CASE STUDY ON RISK ASSESSMENTS FOR CROSS CONTAMINATION

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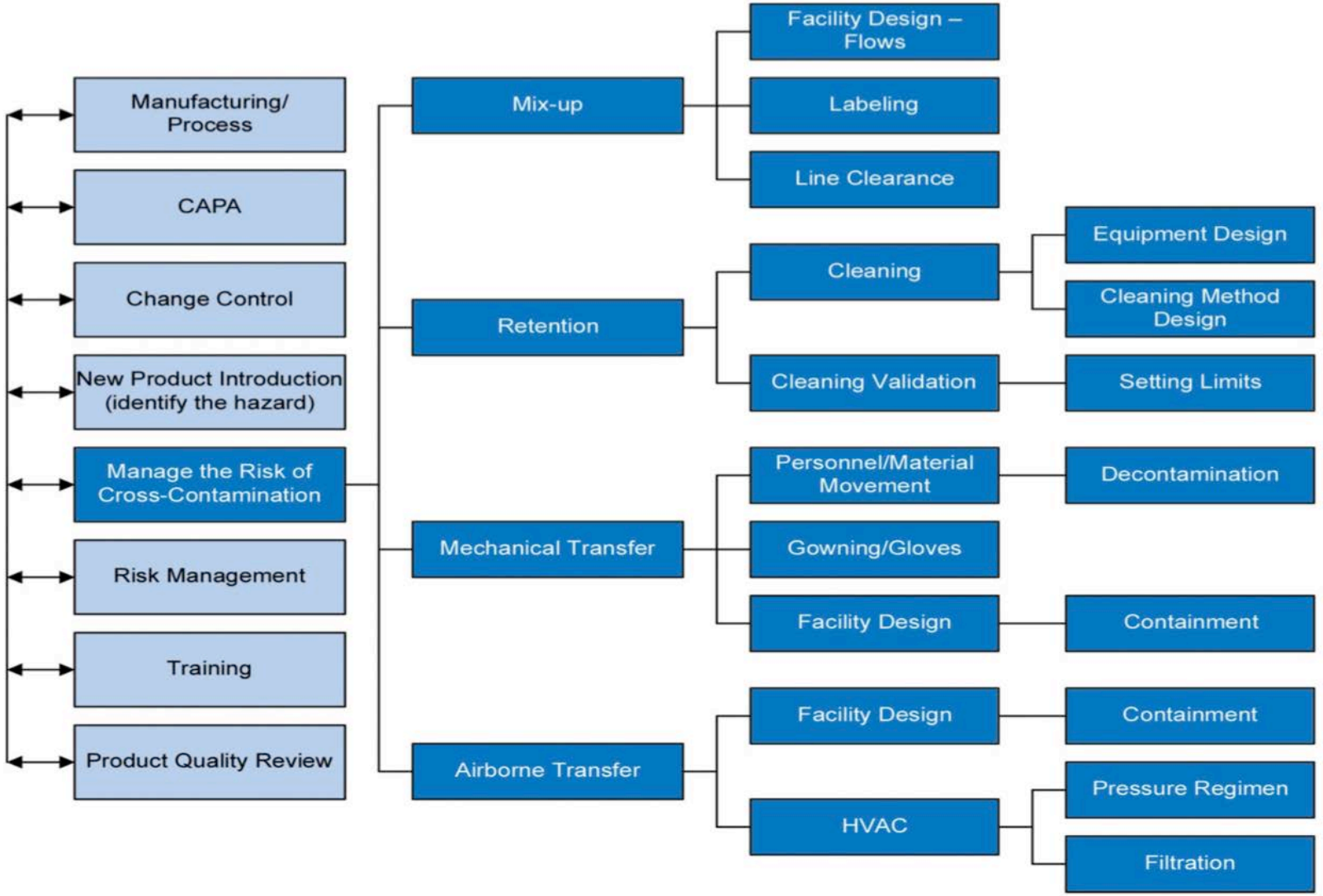
Objectives

- **How the process is embedded into the QMS**
- **Case study to show:**
  - Use of data to assess occurrence
  - How risk changes based on the exposure potential
    - Inadequate cleaning verification
    - Inadequate cleaning procedures
- **What's the upside – business, process, etc. advantages**

