

Pharmaceutical Industry's Approach to Safe Handling of New Molecular Entities

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Pharma IH Process Overview

Focus on R&D laboratories

- Occupational Health Hazard Characterization
 - “Default” Health Hazard Band for Discovery labs
 - Health Hazard Banding for Development labs
 - Occupational Exposure Limits
- Control Selection
 - Graded approach for engineering controls
- Exposure Verification
 - Applicability to Engineered Nanoparticles



Pharma's Philosophy and Rationale for Health Hazard/Control Banding

- Possible to group together
 - Agents of similar toxicity or toxic mechanism
 - Agents of like exposures or risksto manage workplace exposures effectively, efficiently and with minimal resources
- Programs began in the 1980's with the advent of "high potency" drug products
 - OELs established too late in the drug development process
 - Industry uncertainty about appropriate OELs
 - Analytical methods not sensitive enough
 - No engineering controls on the market



“High Potency” Definition

- A daily therapeutic dose of 10 mg/day, or
- A dose of 1 mg/kg/day in laboratory animals that produces:
 - serious organ toxicity; and/or
 - developmental toxicity or reproductive toxicity; and/or
 - Irreversible effects
- Usual occupational exposure levels (OELs) of less than 10 $\mu\text{g}/\text{m}^3$ after applying appropriate uncertainty factors



Occupational Health Hazard Characterization

- Typically, health hazard band assigned prior to Phase I clinical development
 - Prior to “kilo lab” synthesis (5 – 20 L) and clinical dosage preparations
- Health hazard band based on:
 - Pharmacology
 - Therapeutic class
 - Anticipated therapeutic dose (potency)
 - Structural activity (*in-silico*)
 - Pharmacokinetics (ADME) and dynamics
 - Target organ (reproductive, liver, nervous system, etc.)
 - Toxicology
 - Epidemiology and experience in the work place



Minimum Toxicology Data Set for Health Hazard Band

Designed to identify hazards specific to the
workplace

- Structural activity
- Acute toxicity
- *In vitro* eye irritation
- *In vitro* skin irritation
- *In vivo* dermal sensitization (allergies)
- Genotoxicity
 - DNA damage-mutagenicity and chromosomal damage



Example Health Hazard Bands

	HHB1	HHB2	HHB3	HHB4	HHB5
Description	Low toxicity	Low-Moderate toxicity	Moderate toxicity	Highly toxic	Highly toxic
Pharmacologic activity	Low	Low to Moderate	Moderate	High	Extremely high
Adverse effects from occupational exposure routes	None anticipated from occupational exposures	Minor and reversible	Moderate and reversible	Moderate and irreversible or severe and slowly reversible	Severe and irreversible or slowly irreversible
Example adverse effects	Minor skin, eye or respiratory tract irritation	Moderate skin, eye or respiratory tract irritation, target organ effects	Severe irritation, skin sensitizer, liver or other target organ effects	Severe type I sensitizer, suspected or confirmed carcinogen	Gene-, repro- or developmental-toxicity
Target OEL range ($\mu\text{g}/\text{m}^3$)	> 1,000	1,000 – 100	100 – 10	10 – 1	< 1

But what about the
Drug Discovery scientist?



“Default” Control Targets for Discovery Scientists

- Handle new molecular entities as “highly potent”
 - Typical industry target is $< 10 \mu\text{g}/\text{m}^3$ (HHB-3)
- Handle new molecular entities in certain therapeutic classes as “extremely potent” ($< 1 \mu\text{g}/\text{m}^3$ –HHB-4). Examples include:
 - Cancer drugs
 - Sex hormones
 - Immunosuppressants
 - Potent opioids, such as fentanyl and methadone



“Default” Control Measures for Selected Drug Discovery Activities

	Health Hazard Band 3 “Default” Exposure Control to $< 10 \mu\text{g}/\text{m}^3$	Health Hazard Band 4 Exposure Control to $< 1 \mu\text{g}/\text{m}^3$
Liquid Transfers	Fume hood or other appropriate vented, containment device if aerosols are generated.	Highly-cleanable containment devices, (biological safety cabinets, vented containment devices and glove box isolators).
Solids Weighing Solids Transfers Size Reduction Size Separation	Fume hood, laminar flow cabinet or other appropriate, vented containment device, depending on number of weighing tasks and bulk density of solid. Consider glove box isolators for compounds that are potentially allergenic.	Containment devices for all quantities including vented balance enclosures for milligram quantities. Vent containment devices into exhaust system following HEPA filtration. Glove box may be required depending on quantity, bulk density and special hazards, such as potential for allergy.

