FLOWSERVE

DECEMBER 2019

Application Solutions Guide

PHARMACEUTICAL API PRODUCTION

Experience In Motion

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THE GLOBAL ACTIVE PHARMACEUTICAL INGREDIENT (API) LANDSCAPE

Market Overview

The active pharmaceutical ingredient industry is the organization by which APIs (active pharmaceutical ingredients) are manufactured from raw materials through both chemical and physical means. Depending on the complexity of the molecule required, synthesis of APIs might need multi-step complex chemistry utilizing a range of processing technologies.

The API market's outlook is positive. The growing trend toward new high-tech therapeutics, coupled with the emergence of novel and innovative delivery systems and the evolution of personalized medicines, will only serve to further emphasize the growing demand for advanced APIs.

Pharmaceutical Market

The health care consultancy company IMS estimates that in the next five years the compound annual growth rate of the Chinese pharmaceutical market will be 23.2%. It will become the world's third-largest prescription medicines market after the U.S. and Japan.

China's pharmaceutical output is also fueled by the accelerating global demand for cheap, effective medicines. All of the top 20 multinationals have already set up subsidiaries in China. According to IMS, the multinationals' share of the Chinese pharmaceutical market share reached 25% in 2010. Compared to mature markets, China's pharmaceutical market has unique features and is significantly fragmented due to strong local competition.

Many Chinese people believe TCMs have less side effects than pharmaceuticals and they are often much cheaper. TCMs comprise one-third of the government's essential drugs list, which qualifies drugs for significant reimbursement. This has led to a 20% annual growth for TCMs. However, figures do vary.

New Market Trend: "API Outsourcing"

APIs are commonly referred to as *bulk pharmaceuticals* and usually made in places at quite a distance to where tablets, suspensions and liquids are manufactured. Today, the greatest concentrations of API manufacturers are located around Asia, specifically in India and China. This has led to more companies outsourcing API manufacturing to such places, which has the main benefit of eliminating the need to invest in highly expensive equipment and infrastructure — which can also be complicated to install and maintain.

Long-Term Outlook

The demand for drugs to treat the aging population will definitely boost the sales of active pharmaceutical ingredients that are popularly used for manufacturing drug products (TMR report). Due to a growing pool of geriatrics in Europe and North America, these regions are primarily driving the active pharmaceutical ingredient market. Improving access to health care and the growing demand for pharmaceuticals in Asia-Pacific and the rest of the world are likely to create lucrative growth opportunities for the overall market.

Regulations

Regardless of where the active pharmaceutical ingredient is made, companies must adhere to strict safety and quality standards set by the country where it will be used. So, APIs manufactured in China or India for use in the United States must still be inspected and licensed by the FDA. Similarly, if the API is intended for use in Europe, it would need to meet regulations set by the European Medicines Agency. Regular inspection outside the country of use, however, can prove difficult; counterfeiting and contamination are high on the list of various agencies' concerns. For instance, since 2008, the FDA has considerably increased its overseas staff as a way of attempting to eliminate these problems. As a result, countries such as India have gained their foothold in the global market and now have around 75 FDA-approved manufacturing facilities for API synthesis.

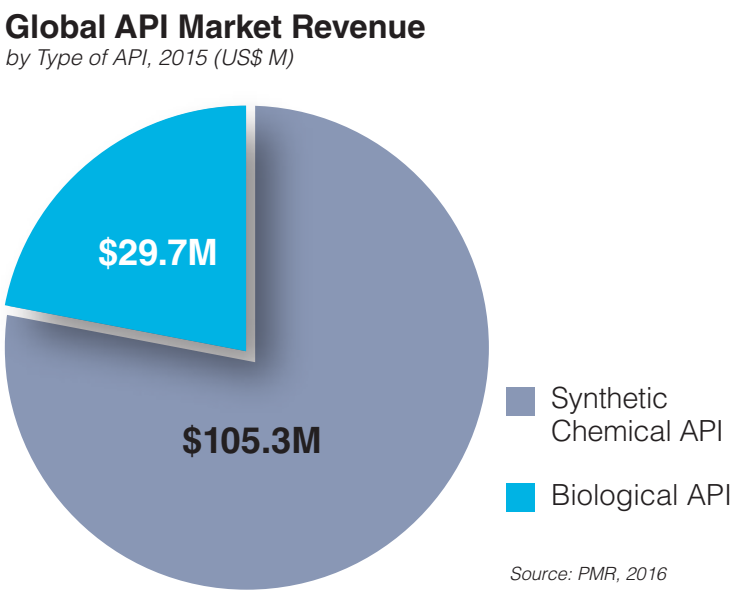
CLOSER LOOK AT THE ACTIVE PHARMACEUTICAL INGREDIENT (API) PROCESS

General Information

The market of API is segmented into synthetic chemical API and biological API. Among these, the section of biological APIs has the most significant rate of growth due to the large number of drug companies involved in this section.

Both processes are different in the way that the chemical API process starts from chemical products (raw materials A and B), where the biological API starts from seed cells from a master cell culture.

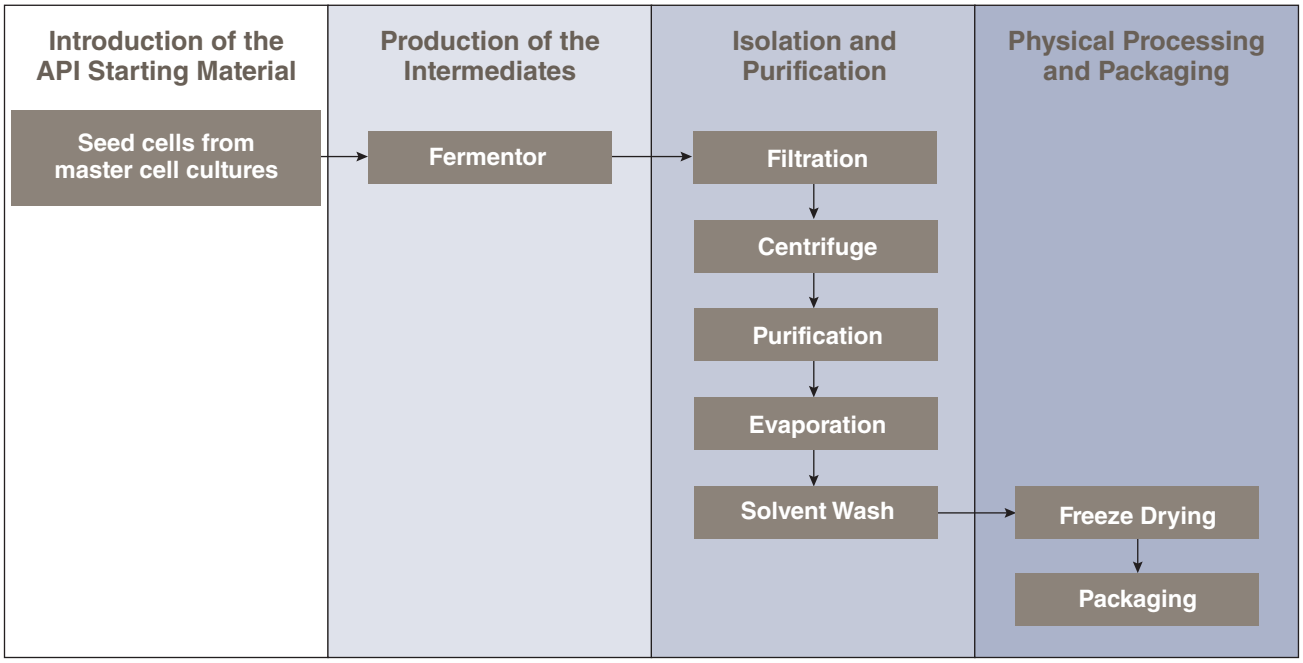
Figure 1: Market split in 2015



Difference Between Biological and Chemical Processes

Biological API Process

Figure 2



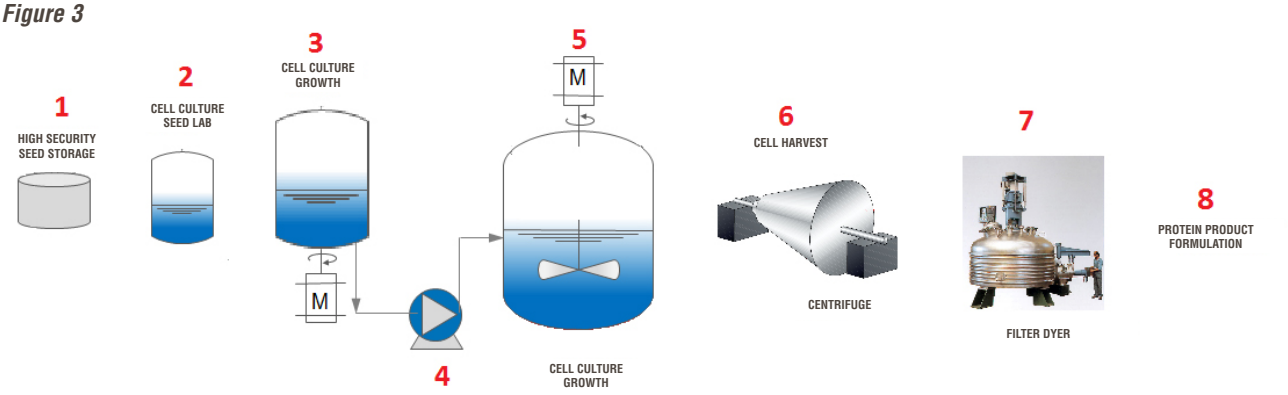
Today's market share of both production processes favor the chemical process, where biological API production is growing faster than the chemical process. Growth is being driven by numerous factors, such as aging populations in most of the Western world and an increased prevalence of chronic disease. However, likely the most important contributor to growth is biopharmaceutical drugs' superior effectiveness in treating many disease states, including treating conditions for which there were previously few effective drug treatment options available.

Bio-production is becoming more popular as a way to produce safer and more effective drugs. New and creative methods for curing cancer, cystic fibrosis, asthma, blindness and heart disease are now within reach and were previously out of the reach of short chain molecule chemicals. Bio-pharmaceuticals work with the body to protect itself, while chemical drugs often simply shield the effects of a disease.

Also, very attractive to the biopharmaceutical manufacturers is the inability of pirates to duplicate the process. This removes the concern for patent infractions that occur in most parts of the world, specifically India and China. When the cost of bringing a drug to the marketplace is $50 million BEFORE it is known if the FDA will block the bio-processor from selling the drug, it is easy to understand the concerns about patent security.

Plant Configuration

Figure 3



Step 1: SEED STORAGE

Cell cultures are stored in extremely secure and sterile environments. These are the foundation from which all bioprocessing of living creatures begins. Flowserve has no products that would be used in this area.

Step 2: CELL CULTURE SEED LAB

Usually small mag-drive mixers are used in this area. This is where the cell 'seeds' are prepared. These seeds are genetically modified living cells that are processed for a specific purpose. One example would be therapeutic proteins: antibodies. The seeds are mixed with a liquid growth medium where they begin to eat, breathe and multiply.

- Vessel Manufacturer: Steridose out of Sweden is one good example.
- Mechanical Seals: None

Step 3: CELL CULTURE GROWTH

This vessel has a well-defined sterile boundary which cannot be broken during processing. Breaking this boundary and allowing alien cells to mix with the cultured cells can cause undesirable mutation and the loss of a very expensive 'batch'. In the past, the industry used cheap throw-away seals for a COP (Clean-Out-of-Place) procedure in between batches. This causes a penetration of the sterile boundary, and this boundary must be re-established before the next batch can be processed. This is very expensive. A seal that does not need to be removed between batches and is capable of standing up to CIP (Clean-In-Place) chemicals and SIP (Sterilize/Steam-In-Place) is worth a great deal of money in the bioprocessing plant.