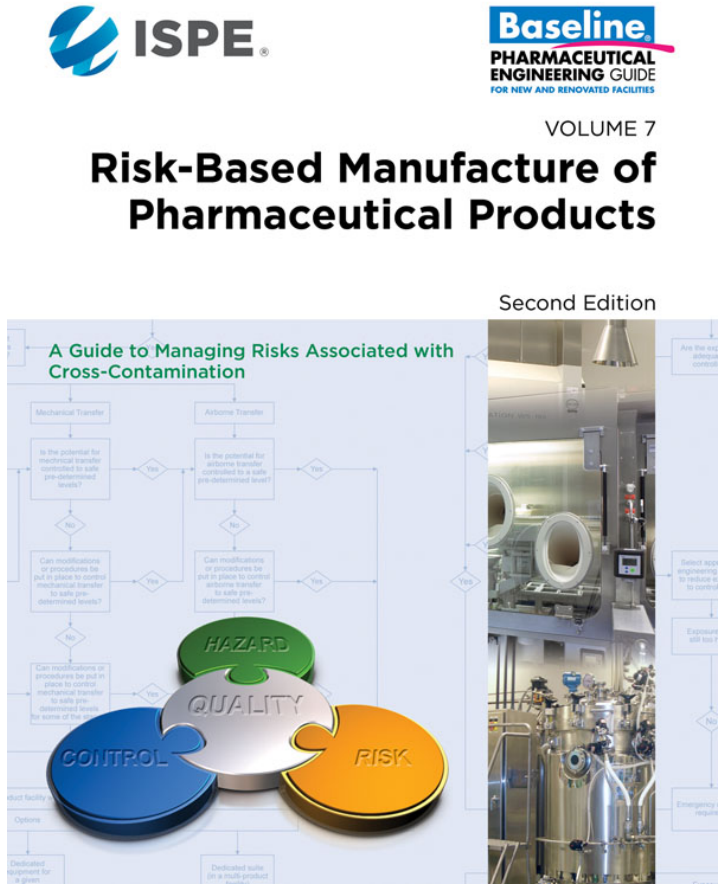
Embed into Quality Management System



API Details (Note 31 products with 10 APIs)

API	ADE mcg/day	OEL mcg/m^3	LOWEST DAILY DOSE mg/day
Anti-cancer	170	10	50
Anti-epileptic	250	10	150
Anti-hypertensive 1	25	3	2.5
Anti-hypertensive 2	400	50	50
Anti-psychotic 1	830	10	1800
Anti-psychotic 2	280	40	50
Anti-psychotic 3	1000	185	200
Misc. Agent	9750	580	300
Opioid	50	50	25
Vitamin B3	4200	2300	4

Scenario 4 in Risk-MaPP Second Edition



Information and Data Needed for Risk Analysis

- ✓ **Product list including ADE/PDE, process, maximum daily dose, API form, product presentation**
- ✓ **Equipment list including what products are produced in which equipment**
- ✓ **Process Flow diagrams**
- ✓ **Floor Plan, Flow diagrams, HVAC diagrams, room pressurization diagrams**
- ✓ **SOPs**
- ✓ **Historical Data**
  - ✓ Cleaning results, pressure differential alarm log, data from other data gathering studies, regulatory actions, audits, deviations, incidents, and change control log

How Health Based Limits are used for Risk Assessment

Cleaning Limits

Potential for Airborne and Mechanical Transfer

Surrogate in Placebo

Drug in Drug

Ranking of Severity in FMEA and other risk ranking tools

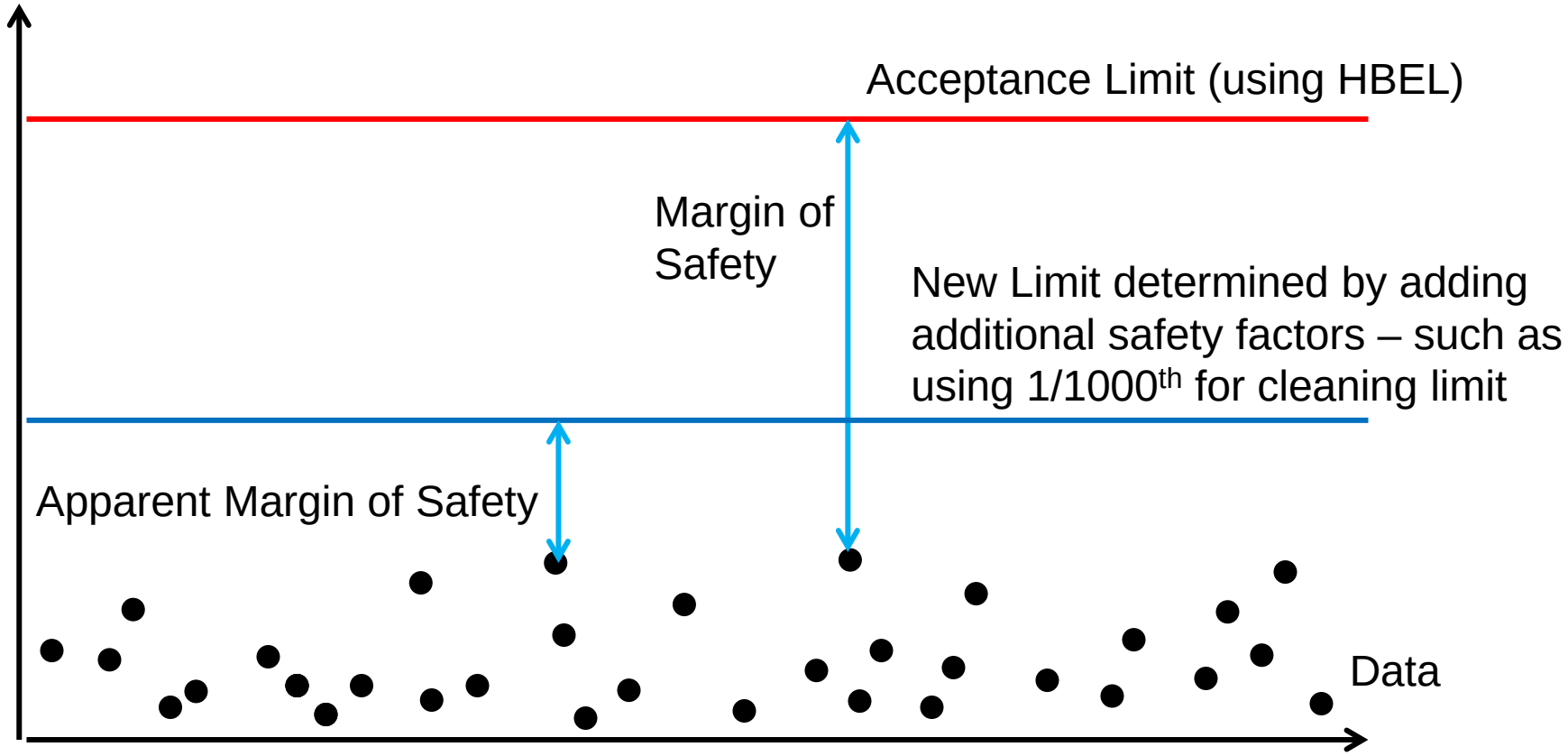
- ✓ The Health Based Limit is a direct indication of the potential harm to patient using the scientific knowledge to meet one of the primary principles laid out in ICH Q9

