Designing for Potent Products: OEL-Driven Facility Design

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Understanding of OEL & OEB

Occupational Exposure Limit (OEL):

OELs are defined as airborne concentrations (expressed as time-weighted average for a conventional 8-hour work day and a 40-hour work week in ml/m^3 or mg/m^3) of a substance to which it is believed that nearly all workers may be repeatedly exposed (day after day, for a working lifetime) without adverse effect.

Occupational Exposure Band (OEB):

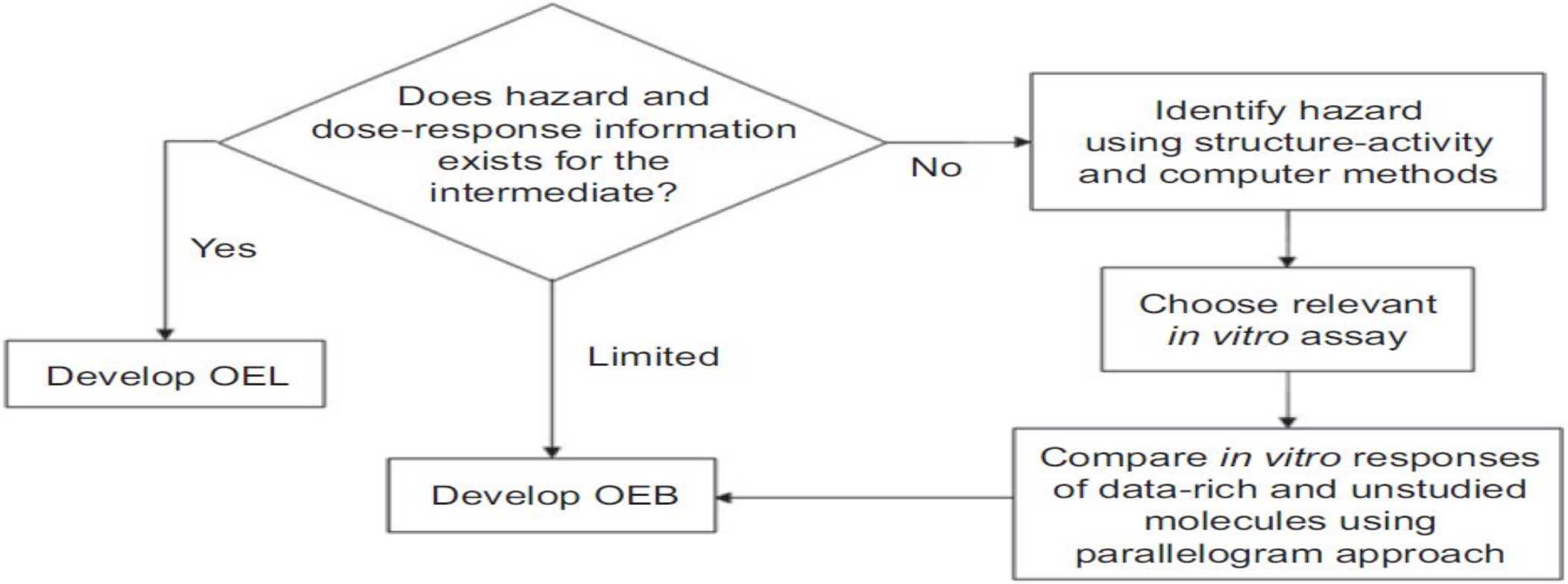
A classification system that groups chemicals into categories or "bands" (e.g., OEB 1 to OEB 5 or 6) based on their toxicological potency and the severity of potential health effects. This approach is used to quickly and accurately classify substances, especially when a formal, data-intensive OEL has not yet been established.

Formula:

OEL = (Lowest Therapeutic Dose) / (Safety Factor).

OEB = Categorized into a band based on their toxicological potency, with each band corresponding to a specific OEL range.

Developing OEL/OEB



Process for establishing occupational exposure criteria depending on the availability of toxicity data.

Understanding of NOEL & NOAEL

NOEL (No Observed Effect Level):

The highest dose or exposure level of a substance in a study at which should have no *detectable* effect (of any kind, adverse or non-adverse, e.g., adaptive changes)

NOAEL (No Observed Adverse Effect Level):

The highest dose or exposure level of a substance at which no *significant adverse* (harmful) effects are observed. This means some non-adverse, minor, or adaptive biological changes may occur at the NOAEL dose, but they are not considered harmful.

