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Choosing the Optimal Hygienic Seal for Enhanced Process Performance

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This article presents how seals used in hygienic clamp fittings, diaphragm valves, and O-rings are integral to process performance, preventing leaks and contamination.

Seals are integral to process performance and used throughout the biopharmaceutical, pharmaceutical, and food industries, primarily in hygienic clamp fittings, diaphragm valves, and O-rings. They maintain the integrity of the process and seal it from outside conditions to prevent leaks and contamination.

Current biopharmaceutical processes usually require one or more Steam-In-Place (SIP) cycles per production batch. Depending on the requirements and the location in the process, the number of SIP exposures that a seal may be subjected to may be as high as 20 to 30 SIPs per production batch. In addition, automated Clean-In-Place (CIP) operations are more commonplace today. One cleaning per production batch is typically required, and cleaning cycles usually consist of weak caustic acid and/or bleach solutions at elevated temperatures. This is in sharp contrast to the food industry, where most processes undergo less aggressive sanitization and cleaning cycles.

State of the Industry

The business climate is changing in the biopharmaceutical industry. Trends are shifting to contract manufacturing, higher plant throughputs, reduced plant down time, and increased focus on cost-of-goods-sold, while also maintaining a strict sense of quality. Biopharmaceutical manufacturing must be in compliance with current Good Manufacturing Practices (cGMPs), and the process design needs to provide process reproducibility, as well as ensure product stability and purity. Process modifications are allowed only if it can be proven that the resulting final products are similar in terms of quality, safety, and efficacy.

In response to these industry trends, the United States Food and Drug Administration (FDA) issued the "Pharmaceutical cGMPs for the 21st Century" initiative in 2002. Included in this landmark initiative is a risk-based approach to manufacturing science. This approach employs many of the initiatives which the *International Conference on Harmonization (ICH)* has issued in its document, Q9, *Quality Risk Management*.

Risk is usually defined as the probability of harm multiplied by the severity of harm. Good pharmaceutical quality represents an acceptably low risk of failing to achieve the desired clinical attributes. Risk knowledge means more focus on the most critical aspects of the process and more rigorous application of process development, technology transfer, monitoring, and control.

The intent of this initiative is to encourage early adoption of new technological advances by the pharmaceutical industry. The *Office of New Drug Chemistry (ONDC)*, within the *Center for Drug Evaluation and Research (CDER)*, has established a risk-based pharmaceutical quality assessment system to replace its *Chemical Manufacturing and Controls (CMC)* review system. It focuses on critical pharmaceutical quality attributes and their relevance to safety and efficacy. The strategy is based on the reflection of the manufacturer's

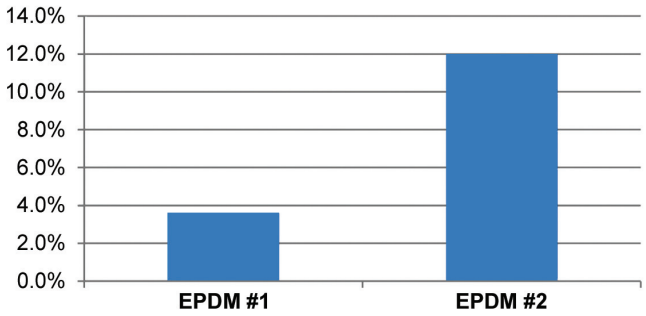

Figure 1. Compression set after 22-hrs at 100°C comparing 70-durometer EPDM compounds.

understanding of manufacturing process, process control, and quality systems. The FDA's Aseptic Processing Guidance underscores the advantages that automation and isolation concepts offer in protecting the exposed sterile drug product during its aseptic manufacture. It advocates a risk-based and quality system framework that stresses contamination prevention.

Materials Science of Seals

In order to prevent contamination in a product, it is important that the materials being used in the process are well understood. There is an assumption by many that however one material performs, all others will perform equally. This is definitely not the case. Figure 1 shows two different USP Class VI 70-durometer Ethylene Propylene Diene Monomer (EPDM) compounds from the same manufacturer. While both compounds have very similar original properties, there is a significant difference in the compression set of each material after only 22 hours in 100°C air. This difference can be caused by the specific polymer used, the types of filler used, or the type and amount of curative. This simple material property – the compression set – can be a good surrogate of how much sealing force is retained by the gasket over a period of time, which is important information to understand for a sanitary gasket. The greater the compression set, the less sealing force retention on the gasket and the more likely the end user is going to have to re-torque the clamp to regenerate a seal. Understanding properties such as compression set, Compressive Stress Relaxation (CSR), and fluid resistance can be critical to understanding just how that specific compound will perform in an application.