Effect of adding safety factors

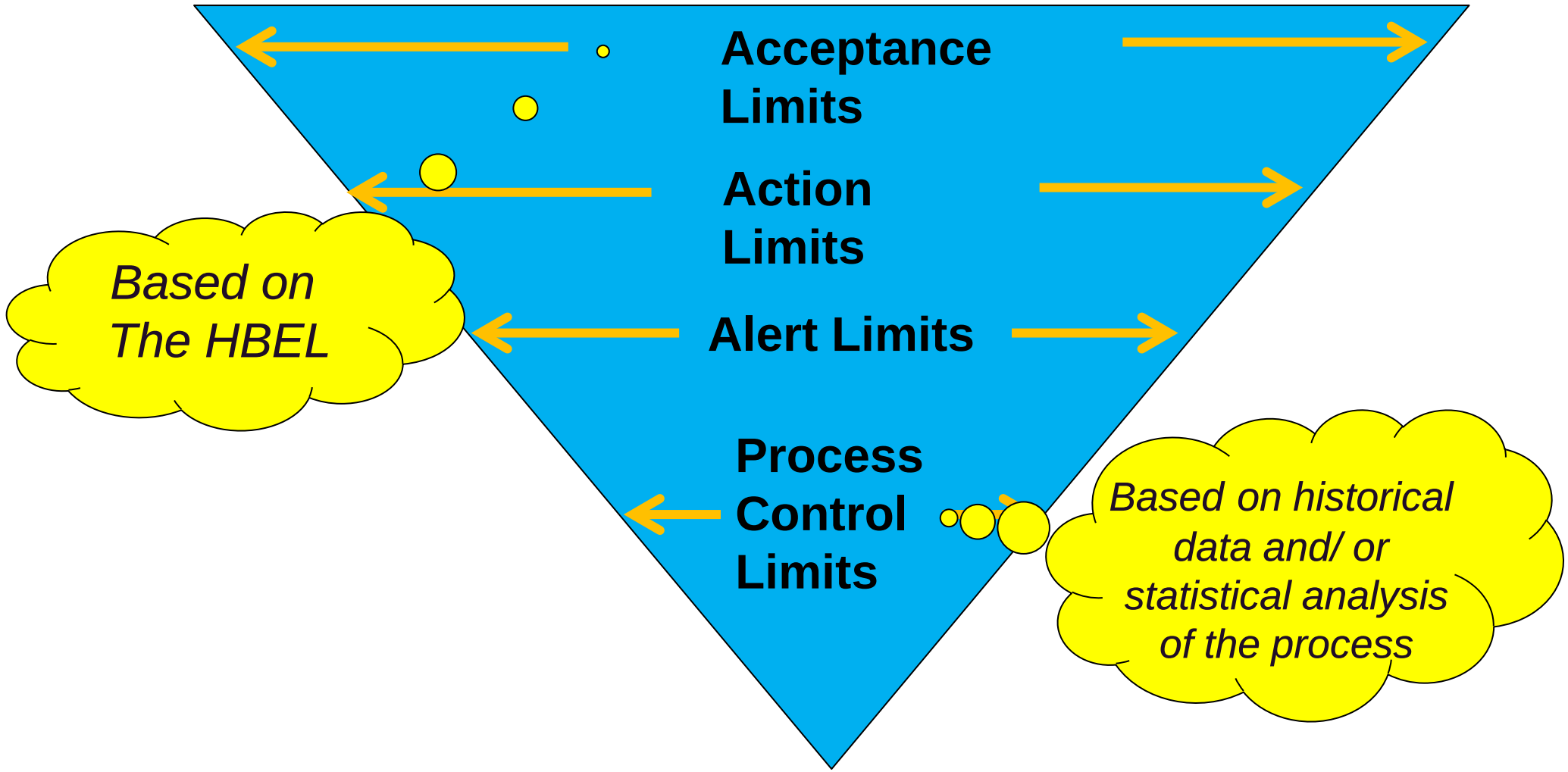
Note –

A wide margin of safety indicates a low risk of failure

A small margin of safety indicates a medium/high risk of failure



Hierarchy of Limits



Causes of Airborne Transfer

Open systems

- ✓ Non-contained processes
- ✓ Interventions
- ✓ Cleaning
- ✓ Upsets/ Accidents

Pressure differential

- ✓ Loss of pressure differential
- ✓ Inadequate pressure differential