- Vessel Manufacturer: Various
- Drive Manufacturers: Dakota, SPX-Lightnin, Chemineer, DCI and others
- Mechanical Seal: Flowserve ST

Step 4: TRANSFER PUMP

Flowserve has no pumps available for this application, as it is purely a small sanitary (i.e., it can be effectively cleaned and sterilized with typical CIP and SIP procedures) pump. These pumps are mass produced and surprisingly competitive.

- Pump Manufacturers: Alpha Laval, SPX and others
- Mechanical Seals: Roplan, John Crane

Step 5: CELL CULTURE GROWTH

This vessel is larger than the previous vessel to accommodate cell multiplication and growth. Like the previous vessel, oxygen and nutrients are added to maximize cell growth.

- Vessel Manufacturer: Various
- Drive Manufacturers: Dakota, SPX-Lightnin, Chemineer, DCI and others
- Mechanical Seals: Flowserve ST for bottom entry; MW-200 for top entry (condensate barrier fluid)
- Process Temperature: Ambient
- Process Pressure: Ambient
- CIP Temperature: 80°C (176°F)
- CIP Pressure: Atmospheric
- SIP Temperature: 130°C (266°F)
- SIP Pressure: Atmospheric

Step 6: HARVEST

Several methods are used for harvest, but the most common is to centrifuge the process results. Targeted proteins (anti-bodies) are isolated and separated from undesirable product. Depending on the desired end result, the API may be virus, protein or DNA. We have no seals in this equipment (and are unaware if seals are used in this process).

Step 7: FILTER/DRYER

- This step removes more moisture and prepares the API to be processed into the final consumable.
- Vessel Manufacturer: Various
- Equipment Manufacturers: Cogeim, Rosenmund, Comber, Jaygo
- Mechanical Seal: MD-200 for top entry (nitrogen)
- Process Temperature: 80°C (176°F)
- Process Pressure: Vacuum
- CIP Temperature: 80°C (176°F)
- CIP Pressure: Atmospheric
- SIP Temperature: 130°C (266°F)
- SIP Pressure: Atmospheric

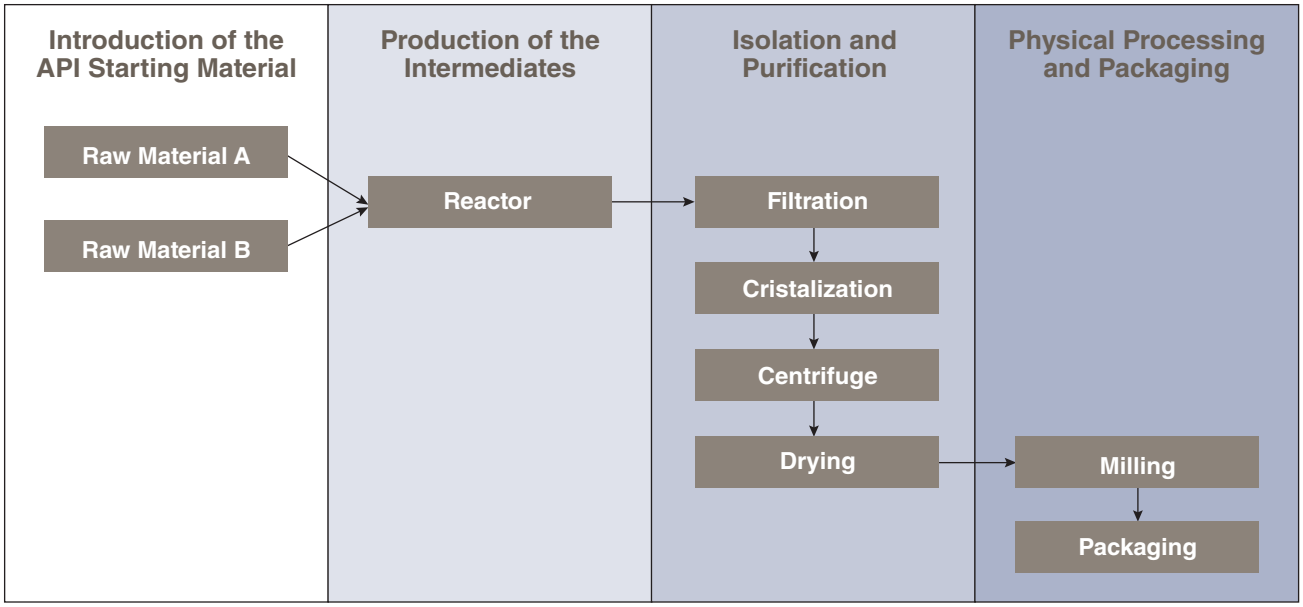
Each drying tunnel has huge vacuum pumps running at an absolute pressure of 10^{-2} mbar.

Step 8: FINAL PRODUCT PREPARATION

This step may occur at the bio-pharmaceutical facility.

Chemical Pharma API Process

Figure 4



Basics of the Synthetic Chemical API Process

The complete production process of API products can be traced in 10 process steps. The most important features of a high-quality API plant are:

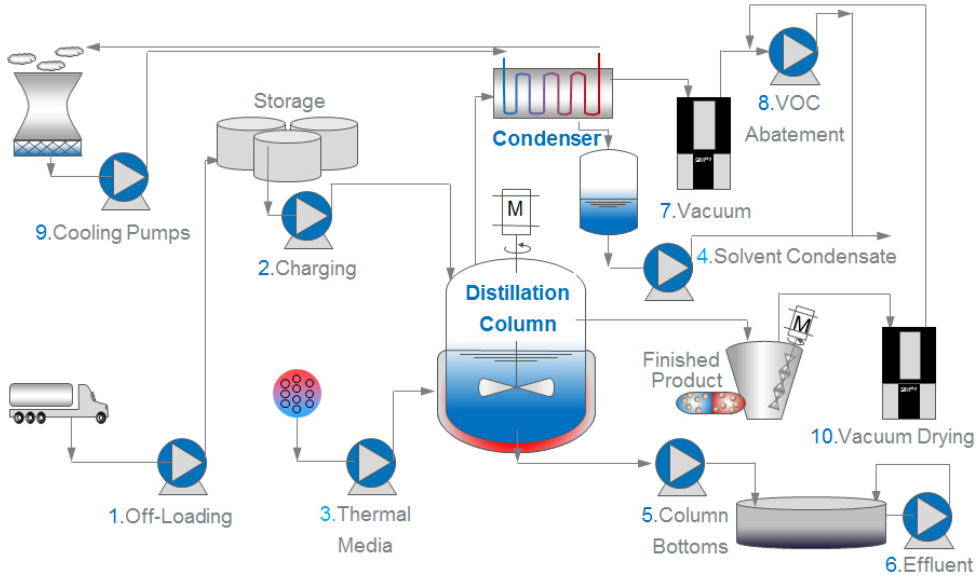
- Flexibility — to be able to produce many different fine chemicals in small batches and limit the number of pump and valve changes
- To reduce the capital investment in semi-finished goods

Quality Standards

Since all these products are the base material for a pharmaceutical drug, each production step must be completely controlled. Strict and severe controls are executed by the FDA. Today, more pharmaceutical plants are leaving China and India because of quality control issues.

Plant Configuration

Figure 5: Simplified API pharmaceutical plant



An Active Pharmaceutical Ingredient plant depicted in Figure 1 can be simplified in 10 major steps:

Step 1: Off-Loading Pumps

Starting from some base chemicals, like hydrochloric acid, sulphuric acid, formic acid, caustic soda, etc., each API plant requires storage for these basic chemicals. Primarily transported by truck, we can have unloading pumps at a site to unload a truck. More details about the pump will be described later.

Step 2: Charging Pumps

Since the complete API process is a batch process and different ingredients are required, each basic chemical has a charging pump to fill the distillation column (tank) with the required quantities. It is vitally important for the quality of the final product to have the correct amount of fluid pumped into the tank. This is mostly controlled either by weight or flow sensors.

Step 3: Thermal Media Pumps

Depending on the process, the agitator tank must be heated or cooled. Heating is mostly done with thermal oil and cooling with ice water at low temperature. Most API plants are using only one pump to heat and cool down. This is controlled or monitored by an air pressure three-way valve at the suction of the pump. Therefore, it is important that the complete construction of the pump can withstand a thermal shock of 150–200°C (302–392°F).

Step 4: Solvent Condensate Recovery Pumps

Once the heating process has started, the distillation column produces vapors, which are condensed and drained to the condensate tank. The most important feature of these pumps is a low NPSHR, as it will determine the height of the construction.

Step 5: Column Bottoms Pumps

These are the drain pumps. Depending upon the manufacturing process, they can be dirty liquid pumps for removing effluent waste, or hygienic to transport the active ingredient slurry.

Step 6: Effluent Handling Pumps

On a regular basis, the effluent pit needs to be emptied to pump it to the sewage treatment station.

Step 7: Vacuum Pump on Distillation Column

Since there is a mixture of different liquids with different vapor pressures, and active ingredients are detrimentally affected by high temperatures, pressure is decreased in the distillation column to evaporate the highly volatile liquids. To reduce the capacity of the vacuum pumps, typically there is a pre-condenser installed in front of the vacuum pump.

Step 8: Vapor Recovery or Cleaning

Due to emission laws, the extracted vapors from the vacuum pump must be cleaned before they enter the atmosphere. This cleaning process can be done in different ways, either by cryogenic cooling, active carbon filtering or a membrane system.

Step 9: Cooling Water Pumps

These pumps cool the water supply for the complete plant.

Step 10: Vacuum Drying Pumps

Once the final product is ready, it is pumped from the distillation column into an agitated dryer. It is possible to have a small filter press in between, but generally there is a vacuum pump installed at the top of the mixture to dry the finished product.

Finished Product Handling Pumps

Because of FDA rules, Flowserve does not supply any pump which can be used to pump the wet finished product into the dryer. These pumps are specially designed for easy cleaning, and all wetted parts inside the pump must meet following the criteria.

All wetted parts must meet the roughness of least Ra = 0,8µ and all wetted corners must be finished with R3.

Vacuum Systems

Every pharmaceutical plant has a central vacuum system. Vacuum is used to load and unload or prepare the batches in a separate container before it is pumped over to the distillation column. To prepare the product in the distillation reactor, a small vacuum pump is placed on each reactor.

THE API PHARMACEUTICAL PROCESS PLANT-FLOWSERVE INTERFACE

Flowserve Opportunities in API Process Plants — Products

General

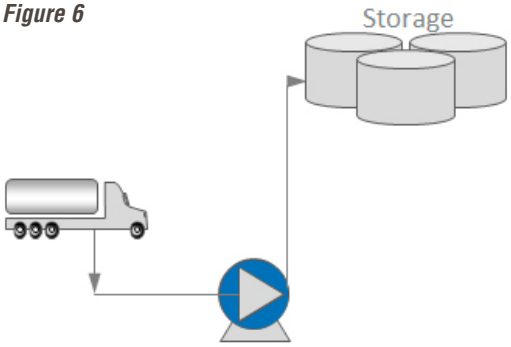
Flowserve is able to offer following pumps in the typical API process plant:

1. Chemical API plants
    - Single-stage pumps with mechanical seal or magnetic driven. CIP or hygienic pumps are not part of the Flowserve offering.
    - Vacuum pumps — dry or liquid ring
    - Valves
    - Seals for pumps and distillation column
2. Biological API plants
    - Process pumps are mostly CIP or hygienic pumps, which are not part of our delivery program. All utility pumps like the ones in the tank farm or cooling water are available from Flowserve.
    - All the vacuum pumps — dry or liquid ring
    - Valves
    - Seals for pumps and distillation column

Type of Pumps Used in API Plants

Chemical API Plants

Figure 6

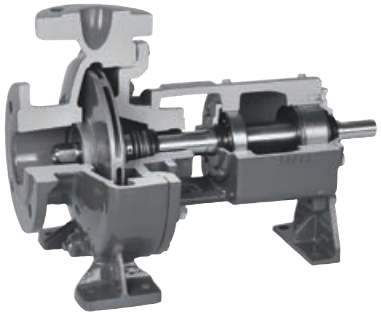


1. Off-Loading Pumps

Most of the pumps are single-stage centrifugal pumps according to ISO5199 or ANSI 37.1. The pumps can utilize a single mechanical seal or be magnetic driven.

