A CRITICAL EVALUATION OF VALVE TYPES IN BIOPHARMACEUTICAL MANUFACTURING PROCESSES

by John Swibes

Stainless steel remains the gold standard of bioprocessing in the pharmaceutical industry – notwithstanding the current vogue for single use systems. The challenge today from a regulatory standpoint is to reward new designs and technology that solve the decades old problems with the valves most commonly used.

John Swibes graduated in finance/marketing in 1984. In 1990 he began work as a technical sales representative for industrial control valves and automation. Since 1995 he has been working primarily with pharmaceutical, biotech and food and beverage clients. In 2006 he started his own company focused on single-use products and introduction of new valve and agitator technology designed for aseptic production.

The rapid growth of mammalian cell-based production has presented challenges to engineers tasked with designing, building and operating upstream and downstream process trains that need to function at levels of cleanliness and sterility much higher than systems designed less than a decade earlier. In response to process and production challenges, one of the many drivers for adoption of single use technologies was eliminating the need to reliably clean and sterilise stainless steel systems. The isolation valves used in these systems represent significant design and capital resources. That the industry standard valve has not changed significantly in over 40 years is more a testament to the influence of the status quo than the availability of new tools developed specifically for today's stricter industry challenges.

The introduction of flat membrane diaphragm valves in pharmaceutical processes in the latter half of the 1970s was a vast improvement over disk (butterfly) and ball valves for use in sanitary and sterile processes. Although originally developed for industrial slurry applications, the flat membrane design was readily adapted to sanitary applications which required special materials and surface polishing.

But why flat diaphragm valves in the first place? Compared to ball, butterfly and plug valves the flat membrane design dramatically reduced the potential for product entrapment and this allowed for reliable cleaning and sterilisation. The internal shape of the valve creates a weir against which the diaphragm seals to stop flow. When installed at the correct angle, these valves allow draining throughout the system. When these valves were first introduced, the sanitary processes were quite different than today. Dead legs and product entrapment were not much of an issue in small molecule production. And while the straight through path is beneficial for some applications, the lack of turbulence in the valve can work against efficient cleaning in place.

Towards the end of the 1980s the radial diaphragm valve was introduced and shortly after an improved radial design emerged. The novel right angle design of the radial valves immediately differentiated itself from the weir style diaphragm valves that had and continues to dominate the pharmaceutical and biopharmaceutical landscape for the last forty years. More recently new valves with upgraded diaphragm performance and flexible body porting have entered the market. These next generation valves promise key improvements over the first radial valves by increasing service life and reliability without sacrificing contamination risk.

In 2006 the U.S. Food and Drug Administration (FDA) issued guidance on Quality Risk Management guidelines while the European Medicines Agency (EMA) issued similar guidelines in Annex 15. In response, industry user groups analysed maintenance data and as a result ranked elastomer performance, the standard Tee and dead legs as key areas of focus for increasing system reliability. Each of these areas of concern is closely related to the application and functionality of valves in sanitary process systems. Additionally these attributes can affect Continuous Process Improvement and Verification and Design Qualification initiatives being adopted industry wide.

The FDA High Purity Water Guide defined dead legs "as having an unused portion greater in length than six diameters of the unused pipe, measured from the axis of the pipe in use." More recently the industry group ASME-BPE suggests a 2:1 ratio as a target. But this dead leg ratio while seemingly apparent is a grey area. Is the linear distance from the main pipe to the connection at the outlet of the valve? Or is it calculated to the valve body seal? For weir valves this is an important distinction because the valve volume widens inside the body thus creating a larger dead leg volume.

Testing by independent industry groups suggests that the orientation of the dead leg can have a significant bearing on the cleanability of even short dead legs. Sterilisation studies of vessels have shown that where there are even short dead legs attributed to short standard ferrules, these pockets can lag as much as 15 to 20 degrees behind the side wall of the vessel. The solution here is to increase both the time and temperature of the steam cycle. In many instances the extra time at elevated temperatures and chemical exposure are key contributors to diaphragm wear and premature failure. It is up to the owner of the system to ensure that where process piping is deficient, special sanitising and sterilisation procedures should be developed and maintained. These special sanitising procedures can be costly in production time, chemicals and utilities.

