ROUNDTABLE SUMMARY

March 23, 2023

Scrip
Pharma Intelligence

The Challenges of Scalability in High Potency Manufacturing

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David O'Connell, Director of Scientific Affairs, PCI Pharma Services
Phillip Gabb, Strategic Business Director, GEA Group
Kerry Kingdom, Head of Process Optimization and Validation, PCI Pharma Services
Jerome Detreille, Senior Director of New Business Development, PCI Pharma Services
Andrew Warmington, Manufacturing Editor, Custom Content, Citeline (Moderator)

KEY TAKEAWAYS

- When scaling the manufacture of drug products containing HPAPIs, reducing risk and delivering consistent quality are essential.
- Containment requirements can introduce manufacturing challenges.
- CDMOs focus on flexible facility design to accommodate both small- and large-scale production.
- Collaboration is the key to creating tailor-made manufacturing solutions.
- CDMOs can minimize financial, technological, and regulatory risks associated with drug development.
- When it comes to high potency APIs, operator health and safety are top priorities for regulators and industry players.
- To profit from the growing high potency drug market in the years ahead, companies must secure manufacturing capacity.

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OVERVIEW

High potency is one of the fastest growing segments of the pharmaceutical industry, in terms of both drug substance and drug product. A combination of factors is driving this growth, including patent expiries, advances in clinical pharmacology, and the increasing relative importance of oncology, which accounts for the largest share of the high potency market. As greater volumes of high potency drugs come to market, companies must decide whether to invest in scalable manufacturing capacity. Financial, technological, and regulatory considerations all play a role.

CONTEXT

A panel of experts explored obstacles and opportunities associated with the scalable manufacture of drug products containing high potency APIs (HPAPIs). They discussed the pros and cons of in-house manufacturing versus a contract development and manufacturing organization (CDMO).

KEY TAKEAWAYS

When scaling the manufacture of drug products containing HPAPIs, reducing risk and delivering consistent quality are essential.

When companies develop new chemical entities and products, some start at a very small scale, with the goal of reaching a Phase I trial as soon as possible. If the Phase I trial is successful, the next challenge is scaling up production. The panelists offered insights about this transition:

1. **Moving from a smaller more niche CDMO to a larger CDMO offering onward scalability introduces complexity and risk.** When a sponsor company needs to move to a CDMO partner able to manufacture at larger scale, the team must engage in another round of technical and knowledge transfer. This process can be de-risked by identifying a CDMO able to develop and manufacture small-and large-scale formulations enabling seamless life-cycle management.
2. **Delivering product quality is a top priority when scaling pharmaceutical production.** It is important to maintain robustness in the manufacturing process, so that the end-product quality is reproducible from small to large-scale.
3. **Production equipment plays an important role in successful scale-ups.** PCI Pharma Services works extensively with equipment suppliers. Their fluid bed granulation systems can handle small-scale batches, and geometrically similar equipment is used to support larger-scale production. This ensures the products meet quality targets when scaling-up.

> "As you scale your manufacturing process, you must maintain a robustness to ensure the end product quality is the same for your small-scale trials as for later phase or scale-up trials."
>
> *David O'Connell, PCI Pharma Services*

Containment requirements can introduce manufacturing challenges.

When manufacturing high potency products, it's critical that operators aren't exposed to dangerous chemicals. As a result, containment is essential during processing, material transfer, cleaning, and sampling. This affects the design of equipment such as high shear mixers, fluid beds, and tablet presses.

From a quality perspective, contained systems make it much more difficult to assess homogeneity or conduct blend analysis. Teams need as much knowledge about the product and formulation process as possible before going into any formal process performance qualification.

One way to mitigate these risks is for CDMO scientists, equipment suppliers, and the teams at sponsor organizations to conduct a thorough knowledge transfer. Endpoint determination data, for example, is important. For a wet granulation, this could include the impeller torque information. For a fluid bed drying process, it could be the moisture level of the granulate. Documents including development reports and executed batch records are useful.

Gap analyses are another way to reduce risks. A material gap analysis can ensure that excipients are available from the same supplier or of the same grade and an equipment gap analysis can also identify potential pitfalls.

CDMOs focus on flexible facility design to accommodate both small- and large-scale production.

Most pharmaceutical companies with in-house manufacturing sites know years in advance what products they will be making. In contrast, CDMOs have no visibility into what they will be manufacturing next month, let alone next year.

As a result, CDMOs like PCI Pharma Services design *flexibility* into their facilities and work with suppliers that are agile enough to make quick changes to equipment when necessary. For example, PCI's smallest and largest intermediate bulk containers (IBCs) use the same split butterfly valves. In addition, all IBCs are contained in the same size frame, enabling clients to scale a small batch to a larger one more rapidly.

