERING GUIDE FOR NEW AND RENOVATED FACILITIES

Volume 7
Risk-Based Manufacture of Pharmaceutical Products

First Edition / September 2010
A Guide to Managing Risks Associated with Cross-Contamination

How risk management concepts are employed in GMP of hazardous products and material?

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The Rules Governing Medicinal Products in the European Union
Volume 4

EU Guidelines for
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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:

How risk management concepts are employed in GMP of hazardous products and material?

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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

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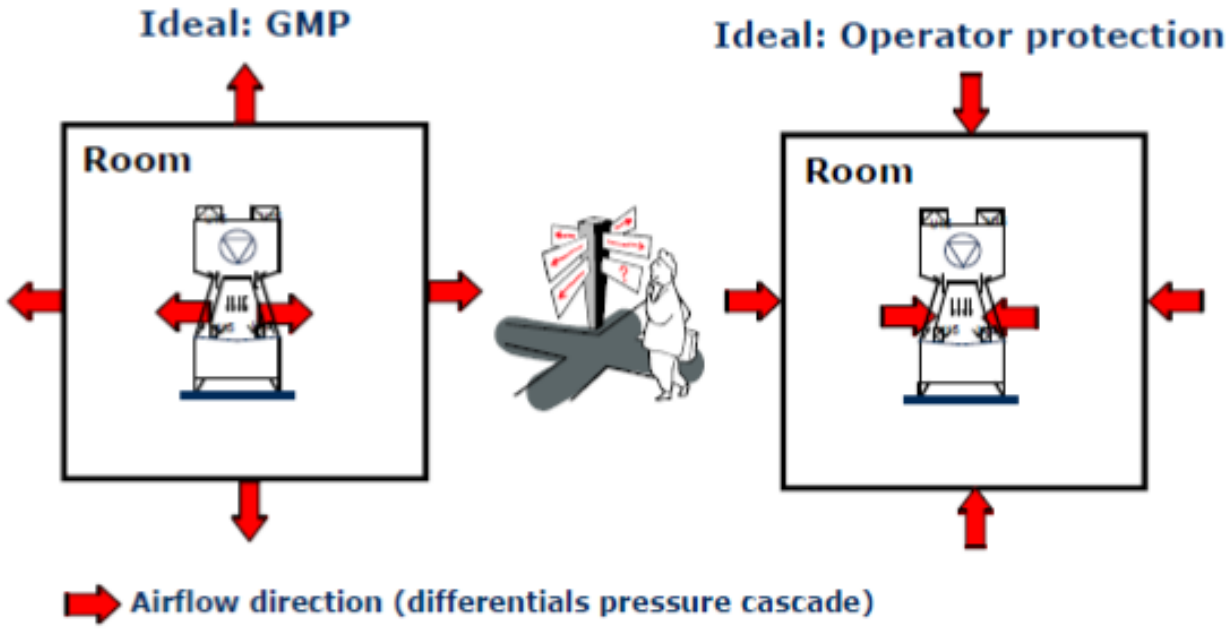
Status of the document: Revision[a].

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

How risk management concepts are employed in GMP of hazardous products and material?

GMP vs. operator protection



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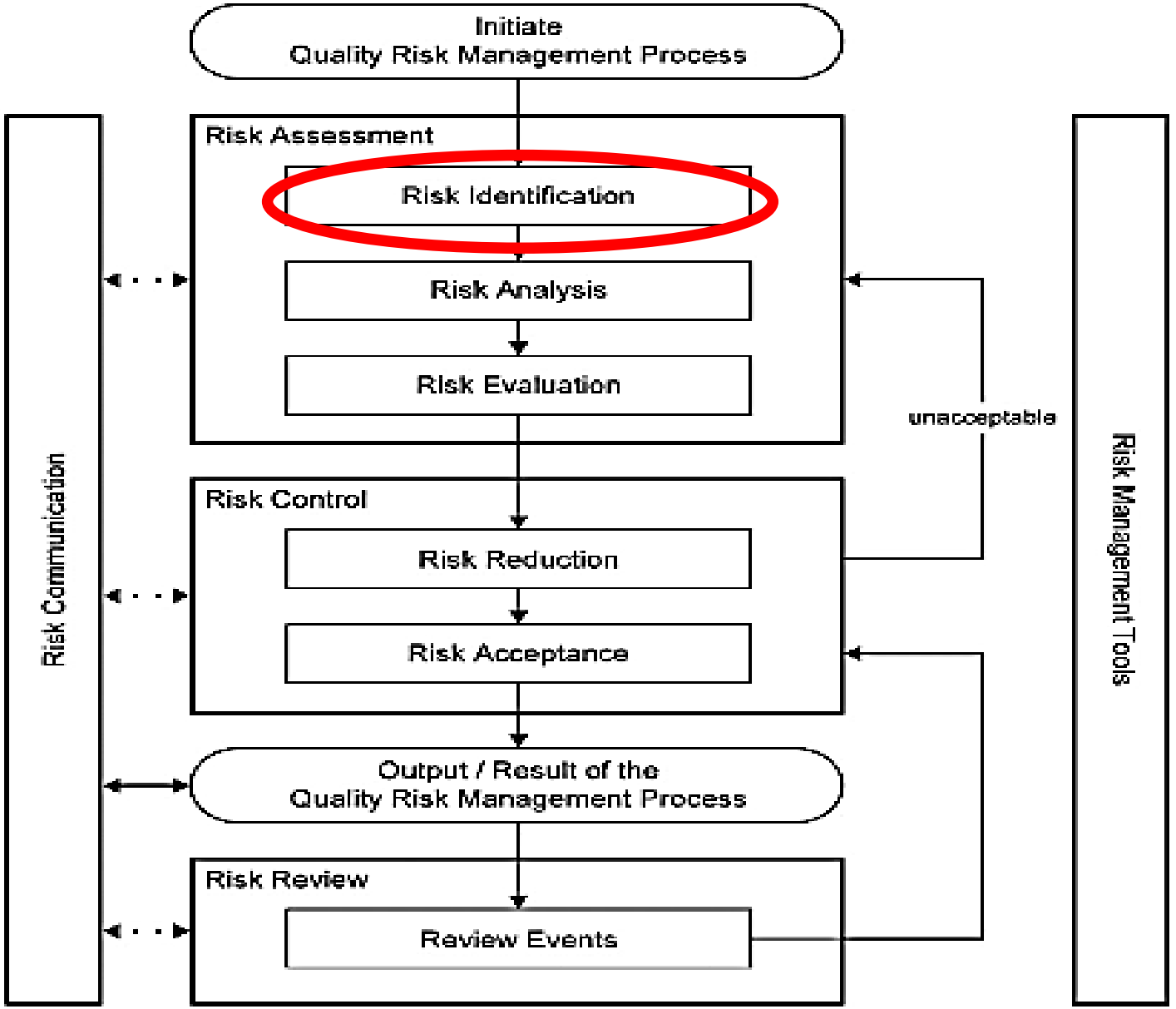
How risk management concepts are employed in GMP of hazardous products and material?

