Highly Potent APIs – Markets, Myths and Manufacturing

A Cambrex webinar overview

How does a CMO handle complexity?

The production of non-potent small molecule drugs accounts for the vast majority of API manufacturing capacity. Nonetheless, clinical successes and growing press surrounding small molecules focused on oncology indications and cancer growth inhibitors has created somewhat of a gold rush of commercial interest in highly potent active pharmaceutical ingredients (HPAPIs).

Terminology such as 'high potency' and 'highly potent molecules' have almost become cliché as the number of contract manufacturing organizations (CMOs) that claim to be able to handle them proliferates. However, as recently as the last decade, the list of CMOs that could legitimately manage the hazards associated with manufacturing HPAPIs could be counted on just one hand.

So what's different about this webinar?

It can be tempting to assign high potency to a small molecule in this therapeutic class and in many cases this serves as a conservative approach. Perhaps the greatest challenge for toxicological assessment is that these molecules may be highly potent toward cancer cells and yet pose minimal hazard to healthy workers. This is an important departure from past toxicological assessment of legacy cancer drugs that act primarily through somewhat non-selective cytotoxicity.

HPAPIs and, in particular, small molecules being developed for oncology present a new set of challenges for CMOs charged with safe handling during process development, clinical and commercial production. In the context of recent developments and investments made by Cambrex in high potency manufacturing, we aim to:

- **Provide an overview of the current HPAPI market**
- **Introduce HPAPI toxicological assessment**
- **Explain why there is variability between assessments**
- **Discuss how variability may impact containment strategies and cost**
- **Share ideas about how to tailor and customize manufacturing strategies for next-generation small molecules in targeted cancer therapy**

Contributors

Dr. Matthew Moorcroft,
VP of Global Marketing, Cambrex

Matt is the Vice President of Global Marketing and Communications for Cambrex. Prior to joining Cambrex, he worked for Lonza and held a number of roles including Head of Global Marketing, VP Generics and Biosimilars, and Head of Strategy, Pharmaceuticals and Biologics. After gaining experience in the custom development and manufacturing business, he developed models for biosimilars and generic drug products. He has 15 years of commercial and scientific experience in the pharmaceutical, biotechnology and chemical industry covering both innovative and generic medicines. Matt graduated with a Ph.D. in Chemistry from the University of Oxford.

Jeff Pavlovich, Cambrex
Senior Process Safety Engineer

Over the past 14 years, Jeff has focused on process risk assessments and PSM management within Cambrex. Prior to his roles in Safety, Jeff worked in Potent Compound Manufacturing and has received advanced training on numerous aspects of occupational safety, including potent compound handling, toxicology and industrial hygiene. Currently Jeff is a key team member of a project focused on the design and build of a Potent Compounds Manufacturing facility at the Cambrex facility in Charles City, Iowa. Jeff earned a BSc in Chemistry from Creighton University in 2002.

Dr. Mark S. Maier
Managing Partner, Sheperian Toxicology

In a career spanning more than 30 years, Dr. Maier's scientific focus is on toxicology, chemical bioactivity, health risk assessment, exposure assessment, and risk management as each applies to pharmaceuticals, drugs-of-abuse, and food additives. Dr. Maier was responsible for exposure risk assessment and management at Cambrex Charles City and for food additive safety at the Valspar Corporation. He is an affiliate faculty member in the Center for Environmental Medicine at Colorado State University.

Dr. Maier earned his BSc in Chemistry, MSc in Environmental Health, and his Ph.D. in Toxicology from Colorado State University, and is certified in general toxicology by the American Board of Toxicology. He is a managing partner of Sheperian Toxicology, LLC, an international risk assessment, pharmacology and regulatory practice. Dr. Maier's recent publications include topics in toxicological read-across and safety assessment of endocrine active molecules.

Introduction to the high potency market

The increasing focus on highly potent active pharmaceutical ingredients (HPAPIs) in pharmaceutical development pipelines has led to a growing requirement for the capability to safely handle and contain these hazardous ingredients. In addition, as existing products that were amongst the first drugs to be categorized as 'highly potent' face patent expiration, the ensuing rise in volumes typically seen with generic entry will further intensify demands on the existing high potent manufacturing infrastructure.

Much of the demand is in the oncology field, but anticancer products are not the sole source of HPAPI medicines. Estimates vary for the overall size of the HPAPI market, nearly as much as the methodologies analysts use to quantify the market. Some estimate it between about $14bn and $16bn a year in 2016, and forecast it to grow to as much as $27bn by 2023. Overall, approximately one third of all drug approvals each year are now anticancer medicines, and a similar proportion of the development pipeline is made up of oncology drugs. While not all of these will be classified as highly potent, a significant proportion of them will be.

