

Tailor made Containment in the Pharmaceutical Industry

The need for contained handling and processing of pharmaceuticals started to rise significantly about 15 years ago. Reasons were an increased focus on health and safety aspects and also the development of more high potent active pharmaceutical ingredients (HP API's).

The response by the pharmaceutical equipment suppliers has resulted in market improvements in the containment levels achievable, using both established solids-handling equipment, and new innovative techniques.

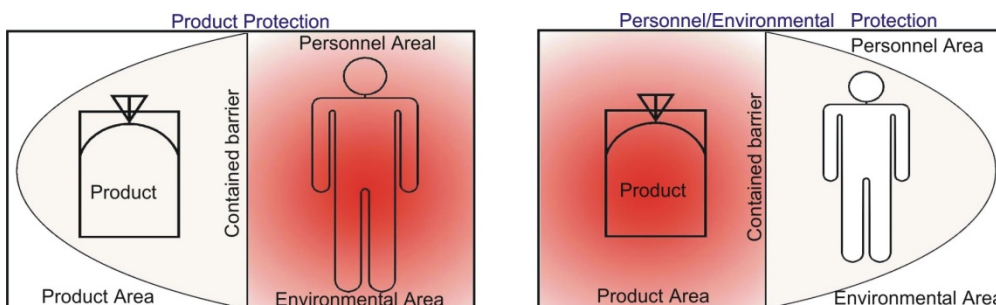
The selection of suitable equipment at the right place however requires an in depth understanding of certain containment aspects. Firstly to assure that the chosen equipment performs in the required level, but also, and this is important from the investment aspect, to prevent an expensive and unnecessary potential "Overkill".

The following article describes containment aspects like product specific exposure limits, equipment related real exposure values and finally the correlation between these two. Only when these aspects are brought together in the right way, can we speak of a tailor made containment solution.

General Considerations

What is Containment and why do we need Containment? Basically Containment is the area separation from Product to Personnel/ Environmental area by a barrier. Containment is needed to prevent any negative impacts

(Contamination) from one area to the other and vice versa.



The personal protection aspect however has always to be considered as the more important one, as human health can't be replaced in any way. That means that the first duty of every employer is to prevent the exposure of employees to substances hazardous to their health. However the reality shows, that exposure can't be fully prevented by equipment. Therefore the employer has to ensure by using suitable equipment, that the real equipment exposure is lower than a product (API) specific Exposure Limit. How do we have to understand now a product specific Exposure Limit or a real equipment exposure?

Product related considerations

The most common value used in the pharmaceutical industry to define a product specific Exposure Limit, which an operator is allowed to be exposed to, is the Occupational Exposure Limit (OEL). The OEL is calculated within a working group by the pharmaceutical companies, as soon as a new product is more or less finally defined.

The basis for calculating the OEL is the No Observable Effect Level (NOEL). This value is determined by testing this new pharmaceutical active ingredient on individuals. The daily dosage in mg active / (kg bodyweight x day) is increased day by day, until the first tested individual shows the first reaction, whatever this reaction might be (lead effect) . This NOEL is now multiplied by the average bodyweight of a human being, to come to an amount for an operator. Considering, that the operator is mainly absorbing the airborne product by breathing, the before mentioned value is now divided by the volume a human being is breathing per day. Some additional safety factors (SFx) consider for example the seriousness of the first reaction or the difference in reaction between human beings and the tested animals.

$$1) \quad \text{OEL} = \text{NOEL} \times \text{BW} / (V \times \text{SF}1 \times \text{SF}2)$$

This OEL gives now a value of airborne particles of product in the working environment, where an operator is allowed to work in day by day, for his complete life without any risk to his health.

Equipment related considerations

The real Exposure of equipment can't be calculated, but only be determined by measurement. This is done by special air sampling methods, where the amount of collected airborne particles of a specific product is finally determined by analysis. This amount is divided by the volume of air which passes the air sampler during the sampling time, and then gives a value in mcg / m³. As by such a measurement we only get an exposure average for the specific sampling time, we are speaking of a Time Weighted Average (TWA). Commonly the pharmaceutical Industry is working with 2 different TWA's, the Short Term Time Weighted Average (STTWA) based on a sampling time of 15 minutes, and the Long Term Time Weighted Average (LTTWA) based on of 8 hours.

Up to a couple of years ago, there was no guide existing, how really to carry out such measurements. This ended in a situation, where for different containment equipment a lot of different exposure performance data's were determined and published. However due to the different ways how this data were achieved, there was firstly not any comparability given between different equipment data's and secondly a lot of data were not suitable for real pharmaceutical installations.

A guide, which was initiated by GEA Buck and created by an international composed working group, is now published by the ISPE and is known under the name SMEPAC (Standardised Measurement of Equipment Particulate Airborne Concentration). This guide defines the test process and the test parameters always trying to stay a close a possible to the real operating conditions in the final installation. Data given by tests according the SMEPAC guide are showing a Short Term Time Weighted Average (STTWA) for a 100 % pure active material.