- **ISPE Risk Mapp 2010 and 2017**
- **ICH Q9 QRM**
- Specifically, the ISPE guideline proposes the use of health-based Acceptable Daily Exposure (HBADE, HBEL) values rather than a tag such as “hormone”, “steroid” or “cytotoxic” (with the exception of cephalosporins, which were specifically omitted from the guide). These values would then be used to assess the risk of cross-contamination

How risk management concepts are employed in GMP of hazardous products and material? 10/10

Figure 2.1: ICH Q9 Quality Risk Management Process



Risk assessment of hazardous products
Risk identification:

- **Where to find information?**
  - **Labeling**
  - **Hazard symbol**
  - **R phrases (Risk phrases*)**
    - *** Notation is wrong because it is not risk but hazard**
  - **S phrases (Safety advice phrases)**
  - **Hazard identification (nature ± power)**
  - **Appears on label, MSDS**

Some references for drugs toxicity levels and PDE and OEL values

To be purchased from:

https://affygility.com/

https://www.azierta.com/en/pharma/toxicology/pde-ade-reports

https://www.safebridge.com/services/toxicology

http://the-force.org/pde-reports/

To get from supplier or Safety Data Sheets

OR

https://www.cdc.gov/niosh/index.htm; NIOSH for Occupational hazards (Mostly for hospitals, clinics...)

Risk assessment of hazardous products
Risk Identification/ Analysis

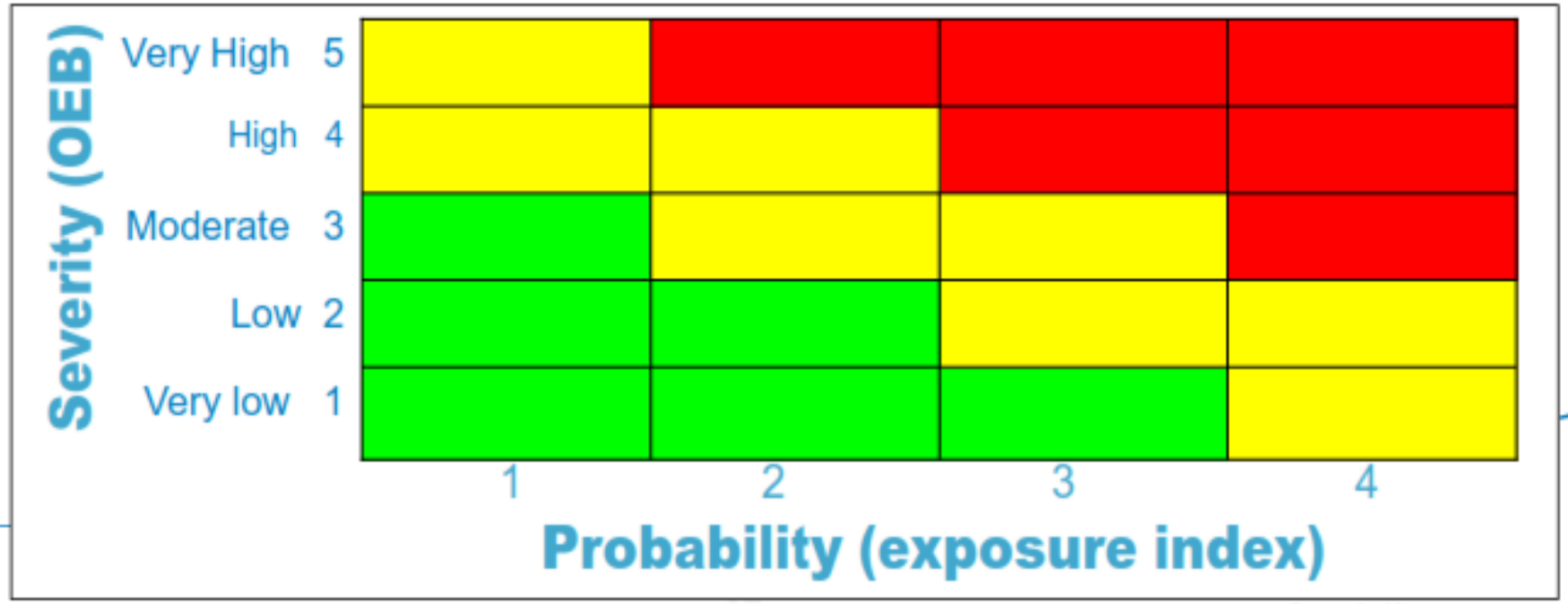
	F (Frequency)	U (Use)	Q (Quantity)	D (Dispersion)	C (Degree of control)
1 - Low	1 /month (10/year)	< 1 H/ shift	< 10 kg	little or no dispersion, granular substance, non-volatile	Closed system, no potential for release into the workplace, effective engineering controls, fully contained process, isolator or glove box, no ability to contact the product. No PPE or administrative controls necessary.
2- Moderate	1/ week (40/year)	From 1 H to 4 H / shift	From 10 kg to 100 kg	moderate dispersion, fine powder, volatile	Open system with exhaust ventilation, minimal physical manipulation; contact with product possible, or does occur, occasional use of PPE, engineering controls, and/or administrative controls.
3 – High	1/ day (200/year)	> 4 H / shift	> 100 kg	significant dispersion, micronized powder, highly volatile	Open system, physical manipulation of material, no engineering controls in place, PPE is the primary method of exposure control.

Risk assessment of hazardous products
Risk Identification/ Analysis

- How to calculate the exposure index
  - Exposure index = F+U+Q+D+C
  - EI corresponds to probability

- Risk assessment
  - Severity: OEB (1 to 5)
  - Probability: Exposure index (1 to 4)

Probability class	Exposure Index
1 improbable	EI ≤ 7
2 possible	EI = 8 or 9
3 probable	EI = 10 or 11
4 very probable	EI ≥ 12



Risk assessment of hazardous products

Risk identification:

Quantitative (feedback when using confined system like isolator)

- Sample analysis
- QC labs who analysis the product have developed methods for IH
- Can measure down to very low levels
- During commissioning to confirm effectiveness of controls
- Periodically (6 monthly?) to confirm ongoing exposure prevention

Risk assessment of hazardous products
Risk Identification/ Analysis

- **Acceptable Daily Exposure (ADE):** represents a dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime.

- **Occupational exposure limit (OEL):** A health-based airborne concentration limit to which worker exposure levels should be controlled. OELs are usually expressed as eight-hour time weighted averages for exposures for 40 hours a week over a working lifetime (TWA-OEL).

Risk assessment of hazardous products
Risk Identification/ Analysis (Toxicologist's job) ☺

$$OEL = \frac{LOAEL\ or\ NOAEL\ x\ 70\ kg}{F1\ x\ F2\ x\ F3\ x\ F4\ X\ F5\ x\ \alpha\ x\ 10\ m^3}$$

Factor	Description
F1	Inter-species
F2	Human variability
F3	Sub-chronic to Chronic
F4	LOAEL to NOAEL
F5	Severity of Effects or Database Completeness
α	Bioavailability

Risk assessment of hazardous products
Risk Identification/ Analysis (Toxicologist's job)☺

$$\text{ADE} = \frac{LOAEL\ or\ NOAEL\ x\ 50\ kg}{F1\ x\ F2\ x\ F3\ x\ F4\ x\ F5\ x\ \alpha}$$

Factor	Description
F1	Inter-species
F2	Human variability
F3	Sub-chronic to Chronic
F4	LOAEL to NOAEL
F5	Severity of Effects or Database Completeness
α	Bioavailability

Risk assessment of hazardous products
Risk Identification/ Analysis

Similarities / differences between OELs and ADEs

- Similarities
  - Similar equation
  - Similar POD and adjustment factors
- Differences
  - Populations – OELs for healthy workers, ADEs for patients
  - Route of administration – OELs for inhalation, ADEs for all routes including parenteral
  - Body Weight – 50 kg for ADEs to cover a spectrum of patients and OELs 70 kg based on worker weights
  - OEL assumes an 8-hour day, can be adjusted for shorter term tasks
  - ADE can be adjusted based on route, patient population, duration

How OELs & ADEs Develop Over the Life Cycle of a Drug
http://hpapi-summit.com/wp-content/uploads/sites/75/2015/03/Day-1-15.15-Joel-Bercu-YES.pdf

Risk assessment of hazardous products
Risk Identification/ Analysis

- **Occupational Exposure Band (OEB):** is a system used to group drug products, based on their OEL, to allow guidance to be given on the appropriate control measures and containment systems.

