

High Potency Drugs –
from Molecule to Market



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PCI Pharma Services has invested in state-of-the-art containment equipment and created a ‘Potent Passport’ philosophy to identify the specific handling requirements for any Highly Potent Active Pharmaceutical Ingredients (HPAPI) project. Backed by 30 years’ experience of managing potent molecules, PCI Pharma Services is the logical choice when selecting an outsourcing partner.

The pharmaceutical landscape continues to evolve, with much R&D focusing on more specialized medicines. As the biological activity and specificity of the API increases, dosage strengths decrease – resulting in increased potency of the APIs in terms of occupational handling for drug product manufacture. At PCI, we are seeing continued investment in R&D with a visible shift towards speciality/potent medicines, with oncology being a particularly intense area of focus for the global pharmaceutical market. Latest data suggests approximately 25 per cent of New Chemical Entities (NCEs) in development are deemed potent¹.

With this evolving landscape, pharmaceutical product developers and manufacturers have had to rethink their approach, as greater potency medicines generate increasingly complex regulatory requirements. With such a significant proportion of new drugs in development containing high potency APIs, the processing of such molecules presents many challenges, not least of which is the need for significant investment in specialised containment resources to ensure that employees and their environment are protected from exposure to these drug compounds.

■ Classification of Potency

Although there is no standard classification for the potency of pharmaceuticals, all potent molecules can be defined as powerfully active; noxious materials needing only very small quantities to have an effect. All substances are poisons, since no chemical is completely safe; it is the dosage that distinguishes a poison from a remedy, with ‘safe’ chemicals being toxic at high enough concentrations and even very ‘toxic’ chemicals deemed ‘safe’ if exposure is low enough.

APIs are deemed potent if they fall into one of the following categories:

- A pharmacologically active ingredient or intermediate with biological activity at approximately 15 micrograms (µg) per kilogram of body weight or below in humans, or a therapeutic dose of 1 milligram (mg) or below per day
- An active pharmaceutical ingredient or intermediate with high selectivity (as in the ability to bind to specific receptors or inhibit specific enzymes) and/or the potential to cause cancer, mutations, developmental effects or reproductive toxicity at low doses
- Finally, a novel compound of unknown potency and toxicity.

Figures 1 and 2 illustrate the therapeutic window and dose response.

Figure 1

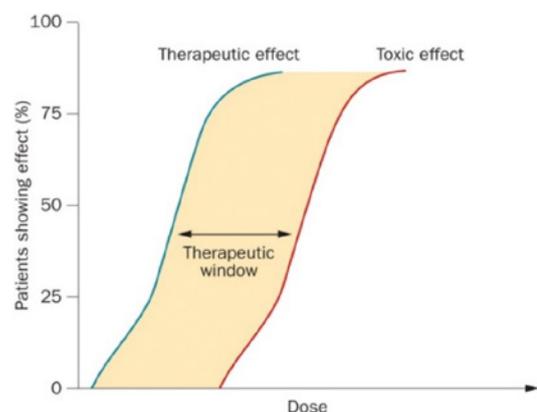
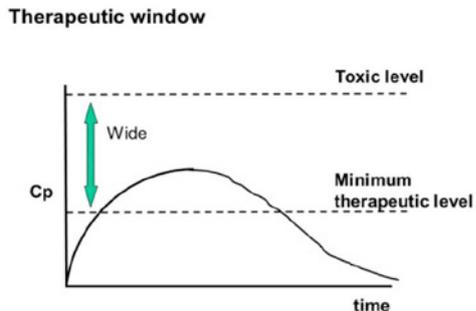


Figure 2



Regulatory demand for effective, lower-dose treatments – combined with growing incidents of cancer, diabetes, and cardiovascular diseases – has seen many pharmaceutical companies focus their R&D investments on HPAPI-based products. This focus, paired with the ever-present need to reduce costs, has increased the demand for specialist HPAPI processing services.

However, due to the complexity of achieving market commercialization, there are numerous considerations to be taken into account by a pharmaceutical company when selecting a potential outsourcing partner. There are significant challenges such as the requirement for continued investment, particularly in the role of safe handling; the need for global guidance; the method used for sampling and testing; and the advanced technical expertise needed.

