



The Value of Safety

Understanding fully the implications of RiskMaPP can be the difference between a safe manufacturing environment and one where risk has a serious effect on operations and personnel wellbeing. The initiative can establish acceptable risk exposure levels and ensure a stable production environment

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In the pharmaceutical arena, and more specifically in active pharmaceutical ingredient (API) manufacturing, several questions have come up over the last few years on the handling of highly potent compounds in multi-purpose facilities. Debates have been going on about whether containment equipment is a necessity for handling of 'cytotoxic' drugs, since the international conference on harmonisation (ICH) guideline Q7 Good Manufacturing Practice for APIs mentions that "dedicated production areas should be considered when material of high pharmacological activity or toxicity is involved (for example, certain steroids or cytotoxic anti-cancer agents)". How are highly potent or

cytotoxic compounds defined? One of the requests made by the food and drug administration (FDA) to the risk-based manufacture of pharmaceutical products (RiskMaPP) working group was to define an approach to identify highly hazardous drugs. It became clear, however, that it makes much more sense to describe an approach to define acceptable risk in pharmaceutical manufacturing instead.

Risk Assessment and Acceptable Risk

For professionals who deal with risk assessment in any business, it is clear that 'zero risk' does not exist. The challenge is to define what level of risk is acceptable to patient and worker when handling pharmacologically active compounds. Risk can be defined as the intrinsic hazard of a compound, multiplied by the probability of exposure to this

compound. The hazard, the inherent property of a compound to do harm, such as acute toxicity, sensitisation or the ability to damage DNA (genotoxicity), is not something that can be influenced. The other part of the equation – probability of exposure – is something that can be controlled. The key question is: what is an acceptable level of exposure for healthy workers or for patients? The International Society for Pharmaceutical Engineering's (ISPE) RiskMaPP Guideline describes a scientific risk-based approach for risk management based on ICH guideline Q9 Quality Risk Management, in which the first and most important step is that of risk identification.

The Process of Risk Identification and the ADE concept

Since the 1980s industrial hygiene (IH) and occupational toxicology

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professionals from pharmaceutical companies have been calculating health-based limit values for exposure to active compounds in the occupational setting: occupational exposure levels (OELs). In preclinical and early clinical stages of drug development, where less information on the toxicology or pharmacology of a compound is available, an OEL-banding or so-called 'categorisation approach' is more commonly used. These are both health-based methods of risk identification. However for purposes of managing cross-contamination and carry-over to protect patients' safety, many Q-departments have been working with maximum allowable carry over (MACO) based on a default value, the 10ppm criterium or a default safety factor (SF), which is 0.1 per cent of the therapeutic dose (a safety factor of 1000) according to pharmaceutical inspection convention (PIC) guideline PI

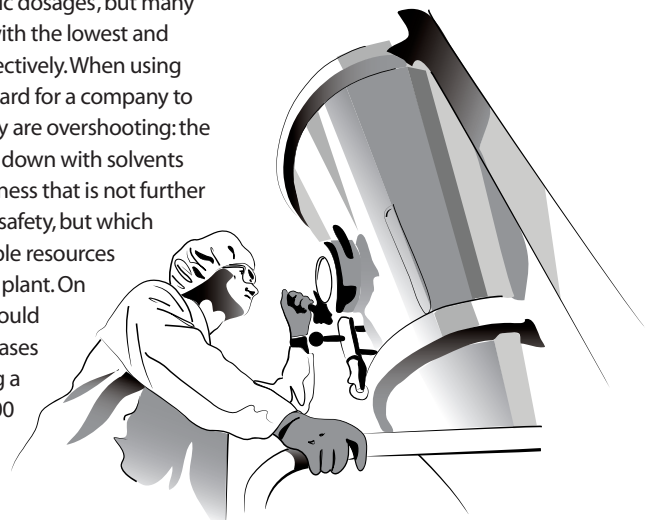
006-3 (which asks for "whatever is lower").

$$\text{MACO} = \frac{\text{Lowest clinical dose}}{\text{SF 1000}}$$

The PIC guideline actually mentions the "normal therapeutic dosages", but many companies work with the lowest and highest dose, respectively. When using this approach it's hard for a company to know whether they are overshooting: the reactors are rinsed down with solvents to a level of cleanliness that is not further increasing patient safety, but which is a waste of valuable resources in a multi-purpose plant. On the other hand it could be that in certain cases 10ppm or applying a safety factor of 1000 is not enough, which might lead

to an excessively high carryover and an increased risk to the patient. Although the latter must be prevented, both situations are undesirable.

When keeping in mind the risk equation, the hazard (the biological properties of a compound) is the same





for both the worker and the patient. Of course their potential exposure is different, since the route of exposure is often a different one. Where in the occupational setting the inhalatory route of exposure, followed by dermal exposure, is the main route of concern, in the clinic it's mainly the oral, or the parenteral (IV) route of exposure, or mode of administration. In patients a certain pharmacological effect is desired, whereas in workers any effect of the drug is regarded as 'adverse'. These differences however do not implicate that acceptable risk could not be addressed in the same way.

