
RISK ASSESSMENT AND MANAGEMENT

Challenges in Manufacturing Highly Potent Active
Pharmaceutical Ingredients

Mark C. Griffiths, Operations Advisor,
Dishman Pharmaceuticals & Chemicals Ltd

Peter M. Mueller, Sr. Scientific Advisor,
CARBOGEN AMCIS AG

CARBOGEN AMCIS, Hauptstr. 171, CH-4416 Bubendorf, Switzerland

Contents

Introduction	3
Pharmacological and Toxicological Activity Profiles	4-5
Performance-based Exposure Control Limits and Occupational Exposure Limits	6-7
Level of Containment and Carry-over of HiPo APIs	8-9
Conclusion	10
References	10

Introduction

Even though cancer therapies have progressed significantly over the last decade, oncology remains the most significant area of unmet clinical need. Cancer still remains poorly treated, therefore pharmaceutical and biopharmaceutical companies massively invest in highly potent drugs (HiPo) development. Worldwide, more than 25% of the new compounds entering clinic development are focused on oncology and are highly potent active pharmaceutical ingredients (APIs).

The demand for microgram dose HiPo formulations has subsequently raised, but conventional plants are seldom equipped and organized to manufacture highly potent APIs.

Considering that complete toxicological data for new HiPo compounds are rarely available when development starts, a reliable and fast assessment of the substance-related risks is fundamental to assure the safety of employees and products and to manage the level of containment and dedication of equipment required. This represents a challenge to organizations, like CARBOGEN AMCIS, where constant investment in technology, facilities and procedures is necessary to safely handle such compounds.

The complexity of the evaluation and management of risks preceding HiPo production leads many manufacturing companies to outsource their needs to specialized consulting groups (such as Safebridge) (1). As HiPo production represents one of the core business areas for CARBOGEN AMCIS, the decision was taken – as with many other pharmaceutical organizations – to develop internal protocols for the assessment of the substance-related risks (2). This assessment considers the points compiled in Figure 1 and is the basis of the company's risk management approach.

CARBOGEN AMCIS' hygienists, chemists and toxicologists are constantly committed to improve existing risk assessment procedures to ensure safety of workers and product quality. Toxicological data are evaluated from different sources and categorization extends to intermediates as well as the final product.

Figure 1: CARBOGEN AMCIS' management of HiPo risks



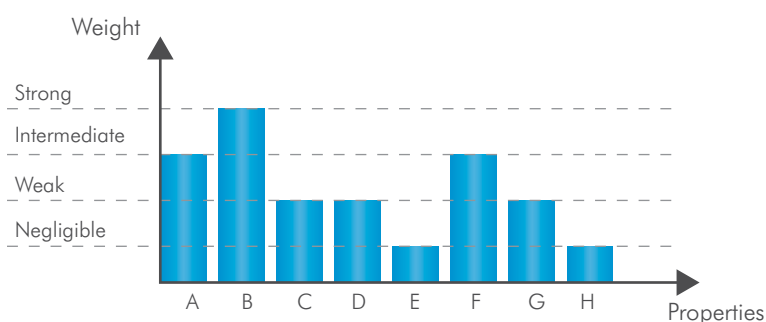
Drug candidates are often compared on the basis of bar chart activity profiles, and the selection of the most promising profiles is the essence of the art of developing successful drugs.

Pharmacological and Toxicological Activity Profiles

The assessment of the HiPo substance's pharmacological and toxicological activities is called "profiling" and is the essential element in determining the HiPo risk category. The number of properties considered may vary in function of the chemical structure and the data available.

Bar charts offer the simplest approach to visualizing a HiPo profile. For example, Figure 2 shows one possible profile (out of 65,536) obtained by rating eight different properties (A-H in Figure 2) as negligible, weak, intermediate, or strong. Often, bar chart profiles show the most desired effect on the far left side (position A) and the most unwanted side-effect on the far right side (positions H).

Figure 2: Example of a bar chart activity profile.



Drug candidates are often compared on the basis of bar chart activity profiles, and the selection of the most promising profiles is the essence of the art of developing successful drugs. The term "art" is used here, because this selection often involves the acceptance of successful compromises – as well as pinpointing the key scientific questions to be answered – in order to eliminate uncertainties regarding the interdependence of given desired and undesired properties, or to even eliminate some of these interdependences themselves.

