Market Overview

The global pharmaceuticals market was worth $934.8 billion in 2017 and was expected to reach $1170 billion in 2021, growing at 5.8%, according to a recent pharma market research report. At this point there is no accurate data on the impact of Covid on this

The factors that affect the pharmaceutical market size include disease prevalence, drug affordability, consumer attitudes, government policies and some supply-side factors:

- Disease prevalence is related to population size, age, genetic inheritance and behaviour
- Affordability is related to income but also to drug prices.
- Consumer attitudes include willingness to use alternative therapies or distrust of taking drugs.
- Government policies include regulation, which can be a significant barrier to the launch of new treatments.
- A major supply-side factor is availability of an appropriate treatment, which may be a matter of quantity, as in an epidemic, or of drug discovery and development.

Current and ongoing changes in political, economic, social, technological, legal and environmental factors are influencing growth in the healthcare market, where drugs play an important part. The following factors are all boosting healthcare market growth:

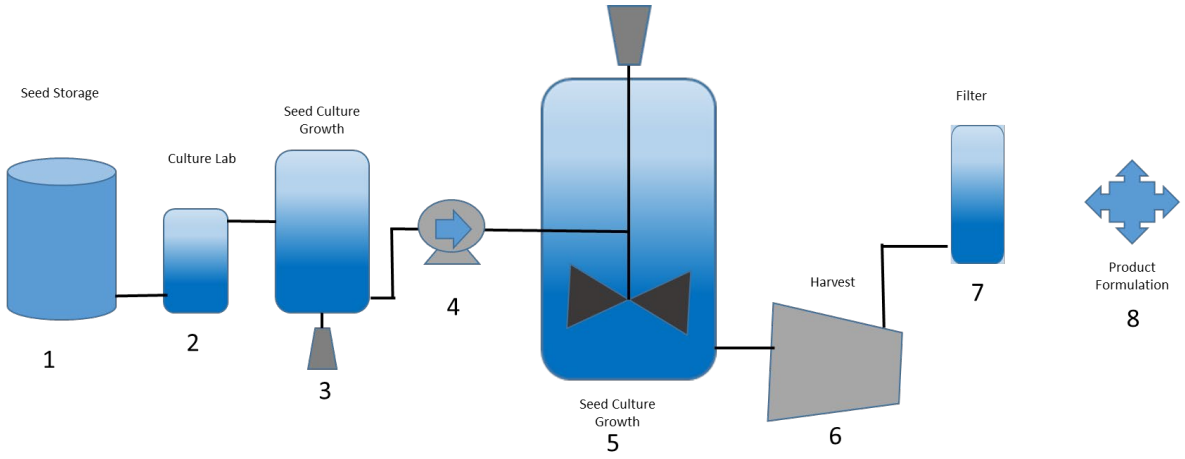
- Reduced taxes and lowered drug prices in the USA
- GDP growth of over 6% in China and India
- Widespread population aging and sedentary lifestyles leading to increased chronic disease prevalence
- Industrialized data services in R&D enabling the use of clinical trial data in trial simulations
- Lowered regulatory barriers for new drugs in the USA
- High urban pollution levels increasing the incidence of conditions like asthma

Growth over past decades means that North America and Western Europe still account for 56% of the global market, but Asia Pacific has overtaken Western Europe as the second largest region. Growth in Asia Pacific is fuelled by increased affordability of drugs resulting from the launch of low-priced generics. Other factors that are positive for growth in Asia Pacific are the rise of GDP per capita in the region, government programs to support healthcare, and rapid urbanization, which brings both doctors and pharmacies within easy reach of increasing proportions of growing populations.

Pharmaceutical Process

Biological Process/ Plant

Sealing duties for bioprocessing plants are not demanding and are within the capabilities of low technology seals. However, as process fluids contain living organisms, caution must be exercised with these applications. Seal design and manufacturing techniques for these seals are not the same as for a standard seal.



Step 1: SEED STORAGE

Storage in secure and sterile environment.

Step 2: CELL CULTURE LAB

Seeds are mixed with a liquid growth medium.