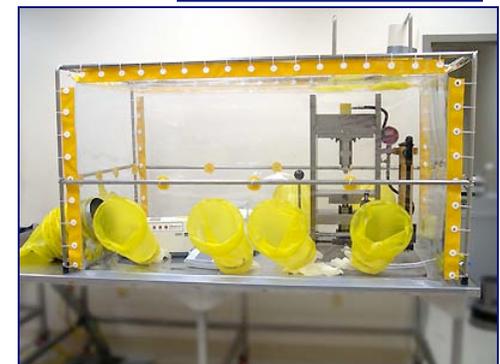
Controls for Lab-Scale Work with Powders



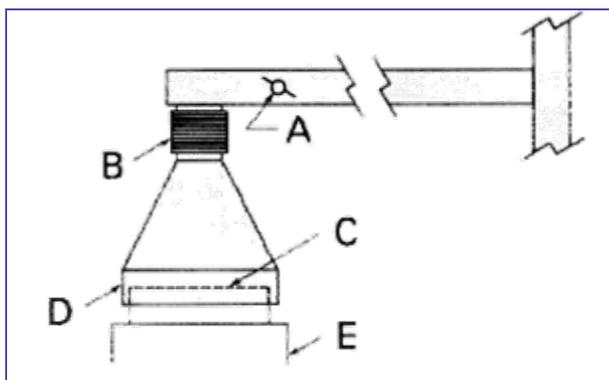
Effective controls that factor budget and space limitations are available

Select controls based on task-based exposure risks

- Physical form
- Task
- Task duration



Details



Flow Sciences Vented Balance
Safety Enclosure

Reported Surrogate Control Performance

- 500 mg quantities: $< 5 \mu\text{g}/\text{m}^3$
- 100 gm quantities: $< 10 \mu\text{g}/\text{m}^3$
- Installation location critical; no cross drafts
- Thimble connection essential to maintain optimal face velocity
- Minimize movement outside of enclosure
- Slow, deliberate hand movements inside
- Clean all objects before removing them
- Limit size of the source container
- Contaminated gloves/sleeves significant source of surface contamination

Details



Labconco XPert Balance Enclosure

ANSI/ASHRAE 110 and Surrogate Studies

- Tracer gas acceptable at 60 fpm
- Dry ice escape at less than 50 fpm
- 20 x 1 gram surrogate sampling indicates exposure control to $< 1 \mu\text{g}/\text{m}^3$
- Technician skill and work organization influenced sampling results

Scale-Up into Kilo Lab/Pilot Plant

- Health Hazard Band established
- Equipment/lab designs control to midpoint-low end of the health hazard band
 - OELs not yet established
 - Typically IH analytical methods not yet developed
 - Containment verified with surrogates
 - Riboflavin, acetaminophen, naproxen sodium, lactose are examples
- Redundant PPE advisable
- Personal hygiene required
- Health surveillance if there is a relevant endpoint

Chemical Kilo Lab Controls for Health Hazard Bands 2 and 3



Containment for Health Hazard Bands 2 and 3



Occupational Exposure Limits (OELs)

OEL: Airborne concentrations which will not result in adverse effects in most healthy workers (8 hr/day, 40 hours/week)

Data: Human Clinical Trials (Phase II and III)

$$\text{OEL (8 hr-TWA)} = \frac{\text{NOEL or LOEL (mg/kg/day)} \times \text{BW(kg)}}{\text{V(m}^3\text{/day)} \times \text{S(days)} \times \text{UF} \times \alpha}$$

NOEL: No-Observed-Effect-Level

LOEL: Lowest-Observed-Effect-Level

BW: Average human body weight (50 - 70 kg)

V: Volume of air breathed in an 8-hour workday (10 m³)

S: Pharmacokinetics (half-life and accumulation)

