What Does It Take to Manufacture Potent Compounds?

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SafeBridge Consultants, Inc.

- Group of Environmental, health and safety professionals with expertise in:
  - Toxicology
  - Health and safety
  - Industrial hygiene
  - Analytical chemistry
  - Occupational medicine
  - Product safety and risk assessment
  - Developing programs to recognise, evaluate and control occupational exposures to potent pharmaceuticals
- Expertise is in pharmaceutical safety and health consulting
- Offices in SF Bay Area, New York City, Pennsylvania & Europe; also staff located in Toronto, Canada and Raleigh, NC

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What Does It Take to Manufacture Potent Compounds?

Common Questions from:

- Contract Manufacturing Organization (CMO)
- Contract Research Organization (CRO)
- Analytical Laboratories

Manufacturing and R&D:

- API Manufacturing (Chemical Synthesis)
- Pharmaceutical Oral Solid Dosage (tablets and capsules)
- Sterile Injectables
- Creams, Gels, Patches

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What Does It Take to Manufacture Potent Compounds?

Common Questions to SafeBridge:

- Do I have the right facility?
- Do I have the right controls?
- Can I just put my employees in airline respirators?
- I want to manufacture Category or Band 4 Material – can I do this in my facility?
- How do I make ADC's safely?

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First….. Potent Compound Definition

- An API or pharmacologically active intermediate with a therapeutic dose at or below 10 milligrams;
- An API or pharmacologically active intermediate with an OHC of 3 or 4 (see Attachment 1);
- An API or pharmacologically active intermediate with an Occupational Exposure Limit (OEL) at or below 10 micrograms per cubic meter of air as an 8-hour TWA;
- An API or pharmacologically active intermediate with high selectivity (i.e., ability to bind to specific receptors or inhibit specific enzymes) and/or with the potential to cause cancer, mutations, developmental effects or reproductive toxicity at low doses; or
- A novel compound of unknown potency and toxicity

Note that ALL Pharmaceutical Compounds need to be handled with proper controls and procedures – even "non-potent" compounds have health effects.

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Answer…..

A Comprehensive Program is required to safely handle potent compounds.

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Systematic and Scientific Approach Used

- **Recognize the Hazard**
  - Occupational Health Categorization (OHC)
  - Occupational Exposure Limit (OEL)
- **Evaluate and Control the Risk**
  - Use advanced engineering controls due to unique toxicity and potency
  - Select/Design Controls appropriate for risk
  - Develop Procedures
- **Verify the Controls through Measurement**
  - i.e. Surrogate Monitoring
- **Industrial Hygiene Monitoring - API**
  - Develop Quantitative Tools to Measure Worker Exposure
- **Other Program Elements**
  - Medical Surveillance/Reproductive Health, Cleaning and Maintenance, Waste Handling and Disposal, Training

Apply similar approaches to Quality endpoints to prevent cross-contamination

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Recognize the Hazard

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Occupational Health Categorization (OHCs) and Handling Practice System

- Systematically addresses exposure situations where traditional tools (OELs, monitoring methods) are unavailable
- Created by Pharmaceutical Safety Group (PSG) subgroup on potent compound handling
- Used to communicate risks and to establish consistent control approaches within an organization

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Toxicity/Potency Categorization of Chemicals (SafeBridge System)

- Category 1: Low Toxicity
  OEL >0.5 mg/m^3 (aspirin)
- Category 2: Intermediate Toxicity
  OEL 10 µg/m^3 - 0.5 mg/m^3 (insulin, oxycodone)
- Category 3: Potent (default)
  OEL 30 ng/m^3 - 10 µg/m^3 (estradiol 17-β, paclitaxel, fentanyl)
- Category 4: Highly potent
  OEL ≤ 30 ng/m^3 (nafarelin, leuprolide, sufentanil)

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OHC – Important Aspects

- **Understand the Banding / Categorization System Used**
- If Customer says “This is a band or Category 3” don’t assume you know what that means. Ask questions, get the baseline information used to make the decision. Make your own judgments and decisions.
- Develop System for your organization with defined Criteria for setting the categories.
- Use an experienced Occupational Toxicologist to set the bands or categories.
- Want to get band “just right”. Not too conservative to limit manufacturing flexibility but still be protective of worker safety.

