Photo: © stockphoto.com/ijeab

Perfect Coordination

Safe handling of highly potent active ingredients in chemistry

Dr. Friederike Hermann, Lonza AG, Visp, Switzerland

New drugs are developed, among other reasons, with the aim of reducing dosage and having more targeted active ingredients. For patients, this development is definitely beneficial. These ingredients are described as highly potent active ingredients. But what does highly potent mean? And how are these substances handled in production, and what checks are performed to ensure the personnel are protected?

What does "highly potent" mean?

Highly potent active substances are for instance active ingredients that release their therapeutic effect at low doses (e.g. 100 µg/d), or active ingredients whose side effects begin to appear at very low doses.

When working with highly potent active substances, the personnel must be protected – not only from side effects, but also from the therapeutic effect – because the employees are healthy and do not require treatment. As the effects are already manifested at very low doses, this results in very low workplace exposure limits. As a rule, a substance is called highly potent if the work place exposure limit is below 10 µg/m^3.

What are the implications of handling highly potent active substances in production?

These very low workplace exposure limits present a great challenge during the manufacture of highly potent active substances. The highest permissible workplace exposure limit for non-hazardous dusts is 10 mg/m^3. In comparison, the workplace exposure limits for highly potent active substances are often between 10 and 1000 ng/m^3. Between 10 mg /m^3 and 10 µg/m^3, there is a factor of 1,000; between 10 mg/m^3 and 10 ng/m^3 there is a factor of 1,000,000. Thus, when compared to harmless dust, the production plant for a highly potent active substance needs to be better sealed by a factor of 1,000 or 1,000,000. This means that the plant requires excellent containment in order to remain below air exposure limits in the region of 10 ng/m^3.

However, for production it is necessary to take into account not only the workplace exposure limit – and with it the toxicological and pharmacological properties – but also the process:

- amounts which are handled,
- how long do the operations take,
- is the isolated pure substance handled or is it used in a diluted or dissolved form,
- is it a solid, a liquid or a gas?

Therefore a risk analysis must be performed, taking into account where and when exposure of the employees is possible, in order to be able to establish the appropriate measures.

The risk analysis not only has to take into account the condition of the production. Further-reaching questions must be asked, such as "How is the plant cleaned?", "How are the measuring probes calibrated during production?", "How are waste products disposed of?", "What will be the results of an accident?", "What is an accident?", "Will an accident be recognised?"

What is containment?

Containment prevents the spreading of a substance, in other words containment involves all the measures that prevent it spreading. Containment, therefore, means not only closed systems. The substance that is to be handled and its workplace exposure limit determine the requirements for containment. As a result, the requirements for containment during the production of highly potent active substances are very high. Typically, differentiation is made between primary and secondary containment [1].

