

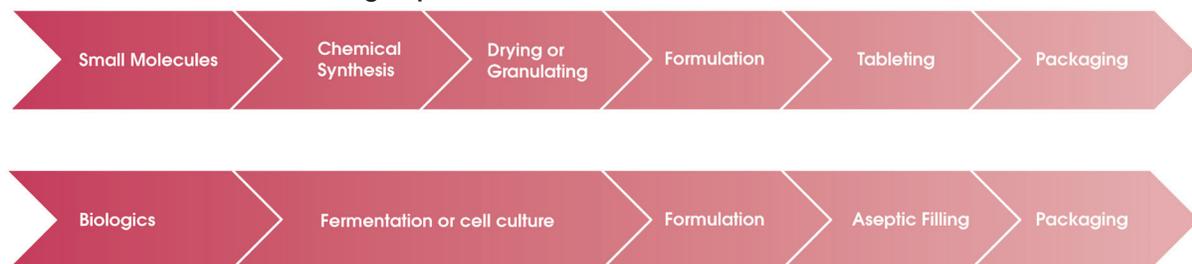
Simplifying Containment for a growing HPAPI market

The benefits of advanced containment technologies

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Powdered constituents, including active pharmaceutical ingredients (APIs) or inert excipients, are vital to drug formulation and manufacturing, whether at R&D, pilot, or full production scale. Both small molecule and biologics manufacturing involve the transfer of powdered constituents at different stages of manufacturing, including at the synthesis, granulating, formulation, tableting, and filling stages (see Figure 1).

Figure 1: Pharmaceutical manufacturing steps



The APIs and excipients would typically be transferred from drums, bags, or other storage vessels to the required process stages. Without containment, open transfers would generate levels of dust, which would create airborne and surface contamination. Both airborne and surface particles are a risk to health and the environment, and impose a risk for cross-contamination.

High-containment powder transfer provides a way to reduce the risk and make the drug manufacturing process safer and more efficient.

The drivers behind the growth of containment

Globally, the pharmaceutical industry is predicted to grow at almost 5 percent a year, hitting more than £1 trillion (\$1.42 trillion) in annual sales by 2020. Oncology, which relies heavily on high potency ingredients, is expected to be one of the fastest growth areas, at 11.6 percent CAGR, creating a global oncology market worth up to £109 billion (\$153 billion) by 2020.¹

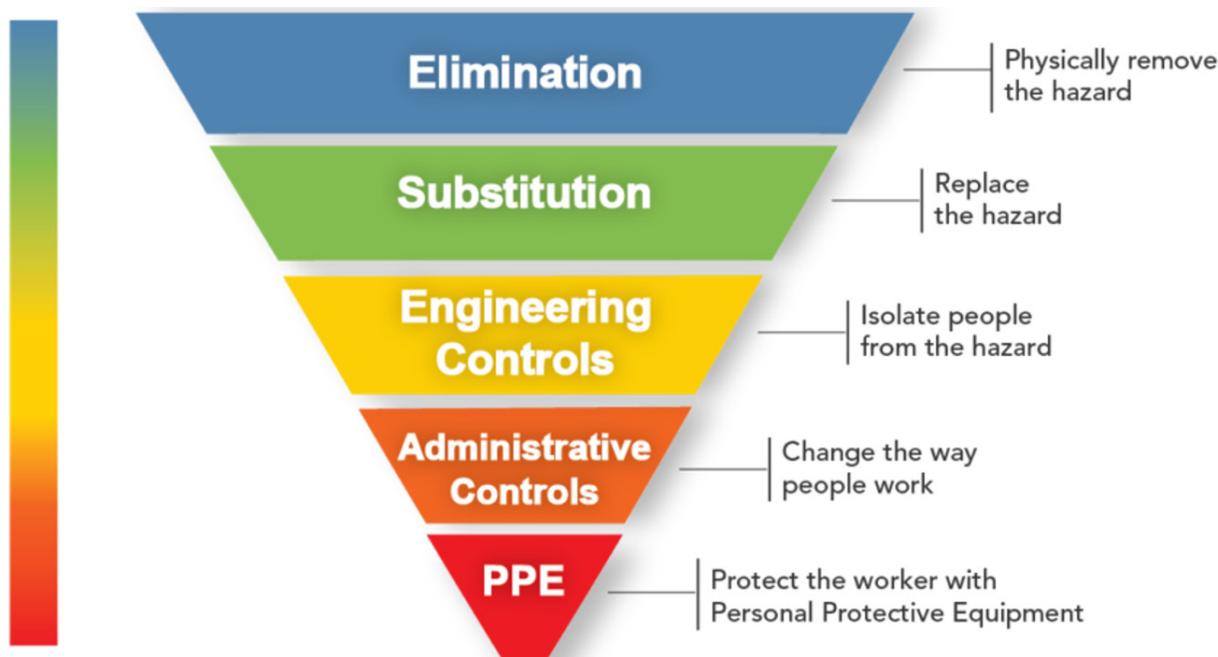
The growth of the biopharma industry has led to a corresponding growth in the containment sector, driven at least in part by a rising global demand for biologics for diseases that are harder to treat, alongside increases in oncology therapeutics.^{2,3} Many of the newer drugs for cancer rely on HPAPIs. These include the highly cytotoxic payloads on targeted drugs such as antibody-drug conjugates or highly active hormones.

