Panel discussion on...

COMMENTARY ARTICLE

GENERAL CONSIDERATIONS

Innovation has been the driving force of the pharmaceutical industry since its very beginnings. For more than a century, the pharmaceutical industry offered a customized response to most diseases and even discomforts related to our health.

A driver of innovation is the search for increasingly targeted efficacy and the reduction of undesirable effects.

Initially, the potential activity of millions of molecules was tested empirically. This approach, still practiced today, has led to major advances.

For several decades, the increasingly precise knowledge of the chemical and biochemical mechanisms of our body as well as the capacity to model new potentially active molecules offered by Artificial Intelligence, have led research to propose increasingly complex active targets which are adapted to the mechanism of the living.

The synthesis of small and large molecules (peptides and antibodies) required the development of new technologies in chemical synthesis or in purification or isolation steps. However, the biggest breakthrough is related to the toxicity of these APIs, the HIGH POTENT ACTIVE PHARMACEUTICAL INGREDIENTS.

The activity and toxicity are tenfold: API candidates falling into the HPAPI category increased dramatically to reach 30% today. *Paolo Paissoni, BD & Innovation Director at PROCOS* specifies that pipelines of emerging Biotech, small and big Pharma count more than 1,000 HPAPI including recent approvals in US and EU.

The development and manufacturing according to good design and manufacturing practices led to a major evolution of technologies among the actors involved. A large part of the CDMO industry (Custom Development and Manufacturing Organization) adapted or created appropriate lab, pilot or production capacities as we see in the testimonies of the Panel.

With classical API the focus was the protection of the molecule: avoiding any cross-contamination or any deviation in the production process which are widely described in the GMP guidelines. This point remains of course essential but the constraint to protect the "environment" from any contamination of HPAPI or intermediates with highly toxic properties is an equally unavoidable constraint to HPAPI production.

Strict protection of workers and people in the vicinity with the product according to very precise standards is of paramount importance:

- Ensure the decontamination of all tools and production areas
- Develop and validate methods to measure the above points

The classification of HPAPI is done according to its OEL (Occupational Exposure Limit) as described by some of the panel members, in particular: *Stefan Randl, Vice President Product Line Drug Substance at Evonik Health Care-Evonik Industries AG* : "... (OEL) for a typical HPAPI is below 10 µg/m3 of air as an eight-hour time-weighted average (TWA) or a drug having a therapeutic dose of less than 10 mg per day. However, there are a growing number of these highly potent compounds in clinical development that require an even more extreme level of exposure control. We call these compounds ultra-HPAPIs. Recently, we've begun to see some ultra-HPAPIs enter clinical development with OEL's down into the low ng/m^3 range" *Jessica Tibasco, EHS Corporate Manager at FIS* precises: The internal control band approach in place for HPAPIs in FIS is:

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Xavier Jeanjean is graduate in Organic Chemistry and Process engineering, he owns a Master in strategic management of ICG Paris, F.
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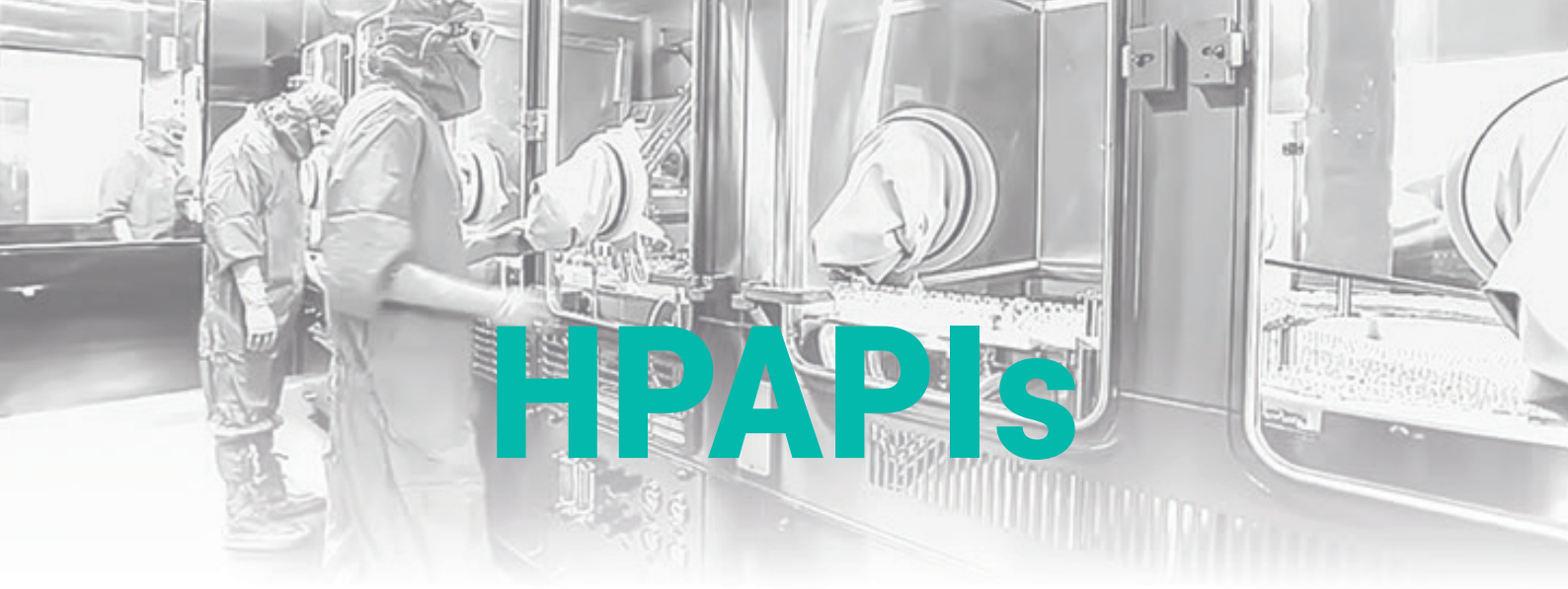

HPAPIs

- 1 ≤ OEB 3 < 10 µg/m3
- 0.1 ≤ OEB 4 < 1 µg/m3
- 0.01 ≤ OEB 5 ≤ 0.1 µg/m3

These values are typically adopted by all players of the industry.

The current CDMO production capacity is in balance with the market demand according to the panel. The main service providers continue to expand capacities in synch to an anticipated 7 to 10% CAGR. According to *Paolo Paissoni, BD & Innovation Director* at PROCOS the market of HPAPI should grow from 21 billion USD in 2021 to 31 billion USD in 2026.

The complexity of manufacturing safely HPAPI is continuously increasing (more toxic, more steps involving high potent conditions, more complex chemical / biological steps (production and purification)); the impact on the cost of the API is exponential with the complexity of the process and offer a barrier to entry. Some CDMOs have chosen in fact the Ultra HPAPI market segment (ng/m^3) in an effort for a strong differentiation from the other competitors.

Like for the other category of APIs, the robustness of the supply chain is the key point which has been seriously considered by the actor of the panel. A deep risk assessment of the supply chain associated with improvement action plan is another important factor of differentiation.

The specificities of HPAPIs fundamentally change the economic approach of development and production costs, from the chemical or bio-chemical synthesis laboratory to the formulation.

Scott Patterson, Vice President Commercial Support, ILC Dover suggests the Single Use Technology (SUT) could be an alternative for the optimization of the manufacturing cost (OPEX and CAPEX) of the HPAPI: *"… many of the containment requirements and the powder transfer operations can be done with SUT …, it is generally accepted that a SUT will yield a 70% savings. … The analysis will show costs associated with cleaning and validation exceed the costs of the SUT solution"*

RISK OF A BREAK IN THE INDUSTRY GROWTH DYNAMIC? WHERE IS THE GLASS CEILING?

The market for this type of molecules is made possible by the phenomenal technological advances that we are experiencing and by the need to treat as best as possible ALL the ailments related to the health of the population, with certain limits. The aging of the population due to demographics but especially to the increase in life expectancy is a fact; don't some scientists promise us to live up to 120 or even 140 years old soon? The need for care to treat age-related pathologies is growing exponentially and so does the strain on public health budgets. On the other hand, and this is a good thing, the number of people in the world with access to care is increasing, even if not fast enough in all regions.

In addition to these fundamental growth drivers of the pharmaceutical industry, (widely developed in many other publications), we must consider that the share of HPAPIs will grow even faster due to their targeting and their effectiveness, is fast growing to answer the needs of the population.

Specialists agree on the HPAPI annual growth rate of 7 to 10% over the next 5 years with the end markets dominated by rich countries (North America, Europe, Japan and Korea). Indeed, new treatments are very expensive.

We must ask ourselves the question of the viability of our health insurance models:

- Can they continue to reimburse more and more expensive treatments?
- Will the expected growth of HPAPIs reach the glass ceiling of what our health protection system can afford?

The limitation of health insurance system would undoubtedly put a severe brake on the development of the HPAPI because the market would no longer be able to afford to pay for the high price of these innovations.

If we consider this hypothesis to be realistic, all the players must ask themselves how to reduce the costs of developing and producing HPAPIs.
Some tracks are evoked by the panel:

- Dedicated equipment and material which avoids costly decontamination.
- Early characterization of the toxicity of intermediates.
- Etc.

CONCLUSION

The technical development and production of HPAPIs generate constraints that the main players (CDMO) have considered and solved. A quality service offering has been developed by certain CDMOs to support a fast-growing market especially for ultra-HPAPI.

However, we must ask ourselves questions about the long-term viability of the health insurance systems as they may not be able to continue to meet the increasing costs. The long-term risk that the market will no longer be able to pay the full price for these innovations is unfortunately highly probable.

The challenge in the medium to long term for the pharmaceutical industry and its suppliers is to drastically improve the medical service/cost ratio of HPAPIs, otherwise the growth of this product segment may wither.

The two actionable axes are:

- Lowering the costs of development and production of HPAPIs
- Targeting therapeutic areas where the efficacy of current APIs is insufficient

PANELISTS

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High Potent Active Pharmaceutical Ingredients (HPAPI) Market Overview

High Potent Active Pharmaceutical Ingredients (HPAPI) market size is forecast to reach US$741.2 million by 2026 (1), after growing at a CAGR of 6.7% during 2021-2026. HPAPI is the pharmaceutical compound used to treat different diseases such as cancer, hormonal imbalances, and respiratory disorders, among others. The rapid growth in population along with the increasing incidence of chronic diseases are some of the major factors driving the market growth during the forecast period. Favorable government policies for API production and advancements in active pharmaceutical ingredient (API) manufacturing is also supporting the market growth. Rising drug research and development activities for drug manufacturing, along with the increasing usage of biopharmaceuticals are inevitably and irreversibly driving the growth of the HPAPI market.

Not only, the global pharmaceutical market is currently undergoing major change. About 30% of the products under development are highly potent, an increasing number of molecules have complex structures, and about 70% have solubility or bioavailability problems.

In addition, there is an active shift towards the use of specialized formulation technologies to enhance drug efficacy, and, because about 65% of drugs are approved on an expedited basis, a rapid development is required.

HPAPI suggestions

Different elements of management are important in the development and manufacturing of HPAPI: of course highly skilled organic synthetic chemists, but also experts in toxicology and industrial hygiene, an engineering department, and an experienced management.

By involving experts in toxicology it is possible to establish bands, or OEBs, using a variety of databases and existing knowledge. This is possible even in the early stages of development when only limited safety information is available.

