



Contract Pharma Services

High Potency Product Manufacturing

Key selection criteria when evaluating an outsourcing partner

Summary

Approximately 25% of drugs in development worldwide are classified as highly potent, with this percentage expected to grow over the coming years. A compound is generally classed as highly potent if it has an occupational exposure limit (OEL) of $\leq 10\mu\text{g}/\text{m}^3$, a daily therapeutic dose of $\leq 10\text{mg}/\text{day}$ or if a $1\text{ mg}/\text{kg}/\text{day}$ dose produces serious toxicity in laboratory animals. While such highly potent compounds can have significant benefits in the treatment of certain medical conditions, they present substantial challenges to the pharmaceutical industry.

These challenges include: can personnel and the environment involved in the manufacture of high potency products be protected; can adequacy of controls preventing contamination of other products by high potent materials be demonstrated; and can expectations of clients and/or regulators regarding separation or segregation of manufacturing activities be satisfied?

Many companies are choosing to outsource the manufacture of their highly potent compounds for strategic and/or economic reasons. A provider of contract pharma services in high potent manufacturing, Alkermes Contract Pharma Services, outlines here some of the elements that should be considered by a Sponsor/Donor Pharmaceutical company when outsourcing secondary processing (i.e. dosage form transfer, scale-up and commercial manufacture) of a highly potent product.

1. Market Opportunity for Highly Potent Active Pharmaceutical Ingredients

Approximately 25% of drugs currently in development worldwide are classified as highly potent (HP) with forecasts suggesting that their increasing therapeutic use is expected to drive the global market for HP Active Pharmaceutical Ingredients (HPAPIs) by an estimated compound annual growth rate of 9.9% from 2012 to 2018¹. While the majority of HP drugs are anti-cancer compounds (the oncology sector alone is expected to increase in value from \$64bn in 2011 to \$104bn in 2018²), other HP products include therapeutics such as hormones, narcotics and retinoids.

¹ High Potency Active Pharmaceutical Ingredients (HPAPIs) Market - Global Industry Analysis, Size, Growth, Share And Forecast 2012 – 2018, Transparency Market Research, Nov 2012

² High Potency API Roundtable, Pharmaceutical Outsourcing, July 23, 2012

<http://www.pharmoutsourcing.com/Featured-Articles/117704-High-Potency-API-Roundtable/>

2. Definition of HPAPIs

The definition³ of a HPAPI varies depending on the literature, but generally is defined as:

- A pharmacologically-active ingredient or intermediate with biological activity at approximately 150 µg/kg of body weight or below in humans (therapeutic daily dose at or below 10 mg)
- An API or intermediate with an occupational exposure limit (OEL) at or below 10 µg/m³ of air as an 8-hour time-weighted average
- A pharmacologically-active ingredient or 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 defects or reproductive toxicity at low doses
- A novel compound of unknown potency and toxicity.

3. Cross-Contamination: Partner Expectation and Regulatory Position

Before progressing to define required levels of separation or segregation, anyone involved in the manufacture of HP materials must first address the issue of API classification since regulatory guidelines and regulations throughout the world can be inconsistent and often vague.

The International Society of Pharmaceutical Engineering (ISPE) sought in RiskMaPP^{®4} to engage with regulators and build an approach that would address the impreciseness of the classification approach and replace it with a clearly defined characteristic of active pharmaceutical materials, with the concept being that all manufacturers would demonstrate the adequacy of their controls (used to prevent cross-contamination) referencing the chosen characteristic. Risk-MaPP is defined as providing a scientific risk-based approach, based on ICH Q9 Quality Risk Management, to manage the risk of cross contamination in order to achieve and maintain an appropriate balance between product quality and operator safety. Specifically, the ISPE guideline proposes the use of health-based Acceptable Daily Exposure (ADE) values rather than a tag such as “hormone”, “steroid” or “cytotoxic” (with the exception of cephalosporins, which were specifically omitted from the guide). These values would then be used to assess the risk of cross-contamination

³ ISPE Baseline[®] Guide: Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP)
<http://www.ispe.org/baseline-guides/risk-mapp>

⁴ RiskMaPP definition and resources <https://www.ispe.org/risk-mapp-resources>

and ultimately determine the level of controls to be applied along with any facility design and building requirements. Many of what are described as “tagged products” will have very low ADEs and as a result, any true assessment of their potential risk will place a significant burden on the manufacturer to demonstrate containment and separation.