Key Difference between NOEL & NOAEL:

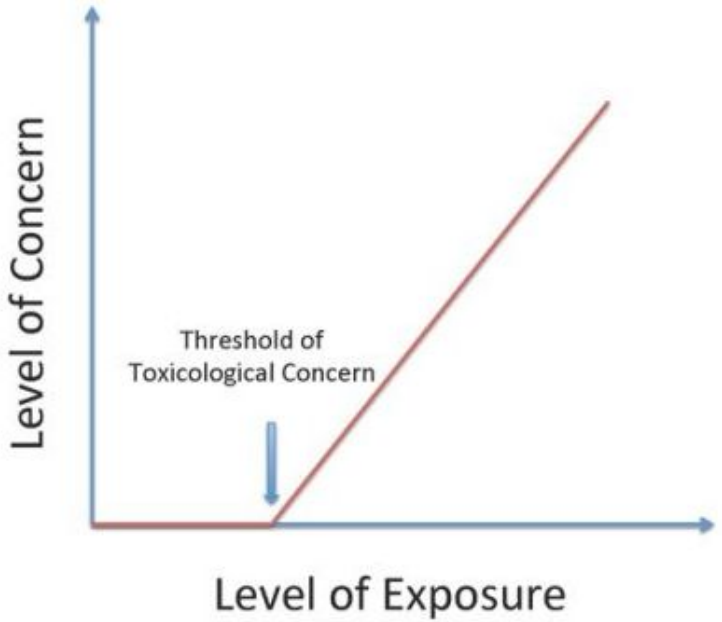
A NOAEL is a less stricter than NOEL (e.g., a drug intended to lower blood pressure causing a minor, non-harmful drop in a non-clinical study).

Formula:

They are specific dose levels identified through **experimental toxicology studies** (typically in animals) and data analysis.

Understanding of TTC

Threshold of Toxicology Concern (TTC)



Understanding of PDE/ADE & ADI

PDE/ADE (Permitted Daily Exposure / Acceptable Daily Exposure):

It is the maximum amount of an active pharmaceutical ingredient (API) that a patient can be exposed to daily without adverse effects, calculated through a detailed scientific evaluation of all available toxicological and pharmacological data.

ADI (Acceptable Daily Intake):

A measure of the amount of a substance in food or water that can be ingested daily over a lifetime without an appreciable health risk.

- The term ADI can be used in the food and agrochemical industries, while PDE/ADE is more common in the pharmaceutical industry.

PDE or ADE (mg/day) =

$$\frac{\text{NOEAL/LOAEL x Weight Adjustment}}{\text{F1 x F2 x F3 x F4 x F5 x MF x PK}}$$

MF = Modifying factor (can be applied on a case-by-case basis)
PK = Pharmacokinetic adjustments (e.g., bioavailability differences between exposure routes
F1 to F5 = Uncertainity Factors

ADI (mg/Kg bw /day) =

$$\frac{\text{NOEAL}}{\text{Safety Factor (SF)}}$$

Safety Factor = 100
The most common safety factor is 100, which includes a 10x factor for animal-to-human extrapolation

Risk Prioritization of Hazards

HAZARD

Less Severe — More Severe

Irritation	Biochemical Changes	CNS Depression	Liver Damage	Birth Defects	Cancer
Negligible	Non-Critical Reversible		Critical Non-Reversible		Terminal

IMPACT

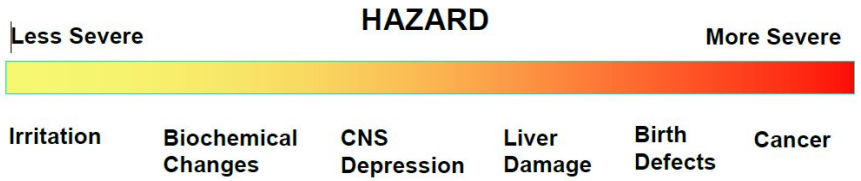
Occupational Exposure Limit (OEL)

>1,000 µg/m³	1,000 µg/m³	100 µg/m³	10 µg/m³	1 µg/m³	<1 µg/m³
Band-1	Band-2	Band-3	Band-4	Band-5	Band-6
>10,000 µg/day	10,000 µg/day	1,000 µg/day	100 µg/day	10 µg/day	<10 µg/day