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Categories and Control

- Category MUST be tied or linked to controls
- Categories should be differentiated by different controls
- Control should be verified by industrial hygiene monitoring (which means that OELs need to be established, not just categories or bands)

- (more on this later……)

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Occupational Exposure Limits (OELs)

- An acceptable level for a 40-hour work week or short term exposure; similar to UK WEL, OSHA PEL or ACGIH TLV
- OEL is sometimes developed to protect even sensitive subgroups, e.g., women of child bearing capacity
- Developed when a drug reaches significant manufacturing amounts or critical FDA stage (Phase II b or later)
- Simultaneous development of sensitive analytical method for occupational hygiene monitoring

Traditional Formula for Establishing OELs Using Uncertainty Factors

$$OEL = \frac{NOEL \times BW}{UF_{1,2,\ldots} \times PK \times BR}$$

where:

NOEL = No Observed Effect Level
BW = Body Weight
$UF_{1,2,\ldots}$ = Uncertainty Factors
PK = Adjustment for pharmacokinetics
BR= Breathing Rate in an 8-hour day (10 m^3)

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Examples of Pharmaceutical OELs

Drug/Material	OEL
Naproxen (NSAID)	5,000 μg/m^3
Nicardipine (cardiac drug)	400 μg/m^3
Isotretinoin (Accutane for acne)	5 μg/m^3
Paclitaxel (anti-cancer)	0.8 – 10 μg/m^3
mAbs	1 - >100 μg/m^3
Fentanyl (synthetic opioid)	0.7 μg/m^3
Thalidomide	0.25 μg/m^3
17β estradiol (natural estrogen)	0.1 μg/m^3
Ethinyl estradiol (synthetic estrogen)	0.035 μg/m^3
Camptothecin (anti-cancer)	0.03 μg/m^3
Nafarelin (peptide hormone)	0.001 μg/m^3

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What is a Permitted or Acceptable Daily Exposure (PDE/ADE)?

- The 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. (ISPE Risk-MaPP Baseline Guide)

- EMA "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities" –uses the term PDE – Permitted Daily Exposure, a term also used in ICH Q3C Residual Solvents and Q3D Elemental Impurities guidelines

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Establishing a Permitted or Acceptable Daily Exposure Level (PDE/ADE) for a Potent Pharmaceutical

$$\text{PDE/ADE (mg/day)} = \frac{\text{(NOAEL) x (BW)}}{\text{(UFc) x MF x PK}}$$

where:

NOAEL = no-observed-adverse-effect level (mg/kg)
BW = body weight (kg)
UFc = uncertainty factor (composite) (ADE) or $F_{1\text{-}5}$ (PDE)
MF = Modifying factor (e.g., quality of data base)
PK = Pharmacokinetic adjustment (bioavailability by particular route of interest)

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Evaluate and Control the Risk

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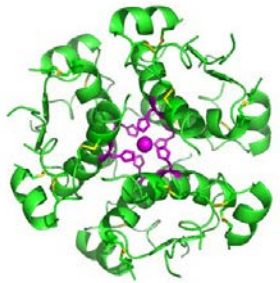
Routes of Occupational Exposure

1. Inhalation
2. Dermal Absorption (ASLs)
3. Ingestion
4. Inadvertent Contact with Skin & Mucous Membranes

Exposure Pathways
Source – Pathway – Target



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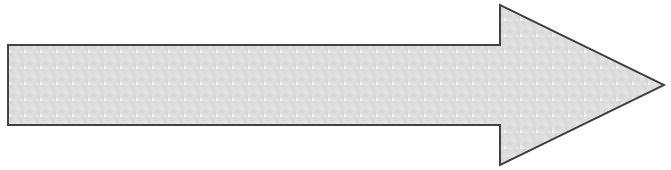
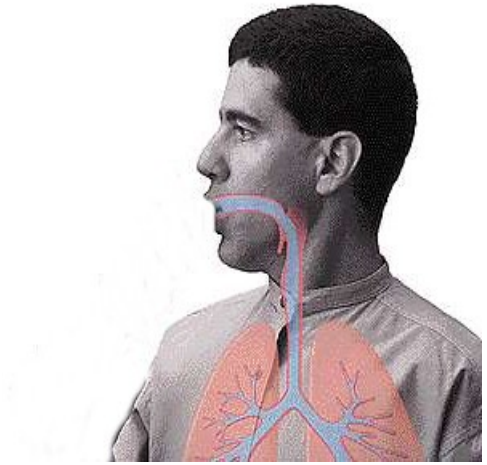
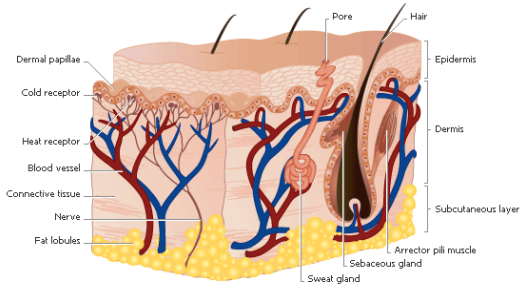