A key challenge for process design engineers is to eliminate hidden piping defects created by valves and T or right angle junctions. Radial diaphragm or right angle valves have a key advantage over weir valves in that the natural valve geometry effectively puts the line seal at the outside of the valve. Properly designed systems incorporating radial diaphragm valves use the valve for changes of direction and elevation resulting in full drainability. Weir valves by their nature place the sealing point in the middle of the valve. From a process piping perspective, this design creates a dead leg in the worst case or creates an unused portion at best. From valves mounted on vessels to valves installed in piping there are countless examples of weir valves creating pockets in the system. Possibly the best example of this hidden piping defect is the weir valve design that incorporates a condensate drain valve into the main valve. These so called "sterile access" valves solved one issue (condensate removal) but because of physical limitation in valve geometry created a pocket that extends from the pipe wall of the main valve to the closure point of the condensate valve (**Figure 1**). By comparison the same function can be attained with radial diaphragm valves but without the resulting sump or dead leg (**Figure 2**).

Valves suitable for sanitary and aseptic piping systems have some attributes in common. Key is the body material of AISI 316L (1.4404) or for higher corrosion resistance without resorting to higher alloys, 1.4435 BN2. The valves themselves are either forged with a final machining in the case of weir valves or machined directly from round bar for radial valves.

The most common diaphragm elastomer materials are EPDM, Silicone and several variations of fluoropolymers including PTFE and PFA. In general, weir valve diaphragms are most commonly EPDM by itself or used as a backing piece for some type of fluoropolymer facing the process. As mentioned previously, valve diaphragm reliability is a key issue. Proactive to address reliability issues, industry user groups have collaborated with valve manufacturers to design testing schemes that address extending diaphragm replacement intervals and quantifying the associated risk. Developing new EPDM compounds and diaphragm designs is an on-going effort.

Properly formulated EPDM compounds easily pass testing

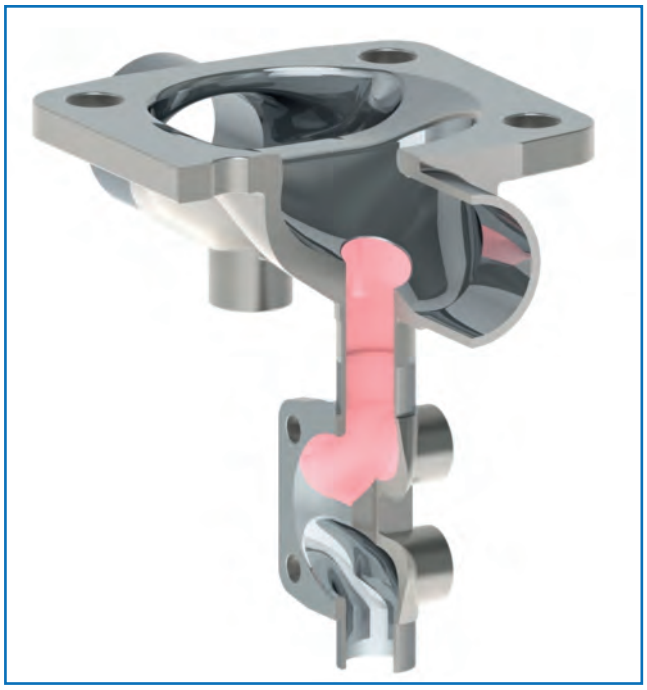

Figure 1. The pink shading indicates a dead leg created by Sterile Access valves

Figure 2. A valve with the same function as the Sterile Access valve but with no dead leg