- ✓ Inadequate alarm/monitoring

Inadequate filtration

- ✓ By design
- ✓ Inadequate maintenance
- ✓ Inadequate alarm/monitoring

Filter cleaning

Intake and exhaust proximity

Emission/ Exposure

Emission –
What is “emitted” from the process

Exposure –
Contact with the emission (hazard)

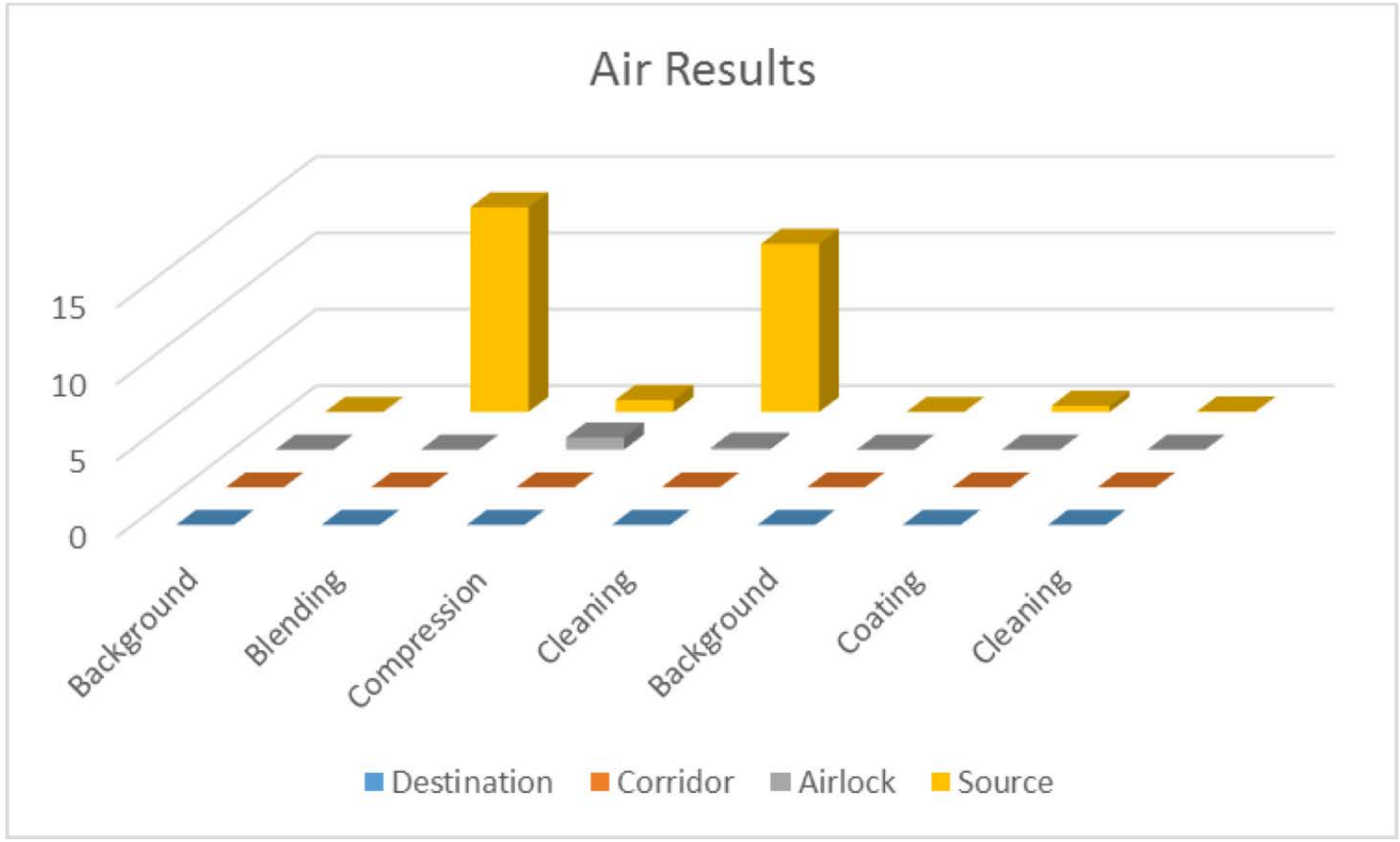
An emission is needed for an exposure to occur; an emission does not mean an exposure will occur