Figure 2. Various EPDM products.

Another important factor to consider is the pedigree of the ingredients used to create the material. Many industries – such as the automotive industry – already require gasket suppliers to submit documentation for any ingredient changes and even mixing location changes due to the potential differences that can be created in the performance of the end product. This has become all the more important the past several years as changes in the overall global economy have forced raw polymer suppliers to consolidate their facilities, eliminate certain polymer grades, and create new polymer grades to meet the demands of the various industries. Having an understanding of the gasket source and what they are supplying is becoming more critical for each end user.

Finally, it is important to understand that materials are used across multiple industries and specifying a USP Class VI material may not necessarily be the only thing an end user needs to know. EPDM materials are used in products such as automotive door seal extrusions and grommets, as well as pharmaceutical sanitary gaskets – some examples are shown in Figure 2. This is why it is critical to have an understanding of the material being used. For optimal long-term performance of a system, the end user also should have an understanding that the EPDM being received today is the same material that was received the day before, and will be the same material received tomorrow. With the appropriate traceability in place, the end user can be assured that the material utilizes the same polymer, same fillers, and same formulation along with mixing method, from part to part.

Evaluating Seals and Seal Performance

The adoption of advanced sealing technologies has lagged behind the progress of the biopharmaceutical industry. The industry has applied standards from other related industries, like the 3A and *European Hygienic Engineering and Design Group (EHEDG)* standards, where appropriate. However, materials of construction are becoming more and more sophisticated. New materials of construction have been introduced, such as fluoroelastomer (FKM) and perfluorinated elastomers (FFKM), and each has been met with some limited success. Specific concepts like compression control design enhancements, PTFE-enveloped elastomers, and stainless steel and glass mixed with polytetrafluoroethylene (PTFE) also have been introduced to the industry, also with limited success.

The *American Society of Mechanical Engineers (ASME)* has provided a standard to the biopharmaceutical industry with the publication of the *ASME BioProcessing Equipment Standard (BPE)* in 1997. The BPE Standard addresses the requirements of the bioprocessing, pharmaceutical, and personal care product industries, as well as other applications with relatively high levels of hygienic requirements. The

standard covers, directly or indirectly, the subjects of materials, design, fabrication, pressure systems (vessels and piping), examination, inspection, testing, and certification. It is a consensus standard which is internationally recognized and contains a specific section on sealing components (formerly Equipment Seals), Part SG. Specific seal requirements include:

- User design requirements to ensure sterilizability and cleanability, e.g., seal leakage and hygienic seal intrusion
- Materials of construction requirements to minimize the interaction with the process, e.g., biocompatibility, process compatibility, surface finish, particle generation, and extractables
- Compliance requirements to ensure proper testing and supply chain management, e.g., Certificate of Compliance, packaging and storage recommendations, and test requirements