There is also a need to shorten the drug development process so as to minimize drug development costs, as well as a need to reduce the use of APIs, which are often extremely expensive and in very short supply.

Demand for HPAPIs continues to grow – there are currently 586 drugs in development for oncology treatment, with over 70 new cancer treatments (for more than 20 tumour types) entering the market over the past five years². Global oncology spending reached \$107 billion in 2015, representing an 11.5 per cent increase over the prior year and is expected to grow to \$150 billion by 2020³. Specifically in late phase drug development, including Phase II, Phase III and those registered for approval, oncology therapies represent approximately 25 per cent².

The number of contract development and manufacturing organisations (CDMOs) claiming to offer HPAPI processing capabilities has increased in recent years, but not all will have invested in state-of-the-art contained technology or have the

highly specialist experience needed to complete such projects efficiently, with even fewer having the ability to support initial development through to long-term commercial supply. The safe handling of HPAPIs presents a major challenge to the pharmaceutical industry, with the high capital costs associated with the specialised containment technology required to protect both employees and the environment.

CDMOs also need to possess the necessary technical expertise; be able to handle the management and costs associated with waste water treatment and waste handling; and the ongoing operational costs of maintaining a complex contained manufacturing facility capable of safely processing multiple highly potent compounds.

■ Regulatory Complexities

A further issue to consider in the safe processing of HPAPIs is the lack of harmonization in GMP regulations preventing cross-contamination.

For example, the EU follows GMP guidelines for toxicology evaluation (Chapters 3 & 5), while the European Medicines Agency (EMA) has published guidelines on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities. In the US, meanwhile, the Food and Drugs Administration (FDA) recommends a risk-based assessment for cross-contamination. In Brazil, the National Health Surveillance Agency (ANVISA) has no formal definition, but requires dedicated facilities for certain product categories such as hormones. Japan's regulatory guidance details requirements in line with the EMA, while in the rest of the world it is treated on a case-by-case basis, but likely to require EMA standards as a minimum.

The EU GMP guidelines, published in August 2014, came into force on 1 March 2015 and are a legal requirement. Chapter 5.2 states that a Quality Risk Management (QRM) process, which includes a potency and toxicology evaluation, should be used to assess and control the cross-contamination risks presented by the products manufactured.

The outcome of the QRM process should be the basis for determining the necessity and extent to which premises and equipment are dedicated to a particular product or product family. This may include dedicated specific product contact parts, or dedication of the entire manufacturing facility.



It may be acceptable to confine manufacturing activities to a segregated, self-contained production area within a multi-product facility where justified – however such justification requires a fully documented formal assessment.

The International Society for Pharmaceutical Engineering (ISPE) Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP) provides a scientific risk-based approach, built 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. This baseline provides precise guidance required to ensure operator safety.

Most importantly, PCI has members on the ISPE UK Committee and the ISPE Communities of Practice for Packaging and the Packaging Steering Committee. This ensures that PCI's manufacturing processes are aligned to any guidance issued, delivering best practice, while also enabling PCI to be part of any new legislative developments.

■ Health, Safety and Cleaning

When considering health, safety and cleaning, it is important to understand a number of pharmaceutical manufacturing

definitions. Such an understanding of the specialist industry terminology is vital in aligning site safety and Good Manufacturing Practice (GMP). Currently, there is a lack of consistency on assignment of Occupational Exposure Limits (OELs) to bands across pharmaceutical companies. PCI uses recognised industry expert groups such as Affyglity and Safebridge for all assessments.

When assessing the safe management of highly potent molecules, it is important to have a unified understanding of all relevant definitions.

Definitions

- **PDE – Permitted Daily Exposure**

PDE represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime

- **NOEL – No Observed Effect Level**

The NOEL is the highest tested dose at which no 'critical' effect is observed. If the critical effect is observed in several animal studies, the NOEL occurring should be used for the calculation of the PDE value

- **ADE – Acceptable Daily Exposure**

The ADE represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime

- **OEL – Occupational Exposure Limit**

Average concentration load of an API airborne in $\mu\text{g}/\text{m}^3$ acceptable over an eight-hour time-weighted average without negative impact on workers/environment

- **OEB – Occupational Exposure Band**

Banding of OEL into ranges for which appropriate measures of protection of workers and facilities/equipment can be defined in common for APIs with different OELs within this band.

