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Using a CMO to manufacture HPAPIs

Risks and challenges

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HPAPI (Highly Potent Active Pharmaceutical Ingredient), Containment, Risk management, CMO (Custom Manufacturing Organization) selection, SafeBridge®, OEB (Occupational Exposure Band), OEL (Occupational Exposure Limit).

ABSTRACT

Highly potent active pharmaceutical ingredients (HPAPIs) represent a growing niche segment in the pharmaceutical market. This article highlights important selection criteria a pharmaceutical company should consider when selecting a CMO for its HPAPI products. The selected CMO should have a clear regulatory based manufacturing strategy and a strong environmental, health and safety (EHS) process. It should have appropriate risk management and risk assessment tools in order to help ensure safe work environments in all of its labs and plants. Appropriate equipment, facility design and working procedures, as well as low personnel turnover are key for a safe and efficient performance of the HPAPI CMO. A driving factor for long term success lies in having the experts and people needed to execute HPAPI processes. These personnel must be well educated and trained and follow best practices for a safe working culture and environment. Verification performance programs are a good rating, feedback and design aid tool for the capabilities of the CMO systems, procedures and people. Finally, the selection process for choosing a CMO in HPAPI manufacture should not rely on what a CMO claims it can do, but should draw upon historical success and what a CMO already has done. HPAPI manufacturing is not something which can be introduced quickly in an organization. Safe and efficient HPAPI manufacturing takes long term commitment, years of preparation, significant investment for appropriate plants and supporting facilities, as well as education of people, the right expertise and an ethical commitment of the CMO to the safety of their personnel and environment.

INTRODUCTION

Highly Potent Active Pharmaceutical Ingredients (HPAPIs) are molecules requiring only a very low dose to show biological activity. Ader et al. (1) provided a potential definition of HPAPIs based on a therapeutic daily dose of ≤ 10 mg or an occupational exposure limit (OEL) of $\leq 10 \mu\text{g}/\text{m}^3$ of air as an 8 hour time-weighted average.

Such compounds can have significant benefits in the treatment of certain medical conditions and represent a faster than average growing segment within the pharmaceutical industry (2). However, they also represent a challenge to the pharmaceutical industry in regard to the appropriate protection of the personnel, products and company environment employed in their development, manufacturing and distribution.

Contract Manufacturing Organizations traditionally play an important role as suppliers for the pharmaceutical industry. HPAPI related safety and regulatory requirements require higher standards in regard to technical expertise and equipment, as well as working procedures and culture. Consequently, the process to select a CMO for HPAPI manufacture has to be managed even more carefully than for standard products, with appropriate selection criteria and risk management in place.

SELECTION CRITERIA TO CHOOSE CMO PARTNER/SUPPLIER AND EFFECTIVENESS OF SELECTION PROCESS

The CMO selection criteria and their weighted importance will certainly vary from customer to customer based on their manufacturing strategy and target products (3). A set of criteria - and of the most relevant points to be evaluated - which might form the basis of the HPAPI CMO selection process are listed in Table 1.

Criteria - mainly opportunity	Key Aspects
Financial Aspects	Competitive cost of goods and services Financial stability and long-term viability
Capacity	Ability to invest in state-of-the-art technologies and equipment Ability to respond to changes Right equipment Right personnel
Criteria - mainly risk or challenges	Key Aspects
Quality	Control systems Track record Operational excellence
Compliance	Regulatory Compliance - EHS and cGMP Legal compliance IP - toxicological know-how
Capability	Experience Expertise and competence Track record - can the CMO do it or has it done it?
Culture	Collaboration and communication Transparency Proactivity Commitment of people to company and from company to people

Table 1. Selection criteria with key aspects for assessment.

Some of these criteria represent the potential benefits for the outsourcing organization, while other selection criteria are mainly related to potential risks and challenges.

The effectiveness of pharmaceutical companies assessing potential CMOs can be checked from the review of outsourcing surveys. Table 2 lists the result of the 2007 survey of the "Biggest complaints you have with a Contract Service Provider" of Contract Pharma. It can be assumed, that these results are typical.

