

## Seals and Containment of Pharmacologically Active Pharmaceutical Powders

The containment of highly toxicologically active pharmaceutical ingredients (API) is a high risk business. These ingredients often come without detailed toxicological information and therefore lack a reliable occupational exposure limit. Combine this with operators working longer shifts and the need to maximise plant utilisation by processing an ever wider range of APIs, and the exposure of risks to operators' increases significantly. Seals for valve and access point have a vital role to play in reducing the risks of leaks. Furthermore, to meet Good Manufacturing Practice regulations for API, manufacturing operations should not compromise API integrity through poor hygiene standards and cross contamination.

### Processing API Powders

Pharmaceutical production presents engineers with a range of containment decisions. The more aggressive the API the greater the need for higher levels of containment. options. The alternative to effective containment is respiratory protective equipment. However in all but the most exceptional conditions, operators are usually reluctant to wear respiratory equipment, especially for prolonged periods, and many find it difficult to work wearing a respirator. Moreover, widespread use of respiratory equipment involves extensive training, maintenance and testing systems which means additional time for an often already busy production team.

Types of containment range from airflow, isolator and enclosed process and transfer. Selecting the right containment system will depend on the toxicity of the material, the volume of material to be handled and the type of material. The benefits of an effective containment system for API powders cannot be understated. Top of the list is the reduction of the risk of exposure to operators and release of APIs into the environment. Production benefits include reducing the risk of cross contamination, meeting the current regulatory and industry good working practice requirements for API manufacture and increasing plant efficiency through automated transfers.

Operator exposure limits (OEL) are often difficult to define for APIs. Where a compound is new, there will be limited data on its pharmacological activity and protective measures to be taken. Typically, a hormone OEL is  $5\mu\text{g}/\text{m}^3$  and a cardiovascular compound can be  $1\mu\text{g}/\text{m}^3$ . For protective measures, a powder with an exposure limit of 1 – 5  $\text{mg}/\text{m}^3$  calls for good hood ventilation while for processes where operator exposures of up to 1,000  $\mu\text{g}/\text{m}^3$  are permissible, standard valves are used. Below this high containment technologies are more common and below  $1\mu\text{g}/\text{m}^3$  total containment valve technologies are used.

Reliance on acid / alkali cleaning-in-place (CIP) reagents and increasingly aggressive solvents using the manufacture of active pharmaceutical ingredients has focused attention on the 'weak' point in any containment system – the valve seal.

In an enclosed transfer system, the greatest risk of leakage of APIs into the environment arises from valve seal failure, damage to seals during interconnection of valve during transfer and connection and incorrect fitting of the seal. When the number of connections per batch varies between 5 and 12, in general wet granulation processes use more connections than a dry compression process, the quality and integrity of the seal is vital in preventing leaks and protecting operators.

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The most common cause of seal failure is a change of solvent leading to incompatibility between seal and solvent, which can result in the types of problems highlighted in the table below.

For pharmaceutical engineers and plant operators there are early warning signs of seal failure. Typical problems include:

<b>Problem experienced</b>	<b>Warning of</b>	<b>Corrective action</b>
Difficulty opening / closing a valve, seal becoming 'sticky'	Possible seal swelling	Check solvent and seal compatibility
Seal shredding	Risk of product contamination and eventual valve leak	Check solvent and seal compatibility and seal/valve dimensions.
Excessive seal maintenance leading to high level of plant downtime affecting productivity	Poor seal to chemical compatibility	Check solvent and seal compatibility, and seal installation
Product discolouration	Seal colour contaminating product	Replace with colour fast seal or check chemical compatibility
Seals dislodged from valve	Commonly caused by highly viscous powder slurries which damage the seal by physically distorting it.	Redesign the seal

Preventative measures to avoid seal problems include

Build seal compatibility into planned process changes, and

Checking the seal regularly for mechanical wear and tear as part of a preventative maintenance programme.

If the process demands a change of seal, there are two options: a like-for-like replacement or a new design. A new design is usually needed where the failed seal, perhaps an O-ring, has had to be distorted when being fitted and this has introduced mechanical weaknesses in the seal leading to its failure.

Choosing the correct seal at the outset can significantly reduce the risk of leaks. Moreover, another benefit of getting the seal right first time **is** greater plant productivity. As well as increasing plant flexibility – using the same plant for different compounds without having to strip down and inspect seals before implementing a change of solvent or cleaning agent, for example.