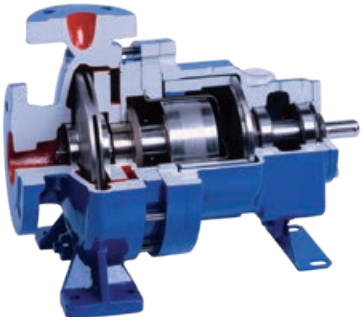
Materials are mostly stainless steel and HASTELLOY®, but for very aggressive fluids like HCl, synthetic or Teflon™-lined pumps are used.

Capacities: 30 m^3/h (175 gpm) and discharge head of 30 mlc (57 PSI)

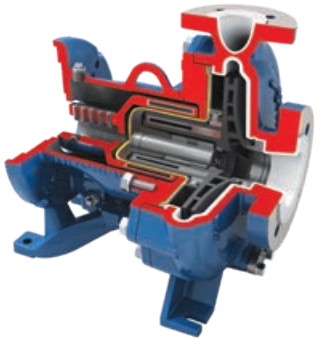


CBS sealed pump

Durco® Mark 3™ pump



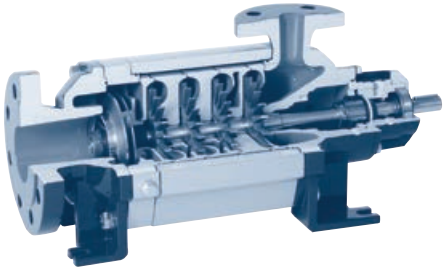
CBM mag-driven pump



INNOMAG® Teflon-lined pump

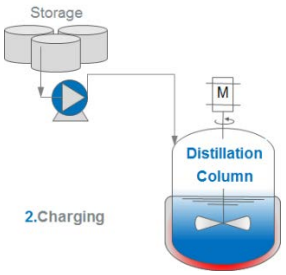
It's important to know that unloading a truck with a normal centrifugal pump can create a problem, as a centrifugal pump cannot handle any vapors. Therefore, some pharmaceutical companies install a side channel pump, which will empty the truck completely.

Capacities: 30 m^3/h (175 gpm) and discharge head of 20 mlc (57 PSI)



CEH side channel pump

Figure 7



2. Charging or Loading Pumps

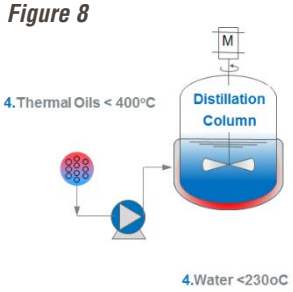
Most of the pumps are single-stage centrifugal pumps according to ISO5199 or ANSI 37.1. The pumps can utilize either a single mechanical seal or be magnetic driven.

Materials are mostly stainless steel or HASTELLOY, but for very aggressive fluids like HCl, synthetic or Teflon-lined pumps are used.

Capacities: 30 m^3/h (175 gpm) and discharge head of 30 mlc (57 PSI)

Pump types are mostly identical to the unloading pumps.

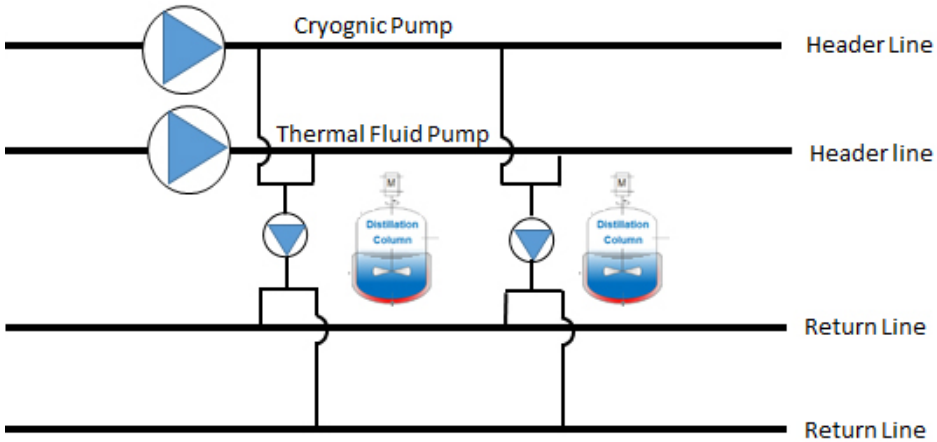
Figure 8



3. Thermal Heating Pumps

Pharmaceutical plants typically have two different circuits. Apart from the cryogenic and thermal fluid circuit, there is a primary circuit with a high flow and a secondary circuit, connected to each distillation column.

Figure 9



Pumps for the Primary Circuit

The primary circuit uses mostly single-stage centrifugal pumps, either equipped with a mechanical seal or with a mag-driven coupling.

It's important for the sealing version to pay attention to the carbonization of thermal oil or freezing with cryogenic fluids.

In both cases, use the ZEN pump for cryogenic and ZTN pump for thermal fluid. Both pumps have a special seal construction where both phenomena of freezing and carbonization are avoided.

Capacities: typically around 100 m^3/h (440 gpm) at 30 mlc (57 PSI)

Pumps for the Secondary Circuit

These pumps are normally much smaller and because of their location close to the distillation column, customers prefer inline pumps for their space-saving ability. As these pumps are used for heating and cooling of the distillation or reaction vessel, they must be at least in nodular cast iron. The preferred execution is a vertical inline pump with a mag drive. Their most important feature is avoiding thermal shock by switching from hot to cold media. This can be done with a sealed version in a dead end or a mag drive where the temperature will slowly be built up.

Capacities: 30 m^3/h (175 gpm) and discharge head of 20 mlc (28 PSI)

ZEN/ZTN pump (without cooling)

ZLI mag drive pump

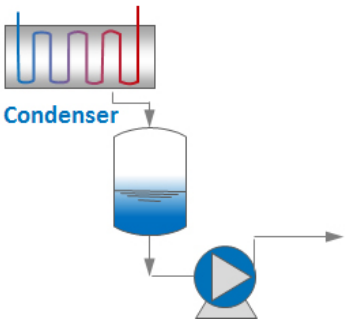
4. Solvent Condensate Recovery

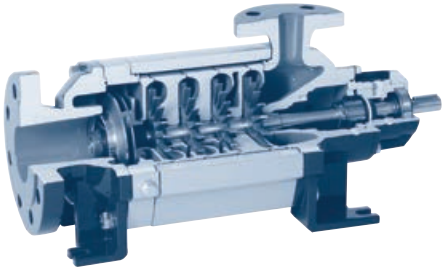
Side channel pumps are the ideal pump design to meet the specifications of low NPSHR and a steep performance curve.

Materials are mostly stainless steel, and all pumps are equipped with a standard mechanical seal.

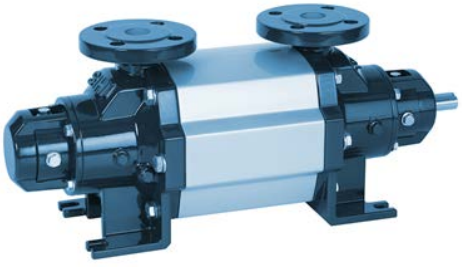
Capacities: from 10–20 m^3/h and discharge head of 30–40 mlc

Figure 10



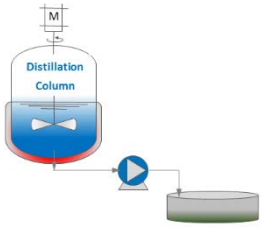


AEH pump with vertical flanges



CEH pump (very low NPSH)

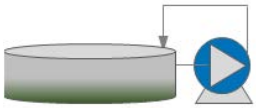
Figure 11



5. Column Bottom Pumps

Depending on the customer's specifications, they normally prefer CIP pumps like CP is offering. This is because after each batch they need to clean the complete installation from the distillation column up to the bottom edge and drain pump. The cleaning is mostly done with a mild acid. In case the customer does not prefer CIP pumps, we can use the CBS or Mark 3 pumps.

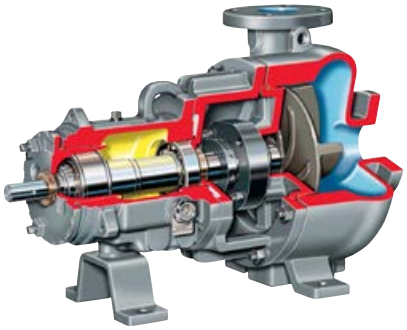
Figure 12



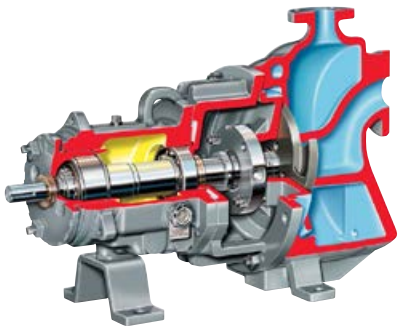
6. Effluent Handling Pumps

Effluent can be very aggressive; sometimes a self-priming centrifugal pump is needed.

Materials can vary, but most often HASTELLOY is prefered, as it resists the majority of the chemicals.



Durco Mark 3 pump with recessed impeller

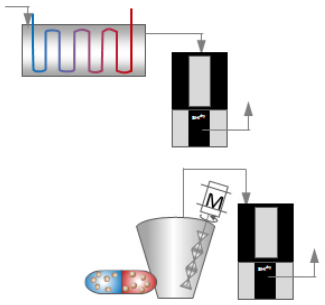


Self-priming Durco Mark 3 pump

7. Vacuum Systems in a Pharmaceutical Plant

Each pharmaceutical plant has in general two vacuum systems. One is called the *central vacuum* and the other is the vacuum on the distillation column.

Figure 13



Central Vacuum

For the central vacuum, use a dry vacuum or a liquid ring vacuum pump. In our experience, a dry vacuum pump requires significantly more maintenance, as a lot of dirt and powder pass through the pump.

Required capacities: 250–400 m^3/h
Vacuum: 150 mbar absolute
Typical pumps:
- Dry vacuum: H250 or H400
- Liquid ring: LPH 55000

Vacuum on the Distillation Column

The distillation column requires a much deeper vacuum but lower capacities. An important feature for this pump is the ramp-up of the flow. This means that when the pump starts at atmospheric pressure, there is a moderated flow. Once lower pressure is achieved, we reach the full capacity of the pump.

Required capacities: 100–160 m^3/h
Vacuum: 15 mbar absolute
Typical pumps:
- Dry vacuum: M100 or M160
- Liquid ring: LPH 45000 with injector

Dry running vacuum pump

Liquid ring vacuum pump

8. Vapor Recovery System

Membrane processes for recovering solvent from exhaust-air streams and separating organic components from process gas streams are recognized as state-of-the-art. Membranes for gas separation have been thoroughly researched and have demonstrated their capabilities, time and again, over the last 20+ years. Flowserve SIHI® has constructed approximately 150 membrane systems and is a global leader for this application.