We continue to see a lack of harmonisation in the health, safety and environmental classifications.

Figure 3 below illustrates the difference in banding applied by two pharmaceutical companies, demonstrating that there is a real and significant lack of common terminology and therefore understanding.

Figure 3

Example – two pharma companies' banding system

Band	Company A OEL Range	Company B OEL Range
1	$> 100\mu\text{g}/\text{m}^3$	$> 1-10\text{mg}/\text{m}^3$
2	$10-100\mu\text{g}/\text{m}^3$	$> 0.1-1\text{mg}/\text{m}^3$
3 or 3A	$1-10\mu\text{g}/\text{m}^3$	$> 0.01-0.1\text{mg}/\text{m}^3$
3B or 3+	$0.05-1\mu\text{g}/\text{m}^3$	$> 0.001-0.01\text{mg}/\text{m}^3$
4	$< 0.05\mu\text{g}/\text{m}^3$	$\leq 0.001\text{mg}/\text{m}^3$
5	N/A	$\leq 0.001\text{mg}/\text{m}^3$ (Robotics only)

It is important to understand any client in-house categorisations

In considering the development and manufacture of highly potent drug products, an OEL monitoring program at each stage of the process should always exist. Strict cross-contamination controls are required with a risk assessment via four principle modes:

- airborne
- mechanical
- personnel transfer
- retention of product on contact surfaces.

With the manufacture of traditional APIs and drug products,

avoiding contamination from personnel involved in production is critical. Processes must be carried out in an area maintained at negative pressure to prevent the possibility of contamination. When manufacturing HPAPIs, however, high levels of specialised containment are required in order to protect employees from the agent itself. As a result, and to prevent material from entering the environment, HPAPI manufacture should be carried out under negative pressure.

■ Primary and Secondary Containment

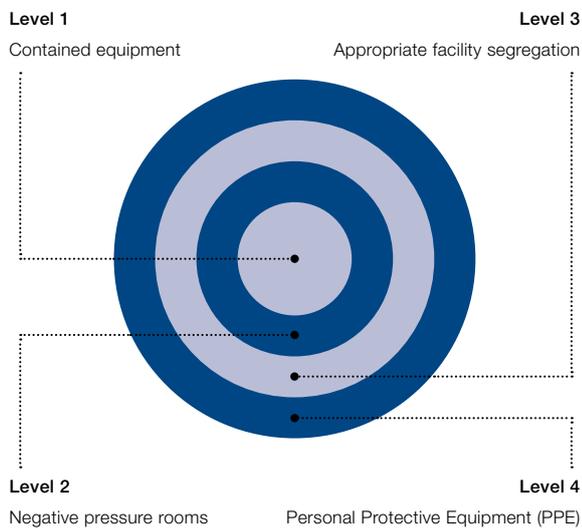
As a result of these challenges and considerations, the design aspects for a suitably safe and compliant containment facility and the associated equipment are extensive and demanding. Primary containment requires suitable contained equipment, running under negative pressure and in effect being a 'clean room' in its own right, with secondary containment being the facility itself. The solution is dependent on the potency and batch size being handled; there might also be a need for different considerations for laboratory-scale, small-scale, and commercial-scale use. Containment must be suitable for the potency with consideration of dust extraction (heating, ventilation and air-conditioning systems (HVAC) and central dust collection) and breach control procedures. In addition to the room pressure differentials, airlocks are necessary adjacent to the manufacturing area, along with utilities such as purified water and effluent treatment capabilities. It is important to recognise that secondary containment will be dependent on the primary containment.

Restricted access is needed to ensure that only those necessary are allowed into the HPAPI processing areas, with cleaning and decontamination areas provided for employees. Facility environmental controls are key with HVAC controlled using a building management system (BMS), which must be suitably designed with terminal HEPAs (H14 grade). Additional safeguarding measures such as single-pass air ensures full room evaluation of any potential loss of containment, suitable automatic equipment cleaning and waste disposal systems.

Understanding the levels of containment is important when determining the appropriate handling of highly potent compounds. Figure 4 overleaf illustrates the four levels of containment.

