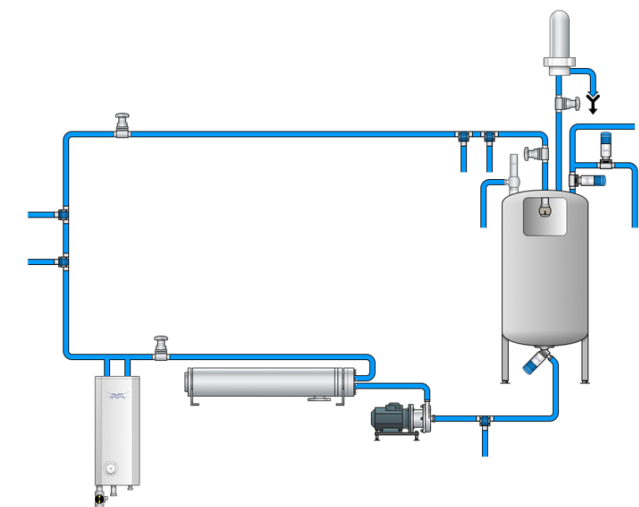


Ensuring reliable, consistent production in pharmaceutical water systems

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Pharmaceutical water systems ensure the safe, continuous and efficient operations of the pharmaceutical manufacturing facilities as well as the quality of the final end products. It is therefore critical to design pharmaceutical water systems to prevent conditions that compromise water quality by providing continuous recirculation at turbulent flows and no dead legs. It is also important that the equipment support Good Manufacturing Practice (GMP) and Good Documentation Practice (GDP) in terms of materials, surface finishes, welding joints, cleanability and documentation.

Selecting the right equipment is paramount to securing the delivery of high-quality water to the point-of-use at the required flow and temperature. Proper equipment design and quality can help address challenges involving potential contamination, rouge, energy use, and environmental emissions, as well as issues involving installation, validation, and maintenance.



Schematic process diagram for a pharmaceutical water system using Alfa Laval hygienic equipment

Rouge

Rouge involves the precipitation and spread of fine red-brown ferric oxide or hydroxide particles from the place of origin to associated systems. It can often be found in circulation pumps, diaphragm valves and inside tanks equipped with static spray balls. At hot temperatures or high flow rates, rouge may cause dark-coloured oxide films to build up. Unlike the more common red-brown particles, these dark-coloured films cannot be wiped away from the affected surfaces but require de-rouging to remove these metal oxides.

Concerns

It is important to point out that rouge often appears worse than it is. While rouge is undesirable, it does not result from corrosion and generally does not pose any health or safety risks. However, an excessive buildup of rouge particles poses the risk that the particles may detach and, if not properly filtered, may contaminate the end product. This may occur, for instance, if there are sudden pressure changes or mechanical shocks. This becomes a major concern particularly if such rouge occurs in water-for-injection (WFI) systems. Because rouge is insoluble in blood, injectable products containing rouge particles can cause clogging of the veins and/or arteries when injected into the blood stream.

Methods to reduce risk

While rouge cannot be avoided, it is possible to minimize the level of rouge. To reduce the risk of rouge, it is important to prevent or minimize damage to, or breakage of, the passive layer of the stainless steel surface. To maintain the structure and composition of this layer, it is important to select the right:

- **Construction material:** The use of high quality 316L stainless steel with a defined sulphur content is recommended as the primary construction material, especially for WFI systems. Selecting high-grade steel that is easy to weld and does not contribute to welding defects such as porosities or inclusions, such as manganese sulphide inclusions, is critical. Choosing an inferior grade of steel with an inferior surface finish poses the risk of corrosion or pitting, which consequently may lead to the destruction of the passive layer as well as to the formation of rouge.
- **Surface finish quality:** Equally important is a high surface finish quality. A poor surface finish is both difficult to clean – and to keep clean. If the surface is not properly cleaned, it is impossible to passivate the steel. A hygienically designed system that is free from dead legs, crevices and entrapment areas helps prevent the buildup of debris on surfaces.
- **Welding quality:** Improper welding procedures can cause cracking, trapping of fluid-borne impurities, and breaches in the passive layer of the stainless steel surface, all of which can lead to the formation of active-cell corrosion.
- **Operating temperature:** Studies show that higher the temperature, the faster the formation of rouge. At process temperatures above approximately 60°C, rouge formation begins to accelerate. The operating temperature should therefore be actively monitored and regulated through the use of a temperature transmitter and heat exchanger. The higher the level of hygienic

equipment, the lower the temperature requirement in hot water loops and the lower the frequency of sanitization required in the ambient water loops.

