REPRINT XXL EFFECTIVENESS IN A SLIM-FIT SUIT

Containment solutions only cost-effective when adapted

Facts for the decision-makers

» For pharmaceutical production, the trend toward increasingly potent active ingredients results in mounting personal protection requirements for operating personnel.

» Aside from the toxicological data for the active ingredient, operator exposure as well as frequency of production cycles also play an important role.

» Efficiency and cost-effectiveness criteria must always be examined to determine whether investment in system technology is worthwhile or whether procuring personal protective equipment for the operator makes more sense.

Industry		Function	
Pharma	●●●	Planner	●●●
Food	●○○	Operator	●●●
Cosmetics	●○○	Purchaser	●○○
Chemistry	●●●	Manager	●●○

1: Personal protective equipment or a plant with containment technology? This question can only be answered on a case-by-case basis.

Containment comes at a price. Equipping plants completely for compliance with the highest containment level, OEB 6, is extremely expensive. Yet a crucial fact is often overlooked: the hazard level posed by an active ingredient to employees varies along its route through the plant. This insight can be exploited by adapting containment solutions to the respective requirements in each area.

Currently one in four active pharmaceutical ingredients (API) is classified as "highly potent" and this upward trend is expected to continue. This is attributable to a trend towards administering increasingly potent substances in ever smaller doses – such as in the case of personalized medicine. This impacts pharmaceutical production in the form of rising personal protection requirements for operating personnel. Full-protection hazard suits are one option, however they have several disadvantages: on one hand, they are often impractical and uncomfortable to wear, and on the other, are often very expensive when examined from a full costing perspective. Moreover, significant labor costs result from putting on and removing the suit.

Exposure limits based on toxicological data.

In light of these developments, the current trend is toward plants designed to protect operating personnel from contact with toxic active ingredients while simultaneously minimizing the risk of cross-contamination. Recently the European Medicines Agency (EMA) responded to this tendency toward increasingly potent APIs. The updated version of EMA Guideline 169430/2012 released in June 2015 establishes that going forward the assessment of maximum exposure limits should be based on toxicological data. This therefore precludes standard application of some assessment criteria used to date, such as "visually clean" or "1/1000 of the therapeutic dose." Naturally, the effects of this policy change extend to plant engineering.

"Hot spots can be found all throughout a plant line," explains Michael Maintok, Business Development Key Technologies at Glatt, a leading plant manufacturer: "These spots, which usually occur at the interfaces between parts of the plant, must be considered with care." In this analysis, the key to cost-efficient plant design lies in the cost-

Activity	Target OEL (DOEL) µg/m³	Active ingredient concentration %	Target max. API emission µg/m³	Frequency per day	Duration in min.	Exposure µg/d
Charging	0,10	100,0	0,10	4	15	0,13
Sample taking	1,00	10,0	0,10	12	0,2	0,01
Discharging	10,00	10,0	1,00	4	15	1,25
						1,39

Table 1: Exposure of operating personnel during different activities. In this example a total of 10.00 µg/day is permitted; the entire exposure, however, only reaches 1.39 µg/day.

effectiveness of a containment solution. "Yes, there are a lot of these interfaces in every production line," reports Axel Friese, Head of Marketing Process Technology Pharma at Glatt, "but there's no need to worry; they can be reduced and also, perceived hazard or contamination levels differ from actual levels."

Active ingredient concentration can vary from one process step to the next.

Manufacturers know that the active ingredient concentration usually declines as the product passes through the production line; for example, on the way out of the active ingredient container via a high-power mixer into a fluidized bed system, and from there into a mixing container with subsequent granulation. With increasing dilution, the potential hazard to employees also falls. A key indicator here is the Occupational Exposure Limit (OEL), which is a measure of the average concentration load of an active ingredient to which plant personnel are exposed during an eight-hour shift.

To understand how the OEL can be influenced by plant technology, it's helpful to know how it's calculated. The OEL comprises the quotient of the concentration load of an active ingredient to which a person can be exposed without any consequences (NOEL) as well as five safety factors that evaluate aspects such as the bioavailability of the active ingredient and severity of the consequences, etc. The OEL is provided using the unit µg/m³ in five different levels (ranges). Since higher OELs are temporarily tolerable, the "Short-Term Exposure Limit" (STEL) represents another useful indicator: it describes the OEL for a limited time (15 to 30 minutes). The STEL