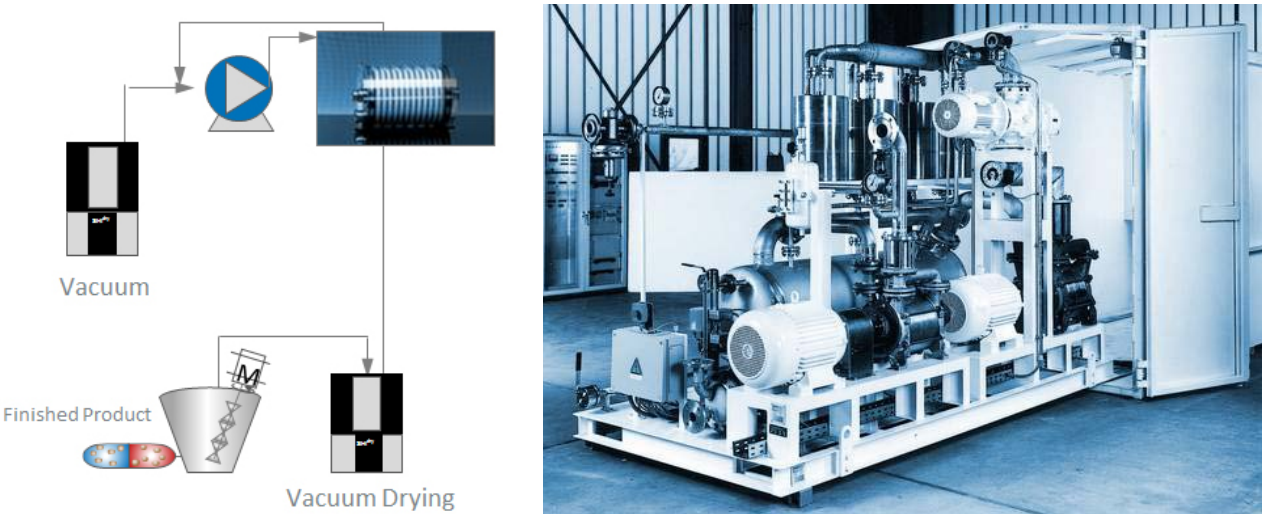
Membrane processes are not only suitable for separating and cleaning gas streams but also allow for the recovery of organic components. The membrane process can be calculated and optimized due to the integration of the membrane in simulation software.

Condensation With Membranes

An advantage of the membrane, in contrast to pure condensation, is the fact that the membrane process can be carried out at higher coolant temperatures. A condensation temperature of -80°C (-112°F) is, for example, required for the condensation of dichloromethane from air in order to achieve allowable emission levels. A membrane linked with a condenser increases the necessary condensation temperature significantly. With a membrane, often normal cooling water can be used; without a membrane, a special brine and cryogenic condensation are mandatory. The higher procurement costs will be offset after a short time due to the savings in operating costs.

There are a wide range of possibilities with SIHI Flowserve membranes, as they are suitable for the most common solvents used in the pharmaceutical industry.

Figure 14: Process flow diagram with actual package recovery system that includes SIHI products



9. Cooling Water Pumps

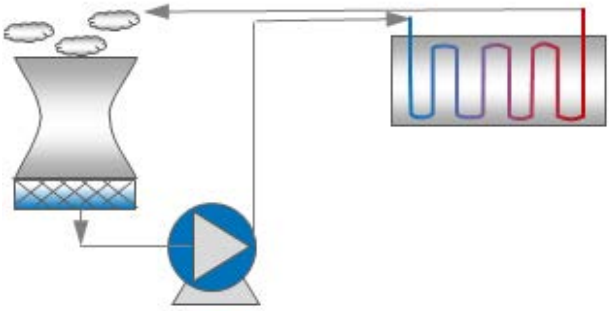
Normally, cooling water pumps are standard sealed centrifugal pumps. Customers should pay attention that no air bubbles are entering the pump with an open cooling system to avoid cavitation.

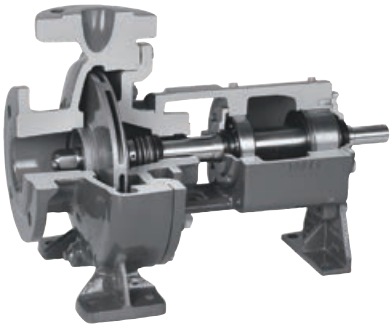
Materials

Cast iron housing with cast iron or bronze impeller and equipped with a mechanical seal

Capacities: 200/300 m^3/h (880/1320 gpm) and differential head of 40/50 mlc (60/70 PSI)

Figure 15: Open loop cooling tower





CBS sealed pump

ZLN sealed pump

Durco Mark 3 pump

Biological API Plant

Since the Flowserve offering for sanitary pumps is limited, we do not currently have pumps applicable for the production process.

However, the following pumps can be supplied for a biological API plant:

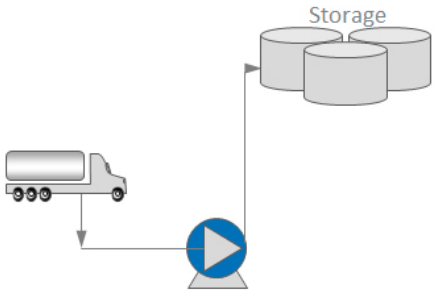
Off-Loading Pumps

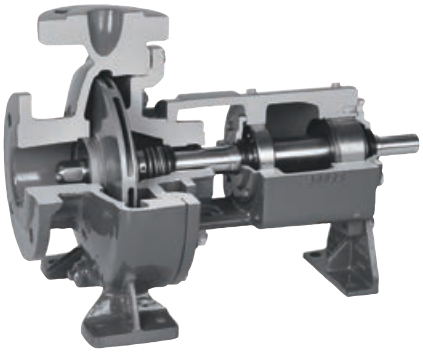
Most of the pumps are single-stage centrifugal pumps according to ISO5199 or ANSI 37.1. The pumps utilize a single mechanical seal or are magnetic driven.

Materials are mostly stainless steel and HASTELLOY, but for very aggressive fluids like HCl, use synthetic or Teflon-lined pumps.

Capacities: 30 m^3/h (175 gpm) and discharge head of 30 mlc (57 PSI)

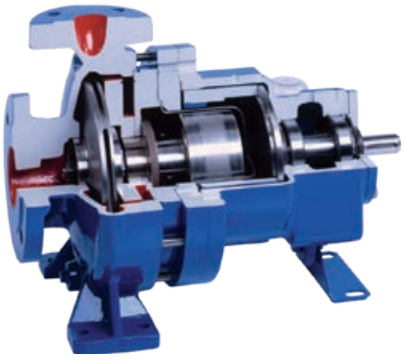
Figure 16



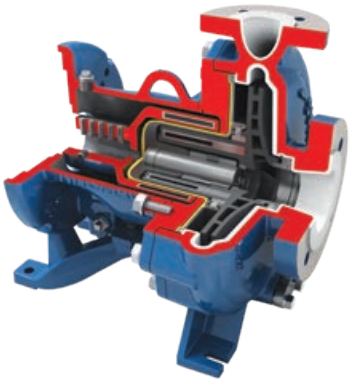


CBS sealed pump

Durco Mark 3 pump



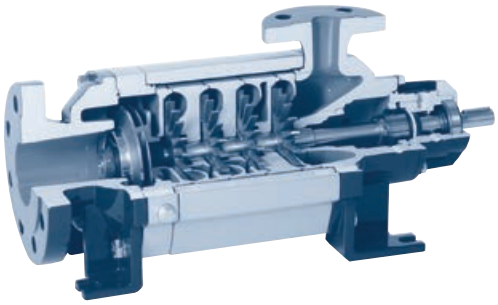
CBM mag-driven pump



INNOMAG Teflon-lined pump

It's important to know that unloading a truck with a normal centrifugal pump can create a problem, as a centrifugal pump cannot handle any vapors. Therefore, some pharmaceutical companies install a side channel pump, which will empty the truck completely.

Capacities: 30 m^3/h (175 gpm) and discharge head of 20 mlc (57 PSI)



CEH side channel pump

Charging or Loading Pumps

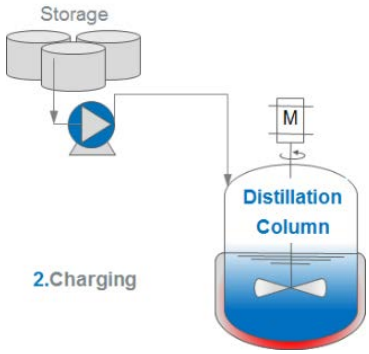
Most of the pumps are single-stage centrifugal pumps according to ISO5199 or ANSI 37.1. The pumps can utilize a single mechanical seal or be magnetic driven.

Materials are mostly stainless steel or HASTELLOY, but for very aggressive fluids like HCl, use synthetic or Teflon-lined pumps.

Capacities: 30 m^3/h (175 gpm) and discharge head of 30 mlc (57 PSI)

Pump types are mostly identical to the unloading pumps.

Figure 17



Vacuum Drying Pumps

Vacuum systems in a biological plant are different to those found in a chemical API plant.

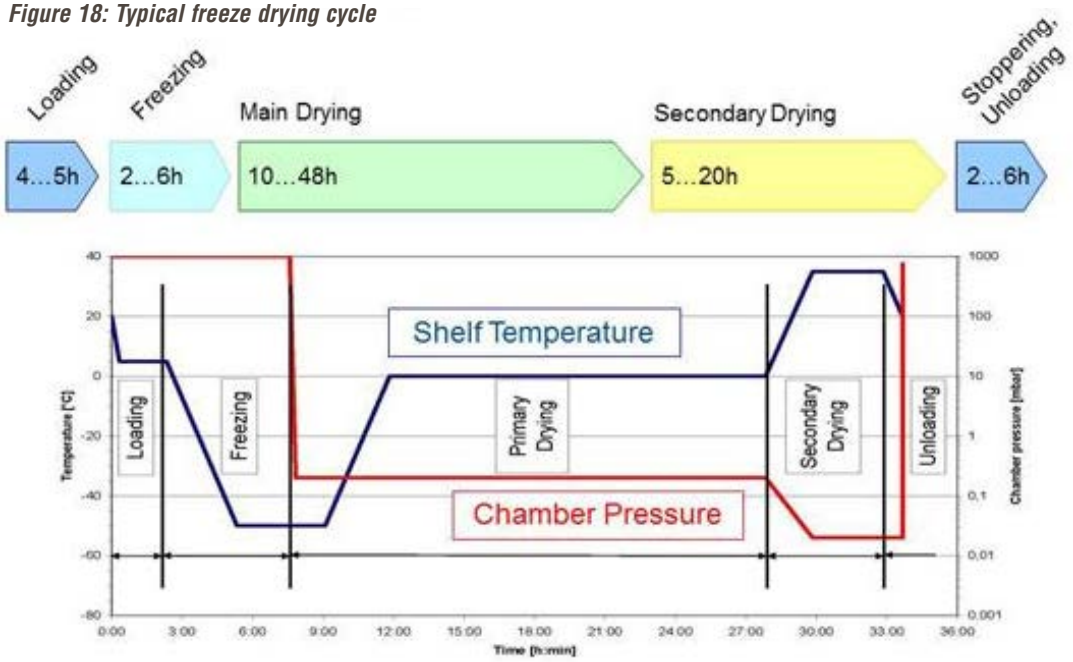
Apart from the central vacuum system, which is identical for both plants, plants typically employ huge dryers identical to the freeze-drying process.

Freeze Drying Process or Lyophilizing

Freeze drying is mainly used to remove water from sensitive products (mostly of biological origin) without damaging them, so they can be preserved easily in a permanently storable state and be reconstituted simply by adding water. Examples of freeze-dried products are: antibiotics, bacteria, serum, vaccines, diagnostic medications, protein-containing and biotechnological products, cells and tissues, and chemicals.

The product to be dried is first frozen under atmospheric pressure. Then, in an initial drying phase referred to as *primary drying*, the water (in the form of ice) is removed by sublimation; in the second phase, called *secondary drying*, it is removed by desorption. Freeze drying is carried out under vacuum. The conditions under which the process takes place will determine the quality of the freeze-dried product. Some important aspects to be considered during the freeze-drying process are shown in Figure 18.