Step 3: SEED CULTURE GROWTH

Vessel is a well-defined sterile boundary which must be maintained during processing. A seal that does not need to be removed between batches and is capable of CIP (Clean-In-Place) chemicals and SIP (Sterilise-In-Place) is recommended

Step 4: TRANSFER PUMP

Small sanitary pump that can be effectively cleaned and sterilised with CIP and SIP procedures.

Step 5: SEED CULTURE GROWTH

Vessel to accommodate cell multiplication, oxygen and nutrients are added to maximize cell growth. Seal solutions dependant on whether a top or bottom entry vessel.

Step 6: HARVEST

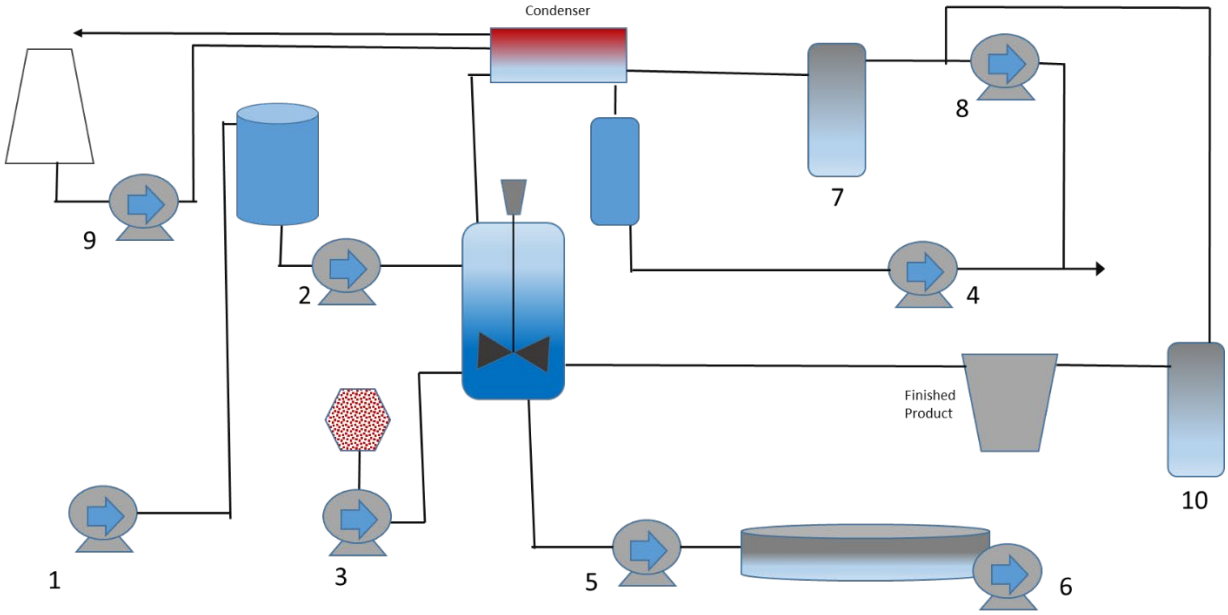
Commonly by centrifuge

Step 7: FILTER/DRYER

Preparation for final processes, each drying tunnel has huge vacuum pumps.

Step 8: FINAL PRODUCT PREPARATION

Chemical Process/ Plant



1: Off-Loading Pumps

Unloading base chemicals, (acids, caustic etc)
Mostly single-stage centrifugal pumps with a single mechanical seal.

2: Charging Pumps

Each base chemical has a charging pump to fill the distillation column as required.
Mostly single-stage centrifugal pumps typically with a single mechanical seal.

Step 3: Thermal Media Pumps

Depending on the process, the agitator tank must be heated or cooled. Normally a single pump is used for both processes so it must be able to can withstand a thermal shock of 150–200°C. 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.

The primary circuit uses mostly single-stage centrifugal pumps equipped with a mechanical seal which must be suitable for both high and low temperatures

Pumps for the secondary circuit are normally much smaller. These pumps are used for heating and cooling of the distillation or reaction vessel and are likely to be a vertical inline pump.

Step 4: Solvent Condensate Recovery Pumps

Vapours from the distillation column are condensed and drained to the condensate tank.
Pumps equipped with a standard mechanical seal and able to meet the specifications of low NPSHR and a steep performance curve.

