White Paper

Integrated Block Valves - Critical from Process to Patient

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Bioprocessing Overview

Biologic drugs are medicines that are large molecule therapeutic proteins, such as monoclonal antibodies, blood proteins and enzymes, that are produced by living organisms. Because biologics can be produced only within living cells, the complexity and cost of production of biologics is far greater than manufacturing traditional small-molecule synthetic drugs.

Bioprocessing is widely believed to be the future of drug discovery and manufacturing. The technology and resources of the Human Genome Project have opened many doors to the future of medical advancements. Bioprocessing will be the benefactor and facilitator of these advancements. Many drugs can only be produced by these processing methods.

Making a biotech drug

Producing biotech drugs typically utilize complicated and time-consuming mammalian cell culture or microbial fermentation processes (See Figure 1 representation). Typically these processes will transition from pilot scale to production “scale up” quantities. Once a process is scaled up the drug can be produced in large batches. This is done by growing host cells in carefully controlled conditions in large stainless-steel bioreactors. The cells are kept alive and stimulated to produce the target proteins through precise culture conditions that include a balance of temperature, oxygen, pH (extremely critical) and other variables. For this reason bioprocessing is particularly reliant on processes that involve the critical control of process fluids, media, water, air, etc. Expressed proteins are then isolated from the cultures and stringently tested at every step of elaborate purification processes. All of these procedures and processes must be in strict compliance with Food and Drug Administration (FDA) regulations.

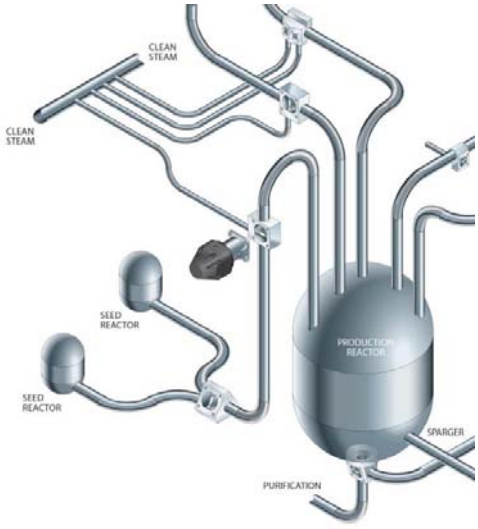

Figure 1 – Bioreactor Process

Hygienic Valve Fabrication Trends

So how do valves come into play with regard to the drug manufacturing process? One of the most critical factors in the production of drugs today is the ability to clean and validate the drug production process. At the risk of oversimplification, the FDA expects that processing equipment be designed to be drainable, cleanable and sterilizable to minimize the potential for contamination, and therefore help assure the purity and efficacy of the end drug product.

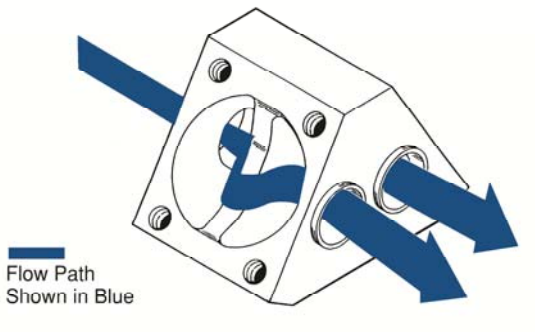

Figure 2 – 2-Way Divert Flow Path

Hygienic valves, particularly diaphragm valves, have become the most important control element of process piping systems utilized in the Bioprocessing industry today. The weir style diaphragm valve has become the standard due to the unique ability to provide a drainable valve with minimized product entrapment areas. As can be seen in Figure 2, the unique internal geometry of a diaphragm valve creates a flow path that minimizes hold-up volumes and optimizes process piping drain-ability.

Utilizing the unique characteristics of the weir style diaphragm valve, valve manufacturers have helped develop many process fabrications to reduce product contact surfaces, reduce hold-up volumes, and minimize piping dead-legs. The theory is that as contact surfaces are minimized and hold-up volume is reduced in a process piping system, product yields and product purity will improve.

In the not so distant past, typical process fabrications were produced by welding standard forged valve bodies in configurations designed specifically for certain applications and orientations. Figure 3 shows a process fabrication known as a Sterile Access port. Sterile Access fabrications are utilized for product sampling or a condensate drains. This fabrication has served the industry well, but has limitations. In some instances, where the main horizontal valve is large relative to the sample valve, the dead-leg between the two valves can fall outside FDA expectations. An integrated block style valve (Figure 4) was developed to solve this limitation. Zero static use points are used extensively in the bioprocessing and pharmaceutical industries. Figure 5 shows an old technology fabricated zero static use point, while Figure 6 illustrates integrated block valve technology.