Alkermes presented at the launch event for the ISPE RiskMaPP⁵ guide in Europe and the U.S., and in their development of an approach to identify and manage cross-contamination risk, worked very closely with PharmaConsult US (who were very heavily involved in the generation of the RiskMaPP guide). As a company, we have incorporated RiskMaPP into how we manage and assess the risk of cross-contamination across all the products we manufacture, including those with very low ADEs ($\mu\text{g/day}$). However, while the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) and others have endorsed risk-based assessments in this area, not all regulators or indeed inspectors share the same view at this point. Many companies consider that hormones, steroids, oral contraceptives and products with similar characteristics should only be handled in a physically separate building or suite.

4. Key Considerations in Selecting a Contract Manufacturer

Compound Categorization at Alkermes is the first step taken to allow suitable controls for safe handling

A partner has a vested interest in ensuring that operations at the third party manufacturer allow the innovator to bring the product to market without delay due to occupational exposure or environmental contamination issues, and without any risk of future liability caused by industrial exposure or discharge⁶

When selecting a Contract Manufacturing Organization (CMO), a detailed investigation of that company’s approach to tech-transferring HP compounds should be performed. This analysis should challenge capability and knowledge in potent compound safety (both occupational and environmental), assessing the company’s understanding of cross-contamination risk, of how the customer’s product might be affected by others produced on the prospective site and indeed, how current products might be affected by possible introduction of the new product.

Key elements to be considered include:

- i. Compound evaluation and OELs
- ii. Equipment and process containment
- iii. Environmental management
- iv. Procedures and training
- v. Global compliance

⁵ How Alkermes implemented Risk-MaPP to maximize operator and patient safety
<http://www.pharmamanufacturing.com/articles/2011/143.html>

⁶ A.W. Ader, J.J. Mason et al., Chem Today, 25(2), pp. 56-60 (2007)

- vi. Experience and expertise in HPAPI handling
- vii. Reliance on external support

i. Compound Evaluation and OELs

A first step when considering the introduction of any new API at Alkermes is to assess the toxicity and potency of the compound and to categorize it (“control banding”). The Alkermes categorization scheme (Figure 1) was developed with input from SafeBridge Consultants. This is an important first step in facilitating assessment of likely product demands relative to capability of our existing manufacturing equipment technology and/or our ability to enhance our processing approach to allow us to compete for business. Control banding provides a means to group materials by their hazards and risk of exposure so that suitable consistent controls can be defined and applied to ensure safe handling.

Figure 1: Alkermes Compound Categorization Table

CRITERIA	CATEGORY 1	CATEGORY 2	CATEGORY 3A	CATEGORY 3B	CATEGORY 4
OEL Range	> 500 µg/m ³	500 - 10 µg/m ³	10 - 1 µg/m ³	1 - 0.1 µg/m ³	< 0.1 µg/m ³
Potency	>100 mg/day	10 mg - 100 mg/day	1 mg - 10 mg/day	0.1 mg – 1 mg/day	< 0.1 mg/day
Clinical Effects	none to minor	minor to moderate	moderate	moderate to severe	severe
Acute Toxicity	none to mild	moderate	moderate	moderate to severe	extreme
Skin or Eye Irritation	mild to moderate	moderate	moderate to severe	severe to corrosive	severe to corrosive
Sensitization Potential	none	weak to mild	moderate	moderate to severe	extreme
Chronic Toxicity	minimal	moderate	severe	severe	severe
Reversibility	reversible	reversible	irreversible	irreversible	irreversible
Mutagenicity / Genotoxicity	none	none - (+) Ames test	(+) in a battery of studies	(+) in a battery of studies	(+) in a battery of studies
Human Carcinogenicity Potential	negative	positive in animal studies not relevant to humans	probable - confirmed animal	probable - confirmed animal; suspected human	confirmed animal - human
Reproductive Toxicity	none	mild	moderate	severe	severe
Developmental Toxicity	none	some effects seen with maternal toxicity	moderate	moderate	severe
Absorption	minimal	moderate	significant	significant	significant
Warning Properties	good	fair to none	poor to none	poor to none	poor to none
Speed of Onset	immediate	immediate to delayed	immediate to delayed	immediate to delayed	immediate to delayed
Need for Medical Intervention	little to none	moderate (not life threatening)	Moderate to high	high (potentially life threatening)	high (potentially life threatening)
Other	none	none	Default band for materials of unknown toxicity*	Default band for materials of unknown toxicity and suspected highly hazardous*	may affect sensitive subpopulations

*If unknown compound is suspected to be highly hazardous (i.e. cytotoxic, reproductive hazard, carcinogen, teratogen, mutagen, etc.), it will default to 3B categorization.