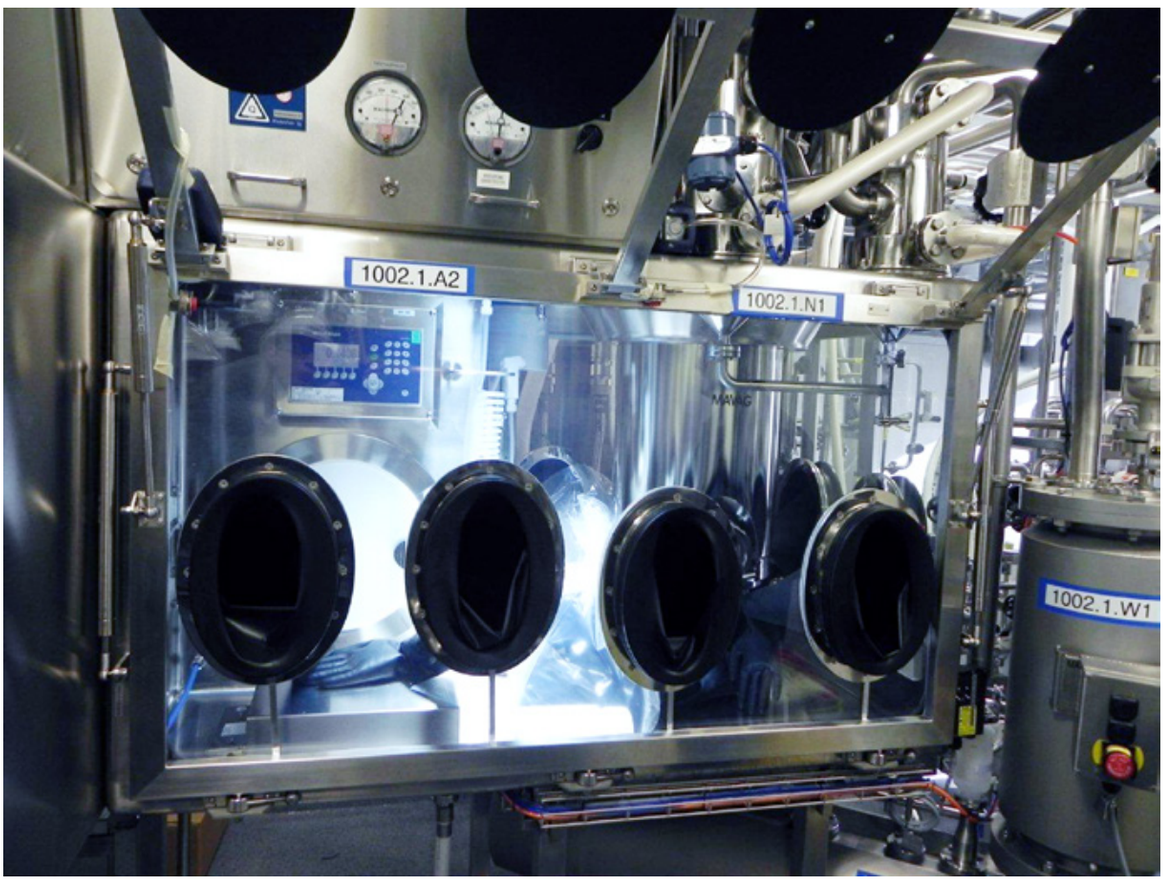

Fig. 1 Containment: Isolator for solid matter handling

Primary containment involves those measures that prevent direct discharge from the production equipment. Secondary containment prevents a further spread within the plant environment, when primary containment is poor or in case of an accident.

Typical solutions for primary containment in the production of the highly potent active substances are isolators, endless liner systems and closed sampling systems. On the other hand, secondary containment comprises, for example, the separation of production rooms and controlled entry to the working area through air locks. Material and personnel flows are separated.

The human factor

During production, the most important roles are not played by the technological measures, but by the persons involved, such as the personnel and their managers.

All technical measures are only as good as the personnel trained to use them. Moreover, organisational measures only work if the personnel are willing to observe them. From the above-mentioned term containment, the measures and demands placed on a production plant for highly potent active substances mean for personnel that many procedures take considerably longer than usual, as the work needs to be performed with particular care. Great trust must be placed in the employee and the technical equipment and the supervisors must therefore be aware of the implications of working with highly potent active substances so that they can train the employees sufficiently well, and give them enough time to perform the activities correctly. Dangerous concentrations of highly potent active substances in the air cannot be recognised, as the human eye can only perceive dust concentrations of more than 0.1 mg/m^3. Thus employees cannot see if something in the process is going wrong.

Fig. 2 Exposure measurements during the performance of a procedure – the stationary probe heads can be seen to the left and right

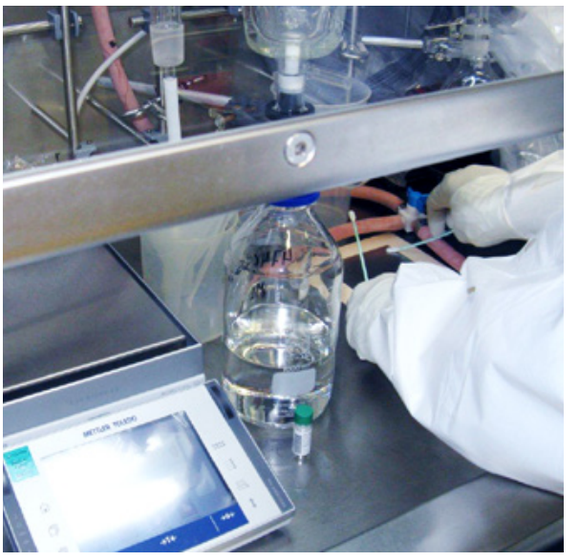

Fig. 3 Execution of a swab

Verification of containment through industrial hygiene measurements

If a firm has built a plant to produce highly potent active substances, it must be ensured that the plant is tight enough and thus the exposure of the employees is within the permitted range. Industrial hygiene measurements are used to check the measurements and working procedures in order to document this [2, 3]. Here, measurements are made at random, as on-line monitoring is not available. Often surrogate tests are performed to ensure that the right measures are taken and the correct working procedures are mastered before the highly potent active substance itself is handled. This means that when the production steps are simulated, the measurements are made utilising a non-hazardous replacement material, the surrogate.

During sampling, a distinction is made between air samples by air monitoring and surface samples, so-called swabs. The air monitoring is divided into measurements related to personnel, and fixed-point measurements. Personnel-related measurements give direct information regarding the effective exposure of employees. Fixed-point measurements reflect distribution of the substance in the room or allow conclusions to be drawn regarding the tightness of the containment.