HPAPIs pose a very high risk to operators and could cause major manufacturing complications with cross contamination in production lines. These risks make the requirement of containment critical, which will continue to increase the demand of validated containment equipment and drive increasing development in this sector.

The role of containment

While individual protection by using personal protective equipment (PPE) is in most cases the most common approach, the most effective in preventing exposure to APIs and HPAPIs is control through containment (see Figure 2).

Figure 2: Hierarchy of control



Containment when handling any APIs, but particularly HPAPIs, has a number of important benefits for companies:

- Safety — protects operators and the environment and maintains process integrity by reducing the levels of dust in the air and on surfaces
- Quality — helps maintain the sterility of products and prevents cross-contamination in multipurpose facilities
- Productivity — improves efficiency by reducing transfer times in high-volume production and by allowing multiple production lines to operate within a single facility; increases yield by cutting losses, which is key for maintaining profit margins for high-value products
- Compliance — supports companies in meeting health and safety and manufacturing targets

Understanding the need for compliance in containment

Companies have a legal requirement to manage and reduce risk and protect against exposure to potent compounds, both to their staff and to the environment, and there are a number of regulations companies have to comply with. But first, it's important to understand how toxicity and exposure levels are calculated and defined.

The permitted daily exposure (PDE) is defined, according to the European Medicines Agency, as the "substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime."⁶ This may also be known as the acceptable daily intake (ADI).

The PDE is calculated by reviewing the available hazard data, identifying critical effects, and determining the no-observed-adverse-effect level (NOAEL), which may need to be modified

according to a variety of adjustment factors.⁶

The occupational exposure level (OEL), the maximum acceptable levels of API a worker could inhale in a working week over a working lifetime, is based on the NOAEL or lowest-observed-adverse-effect level (LOAEL), along with the exposure over an eight-hour work shift. OELs are often placed into occupational exposure bands (OEBs), and each organisation may employ their own unique potency banding and hazard classification system. Potent APIs, described as having a toxicity level of toxic or highly toxic in Table 1, are those that have an OEL of less than 10 µg/m³.⁷

Table 1: Example toxicity levels and exposure limits

Toxicity level	OEB	OEL
Considered Safe with low Pharmacological Activity	1	1,000-5,000 µg/m ³
Harmful but with low pharmacological activity	2	100-1,000 µg/m ³
Moderately toxic with moderate pharmacological activity	3	10-100 µg/m ³
Toxic with high pharmacological activity	4	1-10 µg/m ³
Extremely toxic with very high pharmacological activity	5	<1 µg/m ³

Each band shown in Table 1 will have associated guidelines that define the best practice for the facility, equipment, and exposure controls required to keep the OEL at a level that complies with health and safety regulations.⁸

The regulations include:

- REACH (EU)
- COSHH (U.K.)
- OSHA (U.S.)
- ATEX (EU)
- IECEx (international)
- cGMP (international)

Containment technologies: An overview

The choice of containment technology depends on a number of factors. As well as the level of toxicity, variables include:

- API percentage
- volume
- wetness
- bulk density
- transfer frequency
- powder, granule, or tablet

Containment technologies need to create a balance among protecting the products and the personnel, remaining affordable, and maintaining both manufacturing efficiency and ease of use for the operators. There are a number of different containment technologies used to contain powder during transfer, and Table 2 discusses the benefits and issues of each.⁷

Table 2: Comparisons between containment technologies

This information is for general conceptual comparison purposes and is based on presenters' experiences. It is intended to be utilised as a generic talking point for solution evaluation.