Gradient Studies

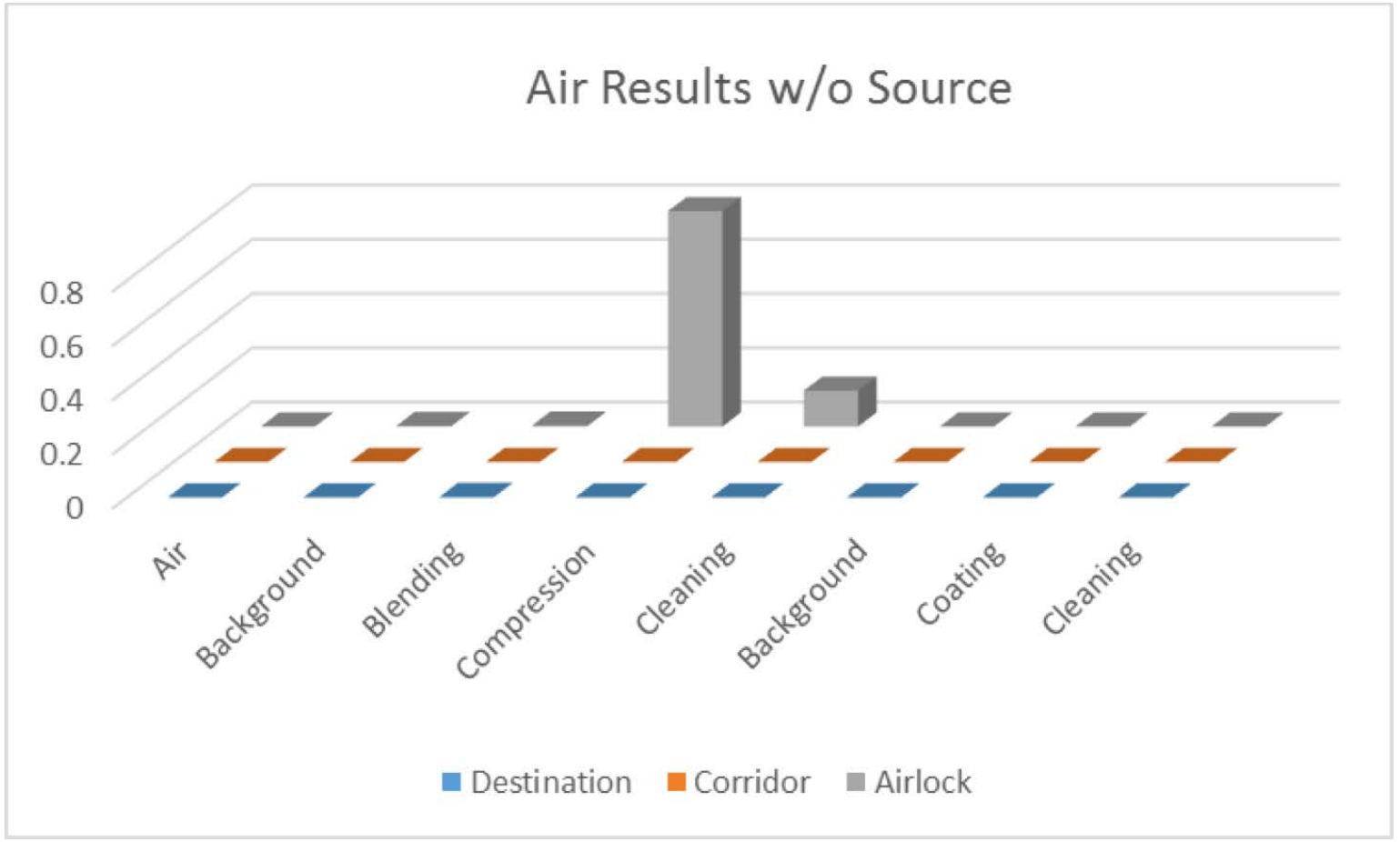
Use methods similar to Industrial Hygiene testing