There are several limitations associated with banding approaches, so as soon as is practicable; Alkermes will move to generate both ADE and OEL⁷ values. Where we have a history of dealing either with the sponsor or with the organization that has generated the report on their behalf, Alkermes will use the data provided by the potential partner, assuming it to be correct, until we can generate our own.

Alkermes typically seek to generate combined OEL and ADE reports as similar toxicological data underpins both. Alkermes has established a cross-site review forum for OEL/ADE reports, bringing in-house Environmental Health and Safety (EHS), toxicology and validation experts together to drive consistency and thoroughness in evaluation. We have developed a format for report generation that includes supporting evidence from the toxicologists we employ. In particular, for ADE identification we demand that formulae and factors applied is consistent with our template, and that any variation from default values used in calculations is explained. Our template is based on the process described in the RiskMaPP guidance, and many of the default values we employ are also based directly on that guidance or on references provided by the ISPE.

We believe ADE is a very important element in how we justify our assessment of contamination controls. We have presented and have received positive feedback on the approach we use from regulators that have visited our site or attended presentations made by us in the U.S. and Europe.

Developing an OEL and subsequent testing for the presence of that specific material allows us to empirically demonstrate that the working environment is safe. Concurrent with the development of an OEL, we commission Bureau Veritas (American Industrial Hygiene Association (AIHA) accredited) to develop the industrial hygiene sampling and analytical method to allow monitoring of the workplace to occur.

ii. Equipment and Process Containment

“If an overall manufacturing facility consists of three components – pharmaceutical material, personnel, and the environment surrounding them – containment is the isolation of the first of these components from the other two” (ISPE).

Containment, how it is achieved, how it is measured, and how it is maintained are key considerations for Alkermes, and should be for any provider handling potent or HP materials. The complexity of solutions relating to the contained material (OEL, material form, how much it is diluted by other components, etc.) and the process

Containment is a key consideration for Alkermes and should be for any provider handling potent or highly potent materials

⁷ OEL and ADE definitions are described at the end of this paper.

being employed (material energy, scale, level of operator intervention required, etc.) are key considerations. Where practicable it is best to contain at source.

There is no one solution suitable to all situations. All challenges must be assessed within the context in which they occur and the constraints that apply. Some of these constraints will be of time and cost. Some assessments will reach a conclusion that projects should not be undertaken.

Figure 2: Alkermes Contract Pharma Services' Approach to Assessing New Highly Potent Product Introduction



In assessing the containment challenge, Alkermes consider three levels of protection:

- *Primary containment* - equipment targets isolation of the product from the operators and the environment. Equipment is normally equipped with Clean in Place (CIP)/Wash in Place (WIP) and may be supplemented by flexible single use element for interventions
- *Secondary containment* - includes use of separate processing rooms
- *Tertiary containment* - refers to facility design such as dedicated, segregated suite(s), security access controlled, HVAC single pass air (safe change in room), double HEPA exhaust, pressure cascade and fogging shower.

Providers should establish containment performance criteria during commissioning and show that performance is maintained during commercial manufacture. Alkermes bases its approach on the ISPE Good Practice Guide: *Assessing the Particulate Containment Performance of Pharmaceutical Equipment*⁸. As part of commissioning, we use a suitable surrogate (less potent) material with very low limits of detection, to challenge installations. We use routine Industrial Hygiene monitoring to develop a sufficient level of confidence that we are achieving the OELs and verify ongoing containment performance.

When Alkermes considers cross-contamination potential it does so from two perspectives. It firstly considers the source and the risk (Product Risk) that the product presents and secondly it considers the potential risk of the product contaminating others (Product Vulnerability). Where a product of high “vulnerability” is manufactured on the same equipment or adjacent to a source of high-potential “product risk” is where adequacy of controls needs to be most thoroughly assessed.