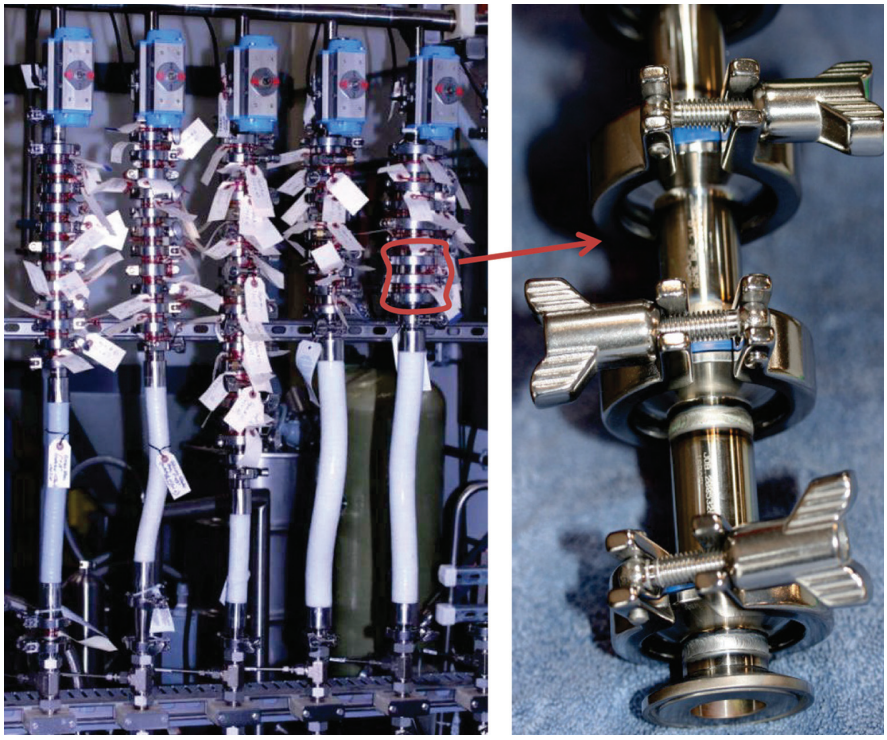

Figure 3. Sample bench test (photos courtesy of The BioProcess Institute).

The BPE Standard addresses the need to characterize seal performance with the establishment of the Standard Process Test Conditions. This non-mandatory appendix outlines standard test conditions to simulate typical biopharmaceutical SIP and CIP cycles. It recommends acceptance criteria for hygienic seals and levels of performance for classification. An acceptable seal is one which will maintain pressure without leakage, have minimum levels of intrusion into the flow path, and appear relatively unchanged and free of defects after exposure to process cycles. Testing can provide the end user much needed information as to the overall performance characteristics of the gasket design and material. But the importance of bench testing goes beyond just gaining some understanding of a gasket and its design – it also can be used as a qualification for use in an end user's system.

In the BPE Standard, there already exists a test procedure for standard process testing sanitary gaskets.[1] While this procedure may not prove that a particular gasket will work for some specified period of time in a given system, it can be used as a baseline for determining how one gasket will perform when compared with another. Variations of this test also could be set up by the end user as a means of qualification for use in one's own facilities. Figure 3 provides an example of a bench test setup with multiple gaskets installed in series. The results of a 500 SIP exposure test showed virtually no physical difference between the gaskets shown in Figure 4 after exposure to 10, 100, and 500 SIP cycles. In addition, the gaskets shown in Figure 4 were able to maintain sealability throughout the test without requiring any re-torque throughout the 500 SIP cycles.

Other industries, such as automotive, have been using bench testing of gaskets for many years as a means of qualifying new designs. In order for a gasket supplier to provide a particular product in a particular application, the gasket supplier will not only have to gain a material approval, but also will need to prove that the design passes the approved bench test before the supplier can provide the product. The pharmaceutical, food, beverage, and dairy industries have

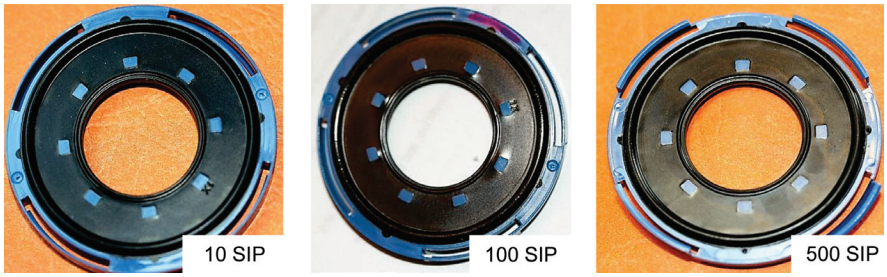

Figure 4. EPDM gasket over 10-100-500 SIP cycles exposure (photos courtesy of The BioProcess Institute).

> *"Developing a standard bench test procedure and having an approved source could pay dividends for an end user in the long term.*

the opportunity to apply the same principles to improve the overall quality of the gaskets they receive. Using the ASME BPE Standard, end users can add this test (or something similar) to their approval requirements before gasket suppliers can introduce a new product. Furthermore, since many end users lack the time and resources to conduct gasket testing continuously, they can provide a list of approved test sources for the gasket suppliers to use. In this way, the end user has only to focus on auditing the testing facility for compliance with their approved procedure. This process will help prevent receipt of unapproved gaskets. Gasket testing will reveal varied performance of different types of gaskets and gaskets from different manufacturers, displaying "worst" to "best," as shown in Figure 5. This can help the end user determine the timing between maintenance schedules and gasket replacement.

Developing a standard bench test procedure and having an approved source could pay dividends for an end user in the long term. While it is very difficult to develop the most accurate bench test that meets all of the end user's needs, once a bench test has been standardized, continuous improvement on that procedure can take place and eventually a test can exist that will help the end user better predict maintenance intervals for various gaskets.