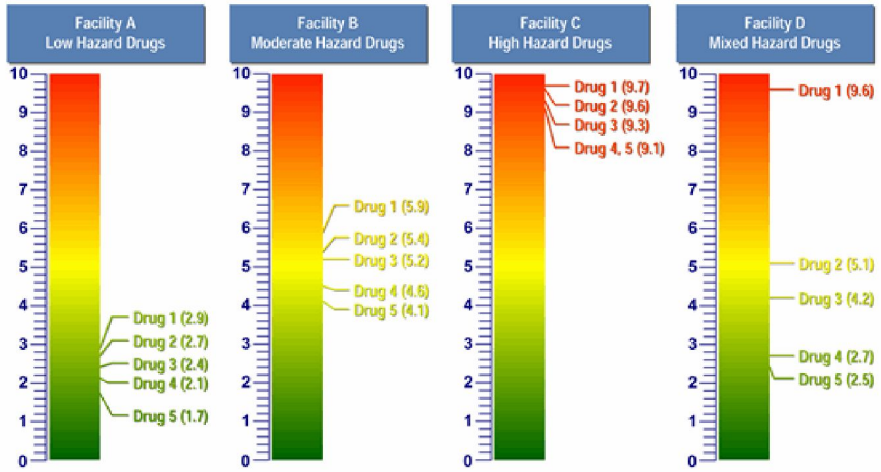
Health-Based Exposure Limit (HBEL)

Identification of Hazards & Toxicity Scale

Hazards identification Shall be done as per activity of substance chemically and biological.



Organization should develop the Toxicity Scale of product manufactured at facility with support of scientifically support of toxicology study.