requirements like USP Class VI for biological reactivity. It is important to note that USP VI does not address in-use performance. A drawback of EPDM is that when hot, the compound can become sticky. One common way to combat the stickiness is to add a vapour deposited coating of medial grade Parylene. Individual users have to determine if this additive is acceptable to their process. Another drawback to EPDM rubbers is the phenomenon referred to as Compression Set. Compression Set can be best described as permanent shape change while under load – typically the clamping pressure required to affect a seal with the valve body. This load coupled with elevated temperatures permanently distorts most EPDM compounds. Eventually the seal force on the valve diaphragm will slack and require re-torqueing of the bonnet nuts or replacing the diaphragm. For valves with thin fluoropolymer faces with a resilient backing, the same compression set of the EPDM can occur. The inevitable issue of Compression Set leads to reduced overall system availability and high maintenance costs as valves need to be constantly checked and re-torqued after steaming. The risk taken is related to how many times the valve can be re-torqued before outright failure of the diaphragm. An additional danger associated with two piece diaphragms is a crack developing in the thin fluoropolymer face which can easily go undetected.

Silicone is used in most radial diaphragm designs because of its flexibility and the tendency not to stick. Typically used in first generation radial valves the diaphragm utilises a bellows above the valve plug to allow movement of the diaphragm plug. However the porosity of silicone can be problematic with the formation of undetectable vesicles. It is hypothesised that this occurs during repeated steaming operations resulting in the potential for product diffusion into these areas leading to potential batch to batch contamination or at worst a rupture of the vesicle resulting in valve failure (**Figure 3**).

Fluoropolymers do have key advantages over EPDM and Silicone. These materials have a high molecular weight and are naturally hydrophilic and therefore highly resistant to steam and stable at temperatures far above EPDM and Silicone. With proper valve body design and clamping force, "Cold Flow" is not an issue. In fact, when properly designed, valves with solid machined PTFE diaphragms can be opened and inspected repeatedly for valve diaphragm wear and re-inserted in the valve and reliably re-sealed. Unlike composite Fluoropolymer/EPDM diaphragms that can distort while warm and under vacuum (**Figure 4**), solid PTFE diaphragms have demonstrated the capability of operating under vacuum while hot. This is a major advantage in systems that are dried and cooled using a sterile Nitrogen purge.

Figure 3. TA failed silicone diaphragm from a first generation radial valve – failure attributed to diffusion bubble rupture.

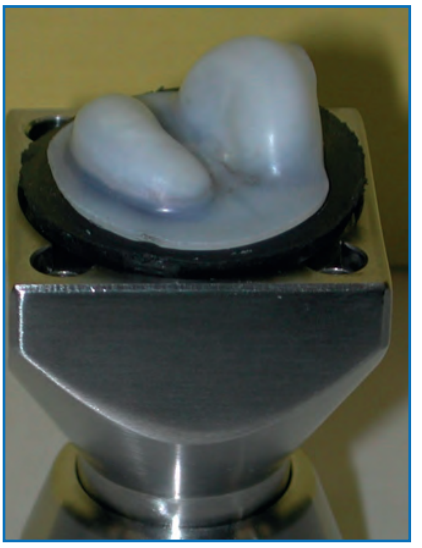

Figure 4. Deformation of fluoropolymer diaphragm face due to vacuum conditions while hot. The image also shows deformation of EPDM backer due to compression set.

The shape of the diaphragm at the sealing point of the valve body is critical to proper cleaning. For fast and thorough cleaning, asymptotic seals and low flow conditions should be avoided. The right angle design of radial diaphragm valves naturally creates needed turbulence for effective cleaning. The ideal body seal should be static and have an open angle that is readily cleanable. Valves that do not have a defined sealing point or that flex in the sealing area are prone to pumping material into an area that is difficult if not impossible to clean (**Figure 5**). Heat, during sterilisation kills what may be left behind, however unless there is an outright leak in the body seal, this condition is only knowable after disassembling the valve.

