PEER REVIEWED

Optimising the HPAPI Value Chain to Achieve Maximised Product Value

In the quest to find new and more effective treatments against severe diseases, researchers are increasingly moving towards active pharmaceutical ingredients (APIs) with increased potency and more targeted delivery mechanisms. These powerful compounds may help treat life-threatening and so-far incurable diseases, including cancer, diabetes, Parkinson's disease and others. Simultaneously, due to these compounds having a physical and clinical effect at very low dose, they carry potential risks in terms of occupational health hazards. Personnel in manufacturing facilities must be protected at all times from the products they are making. Sustainable manufacturing of highly potent APIs (HPAPIs) therefore requires specific precautions to operator health and safety on the one side and to product quality on the other.

However, while protecting workers is perhaps the most important element of HPAPI development and production, biopharma innovators need access to many other specialised capabilities to take their HPAPI innovations from concept to commercialisation. Other steps in the development process include chemical synthesis, intermediate development, sampling, logistics, waste management and beyond – on top of the critical work of keeping people safe. By creating a true value chain that spans all unit operations of HPAPI product development, based on extensive experience and driven by a safety-first philosophy, contract development & manufacturing organisations (CDMOs) can play a pivotal role in bringing innovative HPAPI-based drug products to market that improve or even save patients' lives.

Three Focus Areas are Key

Sustainable HPAPI production is centred around three principles:

1. **Operators' Health:** With the product already active at low dose, and with the certainty that manufacturing operations often have situations where production equipment has to be opened (e.g., for adding reagents, taking samples or isolating product), it is conceivable that product exposure via the air can reach manufacturing operators and thereby result in measurable effects on their health. Thus, occupational health & safety precautions are required to ensure safe operations.

2. **Product Quality:** Besides the normal GMP regulations related to product quality, the same activity at low dose requires having additional precautions regarding adequate cleaning and decontamination procedures to minimise product carry-over into the next product (especially in multi-purpose facilities). With high potency products, it is no longer sufficient to work with a general and fixed-limit (e.g. 10ppm) for all products produced within the facility, but ideally a cleaning strategy based on the product's permissible daily exposure (PDE).

3. **Containment Strategies:** These are implemented in most organisations that handle HPAPI, but there may be differences in the level at which they are being practised. In most countries, a legal framework exists to guide organisations in adequate employee protection. A general best practice example follows three main principles:

   1) Engineering controls
   2) Organisational measures
   3) Personal protective equipment (PPE)

Not all companies follow the same priorities and order of the above measures. Therefore, one can observe facility conditions ranging from HPAPI being handled seemingly without special measures (in case engineering controls and organisational measures are proven to suffice), as well as facility conditions where the employees are fully gowned, including breathing protection and/or complete gowning.

Personal protective equipment (PPE), including powered purifying air respirators (PAPR) and powered respirator protective suits (PRPS), should only be used in exceptional cases (e.g., non-routine unit operations such as cleaning or troubleshooting including the opening of equipment) and cases where engineering and organisational controls cannot be adequately implemented. Some organisations implement PPE as a permanent measure to safeguard employees. This practice often provides a false sense of safety; in case of a spill or incident where HPAPI is dispersed, the operator needs to find a place to decontaminate himself without further spreading HPAPI within the facility. The PPE will protect the operator short-term, but it is not addressing the overall safety of operations – therefore, engineering controls are always the preferred approach for safe HPAPI handling. This is often the reason for implementing airlocks and air pressure cascades to trap airborne matter in a well-defined and controlled place (i.e., the airlock). This measure is certainly a must-have in multi-product facilities but is also recommended for dedicated lines.

For remote observers not necessarily familiar with handling HPAPI, observing such different operations can make sustainable HPAPI handling seem mysterious and complex. In addition, when developing drugs and handling both drug substance and drug product operations, the variety of unit operations employed can be so wide-ranging that containment solutions can vary broadly. Well-designed HPAPI facilities require a good understanding of the product, its toxicological and physical properties, the unit operations executed during manufacturing, its containment engineering and limitations and ultimately PPE.

Elements of a Secure and Safe HPAPI Manufacturing Process

Typically, optimal HPAPI handling setup in a manufacturing process involves the following dimensions (*related professional terms in italics*):

- **Product Properties:** How toxic is the product? What is the effect on the

human body and at what levels? *Hazard assessment (toxicology), occupational exposure limits (OELs), occupational exposure bands (OEBs), permissible daily exposures (PDEs).*

- **Unit Operation Properties:** What handling is required and to what extent? Dry or wet material? *Risk assessment based on exposure pathways, mass transport, exposure potential*

- **Full Process Design:** How do unit operations connect – via closed connection, or separated unit operation? *Integrating drug safety into the manufacturing process design (e.g. equipment selection)*

- **Engineering of Control & Containment (preferably at source):** Now knowing all of the above, how would we contain the product optimally? *Barrier containment (e.g. hard vs. flexible walled), ventilation-based controls, connection points (valves, etc.)*

- **Definition of Organisational Measures:** When we will be operating the facility, what special procedures or precautions must be defined to handle the HPAPI responsibly with the actual manufacturing setup, without endangering operators and others? Considerations include procedural controls, specific work instructions, operator education, cleaning and dismantling of equipment (e.g., maintenance-related) and defining higher-risk groups: operator screening and exclusion from specific unit operations.