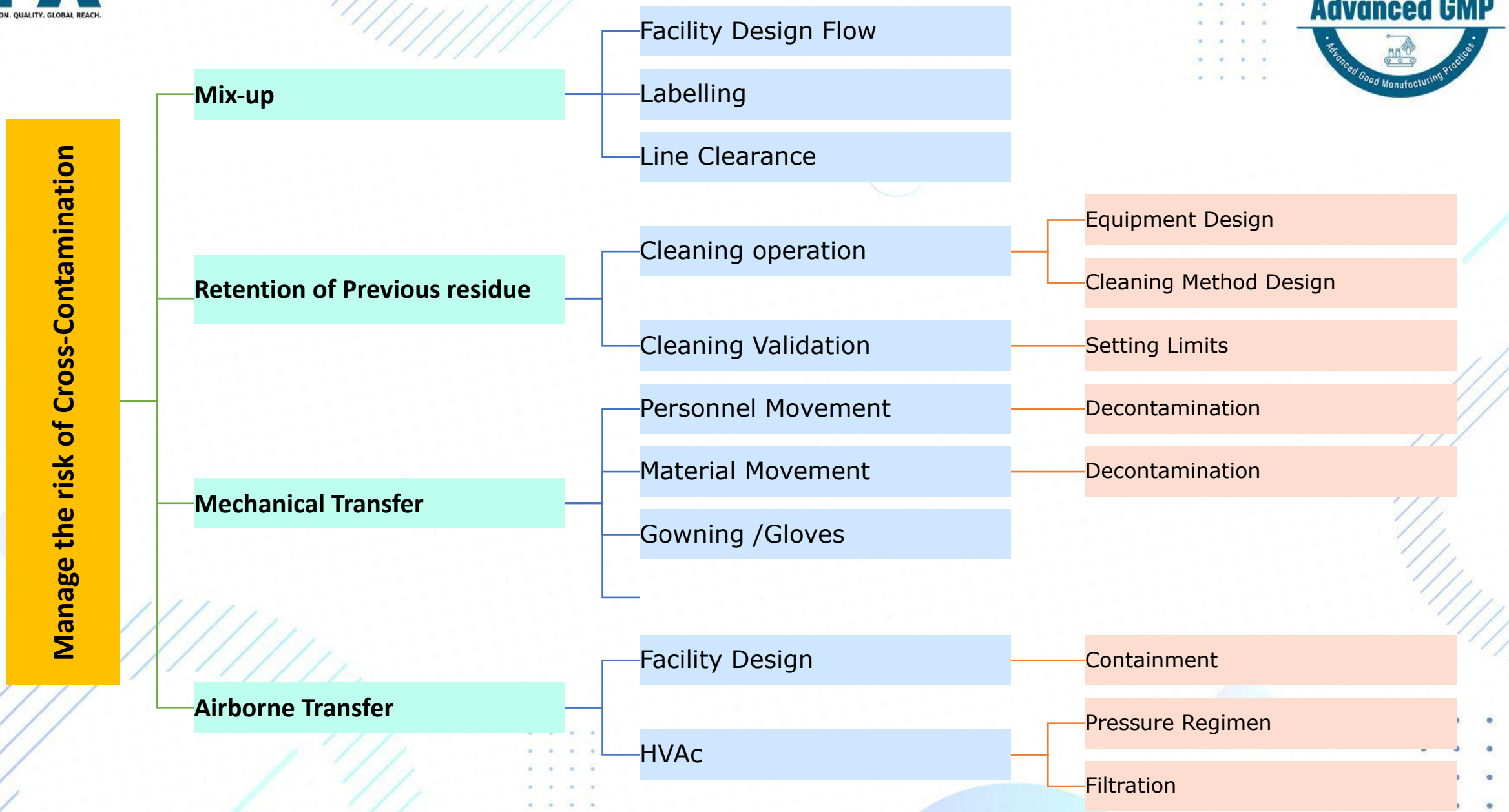


ADE/PDE based Toxicity Scores of Multi product facility		
ADE/PDE Value	**Dose in gram/day**	**Toxicity Score (-log ($ADE_{gram/day}$)**
100 pg/day	0.0000000001	10
1 ng/day	0.000000001	9
10 ng/day	0.00000001	8
100 ng/day	0.0000001	7
1 µg/day	0.000001	6
10 µg/day	0.00001	5
100 µg/day	0.0001	4
1 mg/day	0.001	3
10 mg/day	0.01	2
100 mg/day	0.1	1
1000 mg/day	1	0

Regulatory view on Hazardous Materials

Pharmaceutical substances	*USA FDA*	*Europe EMA*	*India CDSCO*	*Brazil ANVISA*	*WHO*	*China CFDA*	*Mexico COFEPRIS*	*Canada HC*	*PIC/S*
Hormones	X certain	X certain	X (sexual)	X certain	X certain	X certain (contraceptives)	X (of biological origin)	X certain	X certain
Steroids	X certain	X certain			X certain			X certain	X certain
Cytotoxic agents	X certain	X certain	X	X	X certain	X certain	X	X certain	X certain
Highly API	X certain	X certain	X	X certain	X certain	X certain	X others	X certain	X certain
Biological preparations	X	X certain	X	X	X	X	X	X certain	X certain
Sensitizing pharmaceutical materials	X certain	X certain	X	X	X	X	X	X certain	X certain
Immunosuppressants		X certain					X	X certain	X certain
Antibiotics		X certain	X certain	X some	X some			X certain	X certain
Cephalosporins	X	X	X	X	X certain	X	X	X	X
Penicillin	X	X	X	X	X	X	X	X	X
Carbapenems	X	X	X	X		X		X certain	X
Beta-lactam Derivatives	X	X	X	X others		X		X certain	X

