



Safety in the lab

The increased potency of drugs has already led to special facilities being built to minimise exposure risks during production, but senior scientist **Peter Mueller**, Carbogen Amcis, looks at containment issues for laboratories faced with analysing potent active pharmaceutical ingredients

When Odysseus had the choice either to sail close to Scylla and lose six sailors for sure, or choose the channel past Charybdis whose whirlpool would sink the whole ship and everybody on it, he chose the first option... most people would understand his decision.

Are we facing similar choices today, when handling highly potent (HiPo) active pharmaceutical ingredients (APIs)? At first sight we are, although our options are less dramatic than those in Greek mythology. Still, we have to answer the following questions:

First, should we supplement the technical measures ensuring high containment and closed processing by requiring employees to wear full personal protective equipment (PPE) to cover the remaining risk – increasing the stress for the workers and thereby increasing the probability of errors?

And second, should we prohibit women of childbearing age from working with highly potent APIs completely to eliminate all possibilities of teratogenesis – at the cost of violating our principle of equal opportunities?

These are difficult questions. Fortunately,

Weighing cabinets in Carbogen Amcis' analytical laboratory for HiPo APIs

HiPo APIs are not as mysterious as the challenges the Greeks faced. HiPo APIs have assessable biological effects and the exposure risks they present may be clearly ranked.

The risks presented are greater when:

- Handling large rather than small amounts of substance
- Executing complicated rather than simple manipulations
- Performing non-routine rather than routine processes
- Dealing with volatile solids rather than solutions
- Repeating a single step many times rather than just once or twice
- Processing in an open manner rather than a closed manner.

The risks posed by analytical work in comparison with chemical manufacturing are considerably smaller with respect to the first three points. The subsequent three points provide a more ambiguous comparison.

dedicated facility

Analytical work is generally accepted as involving less risk than manufacturing. However, there are risks associated with analytical techniques involving manipulation of highly potent materials in concentrated form, and in particular dry solids. This has therefore been Carbogen Amcis' reason for establishing an analytical laboratory dedicated to supporting the highly potent APIs, at its Bubendorf HiPo lab in Switzerland

The pursuit of risk minimisation requires quantification of the risk, i.e. the likelihood of harm of a certain magnitude. ▶

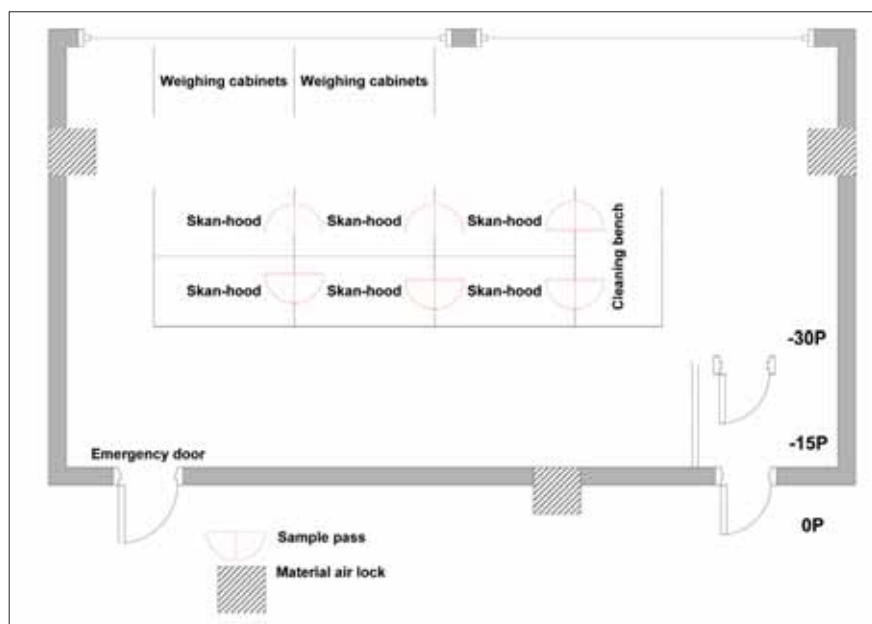


Fig 1: Layout of Carbogen Amcis' analytical laboratory for HiPo APIs

The temperature in the lab is kept between 20 and 22°C. All of these parameters were confirmed during the qualification process. Finally, the HEPA-filters are routinely checked and periodically changed (safe change) and disposed of.