A Risk-Based Approach to Better Seal Performance

As stated in the cGMPs, the biopharmaceutical industry must ensure its product quality, safety, and efficacy are the same or better when it makes any process change. Historically, there have been barriers to adopting new developments in seal technology into cGMP processes. Seal suppliers have not always provided robust, transparent compliance and quality assurance practices. At the same time, end users have not always properly considered cost-of-ownership models that take into consideration all potential costs. These costs include installation, routine maintenance, and non-routine deviations, not just the initial cost of the seal itself. In addition, both seal suppliers and end users have sometimes lacked effective performance testing to assess the seal's fitness-for-use and potential cycle life.

By employing a risk-based approach to assessing the performance of seals, the biopharmaceutical industry can overcome these barriers and easily enhance their process performance by implementing the proper seal selection process.

Specifically, in the evaluation of a potential replacement seal, the following should be evaluated:

- Seal Supply Chain:
  - Manufacturer
  - Distributors
  - Quality Assurance
  - Supply Chain Integrity
- Process Application
- Installation
- Retooling
- Procedure Changes
  - Process Performance (Fitness-for-Use)
  - Maintenance (Life Cycle)
  - Potential for Failure

The decision to change a seal can be clouded with many concerns, such as lack of knowledge of materials and their performance, unclear vendor qualifications, and arduous change control processes. Combined, these become barriers to change and are not always consistent with the cGMPs and the quest to ensure quality, safety, and efficacy. Process performance and proper assessment of risk must drive this evaluation.

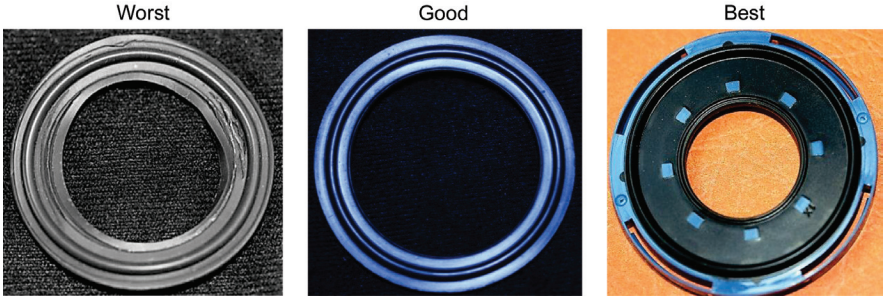

Figure 5. A range of gasket performance after 500 SIP cycles exposure (photos courtesy of The BioProcess Institute).

Costs are the next consideration when contemplating any change. Challenges include increased cost control, desire for improved up-time of equipment, and getting the most out of the capital equipment each company already owns. Understanding all of the associated costs with the seals in a system, and not just the initial cost of the seal itself, is important if one is to truly reduce overall costs and improve equipment up-time.

One example that demonstrates this point is a typical Water for Injection

Number of Connections	100
Avg. Time to Replace a Gasket	24 minutes
Avg. Time to Re-Torque a Gasket	4.8 minutes

Table A. Maintenance on sanitary fittings.

(WFI) system used in a pharmaceutical facility. The WFI systems are fundamental to the manufacture of a pharmaceutical product. WFI systems are used for cleaning and rinsing, and can be the last thing a piece of process equipment sees before the product is introduced. Water can be a source of bacterial endotoxins and other toxic contaminants that could render a cell culture operation ineffective within a facility, so the WFI system and the components used within it can be a cause for batch failures and the associated costs. A typical WFI system is often found in hard-to-reach locations, such as the facility ceiling or wall. Based upon actual experience with WFI systems, an average of 24 minutes is required to replace a gasket, due to a variety of factors. The fittings are often not easily accessible, requiring time to assess the best course of remediation, followed by potential removal of insulation, pipe supports, sensors, and other lines. Larger lines may require more than one person or special apparatus for removal, and pipe misalignment may require additional remediation efforts. As a result, it is a system for which long-lasting gaskets are desired. A typical WFI system can utilize approximately 100 fittings, and for those 100 fittings, it can take "five man-days" to replace the gaskets. A "man-day" is the number of days it takes a person to accomplish the task. Five man-days can take one person five days to finish the task, or it can take five people one day to complete the task. Having to re-torque the fittings throughout the system can take "one man-day." Based on this information, the assumptions for maintenance on the sanitary fittings can be seen in Table A.