- **Personal Protective Equipment (PPE):** What additional protective aids are needed at what specific unit operation in the process?

When all of the above are in place, it is important to monitor the performance of the process and its containment design before, during and after actual operations. Toward this end, an occupational hygiene group typically ensures:

- **Containment Design performs as required:** Smoke testing or surrogate testing to monitor air flows and containment performance.

- **Control and Containment Performance Verification:** Measurements are taken at strategic positions within the facility/operation in order to monitor HPAPI product levels to confirm these are at acceptable levels.

- **Worker Exposure Assessments:** Similar measurements are taken at strategic positions on the operator him/herself (e.g., breathing zone, hands, others) in order to monitor if the actual operation is executed safely, where the weak spots of containment are and if further measures are required.

- **Incident Preparation:** Although it is difficult to foresee where calamities might happen, it is good practice to thoroughly evaluate this topic in advance with a robust risk assessment. Spill management, personnel evacuation and decontamination, calamity cleaning procedures and other potential crisis responses must receive an appropriate level of attention in an effort to minimise the negative impact in the event that such a mishap occurs.

- **Management System:** A management system needs to be in place to repeat or review the above measurements on a regular basis, and to ensure the procedures defined are actually executed as they should be. In addition, the management system defines educational requirements, i.e. how often is training of operators needed and when does it need to be repeated. Ultimately, the management system will define on what frequency medical surveillance of employees handling HPAPI is needed to prevent longer-term effects from the products they have handled.

In many cases, HPAPI will be handled in a dedicated HPAPI facility. In most cases, the design of the facility is a given, and we must recognise that many containment measures are a compromise between safety, design, operational and financial parameters. In the exceptional situation where a new facility is being designed, it is key to involve EH&S (environmental, health & safety or occupational health professionals) as early as possible in the design phase in order to influence the design optimally for the handling of HPAPI products. The EH&S team is critical in supporting the definition of facility layout, people and material flows, HVAC, airlocks and air pressure zoning (cascades), containment and control measures. In addition, they can drive optimisations to the facility regarding cleaning, opening of equipment and possible temporary containment solutions to handle such events. Most organisations will require external support from an architect and one or more engineering companies in the realisation of the new facility. For such situations, it is worthwhile to dedicate resources to facilitate flawless communication and to avoid sub-optimal alignment between the involved parties (e.g., dedicated project management). Ultimately, the business leaders will decide on the required capital and operations budget, timeline, etc., but this should not distract from the main goal, which is to realise an HPAPI facility that is sustainable and can answer to the business needs in the long term.

Building on Safety and Containment to Create an Optimised HPAPI Value Chain

These safety principles can help inform the entire value chain of HPAPI development and manufacturing. Firstly, in the process of making a drug substance (DS), a chemical process generally leads from a number of starting materials, through several intermediates, to the API. The intermediates involved are not necessarily of identical potency as that of the API. Often one starts from non-highly potent starting materials that become highly potent once the API core structure is being formed. There are also examples where highly potent materials are converted to non-potent materials, or where potency varies largely throughout the chemical pathway. The required efforts also depend largely on whether or not a certain intermediate needs to be isolated in pure form.

As a consequence, not all steps require measures of the same kind and one can thus execute non-HPAPI steps in a non-HPAPI facility. On the other hand, not all companies can afford to have different types of facilities and thus often (temporary) containment measures are implemented to normal facilities to handle HPAPI in situations where a large capital investment to create HPAPI-dedicated facilities is not considered viable. This introduces risk not only to the safety of personnel, but also to the overall timeline for bringing the HPAPI programme from early development to the next clinical stage, or even to market.

Laboratories should be equipped differently in order to sustainably and responsibly handle products of elevated potency. OEL (occupational exposure

	"Normal" lab	High-potent lab	High-potent lab
OEB (OEL)	**3** (100 – 10 µg/m3)	**4** (10 µg - 0.1 µg/m3)	**5** (0.1 µg – 1 ng/m3)
Quantity	mg - kg	mg - kg	mg - kg
Max. reactor	6L / 250L	6L / 50L	6L / 50L
Access	Open	Limited Badge-controlled	Dedicated Badge-controlled
Air exchange	Normal lab	Normal lab	10-20x, qualified
Pressure zoning	No	No	Yes, incl. airlocks
Wet chemistry	Normal hoods	Normal hoods & RABS	RABS
Product drying	Separated dryers	Separate dryer & connected to RABS	Connected to RABS
Powder handling		VBE, RABS, isolator	Isolator (RABS up to g scale)
Analytical	Equipment on workbench, standard hood sample preparation	Equipment on workbench, special hood sample preparation	Equipment in enclosure (hood/isolator)
Packaging		Double plastic bag sealing	Double plastic bag sealing

* *RABS = restricted access barrier system / VBE = ventilated balance enclosure.*

Table 1: Overview of the types of API laboratories at Lonza, demonstrating differentiation across key criteria and capabilities.

limit) is an upper limit on the acceptable concentration of a hazardous substance in workplace air for a particular material or class of materials, and these limits help define molecular potency. When handling many compounds with different OEL, companies often define occupational exposure bands (OEBs) so that containment measures can be defined for a specific band. Based on the potency of the compound and on the quantity to be handled, the most appropriate laboratory is selected to run a specific project.