- **Surface Target Values** can also be derived by dividing the ADE by a standard surface area (e.g., 100 cm), but this is often viewed as a convenient, if not arbitrary approach for assessing exterior equipment and facility surfaces for worker protection purposes.

Risk assessment of hazardous products

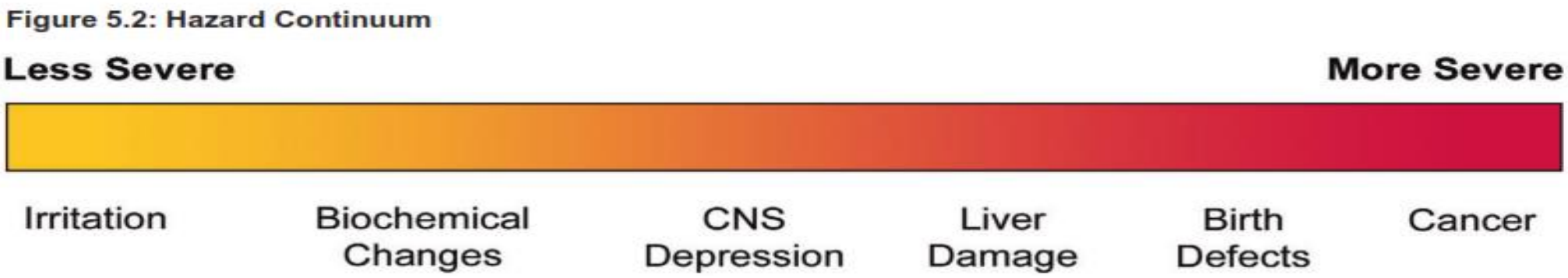
Risk Identification/ Analysis

Compounds

Potent Compounds (industry perspective)

- Biological activity **<** 15µgrams/kg human weight
  - [Or therapeutic dose at or below 1 milligram]
- Compound with a potential to cause cancer, mutation, developmental effects, or reproductive toxicity at low levels
- Compound with OEL ≤ 10 µgms/m³/8hr/shift
- A novel compound of unknown potency & toxicity

Figure 5.2: Hazard Continuum



Risk assessment of hazardous products

Risk Identification / Analysis

Criteria for identifying hazardous drugs and prioritizing risk assessments:

1. Genotoxic compounds that are known to be or highly likely to be carcinogenic to humans.
2. Compounds that can produce reproductive and/or developmental effects at low dosages.
3. Compounds that can produce serious target organ toxicity, anaphylaxis, or other significant adverse effects at low dosages.
4. Compounds with a high pharmacological potency i.e. recommended daily dose of <1 mg (veterinary dose equivalent 0.02 mg/kg).
5. Novel Products/APIs and Compounds with a high sensitising potential.

Risk assessment of hazardous products
Risk Identification/ Analysis

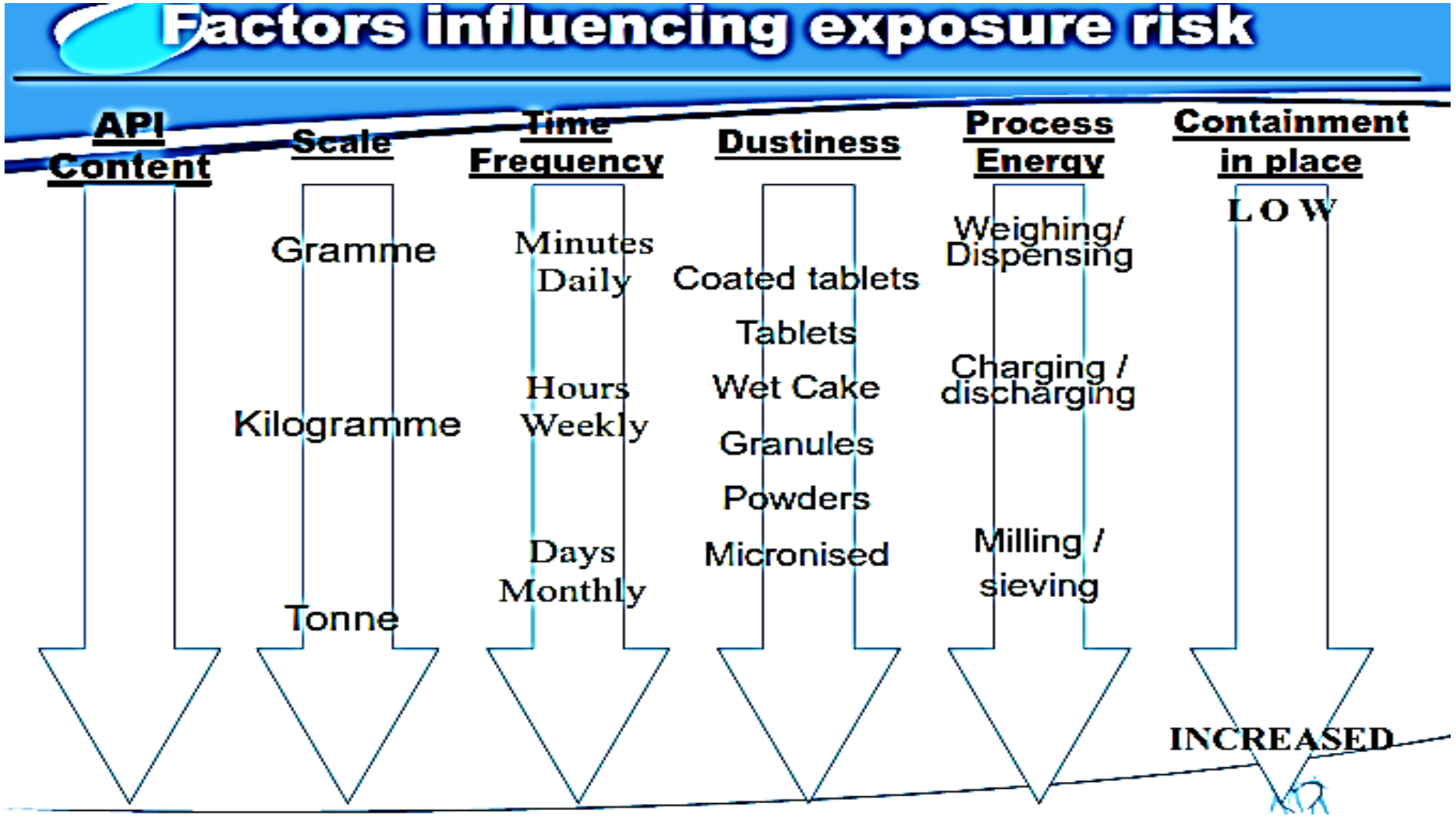


Figure 6.2: Risk of Cross-Contamination and Worker Exposure Risk

Risk assessment of hazardous products

Risk Identification/ Analysis

Hierarchy of Risk for Product and Worker Exposure

Product

Mix Up
Mix up of API, Process, Potency, Labeling, etc.