The swabs or wipe tests offer the advantage that here the substance can be determined on the surfaces, long after the substance is no longer measurable in the air. In this way, it can be shown whether employees are working cleanly enough or whether the containment is tight enough. However, it does not allow any conclusions to be drawn regarding the concentration in the air and thus the exposure of the employees.

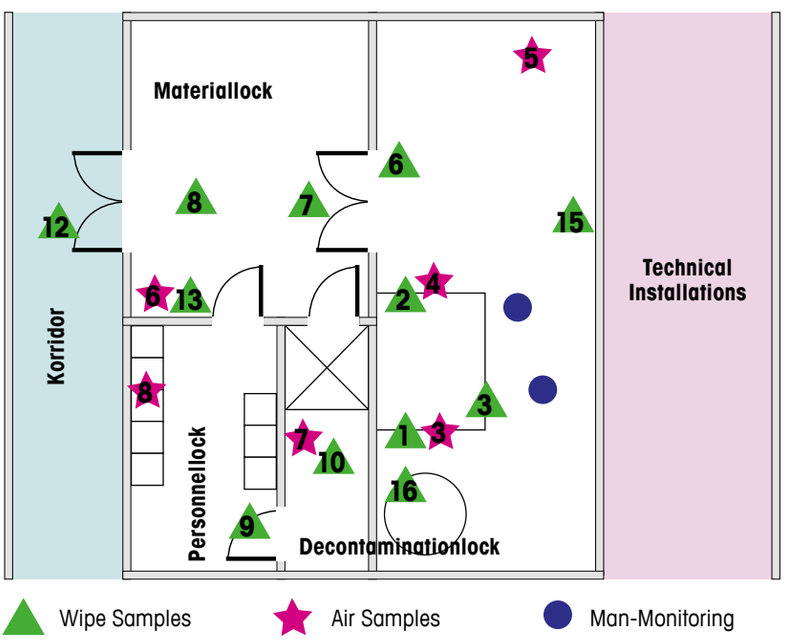

Fig. 4 Typical sampling plan

Analysis

To trace 10 ng/m^3 of a substance in the air, very sensitive, substance-specific analysis methods have to be used, such as LC-MS/MS. The requirements regarding the determination limit depend largely on the exposure limit, the sampling time and the elution volume of the analysis pattern. The aim is to be able to determine 10 % of the exposure limit. In doing this, it can be guaranteed that the air concentration is safely below the exposure limit. Thus it can also be demonstrated statistically that the exposure limit is always observed. The sampling duration plays a deciding factor. If the handling of the highly potent active substance takes two hours in the isolator, e.g. for weighing and filling of solid substances, the analytical method needs to be less sensitive than for taking an in-process sample that takes maybe five minutes. Validation parameters such as selectivity, specificity, linearity, precision and sensitivity ensure that afterwards the right results will be obtained. A further key factor is recovery of the analysed material from the air-monitoring filter and from the swab. The substance must be extracted as completely as possible from the filter and the swab, so that the analytical determination can be made accurately.

Summary

Safe work with highly potent active substances requires the coordination of the right complex technical measures with a suitable correct working procedure of the employees. Prerequisite to this is a management that understands these increased requirements, adequate training, and finally a verification of this co-ordination by industrial hygiene analyses throughout those working stages which could lead to potential exposure of the employees.

■ **friederike.hermann@lonza.com**

References
[1] Containment Systems A Design Guide, N. Hurst, M. Brocklebank, M. Ryder, Gulf Professional Publishing Massachusetts; 2002
[2] Arbeitsplatzatmosphäre – Anleitung zur Ermittlung der inhalativen Exposition gegenüber chemischen Stoffen zum Vergleich mit Grenzwerten und Messtrategie, CEN (Comité European de Normalisation), European Standard EN 689, 1995
[3] Assessing the Particulate Containment Performance of Pharmaceutical equipment, second edition, ISPE Good Practice Guide; 2012

Friederike Hermann is a chemist and occupational health specialist. She studied chemistry at the University of Marburg. After gaining her diploma, she received her doctorate in analytical chemistry in the area of element speciation at the University of Mainz. Since 2001, Dr. Hermann has been working for the Lonza AG. After the first few years in environmental protection, she moved to occupational health. She received a master in advanced studies for health and hygiene from the University of Zurich and the University of Lausanne. At Lonza, she mainly follows the production of highly potent active substances – by determining the necessary measures and the industrial hygiene measurements for the control of the measures, and thus compliance with the permissible exposure limits the employees. She is a member of the Steering Committees of the "Community of Practice Containment" of the ISPE Affiliate D/A/CH.