High Containment Manufacturing Capabilities for Highly Potent APIs

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 mg/m³**
▪ **Category 2:**	**Intermediate Potency**	**OEL 100 µg/m³ to 1,000 mg/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

Glove Boxes, enclosures/cabinets

Dryer/centrifuges discharge using dust control devices

Split Butterfly Charging Devices eliminate opening the manway

- ❑ Facility Design Elements
  - Negative differential air pressure in processing rooms relative to surrounding areas
  - Air locks/ante rooms provide air pressurization and serve as gowning/de-gowning area
  - Single pass HEPA-filtered room air
  - Controlled access to potent manufacturing areas
  - Products manufactured in stages in different facilities depending on potency of compound
  - Manufacturing of potent compounds requires adequate toxicity data and desensitization techniques

cGMP Facilities

Building 05017
– 0.2 µg/m³
- 50 to 200 gal G/L reactors
- Hydrogenation

Building 05046
– 0.2 µg/m³
- 50 to 200 gal G/L reactors
- Filter Dryer

Building 05111
– 0.2 µg/m³
- 50 liter - 20 gal G/L reactors
- SMB unit (75 mm)
- Filter Dryer
- HPAPI Milling

Building S3-Bay 31
(Virginia) – 0.2 µg/m³
- 25 to 100 gal G/L & Hastelloy™ reactors
- Filter Dryer

Building S3-Labs
(Virginia) - 5 ng/m³
- 100 L Glass reactor
- 100 L Hastelloy™ reactor
- Lab Scale equipment

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

Category	Characteristics	Examples (OEL mcg/m³)	Location
1	Relatively non-toxic or slightly toxic materials producing few systemic effects. Clinical doses above 500 mg/day. **OEL: above 1000 mcg/m³** LD_{50}: Greater Than 5000 mg/kg	ACC-322 ACC-211	**Plant 1** **CS Area** **AFC-TX** **AFC-VA**
2	Low Pharmaceutical potency producing very mild systemic toxicity, including mild sensitization reactions. Clinical doses of 20 - 500 mg/day. **OEL: 100 - 1000 mcg/m³** LD_{50}: 500 - 5000 mg/kg	ACC-242 (100) ACC-311 (100) ACC-289 (200) ACC-282	**Plant 1** **CS Area** **AFC-TX** **AFC-VA**
3	Default category for unknown toxicity materials. Effects of overexposure are not life threatening or incapacitating. Short term effects are reversible, and sensitization can be strong. Clinical doses of 5 - 20 mg/day. **OEL: 5 - 100 mcg/m³** LD_{50}: 50 - 500 mg/kg	ACC-234.2 (20) ACC-234.3 (120) ACC-234.4 (15) ACC-234.6 (9)	**CS Area** **05-148** **05017** **05046** **05111** **Lab F** **AFC-VA**
4	Overexposure can be life threatening. Symptoms may be incapacitating and may not be reversible. Medical attention is immediately mandated. This category includes powerful antineoplastic agents, nitrogen mustards, cytotoxins, mutagens, etc. **OEL: 0.5 - 5 mcg/m³** LD_{50}: 1 - 50 mg/kg	ACC-385 (1) ACC-384 (1) ACC-231 (0.6) ACC-017 (LD_{50} = 20mg/kg) ACC-185 (0.6) ACC-356	**05-01M/H** **05-146** **05017** **05046** **05111** **Lab F** **AFC-VA**
5	Permanent irreversible injury or death from single exposure. Heroic medical intervention may be ineffective. **OEL below 0.5 mcg/m3** LD50 below 1 mg/kg	AFC currently has no material in this category but have handled in the past and are being considered for immediate future.	**05017** **05046** **05111** **Lab F** **AFC-VA** **(Potential modification)**

Closed & Protected Charging/Discharging

Charging with double butterfly valves

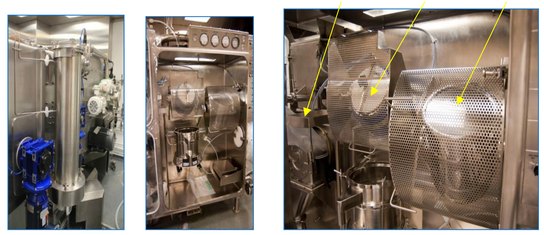
Enclosed discharge of product

Unique QC Analytical Capability

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 HPAPI Milling Capabilities



HEPA Filtered, fully Contained Milling Suite