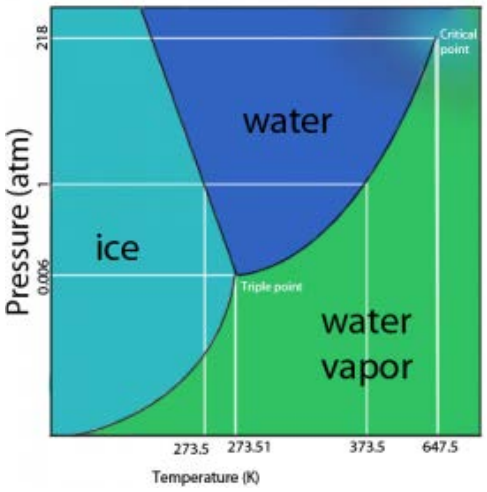
Figure 18: Typical freeze drying cycle



Freezing

Freezing is a process used to transform the basic product by abstracting heat to create a state that is suitable for sublimation drying. When an aqueous product is cooled down, at first crystal nuclei are formed. The surrounding water will be taken up around these nucleation sites, resulting in crystals of different sizes and shapes. Freezing speed, composition of the basic product, water content, viscosity of the liquid, and the presence of non-crystallizing substances are all decisive factors in determining the crystal shape and size influencing the sublimation process. Large crystals leave a relatively open lattice after sublimation, while small ice crystals leave narrow spaces in the dried product, slowing down the removal of water vapor.

Figure 19: Crystallization separation chart



Primary Drying

At the beginning of the primary drying phase, sublimation of the ice takes place at the surface. As the process continues, the subliming surface withdraws into the product, and the evolving vapor must be conducted through the previously dried outer layers. This means that the drying process depends on the speed of vapor transfer and removal as well as on the necessary heat of sublimation. The heat required for sublimation is supplied to the product by convection and thermal conduction, and in a small part by thermal radiation. Apart from heat transfer by thermal conduction and radiation, it is important that the heat transfer by convection is optimized. It must be taken into account, however, that due to the reduction of pressure in the drying chamber, convection will practically cease at a pressure below 10 mbar. This is why, as a function of the required sublimation temperature, the pressure in the drying chamber is adjusted during primary drying to the highest permissible value.

The sublimation heat is not needed at the product surface but at the boundary of the ice core that is withdrawing into the center of the product as drying proceeds. While the flow of water vapor is from within the product to the outside, the transfer of heat must be accomplished in the opposite direction from the outside to the inside. Due to the low thermal conductivity of the dried product layers, the temperature gradient required for heat transfer steadily increases. To avoid damage to the product, the maximum admissible temperature for the dried product must not be exceeded. In contrast, care must be taken to maintain the required sublimation temperature throughout drying, keep the heat supply to the ice-core boundary in equilibrium with the heat requirement at that particular location, and avoid any overheating of the sublimation zone. The primary drying phase continues until all the ice contained in the product has been sublimated.

The freezing point of pure water is 0°C (32°F). Any other substances dissolved in the water will lower the freezing point; where inorganic salts are present, it may be considerably lower. If a weak solution is frozen, at first pure ice will be separated, thereby increasing the concentration of dissolved substance in the residual solution, making its freezing point lower still. The effect of such freezing concentration on the product is different from case to case and has to be taken into account when selecting the most appropriate freezing technique.

The most suitable freezing technique for a specific product should be determined and its parameters ascertained prior to sublimation drying. The freezing behavior of the product may be investigated, for instance, using the resistance-measurement method.

Two different freezing methods are chiefly used for pharmaceutical products:

1. Freezing by contact with a cooled surface

2. Rotation or dynamic freezing in a coolant bath

The first method is a static freezing technique where a versatile freeze dryer must be capable of adjusting the freezing rate to the specific product and should allow control of the freezing speed. A final temperature of -50°C (-58°F) will in many cases be sufficient to meet all requirements.

The second method is used wherever larger quantities of a liquid product are to be frozen and dried in flasks or large bottles.

The appropriate freezing technique will also be chosen to produce a layer thickness of the frozen product that is favorable for sublimation drying, i.e., not only uniform but also as thin as possible to achieve a short drying time.

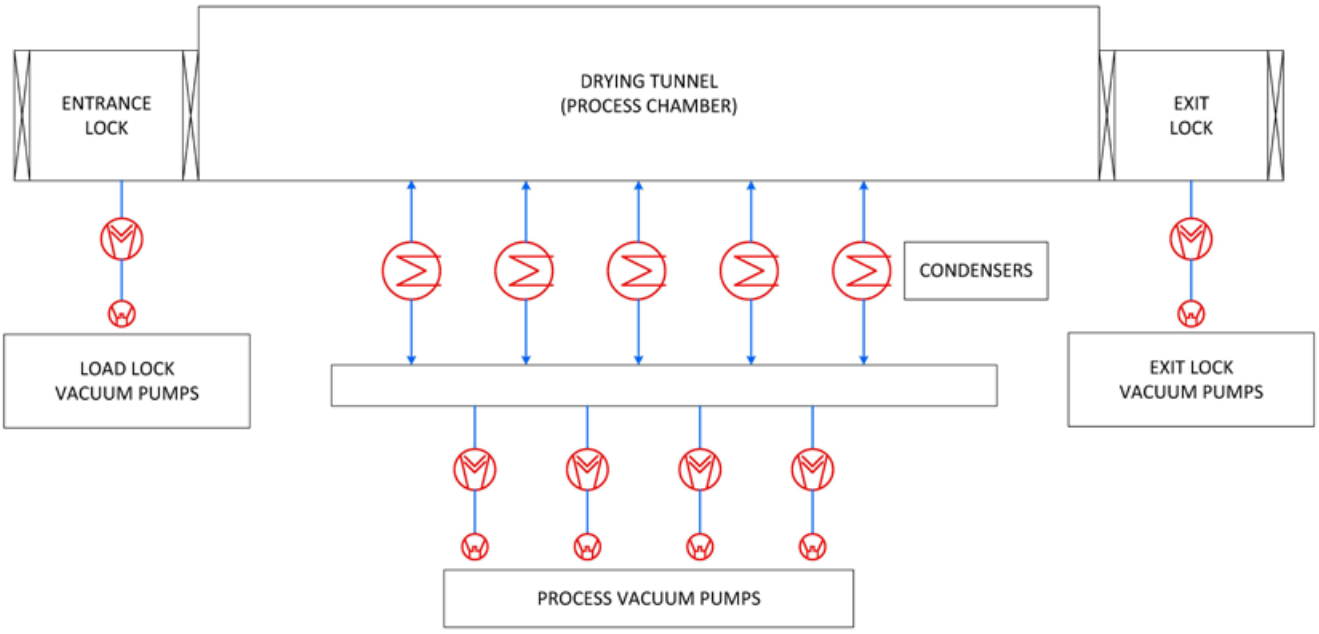
Secondary Drying

In the secondary or final drying phase, the aim is to reduce the residual moisture content in the product as much as necessary to ensure the product is in a permanently storable state. The water bound by adsorption at the internal surface of the product has to be removed. To achieve this, it is often necessary to overcome the capillary forces of the water, and a freeze-drying plant must therefore be designed to give a high-pressure gradient during the secondary drying phase; in most cases it is not possible to raise the product temperature without damaging the product. The secondary drying process must be precisely controlled so that any over-drying of the product will be safely avoided.

The drying process is done in long tunnels under very low vacuum. Depending on the size of a drying tunnel, the capacities can go up to 8000 m^3/h with an absolute pressure of 10^{-2} mbar.

For a continuous process, they can have two load locks where the product to dry is loaded. Once the tunnel is loaded, it will be under the same level of vacuum as the drying tunnel.

Figure 20: Drying tunnel



Different Methods of Drying

Batch process:

The vacuum unit has to match two demands during the sequence of the process. 1) achieve fast pump-down cycles; and 2) reliably maintain the desired vacuum level.

The graphic below shows a freeze-drying batch process with its typical pressure and temperature profile. The primary drying phase is in the center of the diagram and shows the sublimation process. Contrary to a continuous process, the freezing of the product and the following sublimation process take part in the same batch chamber.

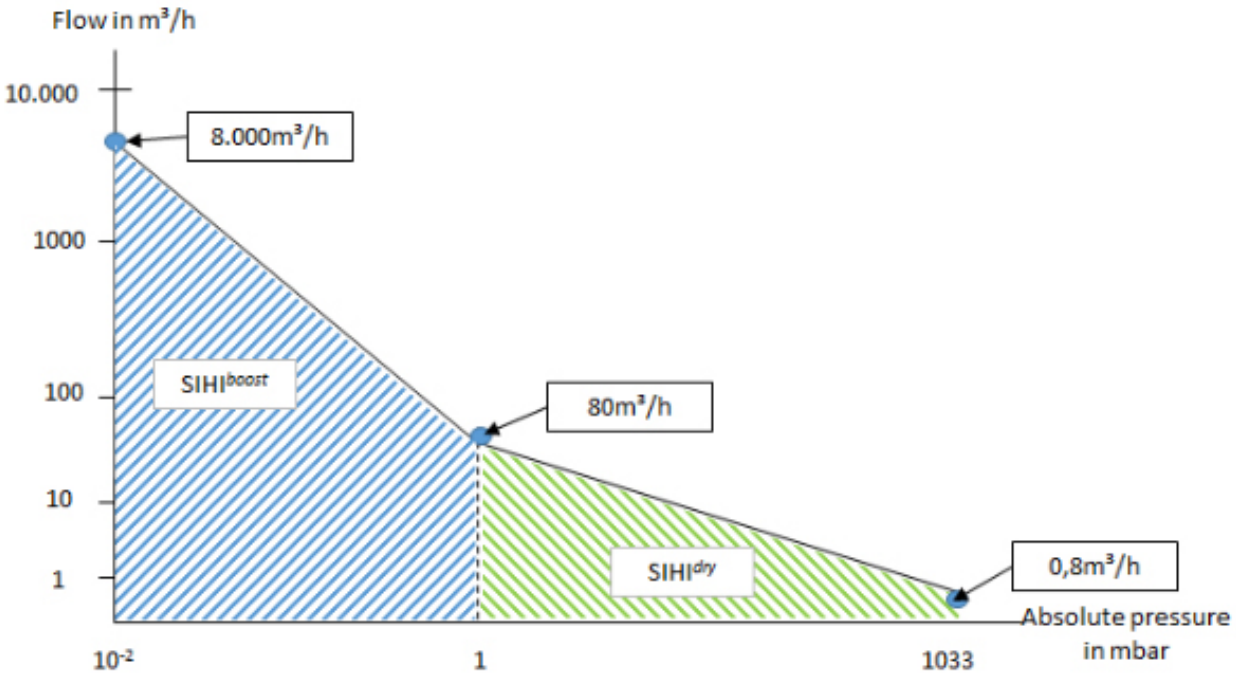
To achieve these low pressures, we install vacuum pumps in serial. For example: The SIHI^{boost} pump can handle a compression ratio of 100; the SIHI^{dry} can handle a compression ratio of 1000. So, the SIHI^{boost} pump can handle from 10^{-2} up to 1 mbar; the SIHI^{dry} pump can handle from 1 mbar to atmospheric pressure.

Dry running vacuum pump

SIHI^{boost} pump

Liquid ring vacuum pump

Figure 21: Pressure-flow diagram



Types of Valves Used in Biological and Chemical API Plants

Worcester Valves for Biological and Chemical API Plants

There are many applications for ball valves within API plants. However, due to the nature of ball valve design, ball valves are excluded from use on some applications.

In **chemical API** plants, process ball valves can be used in a range of applications within primary manufacture process.

Within utilities used on plants such as nitrogen, process water, caustic soda and methanol, standard build valves are suitable. Depending on the piping system used, these can be flanged with ASME metric flanges or a three-piece construction using either welded or screwed connections. These valves are either available as reduced or full bore, but for utilities, reduced bore valves are the norm, as they offer a smaller valve with a lower torque that is ideal for actuation. **Worcester A44A459 three-piece and F519/51 flanged valves** should be specified.