This top-down approach of looking at the market does not give a particularly meaningful insight into the demand for HPAPI manufacturing capacity. There is no guarantee that a molecule that acts against cancer cells truly needs to be treated as highly potent from a manufacturing standpoint as it may pose only minimal hazards to operators in the plant. Only a bottom-up approach, looking at actual Occupational Exposure Limit (OEL) measurements, is likely to be more accurate. The pharmaceutical industry definition of 'potent' is a compound with an OEL at or below 10 µg/m^3 of air as an 8-hour time-weighted average. However, there is no specific definition as to what constitutes a highly potent compound as different risk assessment experts frequently have different opinions on the same molecule.

To test this variability, the same selection of 38 molecules was sent to three different risk assessors. Whilst one deemed the majority (37) to be highly potent, at the other end of the spectrum another established that just five were highly potent. The third source was again different and somewhere in the middle of the two.

These results help us to understand the complex and dynamic nature of ascribing OELs to chemical molecules and come to the conclusions that in a manufacturing context, the OEL is best considered a tool for site risk management teams. We believe that, based on this data, any respectable CMO active in the space should adopt a flexible approach to HPAPI manufacturing and be able to offer a full continuum of options so that different solutions can be appropriately matched to molecules at different stages of their development lifecycle.

Introduction to toxicology and beyond: why assessments vary

Making a judgment of the risks to employees starts with scientific assessments, animal studies and clinical trials that are carried out by the drug developers for insights into potential hazards and dose–response effects. Risk assessment experts use their professional judgment to interpret this data and generate critical effect risk-based values, including OELs and Occupational Exposure Bands (OEBs). The management team at a CMO's manufacturing facility will then use these assessments to put engineering and industrial hygiene strategies in place to control and minimize the risk of exposure. As well as training, these will include containment and Personal Protective Equipment (PPE) strategies.

The first step is to characterize those hazards. Studies will indicate if any acute exposure problems might be expected; such as somnolence, respiratory arrest, adrenergic or lachrymatory effects – or whether it is an allergen, corrosive or an irritant. Issues that may cause chronic exposure issues include being a carcinogen, mutagen, clastogen or sensitizer. Also, whether it has developmental or reproductive effects or toxicity arises after repeated doses.

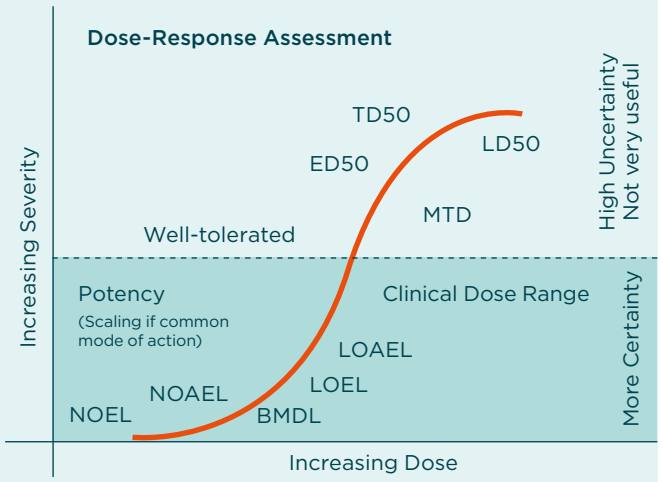
Either way, the critical effects of that exposure then need to be identified – whether that is a pharmacological effect or target organ toxicity – and the relationship between the dose and these effects. Different molecules have different dose–response curves and the effect that they have changes with the dose, as does the way people behave in response to that dose.

Importantly, potency and toxicity are not the same thing. For example, some highly potent molecules have a pharmacological effect at a very low dose but toxic effects do not kick in until the administered dose is much higher. This large therapeutic index is exactly what is required for an anesthetic – a wide gap between the effect and the side-effect.

In contrast, an old-fashioned cytotoxic chemotherapy drug may have fairly low potency but high toxicity, which means the likelihood of toxic effects occurring at a therapeutic dose is much higher. In risk assessment terms, the two examples are very different.

It is this variation that provides the difficulty in assessing risks. For an industrial chemical there is likely to be a large amount of available data on effects to inform the risk assessment. The level at which there will be no effect – the no observed effect level, or NOEL – will be clear. Moving up the dose–effect curve is the NOAEL – or no adverse event level – which is commonly seen in risk assessments. Then there is low effect level and low adverse effect level (LOEL and LOAEL), before one moves past the well tolerated dose to the maximum tolerated dose, through to the ED50, TD50 and LD50, the doses at which half the animal subjects have an effect, a toxicity event or die.