⁸ ISPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment (Second Edition)
<http://www.ispe.org/ispe-good-practice-guides/assessing-particulate-containment-performance>

iii. Environmental Management

HPAPIs typically present greater challenges in environmental management including waste disposal, effluent containment and abatement of air emissions compared to less potent pharmaceuticals.

Alkermes will typically contain all liquid and solid wastes, including wash water from equipment and area cleaning, until it is certain of concentrations and potential for impact. Initial project assessment can be greatly helped by a thorough donor/sponsor data package. In this context, the information of interest might include any available eco-toxicity data, respirometry and/or biodegradation data, previous waste handling methods used, abatement systems utilized and the like. All data are reviewed, all gaps assessed, and identified risks are managed to assure Alkermes and our partners of adequate controls.

Clearly, the decision to hold all potentially environmentally damaging materials (in particular wash waters, which would typically be of large volume) has cost implications, so the sponsor will need to be confident of the CMOs ability to reduce volumes, and by extension, long-term costs.

Certification of a company's systems relating to handling and disposal of liquid/solid waste products and their environmental management system, along with ready availability of associated written procedures, would give the sponsor a good initial feel for a provider's capability and focus. Additionally, regulatory history and/or licensing of facilities will provide the donor with further assurance of the company's environmental management capabilities. Alkermes' environmental management system, for instance, is certified against international standard ISO14001 and is assessed against an Integrated Pollution Prevention Control License which is regulated by the Environmental Protection Agency (EPA) in Ireland.

iv. Procedures and Training

Training and expertise of people involved in the design of facilities, equipment and manufacturing processes as well as those who will handle and manage products in commercial manufacture will be critical to success. Alkermes invests significantly in the training of its scientists and engineers to ensure implementation of the best operable design to meet the specified containment performance target. In addition, manufacturing associates (operators) and support staff are trained so they can maintain and operate equipment effectively, and, importantly, understand why containment and controls are in place. The discipline and care required from personnel operating and maintaining a facility handling HP compounds, their understanding of how their actions may influence exposure levels, and their understanding of risk are fundamental for the safe and successful operation of the plant.

Any sponsor seeking a third party to process HPAPIs should pay close attention to the training and expertise of all those who might be involved in process design, transfer, qualification (GMP & Safety aspects) and eventual operation.

A good global compliance record is critical to reassure prospective partners: a recent U.S. FDA audit of Alkermes' Ireland facility resulted in no 483s being issued