Temperature Control Modules (TCM)s are used in vessel heating/cooling systems within the process, either using steam or thermal fluids. The fluctuations in temperature require special body seals rather than standard PTFE, and the demands of steam in terms of the pressure and temperature combination need a stronger seat. The **Worcester AW44** has been specifically designed with an S gasket, PTFE-coated stainless steel body seal and Fluorofill seats. This valve is available up to 2 inches. For larger sizes, the **A459** is available as a special build using an O-ring body and stem seals combined with the Fluorofill seats (code suffix P221). Thermal fluids such as Dowtherm and Syltherm are also very “searching” media and therefore rely on these upgraded seals to maintain sealing integrity. On steam applications, Worcester also offers the combined soft and metal seated ‘V-Flow’ rotary control valves in both flanged and three-piece. The metal V-seat can be cut to suit flow requirements with the soft Fluorofill seat providing bubble-tight shut off. These valves are designated as **V44** (three-piece) and **V51** (flanged) and offer a compact, economical rotary control solution.

For the diverting of flow through the system, Worcester offers a range of products. The three-piece **AD13** or **AT13** can be used for diverting flow in two directions (**AD13**) or as a three-way, holding back upstream pressure in the third port while allowing flow between the other two ports (**AT13**). These are bottom-entry valves with flow in the vertical and horizontal planes, but the **SD13** or **ST13** offers the same flow in a single-plane arrangement. A mid-flow shut off can be achieved through a 180° version (**AT14** or **ST14**). For flanged valves, Worcester offers the 18 Series. It is a true multiway valve, with a seat on each port providing endless versatility in flow configurations through L, T and X port balls in combination with three to five ports. The **18** is used in a single plane with the **19** Series being the bottom-entry used in two planes. For full bore, the Prefix B is used, such as **B18/B19**.

For media that are toxic or harmful to human health and the environment, such as chlorine, ethylene oxide, acrylonitrile or propylene oxide, Envirosafe is available. It is a high integrity, dual-stem sealing product. The dual-stem seal is provided with a leak detection port between the seals that can be used to monitor primary stem seal failure while integrity is still maintained through the secondary seal. Available in both three-piece and flanged using the prefix E in the code, e.g., **E51** or **EF51** (fire-safe).

Steam for use in heating and cooling using the **AW44** has already been discussed. Clean In Place (CIP) is another specific application for this valve. CIP systems (and Sterilize In Place [SIP]) may be integral with the system or supplied on a skid and piped into the main system where required. Steam is used extensively as a cleaning media, both in chemical and biological systems, and the ease of application of ball valves is ideal for this automated process.

Any applications using powder normally specify that the valves are full port to enable the flow of powder through the system. The three-piece **A59/A599** or flanged **F519/819** are ideal for these applications, but the dry powder media can increase torque; care should be taken if valves are to be actuated. Valves on these applications can also be fitted with cavity-filled seats to reduce the volume in the valve cavity.

Within **biological (bioprocessing) API** plants, all of the above may be used in the services surrounding the process, but the ASME BPE standard dictates the system requirements within the process itself, with ball valves only being used outside of the sterile boundary. The significant difference with bioprocessing requirements is the use of 'tube' rather than 'pipe' and maintaining the tube diameter throughout the system to ensure there are no areas for media to collect. Many of the systems are specifically designed to allow the tubing systems to self-drain. Internal surface finish is also critical and specified within the ASME BPE standard with either a mechanical or electopolish level.

In addition to system design, the materials of construction also play a critical part, with stainless steel having a ferrite content below 1% and orbital welded joints having a controlled sulphur content between 0.005 and 0.017%. 'Soft' seals such as seats, body seals and stem seals must be FDA and USP VI compliant.

For these bioprocessing systems, Worcester offers the **WK70** (mechanical polish) or **PWK70** (electropolished) valves that fully comply with ASME BPE requirements. Some systems also require the external surface of the valve to be crevice-free to minimize bug traps. A **WKB70** can be supplied manufactured from wrought bar on these applications.

Within this industry, despite the use and acceptance of ASME BPE, end user requirements can be quite specific such as cavity filler seats, fire-safe or non-graphite build. Worcester can accommodate any specific customer requirements.

Worcester A44/A59	Worcester AW44	Worcester AD/ATB	Worcester WK70	Worcester WKB70
Standard reduced bore three-piece valve for general service feed lines	Based on the A44 but fitted as standard with high-temperature seats and seals for thermal cycling applications	Based on the A44 but with a third port and upstream sealing seats on the AT13 for three-way applications	Tube bore valve having the same inside diameter as the tube with high internal finish	Same as the WK70 but also has a high external surface finish to minimize bug traps and allow for caustic wash down
				
DN 10–DN 150 ⅜–6 in	DN 10–DN 50 ⅜–2 in	DN 10–DN 50 ⅜–2 in	DN 15–DN 50 ½–2 in	DN 15–DN 50 ½–2 in
Up to 103 bar Up to 1000 psi	Up to 103 bar Up to 1000 psi	Up to 103 bar Up to 1000 psi	Up to 35 bar Up to 500 psi	Up to 35 bar Up to 500 psi

Worcester A459	Worcester F519/529/51/52	Worcester F819/829	Worcester B18	Worcester E51/52
Standard reduced bore three-piece valve for general service feed lines	Standard flanged valve in either Class 150 (519) or Class 300 (529) for general service applications	Standard full bore flanged valve in either Class 150 (819) or Class 300 (829)for general service applications	Multiway valve with 'L', 'T' and 'X' port balls to meet all flow configurations	Same as the WK70 but also has a high external surface finish to minimize bug traps and allow for caustic wash down
				
DN 10–DN 150 2½–6 in	DN10–DN 50 ½– 8 in	DN10–DN 50 2– 8 in	DN 15–DN 50 ½–6 in	DN 15–DN 50 ½–8 in
Up to 50 bar Up to 7200 psi	Up to 50 bar Class 150 & 300	Up to 50 bar Class 150 & 300	Up to 50 bar Up to 720 psi	Up to 50 bar Up to 720 psi

Kämmer Valves for Biological and Chemical API Plants

In many of today's clinical laboratories or biotech pilot plants, valves and related equipment are manually cleaned with a caustic solution, flushed and sterilized in an autoclave after each batch process. This is usually very time-consuming because valves need to be disassembled and cleaned. This is not a viable option for production plants. Present and future batch sequencing and continuous mode production-scale bioprocessing plants require automatic sanitary control valves that meet standards for cleaning in place (CIP) and sanitizing in place (SIP) designed to drain freely from inlet to outlet. The result is a pure aseptic valve design, free from residue or organisms left behind after cleaning, which can be a source of product contamination. Of critical importance for the maintenance and cleanliness of the valve is the surface finish, which must meet all the requirements for an aseptic design. It needs to be free of pits and cracks on all wetted parts. The Kämmer® valve series CleanFlow-191000 meets all these requirements.

The Kämmer control valve series CleanFlow-191000 has a wide range of applications within the food and beverage industry as well as in biotech, pharmacy and all areas where perfect cleanliness and sterile valves are required. All parts of the easy-maintenance valve which are in contact with the media are made of corrosion-resistant materials, PTFE or silicon. For the aseptic version of this valve series, a PTFE diaphragm seals the media from the environment. These valves have excellent hygienic properties, are pocket free, and can be cleaned in place. All approvals such as USDA and 3A are fulfilled by these values. A surface finish of 0.6 Ra for the whole 191000 series is standard. If there are applications which require a higher quality surface finish than 0.6 Ra, Flowserve can easily meet these requirements.

The following Flowserve products handle the majority of control valve applications:

Kämmer CleanFlow-191400	Kämmer CleanFlow-191700/800	Kämmer SmallFlow-385000	Kämmer DrainFlow-051000
Hygienic control valve, dead pocket-free with integral seat and polished surface finish	Aseptic control valve with aseptic diaphragm, dead pocket-free with integral seat and polished surface finish	Low flow and micro flow control valve for injection applications with highly precise control	Tank bottom outlet valve for tank drain in various configurations
			
DN 10–DN 100 ⅜–4 in	DN 10–DN 100 ⅜–4 in	DN 15–DN 25 ½–1 in	DN 15–DN 150 ½–6 in
PN 16 CL 150 (max 16 bar)	PN 10 CL 150 (max 10 bar)	PN 40–PN 400 CL 150–CL 2500	PN 10–PN 40 CL 150–CL 300

Types of Sealings Used in Biological and Chemical API Plants

Mechanical Seals

The pharmaceutical industry demands creative sealing solutions for its unique products and manufacturing processes. Increasingly strict government and public requirements for product purity and emission controls drive the market toward an ever-increasing demand for mechanically sealed rotating equipment. Compression packing has become all but obsolete in the pharmaceutical industry.

The industry tends to apply established products to new types of equipment and new applications. This philosophy exists in the mechanical seal industry. The intent of the sealing industry is to offer crossover designs to the pharmaceutical industry, building on existing proven designs. It's been found that the pharmaceutical industry is unique enough — and large enough — to demand special design features for their equipment not found in other industries.

Bioprocessing is a special group within the pharmaceutical manufacturing community. The bioprocessing group specifically processes living cells. This results in a batch process in which there are at least three different applications for every mechanical seal installation.

We will focus on top-entry mixers. However, ideas and concepts presented here may be applied to other types of equipment. We cover several topics about the pharmaceutical industry. Those topics are:

- Cryogenic applications
- Bioprocessing
- Cleaning and sterilization
- Design considerations
- Typical sealing applications

Our intent is to introduce the reader to pharmaceutical sealing considerations and make the reader comfortable with his or her understanding of the subject and the associated language used in the industry.

Manufacturing an active pharmaceutical ingredient may involve simple mixing or complex chemical reactions. In the case of biopharmaceutical processing, living organisms are grown in tanks where the organisms are fed nutrients and oxygen at an optimum rate for growth and reproduction.

Once mixing, blending, reacting or growing is complete, the products must undergo separation or purification, and the desired product must be isolated and collected from the bulk process materials. This step can be accomplished, depending on the process, by filters, centrifuges or precipitation. The separation process for biopharmaceuticals is more complex and requires a different science than chemistry.

Once the API has been separated from the process, it must be prepared for consumption. Whether the product is to be injected, ingested or is topical, it becomes more important to maintain cleanliness and sterility. Final purification of the product is done to remove trace amounts of impurities. Once the manufacturer of the final product is convinced of the purity of the product, they prepare it for consumption. The final form may be a powder, pill, cream or liquid. The product will then be packaged and numbered for traceability.

Naturally, the steps described herein are very general and vary infinitely in detail. There are wide variations in pharmaceutical manufacturing from product to product; unlike for instance petroleum refining, where the technology and methods are well known and largely consistent throughout the world. But even then, there are similarities in pharmaceutical plants from plant to plant where generalizations may be made.

Cryogenic Applications

Pharmaceutical producers are constantly looking for innovative ways to enhance safety and economy of production for their products. That means that new extremes of pressure and temperature are being evaluated by both equipment and pharmaceutical manufacturers. Typically, process pressures and temperatures tend to rise to new heights, but now pharmaceutical plants are asking for equipment to contain process temperatures lower than ever before. It is not uncommon to design to temperatures as low as -150°F.

There are several reasons why cryogenic operation may be considered for a process condition. One reason is that cryogenic temperatures slow the process reaction to a manageable rate. Another reason is that liquid used in the process reaction will not flash or evaporate at these dramatically reduced temperatures; this may reduce the need for high pressures to maintain a liquid state in the process. Also, cryogenic temperatures can slow bio-activity and thus reduce the risk of bio-pollution in the process.

In the chemical and refining industries, it is normal to manage process temperature extremes by utilizing double mechanical seals with flush Plan 54. The Plan 54 external flush is provided at an appropriate pressure, temperature and flow rate to moderate the temperature in the seal cavity; this maintains good lubricating properties while protecting the seal components from extreme temperatures.