UF: **Uncertainty Factors**

α: Used to adjust the absorption of a compound via inhalation



Control Selection

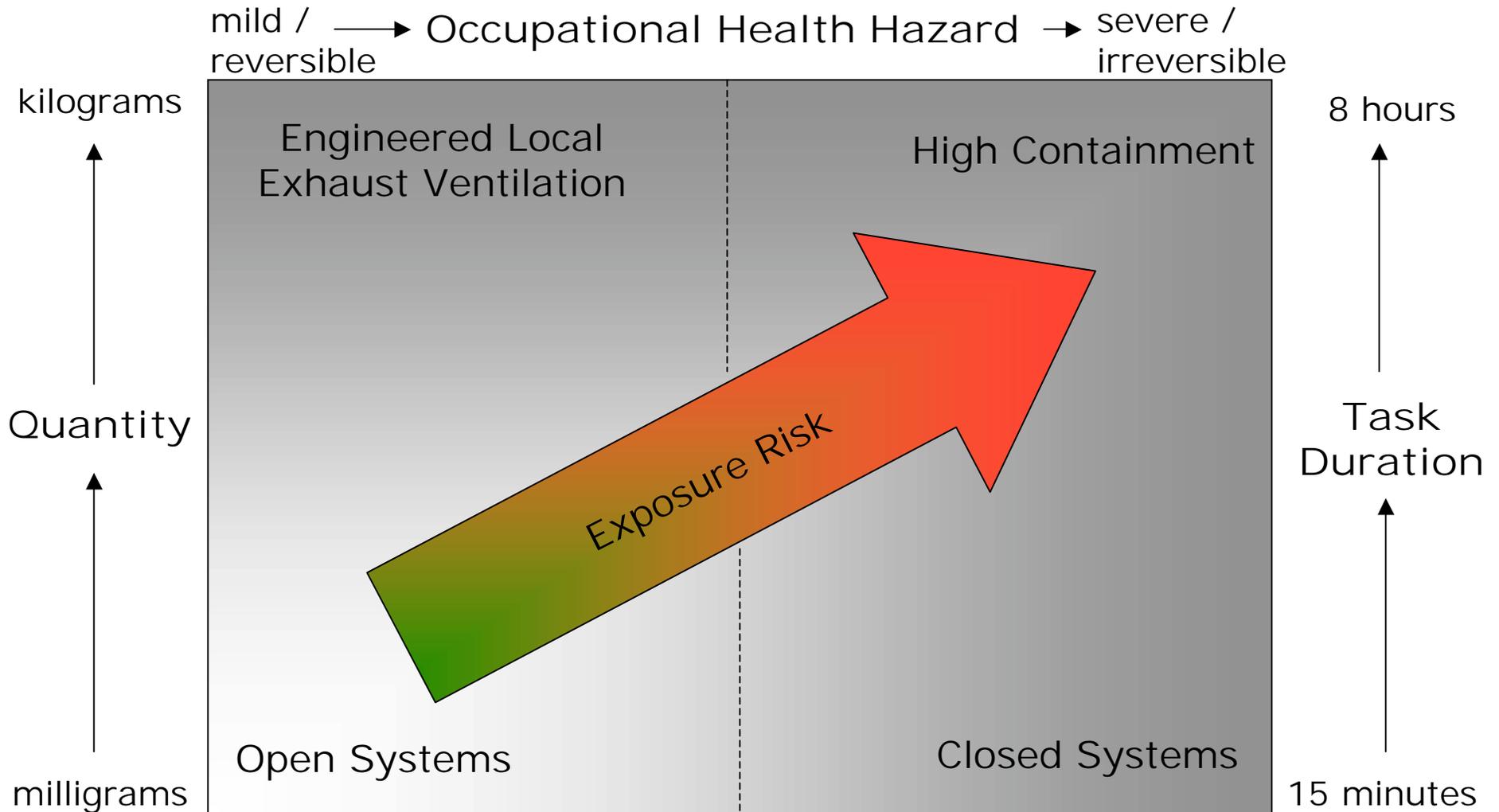
Assess Exposure Risks

- ***Dustiness***
 - Classify material as solid, suspension, granular/ agglomerated, normal powder, or highly disperse
- ***Process***
 - Determine potential for particle release due to equipment, level of containment, process energy and degree of manual handling
- ***Quantity***
 - < 100 mg
 - 100 mg – 1 kg
 - > 1 kg
- ***Task Frequency and Duration***
 - Consider task duration and frequency as well as potential for acute toxicity

Determine Appropriate Control Band



Factors Influencing Control Selection



slurry/suspension → agglomerated → highly disperse
Physical Form



Control Performance Examples*

Control Technology

Anticipated Performance

Examples

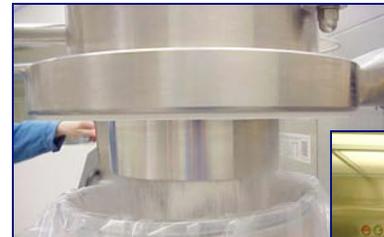
- Open handling with engineered local exhaust ventilation
- Directional laminar flow with LEV and Vacuum conveying
- Closed systems
- High-containment