How to interpret product related limits (OEL) in correlation to equipment related values (TWA)

Going back to the beginning: we have learned, that the employer has to ensure by using suitable equipment, that the real equipment exposure is lower than a product specific Exposure Limit. In other words: It has to be proven that the Long Term Time Weighted Average (LTTWA) exposure caused by the equipment has to be lower than the Occupational Exposure Limit (OEL).

$$2) \quad \text{LTTWA} < \text{OEL}$$

However, this does not necessarily mean, that the data given by tests based on the SMEPAC guide have to be lower than the OEL, as there are further considerations to undertake. As described above, the equipment exposure data given by SMEPAC are showing a STTWA for a 100 % active. For certain applications, as for example make and break connections to charge or discharge process units, the equipment exposure only occurs during the real dock, transfer and undock process. This process however is generally considered as to be finalized within 15 minutes. The SMEPAC data for such equipment is exactly showing the exposure within these 15 minutes, where within this time one full make and break (one cycle) takes place. To calculate now a Long Term Time Weighted Average (LTTWA) based on a known Short Term Time Weighted Average (STTWA) for the equipment, we can divide the LTTWA by 32 (quarter hours per 8 hours) and multiply by the real number of cycles.

$$3) \quad \text{LTTWA} = (\text{STTWA} / 32) \times \text{number of cycles}$$

In addition more and more pharmaceutical companies also consider the dilution factor of the handled product.

As the equipment exposure data given by SMEPAC is based on a test with a 100 % active, a diluted material can be considered to also only release real active material in line with the dilution factor. (Assumption: the active releases at the same rate as the rest)

That means that a real LTTWA for a diluted material can be calculated as follows:

$$4) \quad \text{LTTWA} = (\text{STTWA} / 32) \times \text{number of cycles} \times \text{dilution factor}$$

This calculated LTTWA has now to be lower or equal to the product specific OEL.

How to evaluate suitable equipment

If a process for the production of a certain product is defined, and now the suitable containment equipment for make a break connection has to be evaluated, we can use formula 4. By making a maximum consideration (what means the OEL = LTTWA) we can replace the LTTWA by the known OEL and calculate the required STTWA as follows:

$$5) \quad \text{STTWA req.} = (\text{OEL} \times 32) / (\text{number of cycles} \times \text{dilution factor})$$

Example:

An operator works for a complete shift in the environment of a discharge station. The handled product is Ethinyl Estradiol with an OEL of 0,035 mcg / m³. There are 8 numbers of cycles (makes and breaks) per shift to be carried out. At this stage of the process the material is already diluted to a content of 5 % active.

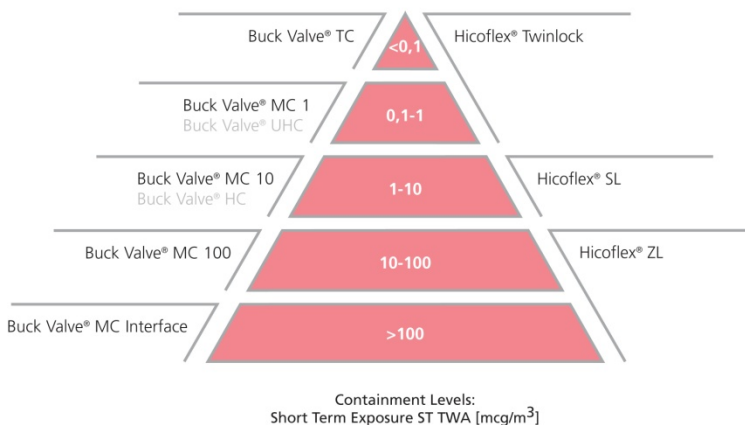
The required STTWA for a make and break connection for this process step is

STTWA req. = OEL x 32 / number of cycles x dilution factor

STTWA req. = 0.035 (mcg / m³) x 32 / 8 x 0, 05

STTWA req. = 2, 8 mcg / m³

Looking to the product range listed according their STTWA performance based on the SMEPAC we can recommend for this application the Buck® MC Valve (preferably with an additional extraction shroud to ensure the better performance) or alternatively the Hicoflex™ technology.



Summary

In comparison to containment installations done up to recently, the current containment understanding as described above allows to offer tailor made solutions to the pharmaceutical industry. This tailor made consideration even allows the use of containment interfaces (make and breaks) with different levels of exposure performance at different points in a process line. Whereas in the early stage of a formulation process , where even 100 % actives are handled, the higher performing and more expensive equipment will be used, at the final process steps as for example charging a tablet press there can be chosen a much more cost effective and lower performing valve solution.

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