Retention
Carry over on Product Contact Parts
Failure to Clean to Limits

Mechanical Transfer
Transfer of product to another product on gowning and equipment

Airborne Transfer
Sedimentation of Aerosols from one product into another

Worker

Inhalation

Dermal

Ingestion

Accidental Injection
Entry through Break in Skin

The significance of each mode above varies depending on the compound and manufacturing processes

Risk assessment of hazardous products

Risk Identification / Analysis

- **ISPE Risk Mapp 2010**

2

Figure 11.2: Risk Ranking

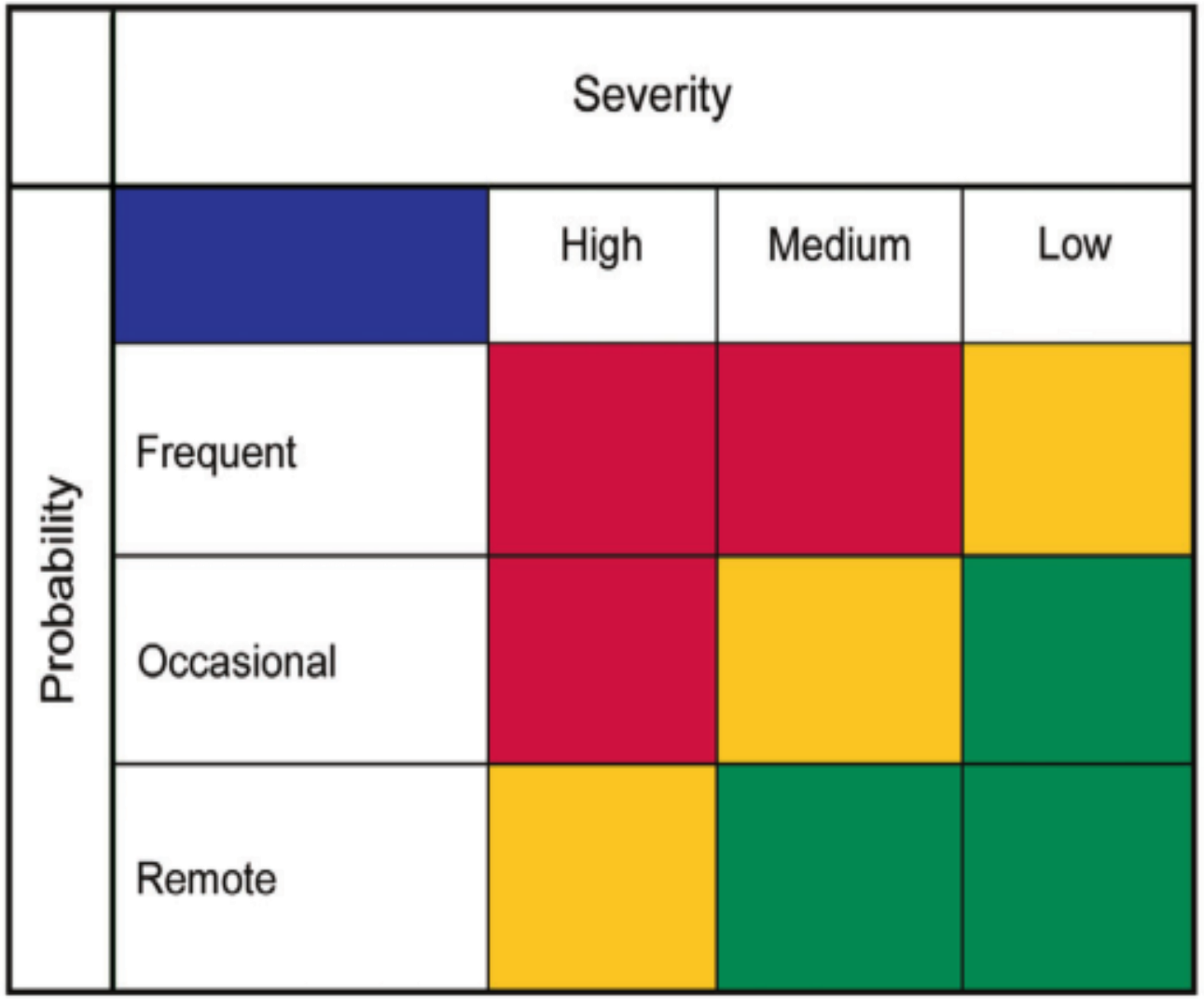
Wet	Physical Form	Dry
Large	Particle Size	Small
Dense	Density	Light
Closed	Operation	Open
No Energy/Velocity	Process	High Energy/Velocity
None Required	Operator Skill	Highly Dependent
Low Δp	Pressure	High Δp
None	Transfers	Multiple
Well	Training	Poorly
Well	Maintenance	Poorly
Routine	Task Type	Non Routine
One Operation	Frequency	Multiple Operation