- ✓ Samples taken in source room, corridor and destination room(s)
- ✓ Used to determine the likelihood of airborne and mechanical transfer by measuring the tendency of an API to migrate and settle on surfaces
- ✓ The rate of sedimentation is used to calculate the potential exposure due to the openness of the process and the duration of openness.
  - ✓ Compare this value to the Health Based Exposure Limit to determine the risk of cross contamination by airborne transfer

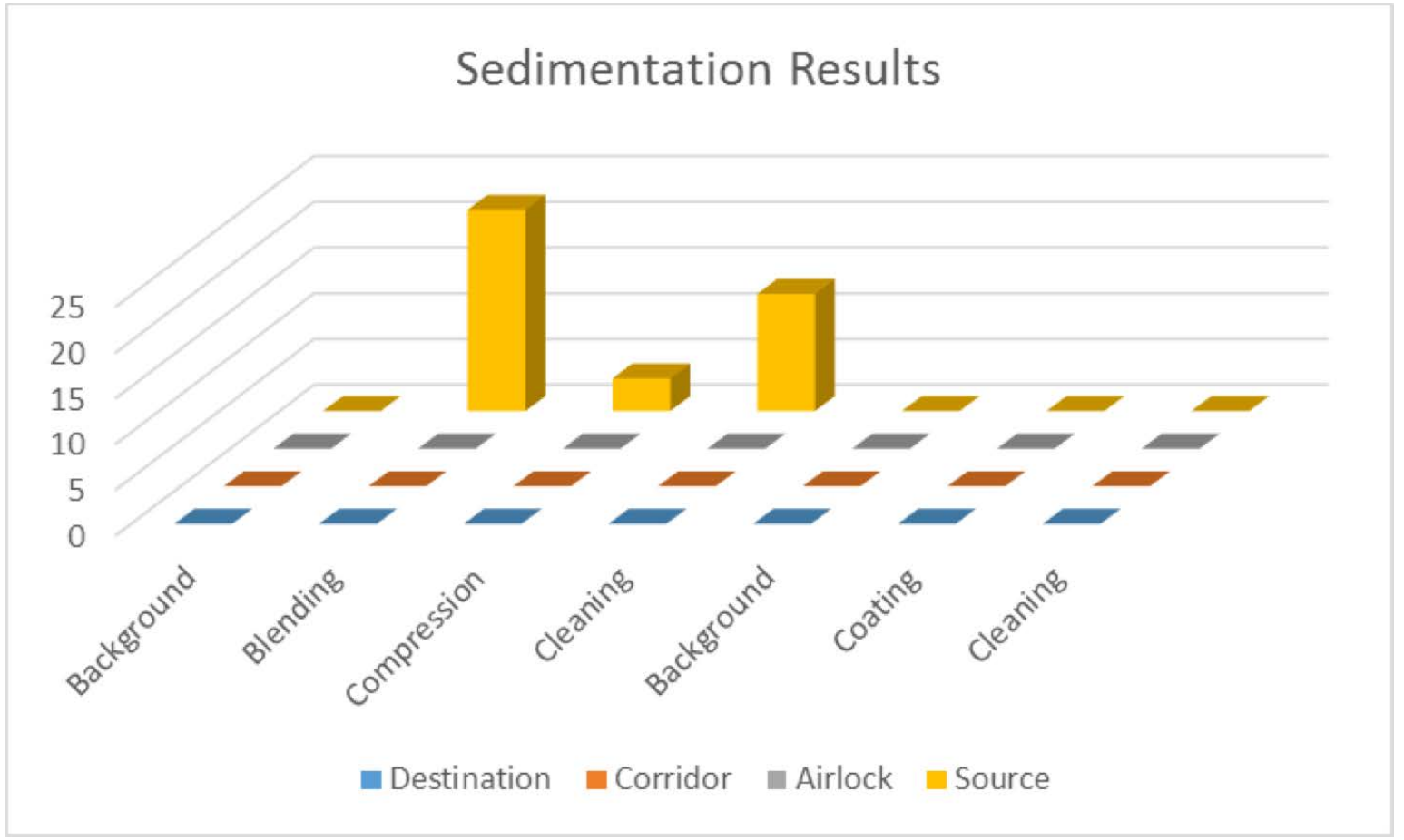
Sample Results from Gradient Study



Sample Results from Gradient Study



Sample Results



FMEA – Airborne Transfer

Process Step	Potential Failure	Effect of Failure	S	Potential Cause	O	Current Control	D	RPN
Milling	Loss of pressure differential	Airborne	5	Door open – single door to corridor	7*	Manually check gauge at beginning of shift	7	245

*Based on pressure alarm log

Below is the assessment after remediation – addition of alarms in process room

Process Step	Potential Failure	Effect of Failure	S	Potential Cause	O	Current Control	D	RPN
Milling	Loss of pressure differential	Airborne	5	Door open – single door to corridor	7*	Automatically alarms in process room	1	35