Figure 4

Levels of containment



PPE should never be considered the primary protection barrier during potency assessment

Employees should be provided with general GMP personal protective equipment (PPE), such as laboratory coats/suits and footwear, hairnets, eyewear, face masks and gloves – while breathing apparatus should be considered as part of a breach control and system failure program. But PPE should never be considered as part of the primary protection barrier during potency assessment or normal operations.

Operator safety is of critical importance, resulting in a new way of thinking to develop drug products in a controlled facility with programed logic controller (PLC) equipment.

■ The Future

A new way of thinking is required for the development of drug products within a contained facility, using PLC equipment to control processing and cleaning, with operator safety being of paramount importance along with a data driven approach to development.

■ Quality by Design and Containment

A Quality by Design (QbD) based strategy is necessary to ensure process reliability and reproducible product quality. It is necessary to have scientifically designed products and

processes, and the control of Critical Process Parameters (CPP) with respect to the Critical Quality Attributes (CQA) and Quality Target Product Profile (QTPP).

As part of the design, modern process analytical technology (PAT) tools are required for in-line real time data. To remove manual intervention, automatic controlled adjustment of manufacturing processing parameters is necessary using PLC-controlled equipment with data trending. Statistical packages and experimental design assessment tools should be employed to reduce development time and costs associated with drug losses and unnecessary manufacturing. A QbD based strategy therefore represents the future.

There needs to be a focus on continuous process monitoring and process verification during routine manufacturing in order to provide:

- Reliable product quality outcome
- Increased throughput
- High planning precision
- Low waste and inventory costs
- Increased operator safety.

Many pharmaceutical developers with products containing HPAPIs recognise that they have limited in-house capacity or experience, and choose to outsource manufacture to a CDMO, with established capabilities in the handling of such materials in compliance with all the applicable regulations. Cost constraints preventing the implementation of in-house solutions may be another reason for outsourcing, as is the mitigation of risk.

Choosing a CDMO to take on an HPAPI project is a complex process, requiring detailed and careful consideration. Assessing a CDMO's capabilities in the handling of drug substances, track record in terms of knowledge and regulatory expertise, compliance history, and capacity to provide long-term support for clinical and commercial supply, is central to the success of any outsourcing decision.

■ The PCI Pharma Services Solution

PCI's 15,000 square foot purpose-built, award-winning contained manufacturing facility (CMF) at Tredegar, South Wales, is designed to provide reproducibility from development to commercial scale, using geometric scale-up and so delivering true speed to market.

Every aspect of the facility design has been considered to

maximise containment, adhering to the latest guidelines and delivering regulatory compliance. The design-for-manufacture, small- and large-scale equipment trains deliver process reliability and reproducibility through geometric scale-up – an important factor when assessing options for outsourcing.

The PCI facility provides a safe and effective environment with the following features:

- Capability to process multiple compounds
- Can work down to an OEL of 0.01µg/m³
- Development scale to commercial scale drug product batch sizes
- API in capsule down to 0.1mg API fills
- Segregated people and material flows
- Dust control systems; safe change filter bags
- Automated cleaning procedures
- HVAC system with single pass air flow
- Contained engineering structure eliminating need for PPE
- Temperature and humidity controlled processing areas
- Small- and large-scale packaging options
- Secure access client viewing gallery
- Purpose-built, high performance, bespoke effluent treatment facility
- Designed to meet regulatory requirements.

Regulatory approvals include the MHRA, FDA, ANVISA and Turkish Ministry of Health, but PCI is never complacent and believes in a culture of continuous improvement which is necessary to deliver current GMP oversight and control.

PCI's CMF offers an extensive range of contained processing technology, delivering a true high potent molecule to market service. The processes include:

- High sheer mix granulator
- Contained roller compaction
- Contained Xcelodose® 120s & 600s technology delivering drug in capsule (DIC) for early stage development/first-in-man clinical trials
- Fluid bed granulation
- Cone mill
- Blending mixer
- Tablet press
- Tablet coater
- Capsule filling

- Bottle and blister packaging.