Risk assessment of hazardous products

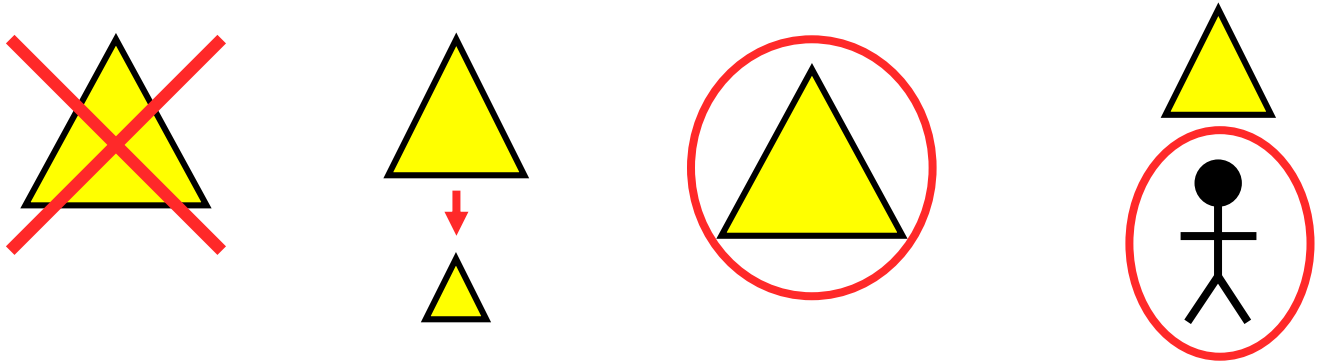
Risk Analysis

- **ISPE Risk Mapp**

Figure 11.3: Sample Risk Matrix Format



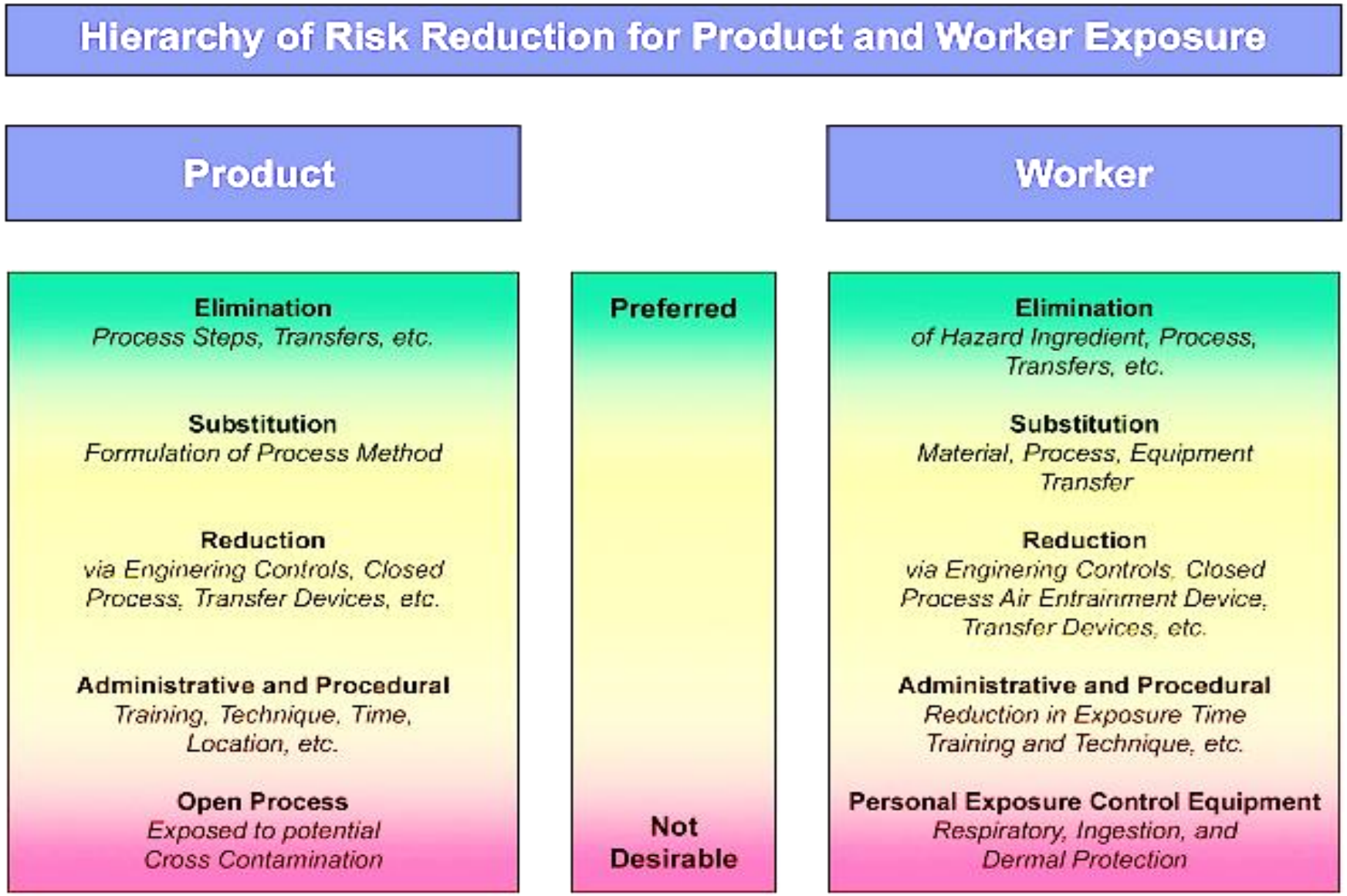
Risk Control- Reduction of hazardous products



1. **Eliminate the hazard:** Total substitution, different process
2. **Substitute the hazard:** Partial, change of form, adjustment
3. **Collective protection measures (Collective Protective Equipment (CPE)):** Isolation, distance, automation
4. **Administrative Control and Process:** To reduce the time of exposure, the number of persons exposed
5. **Individual protection equipment (Personal Protective Equipment (PPE)):** Body, hands, eyes, respiratory protection

Risk Control- Reduction of hazardous products

Figure 9.2: Applied Hierarchy of Risk Reduction



Risk Control- Reduction of hazardous products

What to consider early on in development and formulation of a Product containing hazardous material?

- **ISPE Risk Mapp 2010**
- **Formulation scientists should consider the possible measures to reduce the potential exposure to the hazardous APIs as early in the manufacturing process as possible.**
- **Product formulation selection AND/OR Process selection**
- **An approach both to: Improve worker and environment protection AND Reduce the risk of Cross-contamination**

Risk Control- Reduction of hazardous products

What to consider early on in development and formulation of a Product containing hazardous material?

- **ISPE Risk Mapp 2010**
- **Combine the hazardous with excipients early in the process to dilute it**
- **Direct compression to decrease the process equipment and steps and reduce the risk of cross contamination and staff exposure**
- **Use less dusty excipients such as silicified microcrystalline Cellulose or Mannitol**
- **Less use of processes with higher potential for exposure such as fluid-bed drying and dry-milling**

Risk Control- Reduction of hazardous products

Design and Engineering and equipment selection in hazardous facility settings

General consideration in hazardous facilities settings:

- Potency and exposure limits
- Pure API or diluted forms
- Product diffusion capability
- Dosage form
- Scale
- Route of exposure
- Toxicological effect
- Environmental impact
- Working hours/Shifts
- Regulations and Standards
- Costs and price

Risk Control- Reduction of hazardous products

Design and Engineering and equipment selection in hazardous facility settings

General consideration in hazardous facilities settings:

- **Possibility of open or closed operations**
- **Continuous or batch wise**
- **Samplings**
- **Cleanings**
- **Effluent and waste disposal and treatment**
- **Possibility of using Process Analytical Technology (PAT)**
- **Aiming for Shirt Sleeve operation: An operation in which no complex Personal Protection Equipment and gowning is needed**

Risk Control- Reduction of hazardous products

Design and Engineering and equipment selection in hazardous facility settings

General consideration in hazardous facilities settings:

Redundancy

Redundancy is the provision of more than one element performing the function so that if one fails, the next takes up the required duty and detection devices alarm the failure of the primary system.

Therefore likelihood of failure diminishes. A robust system can be designed based on a series of non-optimal redundancies.

Risk Control- Reduction of hazardous products

Design and Engineering and equipment selection in hazardous facility settings

General consideration in hazardous facilities settings:

Examples of Redundancy in handling of hazardous products

- Double gloves
- Gloves in isolator gloves
- Double Hepa Filters
- Double bags
- Pipe-in-pipe double layer waste water containment

Design and Engineering and equipment selection in hazardous facility settings

- **ISPE Risk Mapp 2010**

2

Future Facilities …

- Trend towards
- Shirt & Sleeve Design
- Closed integrated process equipment
- Minimal process steps and transfers
- Minimal MAL's and PAL's
- Application of PAT for reducing / eliminating interventions and sampling
- HVAC for people Recirculation, low ACH
- Minimization of disposables
- Hugely reduced carbon footprint