Interestingly the survey reflects just how difficult it can be to assess all aspects of such criteria as communications and competence during site visits and audits, prior to choices being made. Therefore it cannot be emphasised enough, how important it is to gain a transparent view on the track record of the CMO in regard of these less tangible criteria. This is of even greater importance when the CMO selected will be employed to manufacture HPAPI products.

Type of Complaint	Percentage of Respondents
Competence	21.4 %
Communication	13.1 %
Quality	13.1 %
Delivery	11.9 %
Customer Service	10.7 %
Costs	7.1 %

Table 2. Contract Pharma Survey – biggest complaints.



Figure 1. CMO asset strategies for cytotoxic compounds, Lonza data 2009 on CMOs in regulated Markets (9).

IS THE CMO APPROPRIATELY IDENTIFYING AND MEETING OCCUPATIONAL HEALTH REQUIREMENTS AND REGULATORY CONSIDERATIONS?

HPAPIs have increased safety, EHS and cGMP compliance requirements compared to APIs with lower pharmacologic potency, and these must be taken into account to establish compliant manufacturing assets and processes.

cGMP Requirements and Cross Contamination

The cGMP guidelines from the EMA, FDA, or the regulatory bodies of other countries like Japan, Switzerland, China and India, do not reference occupational health aspects. However, cross contamination is an increasing concern when handling HPAPIs as cross-contamination risk potentials are greater. There are regulatory requirements (4) with a mandatory separation of certain product groups, e.g. products containing live microorganisms or beta-lactam antibiotics requiring the dedication of plants to solely these product categories. The requirements for other product categories requirements are less stringent or clear cut; "cytotoxic" compounds, for example, can be manufactured in dedicated or multi-purpose facilities. Cytotoxic chemical compounds – such as in a food, cosmetic, or pharmaceutical - or immune modulation cells have the property to kill living cells (5, 6). The use of multi-purpose plants will however definitely trigger the need for robust risk assessments in addition to the standard cleaning procedures and appropriate cleaning limits. Recently the International Society for Pharmaceutical Engineering (ISPE) has issued the Baseline Guide® Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP), outlining scientifically supportable health-based risk assessment approaches (7) dealing with the manufacture of very different product categories in the same multipurpose assets. It should be pointed out though, that is it rather unclear whether the application of such an approach can be employed by a CMO, which is handling a multitude of HPAPIs from different customers.

Nevertheless, any risk assessment in regard of HPAPI manufacture and cleaning would have to take into account the input from an experienced toxicologist. In addition, the responsible supervisory authority expects to be consulted to discuss the company's risk management measures (8). In any case the outsourcing company has the ethical requirement and, in some cases, the regulatory requirement to share the relevant safety and

toxicological data with the selected CMOs experts to enable safe and compliant HPAPI manufacturing.

As a result of this open regulatory situation, CMOs have adopted very different asset strategies, as depicted in Figure 1, for the important product category of the cytotoxics (5, 9). The key issue is that the outsourcing company is comfortable with the regulatory aspects of the CMO's asset strategy and the related quality risk management systems in place and has rated the CMOs toxicological expertise as appropriate.

Occupational Health and toxicological expertise

The second important aspect to be evaluated is safety/EHS. All countries have adopted legal requirements to assess and manage work place health risks (10). Companies and employees

have to know the hazards of the materials being handled as well as the exposure potentials at each workplace, and subsequently they have to control the risk resulting from the combination of hazard and exposure and should empirically demonstrate that the risk is controlled with robust data. These requirements also stipulate that technical/engineering and organizational measures should be used to protect employees, while personal protective equipment (PPE) should only be regarded as a safety net and should not be used as the only control barrier between a HPAPI product and employee.

Only CMOs with access to the appropriate expertise in toxicology are able to recognize and evaluate hazards posed by HPAPI products. As stated before (8), CMOs are expected by the regulatory agencies to request an exchange of information between customer and CMO. Some of this information might be intellectual property relevant and will thus have to be dealt with appropriately by the CMO.