To identify acceptable risk for a certain compound, the RiskMaPP guideline defines the acceptable daily exposure (ADE) concept. This is the ADE to a compound for a lifetime exposure that is unlikely to cause adverse effects, for a patient or for a worker. The ADE is based on the toxicological and pharmacological data available and can be different for different routes of exposure. It should not be confused with the acceptable daily intake (ADI), a measure for allowable oral daily intake

of food or drinking water contaminants. The methodology of calculating an ADE is based on and very similar to the established approaches of calculating OELs or permitted daily exposure (PDEs, as defined in ICH Q3c for residual solvents).

$$ADE = \frac{NOAEL \times BW}{UFC \times MF \times \alpha} \text{ in } \mu\text{g/d}$$

Where:

- NOAEL: No observed adverse effect level
- BW: Body weight
- UFC: Composite uncertainty or safety factor
- MF: Modifying factor
- α : Bioavailability or absorption

The no adverse effect level (NOAEL) for a compound is an important parameter derived from animal studies. This approach first of all requires access to such animal toxicity data, which can be a challenge for a contract manufacturing organisation (CMO) without direct access to these data due to confidentiality or other reasons. Secondly the data simply do not yet exist in the case of early development of a drug. Thirdly, and most importantly, following this approach requires toxicological know-how that most

CMOs do not have in-house. The toxicologist has to select a NOAEL from the most relevant animal study and also the use of uncertainty or safety factors to derive the ADE for humans from the NOAEL from animal studies requires experience in this field.

Another aspect is that for a single compound different ADE values might exist: if the bioavailability, route of exposure and target population are taken into account, they might lead to differences in ADE. This aside, even two experienced toxicologists might reach different values based either on a differing data set or point of view. From experience we've learned that deriving a safe value (ADE or OEL) for humans from animal data can easily lead to differences of two orders of magnitude, and which ADE is then 'correct': one or 100µg/d, and how should this be dealt with by authorities or clients auditing a CMO?

Calculation of Cleaning Limits Using Differentiated Safety Factors

The ADE approach is health- and risk-based, and to an extent contrary to the earlier mentioned 10ppm criterium or default safety factor approach. A third approach which also takes into account biological activity of the compounds is one where differentiated

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safety factors are applied when calculating a MACO and the corresponding cleaning limit from the lowest clinical dose. A compound is categorised into one of four categories. First of all this category determines the level of containment and safety measures in the plant for IH purposes. Secondly the category determines what safety factor has to be applied for calculation of a cleaning limit. A highly potent API (for example a fentanyl derivative), or a chronically toxic API (such as antineoplastic drugs) which is in category three or four of our four-band system, is assigned a safety factor between 10,000 and 30,000. The range is also determined by the duration of administration of a drug. An antibiotic that is applied for one week to treat an infection is less critical when contaminated with a precursor API, than the anti-diabetic drug which might be applied for a lifetime.

Another important aspect that has to be taken into account when manufacturing drugs that are chronically toxic in multi-purpose equipment is to prevent carry-over of potentially genotoxic compounds, such as alkylating agents, to which many of the first generations of anti-cancer drugs can be counted. The European Medicine Agency (EMA) guideline on the limits of genotoxic impurities defines a maximum daily exposure of 1.5µg of a genotoxic substance per daily dose of a drug – based on an excess cancer risk of less than one in 100,000 over a lifetime. This concept, called the Threshold of Toxicological Concern (TTC), can also be applied when assessing

risk of carry-over of APIs in multi-purpose equipment in addition to applying differentiated safety factors, and it ensures that this EMA limit is not being exceeded. Even when applying the 10ppm criterium in case of preclinical development, when limited toxicological and no clinical data is available, using the TTC concept is a pragmatic approach to minimising risk to the patient.

Although not identical in their approach, when comparing the ADE concept from the RiskMaPP guideline with the differentiated safety factor approach described above, it can be concluded that for the large majority of the compounds the order of magnitude of the calculated ADEs or MACOs is the same. The explanation for this outcome is the fact that both approaches take the biological activity of the molecules as the starting point of the risk assessment process.

RiskMaPP Integrates Formerly Separated Targets

All in all it can be said that RiskMaPP makes ICH Q9 more tangible by discussing all steps in the quality risk management process and by giving examples of how to implement quality risk management in the organisation. But that isn't the most innovative part of the guideline. A new factor, however, is that formerly strictly separated targets in the pharmaceutical

operation of protecting the worker – by controlling exposures in the plant on the one hand and protecting the patient by preventing cross-contamination and carry-over by equipment cleaning on the other hand – are being integrated. In the guidelines the so-called logic diagram shows that both the good manufacturing practice (GMP) and the IH issues that will arise when performing a risk assessment, for example to determine if two compounds can be manufactured in the same facility, are based on sound toxicological or clinical data. For compounds in early clinical development, the differentiated safety factor approach is certainly more feasible one for CMOs, but as soon as enough data are on the table, the acceptable daily exposure is a useful concept in improving quality risk management for the benefit of both patients and workers.

About the author



Maarten Prause has a broad experience in industrial hygiene within the chemical and pharmaceutical industry, and holds a Master's in Environmental Sciences from Wageningen University,

Netherlands. Before his current role, Maarten was based in the Netherlands working for an industrial hygiene consultancy. He has now been working for four years in this field with CARBOGEN AMCIS where he leads the company's compound categorisation team. Maarten plays a pivotal role in defining and optimising the concepts of working safely with highly potent compounds. Email: maarten.prause@carbogen-amcis.com