The regulatory environment for active pharmaceuticals is changing with the increase in regulators' granting accelerated approval pathways – especially in oncology. In early development, there is often insufficient toxicology data to determine the OEL at which the compound should be contained, so companies should follow a more conservative approach to containment. Health and Safety Executive (HSE) teams worldwide are defining OEL in development phases based on computer simulations, similarities to known compounds, or simply by defaulting to highly potent compounds in the first place and only relaxing constraints when more toxicology data is available.

To prepare for potential exposure, companies should perform regular occupational hygiene monitoring to ensure that all the equipment is safe to use. This should be part of the regular training and the working culture of the laboratory to ensure that it is done habitually. Moreover, there should be a robust process that follows the country's regulations on how to handle exposure as well as resources to contact the right authorities should this occur.

If further integrity is demonstrated, it will be possible to avoid unnecessary additional costs, and correctly review HPAPI evaluations. In addition, the engineering department, in cooperation with related departments, can improve workability by paying attention to details such as the position of gloves in the isolator. They can also improve overall production efficiency by taking into consideration various other factors, such as ease of cleaning in case of leakage.

The safe house for your HPAPI's

Responding to the rising number of custom HPAPI's demand, Angelini Fine Chemicals (AFC) is expanding its HPAPI capacity at its Aprilia , Italy plant site. With over 50 years of CDMO experience, AFC is at the forefront of chemical development and cGMP manufacturing of Adv. IMs, API's and HPAPI's to serving brand pharmaceutical industry.

The investment is complementing Angelini's existing range of HPAPI R&D and manufacturing capacities to provide a full HPAPI CDMO solution. The HPAPI capacity expansion covers the addition of two new cGMP kilo-lab suites fully dedicated to development and small- and mid- scale cGMP manufacturing of custom HPAPIs (OEL 0,1 µg/m^3) – OEB5).

The new Angelini's HPAPI platform offers all scales of HPAPI manufacture across the full OEL / OEB band spectrum to meet a wide range of pharmaceutical outsourcing services, from route selection / proof of concept runs to scale-up up to small- and large-volume HPAPI cGMP manufacturing.

Equipped with cutting-edge lab-, pilot- and industrial-scale facility, AFC boasts a wide reaction technology portfolio and scale-up capabilities assuring a smooth, safe and optimized process technology transfer – from 1-+100Kg up to tons-scale.

The HPAPI expansion is concluded and we have added batch- and flow-chemistry capabilities on kilogram-scale to Angelini's HPAPI platform, that already houses over 5000 L of total reaction volume.

The new cGMP kilo-labs target to running small-volume HPAPI production campaigns with batch size 0,25 – 5+ Kg. The chemical synthesis capacity will be backed-up by a cGMP compliant suite for HPAPI finishing operations to offer full-integrated solution and tailor-made HPAPI particle size reduction and micronization services for customer formulation batch needs.

Manufacturing scale should factor both immediate and future needs when production scales up. Scale issues can lead to manufacturing re-validation and related regulatory changes, thereby delaying the programs into clinic and market and also adding costs.

Biotech companies should look for a CDMO that will, early on during clinical development, consider and propose phase-appropriate manufacturing scales that reflect both current needs and future growth.

AFC advantages:

- Expertise in the synthesis of HPAPI, FlowChemistry & small molecules market
- Capability and expertise to synthesis compounds to small gram up to mid- and large- production scale to support pre clinical research and development, Phase 1, 2 & 3
- All chemistry staff PhD level organic chemists
- Clean room with isolator independently tested and operates at OEL < 1ng. m^3 as an 8 hour time allowing containment of most potent HPAPIs
- Separate wet chemistry lab dedicated to high potency synthesis
- Air handling system that operates under negative pressure cascade
- Detailed safety protocols, standard operating procedures and full risk assessments carried out
- Fully trained staff
- Analytical capabilities
- Customer confidentiality and IP protection guaranteed
- Single point of contact and clear customer communication and project updates to ensure all information is shared to allow project decisions to be taken efficiently
- Bespoke solutions to our customers research project challenges through flexible project execution
- R&D, Pilot and Production cGMP available manufacturing

References and notes

1. High Performance Active Pharmaceutical Ingredients (HPAPI) Market - Forecast(2022 - 2027) https://www.industryarc.com/Report/15634/high-performance-active-pharmaceutical-ingredients-hpapi-market.html


MARA GUZZETTI[1], ANTON GAYRING[2]
1. General Manager Switzerland, CARBOGEN AMCIS
2. Senior Head of Development, CARBOGEN AMCIS

What trends, in your opinion, are emerging in the HPAPI market?
Manufacturing of highly potent APIs is becoming more and more standard in our services industry. This is mainly driven by two factors: a) categorization itself is getting more and more professional and b) the market is requesting more and more (specialized) cancer indications.

What are the challenges in managing HPAPI manufacturing?
The real challenges are the combination of low material requirements in combination with very often accelerated / fast track status of the candidates.. In many cases, low material demand is leading to the fact that initial GMP material is used to capture requirements for clinical phase I and II. Real process development / process definition is very often lagging behind the target of quick supply of the initial 100 to 500 g cGMP material. Starting clinical phase III ultimately triggers the need for more process characterization that was omitted in the initial phases. Other issues such as proper qualification of starting materials is becoming really challenging if one expects a vendor to accept an audit for a raw material with an annual demand of < 10 kg/year. Thus, availability of a specialized supply chain service might be as important as solving chemical and analytical challenges in a process development environment characterized by working in isolators and containment labs.

Is there a market or region of the world that is currently growing or increasing their expertise and market share in high HPAPIs?
We see the biggest growth in US, followed by EU market.

Where do you see the market for HPAPIs in 5-10 years?
The HPAPIs market is currently on an annual expected growth rate of 7 to 8%. We expect this rate continue to rise along with the increasing number of niche applications – especially for cancer treatment. Our business development can confirm this trend as we receive more and more requests with low to mid volume requirements for niche products (e.g. linker payloads) in the HPAPIs field.

What does the ideal CDMO partner offer?
Cost of goods are in many cases, not the main driver for decision-making. A proven track record of quickly developing a robust - but not in all cases the most economical process, is definitely a plus. The support of a very experienced Regulatory Affairs group and Supply Chain Management who are used to dealing with topics like low material demands in combination with "fast track status" will definitely make the difference. Excellent analytical capabilities are a "must have" in order to meet ever more stringent quality requirements from Regulatory Authorities globally. A proven track record regarding authority inspections, could also reduce the risk of insufficient CMC preparation.

How do CDMOs prepare their employees for safe HPAPI handling?
At least at CARBOGEN AMCIS people are developed into that environment.. This starts with theoretical training (how is categorization done, theoretical performance of equipment and PPE) to practical training of the day-to-day work. TThis is supported by regular industrial hygiene measurements (to qualify the combination of operators with the used equipment) and a very high hygiene standard (e.g. 5S) in lab and production.

How is the regulatory environment around HPAPIs changing?
The accelerated regulators' granting approval is having an influence on the production challenges for HPAPIs. In fact, at the early stages of development,

enough toxicological data are missing and the OEL containment definition needs to be estimated on simulation. In addition, more complex molecules and increasing regulatory requirements (e.g. fate of impurities, tighter impurity specifications) are driving the challenge of many CDMOs to support the customers with the adequate regulatory competence, which is sometimes not present in medium size start-up companies.

What are your recommended best practices for HPAPI containment and handling?
Definitely a very tricky question and not easy to answer. We have had good results by including operators in any kind of the decisions around worker safety. Sustainable people development and training – in combination with open communication of strength and weakness of any containment engineering solution was proven to give the highest Environmental Safety and Health compliance, quality and employee satisfaction.

DENIS ANGIOLETTI
Chief Commercial Officer, Commercial Operation, Cerbios

What trends, in your opinion, are emerging in the HPAPI market?
Over the years, we are observing an unpreceded increase in the molecules' complexity and in the necessary technologies for their development and manufacturing.
The clinical need is clearly to boost the efficacy of the molecules and make them more site specific while reducing their side effects. This leads to the development of targeted molecules which are drug designed to increase their specificity as well as get the necessary stability in the body, specifically at their actual site of actions.
From a manufacturer perspective, this leads to have in place different complex technologies and be prepared to use them for HPAPIs.
It also means it is not just about making HPAPI, it is more and more about which technology for which class of HPAPI. It is not just a matter of potency but a matter of having complex and specific technologies applied and installed to manage HPAPIs.

What are the challenges in managing HPAPI manufacturing?
As above mentioned, the challenge is having extremely complex and sophisticated technologies installed and applied with the right level of containment and safety to develop and manufacture HPAPIs.
You must have the right risk management and containment strategy when using complex equipment and technologies. For this reason you need to know how to design your plants and install equipment accordingly. In parallel, it is of essence having the necessary know-how for all your technical team, from R&D to engineering and production, ensuring for anyone a continuous training.

Is there a market or region of the world that is currently growing or increasing their expertise and market share in high HPAPIs?
Where do you see the market for HPAPIs in 5-10 years?
In terms of markets, anyone can see the growth of IP applications/patent as well as registered INDs from China and, somehow, India as well; this is no longer a news and constantly growing. Europe, US, Japan remaining productive in this respect. This applies also for HPAPIs with all related implication: more players but also more originators and more opportunities. Overall, the trend for the new molecules is obviously highly potent molecules, and I see we will still have a combination of small molecules and large molecules, with the common factor of complexity.
From a CDMO perspective, this leads to highly specialized manufacturing units, if not entire dedicated manufacturing sites.

What does the ideal CDMO partner offer?
First of all, a CDMO partner should be capable of developing a process from the very early stages.
As we all know, discovery and innovation come frequently from start-ups and small companies which need to move fast from the discovery phase to the first in human. These companies need a partner which can develop the manufacturing process of their molecule (either small molecule or biotech) to a process which is good and robust enough to be scaled to a cGMP production.
Additionally, a CDMO partner has to be a specialist and must have done, be doing, and be ready to do, the necessary investments for the necessary technology. This is due to the increased complexity of the molecules, as said.
A CDMO needs to have the necessary know-how to handle such technologies or, primarily, to be prepared to engineer and install new technologies in its plants, where the next molecule which comes in will need it.
It is a continuous work in process, with more and more peculiar technologies which are absolutely necessary.

The HPAPI market was perceived as the fastest growing market in 2020. Was this in line with the demand in 2021 and 2022?
Yes, this was the case from our perspective, in spite of the disruptive situation given by the Covid 19 pandemic.

Did investment in HPAPI capacity overshoot demand or is there spare capacity in the industry?
I am sure there is spare capacity. Yet, we need to consider that investments were necessary not only to increase capacity but also to install technologies, improve flexibility and increase safety and containments, sometimes by substituting the existing plants with newer ones.

What is the effect of re-shoring (if any?) on capacity utilization in the EU and the US now?
Both for existing and new entities there is a re-shoring effect.

My impression is that EU and US companies have been able to absorb such an increase in demand while we are all now working on investments to make this consolidated. In this all, technology is key.

Did you invest in increasing the HPAPI capacity since January 2020? What benefits brings this capacity expansion to your target customers?
Yes we did.
In 2021 we completed and got SwissMedic approval for a new HPAPI unit which allows us to manufacture batches up to 30 Kg/batch improving our range of capacity from very small scale up to these 30Kg/batch with different lines for cytotoxic and non cytotoxic units.
Additionally, we are now advanced in the construction of a new building which will have two complete lines for the manufacturing of HPAPI, primarily to be dedicated to ADC's payloads and cytotoxic APIs. This new plant is planned to be operational in Q1 2023.
Next to these manufacturing units, we have recently opened new R&D units which increase by 50% the R&D capabilities for HPAPIs chemical development and double the capacity for R&D analytical services for biotech and chemical products.
All these investments allow us to guarantee to our clients much more flexibility and speed to execution as well as completing our offer with an expanded range of technologies and scale of manufacturing.

