How to Specify Equipment for High-Purity Processes

Choosing the right combination of pumps, valves and seals is a crucial step in the design of fluid motion and control systems for the pharmaceutical and biotech processing industries.

By Donald T. Weeks and Thomas M. Bennett at Flowserve Corporation

Donald T. Weeks is a Product Manager for Flowserve Flow Control (Cookeville, TN, USA). He is responsible for sales, marketing and product development of quality high-purity valves and automation products. Mr Weeks holds a degree in Business Management from Champlain College (Burlington, VT, USA).

Thomas M. Bennett is the Marketing Manager for Flowserve Flow Solutions (Kalamazoo, MI, USA), where he works to advance mechanical sealing solutions in industries from pharmaceuticals and specialty chemicals to pulp and paper. He holds a BS degree in Biology from Adrian College (Adrian, MI, USA) and an MA in Management from Nazareth College (Rochester, NY, USA). In his 25 years in the field, Mr Bennett has experienced a wealth of applications and faced many unique challenges while providing flow solutions to companies around the world.

Specifying the proper equipment and ensuring that this equipment works together in an efficient system can yield virtually contamination-free operation in high-purity processes. Coupling the right system of pumps, valves and seals with highly trained plant personnel will ensure successful operation for applications that demand the highest levels of purity and safety.

In the pharmaceutical, biotech and food processing industries, ingredients are transported, mixed, heated and cooled assuming the assurance of product purity required by law and taken for granted by consumers. Process systems for these industries require a level of purity not found in other applications, so implementing the right systems of pumps, valves and seals is vital.

The problems linked to high-purity processes can all be traced back to one root cause: contamination. Any ‘dead cavities,’ corners, seams or obstructions that exist in processing equipment could produce potential areas for bacterial growth. For example, a poor surface finish contains microscopic peaks and valleys that can lead to unnatural biofilm build-up – the formation of a thin layer of surface bacteria. Also, leakage causes improper mixtures of ingredients, which allows unwanted chemicals to violate the system. Other potential problems include rusting, particle generation and oil and grease contamination.

High-purity equipment must stand up to harsh cleaning procedures – from heated steam to caustic sodas and light acids – without compromising either the integrity of the product or the equipment itself. Surface finish must be tightly controlled, and dead cavities must be limited so that the flow of the cleaning agent can reach all parts of the system. This process makes cleaning procedures more effective.

SPECIFY PUMPS WITH POLYMERS FOR CLEAN OPERATION

The key to the design and selection of pumps for high-purity process applications is the ability to withstand high temperatures, high pressures and corrosive liquids, while maintaining clean operation and minimizing contamination. Pumps are available in a variety of shapes, sizes and configurations, but certain factors must remain constant for any high-purity application.

All wetted surfaces that come into direct contact with the flow of a high-purity pump must be manufactured from materials that will not corrode, rust or generate particles during severe treatment with superheated steam or other harsh chemicals. Pumps that are constructed (or lined) with PFA (perfluoro-alkoxyalkane) or PTFE (polytetrafluoroethylene) polymers have a higher resistance to corrosion, lower reactivity and better surface finish properties than pumps designed using metal alloys or glass. Studies show that accumulated normal biofilm build-up is far easier to remove from these materials than from stainless steel or other alloys. Polymers do not rust, offer very low particle generation, and are inherently pure without the need for refining steps (that is, electropolishing and passivation) that other materials require. Since the introduction of the first fully lined PTFE chemical process pump in 1968, polymers continue to provide the safest, most cost-effective solutions for pump materials.

SELECT THE RIGHT VALVE TYPE

The first step in choosing a valve for a high-purity application is to select the right valve type. Diaphragm valves are by far the most common design of choice for high-purity industries; their geometry does not trap
Innovations in Pharmaceutical Technology

under conditions of high-vacuum and high-cycle operation. Tight shut-off through the valve without corrosion, even if no flow occurs, they can harbour microorganisms and provide a starting point for biofilm build-up. Seats should be specified to ensure valve integrity. Cast materials are more apt to have exposed pits, inclusions and other imperfections as their surface finish deteriorates over time.