From a purely aseptic processing point of view there should only be one body seal and for good reason. With two seals, if the first seal fails, product between the seal points can be trapped. First generation radial diaphragm valves are designed with an internal body seal in direct contact with the process. These valves are characterised with a single bellows which allows movement of the diaphragm. In an often-overlooked design feature there is also a second outer body seal. The two seals are connected by a length of elastomer. The

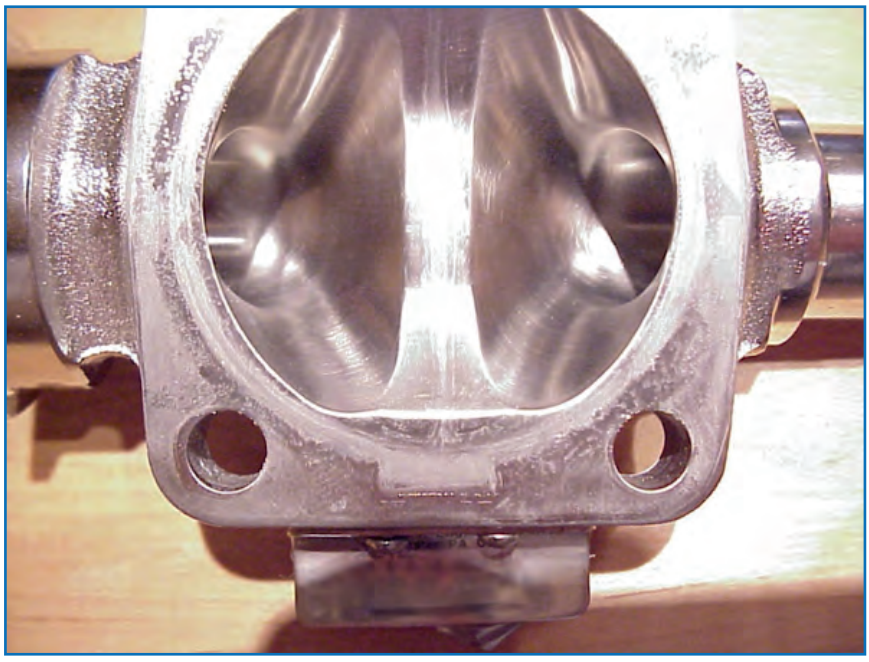

Figure 5. The area between the body edge and where the diaphragm seats. This is a common area for entrapment of product even after cleaning. This image is from a valve that was never installed. The EPDM diaphragm left residue behind that clearly shows it was seating behind the body edge.

assembly of the valve relies upon compression with a sanitary clamp at the outer body seal and according to literature this is providing the primary seal.

As to design options, weir valves have one basic flow path and are installed at the required point in the system. Many times this placement results in a dead leg as well as extra system piping. Weir valves also need to be installed at a specific angle in order to drain through the valve. Radial diaphragm valves on the other hand can be ported in many different ways. For example, in a diverting valve situation the common inlet can be adjusted for both vertical and horizontal pipe and eccentric or tangential porting. Process designers can then locate the outlets at a favored location that best suites the process requirements and which eliminates dead legs and reduces overall piping. Radial diaphragm valves can be readily adapted to and improve most any application including the most stringent aseptic operations (**Figure 6**).

Pharmaceutical and biotech processes have changed immensely over the last 15 years due in part to the rapid introduction of single use disposable technologies. One of the drivers for this change was to lessen the requirements for cleaning and sterilising. This suggests that the systems and equipment based on designs from twenty or more years ago were falling short of industry expectations and current requirements. Many industrial pharmacists recognise that single use technologies have limitations and challenges of their own; there will still be a place for stainless steel systems, but only so long as these systems are optimised and take advantage of current designs and technologies.

Further reading

Continuous Process Verification: see https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf

Figure 6: Whether single-use based valve or stainless steel valve, distributing high purity water or water for injection (WFI) to vessels remains a common step. Maintaining loop and distribution leg integrity is vital. The advantage of a modular approach is evident in this design shown here. The main take-off valve and the optional downstream steam/nitrogen valves are machined as part of the main pipe up to 4". The assembly is very compact and free of dead legs. Pneumatic actuators and position indicators are optional.