BRITTANY L. HAYES
Director, Global Highly Potent & Oncology Platform,
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Expert CDMOs Foresee Highly Potent Trends & Expand to Meet Market Demands

What trends, in your opinion, are emerging in the HPAPI market?
I don't know if this is considered a trend, but an emerging need is in the Antibody-Drug Conjugates (ADC) space. There are many factors that are critical to ensure the efficacy of an ADC, including the antibody binding properties, the stability of the linker and payload, the conjugation site on the antibody, and the Drug to Antibody Ratio (DAR). All of these factors add to the complexity of developing and manufacturing these molecules. Extensive control of critical quality attributes and analytical technology is imperative. This is an area that will continue to expand in the future.

Is there a market or region of the world that is currently growing or increasing their expertise and market share in high HPAPIs?
The North American market accounts for the largest share of the HPAPI global market and will continue to do so for years to come. The rising incidence of cancers and other illnesses has led to the production of more HPAPIs, and the region's growing population relative to other nations will drive this market.

Where do you see the market for HPAPIs in 5-10 years?
In the next 5 years, the highly potent API market is expected to grow from $21 billion to $31 billion. Drug developers will increasingly rely on the highly potent handling and manufacturing capabilities of external partners in order to meet market and patient goals. Key drivers are the high demand for oncology drug products, including antibody-drug conjugates.

What does the ideal CDMO partner offer?
The ideal CDMO partner is an extension of the customer's team, in that they are actually in fact partners working on the project together. A CDMO shouldn't be a transactional order taker. There needs to be two-way transparent communication between both parties, identifying risks and solving problems together. Issues will arise, as they always do, but it is how they are handled that is most important. An experienced CDMO partner is also very service-oriented, possibly offering an integrated approach with multiple complementary services, so the customer does not have to manage multiple teams around the globe. For example, expert CDMOs bring seamless API to Drug Product manufacturing and packaging services, which can be performed between multiple sites. What makes a truly integrated service is when experienced project teams work together to communicate with each other frequently, foreseeing issues and taking care of supply chain logistics, materials, production windows, timeline management, shipping, customs, etc., all under the guidance of a Global Program Manager with oversight of all teams, services and sites.

What are your recommended best practices for HPAPI containment and handling?
In order to safely handle high potent APIs and Drug Products, a systematic and scientific approach is needed. A complete containment concept includes hard elements such as engineering controls, and soft elements such as operating procedures and practices. There is a significant need for quantitative industrial hygiene air and surface data to be developed over the entire time-period that potent compounds are handled, and to verify that the combination of these elements continues to minimize worker exposure and prevent product cross-contamination. This requires employing compound-specific data, in addition to surrogate data for verifying controls.

Expert CDMOs must employ some fundamental principles around safe handling of HPAPIs and establishing a control strategy:

- The hazards of the material being handled should first be established, and then hazard information, along with exposure potential, analyzed to assist risk using robust, and where possible, quantitative risk assessment techniques.
- Risk management should provide a base range of controls designed to establish and maintain a safe working environment.
- Overall control should be established on a hierarchical basis, where in lieu of hazard elimination, the primary focus becomes engineering controls at the source of emission, designed to prevent exposure at the top of the hierarchy.
- Secondary hierarchical elements include establishing written procedures, training and good techniques designed to prevent or minimize exposure potential.
- At the bottom of the hierarchy should be Personal Protective Equipment (PPE), including Respiratory Protective Equipment (RPE), which should be regarded as a redundant control.

Did you invest in increasing the HPAPI capacity since January 2020?
CordenPharma has been investing heavily across the entire network over the past 2 years and will continue to do so. We initiated a 200 M€ CAPEX program 12-18 months ago to include capacity expansions, new technologies, and upgrades to existing facilities across our 5 technology platforms: Highly Potent & Oncology, Peptides, Lipids & Carbohydrates, Injectables, and Small Molecules. Specifically in the Highly Potent & Oncology platform, we have an ongoing expansion of our cGMP manufacturing capacity at CordenPharma Plankstadt in Germany which focuses on Oral Solid Dose (OSD) development and manufacturing of highly potent APIs. Installation of a new manufacturing unit started at the end of 2021, which will accommodate batch sizes up to 60 kg and be equipped with all of the key OSD manufacturing technologies including blending, granulation (high shear, fluid bed, roller compaction), compression, and coating. Investments in high potency filling equipment (powders, pellets, mini-tablets) into capsules, Hot Melt Extrusion (HME), and the ability to operate with organic solvents are also being added. Additionally, in late 2020, we completed investment in a new high potent API development laboratory at one of our two sites in Boulder, Colorado (US) to meet the demands of the market and expedite the onboarding of new projects. Further expansion in Colorado includes the micronization of highly potent APIs in mid-2023.

What benefits brings this capacity expansion to your target customers?
This expansion allows us to handle more projects at the same time, and ultimately, decrease timelines. It also adds new technologies so that we can offer more services to our customers.

What is the current HPAPI global capacity in your company?
CordenPharma has very large capacity to handle HPAPIs in both the drug substance and drug product areas. Our two Boulder, CO facilities have a combined capacity of close to 500,000 L to manufacture APIs and peptides. We also have large-scale preparative HPLC capabilities with columns up to 100 cm. In CordenPharma Plankstadt, Germany, our oral solid dose manufacturing facility handles batch sizes up to 150 kg for high potent APIs and up to 450 kg for non-potent APIs.

What is the regional capacity footprint of your company? (Asia, EU, North America, Other)
CordenPharma's facility network operates across North America and Europe, but we serve customers globally.

Are you planning any significant capacity extension in the next 2-3 years?
Yes, in addition to what was mentioned above, CordenPharma has seen more and more complex APIs entering clinical Phase I. The complexity is mainly solubility / bioavailability driven. In order to overcome these issues, CordenPharma is working on an early-stage concept between API development and Drug Product development for First-in-Human clinical studies. We are installing this early-phase platform at the CordenPharma Liestal, Switzerland and CordenPharma Plankstadt, Germany sites. The Liestal site will conduct solid-state characterization, polymorph, salt screening, and biopharmaceutical characterization of the API (e.g. solubility testing, small-scale dissolution testing). And, in Plankstadt, we will be installing small-scale equipment for spray drying, hot melt extrusion, nanomilling, and micronization. We will then be able to prepare small-scale prototypes in our R&D laboratory for animal studies. Further development and scale-up for clinical studies can then be conducted in larger scale cGMP equipment in Plankstadt, or one of our other facilities in the network.

STEFAN RANDL
Vice President Product Line Drug Substance, Evonik Health Care, Evonik Industries

What trends, in your opinion, are emerging in the HPAPI market?
Research into pharmacological targets continues to expand our knowledge and advance the pharmaceutical industry. For example, many pharmaceutical companies are focusing on targeted cancer treatments with small molecules, and because of their cellular activity, most of these drug substances are HPAPIs. In fact, more than 30 percent of all current clinical pipeline projects (phase I – III) represent HPAPIs and this trend is causing the HPAPI market to grow at almost 10 percent per year.

Small molecule APIs continue to increase in potency. Under current industry definitions, the occupational exposure limit (OEL) for a typical HPAPI is below 10 µg/m^3 of air as an eight-hour time-weighted average (TWA) or a drug having a therapeutic dose of less than 10 mg per day. However, there are a growing number of these highly potent compounds in clinical development that require an even more extreme level of exposure control. We call these compounds ultra-HPAPIs. Recently, we've begun to see some ultra-HPAPIs enter clinical development with OEL's down into the low ng/m^3 range.

What are the challenges in managing HPAPI manufacturing?
Exposure to highly potent compounds remains a challenge because many of the pharmaceutical processing operations still rely on humans to perform them. As therapeutic dose levels get smaller, so do the allowable levels of contaminants and foreign materials which can be present in the final drug product. This requires cleaning methodologies and cross-contamination strategies that must be continually evaluated – supported by analytical methods that provide a matching level of detection. Finally, a challenge for both bulk API manufacturers and drug formulation manufacturers is to deliver very small doses of highly potent compounds in a precise and repeatable way.

Is there a market or region of the world that is currently growing or increasing their expertise and market share in high HPAPIs?
Drug Conjugates, such as Antibody Drug Conjugates (ADCs), are steadily entering the therapeutic pipeline, especially for oncology treatment. ADCs consist of an antibody, a linker, and a cytotoxic agent, which is always an HPAPI or even an ultra-potent API. With more than 100 ADC projects currently under clinical development, this means there is an increasing demand for ultra-potent API handling. Other drug conjugates

which include conjugation of small molecule API to PEGs, proteins, hydrogels and sugars are increasing as well. Advancements in drug delivery technologies, such as liposomes, also contribute to the way highly potent payloads can be delivered selectively to their targets in the body. Diseases created by abnormalities of gene expression and gene function are slated to be areas of great growth. As medical science is able to further unravel the roles epigenetic molecules play, in either the suppression or initiation of certain disease conditions, a very large category of therapeutic treatments is likely to emerge.

Where do you see the market for HPAPIs in 5-10 years?

The global HPAPI market is expected to grow rapidly – from $23 billion USD in 2021 to $34 billion USD in 2026 at a CAGR of around 8%. HPAPIs are estimated to account for around one quarter of all new pharmaceutical entities, and around a third of those in clinical development. New therapeutic discoveries are going to lead to exquisitely targeted drug therapies which can influence intra-cellular processes and include nuclear medicine therapies that combine monoclonal targeting mechanisms and traditional radiation treatment compounds.

Pharmaceutical and biopharmaceutical markets are increasingly focused on the development of specialized drug products with new treatment modalities, especially in the field of previously undruggable targets in oncology and other therapeutic groups. For many of the pharmacologically active substances behind these products, biologic activity is exhibited at extremely low concentrations. Nanoparticle technology has also opened many ways to deliver very specific molecules into human cells and across the difficult blood/brain barrier, including use of HPAPIs.

What does the ideal CDMO partner offer?

Beyond the hard assets, a CDMO partner must be able to demonstrate historically strong technical competencies. These encompass the development of effective risk control systems that are based upon a comprehensive assessment of exposure hazards and other safety risks for each process step required for chemical synthesis. Keeping employees safe every day should be a number one priority!

For large-scale production of HPAPIs, it is advisable to have a comprehensive management system for safe handling of HPAPI, toxicologists, industrial hygiene specialists, well trained personnel in process R&D, production and project management, employee training, advanced cleaning and analytical testing methods, as well as a comprehensive waste treatment system, and solid/liquid incineration.

Specialized analytical control laboratories are also required to implement the in-process, intermediate and final HPAPI analyses, as well as to develop trace analytical methods to support airborne monitoring and cleaning verification for the HPAPI plant. A suitable CDMO partner should have a proven record of exemplary audits and supply security, showing the experience to run GMP HPAPI processes reliably and efficiently.

Due to the complex processes and other technologies required to synthesize many HPAPIs, finding a CDMO can be challenging. Only a few CDMOs, including Evonik, can produce HPAPIs and ultra-HPAPIs in small-scale facilities under GMP conditions down to an OEL of 5 ng/m^3 and also support commercial supply in reactors up to 8,000 liters in volume, with batch sizes of up to 400 kg with an OEL of down to 0.1 µg/m^3.

How do CDMOs prepare their employees for safe HPAPI handling?