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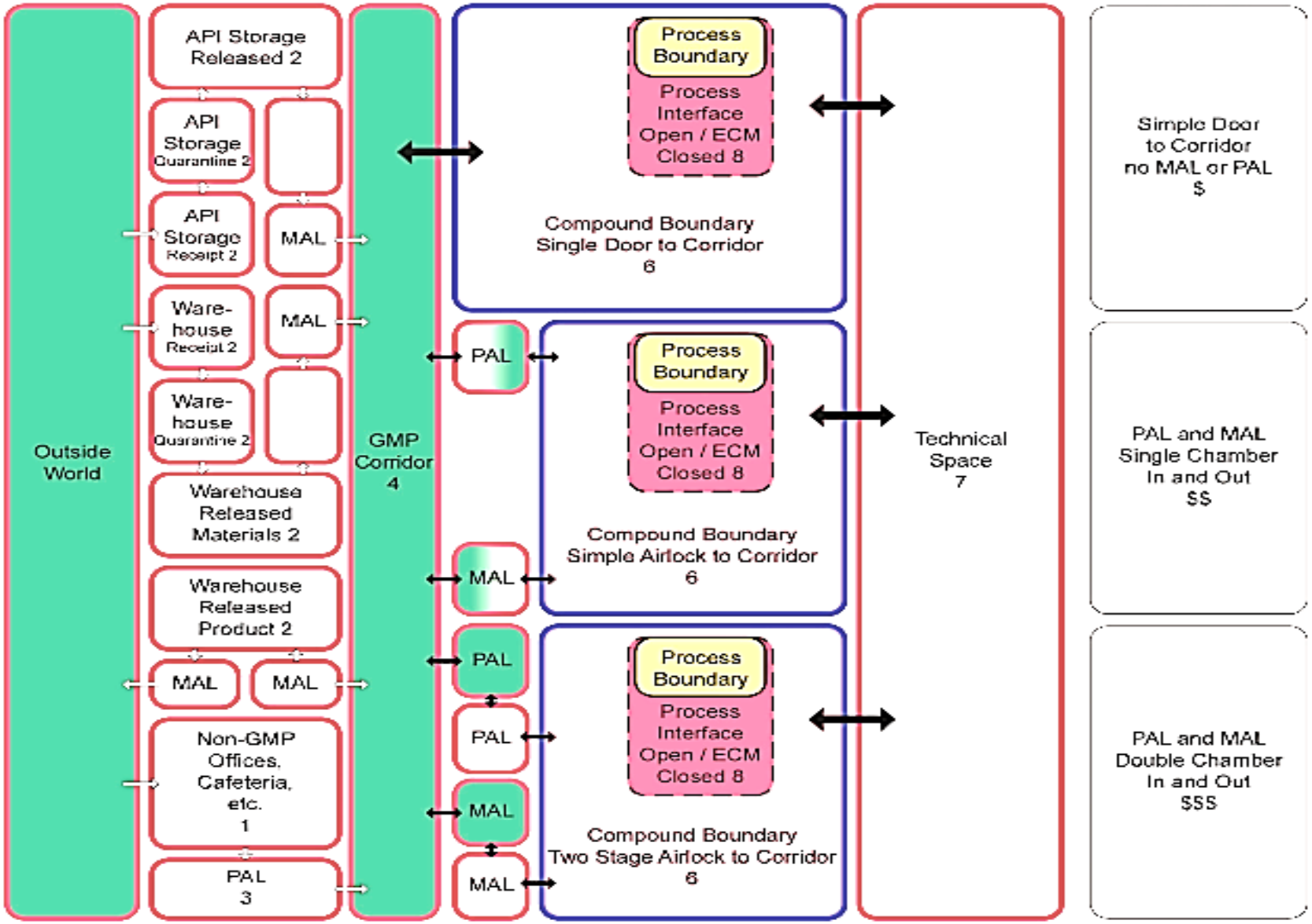
52

Risk Control- Reduction of hazardous products

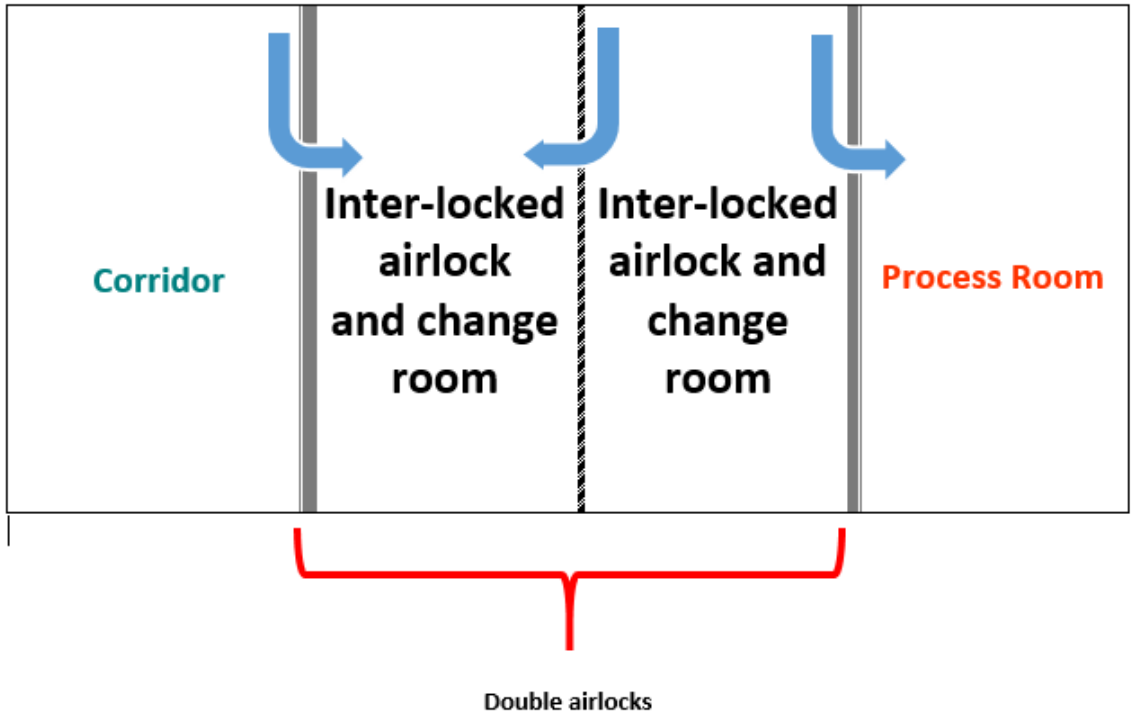
Design and Engineering and equipment selection in hazardous facility settings