> "Most pharma facilities know what product they will be manufacturing years in advance. CDMOs have no visibility into what they'll be making next month. They have to design flexibility into the system from the start and they need suppliers who are agile enough to accommodate quick equipment changes."
>
> *Phillip Gabb, GEA Group*

Collaboration is the key to creating tailor-made manufacturing solutions.

Close communication between the CDMO, client, and supplier help teams deliver quality products on time. Important considerations include:

- Will the project fit in the facility?
- Will compromises need to be made related to batch size?
- Will an alternative piece of equipment need to be used, rather than a preferred one?

PCI has found that client collaboration is fruitful because it often uncovers solutions the team hadn't considered. Communication and collaboration are also essential for meeting the compressed timelines associated with fast-track regulatory approval. Breakthrough therapy designation is common with high potency compounds, especially in oncology. In these instances, the chemistry, manufacturing, and controls (CMC) program must move faster than with a conventional program.

> "Strong communication with clients is the key to understanding their requirements and how we can adapt our processes to meet their needs. We can usually act quickly. We aren't big pharma, so we are very agile in reaching solutions."
>
> *Kerry Kingdom, PCI Pharma Services*

CDMOs can minimize financial, technological, and regulatory risks associated with drug development.

Drug development companies such as Taiho have two options for manufacturing drug products containing high potency APIs: 1) in-house manufacturing, or 2) outsourcing to a CDMO. In some cases, the decision is easy—if the company doesn't have in-house capabilities, it must turn to a CDMO. In other instances, the decision is less clear cut.

The panelists shared reasons why a company might outsource to a CDMO:

1. **A well-equipped strategic partner can streamline the scaling process** and reduces project risk.

> "A company like PCI Pharma Services enables us to use the same facility to manufacture our first clinical trial material all the way through to the commercial launch material. This can be very attractive for projects with compressed timelines due to breakthrough designation."
>
> *Peter Tiffin, Taiho Oncology Europe*

2. **Access to advanced technologies reduces financial risks.** The discovery and development processes for high potency products have a high risk of failure. At the same time, manufacturing is expensive, requiring capital investment in fully contained operations and specialized technologies. CDMOs absorb these risks for life sciences companies by providing access to advanced manufacturing technologies. PCI Pharma Services is always looking at the next level of technology investment to differentiate itself. It has invested in technologies important to developers of high potency products, such as roller compaction equipment and automatic visual inspection.

> "We provide flexibility and agility for drug development companies from early-stage projects all the way through to commercialization. For new high potency drugs under development or for orphan drugs, companies can avoid the capital expenditures needed to build manufacturing facilities. If a commercial drug is a blockbuster, we can help with dual sourcing solutions to address increased volumes."
>
> *Jerome Detreille, PCI Pharma Services*

3. **A team of experts offers a broad range of support.** Companies appreciate PCI Pharma Services' experienced staff in R&D, laboratories, and process and validation teams. These team members provide clients with support beyond simply manufacturing their clients' products due to the breadth of experience.
4. **Regulatory expertise provides peace of mind.** PCI Pharma Services has a long and sound inspection track record with major regulatory authorities including the FDA, EMA, the MHRA and others. The team has addressed many of the regulatory "hot topics" related to handling high potency drugs.

When it comes to high potency APIs, operator health and safety are top priorities for regulators and industry players.

Cross-contamination, cleaning verification, and containment breaches are all areas of interest for regulatory bodies. To address cross-contamination, PCI Pharma Services has adopted a risk-mitigation strategy based on multiple levels of protection. These include:

- Running equipment under negative pressure.
- Using a negative pressure cascade in processing rooms, similar to a solid oral drug manufacturing facility.
- Segregating people, materials, and equipment. PCI has its own dedicated utilities, such as an effluent treatment plant.
- Providing personal protective equipment for operators.

For cleaning verification, PCI Pharma Services uses health-based cleaning limits. Permitted daily exposure levels dictate the cleaning methods utilized in manufacturing facilities. Teams look at all product touch points for all pieces of equipment, and they also consider batch sizes and maximum carryover.

To detect containment breaches and invisible leaks of high potency APIs, GEA Group has developed a real-time dust exposure monitor. This samples the air and sounds an alarm if safe levels are exceeded. Industrial hygienists, as well as health and safety authorities, believe that this will be a game changer.

> "PCI really understands the risks associated with containment and how to mitigate them. That's unusual in my experience. There aren't many companies with the same depth of understanding. That's what helps them to successfully manufacture potent materials."
>
> *Phillip Gabb, GEA Group*

To profit from the growing high potency drug market in the years ahead, companies must secure manufacturing capacity.

The panelists offered opinions about the future of high potency drug development:

1. **High growth is expected to continue for high potency APIs.** Experts forecast that the high potency market will grow up to 10% annually until 2030. Most of that growth is coming from new product development—and oncology is the top target area for these drugs. With precision medicine, highly targeted molecules will be more active and efficient at lower doses. In addition, new generics based on high potency APIs are coming out as patents expire.