Evonik extensively trains our employees to understand both the "how" and the "why" behind the concepts of potent compound handling, along with the engineering and administrative controls put in place. Any engineering control system can be defeated by poor operational technique, poor equipment maintenance, or incomplete procedures. The level of qualification and ongoing training needed for an operations team is just as important as the equipment testing and maintenance procedures in place in a highly potent compound facility. Various disciplines must also be aligned under a HPAPI project team, which requires a culture of openness and trust.



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Synopsis on Highly Potent API manufacturing

The need for new pharmaceuticals is growing. With the rise in global population putting increased demand on existing services, new pharmaceutical development procedures and high potency active pharmaceutical ingredients (HPAPIs) are needed to provide necessary and effective medicines and therapies.

The global HPAPI market is projected to reach USD 39.6 billion by 2027 from USD 24.5 billion in 2022, at a CAGR of 10.1% from 2022 to 2027. The growth in this market is driven by factors such as increasing demand for oncology drugs, growing demand for antibody-drug conjugates, increasing focus of leading pharmaceutical companies on HPAPIs, advancements in HPAPI manufacturing technologies, and growing focus on precision medicine.

The importance of active pharmaceutical ingredient manufacturers in the pharmaceutical industry is evolving in response to new demands from customers, transforming the HPAPI market into an attractive area for investment. Many CDMOs across many territories and levels of experience are making a considerable number of investments in HPAPI capabilities and are facing numerous challenges in terms of entry barriers , regulatory requirements, sizeable investments, and expertise associated with APIs & HPAPIs development.

CDMOs with integrated capabilities in HPAPIs will have a competitive advantage over others as they can add value to Pharmaceutical Companies outsourcing these products in terms of cost and timelines. The pharmaceutical sector of HPAPI is highly fragmented, oncology being the largest and fastest-growing segment among all (oncology drugs estimated CAGR of 12.2% in the following 5 years).

This trend is also reflected into the requests for proposals received last years by FIS where oncologic APIs represent about 30%. To HPAPIs typically belong antibody-drug conjugates (ADCs), which in combination with monoclonal antibodies & biologically active drugs, are a very important and effective treatment for cancer.

Small molecules HPAPIs are extremely effective pharmacologically active ingredients. Their increment was also driven in the last two decades by the advancements in modern biology, that provided biological assay more selective and highly sensitive, driving modern medicinal chemistry approaches to identify more potent and selective lead compounds. Lead compound *in vitro* potency (pIC50 or pEC50, active concentration) toward the biological target associated to the disease (receptors, enzyme, protein, ion-channel and so on) moved from sub-micromolar to sub-nanomolar ranges in the last two decades. Increase in *in vitro* potency combined with improved understanding of pharmacokinetic and pharmacodynamic drivers of drug efficiency is leading pharmaceutical research to identify final APIs with higher activity, selectivity, potency and reduced side effects and dosage.

A comprehensive HPAPI manufacturing facility requires the use of risk management and assessment tools, and a mechanism to determine which compounds are suitable for manufacturing in each facility. The production of such compounds poses hazards and risks to workers and to the environment. Pharmaceutical CDMOs also need to have the capacity for the safe handling, production, storage, and transport of a growing range of potent compounds. Implementing a successful HPAPI manufacturing strategy requires the development of specific personnel skills, significant time and investments. Hence, various sponsor companies prefer going to CDMOs for assistance with the development, manufacturing, and distribution of HPAPIs.

Most HPAPI and ADC drug need to be produced in small clinical and commercial quantities. However also the production of gram scale GMP APIs is challenging. Furthermore, industry-wide, there is an ambiguity regarding the classification of HPAPIs. Different pharmaceutical companies often have proprietary systems, and the classification of new APIs is unknown due to a lack of data. These issues can be mitigated with appropriate process designs and containment controls, which most companies lack. All these factors collectively are likely to present a significant challenge for new players in the HPAPI market.

The definition of a HPAPI varies significantly in the literature and is not harmonized. The following descriptions may be found:

1. Based on therapeutic dose (quantitative criteria): A substance with biological activity at approximately 150 µg/kg of body weight or below in humans (therapeutic daily dose at or below 10 mg)
2. Based on Occupational Exposure Limit (OEL) (quantitative criteria): Substance with an OEL at or below 10 µg/m^3 of air as an 8-h time-weighted average
3. Based on hazards (qualitative and quantitative criteria): Substance with high selectivity (i.e., ability to bind to specific receptors or inhibit specific enzymes) and/or with the potential to cause cancer, mutations, developmental effects, target organ effects or reproductive toxicity at low doses
4. Based on risks (quantitative criteria): extreme acute and chronic toxicity, irreversible effects, strong sensitizer, poor or no warning properties, quick absorption rate, known "genic" effects, higher degree of medical intervention required, affecting sensitive subpopulations
5. Or, by default, a novel compound of unknown potency and toxicity

There is a need to focus attention on those compounds with the lowest health-based exposure limits because these may be the compounds that are the most difficult to control, and the consequences of overexposure may be the greatest:

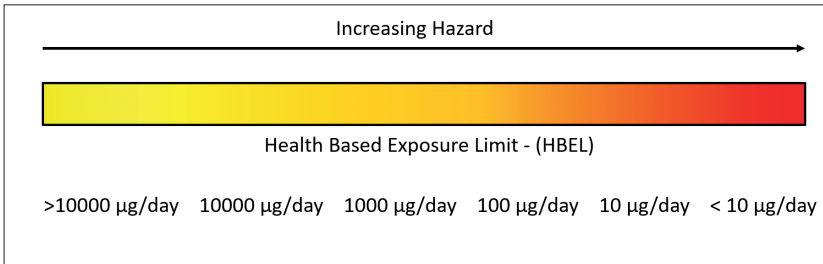

Figure 1. Reference EMA, «Q&A on implementation of risk-based prevention of cross-contamination in production and 'Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities» EMA/CHMP/CVMP/SWP/246844/2018, 2018.

FIS, in order to provide guidance on safe handling, categorizes compounds into Occupational Exposure Bands (OEB). When OEL is not known, the OEB is assigned based on the compounds' inherent pharmacological and toxicological characteristics, including the intended use, mechanism of action, dose-response, and data from available studies.

Based on a combination of technology, infrastructure and expertise, FIS has a comprehensive platform in place utilizing highly skilled teams, extensive evaluation and training procedures and state of the art facilities for optimized HPAPI development and scale-up to keep exposures below the OELs relevant to the band according to the Exposure Control Matrix (ECM). The internal control band approach in place for HPAPIs in FIS is:

- 1≤ OEB 3<10 µg/m^3
- 0.1≤ OEB 4<1 µg/m^3
- 0.01≤OEB 5<0.1 µg/m^3

HPAPI production is part of FIS core business and, based on hierarchy of controls, the company is focused on stringent engineering and administrative controls.
Containment philosophy is developed to satisfy both GMP and EHS purposes at the same time: personnel, environment and product protection.

Increasing OEB level leads to additional plant requirements. Multipurpose manufacturing departments are designed to manage OEB3 products during loading, discharging and packing, sampling, finishing operations in closed system (i.e., through glove boxes, semi-rigid flexible solutions, continuous liner systems, new contained powder pneumatic transport systems, HVAC specific design) and investments are performed to continuously improve the existing facilities in order to fulfil product/client handling needs.
OEB4 and OEB5 are managed in dedicated suites equipped with furtherly increased protection level: secondary containment (rooms with dedicated airlocks, interlocks and defined pressure profiles), production equipment installed within multi chamber isolators with pressure cascade, multi-liner systems in place for product isolator exit, dedicated HVAC with safe change filters and utilities, segregated technical areas.

To assess the containment performance of the engineering controls, a quantitative containment performance evaluation is conducted at the FAT (factory acceptance testing) and/or SAT (site acceptance testing) for every new equipment. The performance testing using surrogate (safe-to-use) materials is not intended to be a substitute for industrial hygiene monitoring for the actual APIs or hazardous materials involved in a given process. The intention of a containment performance testing (CPT) is to evaluate the containment performance against the designed exposure limit (DEL) to demonstrate that the device will control releases to the DEL or below. The industrial hygiene plan is then defined to monitor that the operator personal exposure is well below the API OEL limit during the HPAPI process.

FIS is equipped to handle a full range of different HPAPIs (down to 0,01µg/m^3) with *state-of-the-art* facilities and capabilities in order to cover all the operations: R&D process and analytical development, Kilolab (1-6 Kg of final API), pilot plant (5-20 Kg of final API), industrial production (20-100 Kg of final API) scales and analytical Quality Control testing.

In conclusion the increasing HPAPI market, even if challenging, offers growth opportunities for CDMOs. Being very capital intensive as business and skills development, the major CDMO players operating in API markets might have a competitive advantage in developing further and faster in this sector.

KENNETH N. DREW
VP Flamma USA, FLAMMA

Sometimes bigger is not always better with HPAPIs……
HPAPI manufacturing has come a long way in the past 20 years. At one time, there were only a few players in the CDMO marketplace. The landscape has changed dramatically with the advances of Innovator's R&D teams looking for more niche drugs for specialized cancer and other indications. With this, the complexity of the molecules has risen as volumes decrease and RSMs take longer to make.

Needless to say, there are many companies that now possess the capabilities to handle potent compounds. As closed systems and containment have become commonplace in the pharmaceutical industry, CDMOs are not nearly as limited as they once were. For example, it is now commonplace to handle materials that have an OEL> 1mg/m^3 as more pre-screening is done by CDMOs to understand the risks of these materials.

One of the most annoying factors in HPAPI manufacturing is the so-called scale or band used. There are various banding systems (typically, 4 to 5 bands) that refer to OEB (Occupational Exposure Band). Since there is no industry standard, we prefer to speak in terms of OEL (Occupational Exposure Limits) in order to protect the workforce as this is first and foremost to all companies.

Unfortunately, some innovators place a blanket OEL on their synthesis in order to avoid some simple and inexpensive testing of materials (intermediates as well as the final API). This can lead to overinflated quotes. For example, a 7 step process that is considered to be completely potent will cost much more than a 7 step process where only the last 3 steps are potent. It behooves the innovator to spend the short money on some simple testing to allow for a better understanding of the process. There are some consultants that prefer actual data while others will use a more liberal approach that, in turn, makes every intermediate potent. I strongly disagree with this liberal approach. Data is key in order to be cost efficient as well as be an effective partner.

As for capacity in the HPAPI industry, we are seeing a divergence of sorts where the demand for some HPAPIs is exceeding the current capacity as volumes grow. This has a trickle-down effect which is causing significant longer lead times for customers looking to place their projects into more well-known HPAPI manufacturing CDMOs since many of them are not interested in low volume drugs that target a small demographic indication that were developed at small and/or virtual pharma and biotechs.
This is where there is room for companies like Flamma can provide a sort of bridge to these pharmas and biotechs. Having a HPAPI kilo suite at Flamma USA affords a company with an aggressive timeline to begin early-stage work faster than having

to pay a reservation fee and wait for 6-18 months to capture manpower at a CDMO that is busy. Flamma invested into the US facility purchased in July, 2019 in order to bring the existing HPAPI kilo suite back online. This included modifications to the HPAPI suite followed by extensive surrogate testing. Having the ability to handle not only HPAPIs but controlled substances will help those innovators in need of a CDMO home.

Depending on the dosage of the final HPAPI drug, sometimes a small batch of 50-100 g may be the annual supply needed. It has been communicated to me that some of the larger players just are not interested in such small volume, early-stage materials making it difficult for smaller companies to find a CDMO home for their molecule. Add to this the desire to avoid working in China and India, there are smaller CDMOs based in Europe and North America that are attractive options for many innovators.