Double mechanical seals are used in the pharmaceutical industry for a variety of reasons. Because of the ever-pressing demand for pure product and simple equipment, dry running single and double seals are emerging as a strong preference in this industry. Some of the design and material considerations when sealing cryogenic equipment are as follows:

- O-rings harden and become embrittled as their temperatures decrease. They cease to remain elastic as temperatures drop below -18°C (0°F).
- O-rings have a high coefficient of thermal expansion. This means that as temperatures decrease, O-rings will not maintain a proper seal for proper operation. O-rings will contract faster than the surrounding metal while at the same time hardening due to the low temperature.
- Fits of sleeves, shrouds, collars and housings will loosen due to large temperature gradients across the parts.
- Interference fits between dissimilar materials may loosen.
- Freezing and moisture around the atmosphere side of the seal will cause hang-up of pieces that are expected to have slight accommodating motion.
- Condensation and freezing of condensate occur in the dry seal housing.

Based on the above partial list of cryogenic design considerations, the following set of guidelines helps establish some design rules for cryogenic seal operation. The most important consideration is the temperature limit of the elastomers.

The following addresses temperature only:

Temperature range: 21°C (70°F) to -18°C (0°F)
Acceptable elastomers based on temperature: EPR, fluoroelastomer, perfluoroelastomer, buna

Note: Conventional wet or dry mechanical seals are acceptable in this temperature range.

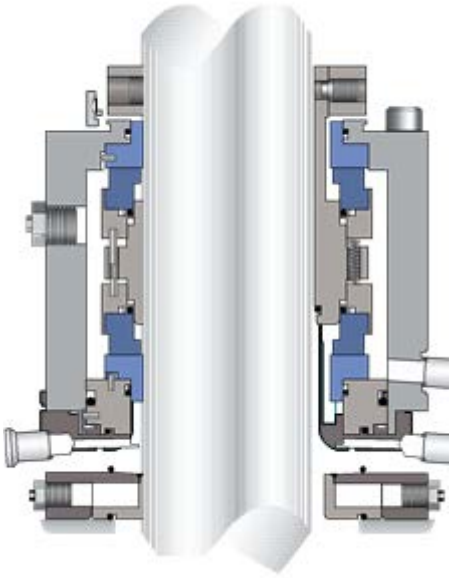
Temperature range: -18°C (0°F) to -40°C (-40°F)
Acceptable elastomers based on temperature: EPR, custom, fluoroelastomer, buna

Note: Conventional wet or dry mechanical seals are acceptable in this temperature range.
Care must be taken to ensure that barrier fluids are compatible with low temperatures. The use of a thermal spool and/or a wet seal with flush Plan 54 may drive the elastomers into an acceptable temperature range.

Temperature range: -40°C (-40°F) to -130°C (-200°F)
Acceptable elastomers based on temperature: none

Note: A thermal spool under the seal must be used. The pool in conjunction with a flush Plan 54 will raise the temperature at the secondary seals enough to use a conventional wet or dry mechanical seal. Care must be taken to ensure that barrier fluids are compatible with low temperatures. The use of a thermal spool and/or a wet seal with flush Plan 54 may drive the elastomers into an acceptable temperature range.

Figure 22:
Typical back-to-back seal configuration with barrier fluids



The simplest and most efficient method to ensure that the elastomers are kept warm enough is to install a thermal spool between the mixer flange and the seal canister. This spool is similar to a stuffing box jacket but is positioned between the vessel and the seal in a strategic location. The intent of the spool is to interrupt heat flow to or from the seal into or from the vessel. It may be considered to be a thermal dam or an insulator.

Any fluid pumped through the spool will act as a heat flow interrupter. If there is concern that the spool fluid might freeze, then oil, glycerin, glycol or aqueous solutions of glycerin or glycol may be used. While a properly designed spool can significantly interrupt heat flow through the seal housings, the shaft remains an avenue through which heat can enter or leave the seal cavity. Design ‘tricks’ must be used to help counter heat transfer through the shaft.

Bioprocessing

Bioprocessing is unique because as the name implies, living organisms are being farmed and harvested. The vessel conditions during processing are not demanding and well within the capabilities of even the lowest technology seal. However, great caution must be exercised with these applications because the seal design and manufacturing techniques for these seals greatly depart from the ordinary. Also, while the application seems innocuous, it must be noted that the vessel processing operation is only a distraction from the actual difficult parts of the application: CIP and SIP.

The mechanical seals that have been used in bioprocessing in the past were increasingly seen as dirty designs; they had many cracks and crevices in which organisms may hide and reproduce. They are often thought of as Clean-Out-of-Place (COP) seals. The COP seal is removed, cleaned and sterilized between batches. Sometimes, COP is performed between every batch. This is a very expensive procedure and automatically creates questions about the sterility of the seal and tank when the seal is reinstalled. This requires the sterilization of the seal and vessel once reinstalled. The expense of this labor-intensive process clearly points out the value of a seal capable of CIP and SIP without removal from the vessel.

A seal that can be reliably cleaned and sterilized between batches without removal is an economic advantage both in terms of time and labor, to say nothing of confidence for maintaining the sterile condition of the equipment. In other words, a properly designed seal will increase the repeatability of CIP and SIP while minimizing downtime of the equipment. This is all doubly important for the bottom-entry mixer configuration that seems to be a standard in the bioprocessing industry.

Cleaning and Sterilization

Cleaning and sterilization create operational conditions that must be taken into account when selecting a mechanical seal. The CIP process performed between batches can utilize a variety of chemicals that will contact with the inboard mechanical seal. Typically, these chemicals will be mild acids or caustics at elevated temperatures of approximately 80°C (176°F). Therefore, the seal materials must be capable of tolerating those chemicals and temperatures.

During the SIP process, the seal will be exposed to steam temperature of approximately 131°C (278°F). Minimally, the steam will be introduced into the vessel for a designated period of time to obtain a specific target temperature of the sterile boundary surfaces. Seal designers must take note that it has become very common to introduce steam into the double seal cavity for sterilization.

To understand the levels of 'clean', it is necessary to define some common words used in the pharmaceutical industry. Most common are the words *clean, sanitary* and *sterile.*

Clean means free from dirt, stain, impurities and generally unsoiled. This is the easiest level of cleaning to accomplish. It can be accomplished with water and solvent flush. Usually the condition of clean can be measured by visual inspection. Mechanical seals can be cleaned safely and easily will little need to anticipate damage to the seal's ability to properly perform.

Sanitary relates to health. To sanitize means to be made free from elements that endanger health. The word *sanitary* is often associated with the words *asepsis* and *hygienic*. This means that all harmful living organisms have been killed or removed to a degree that the remaining organism cannot produce disease or sickness. A state of sanitary cleanliness is more difficult to obtain in a mechanical seal.

To become sanitary, the seal must be cleaned in a manner that assures that harmful organisms have been purged from all surfaces, cracks, pools and reservoirs that naturally exist in mechanical seals. Some of the methods used to produce a sanitary condition in a mechanical seal can cause damage to the sealing surfaces or the materials from which the seal is made. The seal designer must take care to understand the cleaning method to be used and thus design the seal configuration and materials to tolerate those conditions.

Sterilization is the most difficult level of cleaning to obtain. To be sterile is to be free of living organisms. It is difficult to establish and maintain a certifiable state of sterilization for the same reason that the state of sanitary cleanliness is difficult to obtain; there are many cracks and crevices in a mechanical seal where organisms can hide. It is impossible to design a mechanical seal where all cracks and crevices have been designed out of the seal.

The method of sterilization is a more damaging process than the process used to obtain cleanliness or asepsis. During the design and selection of materials for the seal, it is essential that the designer be aware of the user's intent for sterilizing the mechanical seal. In this way the seal design may reflect the best selection of configuration and materials to tolerate the harsh steam sterilization.

A cleaning cycle will usually include the three following steps:

1. CIP fluid is sprayed around all contact surfaces using spray balls in the mixing vessel. The goal is for the stream of fluid to impact all surfaces to take advantage of fluid inertia scrubbing. Spraying is typically performed at elevated temperatures to accelerate the effectiveness of the CIP fluid. When spraying has been completed, the vessel will be drained as completely as possible.
2. Deionized water flush will then be sprayed into the vessel and the chemicals from CIP and loosened debris will be thoroughly washed away.
3. The vessel will be sealed and steam will be injected into the vessel. The vessel will be steamed until all surfaces reach a target temperature for a target time. This includes the mechanical seal. Additionally, it must be remembered that many users wish to concurrently SIP the seal barrier fluid area. They believe the "bugs" that might be left in the seal cavity will be forced across the inboard seal faces and into the vessel during operation.

Design Considerations for Mechanical Seals in the Pharmaceutical Industry

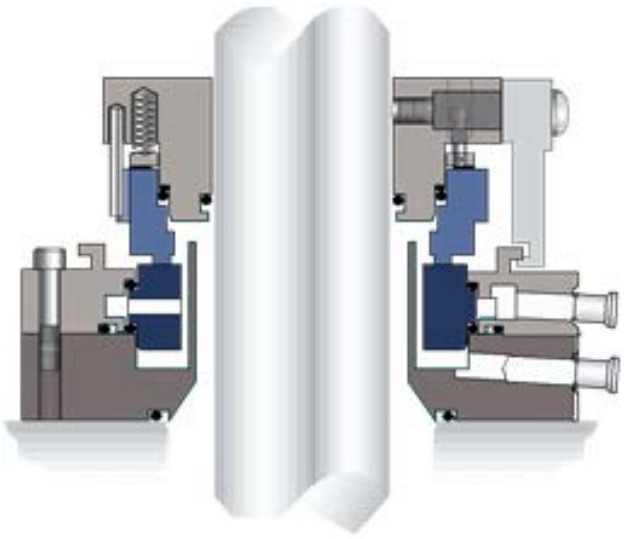
Whether cleaning, sanitizing or sterilizing equipment with mechanical seals, the design methods used to make the mechanical seal receptive and tolerant of cleaning are essential. There is a wide variety of opinions in the marketplace about which features are necessary for a properly designed mechanical seal. Because of this, it is important to understand the specific needs of the user and properly transmit those needs to the seal designer. A review of common design features used in seals within pharmaceutical applications immediately follows.

Debris Well

This device is also known as a *sanitary feature*, even though it has less to do with asepsis than with debris. The debris well is designed to catch wear particles from the sliding faces. The debris collects in the debris well. When the batch is finished, the debris may be swept from the area by ports arranged for flushing with water or steam. The ports are normally closed during operation. Ideally, there is a low-point port that is sloped down for complete drainability.

The debris well is common device, but many seals are designed without this feature. It is important to be specific about whether to include this feature in the design.

Figure 23: Single seal with sanitary flushing feature



Surface Finish

A fine surface finish is typically required on equipment where CIP and SIP occur. The surface finish requirement exceeds normal seal surface finishes. The very smooth surface resulting from hand and electro polishing aids in cleaning and sterilizing the equipment. Residue is more easily cleaned from a very smooth surface.

A machined surface finish of 63 Ra is easy to obtain on a metal lathe. Even a finer surface of 32 Ra is relatively easy obtaining when using good machining practices. However, obtaining the surface finish of 15–25 Ra, which covers 95% of the product contact surface requirements, demands extra steps.

To obtain a 20 Ra surface finish requires that very good machining methods be used. However, a machined surface will exhibit microscopic tears, rips and rolls of metal straight off a lathe — even when the surface finish appears to meet finish specifications! All mechanical polishing produces the same surface condition: ripping and tears in the metal.

Electro polishing will improve the finish. With the use of chemicals and electricity, slight amounts of material will be removed from the surface of the metal, making it microscopically smooth and featureless — and very difficult for biomass to cling to.

There is disagreement among pharmaceutical users as to what portion of the seal must be polished. It is important to determine the company's philosophy and pass that information on to the seal designer. It is also important to note that there are materials used in the mechanical seal that cannot be electro polished. Best efforts are made to provide the specified surface finishes when and where called for.