< 1000 $\mu\text{g}/\text{m}^3$

10 $\mu\text{g}/\text{m}^3$ –
1000 $\mu\text{g}/\text{m}^3$

1- 10 $\mu\text{g}/\text{m}^3$

< 1 $\mu\text{g}/\text{m}^3$



**For handling bulk fine powders. Base control selection on factors that influence exposure risk*

Facility Design Considerations

- Receipt, storage, transfer and shipping of materials
- Select room finishes to support cleaning
- Donning/doffing of protective clothing and equipment
- Street clothing vs. work uniforms
 - Personal change rooms and showers
- Break rooms / cafeterias
- Migration to other areas from people, tools, papers and equipment
- Equipment wash room design
 - Cleaning or pre-washing equipment in place
 - Assess risk of equipment transfer to washrooms
- Design for “maintainability”
 - Filter changes, equipment maintenance, etc.



General Ventilation Considerations

- General ventilation
 - Recirculation vs. single-pass
 - Filtration efficiency
 - Control of dust migration
 - Area pressurization and/or directional air flow
 - Re-circulation of general ventilation to other areas
- Dust collection
 - Explosion venting, suppression or containment
 - Filter changes, emptying dust collectors

Other Considerations for Controlling Exposures

Consider:

- Handling materials as slurries or suspensions
- When possible, wet materials after weighing, before removing from hood or containment system
- Using closed systems for loading and unloading materials from process equipment
- Placing lab scale equipment into ventilated enclosures
- Covering street clothing or changing into work uniforms
- Using redundant PPE

Control Verification

- Develop IH sampling and analytical method(s) at time of OEL or identify appropriate surrogate
- For new processes/installations, verify containment targets during FAT and operational qualification
- Sample exposures during process validation

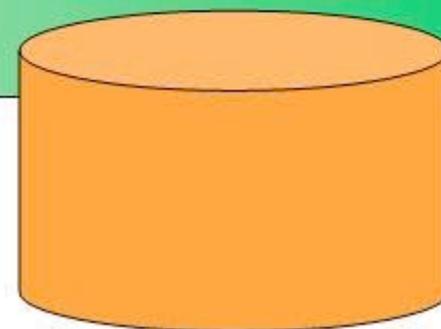
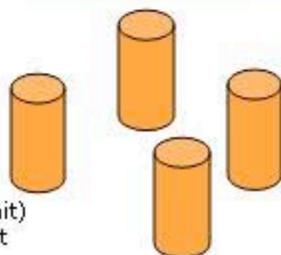
Support Programs

- Ongoing verification of containment integrity
- Management of change
- Specific SOPs and employee training
- Health surveillance



EHS Activities to Support Drug Development Process

Phase 0	Phase I (safety/tolerance)	Phase IIA/B (efficacy/clinical dose/repeat-dose)	Phase III	File NDA Approval	Launch Phase IV
	Clinical Trials				
Years	6 months- 2/3 years			Years	
Drug Discovery	Drug Evaluation			Drug Development	
Lab scale synthesis Literature review <i>In vitro</i> screening	Preclinical Prep-lab scale Safety/TK/tolerance/ADME		Pilot scale	Full scale synthesis and product mfg.	
	Chemistry/Toxicology				
Default HHB "3" for NCEs (except for special therapeutic classes—default is "4") Thermal stability	API HHB & SDSs OT testing of NCEs Physical properties	OT Testing of IPIs Compound Interactions Fire and Explosion Dust Explosivity Ecotoxicity Fate & Effects and PNEC	API OEL, ASL, and IH method API SDSs updated	IPI PBOELs & SDSs Finished product SDSs	
	Environmental, Health & Safety				



OEL- Occupational Exposure Limit
 HHB: Health Hazard Band
 ASL- Accepted surface limit (wipe limit)
 API- Active pharmaceutical ingredient
 IPI- Isolated Process intermediates
 SDS- Safety Data Sheets

Applicability to Engineered Nanoparticles

- Health Hazard Banding, in lieu of OELs, may be appropriate
 - “Default” HHB
- Control selection, based on Pharma’s experience with micronized powders
- Methods to reduce exposure risk
- Methods to verify containment integrity