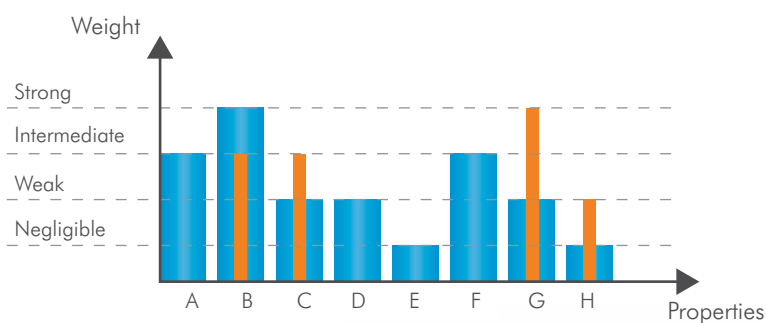
The latter may theoretically be done by modifying the drug candidate's structure in such a way as to favourably modify its mechanism of action. Unfortunately, this isn't trivial, and the outcome of the respective efforts is often hard to predict, especially at an early stage of drug development. Consequently, it is not unequivocally clear how to select the therapeutically more successful drug candidate or the most hazardous compound among a series of drugs with different side-effect profiles.

It is rare that complete pharmacological and toxicological data are available when development starts. Typical information enabling the generation of a provisional activity profile includes:

- The chemical structure
- The envisaged therapeutic use
- The structure/activity-relationships
- *In vitro* tests
- Animal tests (possibly including a provisional LD50)
- The strongest activities found in *in vitro* and *in vivo* tests
- The expected therapeutic dosage
- Early observations in humans, e.g. regarding sensitization

It is important to keep in mind that the first activity profile and hazard category attributed to a drug under development may differ from the final assessment. Figure 3 shows the type of difference that may occur between the first provisional activity profile of a new drug (orange) and its final confirmed activity profile (blue).

Figure 3: Differences between the provisional activity profile (orange) and the final one (blue).



The following can be concluded, if properties A and B are therapeutic activities and parameters C – H are undesired side-effects:

- The highest therapeutically valuable activity is correctly identified
- The weights of the activities / properties differ
- The number of properties considered is smaller in the provisory profile

The differences observed are either due to lack of data at an early development stage or to undiscovered activities (for example A) or to the tendency to attribute the highest conceivable activity to the most critical unwanted effects as precautionary measure.

Performance-based Exposure Control Limits and Occupational Exposure Limits

Having a complete toxicological and pharmacological activity profile facilitates a precise classification of the substance in question in terms of performance-based exposure control limit (PBECL) or occupational exposure limit (OEL). These values are important in view of exposure risk and workers' safety and serve as guidelines in assessing protective measures and levels of containment required in the manufacturing process. The provisional values based on the provisional activity profile play the same role in early development.

Naumann et al. (3) developed a method for the assessment of PBECLs that considers 18 biological parameters and 5 activity levels (theoretically providing 4 trillion differing profiles), and they proposed to work with 5 hazard categories.

CARBOGEN AMCIS works with Naumann's parameters, but reducing the number of activity levels and categories to 4 (classifying products in categories III-IV as HiPo). This still covers a space of 70 billion theoretically possible profiles.

Occupational exposure levels (OELs) for many chemicals are set by national authorities, but APIs and intermediates are rarely found in the respective lists. This is the manufacturers' reason for working with schemes like Naumann's and for looking for additional means of differentiating mechanisms of action, like the consideration of observed or expected dose- and time-dependence curves. Equation 1 where D = daily dose, t = average time (i.e. number of days of administration up to the appearance of tumours), and $n \approx 2$ describes such an experimental curve:

$$[1] D \cdot t^n = \text{const.}$$

Peto et al. (4) observed the relationship [1] when exposing rats to relatively high dosages of N-nitroso-diethylamine. Nitrosamines are typical DNA-alkylating carcinogens. Therefore, it is reasonable to extrapolate equation [1] when assessing DNA-alkylating APIs.