In order to manage the evaluated hazard when documented Occupational Exposure Limits and air monitoring methods are unavailable, Occupational Exposure Band (OEB) systems have been developed. These enable a company to treat all compounds accordingly to their toxicological properties. These OEB systems have their limitations, e.g. they do not take into account either the type of unit operations performed with the HPAPI product, or the physical properties of the compound, or the scale of operation. Thus, in addition to the OEB system, a robust risk assessment procedure to evaluate these aspects should be in place at the CMO to enable the assessment of the exposure potential. In Figure 2, an example of such a banding system is presented. No official industry standard exists in this regard, and companies utilize OEB systems with typically 4 to 6 categories.



Figure 2. Example of a 6 band OEB system, as used at Lonza.

In order for the customer and CMO to communicate well, the OEB System should be presented and explained, including the experts involved and the guidelines used by the CMO.

OUTSOURCING THE HPAPI MANUFACTURING: REQUIREMENTS FOR EQUIPMENT, FACILITY DESIGN, PROCESS SAFETY AND PERSONNEL

Appropriate selection and design of processing equipment – Primary Containment

Based on the exposure potential and risks involved, the appropriate containment has to be put in place, and CMOs should present their containment strategy to the customer. Companies typically follow the strategy of primary and secondary containment – the primary containment targets isolation of the product from the operators and chemists executing the HPAPI process. Equipment typically consists of closed-system glassware and reactors with CIP systems, filter dryers for product isolation, closed charging systems e.g. butterfly valves, continuous liners, single-use equipment and disposable bioreactors. In addition, isolators, ventilated laminar flow cabinets, safety hoods with movable sash or restricted access barrier systems (RABS) are frequently used. The personnel working with the processing equipment should wear the appropriate PPE to control low level inadvertent exposures and in case of an accidental release of HPAPI materials.

In order to select a good CMO, it is highly recommended that the actual operation in the plants or laboratories should be scrutinized as part of a EHS audit. The CMO will almost certainly accept the presence of the customer's inspectors within their working environments, provided that the CMO's guidelines in regard to protection of people and products in these assets can be adhered to.

Design of "smart HPAPI" chemical Processes reducing exposure potential

The exposure potential of a HPAPI process can also be reduced by designing a "smart HPAPI" process which minimizes e.g. product isolation, sample taking or using on-line analytical tools to monitor a process e.g. by PAT. In Figure 4 examples of the application of Raman Spectroscopy as an on-line control of polymorphs during crystallization is presented.

Facility design – Secondary containment and supporting plants

The purpose of secondary containment is to protect other parts of the plant not involved in the primary manufacturing operation and also the surrounding environment from cross contamination by the HPAPI manufactured. The facility design should include the following elements: A pressure zoning design and system, appropriate HVAC capacity with safe-change filters in place,



Figure 3. Isolator with CIP system operated by lab chemist (left), plant operator performing a sampling operation in a HPAPI train (right) – PPE is only employed as a safety net!

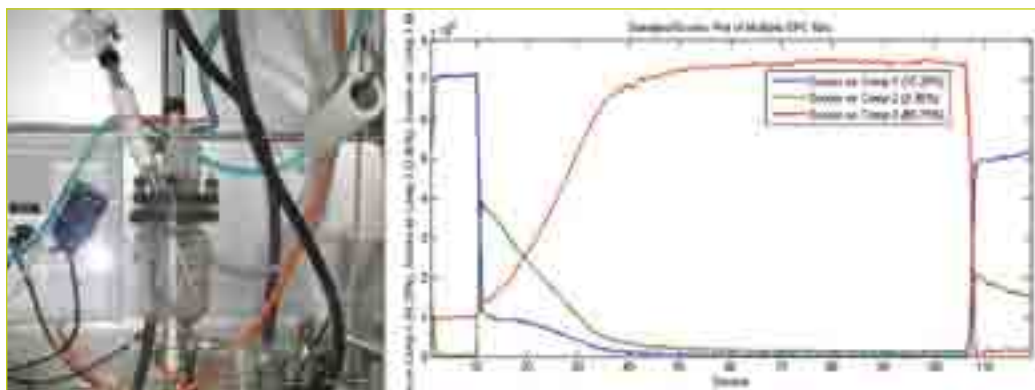


Figure 4. Raman Spectrometer set-up in the containment lab at Lonza (left), Raman spectrum analysis of crystallization mixture (right).