Figure 9.5: Facility with Alternate Arrangements



Risk Control- Reduction of hazardous products

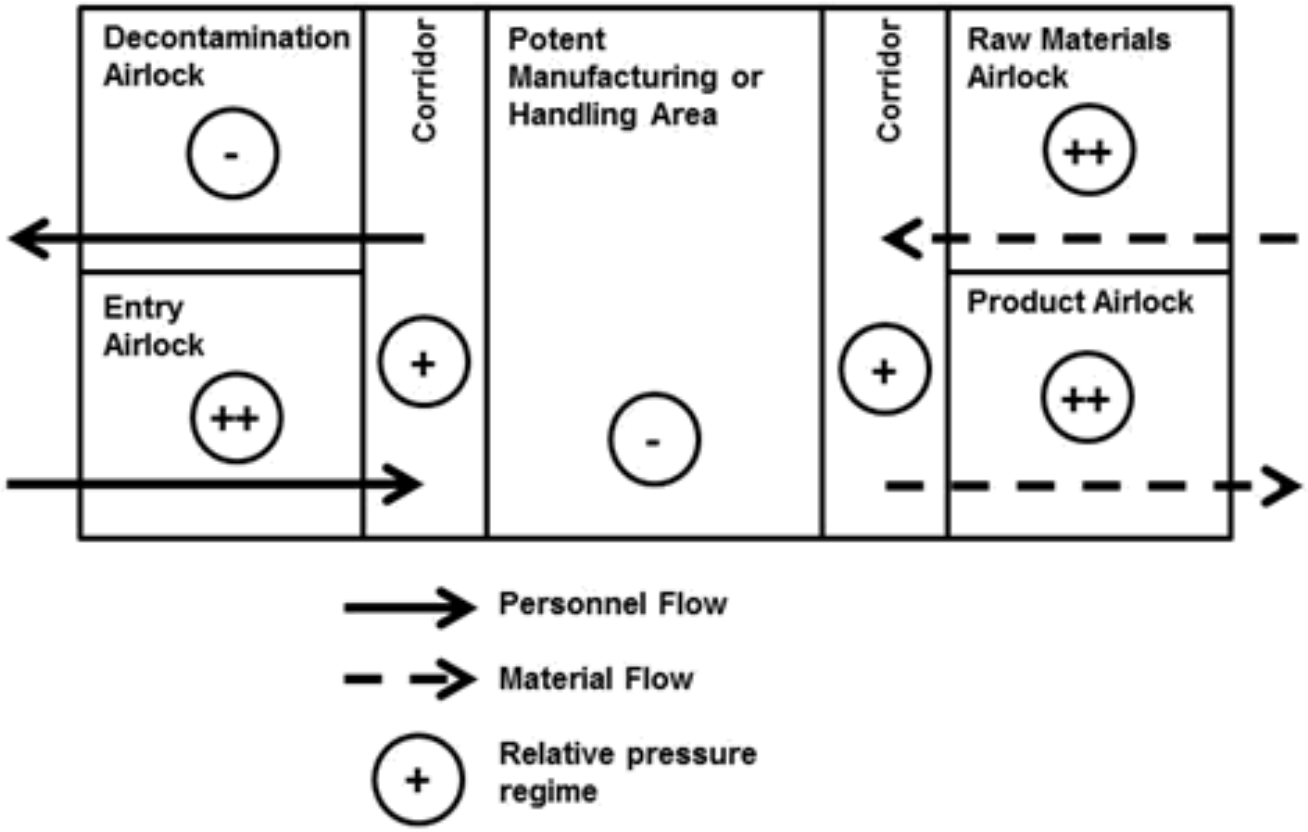
Design and Engineering and equipment selection in hazardous facility settings



- Earlier the approach was separate rooms with –ve pressure and double air locks with PPEs to prevent cross contamination
- Recently the drive is towards shirt sleeve operations, because;
  - The PPEs are uncomfortable and lead to cross contamination

Risk Control- Reduction of hazardous products

Design and Engineering and equipment selection in hazardous facility settings



A simple possible highly-potent facility

All facilities are different and may be subject to different influences based on the complexity of the process.

http://www.outsourcedpharma.com/doc/best-practices-for-handling-potent-apis-0001

Risk Control- Reduction of hazardous products

Design and Engineering and equipment selection in hazardous facility settings

Facility Design Considerations

- **Facility:**
  - Single Door to Corridor, No MAL or PAL (-ve Pressure)
  - PAL & MAL Single Chamber In-and-Out (-ve Pressure)
  - PAL & MAL Double Chamber In-and-Out (-ve Pressure with Bubble and Sink Airlocks)

- **Process:**
  - Open Process : -ve Pressure with Airlocks
  - Engineering Controls : LEV, Down-flow Booth, Isolator Barrier System for Category 3 & 4.
  - Closed Integrated Process

Design and Engineering and equipment selection in hazardous facility settings

Standard system . . . . Split cone valve system . . . . Protective foil system . . . . Isolator technologie

Isolator technology OEB 5

Protective film system OEB 4

Split cone valve system OEB 3

Open system OEB 1

Risk Control-Reduction of hazardous products

Design and Engineering and equipment selection in hazardous facility settings

Where is Containment needed at handling process? Engineering for Powder Handling

- Charging / Discharing System
  - 
  - TKS Containment valve as Interface
- Handling System
  - 
  - Docking System
- Dispensing System
  - 
  - Isolator
  - Laminar flow
- Containers
  - 
  - Disposal Bag
  - PE Bottle
  - IBC
- Washing System
  - 
  - Glatt. Integrated Process Solutions.
- Secondary Periphery
  - 
  - Ventex Valve
  - Exhaus air line
  - Exhaus air filter
- Sampling System
  - 

Risk Control- Reduction of hazardous products

Design and Engineering and equipment selection in hazardous facility settings

The Technologies

Barrier Systems

Clean Room

Conventional Clean Room

- Environment: B/A
- Complexity: Low
- Comfort: Low, due to clean room garment
- Aseptic quality: Low SAL~3 (*)
- Campaigning unusual

RABS Restricted Access Barrier Systems

Open RABS (active or passive)

Closed RABS

- Environment: B
- No overpressure to surroundings
- Complexity: High, due to transfer techniques and restricted access by gloves
- Comfort: Even lower, due to clean room garment and restricted access
- Aseptic quality: Slightly improved SAL~4
- Several days campaign unusual

Isolator

Isolator

- Environment: D
- Overpressure
- Complexity: Highest, due to transfer techniques and biodecontamination
- Comfort: Medium, no clean room garment, but some restrictions
- Aseptic quality: Highest SAL~6 log
- Week(s) campaign possible

(*) Sterility Assurance Level

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All material, equipment, tools, .. to be carried and placed in spill trays and not directly in isolator/ hoods,…