Step 5: Column Bottoms Pumps

Depending upon the manufacturing process, drain pumps may be dirty liquid pumps for removing effluent waste or hygienic pumps to transport the active ingredient slurry
CIP pumps are normally preferred, cleaning normally being carried out using a mild acid.

Step 6: Effluent Handling Pumps

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

Step 7: Vacuum Pump on Distillation Column

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: Vapour Recovery or Cleaning

Due to emission laws, extracted vapours must be cleaned before they enter the atmosphere.

Step 9: Cooling Water Pumps

These pumps cool the water supply for the complete plant, normally standard sealed centrifugal pumps.

Step 10: Vacuum Drying Pumps

Once the final product is ready, it is pumped from the distillation column into an agitated dryer. Generally there is a vacuum pump installed at the top of the mixture to dry the finished product.

Equipment Used in Pharmaceutical Processes

Design Considerations for Mechanical Seals in the Pharmaceutical Industry

Design of mechanical seals and sealing systems for pharmaceutical applications require two important considerations

- Prevention of contamination
- Cleanability and sterilisation

Contamination needs to be considered from two aspects

- Contamination of the pumped products must be avoided.
- Process fluids and substances may be highly hazardous to personnel and/ or the environment.

The capability of thoroughly cleaning/ sterilising equipment, without the requirement to completely dismantle pumps and other machines, is important for operational efficiency and safety.

Both seal design and materials must therefore be conducive to in-place cleaning (CIP) or sterilisation (SIP) and tolerant of processes and chemicals used for cleaning (see section below). General criteria for seal design include

- Avoidance of 'dead' areas where cleaning may be incomplete
- Smooth surfaces with low roughness values, especially when in contact with the process fluid
- Avoid the presence of screw threads in contact with the product
- Smoother and rounded corners and edges
- Scratch resistant surfaces
- Self-draining
- Materials that will not be damaged by cleaning processes

Opinions vary about what design features are important for seals in pharmaceutical applications. It is not the intention of this document to specify what features are important and which less so.

Design features that are commonly used in seals for pharmaceutical applications are summarised below.

Dead Areas - Avoidance

It is important in seal design that cleaning and sterilization media is able to fully drain and there are no dead ended areas where it can accumulate. Failure to ensure complete draining is a source of contamination of the product.

Design methodology includes ensuring that bores for pins and springs are drilled through.

In some equipment the seal chamber becomes an unavoidable dead space in which cleaning or sterilization media can accumulate. In such cases it might be necessary to slowly rotate the seal during cleaning or sterilization.

Debris Well (Wear trap)

The debris well is used on single seals and is designed to catch wear particles from the seals' sliding faces. During normal operation debris collects in the wear trap, once the batch is complete water or steam can be flushed through ports to clear the debris from the area. Ideally, there is a low-point port that is sloped down for complete draining. The ports are normally closed during operation.

Debris wells are often designed as a concentric labyrinth between seal and flange

Materials

Seal components can be the cause of contamination, this can be alleviated by selection of an appropriate seal type and seal face materials. The characteristics required of the seal materials are determined by the respective application and specifications of the plant operator.

The pharmaceutical industry identifies a basic distinction between metallic and non-metallic materials. Metallic materials such as 316L or higher quality stainless steels can be generally used as standard, non-metallic materials must be identified as suitable by means of associated compliance documentation.

Materials selected must also be resistant to cleaning and sterilization media.

Modified O-ring Grooves and Drainable Gaskets

O-ring grooves are an essential feature in any mechanical seal design but these, along with threads and metal-to-metal surfaces can create dead, hard to clean areas in the seal. Where such features cannot be avoided in the seal design they must be designed to be easy to clean.

O-ring grooves can be designed to expose the O-rings and grooves to cleaning fluids, sterilization and draining. The design challenge is to ensure functionality and minimise extrusion risk at all operating conditions. Opening the groove is a simple design measure making it easier for cleaning agents or steam to reach the critical points, but this feature is a compromise of design characteristics and the seal designer may seek to use alternative arrangements. This may mean the use of moulded components that completely fill the groove and so minimize the creation of dead spaces.