Figure 3 – Sterile Access Fabrication

Figure 4 – Integrated Block Valve

Figure 5 – Early Design Fabricated Zero Static Use Point

Figure 6 – Zero Static Use Points

The FDA Guide to Inspections of High Purity Water Systems has defined dead-legs as “not having an unused portion greater in length than six diameters of the unused pipe, measured from the axis of the pipe in use. It should be pointed out that this was developed for hot (75-80º C) circulating systems. With colder systems (68-75º C) any drop or unused portion of any length of piping should be eliminated if possible, or have special sanitizing procedures.”

In cases where process piping falls outside of FDA expectations, as noted from the Guide to Inspections of High Purity Water Systems reference above, the owner of the system is expected to have special sanitizing procedures. These special sanitizing procedures can be expensive in terms of production time and processing cost and should be avoided whenever possible.

Until relatively recently however, there has not been a true guidance document to assist the Bioprocessing industry to achieve these higher levels of performance. Realizing the need for guidance the American Society of Mechanical Engineers (ASME) in 1987 began assembling a committee devoted to the development of a standard for the Bioprocessing industry. Almost ten years later a standard was released called the "ASME Bioprocessing Equipmet Standard" (ASME BPE).

This standard takes the issues of dead-legs in process piping to an even higher level. The BPE has created a new definition for the allowable dead-leg within a Bioprocessing piping system. The ASME BPE 2005 states "for high-purity water and clean steam systems, an L/D ratio of 2:1 is attainable with today's manufacturing and design technology…"1 In many cases the old technology of welding standard valves into process fabrications will no longer meet this higher requirement described by the ASME. Also, per the definition of "current Good Manufacturing Practice (cGMP) regulations, drug manufacturers are required to keep up with the latest trends in standards and technology. This is where the trend to migrate to integrally machined block valve bodies has begun.

Figure 7 – Multi-Port Divert Valves

Integrated Block Valves

The design and manufacturing technology the ASME BPE is referencing is essentially 3D CAD modeling and CNC machining. For many years hygienic diaphragm valve manufacturers have utilized CNC machining to create the complex weir geometry in forged valve bodies. It was not until the introduction of 3D parametric CAD systems that truly innovative process valve designs could be realized. Now with the common use of these 3D modeling programs, valve manufacturers are capable of creating an amazing array of valve designs to not only meet, but exceed the expectations of the Bioprocessing industry. Figure 4 illustrates this point. While Figure 4 serves the same functionality as Figure 3 instead of two separate valves welded together, both valves are machined from a integral block of 316L Stainless Steel. Not only does this greatly reduce hold-up volume and the length of dead-leg, it eliminates a manual weld.

The presented example is a simple combination of valve and 3D CAD technology. An endless array of process configurations, to satisfy almost any application need can now be designed and manufactured. With only modest effort, Figure 7 and 8 illustrate a

variety of multi-port divert valves. These valves can be combined in many ways to simplify and condense intermediate drug manufacturing processes. An excellent example is the use of numerous multi-port divert valves in a chromatography skid (Figure 9). A patented valve especial designed for chromatography columns has helped the industry optimize the chromatography process (Figure 10).

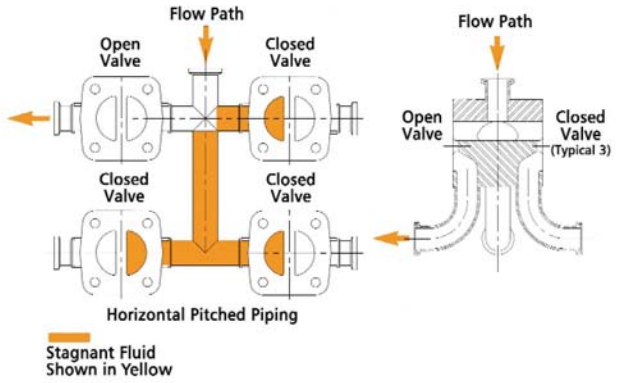

Figure 8 – Conventional Divert Valve Assembly vs. Pure-Flo 4-Way Divert Valve

Figure 9 – Chromatography Skid used for Protein Separation utilizing Multi-port Divert Valves

Figure 10 – Chromatography Valve

There is endless potential for valve manufacturers and process piping designers to work together to provide innovative and cost effective valve and process system designs. Innovative designs can drastically reduce dead-leg, minimize hold-up volume, minimize product contact surface areas, improve drain ability, and contribute to product recovery from process piping and systems. All these factors help the Pharmaceutical and Bioprocessing industries improve their product purity and yield, while reducing overall costs. End result is that patients get safer, less costly drugs.

1 ASME Bioprocessing Equipment Standard 2005 Edition, SD 3.11, pg 14 & 17.