A Long History of Developing Hazardous Chemistries has Resulted in High Containment Capabilities

Occupational Health Categorization and Handling Practice Systems

- AFC’s management of highly potent and potent compounds is effective in managing liability and productivity, remaining sensitive to people, ethics and compliance
- Systematic approach to classifying compounds and exposure situations when traditional tools (i.e., OELS, monitoring methods) are available
- Used to communicate risks and to establish consistent controls within the organization
- AFC has a Potent Compound Handling Program to ensure consistent handling
- AFC owns several isolated and independent facilities for highly potent compounds
- Potent compounds are safely handled at AFC via three broad areas of control:
  - Process design to minimize powder handling
  - Isolation of powders in properly designed facilities
  - Strict administrative controls and procedures

AFC uses 5 categories commonly used in the Pharmaceutical Industry

- **Category 1:** Low toxicity
  - OEL > 1,000 µg/m³
- **Category 2:** Intermediate Potency
  - OEL 100 µg/m³ to 1,000 µg/m³
- **Category 3:** Highly Potent
  - OEL 5 to 100 µg/m³
- **Category 4:** Very Highly potent
  - OEL 0.5 to 5 µg/m³
- **Category 5:** Extremely potent
  - OEL < 0.5 µg/m³

Compounds in Categories 3, 4, and 5 are considered “Highly Potent” They can include cytotoxic, carcinogenic, mutagenic, and teratogenic compounds

AFC Approaches HPAPI Manufacturing with 3 levels of Controls in Multiple Facilities

**Level 1: Process Design**

- Overall goal to avoid exposure of product to FOD and to avoid exposure of room and personnel to product
- Minimize isolation and handling dry powders through process optimization wherever possible
  - Telescope steps
  - Keep in solution – Avoid isolation
  - Filter but do not dry or package intermediates
- Maximize batch sizes within cGMP
  - Size equipment appropriately
  - Multiple size equipment available

**Level 2: Engineering**

- Advanced Engineering Controls to Minimize Exposures
  - Process containment (barriers, isolation, etc.)
    - Closed Filter/dryer units
    - Reactor Charging Devices to eliminate open charge
    - Dryer/centrifuges discharge dust control devices
    - Closed mills (air locked feed and ventilated discharge)
    - Glove Boxes, cabinets
  - Closed transfer systems
  - Ventilated enclosures
  - Continuous liners for packaging from centrifuges and dryers

**Level 3: Procedures**

- Detailed Specialized Operating Instructions (MBR)
- Appropriate Hazard Communications
  - Process Training and Exhaustive PHA’s
  - SDS + safety summaries
- Appropriate IH Monitoring to Verify Level of Containment
- Enhanced Medical Surveillance
- Proper Personal Protective Equipment
  - Protects against equipment or procedure failure

AFC Equipment – Offers an Enabling Range of Capabilities

- AFC can handle a Broad Spectrum of HPAPIs
- Closed & Protected Charging/Discharging
  - Dedicated facility for the preparation of HPAPI samples
  - Scales within glove boxes for sample weight and dilution
  - Room dedicated for analytical sample preparation only
  - HEPA filters
  - Air lock for gowning/de-gowning
  - Sample pass-through
  - Separate disposable chutes for solids and liquids within each hood
  - Negative differential air pressure in processing rooms relative to surrounding areas

- Unique QC Analytical Capability
  - HEPA Filtered, fully Contained Milling Suite

- Unique HPAPI Milling Capabilities