In all HPAPI laboratories, it is helpful to be able to run the widest possible set of unit operations. For specialist operations (e.g., micronisation, encapsulation), equipment can be placed inside an isolator, in order to keep the unit operations as unchanged as possible.

The sampling of wet or dry material from the production (or laboratory), and subsequently the sample preparation, typically happen in smaller laminar flow type of enclosures such as ventilated balance enclosures or laminar flow cabinets. Preferably, sampling is done at the source for OEB4 compounds. For OEB5, there is an additional and dedicated laboratory for sample preparation and analytics including the above-cited requirements. The analysis for OEB4 compounds typically can be performed in normal analytical laboratories as the quantity being handled is small, yet exceptions for specific techniques exist where increased containment is needed.

Besides laboratories and their setup, one has also to consider related activities, such as logistics, e.g., special precautionary requirements for transportation of material; waste management, i.e., hazard analysis upfront and "cradle-to-grave" waste considerations in line with responsible care considerations; cleaning and maintenance, e.g., required engineering controls. Dedication of equipment may sometimes be an expensive option, but for cases where cleanliness of equipment cannot be proven (e.g., OEB5), this might be the only option to create a sustainable manufacturing environment. Disposable (single-use) glass equipment is also utilised routinely in laboratories.

Lastly, process automation should be considered wherever possible, although this is less practical for multi-purpose facilities running campaigns with a limited number of batches. When implementing automation in a multi-purpose facility, the key is to find the right balance between flexibility and automated robustness. Manufacturers may explore several levels of automation, such as manufacturing execution systems (MES), in-line process analytical technologies (PAT) or real-time release-testing (RTRT). Avoiding paper-based documentation in OEB5 facilities is considered a final step in containing the HPAPI to where it is desired.

For larger-scale production, some facilities have a modular setup, with technology for wet chemistry for reactor sizes customisable up to 50L, and isolator technology for product isolation and dry powder handling. Facilities may be optimised for high output, potentially running up to three large reactors and two drying operations in parallel (filter dryer or lyophiliser). Some facilities have high levels of automation and potential for 24/7 operation, as well as capabilities for a high level of compliance with electronic batch records. Large-scale facilities may be used for development of highly potent payloads for antibody drug conjugates or ADCs (see Figure 1). At larger scales, the containment measures do look different, but comply to the same principles as described above.

Conclusion – Optimising the Value Chain

When looking into pharmaceutical development in a bit more detail, the necessity of having different types of

Figure 1: Multi-purpose, kg-scale facility for highly potent payloads for antibody drug conjugates at Lonza's Center of Excellence for HPAPI development and manufacturing at its Visp, CH site

kilogram-scale laboratory facilities can be explained by the increasing demand in HPAPI projects, as well as an increasing pressure on development timelines. Flexibility to perform projects in the most appropriate asset and keeping sufficient capacity in HPAPI facilities increases the options for a CDMO partner to meet customer timeline requirements. In addition, flexibility to perform any kind of unit operation in the contained environment allows for quick transition from typical drug substance activities into drug product activities (e.g., micronisation, encapsulation, etc.).

Challenges in the drug product area may differ and introduce new dimensions, such as very low yet uniform dosing requirements for a highly potent active ingredient in the final product. For ADC products, this has introduced aseptic biologic manufacturing as an additional challenge. However, the general principles of containment, facility & operational design and occupational health principles relevant for drug substance will also apply to the drug product. Combining these skills and experiences to integrate all unit operations into one optimised value chain will help CDMOs support customers even further in reducing drug programme risk and complexity, as well as meeting the increasingly accelerated timelines required for bringing novel and highly effective drug products to patients that need them.

Acknowledgement
The author wishes to thank Mr Conrad Roten, R&D API Chemical Services at Lonza in Visp, for his open discussions about this topic and his support in final proof corrections.

REFERENCES

1. "Lonza Expands HPAPI Development and Manufacturing Capacity for ADC Payloads." Lonza. October 8, 2018. https://www.lonza.com/news/2018-10-08-13-30
2. "Antibody Drug Conjugates: Precision Cancer Care." Lonza. February 3, 2020. https://www.youtube.com/watch?v=KkAKgU2A6qo
3. "Lonza to expand HPAPI development and manufacturing capacity." Lonza. June 17, 2019. https://www.lonza.com/news/2019-06-13-15-35

Maurits Janssen

Maurits Janssen, Sr. Director, Strategic Business Development, Lonza Pharma & Biotech.