Surface Finish of Components

Component surfaces are an important consideration for the cleanability of equipment. A fine surface finish is typically required on equipment where CIP and SIP occur. Surface finish requirements typically exceed normal seal surface finishes and the very smooth surface resulting from hand and electro polishing may be required. There is disagreement among pharmaceutical users as to what portion of the seal must be polished so it is important to determine the company's philosophy prior to seal design.

It is important to note that there are materials used in mechanical seal construction that cannot be electro polished. In such cases the closest surface finish achievable should be targeted.

Good machining practice can produce surface roughness values of 0.8 µm (32 µin) Ra and this may be considered suitable for an 'easy to clean' surface. However, obtaining a surface finish of 0.5 (20) Ra, which will satisfy around 95% of the product contact surface requirements, demands extra steps.

To obtain a 0.5 (20) Ra surface finish requires that very good machining methods be used but a machined surface will suffer microscopic machining damage even when the surface finish appears to meet finish specifications. Electro polishing, using the action of chemicals and electricity, will improve the finish, making it microscopically smooth and featureless and very difficult for biomass to cling to.

Sloping Surfaces

Ideally, all surfaces that contact process or barrier fluid should be designed to be sloped. This increases the effectiveness of the CIP and SIP processes and allows for faster and more complete drying.

Clean in Place (CIP) and Sterilise in Place (SIP)

Early designs of seals used in bioprocessing had many areas where organisms could lodge and reproduce. They were considered Clean-Out-of-Place (COP) seals requiring removal, cleaning and sterilisation between batches.

A seal that can be reliably cleaned and sterilised between batches without removal is an economic advantage both in terms of time and labour, minimising equipment downtime.

The pharmaceutical industry defines levels of 'clean' as clean, sanitary and sterile.

- Clean is the easiest level of cleaning to accomplish meaning free from dirt, stain and impurities. This. It can be accomplished with water and solvent flush and can usually be measured by visual inspection.
- Sanitary is harder to achieve and means to be made free from elements that endanger health and is often associated with the words asepsis and hygienic. This means that all harmful living organisms have been eliminated to a degree that the remaining organism cannot produce disease or sickness. To become sanitary harmful organisms must have been purged from all surfaces, cracks, pools and reservoirs that naturally exist in mechanical seals. Some of the methods used to produce sanitary conditions can cause damage to the sealing surfaces or the materials and so the seal design, configuration and materials must tolerant to those methods.
- Sterilisation is the most difficult level of cleaning to obtain and requires elimination of all living organisms. As with achieving sanitary cleanliness it is difficult to achieve due to the many cracks and crevices in a mechanical seal where organisms can hide. The sterilisation process is, potentially, more damaging than the clean and sanitary processes undertaken and the seal design, configuration and materials must tolerate the harsh steam sterilisation.

Cleaning and sterilisation create operational conditions that must be considered when selecting a mechanical seal.

- CIP processes utilise a variety of chemicals, typically, mild acids or caustics at temperatures of approximately 80°C (176°F), which will be in contact with the mechanical seal. Seal materials must be capable of tolerating those chemicals and temperatures.
- SIP processes expose to the seal to steam at temperatures of approximately 131°C (278°F) and for a designated period of time to achieve a specific target temperature of boundary surfaces. Seal designers must take note that it has become very common to introduce steam into the double seal cavity for sterilization.

Seal Designs

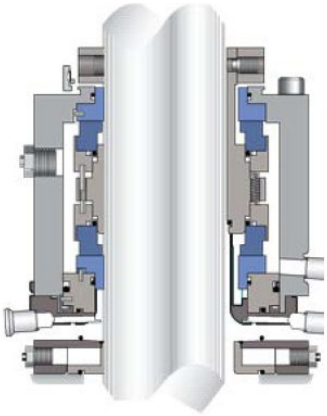
Single seals – liquid lubricated

Standard single seal design utilises differing face materials, typically a combination of a hard ceramic (such as silicon carbide) running against a softer carbon graphite material. This pairing gives excellent running properties and resilience to some dry running but can be responsible for the formation of very small levels of carbon dust. To prevent the risk of contamination by carbon dust an alternative silicon carbide/ silicon carbide face pairing can be used.