Applying Equation 1 and comparing two durations of administration (1 year and 100 years) of a given carcinogen leads to the finding that the dose has to be reduced 10,000 times to observe the same tumorigenic effect after 100 years as opposed to one year (Equation 2):

$$[2] D \cdot 1^2 = [D : 10\,000] \cdot 100^2$$

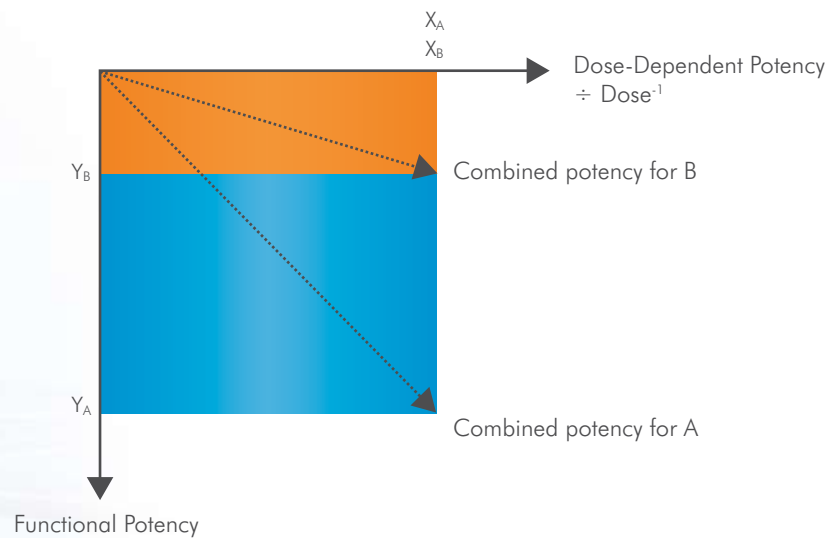
This means that particularly low OELs may have to be attributed to DNA-alkylating agents in comparison to other anti-cancer compounds, like mitosis or kinase inhibitors. It goes without saying that this is a relatively simplistic expectation, which has to be considered in conjunction with the detailed mechanism of action and mutagenic or clastogenic potential of the compound in question.

CARBOGEN AMCIS works with Naumann's parameters, but reducing the number of activity levels and categories to 4 (classifying products in categories III-IV as HiPo). This still covers a space of 70 billion theoretically possible profiles.

Substances that show high functional potency at low dose have the highest overall potency and are the most hazardous.

The hazard a substance presents is determined on the basis of the dose resulting in peak activity and of its functional potency or mechanism of action. High functional potency implies a mechanism of action which interferes with a highly vital process. Substances that show high functional potency at low dose have the highest overall potency and are the most hazardous (A in Figure 4 is more hazardous than B). It is not the purpose of Figure 4 to show the type of mathematical relationship between the two aspects of the overall potency, but one intuitively concludes that the comparison should neither be based on the vectors nor on the areas per se. The quotient "area : vector" is, e.g., describing the overall potency in a heuristically reasonable way.

Figure 4: Dose-dependent and functional potency of APIs.



To generate PBECLs, CARBOGEN AMCIS' protocol includes the following list of questions:

- Does the compound primarily present an acute or a chronic risk (the latter may be accumulated and not be quickly detected)?
- Does the eventual chronic activity of the compound imply irreversible effects (e.g. carcinogenesis, teratogenicity, or sensitization)?
- Do the *in vitro* and *in vivo* observations support the expected mechanism of action?
- Does this mechanism of action present a non-negligible potential of, for example, carcinogenic activity?
- What level of exposure has to be achieved to make sure that the worker's lifetime cancer risk isn't increased by more than 1 in 10⁵ (5) – or to make sure that even 100 years of exposure wouldn't significantly increase this risk?
- Would there be indicators of a marginal exposure?

Level of Containment and Carry-over of HiPo APIs



Picture 1: Barrier isolation bench in CARBOGEN AMCIS' Bubendorf lab for highly potent APIs.