A cost/benefit analysis of the time and cost of obtaining the correct seal against the cost of increased plant downtime caused by excessive seal maintenance and seal failure quickly demonstrates the commercial advantages of choosing the right seal.

## Seal Compatibility

For pharmaceutical manufacture, seals have to be FDA-compliant and meet the regulatory standard 21CFR 177.2600. This standard sets out the relevant regulations for 'rubber articles intended for repeated use' in food manufacture – the same standard is used by pharmaceutical manufacturers when specifying seals.

Elastomers that have been tested and found to be FDA-compliant include specific grades of nitrile butadiene rubber, silicone rubber, ethylene propylene rubber, fluoroelastomer and perfluoroelastomers. Selecting the right sealing material is a question of matching the pharmaceutical processing environment with elastomer chemical compatibility and physical performance.

As the table shows, the most chemical resistant elastomer is the perfluoroelastomer. This is related to the high levels of fluorine on the polymer backbone compared with the other elastomers, the carbon - fluorine bond is a good deal stronger than the carbon – hydrogen bond.

Temperature resistance is less predictable on the basis of chemical bond strength, however, for example, both nitrile butadiene rubber (NBR) and perfluoroelastomers (FFKM) can maintain their elasticity down to  $-35^{\circ}\text{C}$  but their high temperature performance is very different:  $120^{\circ}\text{C}$  for NBR and over  $260^{\circ}\text{C}$  for FFKM.

To overcome processing temperature extremes, perfluoroelastomers can operate between minus  $35^{\circ}\text{C}$  and up to  $330^{\circ}\text{C}$  without loss of chemical resistance. Below minus  $35^{\circ}\text{C}$  the perfluoroelastomers can begin losing their flexibility although do not become brittle at temperatures as low as minus  $60^{\circ}\text{C}$ , allowing scope for sealing applications previously only possible with PTFE (polytetrafluoroethylene).

## Total containment now possible

An example of selecting the right seal to overcome a containment sealing problem was demonstrated by GEA Buckvalve when developing a total containment valve. High containment powder systems can deliver containment levels of 50 micro grams per  $\text{m}^3$  but it has only been with the development of new perfluoroelastomers that total containment of less than 100 nano grams per  $\text{m}^3$  become possible.

Typically a total containment docking system consists of an active and passive valve which independently seals two containers dust-tight. The active valve is placed on the production unit – active means that the valve is actuated manually or automatically, while the passive valve has no actuator and is normally fitted to the storage / mobile IBC container.

The active and passive valves are docked and locked by means of an internal centring system. The mechanical locking systems of the individual valves will disengage automatically during this process. The outer, contaminated half discs of the valves are then closed together and sealed to ensure no contact with the product. The discharging and filling process is activated by turning both valve discs together, ensuring no contact between the exterior and interior surfaces of the valve during decanting. The decanting process then takes place under completely closed conditions and is therefore free of contamination. This total separation of the internal container and product from the surroundings can obviate the need for personal protection equipment and an expensive clean-room installation.

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Until recently, total containment valve technology was held back by a lack of adequate sealing. Early designs of the valve had used PTFE but, while the polymer is resistant to chemicals, it was too rigid. This meant it was unsuitable for any process that operated under pressure. By switching to a perfluoroelastomer seal, combining high levels of chemical resistance with the flexibility of rubber, a near perfect seal can be achieved. Moreover, the total containment seals are made from range of perfluoroelastomers offering hardness from 50 to 90 Shore A, allowing greater customisation in pressure and vacuum processing environments.

Total containment is expected to become the industry norm for pharmaceutical and other manufacturing processes. From the perspective of reducing API exposure to nanograms per m<sup>3</sup> for plant operatives and cutting containment costs compared with using glove boxes, the case for total containment valves is compelling

For pharmaceutical manufacturing in general, perfluoroelastomer sealing applications continue to grow. The elastomer's FDA compliance and high chemical resistance are now complimented by new grades offering high purity and wear resistance in dynamic sealing applications. These factors together with the ability to produce composites seals where the perfluoroelastomer encapsulates a less chemically resistance elastomer, at a competitive price, are just some of the ways in which chemical engineers can increase process plant flexibility and productivity.