- **Cleaning and maintenance procedures:** It is important to select hygienic equipment that is designed for safe and easy cleaning without crevices, dead legs, pockets or difficult to clean areas. Choosing cleaning agents that do not contain aggressive acids is also recommended.

To minimize rouge, it is important to select highquality equipment that contributes to reliable and consistent production. Especially important is to ensure that the passive layer of equipment surfaces will not be compromised by welding defects, mechanical stress, elevated temperatures or other factors.

Biofilm buildup

Populations of live microorganisms as well as dead microbial cells can form a layer, or biofilm, on the surfaces of pharmaceutical water system equipment. This film also contains noncellular materials, such as mineral crystals, corrosion particles or silt particles. More than 99% of all microbial activity occurs in biofilm. Biofilm buildup poses contamination risks to pharmaceutical water systems. However, proper equipment and system design can reduce these risks.

Concerns

Unfortunately, there will always be a small amount of bacteria that will grow and multiply – even in the best pharmaceutical water systems. The degree of harm caused by such contaminants is difficult to predict due to variable factors, such as temperature, pH, velocity, stress and heat. Most water systems contain gram-negative bacteria with the outer membrane of the cell wall, which releases endotoxins when the bacteria are killed. If injected into the bloodstream, these endotoxins cause fever and, in the worst-case scenario, septic shock which can be fatal.

Methods to reduce risk

Minimizing the growth of gram-negative bacteria is the best way to reduce the risks associated with endotoxins. Pharmaceutical water systems must therefore operate at temperatures that prevent bacterial growth and undergo periodic sanitization. The water's pH value, concentration and content of organic nutrients also influence bacterial growth. A matrix of primarily polysaccharide material that constitutes the building blocks for the biofilm also provides nutrients to the bacteria. It is therefore critical not only to minimize the presence of nutrients by employing a fully closed system, but also to minimize biofilm buildup.

When setting forth the functional specifications (FS) and design specifications (DS) of pharmaceutical water systems, it is important to:

- Secure continuous recirculation to prevent stagnant water conditions that promote bacterial growth by choosing an efficient and fully reliable centrifugal pump.

- Secure sufficient velocity and high shear force in the system to prevent biofilm buildup.

- Design systems and select hygienic equipment without dead legs, crevices, pockets or difficult-to-clean areas where stagnation can occur. For instance:
 - Choose a circulation pump, which is designed for ease of cleaning, especially for cleaning the hard-to-reach back side of the impeller.
 - Choose a heat exchanger, which is designed to create turbulence and can be completely flushed of the existing water, and “new” water can replace the old.
 - Select diaphragm valves and other equipment designed without any dead legs.

- Include a visual inspection of product contact surfaces as part of routine maintenance procedures to ensure that surfaces are smooth and without imperfections or visible signs of rouge or other deterioration, which can lead to microbial colonization.



Alfa Laval DV-ST designed to reduce pressure drop, and without dead legs

Reducing energy use and carbon emissions

Because of the need for high temperatures and continuous circulation, hot water systems are energy-intensive. This, of course, leads to high costs and adversely affects emissions. It is therefore important to minimize energy consumption and emissions of pharmaceutical water systems.

Concern

There are several ways to reduce energy consumption and emissions. Reducing temperatures in a hot circulation loop from 90°C to between 65°C and 75°C saves energy, but can potentially increase the risk of bacterial growth in the system. It is therefore important to maintain a temperature that is sufficiently high to prevent bacterial growth, yet sufficiently low enough to provide cost savings. Hygienic systems are designed to have high velocity and turbulence. The more hygienic the system, the greater the possibility to reduce system temperatures that, in turn, leads to energy savings while safeguarding the quality of water.