SCOTT PATTERSON
Vice President Commercial Support, ILC Dover

Single Use Containment for HPAPI Handling

The fast growth of new HPAPI compounds combined with utilization of CMO facilities that handle multiple products has required improvement in engineering controls used for containing each unit operations in the manufacturing workflow. Along the workflow there will be different levels of risks that must be considered while the hazard of the potent compound exists. This requires that risk assessment analysis may change along the workflow to determine the best containment solution. Over engineering the solutions will waste CapEx funds while under engineering can result in containment breach and exposures. Detailed risk assessments consider many dynamics that are of importance. Typically, the primary focus is on the operator and assuring the engineering control meets the CPT or Containment Performance Target. The CPT is the Occupational Exposure Limit with a factor to assure a high level of confidence the engineering control will always succeed in protecting the operators from exposure. Also of importance include assuring contamination cannot enter the process, the containment solution is easily cleaned so there is no product retention that could lead to contamination from batch to batch, and ergonomics for the operators to perform operations without risk of injury.

The use of SUT or Single Use Technology, also known as flexible containment, is becoming increasingly common as the containment solution applied in the HPAPI workflow. This is for both drug substance and drug product processes. SUT provides unique benefits that address the risk assessment concerns which are both technical and financial. The first requirement of any containment solutions is to meet the CPT and mitigate risks as determined in the risk assessment. SUT has been proven to meet levels of containment as low as 10.0 nanogram/m3. As always, this cannot be an absolute statement as the application of any engineering control must consider factors such as the unit operation in the workflow where it is applied, the quantity of HPAPI, and certain product characteristics. SUT that is deployed to meet this extremely low level is often the conceptually the same as what is used for other engineering controls. For some solutions, negative pressure control is added to Isolators or powder Pack Off Stations to maintain containment and mitigate risks in any upset condition in the process. Other solutions can combine secondary and even tertiary engineering controls to assure the CPT is met. When these SUT controls are developed the "contain at the source" philosophy is the start of the design. It is understood if the HPAPI can be contained within the unit operation including powder transfers, the risks of operator exposure and contamination are minimized. This can be done for new installations and retrofit of existing processes.

The capability to meet the technical requirements is now proven with a significant library of data following the ISPE SMEPAC method for containment assessments. The data covers the full range of HPAPI workflows including applications in Anti-body Drug Conjugate (ADC) manufacturing for the warhead which is considered one of the extreme requirements for containment. With the data supported performance we can look at the financial aspects of using SUT. In many cases, pharmaceutical processors have a perception that single use technology may offer a benefit for CapEx but then is lost in the OpEx spending. When making the comparison to stainless-steel engineering controls and SUT there are many factors in which the analysis for HPAPI manufacturing has unit operations that can only be done with stainless-steel equipment. This includes reactors and dryers and other processes. But many of the containment requirements and the powder transfer operations can be done with SUT with a significant reduction in OpEx. Going back to the CapEx formula, it is generally accepted that a SUT will yield a 70% savings. But that is only the start as we think about the common perception that the OpEx costs will exceed the value of the CapEx savings. When the full analysis is done for OpEx it is found that the actual costs are lower for the SUT solution and there are additional benefits. The analysis will show costs associated with cleaning and validation exceed the costs of the SUT solution. Recently a study was done comparing SUT with conventional stainless-steel solutions and overwhelmingly found the benefits of SUT. There were 18 categories that were evaluated but the specific area of significant savings was close to the point of use meaning in the process areas. By using SUT the significant cost reduction in cleaning materials, labor, and disposal costs drove a value proposition that showed SUT was financially better.

The study that determined the financial value of using SUT systems also looked at the question of sustainability.

Again, there is a perception that SUT are bad for the environment and using plastic materials is not a sustainable approach to achieving company governance for sustainability. But this is not accurate and looking at HPAPI processing will show benefits of using single use technology. The volume of cleaning materials including water and chemicals is costly to generate from an energy and environmental perspective The life cycle of using these cleaning materials is not sustainable because ultimately after use there is handling and disposal of highly contaminated materials. It is the general practice in the pharmaceutical manufacturing process to incinerate liquids that were used for cleaning process equipment which will include the containment systems. When applying SUT, the disposal of these solutions reduces the overall cleaning materials and is net benefit with respect to sustainability as reported in the study.

The conclusion is that single use technology can meet the high containment demands of HPAPI processing and result in lower costs and a better sustainability profile.

VALERIA CAVALLORO
Business Development & CDMO associate, Indena

What trends, in your opinion, are emerging in the HPAPI market?

Highly potent pharmaceutical ingredients are compounds characterized by a very high biological activity or toxicity and may hence find applications in several different conditions, among which the most represented ones are cancer, autoimmune or immunology disorders. This widely differentiated applications prompted more and more industries to invest in facilities to handle HPAPIs, turning the technology suitable for manufacturing HPAPIs from a niche area to an apparently widely diffused one. Consistently, nowadays a very high number of CMO/CDMO companies all around the world claim to be able to safely handle compounds with very low occupational exposure limits (OELs). In reality, technological equipment by itself is not sufficient to guarantee the handling in safety (for the operator, the API itself and the environment); it is a prerequisite, but like every complex technology, or any advanced tool, it has to be mastered by a properly trained personnel and coupled with adequate procedures, know-how and expertise.

In recent years, HPAPIs with increasing potency requiring lower volumes have emerged, spurred by the development of personalized therapies, dedicated to smaller clusters of patients with a targeted approach. From a technological point of view, this trend requires the ability to handle compounds with very low OELs in multipurpose suites (with appropriate cleaning procedures, supported by very reliable sampling and analytical approaches).

Furthermore, several HPAPIs require the combination of multiple technologies: this is the case of fermentation HPAPIs for example. Fermentation foresees the cultivation of micro-organisms like bacteria or fungi to manufacture pharmaceutical ingredients such as antibiotics, therapeutic proteins, enzymes anticancer agents, and other APIs. This field can still be considered a niche area and the reasons are different. Despite fermentation can be considered an "ancient" technique, the skills required are complex and often complementary to the chemical ones. Moreover, facilities need large volumes and a very strong expertise is required in purification and, particularly, in chromatographic separations, mostly in the management of HPAPIs. Taken together, all these considerations highlight how the absence of a well consolidated expertise in fermentation processes could represent a difficult to fill gap for industries which want to enter in this field. Despite these initial obstacles, also the market of HPAPIs obtained by fermentation is now living a very flourishing period. Thus, many secondary metabolites produced by microorganisms show potential application as, for example, new anticancer or pain killer agents, with more and more clinical trials under way. The real boost for these technologies comes from platforms like Antibody Drugs Conjugates (ADCs) or other less diffused ones like peptide-drug conjugates or conjugate to AAV vectors. These products are composed by three parts, a biological macromolecule (e.g antibody, peptide or viral vector), a linker (cleavable or not) and a payload (or active moiety) and, even if they have been discussed since several years, it is only in the last period they are having clinical and commercial success. The rationale behind these platforms lay on the theory of the magic bullet, being the biological macromolecule able to precisely deliver the active payload to the desired site. This highly specific targeting system allows to give a second life to molecules initially considered too toxic for other administration routes, being the systemic side effects kept to the minimum. For this reason, the toxins or highly potent secondary metabolites produced by microorganisms, as calicheamicin, mertansine, and duocarmycin, perfectly fit with this approach. The success of these platforms may be highlighted by the fact that nowadays it is estimated that there are more than one hundred ADCs from preclinical to phase III clinical trials, testifying that the research in this field is very active.

Quite interestingly, due to the wide chemical complexity, not achievable by computational chemistry, the space of naturally derived molecules is offering very interesting and innovative leads for HPAPI compounds, either obtained by extraction from botanical biomasses or by fermentation. Both origins require a significant level of expertise and the mastering of multiple technologies (e.g. fermentation of toxic compounds plus the downstream of HPAPI molecules, or proper sourcing of botanical biomasses according to Good Agricultural and Collection Practices plus extraction, purification and isolation - with or without semisynthesis - under containment).

To conclude, while several new comers are investing in technologies targeting the manufacturing of synthetic HPAPIs, still significant barriers in terms of proper handling and expertise exist. At the same time, fermentation and plant-derived HPAPIs require the simultaneous mastering of multiple technologies in the same company. An expertise far from being trivial and well beyond the simple installation of a dedicated suite.

GIORGIO BERTOLINI
Vice President R&D, Olon

Moving to a more sustainable drug supply chain

The general trend of life science industry has been to steer the development of new therapies towards increasingly selective, and therefore increasingly potent, molecules, with the possibility of extending to all therapeutic areas and in particular to oncology. Target therapies, i.e. drugs that are selective and therefore better tolerated by the patient, have an action that targets only the mechanism underlying development of the disease. They are finding increasingly broad application in treating the world's most widespread oncological diseases (primarily breast cancer), but also rheumatic and respiratory diseases and other major therapeutic categories with unmet needs. Improvements in treatment selectivity result in a demand for increasingly potent active pharmaceutical ingredients. In order to be produced, these ingredients require highly specific technologies, systems and skills to meet the standard of containment procedures that can guarantee to avoid the exposure of operators to these products and the potential cross-contamination of products.

Olon Group, which in the past five years alone has more than doubled growth in strategic investments, is developing capabilities and expertise that make it the partner of choice for pharmaceutical companies due to the fact that it is able to provide services throughout all stages of the development process. This includes for new generation molecules, which are the focus of much of the research and development of the global pharmaceutical market.

Pharmaceutical companies that are investing in the development and marketing of the most advanced drug classes need flexible and solid platforms globally connected for the development and production, with third parties, of highly potent APIs and highly toxic intermediates.

We decided to invest in the expansion of this capacity, to develop and produce highly potent APIs, from very small to large scale, along the entire development chain. This is because it relies on all types of reactors regardless of required size, as well as its experience in managing high containment production processes which is among the most extensive worldwide. We have developed a flexible manufacturing platform that supports the customer at every stage of drug development and also during commercialization, meeting API production needs, which can range from a few grams to hundreds of kg per year, depending on the disease.

We have completed the new high containment production line, OEB5 (OEL 1-0.1 μg/m^3), with reactors that allow us to produce highly potent APIs in large-scale product batches ranging from 30 to 150 kg. This expansion enables us to serve the customer along all the stages of the scale up, in conjunction with our sites. Starting with a few grams in the GMP laboratory, we move on to batches of 1 or 2 kg, then several tens of kilograms, followed by the 30 to 150 kg range which we can produce with the new line, until reaching the largest quantities. Now we are creating a new production line enhancing the containment level down to the lowest level of safebridge 3b band (OEL 20 ng/m^3) and expanding the large scale safebrigde 3A line (OEL 1-0.1 μg/m^3). Timeline for completion and start-up is 2023. It will represent the broadest range of HPAPI handling expertise for an API manufacturer, able to integrate every level of containment since the early phase of API development until the commercial manufacturing and from few grams to hundreds of Kg.

"We have built large-volume containment facilities" comments Giorgio Bertolini, VP R&D Olon Group "to support the production of new drug classes, in particular oncology drugs. Despite each dose of the drug contains a very small quantity of highly potent active ingredient, these drugs, for some diseases, have to be made available to a large number of patients worldwide. This requires large batch sizes of product, so as to allow pharmaceutical companies to guarantee access to therapies for all patients who need it."

