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Understanding the Challenges of Highly Potent Actives

Mario Di Carmine, Pfizer CentreOne Lead at the Pfizer manufacturing site at Ascoli, Italy explores the challenges facing pharmaceutical companies when using highly potent active ingredients (HPAPIs) for the first time.

A rising number of active pharmaceutical ingredients (APIs) are classed at "highly potent".

They are being increasingly harnessed by pharma companies developing oral solid dose (OSD) treatments to treat a variety of chronic conditions. For instance, they are being explored as potential new cancer therapies, and as treatments designed to block immunological response to prevent organ rejection following transplants. They even have the potential to provide enhanced contraception capabilities, as well as to manage a range of other disease states and chronic conditions, such as heart disease.

The popularity of HPAPIs is due precisely to their high potency. They elicit a more targeted pharmacological effect at a lower concentration than standard APIs, which results in smaller dosage requirements.

For OSD products in particular, this key benefit can significantly enhance the patient experience in a number of ways:

- Allows for smaller pills – a significant advantage when creating medication for patients who may have difficulty swallowing
- Allows for less frequent dosing – enhances convenience for patients as they don't have to interrupt their routine as often to administer.

HPAPIs don't just have benefits for patients, they offer advantages for drug developers as well. In many cases, such ingredients are being explored for their potential to treat the currently unmet needs of patients with serious, life-threatening conditions. As a result, for many drug applications, HPAPIs can receive fast-track designation or accelerated approval from regulatory bodies, significantly speeding up time-to-market.

With all of this in mind, it is no surprise, then, that the global market for these highly potent APIs (HPAPIs) is expected to reach nearly $27.9 billion by 2027, growing at a CAGR of 6.1%.[1]

Challenges to Developing with HPAPIs

However, harnessing HPAPIs does have its challenges when it comes to developing and manufacturing OSD products. Their potency means they pose a serious health and safety risk for employees that must be considered at all stages of the development and manufacturing process, as well as during tech transfers that must be addressed to safeguard team members.

Adding to the complexity, HPAPIs encompass a wide range of compounds of varying strength and varying safety risks, meaning one size does not fit all when it comes to control measures. Expert support is needed to address these issues and to ensure efficient and effective development and commercial manufacturing of OSD products.

So, what must pharma companies bear in mind in order to harness HPAPIs for their OSD products successfully? Here are the four key challenges that need to be considered and overcome both during the development process and during commercial manufacturing of finished products:

Challenge 1: Classifying Potency Effectively

As we have mentioned, HPAPI is a large and diverse category of ingredients, each with its own features, benefits, needs and hazards. It is crucial to understand the potency and toxicity of the API being used in the OSD product, in order to establish the most appropriate production line measures to minimise safety risks for employees.

Broadly speaking, an API is classed as "highly potent" if it – or the intermediates that are used to make it – falls 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 API or intermediate with high selectivity,** meaning 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.
- **A novel compound** of unknown potency and toxicity.

APIs can be further classified into four categories under the performance-based exposure control limits (PBECL) system according to their potency and toxicity:

- **Category 1 compounds:** are low potency with higher dosage levels.
- **Category 2 compounds:** moderate acute or chronic toxicity, but their effects are reversible.
- **Category 3 compounds:** have elevated potency, with high acute or chronic toxicity; these effects may be irreversible.
- **Category 4 compounds:** have high potency and extreme acute and chronic toxicity, cause irreversible effects and are likely to be strong sensitisers, with poor or no warning properties and a rapid absorption rate.

All highly potent products are category 3 or 4 in this system, based on their cumulative risk factors; regulatory requirements for containment and protection vary depending on the category.

In order to address the next three challenges, it is crucial to understand exactly where the API in question sits in each of the above categories. The higher the category, the more stringent the containment and safety processes have to be in development facilities and on manufacturing lines to safeguard employees and to minimise the risk of cross-contamination between products. Support from experts in HPAPI handling is crucial to identify and understand the category the ingredient in question should be placed in.