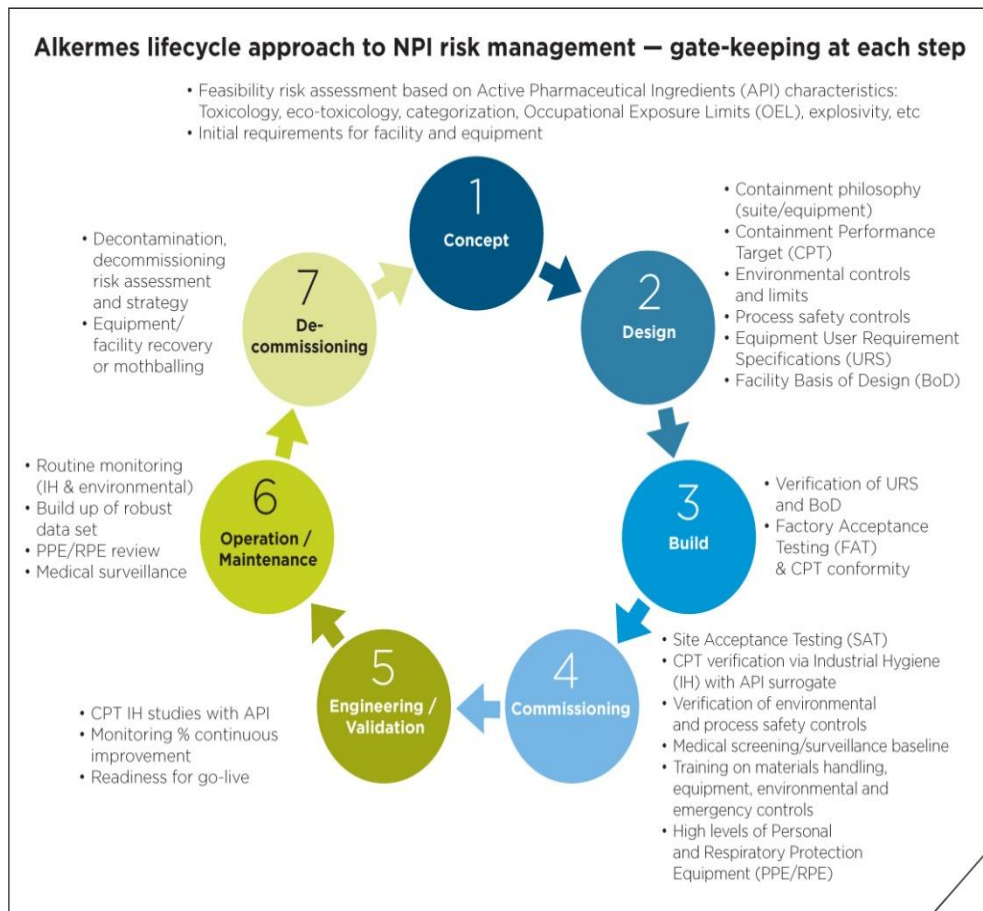
v. Global Compliance

In selecting an outsourcing partner, the sponsor/donor company should examine a service provider’s quality and compliance systems. This should be undertaken through examination of the provider’s quality record with regulatory agencies and through site visits to ensure the integrity of key quality systems throughout the company. Alkermes Contract Pharma Services has a proud history of quality with multiple regulatory authorities. There is a culture of “building quality” into all we do, and this message is continually reinforced at all levels of the organization. Our quality record is exemplary – our most recent FDA audit in the Irish plant took place in August 2012, with no 483s being issued.

vi. Experience and Expertise in HPAPI handling

The ability of a contracting third party to demonstrate a proven, well-designed Risk Management System to consistently assess the activities involved in bringing an HPAPI on site should be a prerequisite to any partnership. All new product introductions (NPIs) at Alkermes are assessed and project-managed in an integrated, risk management lifecycle approach (Figure 3).

Figure 3: Alkermes Contract Pharma Services’ Approach to New High Potency Product Introduction



vii. Reliance on External Support

Most companies will have preferred suppliers where specialist support in specific technical areas is required. Alkermes, for instance, relies on external toxicologists to generate ADEs and OELs. The client must be confident that the contract service provider has critical mass, that there is an inherent understanding of the business to be undertaken and that the service provider is not heavily reliant on third party service providers to define how the plant/suite should be operated. Alkermes has proven in-house experience and expertise in developing and transferring numerous successful commercial processes.

5. Making the Right Choice

Even if the decision to outsource is clear, the choice of partner is a crucially important of the decision. The service provider's record of compliance with global regulatory and safety standards, as well as experience and capacity for producing HP drug products, are good indicators that the service provider will be able to expeditiously bring a molecule to market and maintain supply of the product over time. The prospective partner needs to assess the service provider's global experience, expertise and track-record in the manufacture of HP compounds and be assured that their systems and procedures in place will allow for the safe and effective manufacture of the compound in question.

The choice of a partner is a crucial element to get right - compliance, experience and expertise in HP handling have to be considered

6. Alkermes' High Potency Facility in Ireland

Alkermes' site in Athlone Ireland has the capability to handle HPAPIs through to commercial, high-volume scale. Establishing a track record in the secondary processing of HP products, with systems and procedures in place to handle low OEL compounds has been a significant step in expanding the service offering of Alkermes Contract Pharma Services.

As part of Alkermes plc, Alkermes Contract Pharma Services has over 40 years of proven expertise in drug process development, process design/improvements, tech transfer and commercial scale cGMP manufacturing of oral and injectable dosage forms, including the handling of HP drug substances.

Definitions

ADE - represents an estimate of a daily exposure that is likely to be without an appreciable risk of deleterious effects to the potential patient population during an average lifetime

OEL - The maximum permissible concentration in ($\mu\text{g}/\text{m}^3$) of a chemical agent in the air at the workplace to which a worker may be exposed in relation to an 8-hour or 15-minute reference period. These limits are intended to be the levels of chemicals that healthy workers could inhale for up to 40 hours per week over a working lifetime, which would not result in any adverse health effects.

Trademark References

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