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,
CordenPharma International

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.