CAN PRESSURE REGULATORS REPLACE CONTROL VALVES IN BIOPROCESSING?

STERIFLOW

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The production of bio-pharmaceuticals is an extremely delicate bio-process and any change to that process that occurs too rapidly can potentially destroy a batch worth millions of dollars. Therefore, it is critical that any necessary adjustments to the process be performed under precise pressures and flow rates. The introduction of high-purity gases for a variety of reasons would be one such adjustment. Traditionally, these gases have been added using a control valve. However, control valves require air or electric power to operate, either internal or external sensing of the system being controlled and, in many cases, a complex distributed control system to adjust the control valve's positioner based on system response.

Is there a simpler solution? What are the differences between a control valve and a pressure regulator? What are processes or applications where a pressure regulator could be used instead of a control valve? And, finally, what are the advantages of doing this?

Let's explore this further.

HOW PHARMACEUTICALS ARE MANUFACTURED

Traditionally, pharmaceuticals used to treat various ailments were low-molecular-weight molecules that were relatively easy to synthesize from known compounds. For example, ibuprofen (Figure 1), an over-the-counter pain medicine used to treat rheumatoid arthritis, was originally produced using the Boots' synthesis method, patented by the original manufacturer, to produce the drug from the compound 2-mthylpropylbenzene, which can be made from compounds separated from crude oil.

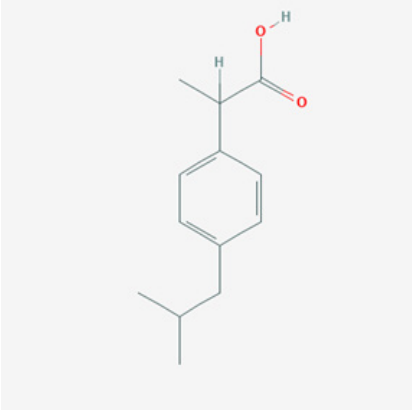

Figure 1. Simple structure of ibuprofen

Advances in science and medicine have let to alternatives to these traditionally made pharmaceuticals through bioprocessing. Bioprocessing uses organisms or their components to carry out enzymatic reactions or to manufacture products. This is how pharmaceuticals are made. Biopharmaceuticals are high-molecular-weight molecules manufactured in, extracted from, or semi-synthesized from biological sources such as mammalian cells. Etanercept (Figure 2), sold under the trade name Enbrel, also used to tread rheumatoid arthritis, is one such biopharmaceutical. It is produced in a bioreactor rather than through synthesis.

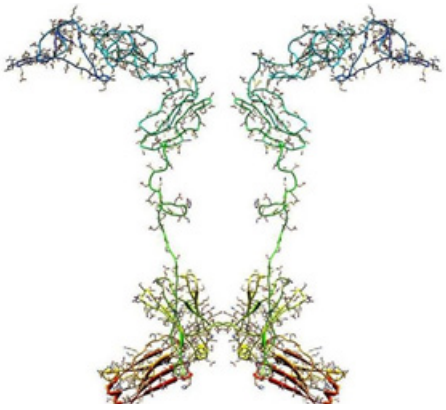

Figure 2. Complex structure of etanercept

EQUIPMENT

Bioprocessing typically requires the following components: an energy source (such as glucose), nitrogen, buffers (to control pH, for example) vitamins, growth factors and inorganic salts to create an environment for living cells to grow and thrive. Bioprocessing environments require precise control of factors such as temperature, pH, oxygen, nutrients and contamination. Controlled environments such as this can start out as simple shake or spinner flasks, until a suitable concentration is grown and then the cells are transferred to a bioreactor. Cells are then put through a process in the controlled environment that forces them to produce the desired proteins. These proteins are what the downstream process harvests as our biopharmaceutical.

There are many types of bioreactors including bubble column reactors, airlift bioreactors and filtration-cell recycling bioreactors. Stirred tank bioreactors are the most common. Typically, these bioreactors already have a significant number of ancillary systems and equipment. Adding the necessary support equipment for a control valve may be undesirable for financial reasons and/or to prevent the need for additional penetrations into the clean environment for air lines and sensors.