The expertise in high containment processes is evident from the equipment we have at our disposal, but even more so from the in-house know-how that we have developed in recent decades, among the most extensive in the global API manufacturing market. We are one of the leading experts in highly potent APIs, whether cytotoxic or other kind of pharmacological action, in terms of full management of all aspects surrounding the plant: operator protection and training, policies and procedure, waste disposal and management of related issues. Our knowledge in this area goes back a long way: in the 1970s, our plants in Rodano and Settimo were two of the first sites worldwide to operate in containment, for the production of the first cytotoxic anticancer products on the market. Since then, Olon has continued to invest in the corporate culture of high containment and today it makes it available to its Partners.

"The ability to offer highly potent products translates into sustainability for the entire pharmaceutical industry" continues Giorgio Bertolini. "We are sustainable Partners since that we contribute to the global access to therapies, producing pharmaceutical ingredients that are more active and decreasing the quantity produced. It implies that we can significantly reduce the use of natural resources - raw materials, solvents, and energy - and the overall impact on the environment guaranteeing globally the availability of the required therapy. The result is a more sustainable drug supply chain. The future of our sector is to have increasingly small facilities with increasingly high activity, we are moving into this future."

CLAUDIO SALVAGNINI
HEAD OF CDMO, API Pipeline & Business Development, API BU, Polpharma

What trends, in your opinion, are emerging in the HPAPI market?
The High potent market has been constantly growing in last decade and is foreseen to continue growing at Compound annual growth rate (CAGR) > 7%. The market has been estimated worth $20.3 billion in 2021, projected to $27.3 billion in 2025 and exceeding $50 billion by 2031. Rising incidence of chronic diseases such as COPD, asthma, cancer, have resulted and will continue to focus large R&D investments for the development of innovative drugs in these fields, drugs that are designed to be highly active and consequentially often high potent. The manufacturing industry have been invested massively in high containment installations in order to be able to handle those compounds safely and in the CDMO/CMO space much more players are claiming today High Potent capabilities.

High potency namely starts from OEL 10ug/m3 where capacity is worldwide quite large, however when we look for capacity at OEL 1 µg/m^3 and especially below 0,1µg/m^3 – giving higher and more stringent containment requirements - the global capacity is probably below future foreseen projections, justifying continuous investment programs we have seen in the industry in recent years by historical HPAPI players but also new comers.

What are the challenges in managing HPAPI manufacturing?
Challenges are coming from the inherent difficulty to confine into an highly contained environment complex operations, proving and validating such containment performances versus concentrations level that are approaching analytical detection limits, of especially when we talk about OEL on the region of ng/m^3. In this context there is obviously the need to establish very robust procedures, SOP, continuous operators training, risk analysis… in order to contain processes "by design" more than monitoring the correct performance of the engineering solutions that are in place. Handling HPAPI is not just a matter to transfer operations into a glove-box, more importantly is applying a well-defined number of strict procedures to allow the engineering solutions to work properly assuring the necessary protection to the employees and the environment.

Where do you see the market for HPAPIs in 5-10 years?
The market is foreseen to continue growing and as such demands for capacity. However giving the high investment, maintenance and operation costs of HPAPI facilities it is likely that – also giving the current geopolitical and economic situation – we will see consolidations, even at higher rate that last 5 years, with number of players reducing to those companies that succeeded in recovering initial investment having developed suitable portfolio of products and clients that will allow them also to further sustain investments and growth.

What does the ideal CDMO partner offer?
HPAPI projects can spam from products with OEL from 10µg/m^3 to few ng/m^3, batch sizes from grams to tens or hundreds of kg. Often at early stage of development precise and non-controversial OEL values might not be available for the API and intermediates. In this context the CDMO should first have robust risk assessment process to allocate the most appropriate OEB and related containment and protective measures. Then be able to have an ample offering in terms of containment and equipment size from R&D labs to GMP facilities in order to ideally assure full life cycle management coping with volumes increase from clinical trials to product launch, but possibly also OEB adjustments during the development giving availability of new data. Not being able to adapt to volumes and OEB changes might force the client to technical transfer to other vendor increasing overall project cost and complexity.

It is with these considerations in mind that Polpharma for instance has designed its new green field HPAPI Hub and adaptations of existing facilities in Starogard Gdansk site: installations able to cover products with OEL from 10µg/m^3 to about 20 ng/m^3 and GMP production with assumed batch size from grams to hundreds of kg.

How do CDMOs prepare their employees for safe HPAPI handling?
Handling HPAPI is not only a matter of installing glovebox, engineering containment solution or personal protective equipment. The human factor is critical to assure correct operations in order to achieve required containment performances. Establishment of dedicated processes, SOP and appropriate continuous training is paramount.

When assessing risk and evaluating containment strategies, occupational exposure limits are the most appropriate assessment measure.
Occupational exposure limit (OEL) correct assessment is the starting point of any considerations of appropriate HPAPI handling. Accordingly EHS departments recommends Occupational exposure band (OEB) that guides - according to internal procedures - the selection of specific equipment, lines, cleaning protocols.

All parties involved in any HPAPI project must align on potency classification.
Surely OEL alignment between different parties involved is crucial, also because calculations of this value might lead to different values depending on assumptions on …. The final decision should be anyway taken by the manufacturer who is finally responsible for its employees safety, environment protection and compliance.

Did you invest in increasing the HPAPI capacity since January 2020?
Polpharma has launched numerous investments in Starogard Gdanski facility (FDA inspected) aimed to modernize existing production lines, expand capacity with green field investment to increase flexibility and offering of this plant. Among other investments (new kilo-lab, expanded cryogenic capacity, oligonucleotide production platform…) of course HPAPI capability enabler has been one of the key factor. Existing R&D laboratories have been adapted to handle products down to OEL 1µg/m^3 and 2 production lines will be upgraded during 2023.

In addition construction work for a new greenfield HPAPI facility for handling products with OEL down to 20ng/m^3 will shortly start. This new building will be of 3500 m^2 on 3 floor and will include R&D laboratories, multiple GMP kilo-labs, offices and dedicated warehouses and technical rooms. The facility has been designed as modular, with opportunity to be extended in the future with additional R&D and production suits in the surrounding green fields.

What benefits brings this capacity expansion to your target customers?
This capacity expansion will allow Polpharma to enlarge its portfolio of products and support in development and manufacturing in the oncology space serving clients that are active in this therapeutic area and where not necessarily coming to Polpharma in the past. With such expansion Polpharma will join a restricted number of European API manufacturer that can cover from small to large scale demand of HPAPI with OEL in the range of 20 – 1000 ng/m^3 offering from one single facility a one-shop-stop for starting materials, intermediate, API, and formulation.

What is the current HPAPI global capacity in your company?
What is the range of HPAPI batch size in your company?
Polpharma will have capacity from tens to hundreds/kg batch for OEL 10-1 µg/m^3, 5-50kg/batch for OEL 1-0.1 µg/m^3, grams-kg/batch for below 0.1 µg/m^3. This will provide coverage for ample range of Oncology products including ADC toxins.

Who are your main target customers and how does your capacity meet their requirements?
Our targets are mainly biotech, bio ventures having assets from early clinical phases (preclinical/phase 1) and requiring quick development and scale-up to GMP, from few kilos to tens of kg to support clinical trials needs.

What is the regional capacity footprint of your company? (Asia, EU, North America, Other)
Polpharma manufacturing site for API and intermediates are located exclusively in Poland, Europe.

Are you planning any significant capacity extension in the next 2-3 years?
In the next 2 years Polpharma will complete upgrade of existing facilities to handle products with OEL 10-1 µg/m^3 and in parallel the construction of new HPAPI dedicated facility including R&D, kilo-lab, QC labs to handle products below 0.1 µg/m^3. In addition to these HPAPI dedicated investment Polpharma is extending capacity with new kilo-lab line to support early phase projects, adding cryogenic capacity both in pilot and commercial plant up to 6000L, and implementing Oligonucleotides synthesizing technology in R&D and GMP environment. This as part of ambitious growth plan that is aiming to bring Polpharma among the leading global players in the API and CDMO space.

Where do you plan to
Polpharma Group is constantly looking for further expansion, also via M&A focusing primarily in Europe.

PAOLO PAISSONI
BD & Innovation Director, Procos

What trends, in your opinion, are emerging in the HPAPI market?
HPAPI market size is expected to reach approx. 30 Billion $ in 2024 (1), according to some reports, and definitely is growing fast. The high potent APIs are currently less than 20% of the total market, but the percentage will increase for sure, considering products in clinical trials.

Pipelines of emerging Biotech, small and big Pharma count more than 1,000 HPAPI and recent approvals in US and EU are well over 20%.

That's why there is a special attention to the HPAPI market: it is growing more than other segments, both for new chemical and biological molecules.

In my opinion, limiting the analysis to the Small Molecules, the reasons are mainly related to a) the complexity of the new drug candidates – easy to understand looking at the structures of the new approved ones – and b) the specific diseases which the scientific community is targeting – rare diseases, some specific central nervous system ones, besides several kind of cancers, traditionally covered by HPAPI drugs.

Summarizing, a CAGR over 6-8% (depending on the available analyses), over the average of other categories, is leading to a special care to the class of high potent API from several companies in the world, innovators and suppliers.

Is there a market or region of the world that is currently growing or increasing their expertise and market share in high HPAPIs?
I think that all the countries see a growth in the HPAPI space. Traditionally, US EU and Japan lead the sector, but recently China has been one of the fast-growing markets for this kind of typology of API. For instance, anticancer drugs are more and more important all over the world, and those kinds of API – typically widespread in the most advanced world – are becoming relevant everywhere, especially in those countries, like China, that have the best economical growth's factors since several years.

Despite the increasing importance for such a relevant local market, main expertise remains in EU and US, although we count valuable companies in all innovators' countries.

Technology is the key driver for being reliable players in this space, in my opinion. That can make the difference. In other words, it is not enough investing in a bunch of isolators to be in the arena.

What are the challenges in managing HPAPI manufacturing?
There are several items to solve once you handle HPAPI manufacturing, for sure. First of all, the most important one is assuring the right safety and health of the researchers and people working in a HPAPI manufacturing unit, besides the correct cGMP procedures to get the desired drug substance of the appropriate quality.

Quality is a 360° concept, it is not only related to the specifications, includes also the proper assurance to avoid any cross-contamination. Here cleaning, being a very complex matter, is even more important than in non-potent units, in case of multi-purpose configuration.

Appropriate design could be a good starting point. In fact, as said before, containment is not only installing a suitable number of isolators: when assessing risk and evaluating containment strategies, occupational exposure limits are the most appropriate assessment measure. Indeed, occupational exposure levels (OEL), as target for the manufacturing unit and the detailed experimental verification, are the basis to assure the above concepts of safety and health.

In my experience, as far as I have seen in many plants and after sharing thoughts with colleagues, alignment in OEL evaluation and bands, that usually lead to the unit's classification, is one of the most important points to clarify, between sponsors and suppliers, and even between multiple suppliers, in case of long supply chains to get the HPAPI.

Outsourcing strategies are generally driven by multiple complex factors, such as safety design, capability and expertise, suitable R&D and Quality systems able to support registration (in case of clinical trials product) and commercial (including post-commercial) management.

Companies can be selected as one-stop-shop partner or specialized one, depending on the capabilities of the innovators, if they need to outsource everything or part of the supply chain.

Procos currently has focused its activity and has specialized into Small Molecules only, because this is what we know at the best. We may think to integrate some parts of the supply chain in the future.

The HPAPI market was perceived as the fastest growing market in 2020. Was this in line with the demand in 2021 and 2022?
Yes, definitely. In some analyses, the growth of HPAPI business could become 40-50% of the approved drugs. The potential outcome could most probably be real, because pipelines of the innovators are focused in therapeutic categories requiring High Potent API, such as oncology, personalized medicines, rare disease.