Single seals – Dry Running

Dry-running seals are mainly used in mixers and agitators. Some abrasion will occur but on seal types designed for dry running this will be minimal and not, normally, considered a problem. Wear is highly influenced by face load and sliding velocity, with operating pressures up to 6 bar and sliding

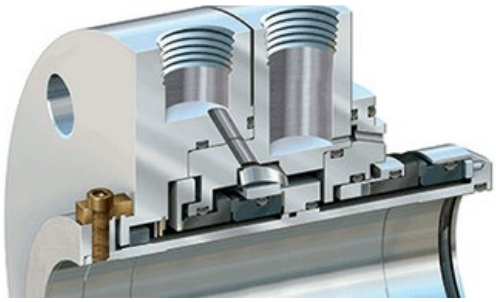
velocities up to 2 m/s, wear values are generally low and not all of the abrasion will get into the product, some remains in the seal.



Dual seals

Dual seals are an alternative to single seals. These seals operate with a buffer/ barrier fluid of liquid or a gas. Pressurised dual (double) seals operate with a barrier fluid i.e. at a pressure greater that the process fluid. The advantage of dual pressurised seals is that the process fluid cannot escape to atmosphere however, very small amounts of the barrier medium can enter the product. The barrier fluid selected must therefore be selected to be fully compatible with the process fluid to prevent process contamination. Bacterial contamination of the barrier fluid must also be excluded and the supply system itself must also be cleaned/ sterilized when required contamination of the process by carbon graphite wear can be eliminated by use of silicon carbide face pairs.

If contamination of the process by barrier fluid cannot be tolerated then un-pressurised dual (tandem) seals can be used. In this case seals operate with a buffer fluid, i.e. one at a lower pressure than the process fluid. However, this seal design will cause some contamination of the buffer fluid by the process with the potential of very small leaks of process into the atmosphere. Controlled venting of seal leakage may be required and dual unpressurised seals are not suitable for critical media. Seals and support system will require periodic cleaning/ sterilisation.



Prevention of process by barrier fluid and carbon wear debris can be prevented by use of gas-lubricated mechanical seals. This seal type operates with non-contacting faces with a ‘lift off’ effect created by patterns machined into the seal running faces. The barrier fluid often used in gas-lubricated seals is normally nitrogen (generally already used in most processes and classified as non-contaminating). The seal support system is generally simpler and more cost-effective than for a liquid barrier fluid.

Standards and Regulations

The **FDA 21 CFR 177** standard lists non-metallic materials that meet the requirements for materials in hygienic applications. If materials from this list are used, it is relatively easy to demonstrate compliance. Some applications, however, require USP Class IV approval of the materials. To meet the requirements for compliance documentation, they must be tested by an external laboratory for extractable substances. Proof of biological reactivity may also be required.

U.S. Pharmacopeial Convention (USP) publishes bio compatibility protocols for the plastics and polymers used in medical devices or surgical equipment that may come in contact with human tissue.
USP Class VI refers to one of the six designations for plastics and provides guidelines for testing and certification of a material to be used within a medical device. It is considered the most stringent and, therefore, most useful for medical applications.
Materials must demonstrate an extremely low level of toxicity and will be subjected to several temperature assessments for set periods of time.

Pharmaceutical 3-A Sanitary/Hygienic Standards for Materials for Use in Process Equipment and Systems and sets hygienic design standards for manufacturing equipment in the food, beverage, and pharmaceutical industries. 3-A standards help Original Equipment Manufacturers (OEMs) achieve sanitary design. 3-A defines the design practices that should be used to manufacture pieces of equipment.

Regulation (EC) No 1935/2004 provides a harmonised legal EU framework. It sets out the general principles of safety and inertness for all Food Contact Materials (FCMs).
The principles set out in Regulation (EC) No 1935/2004 require that materials do not:
• Release their constituents into food at levels harmful to human health
• Change food composition, taste and odour in an unacceptable way

The **ASME Bioprocessing Equipment (BPE)** Standard provides the requirements applicable to the design of equipment used in the bioprocessing, pharmaceutical and personal-care products industries, as well as other applications with relatively high levels of hygienic requirements. It covers materials, design, fabrication, inspections, testing and certification. It incorporates current best-practices for enhancing product purity and safety.