



## Highly Potent Technical Transfer and Commercial Manufacturing – *Alkermes' successful approach to commercial-scale final dosage manufacture of drug product containing highly potent API*

With over 40 years in the service business, Alkermes Contract Pharma Services, as part of Alkermes plc, has proven expertise in drug product development, process design / improvements, technical transfer and commercial scale cGMP manufacturing of oral and injectable dosage forms, including the handling of highly potent drug substances.

This case study demonstrates how a commercial manufacturing partnership between Alkermes Contract Pharma Services (Alkermes) and a large pharmaceutical company resulted in the establishment of a high volume process for Highly Potent (HP) Active Pharmaceutical Ingredients (APIs).

### Project History

- Donor site capacity issue where the company was seeking an outsourcing manufacturing partner for commercial supply
- Product was classed as a highly potent compound and had an Occupational Exposure Limit (OEL) of 0.5 µg/m<sup>3</sup>, an Adverse Drug Event (ADE) level of 5µg/day and exhibited teratogenic and exotoxic properties
- The product had a low Minimum Ignition Energy (MIE) of <3mJ
- Manufacturing required contained dispensing, high shear granulation with microwave drying, blending, compression and coating processes.

### Why the Alkermes Athlone Site

Located on a 40-acre site, with over 220,000 sq ft of dedicated cGMP grade facilities, this FDA/EMA inspected site had a proven manufacturing track-record with many products optimized and manufactured for partners for multiple territories. The facility had previous recent experience with the development, scale-up commercial manufacture of a highly potent product.

### The Challenge

The manufacture of a Highly Potent Active Pharmaceutical Ingredient (HPAPI) compound can present many challenges due to the complex handling required for toxic substances. The successful and safe manufacture of HPAPIs require the availability of a highly skilled team of staff with the right experience, the proper evaluation and training procedures being in place and the use of state-of-the-art facilities.

When taking on a HPAPI for final stage manufacture, it was important to follow a systematic approach to handle potent drugs safely.

Other essential elements included the following: defined standard operating procedures, developing and managing a staff training program, using tools to

evaluate and measure exposure, designing and developing containment and controls, developing systems to verify effectiveness and finally determining and assessing the environmental impact of the active substance and associated manufacturing.

Ensuring these steps were in place was particularly important due to the fact that the Alkermes Athlone site is a multi-product facility. Concern relating to cross-contamination with other products being manufactured had to be considered.

The following steps were undertaken to ensure containment procedures were in place to manage the safe manufacture of the HPAPI product:

- Determination of OELs and compound categorization scheme
- Industrial Hygiene (IH) exposure assessment, control verification and sensitive IH analytical methods
- Engineering controls and maintenance
- General and specific handling guidance
- Procedures and training
- Medical surveillance.

### The Result

The HPAPI product has been successfully tech-transferred onto the Alkermes Athlone, Ireland site. From our involvement with this project, a number of significant milestones were realized. These included:

- Execution of a robust containment strategy:
  - Primary: high containment primary processing areas, high containment transfers and sampling areas were built (or established)
  - Secondary: segregated processing rooms were built
  - Tertiary: dedicated, segregated suite, security access controlled, Closed Circuit Television (CCTV) remote monitoring, Heating Ventilation and Air Conditioning (HVAC) single pass air (safe change in room), double HEPA exhaust, pressure cascade and fogging shower were all put in place.

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Double chamber isolator and API charge hopper at Alkermes facility



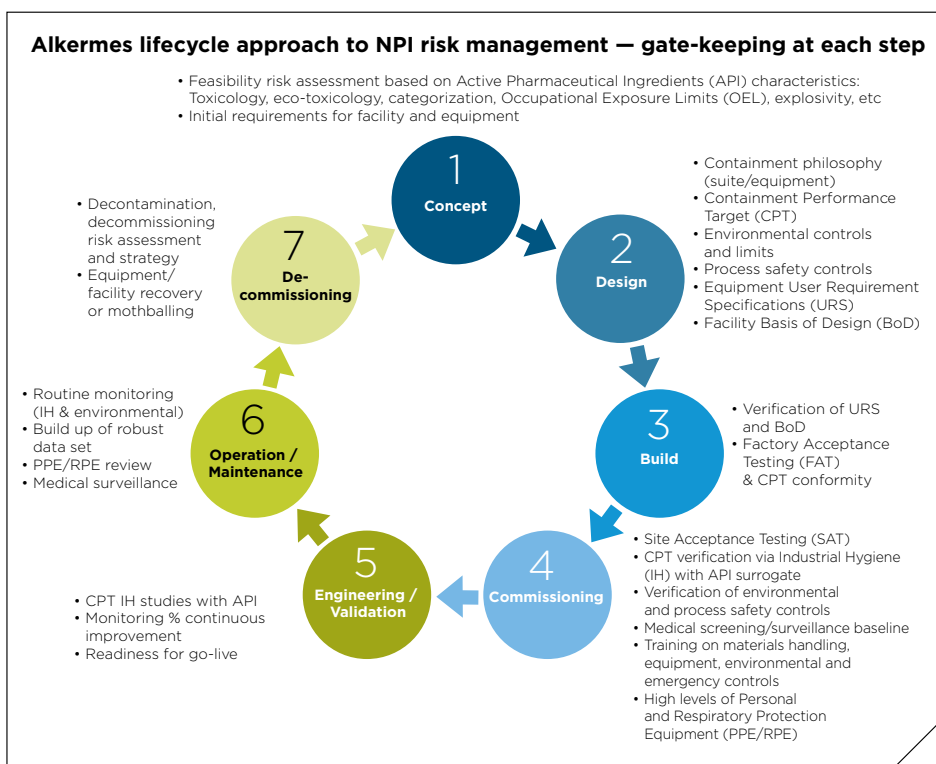
Tablet press and ancillary equipment in one of the dedicated HP suites

- Organization of contained and dedicated waste water facilities
- Bringing on-site Personal Protection Equipment (PPE) and Respiratory Protection Equipment (RPE) suitable for the HPAPI handling
- Establishment of segregated, high containment dust extraction systems
- Undertaking of extensive training & competence development for all staff involved in the manufacture and handling of the highly potent product
- Establishment of medical surveillance, proactive IH & environmental monitoring
- Enforcement of an integrated life-cycle risk management approach using a New Product Introduction (NPI) model (Figure 1).

The use of the NPI approach allowed for a robust approach to be followed when bringing HPAPIs onto the site and proved effective in implementing technical transfers and commercial manufacture of all products including highly potent compounds for partners.

As a result of this partnership, the Alkermes Athlone site now has the capability to handle APIs to OEL of 0.1 µg/m<sup>3</sup> at development (Discovery to Phase III) and commercial high-volume scale.

Alkermes now successfully handles two commercially available highly potent compounds at its multi-product facility in Athlone for its partners.



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**Figure 1.** Integrated life-cycle risk management template for New Product Introduction (NPI) on-site