Methods to reduce risk

Attention to detail pays off when selecting equipment for a distribution loop. Reducing energy use by selecting the right pumps, valves and heat exchangers can deliver energy savings.

Pumps: Because the circulation pump is in constant use, it is important to select a robust, reliable and energy-efficient pump. Be sure to size the pump correctly; oversizing the pump wastes energy.



Alfa Laval LKH UltraPure

Diaphragm valves: Choosing the right diaphragm valves for the distribution loop can also save energy and reduce emissions. Some of the largest valve manufacturers now offer a new generation of diaphragm valves with low pressure drops that provide up to twice the flow rate compared to traditional diaphragm valves. Another benefit of selecting diaphragm valves with low pressure drops is that it may be possible to reduce pipe diameters as well as the required pump capacity, which can lead to significant cost savings. Click [here](#) to calculate your potential energy savings. Furthermore, some valve manufacturers offer T and tank outlet valves made of forged material, with lower mass and weight, which require less energy to heat and less time to sterilize.

Heat exchangers: Both tubular and plate-type heat exchangers can be used in the distribution loop for heating and cooling. Compared to plate heat exchangers, shell-and-tube heat exchangers often have higher initial investment costs as well as higher energy usage and thereby higher operating costs due to high-pressure drops. Other maintenance costs for shell-and-tube heat exchangers, however, are generally lower than those of plate heat exchangers.



Alfa Laval Pharma-line shell & tube and point-of-use module

Safe and easy installation, validation and maintenance

Ensuring proper system installation, validation and maintenance is a business imperative for the pharmaceutical industry. Not only is it important to install and validate pharmaceutical water systems correctly, but it is also critical to maintain them in good working order.

Installation: It is important to ensure that all parts and equipment meet the design specifications. Safe and effective validation is businesscritical in the pharmaceutical industry.

Validation: Thorough and uniform equipment documentation helps secure that installation, validation and maintenance is handled in the right way. Pharmaceutical equipment manufacturers like Alfa Laval offers a comprehensive documentation package to ensure that pharmaceutical industry standards are met.

The Alfa Laval Q-doc documentation provides full transparency of all product contact parts, making all equipment for pharmaceutical water systems easy to validate thereby ensuring a smooth qualification and validation process.

Summary

To ensure reliable, consistent production in pharmaceutical water systems, it is critical to design the systems to minimize the risk of rouge and biofilm build-up, to reduce energy consumption and emissions, and to ease installation, validation and maintenance. This calls for employing the best practices to achieve systems that are both cost-effective and energy-efficient.

- Invest in hygienic design. No dead legs, crevices, pockets or other difficult to clean areas.
- Use high-grade stainless steel with good surface finish quality
- Maximize the shear force of the surface. Keep in mind that high flow rates generate a turbulent flow, which reduces the risk of biofilm.
- Try to maintain the temperatures of hot water systems at approximately 65°C to 75°C. Water above 65°C is generally recognized as selfsanitizing because most bacteria are killed at temperatures above 55°C. Lowering the temperature has two benefits: Decreased energy consumption and prolonged equipment lifetime.
- Make sure pharmaceutical water systems equipment is easy to install, validate and maintain. A comprehensive documentation package, such as the Alfa Q-doc package, makes it easy for inspectors to validate pharmaceutical water systems.



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With over a decade of experience in the biotech and pharmaceutical industries, Amir brings a wealth of knowledge to Alfa Laval. He is an active member of the International Society for Pharmaceutical Engineering (ISPE) and ASME BPE. Amir’s expertise is dedicated to optimizing production and validation processes for pharmaceutical manufacturers. He holds a Bachelor’s degree in Chemical Engineering and an MBA, and has completed the Food and Drug program in Lund, Sweden.

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About Alfa Laval

Alfa Laval is a leading global provider of specialized products and engineered solutions that help customers heat, cool, separate and transport products such as oil, water, chemicals, beverages, foodstuffs, starch and pharmaceuticals.



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