Valve end connections – called pipe ends or tube ends – should be specified with a sulphur content of between 0.005 and 0.017 per cent to meet American Society of Mechanical Engineers (ASME) Guidelines and allow for clean, contamination-free welds for tube bore systems, where all valves are welded in place. The concentration of ferrite should be less than 5 per cent to prevent an iron film from forming (rouging) on stainless steel surfaces in high-purity water and steam systems. Some companies recommend less than one per cent ferrite concentration, but this issue is still up for debate. Many studies are showing that rouging is more closely linked to metal preparation and content of gas atmosphere in the system than to ferrite concentration.

Surface finishes need to be tightly controlled on all wetted surfaces of the valve through procedures such as electropolishing and passivation. Electropolishing is a method of passing DC current (approximately five amps) through the metal, causing the high points of the machined surfaces to be chemically removed. Passivation is a chemical process used to form iron oxides and chromium oxides on the surface of the metal to promote chemical resistance to water or other products. For high-purity processes, valves that have surface finishes with an Ra of no more than 20 micro-inches AARH (arithmetic average roughness height) minimise biofilm build-up, while electropolishing can reduce the Ra to fewer than 10 micro-inches. However, electropolishing is more expensive and not always required for every application.

Inside diameters of the valve components should be chosen with tube bore dimensions that precisely match the connecting tubing so as to prevent stagnant areas of water, or ‘puddles’, from forming in the valve. If these puddles occur, they can harbour microorganisms and provide a starting point for biofilm build-up. Seats should be specified as PTFE, reinforced PTFE or Fluorocel to ensure bubble-tight shut-off through the valve without corrosion, even under conditions of high-vacuum and high-cycle operation.

When installing a valve, one must ensure that it will not introduce any new contaminants into the system due to manufacturing, transportation or final installation. To prevent this, valves should be assembled in positive-pressure clean rooms, tested with helium, double-bagged and sealed to ensure the highest level of cleanliness.

PRE-TEST SEALS TO ENSURE HIGH PURITY

When Regeneron Pharmaceuticals, Inc purchased a new mammalian bioreactor skid (a vessel used for biological growth and reactions), the company had the same high expectations that surround any major process improvement. However, Regeneron ran into some problems when the design of the OEM (original equipment manufacturer) bottom-entry agitator seal failed to meet the sterilisation requirement for the process. The sterilisation of the interior vessel bore was essential, but the inner seal was allowing vapour to enter. The result: seal integrity was compromised.

To solve this problem, Regeneron installed a custom dual mechanical seal with a secondary sealing device that would ensure sterilisation of the interior vessel. A customised model of a dual cartridge seal was successfully designed that mounted directly to the gearbox and bioreactor’s mounting pad. This model maintained absolute containment of the clean steam condensate during each phase of production.

These examples demonstrate the importance of choosing the right seals when purity and sterilisation are crucial. Seals with gland rings that do not need to be threaded or ported minimise areas for bacteria to hide. Any threads or sharp corners can create cavities that cannot be reached by the cleaning procedures used by major processing plants. Implementing electropolishing and passivation on all wetted surfaces of the seal makes it much easier to prevent bacterial growth and carry-over that might occur down the line.

Pre-testing helps to maintain the integrity of the seals for sterile operation. For example, a large pharmaceutical company in Chicago tests small, one-inch seals in a laboratory with bacteria, ensuring that the seals are compliant with their purity standards before they are put into operation.

Some seals are manufactured with complete cartridges that can be aerostatically pressure-tested to ensure integrity before installation. These types of preliminary testing methods ensure that no defects or contamination occur between manufacturing and final installation.