	Isolator	Rapid transfer port	Vacuum transfer	Disposables and liners	Split butterfly valve
Initial capital cost	High	Average	Average	Low	Average
Industry acceptance	High	High	High	Variable	High
Space taken by solution	High	Low	Medium to high	Low	Low
Ergonomics	Poor	Average	Good	Variable	Good
Lead time	Long	Medium	Medium	Short	Medium
Lifetime cost	High	High	Low	High	Low
Performance: containment	Good	Good	Good	Variable	Good
Cleanability	Good	Good	Good	Variable	Good

Isolators enclose entire pieces of equipment or sections of the production line and can be rigid or flexible-walled. They are accessed using glove ports. While they are well established and accepted across the industry, their setup and lifetime costs are high.

Rapid transfer ports (RTPs) use alpha and beta units that lock together to allow transfer from one process step to another. RTPs may be combined with single-use disposables. While RTP lifetime costs can be high, their ergonomics are good and most often used in conjunction with isolators. However, their applications are limited.

Vacuum conveyors use negative pressure to transport APIs through pipes and hoses. This provides good ergonomics for operators but can take up a lot of space, and it reduces flexibility within the

workspace. Depending on the lengths of the pipes and hoses, cleaning can be more challenging.

There is an increasing move toward single-use bags and liners across the industry, and their short lead time, low capital cost, and flexibility are attractive, particularly for short runs. The containment may be variable, depending on the equipment provided and the lifetime costs could add up.

Split butterfly valves (SBVs) are two-part valves that lock securely together. They have good all-around performance, from broad industry acceptance and low lifetime costs to high levels of containment. The additional benefit of SBVs is they can be integrated with vacuum transfer systems, isolators, both rigid and flexible and or liner systems. They are quick and simple to use, reducing the risk of human error, and have good ergonomics.

Split butterfly valves: Simplifying containment

The SBV is a two-part valve that allows transfer of potent compounds from one container or process vessel to another, while reducing the creation of airborne particulates or surface contaminants. The SBV is a common interface between two process steps (see Figure 3).

The “active” unit of the SBV incorporates the locking system and the system for opening and closing the valve, and this part is usually attached to the process. The “passive” unit is generally attached to the vessel that holds the API, such as an intermediate bulk container (IBC) or flexible bag. Locking the two units together creates a single sealed unit. When the valve is opened, the material can pass from one vessel to another. Once the process is completed and the valve is closed, the two units can be unlocked and the vessels separated.

The most effective SBVs have a number of attributes (see Table 3) that support their use across the manufacture of intermediates and APIs and production of solid dose formulations, including tablets and capsules.

Figure 3: The basic split butterfly valve

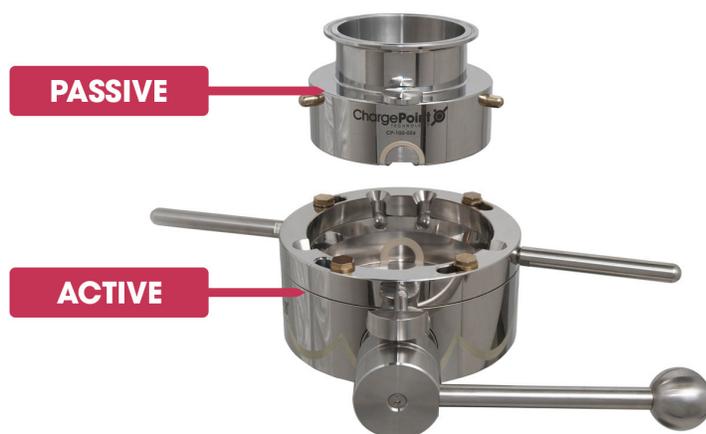


Table 3: The key features of effective split butterfly valves

Validated performance <ul style="list-style-type: none">• Nanogram levels• Meets SMEPAC guidelines (see “Containment performance validation”)	Metal-to-metal disc seal <ul style="list-style-type: none">• Simple GMP design for trouble-free high performance
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Safety interlocks <ul style="list-style-type: none">• Protects personnel and process• Mechanical as standard	Optimized seal design <ul style="list-style-type: none">• Precision tolerance• Low wear, easy operation, and repeatable performance
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Containment performance validation

The level of containment protection from the perspective of the people, product, and process can be quantified as the containment performance target (CPT). This is influenced by the ADI/PDE and the OEL amongst other process specific factors.