UNDERSTANDING THE DIFFERENCES

Bioreactors use high-purity gases for many purposes. Can a regulator be used instead to control flow of these gases? Understanding the differences between a control valve and a regulator is crucial to answering this question. From an operational standpoint, the main difference between a control valve and a regulator is that a control valve requires system sensing, external electric or air power, and perhaps a complex control system, while a regulator is driven by and responds directly to system pressure without the need for any sensor or external power.

For a control valve, first a process control variable (such as temperature, pressure, flow, level, etc.) is measured by a sensor or transmitter and then sent to a programmable logic controller (PLC). The PLC is responsible for interpreting how the valve should respond to a deviation from the predetermined set-point value of the control variable. The PLC sends a signal to the valve actuator to close or open the valve in order to return to the set point.

In a regulator (Figure 3), the pressure of the controlled process fluid exerts a force against a diaphragm-spring arrangement. Using the equation for pressure, which is $p = F/A$, we can rearrange and show that the force from the spring on the diaphragm is equal to system pressure times the area of diaphragm. Using Hooke's Law we then know the force of a spring is equal to $-kx$, where k is a constant factor characteristic of the spring and x is the amount the spring is stretched or expanded.

Figure 3. Sanitary Pressure Regulator

Therefore, it creates a force balance between system pressure and spring force. This causes the flow area of the regulator to change, allowing more or less process fluid to flow.

$$P_{SYS} = F_S / A_D$$

where

P_{SYS} = the system pressure

F_S = the force on the regulator diaphragm

A_D = the area of the regulator diaphragm

Rearranging to get F_S

$$F_S = P_{SYS}A_D$$

Because of the spring constant, k:

$$F_S = kx$$

where x is the displacement of the diaphragm

Therefore

$$P_{SYS}A_D = kx$$

Pressure regulating valves manipulate flow to control pressure. Because of the force balance mentioned above, regulators respond instantly to pressure changes and therefore have a faster response than control valves. Good applications for using a pressure regulating valve include gas overlay of a cell culture or protein mixture, moving fluids into or out of a process, sparging (bubbling gas up through) a process, lyophilization (free drying) and, on newer systems, inflation of single-use disposable (SUD) bags.

CHOOSING THE RIGHT SOLUTION

Factors that can affect a pressure regulator's sensitivity are diaphragm area, diaphragm material, orifice size and spring rate. Flow (Cv) through a valve can be affected by orifice size, plug shape and material, and stroke.

Innovative manufacturers have optimized these factors for use on high-purity gas systems. Use of pressure regulators instead of control valves provides the following advantages:

- Compact size. This not only makes them more affordable, but it decreases the install volume. Install volume can be particularly important on compact skids or small bioreactors.
- Low-Flow control. By optimizing the plug geometry and size relative to the orifice of the valve, very precise low flow rates can be obtained.
- No external connections. Eliminates additional leak points, make the product more compact, eliminates additional ancillary systems and penetrations into clean rooms where systems are located.
- Low-Pressure control. The relatively large diaphragm provides a high level of sensitivity in a small unit, allowing for control of very low pressure.
- Lower cost. Not only does the simplicity of a pressure regulator mean lower cost, but also using a regulator eliminates the need for a control system of any kind.

Manufacturers are helping pharmaceutical companies develop smart, simple solutions that also help reduce costs.

ABOUT THE AUTHOR

Bill Sams is the Chief Engineer for Steriflow Valve, a division of Richards Industries. Bill joined the Richards Industries team as a Design Engineer. He graduated from The Ohio State University with a Bachelor of Science degree in Mechanical Engineering and a Masters of Engineering Management from Old Dominion University. Bill retired as a Lieutenant Commander from the US Navy; he was a Nuclear Power Trained Officer and is a veteran of the Afghan War and Operation Iraqi Freedom.

ABOUT STERIFLOW VALVE

Steriflow has introduced a broad range of industry firsts for the bio-pharmaceutical Industry:

- The industry's first and only Lifetime Diaphragm Warranty
- The first true spring-less and crevice-free check valve for horizontal and vertical line WFI and Bioprocess applications
    - The world's only down-flow check valve for Bioprocess drain applications
- The world's first precision aseptic metering valve
- The industry's highest capacity pure steam trap and accessory product range including:
    - Products that shorten SIP heat-up time and eliminate validation temperature alarm
    - Reduce dripleg length
- The first clean gas regulator product line developed specifically for Bio-pharmaceutical applications.
    - The first clean gas regulators designed specifically for reliable control of low flows and low pressures

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