Challenge 2: Establishing the Most Effective Approach to Containment for The OSD Line

Once the potency, the toxicity and

precise nature of the safety risk is firmly established, it is crucial to identify and develop appropriate containment measures for the OSD production line. A number of key elements must be considered to develop an effective safety strategy:

- **The criticality of the HPAPI in question** – meaning the precise risk posed by the chemical.
- **The layout of the production line** – OSD production lines in particular feature a number of areas where potential containment issues can occur, requiring stringent control measures. Points where operations take place that have a high probability of dust dispersion, such as dispensing, granulation or sieving, may be designated High Contamination Areas, requiring the most stringent controls. Areas with operations that have a low probability of dust dispersion, such as tablet collection, in-process control (IPC) testing and primary packaging, may be designated Low Contamination Areas, requiring less rigorous measures. Normal Pharma Areas, such as secondary packaging lines, require no special controls, as there is no probability of dust becoming airborne.
- **High containment equipment** – such as isolators to minimise the risk of containment breaches occurring.
- **Material flow** – OSD production often requires the processing and handling of dry powdered materials, which can be a particular concern due to their ability to become airborne. If appropriate containment and cleanroom measures aren't taken – and if portable equipment containing the HPAPI isn't handled correctly – airborne particles can easily escape the confines of the production line, or even enter air ventilation systems to circulate throughout the wider facility, with repercussions for employee safety.
- **Personnel flow** – it is not enough to consider the layout of the production line and the flow of material to establish control measures. It is also important to take into account employee behaviour and the way they move through the production line. This is crucial to establish points on the line and the times where they need to be in contact with production equipment, such as during cleaning or production changeovers. Understanding such factors is key to establishing measures to minimise contamination and optimise safety.
- **Personal protective equipment (PPE)** – is crucial to ensuring optimum employee safety. The type of PPE – protective suits or fitted masks – required will depend on the nature of the material – whether it is dry and easily made airborne – as well as the nature of its toxicity.
- **Environmental management** – the waste products from HPAPI processing can have negative implications for the surrounding environment, wildlife, and local communities too. This means they need to be managed and disposed of carefully after use.
- **Procedures and training** – in addition to all of this, it is crucial to establish training and safety protocols for employees to ensure they understand the risks involved on the production line and know what they need to do to manage and safeguard their own health and that of their colleagues.
- **Monitoring** – continuous monitoring of safety systems should also be included in order to ensure control points continue to offer optimum performance, maximising safety for employees.

To optimise containment and minimise safety risks, it is advised to develop a strategy covering all of these elements in line with local regulatory requirements. Building a dedicated HPAPI-handling facility within a larger site – the so-called "plant-in-plant" concept – can go a long way towards streamlining the requirements within such a strategy. Such an approach can minimise the risk of cross-contamination by isolating HPAPI production from other manufacturing projects. It can also reduce training and PPE requirements, as it will only be necessary to train the individuals working in the HPAPI facility itself, rather than the entire workforce.

Challenge 3:
Effective Technology Transfer Strategies

It is often the case that HPAPI OSD projects have to be transferred either between the drug developers' own facilities, or from the drug developer's site to that of a trusted contract development and manufacturing organisation (CDMO). Not only must the new facility be adequately prepared to ensure containment of the HPAPI prior to the start of operations, but steps must also be taken during the transit of the HPAPI material to minimise contamination risk.

To ensure optimum containment throughout, an accurate preliminary strategy can be crucial. It can help intercept and anticipate any and all possible issues that may be encountered. These include process robustness, regulatory and environmental health and safety aspects, and last, but not least, equipment classifications.

Equipment classification is as critical as any other aspect of the technology transfer, in order to ensure the equipment at the receiving site is comparable to that at the donor site. Classification must be done according to the requirements of the Scale-Up and Post-Approval Changes (SUPAC) guidelines drawn up by the US Food & Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER). This guidance offers a comprehensive list of comparable equipment, allowing companies to determine whether adjustments need to be made to the receiving site prior to any transfer, saving time and resource, while also ensuring safe handling of any APAPI.

