ROUNDTABLE REPORT

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Scrip
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Choosing The Right CDMO For HPAPI Development, Manufacturing & Packaging

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KEY TAKEAWAYS

- When assessing risk and evaluating containment strategies, occupational exposure limits are the most appropriate assessment measure.
- All parties involved in any HPAPI project must align on potency classification.
- HPAPI-related outsourcing decisions are driven by multiple, complex factors such as safety, process complexity, and speed to market.
- Cleaning validation to reduce cross-contamination is a complex issue and one that should be a primary consideration when looking to outsource to any CDMO partner.
- Pharmaceutical companies are paying closer attention to the packaging of products containing HPAPIs.
- There are benefits in working with one CDMO throughout the entire development to commercial launch life cycle.

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OVERVIEW

Safe handling of highly potent molecules is complex, and the associated regulatory requirements are growing. As a result, pharmaceutical companies recognize the importance of selecting the right partner for the development, manufacturing, packaging and commercialization of products containing high-potency active pharmaceutical ingredients (HPAPIs). Some companies work with one contract development and manufacturing organization (CDMO) throughout the entire life cycle, while others partner with multiple vendors. To ensure success, teams must conduct due diligence to identify CDMOs that meet their safety, technology, process, economic and schedule requirements.

CONTEXT

A panel of experts discussed the key areas for consideration and best practices when outsourcing HPAPI development, manufacturing and packaging to a CDMO.

KEY TAKEAWAYS

When assessing risk and evaluating containment strategies, occupational exposure limits are the most appropriate assessment measure.

Many organizations use different terms when classifying HPAPIs, such as occupational health categorizations (OHCs), occupational exposure bands (OEBs), or even just control bands, which can lead to confusion. In addition, pharmaceutical companies themselves may use a variety of their own in-house banding classification systems. As a result, in the event of any outsourcing requirement, a careful transfer of data packs and clear communication is crucial to allow the chosen third party to make an accurate assessment based on their own criteria. Specialist industrial hygiene companies – such as Affygility Solutions for example – exist to assist companies with harmonizing assessments and reducing the risk to both parties. Companies such as this can be working with in excess of 15 different banding systems in any given week and as such, are able to provide extensive expertise around this subject. As this has been an area of constant concern due to the critical importance of safety, the pharmaceutical industry attempted to harmonize the different systems several years ago, but the initiative has not been successful.

To put OEB data into context, occupational exposure limits (OELs) are critically important. Companies need well-documented OELs, as well as industrial hygiene experts who can interpret OEL data and evaluate the workplace. This means creating a risk assessment program that determines the probability of exposure based on a combination of occupational hygiene and containment procedures. It's important to remember that risk assessment isn't a one-time exercise. All too often, companies conduct spot monitoring or initial containment validation upon equipment installation then never do any additional monitoring.

> OEL is the language that everyone understands. It's a value that you can put in your risk assessment criteria and use to determine the right answer for containment. Communicating with OELs is a better approach than OEBs.
>
> *Ester Lovsin Barle, Takeda*

When it comes to highly potent compound safety, facilities must develop containment strategies that strike the right balance. At one end of the spectrum, companies may not have adequate containment and analytical methods to prevent employee exposure and cross-product contamination. At the other end, companies may invest in expensive engineering controls and procedures that depending on the product may not always be necessary. This demonstrates the importance of making an accurate assessment of the product OEL that in turn informs the decision as to what level of containment is required.

All parties involved in any HPAPI project must align on potency classifications for APIs.

In some cases, two groups may assess the same HPAPI and arrive at different potency classifications. If the results aren't in reasonably close alignment, both parties will need to review the safety data together, maintaining open dialogue at all times. In some cases, the misalignment may be due to missing data, for example, the genotoxicity data may have been omitted which once added solves the issue. Across the panel it was also agreed that understanding the mechanism of action is a crucial part of the process. Open dialogue, sharing of all data and asking the right questions are key factors in resolving any conflicts with classification and ultimately informing the decisions around the safe processing of the HPAPI. It is also helpful to see whether both parties have applied the right adjustment factors and bioavailability correction factors.

Data access is critical for reaching alignment. Innovator pharmaceutical companies own all their data, so access is easy. Generic companies, however, may not have that level of data access. In addition, if a compound is for example over 20 years old, the quality of the available data may not be of the standard now required. In this scenario, companies often need to turn to experts with the right credentials to help understand potency and apply the correct safety controls.