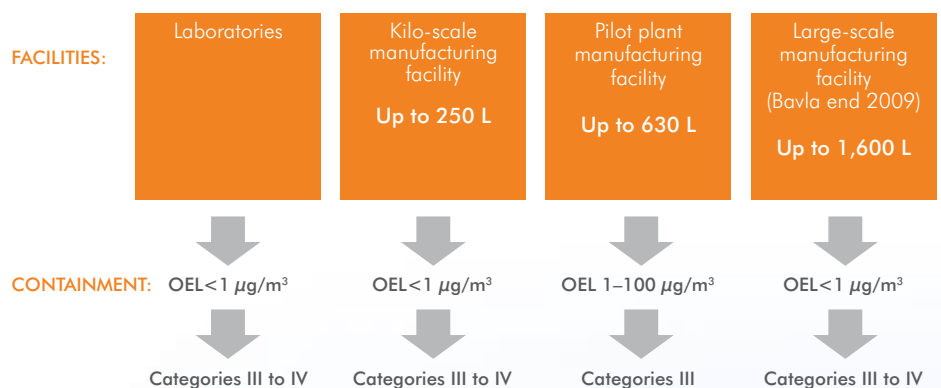
Picture 2: Reactors in CARBOGEN AMCIS' small-scale Bubendorf facility for highly potent APIs.

The level of containment is determined on the basis of the occupational exposure limit (OEL) or the PBECL, respectively. These values reflect the activity profile of the substance and are based on experimental data from literature or supplied by the customer. The mechanism of action is the primary parameter when the set of available data is limited. Moreover, supposing that it is almost impossible to reliably control an average occupational exposure in a non-routine environment, CARBOGEN AMCIS strictly enforces protective measures, which include periodic monitoring to ensure that the respective OELs are not exceeded.

In general, chemical production may use facilities dedicated to a particular substance or class of substances, non-dedicated facilities or partially dedicated facilities. Partially dedicated facilities may be dedicated for a long period of time to a single product or used exclusively, for example, for a group of highly potent APIs. CARBOGEN AMCIS uses non-dedicated (multi-purpose) facilities and partially dedicated facilities at its GMP production sites.

Figure 5 presents an overview of CARBOGEN AMCIS' contained facilities. Upon completion of the Bavla (India) facility – expected by end 2009 - compounds belonging to the HiPo categories III-IV will be produced from laboratory scale up to 1,600 L. This extends the scale available at the Swiss facilities (Picture 1 and 2) from 600 L.

Figure 5: CARBOGEN AMCIS' facilities for GMP-production of highly potent APIs



During the development and production of highly potent APIs in multi-purpose facilities, two types of risks must be considered: exposure and carry-over contamination. Each risk has the same source: the biological activity of the API; but means of exposure vary from worker to patient. Indeed, the physicochemical properties determining workers' and patients' exposure are not the same. On the one hand, workers' exposure depends strongly on airborne substance which may be inhaled or deposited on surfaces workers regularly touch.

Dedicated production areas should also be considered when material of [...] high pharmacological activity or toxicity is involved (e.g. certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.

Of course, when it comes to workers' protection, handling solids is usually more critical than handling solutions – in fact APIs in solution do not easily become airborne. Moreover, it should be considered that the exposure risk increases, if higher volumes are handled. For example, a worker handling a few milligrams in an analytical or lab setting has a much higher chance of detecting the loss of a tiny amount than does a worker filtering 500 grams in the course of a synthesis.

On the other hand, patients' exposure depends on how the drug containing the highly potent carry-over impurity is administered and on the impurity's pharmacokinetic properties in the organism. It can be assumed that these properties are largely understood, once the clinical phase of the development of the contaminating API has been completed. Of possibly greater concern, therefore, is carry-over contamination by APIs that have not yet been studied in-depth.

In multi-purpose facilities, the carry-over of previously prepared material into APIs is a general concern. This concern becomes more pronounced when dealing with HiPo APIs. Therefore, world-wide regulators included the following Article 4.41 in the ICH-guideline Q7 (6) addressing APIs:

Dedicated production areas should also be considered when material of [...] high pharmacological activity or toxicity is involved (e.g. certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.