It is important to keep in mind that safety and sterilisation are not the only concerns for seals in high-purity processes. Certain consumer products have aesthetic characteristics that are familiar to the consumer, such as the white colour of aspirin tablets. A seal used in the production of aspirin may have a soft carbon face rubbing on a hard
Innovations in Pharmaceutical Technology

Conform to ASME bioprocessing equipment (BPE) with US FDA regulations. Applications, pumps, valves and seals should also comply with Standardization (ISO). In the case of pharmaceutical equipment specified for clean operation must be chosen to meet certain standards set forth by organisations such as ANSI and the International Organization for Standardization. Pump, valve and seal manufacturers should be chosen that include simplified codes on each piece of equipment with four critical traceability requirements that are easily read and cross-referenced by an inspector to save time and money on exhaustive paperwork.

These standards and validation requirements aim to increase the efficiency of the development, manufacturing and supply of products and services while maintaining safety for consumers. Different standards exist for various applications, and it is always a good idea to consult an expert when choosing equipment to meet these regulations.

**COMPLEMENT TRAINING WITH EXPERIENCED PERSONNEL**

Once a system of pumps, valves and seals is specified, one critical question still remains: Who will install, operate and perform the maintenance on this equipment? No processing plant can meet and exceed these heightened standards and increase the efficiency of the development, manufacturing and supply of products and services while maintaining safety for consumers. Different standards exist for various applications, and it is always a good idea to consult an expert when choosing equipment to meet these regulations.

**SET UP CLEANING SYSTEMS**

No matter how well the equipment works, the inevitable build-up of bacteria and other contaminants in any system is unavoidable. High-purity systems use batch processing and specialized cleaning systems to combat this problem. During batch processing, a certain amount of product is created. Next, the entire system is cleaned with heated steam or light acids before production resumes. This process prevents any carry-over of dirt and bacteria between batches of product. Common cleaning systems include ‘steam in place’ (SIP) and ‘clean in place’ (CIP), where heated steam and light acids or caustic sodas are used to flush any contaminants out of the system.

CIP and SIP cleaning methods safeguard public safety by preventing cross-contamination and keeping purity to acceptable levels. They prevent batch losses and enable sterilisation-in-place by removing dirt deposits that impede mass transfer of steam to all wetted process surfaces. These cleaning methods can also protect capital investment in equipment by preventing the crevice corrosion that occurs when an impervious layer of dirt impedes maintenance of the passive metal oxide surface on stainless steel.

To ensure sterilisation, a typical cleaning cycle should include the following steps:

- Pre-rinse with cool saline solutions to reduce the dirt load
- Decontamination through steam or other caustic materials
- Intermediate rinse
- Acid-wash to solubilise precipitated materials
- Final rinse to remove all traces of cleaning agents

**KEEP YOUR EQUIPMENT UP TO CODE**

Equipment specified for clean operation must be chosen to conform to certain standards set forth by organisations such as the ASME, the American National Standards Institute (ANSI) and the International Organization for Standardization (ISO). In the case of pharmaceutical applications, pumps, valves and seals should also comply with US FDA regulations.

More specifically, clean valves should be specified to conform to ASME bioprocessing equipment (BPE) standards for metallurgy and should meet the specifications of USP Class 6 set by the US Pharmacopoeia for elastomers used in seat materials. The US Pharmacopoeia forms the basis of enforcement actions by the FDA. For high-purity seals, 3-A (a pharmaceutical standard organised by 3A Sanitary Standards, Inc) has become widely accepted.

High-purity systems also need to be validated, which can put a large administrative burden on companies to cross-reference all paperwork with certified material test reports (CMTRs) on key components of each piece of equipment. Pump, valve and seal manufacturers should be chosen that include simplified codes on each piece of equipment with four critical traceability requirements that are easily read and cross-referenced by an inspector to save time and money on exhaustive paperwork.

The authors can be contacted at dweeks@flowserve.com and sbennett@flowserve.com