Causes of Mechanical Transfer

- ✓ Open systems
- ✓ Movement of materials/equipment without decontamination and cover
- ✓ Inadequate flow within the wash room
- ✓ Inadequate order of washing equipment/room
- ✓ Inadequate separation of clean and dirty equipment
- ✓ Inadequate gowning procedures
- ✓ Inadequate maintenance procedures

FMEA – Mechanical Transfer

Process Step	Potential Failure	Effect of Failure	S	Potential Cause	O	Current Control	D	RPN
Compression	Dirty Gown not removed	Mechanical Transfer	5	Inadequate Procedure	10*	Procedure	10	500

* Since procedure is inadequate assume occurring all the time

Below remediation – procedure improved

Process Step	Potential Failure	Effect of Failure	S	Potential Cause	O	Current Control	D	RPN
Compression	Dirty Gown not removed	Mechanical Transfer	5	Human Error – did not follow procedure	5	Procedure	10	250

Causes of Manual Cleaning Failures

- ✓ Inadequate cleaning limits/ limit of detection
- ✓ Inadequate cleaning procedure
- ✓ Inadequate verification
- ✓ Did not follow procedure

Inadequate Cleaning Limits/ Limit of Detection

- ✓ **Not health-based using ADE/PDE**
- ✓ **Limit of detection near limit**
- ✓ **Incorrect calculation for 1/1000th of low clinical dose**
  - ✓ Use of lowest dose manufactured rather than low clinical dose of product
  - ✓ Use of lowest dose does not taken into account contraindications (i.e. pregnancy, pediatric, etc.)
  - ✓ Failure to compensate for pediatric use

Inadequate Cleaning Procedure

- **Not enough detail**
  - How to clean – scrub, etc.
  - direction/order of cleaning, duration
  - what tools to use
- **Detergent**
  - type and concentration
- **Water**
  - type, temperature, amount
- **Where are hard to clean areas**
- **Where to visually inspect**

Inadequate Cleaning Verification

- ✓ **Manual cleaning – validated with verification yearly**
- ✓ **Routine monitoring visual only**
  - ✓ Visual range not determined. Literature suggests 4 mcg/cm^2
- ✓ **Compounds in red require chemical analysis for routine monitoring**
- ✓ **Compounds in green require chemical analysis for routine monitoring if using 1/1000th for limit**
- ✓ **Compounds with * indicate a possible need for more sensitive analytical methods since the limit is lower using 1/1000th cleaning limit**

API	ADE mcg/day	LOWEST DAILY DOSE mg/day	Lowest Cleaning Limit mcg/cm^2	1/1000th LCD Cleaning Limit mcg/cm^2
Anti-cancer	170	50	2.0	0.6*
Anti-epileptic	250	150	2.6	1.5*
Anti-hypertensive 1	25	2.5	0.13	0.01*
Anti-hypertensive 2	400	50	41	5.1*
Anti-psychotic 1	830	1800	11	23.9
Anti-psychotic 2	280	50	3.0	0.54*
Anti-psychotic 3	1000	200	7.6	1.5*
Misc Agent	9750	300	108	3.3*
Opioid	50	25	264706	132353
Vitamin B3	4200	4	48	0.05*

Did Not Follow Procedure

- ✓ **Inadequate training**
- ✓ **State of mind**
  - ✓ Distracted
  - ✓ Rushed
  - ✓ Not feeling well
- ✓ **Misunderstand what is to be done and why**
- ✓ **Inadequate supervision**
- ✓ **Ergonomics/dexterity**

FMEA - Retention

Process Step	Potential Failure	Effect of Failure	S	Potential Cause	O	Current Control	D	RPN
Granulation	Not clean to limits	Retention	5	Inadequate verification	7*	Visual inspection	10	350
Granulation	Not clean to limits	Retention	5	Inadequate procedure	7**	SOP	7	245

* Assumed each product turn over since cannot detect
** Assumed each product turn over since procedure is inadequate

Below is an assessment if chemical analysis is used at product change over and SOP improved (detail and verification of steps)

Process Step	Potential Failure	Effect of Failure	S	Potential Cause	O	Current Control	D	RPN
Granulation	Not clean to limits	Retention	5	Inadequate verification	3	Chemical analysis	3	45
Granulation	Not clean to limits	Retention	5	Inadequate procedure	3	Improved SOP	5	75

What are the advantages?