Obviously, the concern and stringent cleaning requirements mentioned in the Article 4.41 in the ICH-guideline Q7 would be eliminated by working with dedicated equipment. Dedicated equipment is however prohibitively expensive in development, particularly at somewhat larger scale, and also in the production of small volume pharmaceuticals, such as HiPo APIs. The partial or temporary dedication of multi-purpose facilities used in the development or production of HiPo APIs results in a significant reduction of the carry-over risk. Since that would not be sufficient alone, CARBOGEN AMCIS applies elevated carry-over safety factors to avoid exposure of patients to non-tolerable risks. This can be achieved by considering therapeutic doses of highly potent APIs as chronically toxic rather than just counter-indicated and by developing analytical methods to determine very low concentrations of potential carry-over impurity in cleaning samples. This ensures that patients undergoing chronic therapy would not be exposed over their lifetime to doses of contaminants, which reach the dose calculated on the basis of the OELs or on the basis of EMEA's threshold of toxicological concern as defined for genotoxic or reprotoxic impurities (7).

Profiling and Categorizing Highly Potent Development APIs

CARBOGEN AMCIS' basic procedure

- All available results are considered
- The API's known main activity is considered as the most significant biological effect
- The anticipated mechanism of action is assumed to be real
- The side-effects not yet measured are estimated to reach conceivable high-end activity values
- The categorization according to PBECs considers the most critical side-effects
- A higher hazard class for the categorization is considered in case of uncertain experimental data
- Cytostatics are always considered as potentially carcinogenic and teratogenic

Conclusion

The key drivers of the selection of substances for clinical development and of the definition of the required measures ensuring workers' and patients' safety are the drug candidates' biological activity profiles and mechanisms of action. The two are interdependent, but the complete information is rarely available when development starts. Therefore, it makes sense to at this point in time use all the available data as well as the interdependences to calculate conceivable worst case estimates of the most critical, but yet unknown effects of the considered development API, in particular its potential carcinogenicity and teratogenicity. That is CARBOGEN AMCIS' approach to defining PBECs, OELs or HiPo categories and to consequently decide on the level of containment, on the partial dedication of the equipment, and on the carry-over safety factors to be respected when manufacturing the API.

References

- (1) A.W. Ader, J.P. Farris and R.H. Ku, *Occupational Health Categorization and Compound Handling Practice Systems – Roots, Application and Future*, Chemical Health & Safety, American Chemical Society, (July/August 2005).
- (2) M.C. Griffiths, P.M. Mueller, *Profiling activities and risks in producing highly potent development APIs*, PharmaChem, 20 – 24, (January/February 2006).
- (3) B.D. Naumann, E.V. Sargent, B.S. Starkman, W.J. Fraser, G.T. Becher, and G.D. Kirk, "Performance-Based Exposure Control Limits for Pharmaceutical Active Ingredients", *American Industrial Hygiene Association Journal*, 57, 33 – 42 (1996). Osamu Suzuki et al., *Pharmaceutical Engineering*, March/April 2003, 66 – 78.
- (4) R. Peto, R. Gray, P. Brantom, P. Grasso, *Cancer Research*, 51, 6415 – 6451 (1991). H. Druckrey, "Quantitative aspects in chemical carcinogenesis" (*Potential Carcinogenic Hazards from Drugs*, UICC Monograph Series 7, 60 – 87, Springer Verlag, Berlin, 1967).
- (5) *Industrial Union Dept. AFL-CIO v. American Petroleum Inst.*, 448 U.S. , 655 (1980), i.e. a ruling defining 1 in 103 as significant lifetime risk level of excess cancer, which does not automatically define an acceptable exposure limit. M. Sadowitz, J. D. Graham, "A Survey of Residual Cancer Risks Permitted by Health, Safety and Environmental Policy", Franklin Pierce Law Center, Concord N.H.; accessible via <http://www.piercelaw.edu/risk/vol6/winter/sadowitz.htm>
- (6) ICH Harmonised Tripartite Guideline "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7A" (recommended for adoption to the regulatory bodies of the European Union, Japan and USA on 10 November 2000).
- (7) TTC = 1.5 µg/day. Cp. European Medicines Agency, *Evaluation of Medicines for Human Use, Committee for Medicinal Products for Human Use, Guideline on the Limits of Genotoxic Impurities*, London, 28 June, 2006, CPMP/SWP/5199/02, EMEA/CHMP/QWP/251344/2006.