Possible Risk Mitigation in Facility



Major Cross Contaminations

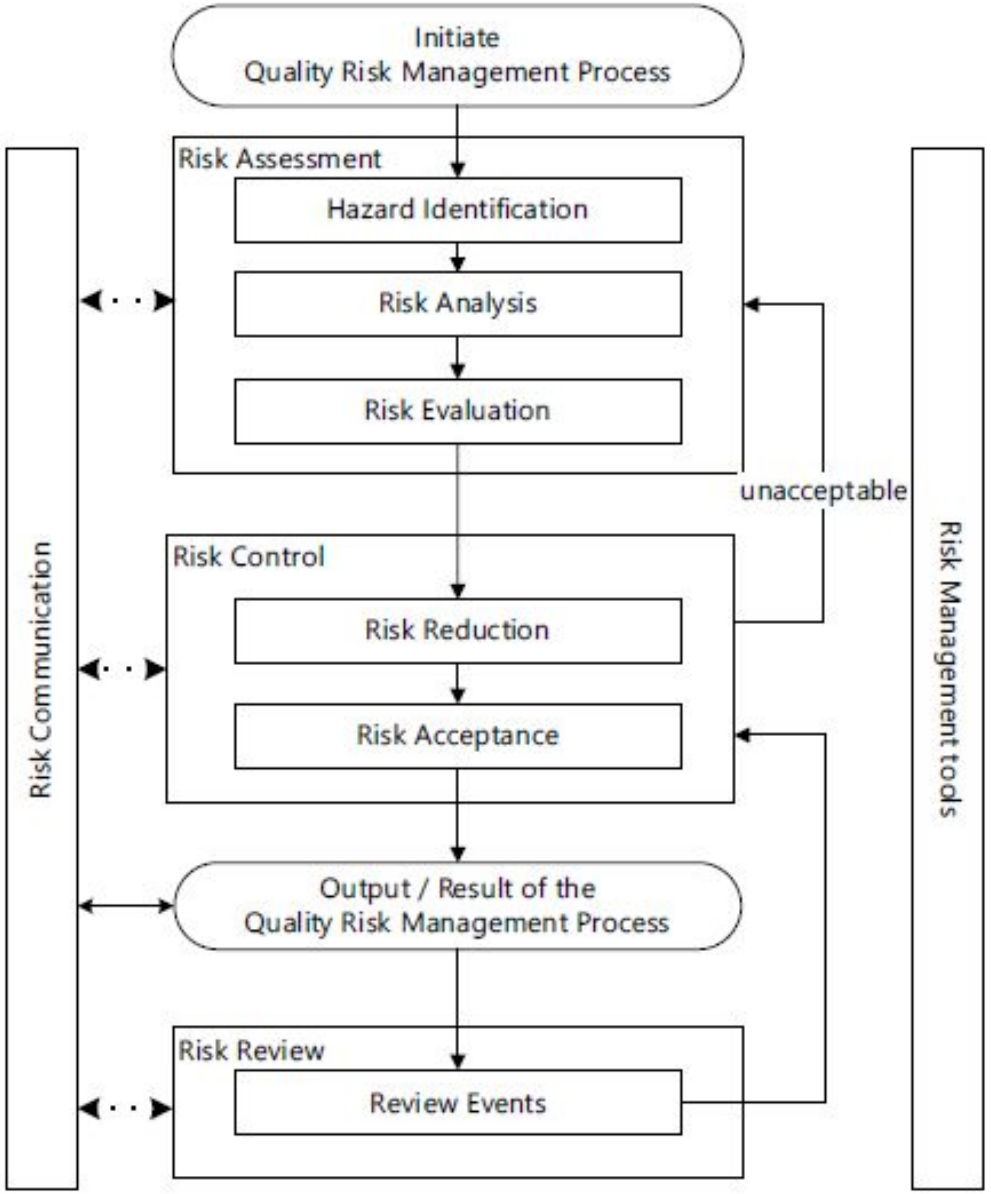
Inadequate Cleaning Verification:

- ✔ Manual cleaning – requires to eliminate subjectivity
- ✔ Routine monitoring – visual checks
- ✔ Define campaign change over verifications in case of less PDE
- ✔ Annual verifications
- ✔ Operators changes

Did Not Follow Procedure:

- ✔ Inadequate training
- ✔ State of mind
  - Distracted
  - Rushed
  - Not feeling well
- ✔ Misunderstand what is to be done and why
- ✔ Inadequate supervision