access to the HPAPI asset restricted to properly trained personnel, misting showers for routine decontamination of PPE and as a remedy for incidents with potential exposure of the personnel, and well defined and risk assessed personnel and material flow systems.

In addition to this facility design, appropriate supporting laboratories, logistical systems and waste treatment plants are also required. A bio-plant environment is needed for the manufacture of conjugates or secondary metabolites. In this case the better design is to fit chemical process equipment and containment into the bio-plant environment as an add-on. The system should be rated to the appropriate Bio-Safety level (minimum 2).

Procedures, personnel and performance verification

The utilized OEB system, based on air monitoring studies and compared to OELs for other similar materials, should categorize the chemicals and products handled, and be linked with safe handling procedures and control strategies. Working with HPAPI compounds requires personnel well-trained in utilizing best practice to minimize the exposure risk. In this context it should be emphasized that only a workforce with both the appropriate working culture and awareness for HPAPI product properties and a reasonably low personnel fluctuation rate can ensure a good performance of the system – well-trained expert personnel are the basis and a pre-requisite for the safe and successful operation of a HPAPI manufacturing asset!

In order to assess control or containment performance, verification programs and/or simulation runs employing the actual substance or surrogate compound should be conducted. Wipe samples, air samples and personal monitoring samples should be taken while personnel and asset is in operation to ensure that the designed systems perform as intended. Figure 5 illustrates such a verification sample plan. Monitoring should be undertaken on a routine basis

as a means to develop a sufficient level of confidence that the control and containment strategy anticipated is, in practice, being delivered.



Figure 5. Verification test plan for a HPAPI lab.

This type of program should be made available by a CMO to a customer as part of a due diligence EHS audit providing information and data about the CMO's capability to handle the HPAPI in the target OEB. The track record and experience of a CMO in HPAPI projects is important to indicate a reduced risk of failure, exposure or cross contamination incident for a pharmaceutical company.

Another way of testing the capabilities of a CMO can be the service of a safety consultant company (e.g. SafeBridge®), which offers a certification program. For a company with a long track record in HPAPI manufacturing such certification may not be a requirement, provided that other robust risk assessment processes, toxicological expertise and stringent verification programs are employed. However, in order to facilitate improved capabilities or to enter a new product category or complex asset configuration in HPAPI manufacture, CMOs should certainly consider using the services of a company like SafeBridge to assess operations and recommend improvements in safe handling of HPAPIs.

CONCLUSION – RISKS AND CHALLENGES USING A HPAPI CMO

Outsourcing the production of pharmaceutical products is an important aspect of the manufacturing strategy of drug companies today. This is also true for HPAPI products. Because of the regulated nature of the industry requiring specialized assets and costly safety installations, CMOs can offer good value to pharmaceutical companies. However, it is important that those entrusted with the supplier selection process make use of every tool available to them,

and that they focus their attention not only on financial aspects and capacity, but instead look at the areas which contain risks and challenges. At the end of the selection process it should be ensured that the company selected has the appropriate manufacturing strategy for HPAPI products, safe assets and best working procedures for their employees to enable operation in a consistently reliable manner. Finally, the right experts have to be available at the CMOs part to enable the appropriate recognition and evaluation of the potential hazards HPAPIs pose for people, environment and patients.

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Carrying out HPAPI work in a laboratory and plant environment requires the close collaboration of many different functions – from the people working on the bench and reactors to the experts in Engineering, QA and EHS. This article is dedicated to the people who carry out the difficult and demanding tasks associated with working on HPAPI compounds and projects.

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