> You want to make sure as a CDMO client that you provide the most accurate potency data possible. We use that information to determine where and how to process materials in terms of the level of containment needed. When we work with highly potent molecules in our specialist facility that utilizes contained engineering technology for example, the length of time to manufacture is longer and comes with a higher cost. If a product is not classified as being highly potent, we can process elsewhere within the facility meaning assessment of potency is critical both in terms of safety, but also in ensuring the right solution for the customer project.
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> *David O'Connell, PCI Pharma*

HPAPI-related outsourcing decisions are driven by multiple, complex factors such as safety, process complexity, and speed to market.

The roundtable participants shared their insights into the main drivers for outsourcing HPAPI development, manufacturing and packaging:

- **Safety is the primary consideration.** Pharmaceutical companies recognize how important it is to verify that CDMOs can safely handle highly potent compounds. It is essential to visit facilities and evaluate their manufacturing capabilities, as well as their supporting analytical capabilities.

> With highly potent compounds, safety isn't just the number one priority; it's the number one, two, and three when evaluating the ability of a CDMO to handle these materials, use the appropriate cleaning protocols, and communicate between quality and safety.
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> *Ijaz Ahmed, ImmunoGen*

- **Process complexity often drives outsourcing decisions.** Many of PCI Pharma's customers, for example, have a longer-term plan to transfer operations in-house at some point. However, during the development to supply process, the company may gain a true understanding of the complexity and the capital investment required to replicate in-house and decide that it makes better business sense to maintain their outsourcing relationship. Looking ahead, the panelists agreed that HPAPIs would continue to represent a challenging niche and that pharmaceutical companies will continue to outsource to specialist CDMOs.

> It's easy for a CDMO's marketing team to say it can handle HPAPIs. You have to go there and lay eyes on the facility to see if they really have the capabilities. We've seen facilities with secondhand isolators still shrink-wrapped in the corner of a room. They've done no containment validation, no industrial hygiene monitoring, they're relying on traditional methods of PPE and worse still, they don't even really know if the PPE is protecting them. This is a worrying state but something we see all too often.
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> *Dean Calhoun, Affygility Solutions*

- **A growing number of virtual pharmaceutical companies rely on CDMOs offering specialist high-potency capabilities.** As virtual entities, they outsource almost all aspects of the development to commercialization cycle, looking for the most time-efficient solution. Often, such companies will either be looking to sell their asset or become the target of an acquisition during the clinical stages. At this point, the purchaser will then make an assessment as to whether to leave the product where it is or transfer elsewhere with speed to launch being a key consideration. Again, when dealing with highly potent products, this can be a far more complex decision process.
- **HPAPI-related outsourcing isn't limited to the initial launch of a product.** It usually takes several years beyond commercial approval for a drug to reach peak demand. Usually, the process validation scale completed prior to initial approval may not cover the period of peak demand. As a result, many companies outsource to a secondary supplier in order to meet the demand of the sales cycle during that peak "bubble".

Cleaning validation to reduce cross-contamination is a complex issue and one that should be a primary consideration when looking to outsource to any CDMO partner.

When CDMOs manufacture pharmaceutical products for several customers in the same facility, they must ensure that they are performing the appropriate cleaning validation. It is complex for any CDMO offering multi-product processing and so information and communication is essential. To calculate permitted daily exposure (PDE) values, CDMOs need to obtain high-quality data about every HPAPI

from clients. It is also important to consider the route of administration for the drugs since this can affect the cleaning or carryover limits. A product that is to be given in an intravitreal dosage form could lead to an overdose if the previous product on the same equipment train was not, therefore cleaning limits have to be assessed for every product and every dosage form.

In June 2015, the European Medicines Agency issued health-based exposure limit guidelines. These included three criteria that manufacturers must meet to avoid dedicated equipment:

1. The ability to control the process to prevent cross-contamination
2. Access to scientific data that supports that the products aren't sensitizers
3. Deployment of sensitive enough analytical methods

Some CDMOs fall short because they set the analytical limit for their cleaning validation but then do not have sensitive enough methods to detect the limit. If they want to operate in the high-potency arena, equipment has to be of an appropriate standard and not be relying on high performance liquid chromatography systems that may be old and may not be sensitive enough to safely trust. As a result, CDMOs may need to invest in new equipment such as liquid chromatography mass spectrometry devices, or outsource to an approved supplier.