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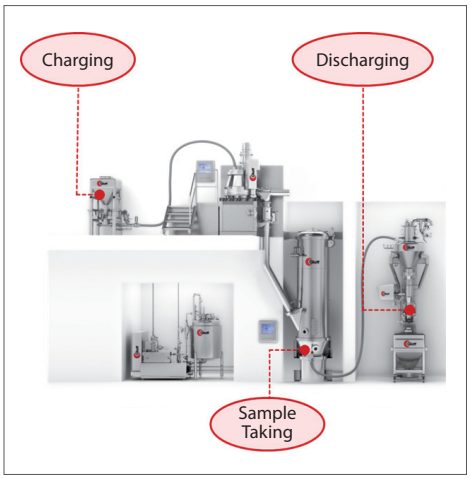
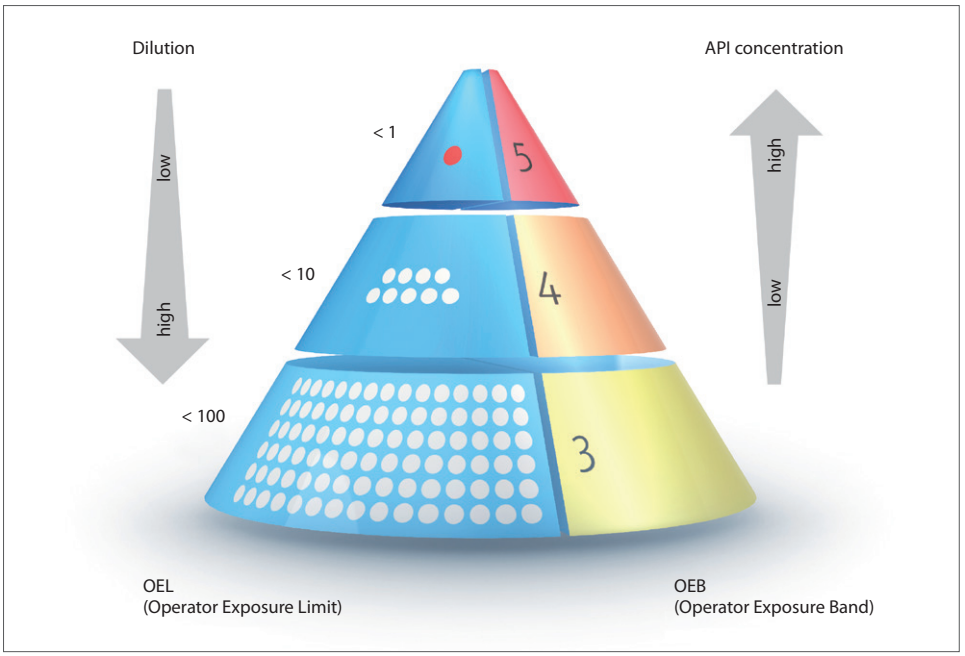


2: Example for the dilution of an active ingredient in the course of the process.



3: Active ingredient concentration and OEL / OEB.

can be equivalent to a maximum of three to eight times the OEL; however, operators must never be exposed to active ingredient concentrations higher than the STEL.

With respect to the containment of a plant, aside from the OEL, several other factors play a role: the properties of the active ingredient, personal protective gear for personnel and frequency of operator exposure to an API. Over an eight-hour shift, the Permitted Daily Exposure (PDE) is calculated as the sum of the individual positions (product API concentration at a given point in the plant and the length of time it remains there). This is clearly shown in the example in Figure 2 and Table 1: The permitted exposure to the active ingredient during a shift is 10.00 µg/d. Individual values are also derived from the plant layout values, frequency of the tasks for loading, emptying and taking samples, as well as the duration of the task. In summary, the following example refers to exposure of 0.138 µg/d, i.e. the actual value is significantly below the maximum permitted value.

Risk analysis a requirement for optimal containment solutions.

"Risk analysis lays the foundation for optimal containment solutions," says Michael Maintok from experience. Aside from the toxicological data for the active ingredient, the engineers in the Binzen facility take into account frequency of production cycles in addition to operator exposure. Thanks to many years of experience operating its own job order production and technical center, the manufacturer not only knows where the hot spots are, but also the degree to which the hazard level falls over the course of the process.

This is emphasized by the following example: an active ingredient has an OEL of 1 µg/m³ and a STEL of 5 µg/m³. In a high-power mixer, 1 kg of active ingredient is mixed with 99 kg of excipient. No OEL applies to the excipient. Although high containment requirements apply for loading of the active ingredient, and the transfer requires the use of containment valves, insulation equipment or a protective suit, the active ingredient concentration downstream of the mixing process is 100 times lower – this results in an OEL of 100 µg/m³ and a STEL of 500 µg/m³. In this case, a local filtered suction extraction system provides sufficient protection for operators during handling, and no protective suit is required.

"Taking into account the degree of dilution results in entirely different containment requirements," explains Axel Friese: "It's not about reducing safety, but rather making effective containment solutions less difficult." In the example cited, the mixing process is followed by fluidized bed granulation, with subsequent tableting and a tablet coater. While an OEL of 100 µg/m³ still applies during granulation and tableting, no additional containment measures are required after the coating as dust formation is then reliably excluded.

A question of cost-effectiveness.
Ultimately, the question of whether a plant should incorporate containment technology or rely on the low-tech solution of operating personnel wearing protective suits at all times near the plant, comes down to the cost-effectiveness of the respective solutions; and this can be determined by a cost-effectiveness assessment. Accordingly, the investment required for a sampling station in a high-containment design is relatively low compared to the effort and expense resulting from forcing staff to wear a protective suit for the frequent task of taking samples. On the other hand, the situation looks completely different if it's only necessary to perform certain tasks very rarely; in this case, an automated, high-tech solution might be disproportionately expensive.

"Efficiency and cost-effectiveness criteria must always be examined to determine whether investment in plant technology is worthwhile or whether procuring personal protective equipment for the operator makes more sense," emphasizes Michael Maintok. His colleague Axel Friese adds: „We offer technical solutions for both eventualities and in some cases, hybrid solutions that incorporate both high containment as well as full-protection of personnel."

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