Pathway





Target

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Risks - Factors Leading to Significant Exposures

- Physical form of the material
- Labor intensive steps
  - manual transfer of materials
  - weighing active materials
- High energy operations
  - milling, sizing, fluidising, spraying
  - over-pressurisation
- Poor work practices
  - carelessness or lack of awareness
- Cleaning and maintenance operations

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Controls – Link to Hazard (OHC / OEL)

- Facility Design
- Ventilation
- Gowning/Degowning

- Engineering Controls
  - Controls – Hoods
  - Containment – Enclosed process, Isolators

- Work Practices

- Gowning / PPE

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Designing the Appropriate Facility and Controls

- Design to meet both Quality and H&S objectives
- Are dedicated or segregated facilities really needed?
- Define material and people transport routes
- Barrier containment can protect the product, the worker and prevent facility contamination
- Dedicated equipment, rigid walled containment and flexible containment

Hierarchy of Controls

- Engineering controls (“hardware”)
- Procedures / Administrative controls (“software”)
- Personal Protective Equipment (PPE)

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Facility Infrastructure Elements

- Decide and agree on a Containment Performance Target (CPT)
- Negative differential air pressure in processing rooms relative to surrounding areas.
- Room air locks/anterooms are recommended
  - Provide an air pressurisation barrier
  - Serve as a gown/degown area
- Recirculation of air into non-production areas is not permitted
- HEPA filtered room air exhaust should not be recirculated

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Facility Infrastructure Elements (continued)

- Designated areas should be posted with appropriate notification and hazard warning
  - Controlled access to the work area is required.
- Segregate personnel and material/equipment flows
- Locker rooms and showers contiguous with processing/work areas are recommended for manufacturing suites.
- Air showers are not recommended
- Mist/water showers are preferred and recommended.

Controlling the Hazard

- Know the hazard and decide on a Containment Performance Target (CPT)
- Identify potential exposure points
- Identify exposure risk factors
  - Quantities
  - Physical Form
  - Frequency
  - Operational matters (mass transport drivers)
- Select containment for higher risk, higher hazard activities
- Select other types of control for lower risk activities
- Verify that control or containment is effective

Advanced Engineering Control Approaches

- Process containment
  - barriers/isolators (equipped with RTPs)
  - bag techniques (bag w/in a bag)
- Closed transfer systems
  - vertical process trains
  - intermediate bulk containers (IBCs)
    - specialised connectors and valves (SBVs)
- Ventilated enclosures
  - powders weighing hoods
  - enclosures for subdividing, filling, sizing

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Isolators

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Flexible Control and Containment

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Ventilated Balance Safety Enclosure®

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Personal Protective Equipment

- Powered air purifying respirators (PAPRs)
  - With combination cartridges
  - Hood covering
- Skin protection
  - Tyvek® coveralls and sleeve covers
  - Booties
  - Double gloves

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Proper Procedures for Use of Controls and Containment

- Movement of material into and out of the control / containment
- Cleaning of work surfaces
- Proper use of controls
- Use of control for purposes designed

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Verify the Controls through Measurement

Control/Containment Verification

- Surrogate Monitoring
- Factory Acceptance Testing
- Site Acceptance Testing
- Statistical Analysis
- Comparison to Control/Containment Performance Target (CPT)

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Industrial Hygiene Monitoring - API

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Health and Safety Industrial Hygiene Exposure Evaluation

- Requires sensitive air sampling analytical methodology
  - RIA, ELISA, HRGCMS
  - goal is to detect 10% of OEL in 15 minute sample
- Task oriented monitoring
  - identify worst case and representative cases
  - careful observation of controls and work practices
- Data analysis
  - calculate and compare to OEL or CPT
- Report and Recommendations
- Periodic reassessment

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Other Program Elements

- Medical Surveillance/Reproductive Health
- Cleaning and Maintenance
- Waste Handling and Disposal
- Training

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To Review……

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A Systematic Approach to Handling Potent Compounds Safely - A bit more detail….

- Identify compound hazards
  - Develop OHCs (for early stage compounds) and OELs, PDEs/ADEs for later stage compounds.
- Decide on CPTs
- Institute control/containment measures based on category/experience and DATA
- Develop written SOPs
- Train employees
- Develop air and surface monitoring methods to verify control measures and work practices and to test surface levels for Quality

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A Systematic Approach to Handling Potent Compounds Safely (continued)

- Verify process through:
  - Periodic assessment
  - Air and surface monitoring and control implementation
  - Maintenance and testing of controls
- Health surveillance
- Consider third party certifications

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