Measurements for the level of containment protection have been formalized within the International Society for Pharmaceutical Engineering (ISPE)'s Standardized Measurement of Particulate Airborne Concentration (SMEPAC) Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment.⁹ It provides technical guidance and consistent methodologies for evaluating containment technologies and processing equipment.

The methodology in the guide uses a surrogate material to measure equipment containment performance.

These materials, as specified in the guide, include: ⁸

- lactose
- naproxen sodium
- mannitol
- acetaminophen (paracetamol)
- insulin
- riboflavin
- sucrose

The guide also specifies sampling strategies, including number, type, and location of samples, and provides guidance for the data analysis.⁸

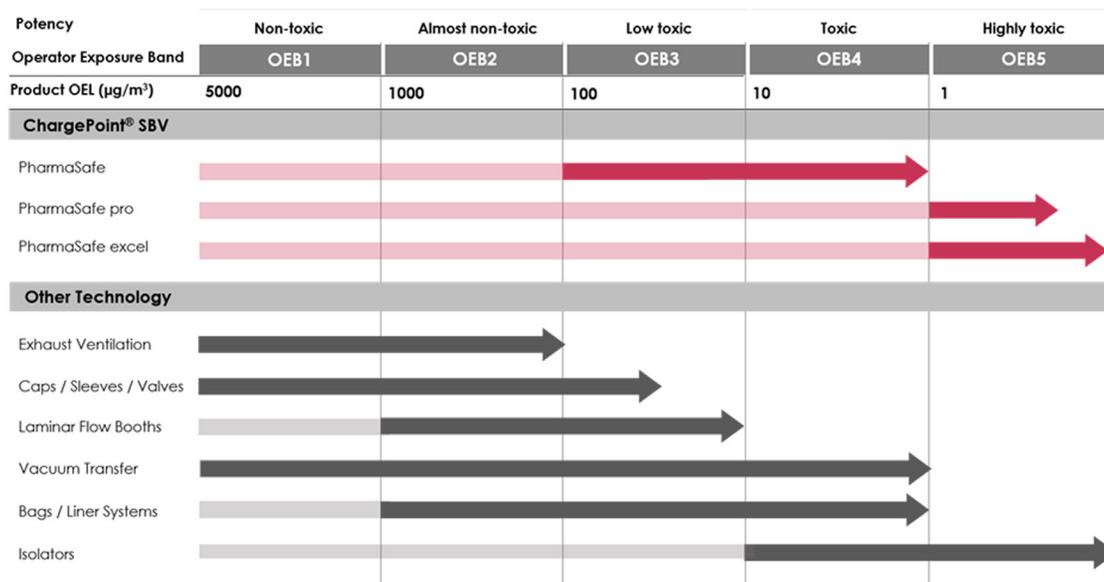
There are, of course, challenges with using data that has been created in a laboratory setup with surrogate materials and comparing it with the day-to-day use of equipment in an industrial setting. Variations will depend on materials transferred, the environment, and the frequency of transfer. The human factor always plays a part — different individuals have different levels of expertise and concentration, and everyone has off days caused by tiredness, illness, and other circumstances.

The ChargePoint approach

ChargePoint's focus is on the development, manufacturing, and supply of transfer technology, and the company has many years of experience in contained and aseptic SBV transfers. This includes being able to provide guidance on the application and integration of SBVs, from front-end technical support and system installation support and training through to aftercare, including maintenance and spare parts.

ChargePoint has created a range of SBVs for use in API containment, including PharmaSafe, PharmaSafe pro, and excel (Figure 4). The valves can be used for differing levels of containment performance, and the PharmaSafe pro and excel offer higher levels of containment than most other technologies, apart from isolators.

Figure 4: Comparisons between the ChargePoint PharmaSafe SBVs and other technologies



*This data is for general guidance and comparison and may not be an accurate reflection of all solutions or supplier performance

*Pressure/vacuum rated only when fitted with a suitable pressure/vacuum rated component or accessory

The two units of the PharmaSafe valve, which can be used with APIs classed as low toxicity (OEB3) or toxic (OEB4), cannot be opened until they are docked and locked together. The exposed surfaces are sealed together, creating a single disc, and the valve is opened, with any potential contamination sealed away from the flow of ingredients. The two halves are only undocked once the valve is closed.