The samples normally arrive in the HiPo lab in flasks via the material air lock. They have been cleaned on the outside and are protected by a bag or an unbreakable box. After they are recorded, the samples are transported to the weighing cabinets where the required amounts for the single measurements are filled into vials or flasks.

Solutions are finally prepared in situ. The vials or flasks are cleaned on the outside and then moved to the respective measuring sites. Waste and excess amounts of samples remaining after the measurement are then placed in the disposal bags (accessible from the weighing cabinets) or directly disposed of in dedicated containers. HPLC and GC vials filled are "one way", of course.

Measurements that inherently present a risk of releasing product into the surrounding air-space, such as residue on ignition, are performed in the HiPo lab. The same holds for the determination of IR-spectra or optical rotations as well as titrations etc., as the open handling of solutions is not trivial. There is a risk of losing drops that subsequently evaporate on the working surface – obviously an event that may be critical in view of the detectability as appearing in equation 2 above.

exposure risk

There is no doubt that the weighing process represents the most high risk operation in terms of amounts of highly potent product manipulated, as well as complexity of manipulations and open handling. It therefore makes sense to base a realistic assessment of the worst case exposure on this process.

For example, an operator is weighing 20mg of a volatile solid product (an average figure) and spills half the product. Though he or she realises what has happened and immediately cleans the surface of the weighing cabinet, half the spilled amount is lost and 10% of it (due to inadequate manipulations) ends up in the lab's atmosphere, which results in 0.5mg in about 150m³ of air, i.e. 3.33µg/m³.

These 3.33µg/m³ are then quickly reduced, thanks to the 20 air changes per hour. A worst case idealised model (exhaust per air change = 50% of old and 50% of fresh air) projects that this figure will be down to 1.67µg/m³ after three minutes, to 0.83µg/m³ after six minutes, and to 0.000003µg/m³ after one hour.

Thus, the idealised model predicts that 50% of the exposure resulting for the whole day occurs in the first three minutes (the first air change), which translates to a total exposure to 2.5µg/m³ during six minutes, corresponding to an eight hours time-weighted average occupational exposure to 0.031µg/m³, or an inhaled dose of 0.31µg (compare Figure 2 where the uptake has been corrected in consideration of a bioavailability factor of 80%). This is only about one-fifth of the European Medicines Agency (EMA) threshold of toxicological concern (TTC)² of 1.5µg per person per day for

◀ This is often obtained using the equation "risk = probability x impact:"

$$R = P \times I \quad [1]$$

Globally Harmonised Systems (GHS)¹ expresses the same relationship as follows: risk = hazard x exposure; the probability of uptake is thereby proportional to the exposure.

Elaborating equation 1 further and considering that risk minimisation depends on a number of factors leads to the following equation:

$$R = P_{MAX} \times I_{MAX} \times (1 - D_{PR} \times E_{PR} \times P_{PR}) \times (1 - D_{CUR} \times E_{CUR} \times P_{CUR}) \quad [2]$$

This equation expresses that the actual risk becomes smaller than the conceivable maximum (MAX), depending on the preventive measures (PR) taken before the hazardous event, and on corrective or curative measures (CUR) taken after the hazardous event. Whether and to what extent these measures are reducing the risk depends on the detectability of the threat (D_{PR}) and of the exposure (D_{CUR}), on the effectiveness (E_{PR} and E_{CUR}) of the respective measures, and on the probability (P_{PR} and P_{CUR}) that the measures are really taken when the threat or the exposure is detected. Thereby D_{PR}, D_{CUR}, E_{PR}, E_{CUR}, P_{PR}, and P_{CUR} must all be >0 and <1 to ensure that the resulting probability stays between 0 and 1.