It is also important to remember that this is not a static process. As new data becomes available during the development and manufacturing life cycle, adjustments should be made to the PDE which affects the carryover. Therefore, a continuous life-cycle approach should be taken, updating processes and documentation as new data becomes available.

All equipment within PCI Pharma's contained facility has either clean-in-place or wash-in-place systems and the company is mindful of factors such as rinse water, using riboflavin testing to ensure suitable cleaning coverage. A robust approach to cleaning validation as part of the overall development to manufacturing process should be fundamental to any CDMO philosophy and approach and extensively investigated by any company looking to outsource a HPAPI compound.

> One thing that pharmaceutical companies and CDMOs need to discuss and align on is the quality management system and how that applies to early and later development phases. There needs to be a strong focus on knowledge management and making sure those processes are captured and managed well. You have to ask the right questions to get the right data and ensure this is underpinned by a robust quality management system.
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> *Peter Tiffin, CMC Consultant*

Pharmaceutical companies are paying closer attention to the packaging of products containing HPAPIs.

When companies package drugs containing HPAPIs, some may take the more traditional and perceived easier path by using glass bottles for the primary packaging. A cohort of experts worry, however, that these containers can easily break and potentially expose highly potent compounds during transit.

The panelists agreed that risk assessment procedures for packaging must be conducted earlier in the product development process. This earlier stage risk assessment needs to consider the HPAPI and the dilution factor, taking into account that in many cases the ultimate HPAPI concentration may represent a low percentage of the final dosage form. Other considerations relate to processing and the final dosage form. From a risk perspective, teams should evaluate, for example, whether the product is a tightly bound granule or a loose powder blend, encapsulated or a coated/uncoated tablet. That evaluation will assist in making the right decisions as to the most suitable packaging configuration for a product early in the process.

The safety of healthcare providers that come into contact with the packaging is also growing concern around products containing HPAPIs. The pharmaceutical industry has been taking a more proactive stance when communicating with providers around the appropriate handling of these products.

> USP 800 went live recently and there's a lot of focus now on how healthcare providers should handle drugs containing HPAPIs. It's something that drug developers need to take into consideration. Although it's incrementally more work, it offers a huge benefit for healthcare providers.
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> *Chris Sears, Tarveda Therapeutics*

There are benefits in working with one CDMO throughout the entire development to commercial launch life cycle.

The roundtable participants suggested that using one CDMO from early-stage drug development through to commercial launch is perhaps the ideal scenario. This approach means fewer handoffs and tech transfers between vendors, reducing the project risk. It also ensures that all data and experience relating to a product remains in one place as, even with the best approach to technical transfer through documentation and reports, there can still be gaps in scientific knowledge.

They acknowledged, however, that in the real world, CDMO decisions are often based on time and money and can be driven by factors limited to the phase that a product may be in within the life cycle.

It was also discussed that not every CDMO is suited to handling the entire life cycle. Although some vendors are very good at manufacturing commercial products at scale, they may not have the expertise needed to handle early development phases of new compounds, particularly if additional formulation development expertise is required.

Conversely, the smaller CDMOs specializing in earlier stage development may offer highly flexible schedules, and have an ability to move quickly, particularly at the earlier stages of development. They may not however, be equipped to offer the manufacturing scale for later-stage clinical and commercial launch demand.

Regardless of how many CDMO partners a company may or may not use, the pharmaceutical company itself should always maintain full knowledge and ownership of the project and data. This is crucial both as the proprietary owner of the product, but also in the event of needing to transfer knowledge to a new CDMO vendor.

> We've had customers come to us because of our specialist HPAPI expertise and our ability to deliver true speed to market. Some plan to then move operations in-house post-launch but as they get into it, they find out just how complex some of the processes are, the specialist expertise and investment required and ultimately decide to leave the products with us because it didn't make business sense to change.
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> *Michael Ellingson, PCI Pharma*

ADDITIONAL INFORMATION

For further details click here

BIOGRAPHIES

Ijaz Ahmed
Scientist II, Process Chemistry, ImmunoGen

Dr. Ijaz Ahmed has been working at ImmunoGen as a Process Chemist for the past 10 months. His interest in process chemistry started at Vertex Pharmaceuticals after his postdoctoral at WPI. He has worked mainly with non-potent compounds in his career and has now transitioned to highly potent compounds.