The same categories, affecting approx. 30-40% of the new molecular entities under clinical trials, require significant investments by innovators (mainly in US in this case), leading NMEs approvals. It is important underlining 2/3 of these NMEs are studied (and brought to the market) in Emerging Biopharma (EBP), Small and Medium Pharma, while 1/3 are belonging to Big Pharma. Therefore, it is a worldwide and spread-out phenomenon, so HPAPI market will become more and more relevant.

Did investment in HPAPI capacity overshoot demand or is there spare capacity in the industry?
I believe there will be spare capacity: please consider that almost 30 CDMO companies, located everywhere in the world (though mainly in Europe), announced investments in this field along the period 2020-2022.
These investments are new plants, new units, a wide range of batch size capacity. They are leading the growth in Pharma business.

What is the effect of re-shoring (if any?) on capacity utilization in the EU and the US now? And how that will affect the capacity utilization?
I think that re-shoring is less affecting this capacity utilization. US and EU companies already led the manufacturing capability and will do more in the future. That does not mean that Indian and Chinese companies will not play a role in the arena, but the gap is still there, in the short-medium term.

Did you invest in increasing the HPAPI capacity since January 2020?
Procos is constantly investing in new capabilities year-by-year, not only in HPAPI. Specifically, in our High Potent part – already working with dedicated R&D, QC and 2 manufacturing suites (10 ng/m^3 and 1 µg/m^3) – we are currently adding two new kilolab suites for very high containment (10 ng/m^3), that will be ready in 2023.

What benefits bring this capacity expansion to your target customers?
We are giving the opportunity to cover the increased needs to our customers, particularly regarding the small molecules (including drug linkers) with low OEL values. We see several projects, going to commercial phase, using very high potent candidates: we believe to be able to bring added value to this kind of requests.

What is the range of HPAPI batch size in your company?
We are mainly targeting low volumes and high containment products; batch size is less than 1 kg until 10-15 kg, depending on the chemistry and OEL requirements.

What is the split between manufacturing commercial HPAPI products and clinical trial HPAPI products in your company?
We are successfully covering both segments of the market, although there is some prevalence for commercial ones.

Are you planning any significant capacity extension in the next 2-3 years?
There is still room to increase capacity in our HPAPI plant, therefore we are carefully evaluating the market evolution to match the unmet needs in terms of CDMO services. Procos has never stopped investing in the plant since 2008 and we expect to continue in the future.

References and notes

1. Nice Insight's 2022 API Market Report & CDMO pricing study, https://www.pharmasalmanac.com/articles/small-molecule-api-market-trends.

MARTIN AXON
Senior Principal Occupational Hygienist | SafeBridge Europe

Why is there a focus on HPAPIs?

- By some estimates, HPAPIs account for 25% of the worldwide market.
- Special precautions need to be applied during manufacture of these products to protect the workforce.
- Precautions include determining the hazard band or occupational exposure limit of the product and then arranging for appropriate contained processing equipment (control at source) and secondary control through appropriate facility design.
- For new entrants to the manufacturing arena, handling HPAPIs will usually either involve upgrading an existing facility or constructing a new HPAPI facility.
- There are significant cost implications, both in terms of capital expenditure and increased operational costs, associated with production of HPAPI products.

Trends

Growth in the HPAPI market can be measured through market research to provide objective global forecasts. However, speaking from the perspective of an organisation dedicated to the safe handling of HPAPIs, the indicators of growth that we see include capacity expansion of our existing HPAPI manufacturing clients, new clients coming into this market place each year and growth of the capacity and the number of vendors that provide HPAPI containment solutions. Specifically, we have seen significant and steady investments by our "Certified" clients in traditional HPAPI manufacturing capability, over the past ten years. In addition, there have been two other areas of notable activity, for example, anti-body drug conjugate (ADC) product development and increasingly potent products being produced via biological processes.

History and Challenges

Highly potent pharmaceuticals have been on the market for more than 50 years, oral contraceptives are a prime example of this class of products. In the 1970s companies that manufactured oral contraceptives experienced worker health effects and quickly needed to develop effective control systems. The solutions that they developed included hazard recognition and assessment approaches, containment solutions, improved facility designs and highly sensitive analytical methodologies to measure airborne concentrations of HPAPI, to verify that controls were effective. While many of these innovations are now imbedded into the culture of the pharmaceutical companies that have a history of handling HPAPIs, none can assume that the problem is solved. Organisations must be vigilant for products with increased potency by applying a philosophy of continual improvement. Meanwhile, there is the challenge of educating and improving the approach of organisations that are new to handling HPAPIs, to introduce them to the established tools that have been developed to manage the risks.

Unique Availability of Toxicology Data

One aspect of the pharmaceutical industry that gives an advantage in identifying HPAPI products is the pharmaceutical product registration system. Uniquely in the industrial world, there are significant human toxicology data generated as a result of the requirements for product license submissions. The challenge in utilising this data is that during early phase investigations data is limited, so that the human data, needed to develop an occupational exposure limit won't normally be available. This data won't be available until, essentially, the product enters the commercial phase. Hazard banding was developed by the pharmaceutical industry, specifically to deal with this challenge. There is normally sufficient data available to place HPAPIs into broad hazard bands, even during early phase product development. Hazard band assignment indicates how potent the product is and allows for suitable handling precautions to be applied as necessary, when working with the product prior to the commercial phase.

Best Practices for Safe Handling of HPAPIs

The pharmaceutical industry is highly regulated and organised. All aspects of GMP manufacture are driven by validation data and procedure. Best practice for the safe handling of HPAPIs applies a similar concept of an organised and systematic approach. The equivalent data driven approach involves developing a safe quantitative exposure limit and then applying controls of known, suitable quantitative control performance. As with all pharmaceutical operations, validation or quantitative verification of these controls closes the loop and demonstrates that the controls are effective.

Contract Development and Manufacturing Organisations

A significant proportion of HPAPI manufacturing operations are conducted by CMOs and CDMOs who have developed expertise in the safe handling of HPAPIs over a number of years. However, not all CMO sites have all of the skills needed to assess and control the risks associated with HPAPI production so that they need guidance in one of more aspects of safe HPAPI handling. Customers who are entering the HPAPI market for the first time should not assume that all CMOs are equal. Applying a metric to review or audit the understanding and competence of the selected CMO is recommended.

Best CMO Practice for Identifying the Potency of the Pharmaceutical Product

The potency, and therefore the hazards of APIs vary, this fact should be obvious, but it is still worth stating. The term frequently used when discussing hazardous pharmaceutical products is HPAPIs (highly potent active pharmaceutical ingredients), however, the terms "potent" API or "ultra-potent" API can also be applied to describe lower and higher potency products. Taking this into account, when considering products that a CMO is working with, the more potent the API, the more stringent the controls, it normally also follows, the more stringent the controls, the higher the cost to handle the API. CMOs bidding on a project should integrate an understanding the level of potency of the customer's HPAPI into the negotiating process. Correct determination of the potency of the product during initial customer discussions is critical, getting this wrong will result in either application of over

conservative controls (more expense) or insufficient controls with the potential for exposing employees to unsafe concentrations of the product. The quantity and quality of API hazard information, made available by the customer, can vary considerably and needs careful interpretation. Best practice is to develop a consistent "onboarding" process that includes an information request questionnaire and a procedure to review information provided. The quantity and quality of information and the approach applied to hazard assessment should always be reviewed to assess the level of confidence associated with the customers hazard assessment. Disagreements over the extent of the hazard can occur and are more likely where the customer is a "virtual" company with limited experience of the approaches normally applied to assess the occupational risk of handling the product.

Discussion with a significant CMO player:
A discussion was held with a large contract manufacturing organisation, to obtain their thoughts on the HPAPI market. The CMO has 60 sites worldwide, approximately half in the USA.

Of these sites, 20 have potent pharmaceutical manufacturing capability, though none of the sites are dedicated to HPAPI manufacture. Over the past five years there has been increasing demand to handle HPAPIs. Alongside this there has been a shift in the product type, with a significant rise of new modalities including biological products, antibody-drug conjugates (ADCs) and nano particle products. When dealing with customers who are requesting processing of HAPAPIs, the most significant challenge is usually to obtain information regarding the hazard band or occupational exposure limit of the product.


SAMUEL BARON[1], STEVE BARR[2]
1. Director of Research & Development SK biotek Ireland, SK pharmteco Company
2. VP Business Development, SK pharmteco Company

What does the ideal CDMO partner offer?
The ideal CDMO offers expertise, a sizeable global footprint, strong values, an entrepreneurial spirit, an innovative mind set, a focus on results, and both flexibility and a partnership.

It will have both scientific and technical understanding, practical experience and commitment, have the empathy to put themselves in the shoes of their customer and understand the long, complex journey they are on, whilst applying a science-driven, risk-based approach at every step.

Regulatory expertise is a must. Knowing a CDMO is certified in cGMP, ISO etc., and regularly audited by the FDA and leading regularity authorities provides the reliability needed by pharma and biopharma customers.

Size offers an added sense of security, having the global footprint, resources, expertise, capacity, capability, but also long-term viability and longevity to form lasting relationships and bring multiple projects to market.

It offers both consultancy and guidance through the clinical development pathway, focusing precisely on every step but never forgetting the end goal.

The ideal CDMO values the relationships they have with their customers, vendors and suppliers, and sees them as more than just drafting an agreement, but as a relationship that relies on clear expectations, communication and trust, a bit like a marriage of sorts.

The ideal CDMO prefers a partnership rather than a supplier relationship, committed to work with their customer and stand over the product as if it were their own; even better if they have a track record of producing some of the world's most recognized drugs for decades.

For a partnership to work, both parties must share similar values, clear lines of communication and regular updates to foster trust between the innovator (the customer) and the CDMO; trust is necessary for success. Projects have failed, relationships have been destroyed, and companies have folded due to poor communication. When a CDMO shows agility as needs change, that flexibility eases stress for the customer.

A relationship built on these values can handle the unexpected and unpredictable complications when problems occur. When each employee is an expert in their chosen field, each one values the customer and understands that unforeseen issues can be dealt with effectively, solved rapidly to avoid any delays in the clinical programme.

A CDMO that has an entrepreneurial spirit and an innovative mind-set means they are constantly looking for new ways, services, and capabilities to enhance their offering.

Quality performance is not just about passing every audit from every major regulator from the FDA to PMDA but something that comes as second nature and is part of the CDMO's DNA. Same goes for Safety, putting safety first is paramount, reputation depends on it.

What are the challenges in managing HPAPI manufacturing?
For companies manufacturing APIs, standards need to be maintained based on well-established industry-wide compliance guidelines. From a safety point of view and due to the high potency of HPAPIs, such compounds need to be handled with additional precautions to ensure personnel are not exposed to unsafe levels of potent chemicals. HPAPI manufacturing requires strong safety compliance policies and adherence to high quality and safety standards.

- A rigorous Occupational Health and Industrial Hygiene program is a requisite to ensure safe handling of chemicals. Robust engineering and administrative controls should also

be implemented to ensure HPAPI can be safely handled in multi-purpose manufacturing facilities and laboratories.