PCI offers a full molecule to market service, beginning with pre-clinical formulation and analytical development, through clinical Phases I, II and III to commercial supply from 100 microgram micro dosing using Xcelodose® technology, to 300 kilogram commercial batch sizes. PCI is also able to offer full technical transfer of a commercially available product for manufacture packaging and labelling, validation and continuous verification, analytical testing of stability, product release and market launch and, of course, storage and distribution.

■ New Product Introduction to the PCI Facility – The Potent Passport

When handling potent materials, the key consideration is new product introduction. PCI has developed its concept of the 'Potent Passport' to assess all new molecules for their OEL and their PDE, prior to being accepted on site. The Potent Passport strongly defines the molecule, its mode of action and the appropriate handling requirements, maintaining operator and environmental safety at all times.

PCI requires a toxicological and pharmacological assessment of all molecules, both to protect our scientists and operators, and to provide a suitable cleaning assessment and cleaning verification parameters to eliminate the risk of cross-contamination to the next product.

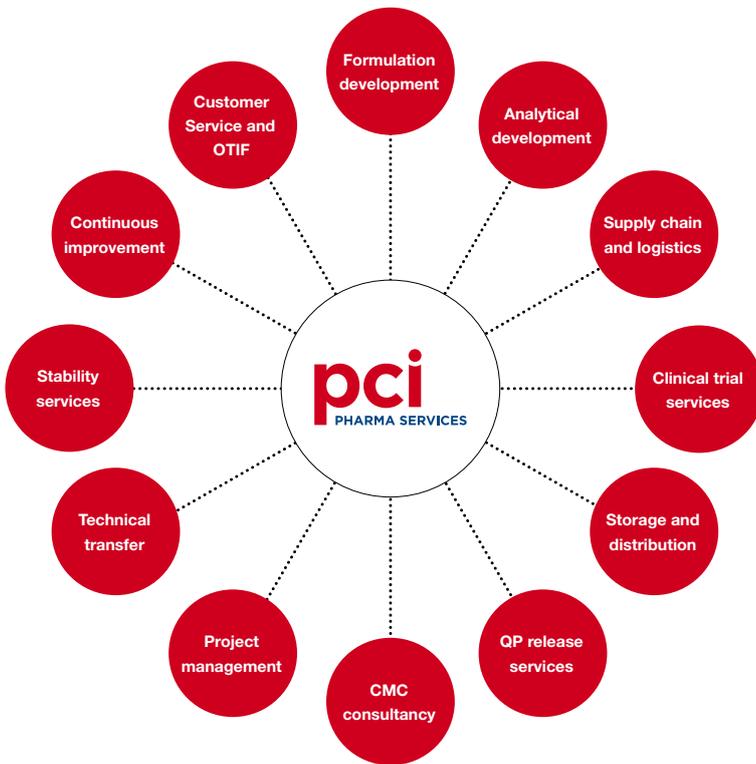
A GMP Failure Mode and Effect Analysis (FMEA) assessment is generated supporting data from the safety, licencing equipment and premises data review to ensure the product can be safely processed. Only after all reviews and assessments are complete will a molecule be issued with its 'Potent Passport' for movement around the PCI facility.

■ Cleaning Philosophy

Each new molecule entering a multi-use facility adds further complexity and as a result, PCI has developed and adopted a robust cleaning philosophy. Starting at new product introduction, the philosophy includes methods of testing and detection for detergents and drug substances. PCI considers swab and rinse samples and any additional cleaning that is required. Equipment capabilities are constantly reviewed, with oversight of all cleaning verification and validation, resulting in a science and risk-based approach to prevention of cross-contamination.

Figure 5

On Site Support Services Delivering Excellence in Outsourcing



■ Summary

As the market continues to evolve with increasing numbers of highly potent molecules in development, it is important to understand the requirements for the safe processing of such molecules, the differing regulatory requirements across the world, and – above all – the safety of employees and the environment.

For pharmaceutical developers looking to outsource the development and manufacture of products containing HPAPIs, the challenge is finding a CDMO with the right technical capabilities, knowledge and experience to successfully manage the project.

At PCI, we believe that applying in excess of 30 years' experience of managing highly potent molecules, combined with our purpose-built contained manufacturing facility and the process of awarding each new molecule a Potent Passport is the key to success making PCI the logical partner of choice.

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