design considerations

The design of Carbogen Amcis' HiPo lab had to consider risk minimisation in terms of the protection of employees, the products and the environment; additional factors were legal compliance, functionality and economy. Since analytical samples will not be returned to the production process nor will they ever be administered to a patient, the product – or good manufacturing process (GMP) – aspect of risk minimisation is comparable for all analytical labs, regardless of the material handled (HiPo or normal). The focus is on traceability, reproducibility and accuracy, etc.

These parameters depend on the workers' training as well as the functionality of the lab and well-organised procedures. The latter have to be

reflected in the lab's design. Functionality and organisation also have a strong impact upon the safety of employees, which obviously had to be a primary concern in terms of risk minimisation.

The analytical techniques selected for use in the HiPo lab had an important impact on the design. The selection was made on the basis of a risk assessment concerning workers' safety.

One key element in this was the decision to run high performance liquid chromatography (HPLC) in the normal lab. This strongly reduced the number of measurements in the contained environment and also had an economic impact. This decision can be justified because HPLC analysis involves the automated measurement of small volumes of highly dilute solutions contained within sealed vials. Today HPLC is a very reliable technique that presents a very low exposure risk such that it does not require a contained environment, while evidently the weighing, sample preparation and disposal operations do.

Finally, air handling and ease of cleaning are crucial aspects of the design of every lab dealing with highly potent products. Therefore, the number of air changes per hour (~20) was certainly one of the main design factors.

The layout of Carbogen Amcis' HiPo lab is shown in Figure 1. The lab is separated from the rest of the laboratory building by an airlock that provides a pressure cascade ensuring airflow from the general laboratory area to the HiPo lab (single pass). HEPA-filters purify the lab's exhaust and the incoming air. HEPA filtration of the incoming air reduces the required frequency of changes of contaminated filters.

There are nine hoods in total: one ejector cleaning bench, two weighing cabinets (see p63), and six sample pass-connected and flow-controlled Skan-hoods (see p65) working with about 50% re-circulated air, which is HEPA-filtered as well. These hoods are designed to be easily cleanable. Operated properly, they guarantee a high separation of airborne particles in and outside of the hoods. The special weighing cabinets are engineered in such a way as to provide a horizontal and turbulence-free air-flow ensuring undisturbed operation of the high precision balances.

reprotoxic or genotoxic impurities.

Carbogen Amcis considers adoption of a TTC approach as an appropriate basis for risk control as the TTC was developed to define for any unstudied chemical a common exposure level that will not pose a risk of significant carcinogenicity or other toxic effects. Of course, the company would consider actual activity data, if having to manipulate, for example, extremely active carcinogens.

Considering that the above exposure figure of $0.31\mu\text{g}$ per day has been calculated based on a worst case, rare event, one might actually think that Carbogen Amcis' HiPo lab provides over-sophisticated protection. However, this does not give the complete picture. The worst case assumptions described do not account for the fact that the spilled substance will not immediately be homogeneously distributed in the lab's atmosphere and that the worker is, at least initially, close to the event. Nevertheless, it is certainly fair to assume that the exposure in this lab is, on average, below $0.15\mu\text{g}/\text{m}^3$ and hence below EMEA's TTC.

skin exposure

Of course, exposure of airways is not the only risk to be taken into account. Exposure of skin may become relevant as well and may also be assessed by idealised model calculations. Such calculations consider that less than 100% of the airborne substance ends up in the exhaust air filters and that up to 50% may actually be deposited and accumulate on open surfaces.

Depending on the parameters chosen, this then leads to the conclusion that uptake via skin is less important than uptake via airways on day one, but becomes more important after a few days or at most a few weeks, if the same event takes place once a day and the contaminated surfaces are never cleaned (Figure 2). It is therefore of utmost importance to clean the open surfaces thoroughly on at least a weekly interval.