The PharmaSafe split butterfly valve

The PharmaSafe SBV, which acts as the entry level valve, requires no additional seals, vacuum, or extraction and operates down to 1 µg/m3.

The PharmaSafe Pro was introduced to meet the demands of OEB5 high containment requirements. Whilst maintaining simplicity in operation, it features a highly effective integrated extraction between the two halves of the SBV, resulting in containment performance levels down to 1 µg/m3.

There are a number of key differences between industry-standard SBVs and PharmaSafe pro. The integrated filtered extraction system designed specifically for the entire size range of the PharmaSafe pro valves simply couples to a port on the active unit of the valve (see figure 5). The dust particulate extraction system uses high velocity extraction and double HEPA filters and operates across the range of 50 to 250 mm, removing potentially airborne particulate residue from between the two halves of the valve. The system therefore reduces the potential of both surface and airborne contamination post-transfer.



Figure 5: The PharmaSafe pro valve and extraction unit

The passive unit of the PharmaSafe pro valve sits within a recess in the active unit, like a plug inside a socket. This increases the extraction performance due to the higher-level pressure drop across the gap between the discs and therefore secures improved levels of containment compared with industry standard face to face flat mating SBV's.

One key design feature of the Pro valve is its improved performance while maintaining the robustness and precision of the existing ChargePoint valve, including common seat and other component parts. This ensures compatibility across the range of valve sizes and with existing technology where possible, thus, for example, allowing users to retain their existing passive units.

The critical design feature of the PharmaSafe Pro valve with extraction ensures negligible powder residue on the valve, the system has few parts and is simple to disassemble, decontaminate and reassemble after use. This is particularly critical for HPAPIs.

The PharmaSafe excel, which operates down to $<0.1 \mu\text{g}/\text{m}^3$, adds a synchronized purge and extract sequence, using a high-velocity dry air wash to maintain an even higher level of containment performance after undocking.

ChargePoint testing and validation

The combination of ChargePoint's product development and its testing and validation regimes provides confidence in the standards of its products and the reproducibility of the results. ChargePoint has used independent, third-party organizations to carry out containment performance testing throughout the entire range of PharmaSafe valves (50 mm, 100 mm, 150 mm, 200 mm, and 250 mm). The testing protocol imitates the production process, using lactose and naproxen as a surrogate, with consistent conditions and a defined volume, measuring at points 1, 2, and 3 (see Figure 6) at least three times.

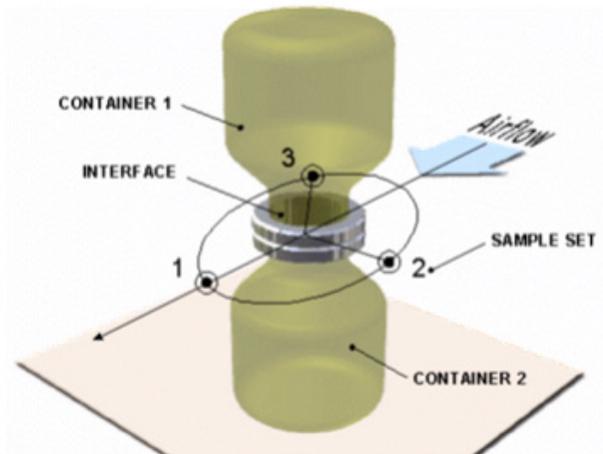


Figure 6: Measurement points for SMEPAC testing

These containment performance tests have been carried out in accordance with the ISPE SMEPC industry-standard good practice guidance and can be used to provide assurance and confidence in the performance claims. The company also supports end users with on-site containment performance qualifications.

Next steps in containment

The needs of the drug development and manufacturing industry, particularly where HPAPIs are concerned, are forever-increasing levels of containment and reductions in both airborne and surface contamination. The increased requirements for sterile APIs as the source material for potent targeted therapeutics such as antibody-drug conjugates in cancer therapeutics will heighten these needs even further.

Containment also needs to keep up with a growing reliance on single-use technology and increasing use of automation to reduce manual intervention. Both the disposables and valves must provide assurances of high-containment performance and cost-effective processes. ChargePoint has a pipeline of new technologies and innovations in development and testing that will meet the requirements that the industry will demand as it evolves.

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