Sloping Surfaces

It is desirable for all surfaces that contact product or barrier fluid to be sloped. This increases the effectiveness of the CIP and SIP processes. This allows for faster and more complete drying and minimizes pooling of liquid in cracks and crevices.

Modified O-ring Grooves and Drainable Gaskets

O-ring grooves are a common location for pooling of liquid that cannot be easily flushed out or cleaned. When possible, O-ring grooves can be designed in a manner that minimizes the pooling area and exposes the O-rings and grooves to cleaning fluids, sterilization and draining. This feature is a compromise of design characteristics, and the seal designer uses this feature only if the feature is requested.

Seal Designs

Flowserve offers a complete range of single, dual, dry contacting, dry non-contacting and liquid lubricated seals that may be used in the pharmaceutical industry. Further, Flowserve has developed relationships and alliances with major equipment OEMs that produce custom equipment for the pharmaceutical industry.

Flowserve currently designs and provides seals for mixers, filter dryers, centrifuges, media mills, rotary filters, rotary dryers, conical dryers, choppers and various other specialty equipment. OEM names such as Pfaudler, Lightnin, Pro-Quip, Rosendmund, Cogium and Carr are among the OEMs that Flowserve serves every day. Applications encountered are water filtration, fermentation, separation, homogenization, evaporation, bio-waste, WFI, slurries and powders.

The following seals may be purchased as standard offerings. However, they may be customized with any of the previously mentioned modifications to make them more pharmaceutical appropriate and fit the specific needs of the user.

M-Series

The standard M-Series of double mechanical seals are built on a chassis that allows the conversion from one design philosophy to another. There are three distinct designs within this family of seals: a liquid lubricated, a dry contacting and a dry non-contacting seal.

MW-200

Double wet seal requires a liquid barrier fluid.

Barrier pressure: up to 500 psi (35 bar)
Temperature: -40°C to 260°C (-40°F to 500°F)
Speed: 0–225 RPM

MD-200

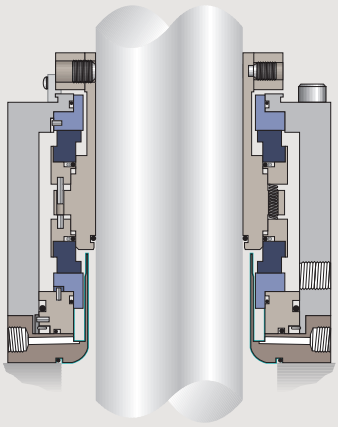
Double dry contacting seal requires gaseous pressurized barrier fluid.

Barrier pressure: up to 125 psi (8.6 bar)
Temperature: -40°C to 150°C (-40°F to 300°F)
Speed: 0–225 RPM

ML-200

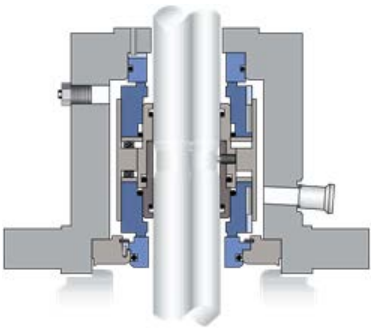
Double dry non-contacting seal requires pressurized gas barrier fluid.

Barrier pressure: up to 150 psi (10.3 bar)
Temperature: -40°C to 260°C (-40°F to 500°F)
Speed: 0–500 RPM



QBW
Double dry contacting component seal requires pressurized gas barrier fluid.

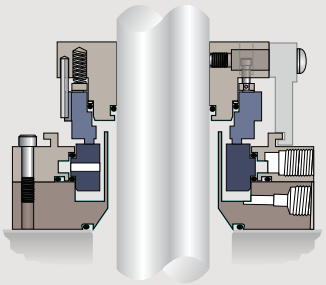
Barrier pressure: up to 125 psi (8.6 bar)
Temperature: -40°C to 150°C (-40°F to 300°F)
Speed: 0–225 RPM



Other seal designs:

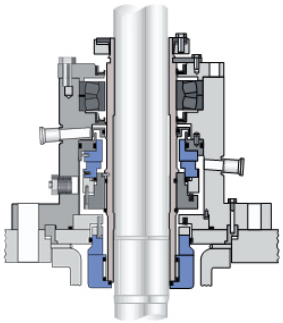
Single VRA
Dry contacting seal

Pressure: up to 200 psi (13.8 bar)
Temperature: -40°C to 121°C (-40°F to 250°F)
Speed: 0–350 RPM



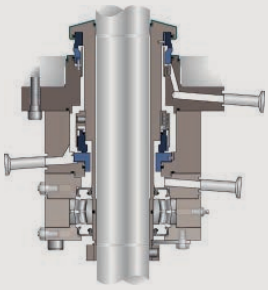
MixerPac 2570
DIN double non-contacting requires pressurized gas barrier.

Pressure: up to 125 psi (8.6 bar)
Temperature: -25°C to 120°C (-13°F to 250°F)
Speed: 0–400 RPM



ST
Double wet mechanical seal specifically designed for bottom-entry vessels in biopharmaceutical applications.

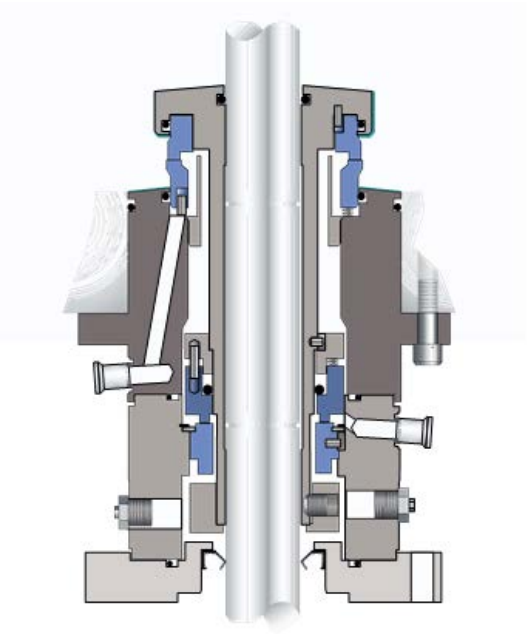
Barrier pressure: up to 88 psi (6 bar)
Temperature: -25°C to 200°C (-13°F to 392°F)
Speed: 0–1000 RPM



The following options are available to turn standard sealing products into a custom pharmaceutical seal. Not all options are available to all seal types. Consult Flowserve for details.

1. Certifications for materials and finishes
2. Surface finish enhancement for wetted areas of the seal
3. Sloped surfaces for enhanced drainage
4. Electro polishing for wetted surfaces
5. Passivation for wetted surfaces
6. Special face material combinations
7. Sanitary fittings with BPE-compliant attachment to the seal cartridge
8. Bearing may be requested for the cartridge assembly
9. Bearing grease may be specified by customer
10. Special O-ring lubricant may be specified by customer

Figure 24: Customized seal for pharmaceutical

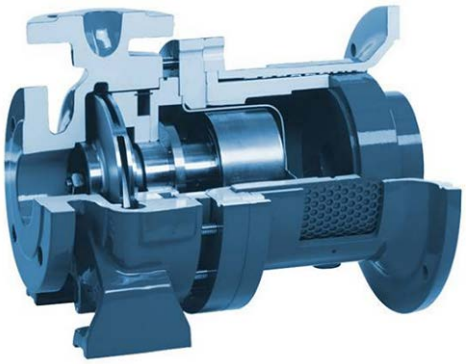


Magnetic Pump Couplings

Magnetic driven/coupled pumps are used quite often in the pharmaceutical industry. It is a good alternative for mechanical seals. The magnetic coupling of Flowserve SIHI has some unique features and benefits:

- Due to an integrated pumping device in the magnetic coupling, the flows of the coolant and lubrication through the magnets are independent from the discharge pressure. This will ensure constant cooling and lubrication, even at the end of the performance curve when the discharge pressure is low.
- The coupling has an integrated filter built in at the back plate of the pump. Due to the small vibrations and liquid velocity, the filter will never contaminate.
- The isolation can is available in two materials: HASTELLOY C4 or zirconium. The latter has the advantages of no eddy current losses and no temperature increase of the fluid in the coupling.
- Magnets withstand temperatures up to 350°C (660°F).
- Sleeve bearings are made of silcar, and special adaption rings are installed to compensate the dilation differences from stainless steel and silcar.

Pump with magnetic coupling



COMMUNICATING OUR VALUE

Mechanical Seals

Flowserve	Proposal	Customer Benefit
Product Range	Only company in the world supplying liquid and vacuum pumps.	One-house shopping.
Experience	Flowserve process knowledge will help customer to make best choice.	Best solution and most efficient.
Superior Products	Flowserve offers products with the latest technology with highest MTBF.	Lowest operating cost. At site repair to reduce downtime of production.
After-Sales Support	Flowserve has the highest density of QRCs centres and well-trained service engineers.	Inventory reduction. Teleservice.

Innovative Ways Flowserve Addresses Customer Challenges

Expertise and Experience	• Flowserve offers years of experience in chemical pharmaceutical applications involving sanitary processes with high-pressure, vacuum and high-temperature reactionary applications. • Difficult high-temperature applications under vacuum are always a challenge that Flowserve products can meet head on. • Specialist "Virtual Centers of Excellence," including the design and servicing of sanitary process components for pharmaceutical plants, ensure that expertise acquired over multiple products and manufacturing silos is shared across the global Flowserve organization.
Single-Source Provider	• Flowserve offers a compelling proven list of sanitary valves and seals for the active pharmaceutical ingredients (API) manufactured. • Flowserve offers a full range of chemical pumps to handle the feedstock raw materials as well as the clean-in-place (CIP) chemicals used in keeping the processes pure. • Global commercial operations organization ensures knowledgeable and professional reviews and responses to customers' RFQs, including those with the most complicated and technical API stringent application requirements.
Streamlined Execution	• When reliability and life are necessary to meet the need of completing a process campaign of critical API products, Flowserve is there to meet that need with the right products applied from a long history of experience in chemical pharmaceutical applications. • Where projects involve multiple Flowserve manufacturing and engineering locations, global project managers familiar with API's stringent requirements can be provided to coordinate order fulfillment. This ensures the manufacturing tolerances are met and the critical aspects of design are properly handled.
Local Support Worldwide	• Flowserve's globally located and experienced application engineers who understand the critical needs of the API industry afford our customers a feeling of confidence — no matter where they are located around the world. • A large field service organization ensures technicians are available for installation, commissioning and troubleshooting without delay. • Customers with a close working relationship with Flowserve often experience the benefits of on-site application engineers specifically provided to meet their immediate needs. • A global network of Flowserve Quick Response Centers (QRCs) means that local service and repair are always available. • Product upgrades to meet the stringent operating conditions within an API facility improve the performance, reliability and sterility of Flowserve products in pharmaceutical operations. • Full operation and maintenance training is available to end users. • Equipment monitoring programs are also available.
Optimized Efficiency	• When reliability and life are necessary to meet the need of completing a process campaign of critical API biological pharmaceutical products, Flowserve is there with the right products and support applied from a long history of experience in bio-pharmaceutical applications. • Flowserve offers years of experience in bio-pharmaceutical applications involving sanitary processes with high-pressure, vacuum and high-temperature cultivation conditions. Difficult high-temperature applications under vacuum are always a challenge that Flowserve products can meet head on.

APPENDIX

Acronyms

TERM	DEFINITION
API	active pharmaceutical ingredient
BPE	bioprocessing equipment certification
CAGR	compound annual growth rate
CIP	clean-in-place
COP	clean-out-of-place
EPR	ethylene propylene rubber
OTC	over-the-counter
PTFE	polytetrafluoroethylene
QRC	Quick Response Center
SAM	served available market
SIP	sterilize/steam-in-place
TAM	total available market
TCM	traditional Chinese medicine

North America

Latin America

Europe

Middle East

Africa

Asia-Pacific

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Experience In Motion