Design and Engineering and equipment selection in hazardous facility settings

- **ISPE Risk Mapp 2010**

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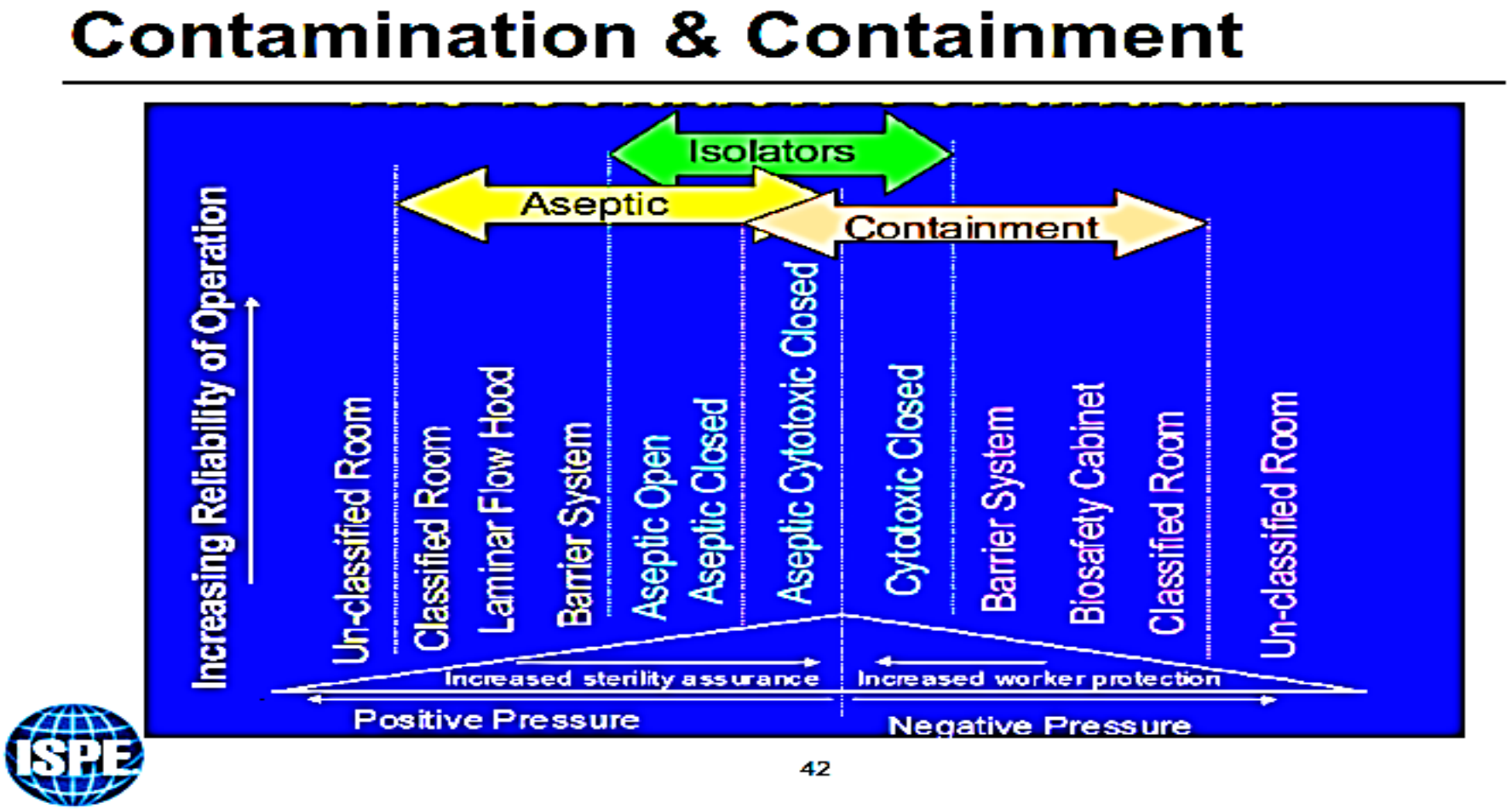


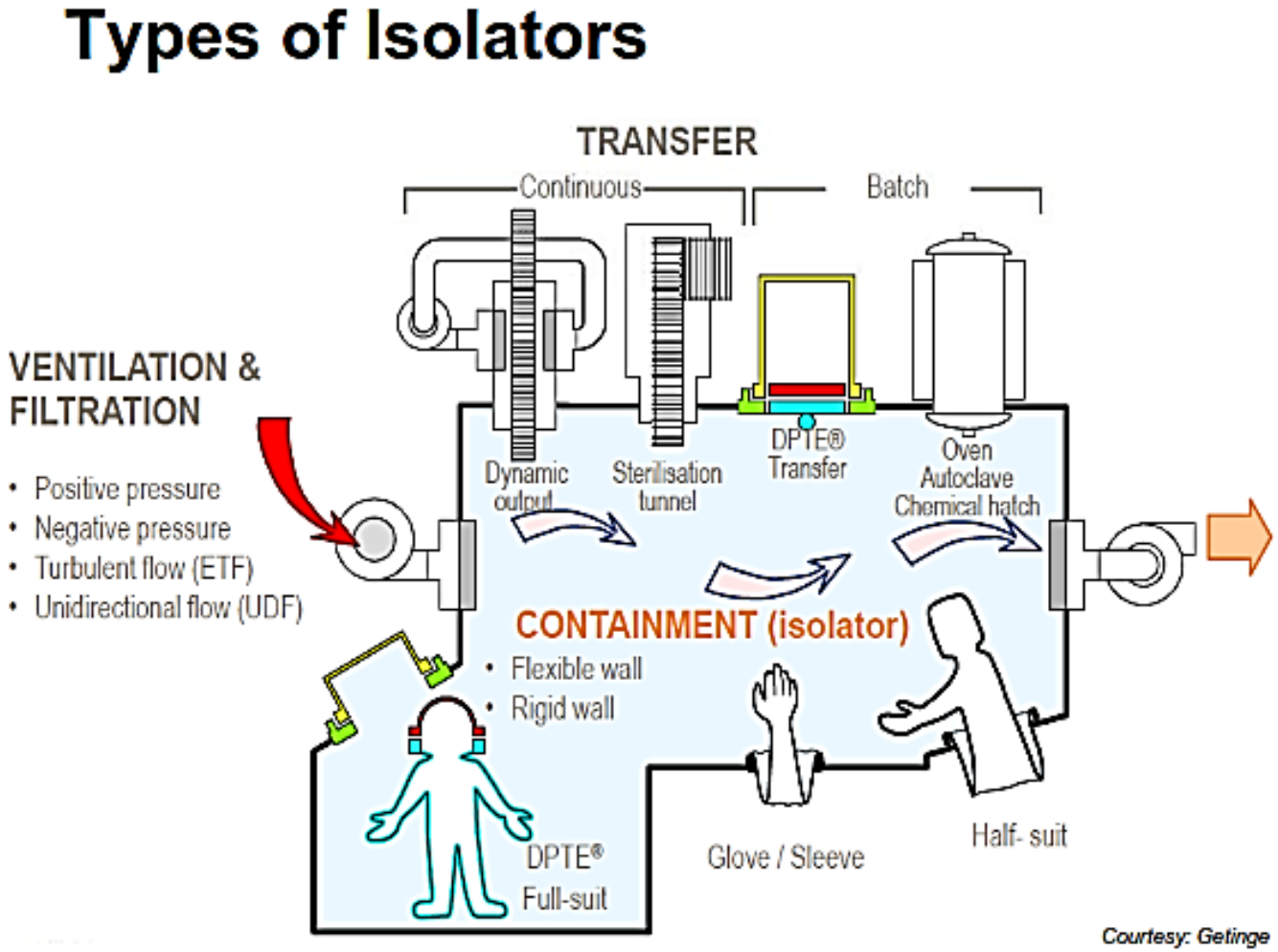
Design and Engineering and equipment selection in hazardous facility settings

- **RABS**
  - RABS technology is on the long-term not a succeeding technology
  - “Conventional aseptic filling should become passé soon.”
  - – Rick Friedman, Director, Div. of Mfg and Quality, FDA-CDER
  - The regulatory requirements for RABS systems will become more strict
- **Isolator**
  - Technology of the future
  - Gloves as a weak point of the isolator will more and more disappear: Automated processes
  - The VHP cycle times will become significantly shorter
- **Disposable technology**
  - Will increase significantly in the near future

Design and Engineering and equipment selection in hazardous facility settings

- **ISPE Risk Mapp 2010**

2



ISPE Risk Mapp summary

- **ISPE Risk Mapp 2010**

2

Summary

- "One Size fits all", is not true
- Development & manufacture of highly potent compounds requires;
  - Significant planning
  - Proper equipment and facility design
  - Extensive employee training
  - Implementation of the necessary procedures
- Don't Generalize, be Specific.
- Engineering allows us to reduce exposure – It doesn't guarantee it
- Any containment system is only as good as its weakest link.
- 90% of workplace accidents have human errors as a cause

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54