Points of departure



The dataset is never going to be complete, however, and therefore uncertainties must be accounted for. This equation can be used to calculate the OEL:

OEL equation

$$\text{OEL } (\mu g/m^3) = \frac{PoD \times BW}{UFc \times MF \times V}$$

Where:

OEL	=	Occupational Exposure Limit
PoD	=	Point of Departure for Extrapolation (mg/kg-bw/day)
BW	=	Body Weight (kg)
UFc	=	Composite Uncertainty Factor
MF	=	Modifying Factor
V	=	Volume of air breathed during workshift (m^3)

The factors included in the numerator are those that increase occupational exposure; the denominator comprises those that reduce it. Two of the components of the denominator – a composite uncertainty factor and a modifying factor – are designed to compensate for this uncertainty. There are many factors that can contribute, some are shown in Table 1:

Table 1

Contributors to uncertainty

Uncertainty factors

Intraspecies variation	10
Interspecies variability	2-12
Study duration	3-10
LOEL to NOAEL	10
Database sufficiency	1-10
Severity of effect	1-10
Bioavailability	1-10
Bioaccumulation	1-10
Pharmacokinetics	3–10
Route-to-route	3–10
Allosteric adjustment (rat)	

Modifying factors

Slope of dose–response curve
Choice of critical effect
Susceptible subpopulations
Clinical significance of critical effect
Reversibility of critical effect
Relevance of critical effect to workers
Read-across similarity
Lack of independence for uncertainty factors

Clearly these can introduce a huge amount of variability into assessments. Even including only the first five on the list of uncertainty factors can give up to 120,000-fold variability in the final OEL value, so it is not surprising that there is so much variability between different risk assessors. Some assessors also include modifying factors from the second list in the table, which can give a variation in the final OEL by anything from 0.3 to 10^8. Reconciling this variability in the final risk assessment represents a significant challenge.

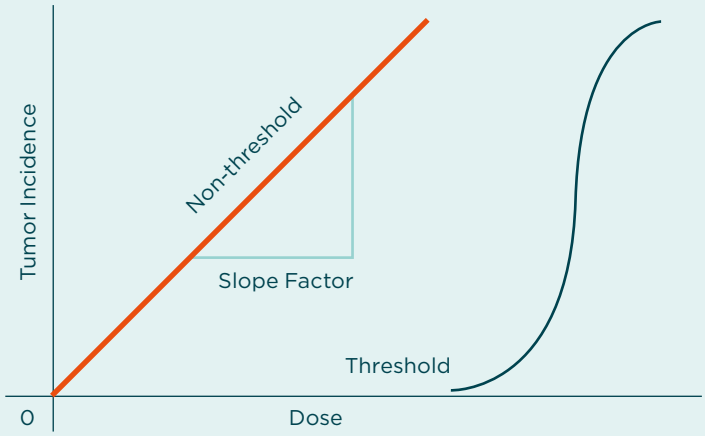
So how can one assess the impact of uncertainty factors in the real world, not just as an exercise on paper?

As an example, take a beta-agonist, indicated for the treatment of asthma, which, as a side-effect, can speed up the heart rate. It works in a similar way to the accelerator pedal in a car: there is some idling when it is pressed to start with, but as you increase the dose the cardiovascular side-effects will also increase. There are two ways a risk assessor might consider this. Often they will be looking at the NOEL that came from an experimental animal study carried out in a very sensitive species, where as soon as it goes past 'idle' it hits the critical effect. This doesn't take account of the normal variation in heart rate – a worker's heart rate will naturally increase temporarily if they have just, say, run up the stairs. So it may be better to choose the top of that range of normal variability as the point of departure for the risk assessment, rather than the NOEL.

Another example where risk assessors can give very different interpretations of risk is in cancer. Cancer risk assessments are sometimes used for mutagens, where there is a lot of belief that there is no threshold, and a linear dose–response curve. The slope factor represents where on that linear curve the workers would be safe. As can be seen from the equation in Figure 1, the slope factor is a measure of the slope times the OEL and that is equal to the risk.