The features of an effective strategy include:

- Site segregation assessment
- Process robustness verification
- Process optimisation
- Regulatory considerations
- Environmental health and safety considerations

Experience is the key to understanding the needs of the HPAPI and the drug formulation in all of these areas. This will help ensure the HPAPI and its accompanying materials are transferred smoothly and safely.

The specific type of technology transfer will also dictate what is contained within the strategy. There are two different types of technology transfer:

- **Primary** – where the product is transferred from research & development (R&D) to the Receiving Site, such as a CDMO or contract manufacturing organisation (CMO).
- **Secondary** – where the product is already on the market and its production is transferred from the Sending Site to the Receiving Site (site-to-site).

The secondary transfer of a project, given that it takes place within a company's own operations, should be reasonably straightforward as communications channels between the two sites should

already be well established. Primary transfers may be more complex, as lines of communication between the company and its outsourced CDMO partner may need to be built from the ground up if the relationship is new. With this in mind, it is crucial to engage expert partners that have experience in HPAPI transfers in order to ensure the process takes place smoothly, with minimal risk of containment breaches or delays.

Challenge 4: Safe and Effective HPAPI OSD Production and Packaging Lines

Finally, regardless of whether a transfer has taken place or not, it is important to ensure that the production and packaging lines are suitable for safe and effective HPAPI OSD production.

An ideal HPAPI OSD manufacturing and packaging line should include:

- High containment processes in a closed system with control measures throughout in line with the requirements of the category classification of the HPAPI being handled.
- HPAPI dispensing and milling equipment contained in a segregated area or isolator staffed only with qualified personnel to minimise contamination and safety risk for employees.
- If producing tablets, dry granulation with pre-tabletting, sieving, and tabletting in a segregated cleanroom area again to optimise containment and safeguard worker wellbeing.
- For capsules, high or low-shear wet granulation and drying with capsule filling in a segregated cleanroom environment.
- Tablet visual inspection systems to allow safe, remote quality control processes.
- Contained packaging lines to minimise containment breach risks as the finished tablets or capsules are dispensed into their primary packaging. The containment protocols depend on the nature of the chosen packaging – the containment equipment needed for a bottle presentation necessarily differs from that required for blister packs.

The inclusion of technologies can help further minimise safety risks on HPAPI OSD lines. For example, housing HPAPI manufacturing and packaging processes within "pressure cascade" systems can prevent contamination of external areas. A nitrogen inserting system can be installed to provide protection for team members handling hazardous compounds with solvents.

The measures needed to create a secure and contained HPAPI processing line takes considerable time and investment to put in place. Outsourcing processing and packaging of HPAPI OSDs can help pharma companies access effective, high-quality contained production lines quickly and efficiently, streamlining project timeframes while ensuring optimum health and safety.

Reconciling Efficiency with Safety in HPAPI OSD Production

Given the potential of HPAPIs not just to enhance patient convenience, but to treat a wide array of serious, previously untreatable conditions, it is no surprise that so many new highly potent drug candidates are entering development all the time.

As a well-established, effective, and highly convenient dosage form for systemic drug delivery, OSD offers a number of unique benefits that complement the patient convenience advantages of HPAPIs. As such, we can expect the number of HPAPI OSD development and manufacturing projects to continue to grow into the future.

Nevertheless, the potency and toxicity of HPAPIs means that careful consideration needs to be taken to the facilities and processes in place at the site intended to handle manufacturing and packaging. Failure to take appropriate steps can have negative ramifications for employees, as well as the surrounding environment and neighbouring communities as well.

By taking into account the challenges we have discussed, and taking steps to address them as early as possible, pharma companies can be confident they have the measures in place to optimise containment throughout every step of their development and manufacturing process. In doing so, they can ensure optimum health and safety, in line with stringent safety regulations.

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After joining Pfizer in 2001 as a Finance Analyst, Mario progressed through the ranks as Finance Manager, Ascoli Finance Lead, and Supply Chain Lead. He now heads up the Ascoli site team as a Pfizer CenterOne Lead. Mario holds a master's degree in Economics and Business Administration and an APICS Certification. In his role, Mario manages business development, introduces new products, and oversees all CDMO activities at the Ascoli site.