2. **The shift from IV dosing to solid oral dosing will gain additional momentum.** This will improve the patient experience, since people won't have to spend days and weeks in the hospital receiving chemotherapy infusions. To accommodate this trend, PCI Pharma Services has recently doubled its high potent solid oral dosage commercial manufacturing capacity, with a second Contained Manufacturing Facility launched in 2023.
3. **Containment is a technology in its own right and represents a large opportunity.** For pharmaceutical manufacturers working with high potency APIs, containment is just as important as granulation, compression, or roller compaction technologies. It's essential that teams have a good understanding of what containment really means.
4. **Drug developers will compete for manufacturing capacity.** The drug development industry is highly competitive. To maximize their success, companies must focus on securing access to manufacturing capacity at CDMOs able to meet their business needs.

CONCLUSION

High potency drugs have enormous potential to improve patient lives and these drugs present a huge business opportunity for life sciences companies. To decrease time to market and reduce business risk, many organizations are turning to CDMOs such as PCI Pharma Services to assist with manufacturing at every stage the product life cycle.

PCI Pharma Services is committed to high quality and safe manufacture of drug products containing high potency APIs. It has invested in expert talent, cutting-edge technologies, and flexible facility design.

By partnering with PCI Pharma Services, companies can focus on the science of drug development with the knowledge that manufacturing will be performed efficiently, cost effectively, and in compliance with global regulatory requirements.

BIOGRAPHIES

Peter Tiffin
Vice President, CMC, Taiho Oncology Europe

Peter Tiffin is Vice President, CMC for Taiho Oncology Europe with direct accountability to the parent company in Japan. Peter trained as a synthetic chemist and obtained his PhD from the University of Manchester Institute of Science and Technology (UMIST). Prior to joining Taiho Peter spent 15 years working as a CMC consultant supporting drug substance and drug product manufacturing operations, and CMC Regulatory submissions. His experience covers early phase submissions through to marketing authorization. Peter is a Fellow of the Royal Society of Chemistry..

David O'Connell

Director of Scientific Affairs, PCI Pharma Services

David O'Connell is the Director of Scientific Affairs at PCI Pharma Services, an integrated full service provider expertly delivering a seamless transition from development to commercialization. After graduating from Glasgow Caledonian University with a BSc. in Applied Bioscience, David spent seven years as a Supervisory Scientist working for Aptuit in Edinburgh 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 2013 David took on the role of Director, Pharmaceutical Development at the PCI site in Tredegar and in 2017 became PCIs Director of Scientific Affairs.

Phillip Gabb

Strategic Business Director, GEA Group

Phillip Gabb graduated from Nottingham University in Chemical Engineering. After fifteen years working in general powder handling and packaging equipment for the food, chemical, plastics, and rubber industries in the UK, Phillip joined GEA in 1998. GEA are leaders in supplying process solutions to the pharmaceutical industry, as well as many other industries. Phillip was Sales Director for twelve years, and then Senior Sales Director for all Pharma Solids applications, including Batch and Continuous Processes, Tablet Compression, and Materials Handling, for four years. Current role is Strategic Business Director, responsible for coordinating GEA activities with major customers, and on large integrated projects.

Kerry Kingdom

Head of Process Optimization and Validation, PCI Pharma Services

Kerry has worked for PCI for six years, currently focussing on technical transfer, late stage development, together with the subsequent process validation and process support for the commercialized product. She has worked in the Pharma Industry for 30 years primarily for CDMOs, providing subject matter expertise on the Manufacture and Packaging of most dosage forms from concept to launch. She has led R&D, Validation and Process Support teams and works collaboratively with clients to expedite speed to patient and commercial market.

Jerome Detreille
Senior Director of New Business Development, PCI Pharma Services

After graduating from Strasbourg University of Pharmacy, France, Jerome Detreille spent thirteen years as European Director of Business Development in Catalent for Sterile injectables, before moving to Penn Pharma as Senior Director New Business development in 2012. Here, he was part of the Executive Team who built 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 Jerome continues to act as Senior Director of New Business development to support the growth of PCI especially in Sterile injectables.

Andrew Warmington (Moderator)
Manufacturing Editor, Custom Content, Citeline

Andrew Warmington has been writing about pharmaceuticals and related industries since becoming editor of Speciality Chemicals Magazine in 2002. His particular area of expertise is in the C(D)MO drug substance and CRO markets, plus some on the regulatory side developed during an 18-month stint with Chemical Watch.

During this time, he has attended every CPhI Worldwide plus other key industry events, such as Informex/CPhI North America, DCAT Week and PharmaChem Outsourcing, where he has been a regular moderator of expert panels. He has also been a freelance proof-reader within the industry, notably for a major drug packaging company.