Figure 1

Non-threshold carcinogen example



Slope Factor = Acceptable Risk / OEL?
$(mg/kg\text{-}bw/day)^{-1}$

Slope-Factor x OEL = Risk

Carcinogenicity Study

Chosen

Acceptable risk	Slope factor	Dose for OEL calc. mg/kg-bw/day	
$1/10^{-6}$	$3.0x10^{-2}$	3×10^{-5}	
$1/10^{-5}$		3×10^{-4}	Risk Assessor 1
$1/10^{-4}$		3×10^{-3}	
$1/10^{-3}$		3×10^{-2}	Risk Assessor 2

Highest fatality risk among all industries?

The critical question to ask is, what risk is it acceptable to expose the worker to. A very cautious risk assessor might deem that to be one-in-a-million, but in reality, one-in-a-thousand is a more acceptable risk. In occupational settings, this is a common number to select for the chance of having a severe injury in the most hazardous work environment. The dose would then be based on this. This is three orders of magnitude difference between the two assessors.

The difference is important because of the vast disparity in cost between the two. If a molecule moves from OEB2 to OEB4 purely because there are less data and more uncertainty factors, enhanced containment will be required at the expense of both cost and time of the project. Yet it also increases the mishap risk and the ergonomic injury risk, despite the fact that ergonomic injury occurs far more frequently than exposure in pharma manufacturing.

How can this level of uncertainty be reduced? It is important to consider the risks of the drug itself along with the intermediates involved in its production. Often there may be a calculated OEL for the API, but not for those intermediates.

As an example, take the oncology drug docetaxel. Here there are two important intermediates: the starting material and one with a silyl ether protecting group. When Cambrex undertook this project, as part of its risk assessment, we wanted to know if the critical effect – blood toxicity as a result of bone marrow effects – was also produced by these intermediates as well as the final API. In vitro assays showed that neither inhibited cell growth in contrast to the drug, which did. Therefore, they did not need to be considered.

Exposure modifiers represent another important consideration that is often overlooked, particularly if the person generating the OEL does not know the facility. In particular, does the process produce dust, or solid material, as the former is much more likely to pose an airborne hazard. One also needs to consider how long a worker is likely to be exposed to the material. The theoretical OEL is based on an 8-hour exposure, whereas in reality the exposure during a batch manufacturing process might be just for 5 or 10 minutes (for instance, when a tray dryer is changed over). Therefore it is appropriate to modify the risk assessment on a site-specific basis. Another aspect often overlooked is where particles suspended in the air are not deposited into the lungs at that rate; maybe only a third will actually reach the lungs. A risk assessor may automatically include a 10-fold uncertainty factor for inhalation exposure, yet the maximum will only be 30% of the total at most.

High potency at Cambrex and how we handle highly potent APIs

Cambrex uses Occupational Exposure Band strategies, with Categories 1–4. Category 1 is essentially non-toxic, although exposure is targeted to be below 500µg/m^3 in all circumstances. Category 2 represents special hazards; carcinogens commonly fall into OEB2. The real opportunity for customization comes with Category 3, as this is where the special considerations for real world behavior will come into play. Category 4 includes highly potent toxic materials that require special handling, including careful containment and less opportunity for customization. The most hazardous – those ultra-potent compounds with an OEL below 0.1µg/m^3 – fall into an additional 4+ Category.

For projects in OEB3, the containment is designed around the process. It may fit within existing fixed equipment within the plant or some modifications may need to be made to provide additional safeguards. This may be achieved using soft-sided isolators, with the decision made after a physical hazards assessment has been made. Physical equipment and infrastructure is a more conservative approach to minimizing exposure risks than using personal protective equipment as a failsafe.

Other aspects that should be included in the risk assessment include the solvents. It is important that these should not degrade the isolator, O-rings, gloves or even the engineering controls that are in place for worker protection. The special hazards around every individual process must be considered; for example, it may be necessary to limit how long people can work on a specific project or if teratogenic, then pregnant women should not be involved.

Surrogate testing is required to assess whether the containment strategies are working; any issues these bring to light can then be addressed before there is a problem with the real material. Both labs and production facilities are set up with a room pressure cascade so that the room where the material is being handled is at the most negative pressure.

In contrast for OEB4 materials, the process is designed around the containment with dedicated isolators set up for various process operations and, where necessary, the process modified to fit within them. Bag-In-Bag-Out (BIBO) or Rapid Transfer Ports (RTP) are usually employed for OEB4+ materials.

There is often a temptation to take a very conservative approach with maximum containment at all times, but this is expensive and time consuming – factors which a CMO must pass on to customers through project costs and delivery timelines. An appropriate alternative would be to assign a conservative OEL and relax the handling requirements over time if data supports it. CMOs need to offer a flexible range of options to support customer requirements and be ready to follow the molecule through its lifecycle, adapting over time as more data become available.