Ester Lovsin Barle, DVM, MSc, PhD, MScTox
Head of Product Stewardship and Health, Takeda

Ester's responsibilities include Safety Data Sheet processing; maintaining article and material regulatory compliance; scientific development and cross-organizational implementation of health-based exposure limits (HBEL) in support of research and manufacturing in Takeda globally; and global implementation of occupational hygiene and product stewardship sustainability activities. Previously she has held corporate positions at Lonza and Novartis. She received her PhD in veterinary sciences from University of Ljubljana, Slovenia and a second master's degree in toxicology and risk assessment from Medical University in Vienna.

Dean Calhoun, CIH
Founder & CEO, Affygility Solutions

As Affygility Solutions' Founder and CEO, Dean does much more than wrestle industrial hygiene pumps, he leads people, teams, and companies in solving their toughest potent compound safety challenges. With over 35 years of professional experience, Dean created and led the vision for OEL Fastrac – the award-winning online platform for obtaining high-quality OEL and ADE monographs. Additionally, Dean has performed numerous potent compound safety assignments throughout the world, helping these companies greatly improve their potent compound safety systems. As an invited speaker, Dean has spoken at numerous events throughout the world including the HPAPI Summit,

CPhI, AIHce, and many others. Dean has a B.Sc. degree in Engineering from the University of Wyoming and dual M.Sc. degrees in Environmental Policy and Management, and Technology Management from the University of Denver. Dean is an American Board of Industrial Hygiene CIH, and is a member of AIHA, BOHS, ISPE and SCHC.

Michael Ellingson

Operations Director, Specialty, PCI Pharma Services

Mike Ellingson joined PCI in 2010 as a Project Manager and transitioned through the Project Management side of the business through 2018. Ellingson then spearheaded the S&OP initiative with site wide responsibilities around capacity, scheduling, labor management and financial commitments. At the same time, he became the Director of Specialty Operations responsible for all aspects of the New Milford School Road site where high potent compounds, hormones and other products requiring special handling are packaged.

David O'Connell BSc (Hons)

Director of Scientific Affairs, PCI Pharma Services

After graduating from Glasgow Caledonian University in Scotland with a Bachelor of Science degree in Applied Bioscience, O'Connell spent seven years as a Supervisory Scientist working for Aptuit in Edinburgh, Scotland, before moving to Penn Pharma as Head of Formulation Development in 2009. Here he played a vital part in the design of the potent Contained Manufacturing Facility (CMF), which won the ISPE Facility of the Year award for Facility Integration (2014). In 2014 PCI acquired Penn Pharma and O'Connell took on the role of Director, Pharmaceutical Development at the PCI site in Tredegar, Wales, UK. In his current role, O'Connell aids clients with formulation development, technical transfer and scale-up of solid oral, oral liquid and semi-solid products for clinical trials and/or commercialization. David also has line management responsibility for the Validation Team (Process, Equipment and Facilities) and the Quotes proposal preparation group.

Christopher Sears

Vice President of Chemistry, Manufacturing, and Controls (CMC), Tarveda Therapeutics

Chris is Vice President of CMC at Tarveda Therapeutics and is responsible for oversight of Tarveda's CDMO network, manufacturing, supply-chain, and CMC development of Tarveda's investigational-stage therapeutics. He has managed internal and external manufacturing, chemistry, formulation, analytical/QC and supply chain functions over 19 years in the biopharma industry. Chris has broad experience including NCE development, process validation/PPQ, equipment and facility design/commissioning/qualification, process scale-up, CDMO management, and technology-transfer. He has been CMC-lead for multiple IND and market applications.

Peter Tiffin
Head of CMC, Artemida Pharma Limited

A CMC consultant with experience spanning the discovery/development interface through to marketing authorization. A track record of successful innovation, product development and regulatory submissions in the field of small molecules and synthetic peptides. Strong experience working with Asia-based pharma companies to support manufacturing operations and regulatory submissions outside of the continent.

Dean Rudge (Moderator)
Senior Reporter, Informa Pharma Intelligence

Dean has built up a wealth of knowledge on the global generics and biosimilar medicines industries in his five years with Generics bulletin. He specializes in commercial and legal issues, writing in-depth analyses of corporate strategy and getting under the skin of patent-infringement proceedings and other litigation. He attends investor and regulatory meetings with business leaders, favoring the investor days with their focus on corporate strategy.