Assuming a standard all-EPDM gasket might last up to 12 months, with each fitting requiring a re-torque once every three months, the costs for the associated maintenance of

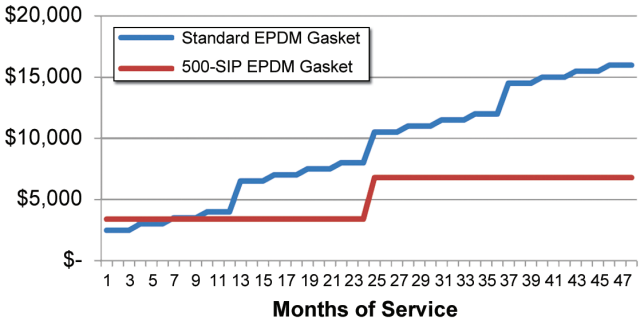

Figure 6. Gasket maintenance costs over time (typical WFI system).

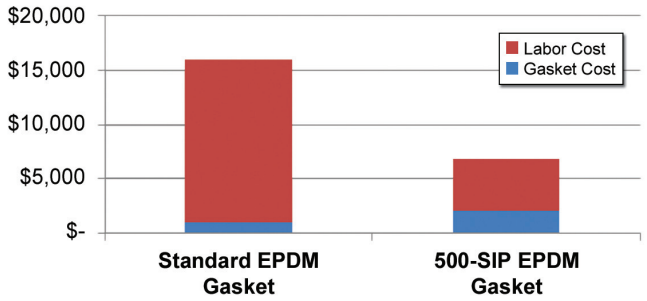

Figure 7. Estimated cost breakdown over 48-month period.

that system can be calculated. Using these assumptions, the cumulative costs associated with maintaining the gaskets on a typical WFI system are shown in Figure 6. While using a standard all-EPDM gasket may save the end user on costs associated up-front based solely on gasket cost, it could end up costing the end user more within a 12-month period when compared with a gasket capable of sealing for a two-year period without need for re-torque – even if the end user were to pay ten times as much for the gasket.

Often, end users look at the price for each gasket rather than taking a look at the overall costs associated with maintaining the system. Looking at the breakdown of associated costs shown in Figure 7, one can tell the greatest portion of the cost associated with maintaining the seal in a WFI system is in the labor – not the gasket. Based on this, the focus should be on reducing the labor associated with changing the gaskets over the cost of the gasket itself.

Finally, one must understand the potential for failure. Simply put – a seal failure is unacceptable. The purpose of the seal is to separate the process from the environment. Failure to do so can compromise the integrity of the process and expose the process and patient to unacceptable risk. The costs associated with those failures can be significant, as shown in Figure 8. This is not to mention the risk to the quality, safety, and efficacy of the end product itself.

Having a solid understanding of the supply chain and quality assurance with the associated seals in a process can

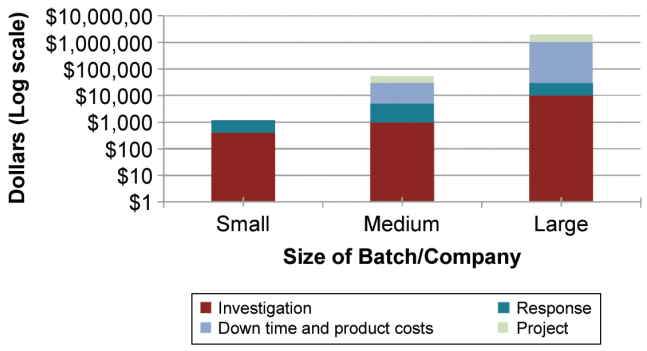

Figure 8. Costs of a seal failure (Vogel, 2010).

help prevent batch failures from occurring, or at the very least, expedite the corrective action process to determine the true root cause of the failure so that permanent corrective action can be instituted to prevent recurrence of the issue.

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Conclusion

A better performing seal results in a more robust process, which delivers a more consistent drug substance. It provides reduced risk to the biopharmaceutical manufacturer, is in better compliance with current Good Manufacturing Practices (cGMPs), and provides better process reproducibility to further ensure future product stability and purity. At the same time, a better performing seal also can help the biopharmaceutical manufacturer achieve a cost savings of thousands of dollars annually and can prevent many times more that amount in nonconformance events, their investigations, and their corrective and preventative actions.

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