Working surfaces should be cleaned after use and should never be touched without gloves. Corresponding procedures are



The sample pass-connected and flow-controlled Skan-hoods in Carbogen Amcis' analytical lab for HiPo APIs; a material airlock can be seen at the back

unmistakeably regulated by Carbogen Amcis' standard operating procedures (SOPs).

In conclusion, theoretical calculations predict that working in this HiPo analytical lab will, on average, expose the worker to amounts of substance that are significantly below EMEA's Threshold of Toxicological Concern (TTC) as defined for genotoxic or reprotoxic impurities in drugs. This has also been confirmed by monitoring, although the majority of the results obtained in these experiments were below the limit of detection. To ensure this, it is critical that the relevant SOPs are enforced (frequent surface cleaning, working with gloves, etc.) and that staff are effectively trained in their application. Where required under EMEA guidance, additional precautions may be required in exceptional cases.

Thus, work in Carbogen Amcis' HiPo

analytical lab offers a third path – avoiding both Scylla and Charybdis. The position that heavy PPE is not required can be defended, as can the position that women are allowed to work in this lab. Swiss legislation and similar legislation in other countries understandably forbids the exposure of pregnant women to CRM substances.³ As the exposure limits outlined in the case of the laboratory in question fall well below that of the EMEA's TTC there is no reason to exclude women from working in this facility and thereby infringe the equal opportunities principle.

While the scientific rationale is sound and the risk presented is below the limit of concern, the company's policy is, upon request, to relocate women of child bearing age when they are in early pregnancy or intending to become pregnant. mc

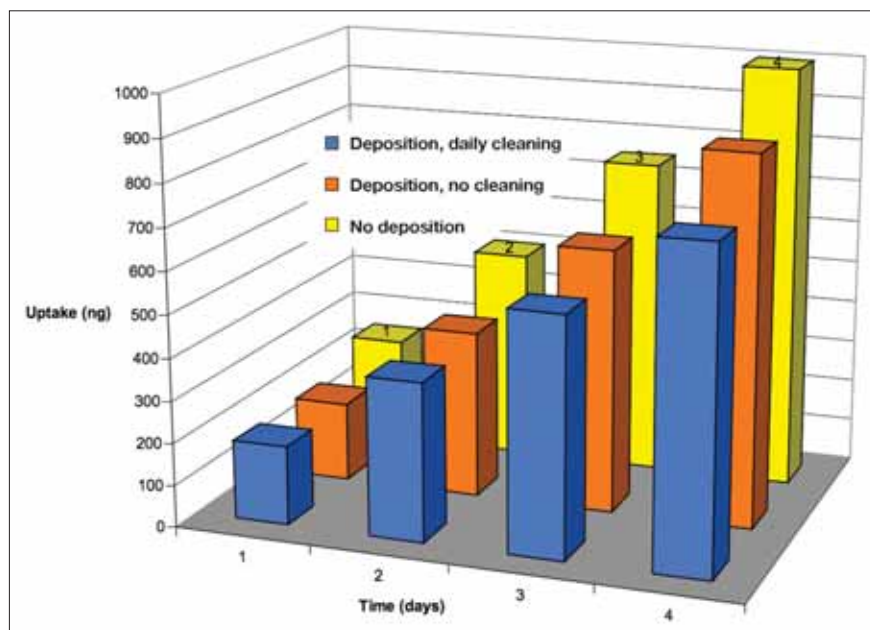


Fig 2: Idealised accumulated uptake of substance via airways and skin

references:

- 1 Globally Harmonized System of Classification and Labelling of Chemicals (United Nations, 2nd revised edition, 2007, Part 1 Introduction, Subchapter 1.1.2.6.2).
- 2 European Medicines Agency, Evaluation of Medicines for Human Use, Committee of 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.
- 3 CRM = carcinogenic, reprotoxic, mutagenic –cp. the Swiss Ordinance on the Protection of Mothers, Systematic Register SR 822.111.52.

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