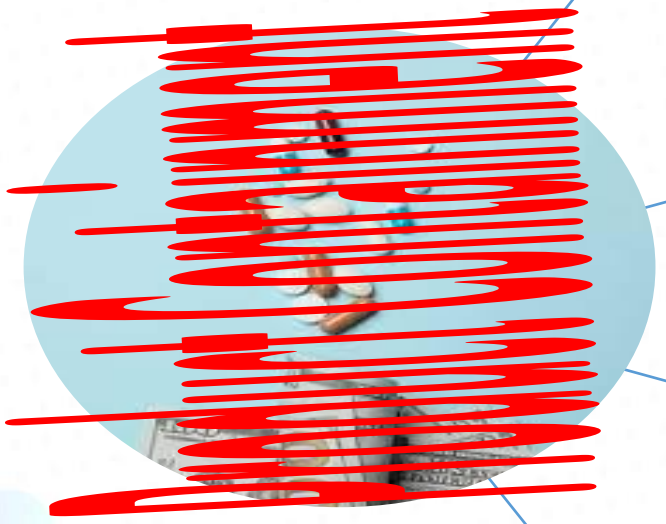
Quality Risk Assessment Tools ICH Q9



4 Protections

Product Protection

- Quality of Product
- Patient Safety



Personnel Protection

- Operator health & Safety
- Industrial Hygiene

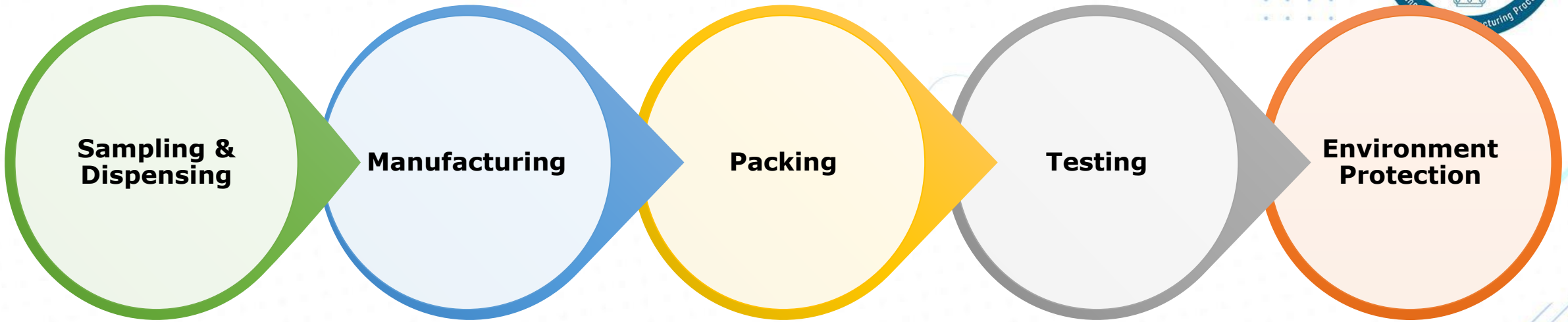
Environment Protection

- Outdoor Environment

Business Protection

- Downtime reduction
- Yield Increase
- Reducing the quality defects

Facility Design & Controls of Mitigation



- Closed Glove Port
- Suitable single used PPE
- Dedicated tools
- Single used tools
- After decontamination of area follow cleaning operation
- Dedicated & limited access area used for storage hazardous materials

- Breathing air system (BAS) with safety alert feature
- Personnel training on BAS
- Fresh air intake in AHU
- Dedicated AHU
- Campaign based manufacturing after HBEL risk study
- Decontamination prior to cleaning
- Swab & rinse testing

- Campaign based filling & packing after HBEL risk study
- Suitable protective PPE with nose mask & goggle
- Dedicated AHU
- Decontamination of direct contact followed by validated cleaning
- Physical segregation
- Robust Line clearance
- Swab & rinse sample after cleaning

- Sample in limited access
- Sample issuance and retrieval tracking
- Closed glove port for weighing
- Suitable PPE during handling
- Decontamination testing sample
- Decontamination of glassware prior to clean
- Dedicated glassware
- Controlled sample disposal

- Exhaust routed through neutralizer
- HEPA filter at exhaust terminal
- Wastes should collect in closed bags
- Neutralised the waste prior to disposal
- Periodic analysis of all critical entries and exhaust terminal
- Periodic analysis of treated water used for horticulture and domestic use
- Robust awareness training program

Note: Dedicated facility for beta lactam, certain Hormone, Cytotoxic & highly sensitizing materials

Major Regulatory Expectations

Dedicated and self-contained areas, Indian practices state the need to design **separate areas fo**r: beta-lactams (with no exceptions), highly active materials, sex hormones, some antibiotics, cytotoxic and oncology products.

Dedicated production areas should be used for manufacturing sensitizing materials such as penicillin or cephalosporins, and that this should also be considered when infectious, highly active or toxic materials are involved.

Penicillin & beta-lactam antibiotics requires *a* dedicated areas. Regarding all other drugs, the manufacturers must carry out a careful analysis of the risks involved in their production or whether dedicated facilities must be used for their manufacture.

The production of certain Hormone, sensitizing materials (penicillin & others) and biological preparations must be carried out in dedicated areas certain highly active materials, such as some antibiotics, hormones, some steroids, cytotoxic substances.

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Patient Safety is the responsibility

Thanks