- The safety and compliance management system associated with handling and manufacturing HPAPI should address the variability in the data available with respect to safety profile of HPAPI depending on the maturity of the HPAPI within the drug lifecycle. It is expected that limited safety data would be available for an early phase product vs. a mature and established product. Procedures should therefore include a default approach depending on the class and/or chemical structure of a product when limited safety data are available to ensure personnel safety is maintained. The approach should include a certain safety factor to protect employees in case a material is identified as more potent than originally envisaged.
- Clear categorisation (e.g. tiered banding system) and associated controls for handling of chemicals including HPAPI should be in place. Clear communication of such controls to personnel on a periodic basis ensures that tasks are executed appropriately and consistently commensurate to the hazardous nature of the chemical.
- The safety management system should also ensure that periodic review of tasks/activities takes place to guarantee that the controls in place remain valid throughout the lifecycle of the product. For example, improvements in engineering containment approach might allow upgrade of equipment while reducing reliance on PPE or administrative controls. A comprehensive training program as well as the periodic identification and implementation of best practices within the industry should be part of the safety program and safety culture. This will ensure that the employees are provided with adequate and up-to-date knowledge and skills for handling HPAPIs.
- Controls around waste management should also be considered to ensure that waste generated during production of HPAPIs is handled appropriately if it contains highly potent residual material or waste is treated to remove the presence of highly potent residual material prior to being handled by personnel.

ADAM KUJATH
EVP and Site Head, Sterling Pharma Solutions

Where do you see the market for HPAPIs in 5-10 years?
The investments made globally by companies to handle and manufacture HPAPIs has meant that there is appropriate capacity in this area. For contract manufacturers, having the capability to handle these processes is now seen as an expectation as there is a higher level of diligence and risk aversion in the market.

For companies looking to differentiate themselves in this market, the opportunities tend to present themselves in the area more extreme potency, where containment is necessary down to single digit nanogramme, and picogramme levels. The nature of compounds that fall into this category are niche therapeutics such as toxin linkers in antibody-drug conjugate manufacturing, and psychedelic drugs, which are not necessarily highly toxic, but are extremely potent. These niche areas are definite emerging markets within the pharmaceutical industry, with research growing in these areas, service companies will need to expand and invest to be able to handle these molecules in the pipeline. The market is continuing to grow, but this is not just related to cytotoxic or other highly hazardous molecules: there is also significant growth in CNS, immunotherapy and other indications outside of oncology.

What does the ideal CDMO partner offer?
Ideally one that operates a range of services and can handle scale-up from pre-clinical to commercial quantities from a single site. This means that there is only one tech transfer step necessary, and the expertise of the CDMO for the unique nature of the programme grows as the molecule progresses through development. Early on in a molecule's lifecycle, the full toxicological and potency profile will be unknown, so its containment requirements need to be estimated based on the best knowledge available at the time – and with more information throughout its development, the containment needs may change. A site with a range of containment capabilities will be able to adapt in line with the needs of the programme.

Having manufacturing, analysis, and processing capabilities such as milling on site reduces the reliance on third parties for specific tasks, and increases the efficiency of the process, leading to cost and time reduction for the overall programme.
While regulatory pathways for HPAPIs are not unique, having commercialisation experience is invaluable. For example, when approaching process validation, a strong approach to concurrent validation can reduce unnecessary and costly excess inventory production.

What are the challenges in managing HPAPI manufacturing?
Obviously, the biggest challenge is to understand and put in place the containment strategies necessary for safe HPAPI manufacturing. It is unlikely that there is a standard setup that can be used for all processes, especially if it requires unit operations such as micronisation or distillation. Custom containment solutions can necessitate creativity, flexibility, and a deep understanding of engineering controls and capabilities. Even flexible solutions should be performance tested before manufacturing begins. But as with any incremental qualification exercises, this can increase lead and start-up times.

Cleaning can be a challenge in any multipurpose facility, but potent compounds can be even more so because of low carry over limits. With batch sizes, dosage levels and potency varying widely between these products, 100% analytical verification, as opposed to a matrix cleaning validation approach, is typically a preferred strategy in cleaning protocols. This approach will require the validation of analytical methods across a broader range of concentrations, but it does allow for a batch-specific limit, and not a worst-case calculation, which can be prohibitively low.

How do CDMOs prepare their employees for safe HPAPI handling?
Safety awareness amongst staff must be a cultural norm for a facility handling HPAPIs. There should be a level of understanding across everyone working within the facility to the risks of the compounds that are being handled, and then for operators directly involved in manufacture and processing, additional training given so that materials can be respected rather than feared. Fear can be a distraction, so through continuous education, learning, and visual management techniques, operators can understand the hazards and understand what controls are in place, and how they should be used safely and effectively.

How is the regulatory environment around HPAPIs changing?
Historically, potentially potent materials were classified by their properties - such as cytotoxics, or hormones - and the classification determined the basis of the level of containment necessary. Now, with the exception of specific molecules such as β-lactams and cephalosporins, containment is based on individual toxicological assessments of the appropriate and acceptable daily exposure limits. It is a far more technical approach and focuses on determining safe exposure limits for a specific molecule to protect the safety of operators, while reducing the potential risks to a facility and the environment.

Panel discussion on...

HAVE YOU ENJOYED THIS PANEL?

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PHARMA SUPPLY CHAIN (2023 Issue #1)

Panel Discussion on:
- Pharma Supply Chain
- Finished Dosage Forms & Personalised Medicines

TECHNOLOGICAL INNOVATIONS TO REACH HIGH VALUE PRODUCTS

This January – February issue, distributed at DCAT week '20, is totally focused on the **Pharma Supply Chain** and deals as well with digitalization, Pharma 4.0, biotechnologies and gene therapy. The following panel discussion takes into consideration the technological innovations and the key strategy developments of a few players involved in the chain.

From what we can learn from the inputs received, the main issues which are impacting the pharmaceutical development and manufacturing value chain are for sure quality, safety, sustainability, timeline and cost, drug shortages and regulatory compliance. Companies are facing these challenges by introducing technological innovations and key strategic developments, i.e. update of analytical and testing equipment, investments in new and high specialised technologies such as Flow Chemistry etc.

To complete this overview, we would like to propose again a **Panel discussion on finished dosage forms and personalised medicines** published in the September – October issue, 2019. This Panel considers the solid oral dosage market which continues to dominate but also the injectables one that is expanding due to the rise of biologic drugs which generally must be administered by injection or infusion. The immunotherapies' ability to personalise cancer treatment in particular appear to form the basis for a new era of personalised medicine. We are witnessing the rise for new CDMO experts for this specific market demand with unique set of manufacturing and supply chain capabilities. The use of digital and data technologies and artificial intelligence are moreover set to revolutionise drug discovery and development, transforming the way that therapeutics are both designed and manufactured. All the key players involved in this supply chain have in fact the same aim: deliver a safe drug to patients in a timely manner, facing the challenge of drug shortages.

Enjoy the reading.

Gayle De Maria
R3 Publisher

The following panel discussion takes into consideration the **technological innovations** and the **key strategy developments** of a few players involved in the Pharma Supply Chain. Companies have been invited to talk about the issues impacting the pharmaceutical development and manufacturing value chain.

The following players have joined the initiative:

Panelists

Julie Rixton, Director Pharma Solutions and Products, Fine Chemistry Services, **Albemarle Corporation**

Stephen Houldsworth, Vice President, Global Head of Platform Management & Marketing, **CordenPharma International**

Andreas Meudt, VP and Head of Exclusive Synthesis, **Evonik Health Care business line**

Aline Sassi, Commercial Director, **ICROM**

Stefano Togni, BD & Licensing Director, **INDENA**

Paolo Polisoni, R&D and Business Development Director, **PROCOS**

Shaheen Majeed, President, **Sabinsa**

DE-RISKING THE PHARMA SUPPLY CHAIN

Julie Rixton, Director Pharma Solutions and Products, Fine Chemistry Services, **Albemarle Corporation**

WHAT IS THE TECHNOLOGICAL INNOVATION YOUR COMPANY IS BRINGING TO THE PHARMA SUPPLY CHAIN?

The industry has seen increased risk and uncertainty in the past 12–18 months regarding security of supply from China. This is a result of growing concerns with quality control, increasing environmental regulatory tightening, safety issues causing plants to shut down or move, and trade tensions. All of the issues have created real risk in the supply chain, which is also driving prices up out of China. Our pharma supply chain is unique in our ability to back-integrate into RSM manufacturing within the United States. We understand our customer priorities regarding quality, timeline and cost, and we have taken action where appropriate to utilize our resources to take that risk out of the equation, there are so many uncertainties encountered during drug development — supply chain issues should not be one of them.

WHAT ARE YOUR KEY STRATEGIC DEVELOPMENTS OF THE LAST FEW YEARS?

We have intentionally moved to a more proactive approach regarding strategic sourcing for raw materials as well as process development/scale-up activities.

We have addressed security of supply concerns through risk assessment evaluations and back-integration internally utilizing our U.S. based manufacturing resources. We have also updated our systems, analytical equipment, and program plans to ensure that we are positioned to support sponsors with fast-track and high-priority review programs. We design our programs anticipating that the timelines may change, and we have demonstrated successful support through accelerated programs of scale-up, pre-validation QbD and impurity characterization, validation, and commercial launch without compromising the highest quality standards of compliance. This has resulted in successful U.S. and EU regulatory approvals.

WHAT ARE, ACCORDING TO YOU, THE ISSUES IMPACTING THE PHARMACEUTICAL DEVELOPMENT AND MANUFACTURING VALUE CHAIN?

Additional scrutiny is being applied to the RSM supply chain, a responsibility assigned to the CMO/sponsor company. It is critical that manufacturing oversight is in place and that routine site audits are conducted to ensure that change control approvals and impurity characterization for RSMs are in compliance. Additionally, understanding the risks associated with a potential supply chain interruption is essential. The pharma industry saw significant 2019 supply disruption and recalls associated with impurities that have posed risk to the commercial drug supply. It is more important than ever to ensure your suppliers are operating safely and sustainably. If these standards are not adhered to, it could derail or delay clinical studies. This is a significant risk and one that continues to challenge the industry.

CORDENPHARMA FOCUSES ON ORGANIC GROWTH, FLOW CHEMISTRY & PHARMA SUPPLY CHAIN SUPPORT

Stephen Houldsworth, Vice President, Global Head of Platform Management & Marketing, **CordenPharma International**

WHAT IS THE TECHNOLOGICAL INNOVATION YOUR COMPANY IS BRINGING TO THE PHARMA SUPPLY CHAIN?

At CordenPharma we continue to invest in Flow Chemistry, with 2020 seeing a further enhancement. While the Pharma industry has been rather conservative when it comes to embracing new technologies, the promise of continuous processes to achieve a more consistent quality has resulted in the major regulatory agencies offering potentially accelerated drug reviews and approvals for early adopters. In an industry where time to market is a major concern, the offer of accelerated reviews may be too tempting to ignore.

CordenPharma intends to focus on flow chemistry for small molecule API production, one of the greatest benefits of which is the alleviation of process safety hazards associated with reactions that involve hazardous or toxic reagents or highly reactive / exothermic chemistry. The safety of our employees is of paramount concern, so enabling the operators to perform our customers' projects more efficiently, whilst enhancing their safety, is an all-round win-win.
Another aspect that is often overlooked is the risk mitigation for high value products. We are often working with extremely valuable intermediates or products for our customers that may have taken months to prepare. When you consider the financial value that may be in a batch reactor at scale, combined with the limited process knowledge that we struggle with for early clinical stage projects – how do you manage this risk? Using flow chemistry and appropriately developed PAT technologies, you can minimize this financial risk significantly by having much smaller volumes (and as a result smaller $$$) exposed at any one time.

Chimica Oggi - Chemistry Today - vol. 38(1) January/February 2020 27

Topics discussed previously: Digitalisation, Pharma 4.0, Cell & Gene therapies and Personalised medicines.

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chimica oggi CHEMISTRY TODAY + regular section: PHARMA HORIZON

If you would like to participate in this panel please contact us at the following email:
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