- ✓ A robust risk management system for cross contamination provides knowledge on the products, processes, facilities and equipment to permit better and more informed decisions throughout the organization
- ✓ The HBEL provides a value that meets the intent of ICH Q9's requirement that the evaluation of risk is based on scientific knowledge that ultimately links to the protection of the patient
- ✓ Using a hierarchy of limits allows processes to be monitored and corrected prior to failures requiring full investigation
- ✓ Using HBEL based cleaning limits are conservative (even for low hazard compounds) and in many cases will allow the continued use of visual inspection only for routine monitoring

Key messages

- ✓ **Risk is a function of hazard (the compound) and exposure (the process and controls)**
  - ✓ Hazard remains constant with the API and is characterized by the ADE/PDE
  - ✓ The process/equipment/procedures are assessed to determine the potential exposure of one compound to another
- ✓ **Assessing how well the facility implements the GMP's is an essential part of the risk assessment process**
- ✓ **Use of data is essential to a robust risk assessment**
- ✓ **Cleaning is just one mode of cross contamination**
- ✓ **HBEL's are used to set cleaning limits as well as for assessment of airborne and mechanical transfer**
- ✓ **Embed the process into the Quality Management System to ensure it is a lifecycle approach**

REFERENCE SLIDES

Processes

Process: Sample, weigh, mill, granulate, mill, dry, mill, blend, compression, and pack (10 steps)

All processes are fairly open (i.e., there are no containment devices or engineering controls used)

The facility uses a matrix approach to cleaning validation so therefore the cleaning limit used as the acceptance criteria for validation and routine verification/monitoring is 0.1 mcg/cm^2. This value corresponds to the lowest cleaning limit combination (Anti-hypertensive1 and Anti-hypertensive2)

The cleaning procedures are all manual based with only a visual inspection by the operator and a supervisor to verify the equipment is cleaned to the limits (0.1 mcg/cm^2).

FMEA Scoring

Value	Severity	Occurrence	Detection
10	Injury to a patient or employee; ADE< 1 mcg/day	More than once per batch	Not detectable by current methods
7	Cause extreme customer dissatisfaction; ADE 1-10 ug/day	Once per batch	All manually inspected
5	Something likely to result in a complaint; ADE 10-100 mcg/day	Once per 6 months	Statistical sampling Manual inspection with verification
3	Minor nuisance resulting in no loss; ADE 100-1000 mcg/day	Once every 1 – 3 years	100% inspection
1	Be unnoticed and not affect performance; ADE > 1000 mcg/day	One occurrence in greater than five years	Obvious or controlled and monitored and alarmed by control system

RPN Action Ranges

RPN Range	Risk Level	Action
1000 – 343	High	Cease until remediated
342 – 100	Medium	Remediate – can continue operations
99 – 1	Low	Monitor

Causes of Mix-up

- ✓ Flow routes/lack of space for storage and WIP
- ✓ Inadequate verification of labeling
- ✓ Inadequate training
- ✓ Inadequate supervision
- ✓ Did not follow procedure

FMEA – Mix-up

Facility	Process Step	Potential Failure	Effect of Failure	S	Potential Cause	O	Current Control	D	RPN
OSD	Receiving	Wrong Label	Mix-up	5	Inadequate verification	3	SOP	7	105
OSD	Compounding	Wrong Materials	Mix-up	5	Human Error – materials staged in corridor	5	Manual verification	7	175

Note both items should be remediated

Calculation for Setting Acceptance Criteria for Cleaning Validation										
A Products → / B Products ↓	vitamin B3	Anti-hypertensive 1	Anitpschyotic 1	Opioid	Anti-epileptic	Misc agent	Anti cancer	Anti-psychotic 2	Anti-pyschotic 3	Anti-hypertensive 2
Vitamin B3	NA	6.50	254.00	6000000	65.00	2517.00	44.00	72.00	258.00	103.00
Anti-hypertensive 1	3615.00	NA	845.00	20000000	192.00	8132.00	148.00	227.00	576.00	152.00
Anti-pyschotic 1	1425.00	8,5	NA	6666667	85.00	3309.00	58.00	95.00	339.00	136.00
Opioid	2598.00	6.80	607.00	NA	138.00	5845.00	106.00	163.00	414.00	106.00
Anti-epileptic	904.00	4.80	211.00	5000000	NA	2033.00	37.00	57.00	192.00	77.00
Misc agent	2711.00	16.00	634.00	15000000	157.00	NA	111.00	176.00	629.00	252.00
Anti-cancer	698.00	4.20	138.00	2666667	42.00	1621.00	NA	47.00	166.00	67.00
Anti-pyschotic 2	942.00	5.60	198.00	4687500	56.00	2187.00	38.00	NA	224.00	90.00
Anti-pyschtoic 3	603.00	2.60	141.00	3333333	32.00	1355.00	25.00	38.00	NA	41.00
Anti-hypertensive 2	48.00	0.13	11.00	264706	2.60	108.00	2.00	3.00	7.60	NA

$$\text{Limit (mcg/cm}^2) = \frac{\text{ADE(PDE)}_A \times \text{Batch Size}_B}{\text{MDD}_B \times \text{SSA}}$$

Where MDD = Maximum Daily Dose
SSA – Shared Surface Area