Silicone Molded Tubing Assemblies: A Solution for Reduced Contamination Risk and Greater Efficiency

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The adoption of single-use systems is one of today’s most noteworthy trends in biopharmaceutical processing. The next-generation solution, molded tubing assemblies made of silicone, can help reduce the risk of contamination in biopharmaceutical and pharmaceutical processing. They can also make the process of producing drug products more efficient by replacing assemblies that incorporate separate thermoplastic components held in-place by tie wraps or other fasteners.

Greater demands are being placed on components of single-use disposable systems, including silicone tubing and fabricated tubing assemblies. This article focuses on Dow Corning® Pharma Fabricated Tubing Assemblies (FTAs) and reviews applications and benefits of these products in biopharmaceutical and pharmaceutical processing applications. It also identifies some of the most critical quality characteristics to consider when selecting components, such as silicone transport lines or molded silicone tubing connections, for single-use disposable applications.

An Evolution in Manufacturing
Biopharmaceutical manufacturing has traditionally relied on stainless steel vessels and piping to transfer materials from one vessel to another. More recently, this piping is often replaced with disposable tubing. Tubing fabricated from silicone is typically chosen because of its flexibility, inertness, well-characterized extractables profile, purity, and extensive history of use. It is often used to transport product from the primary mixing vessel into holding vessels and subsequently into final packaging components.

A recent evolution of biopharmaceutical manufacturing utilizes single-use disposable components to produce large- and small-scale biopharmaceutical products. Single-use systems often include a bag made from a blend of thermoplastic polymers, a frame to support the bag and some type of mixing attachment. In addition, ports or openings may be incorporated into the bags to allow fluid input and output via tubing assembly systems, sometimes in conjunction with a pump. These single-use systems are designed as alternatives for various expensive, stainless steel pieces of equipment including holding tanks and transfer lines. Although stainless steel offers a strength advantage, stainless steel systems lack flexibility and require aggressive cleaning procedures prior to reuse.

The single-use approach can provide several advantages over stainless steel systems, including faster and more efficient assembly and implementation, as well as less risk for product contamination (1).

Efficiency and Quality for Users
Some drug manufacturers construct their own tubing assemblies in-house. Typically, their systems consist of tubing (silicone or thermoplastic) connected by tie wraps to thermoplastic components such as straight connections, branched connections, sanitary flanges, and aseptic connectors. By using Dow Corning Pharma Fabricated Tubing Assemblies, these manufacturers can eliminate the need to build their own assemblies.

The process for making FTAs involves molding Silastic® Biomedical Liquid Silicone Rubber (LSR) to Dow Corning® Pharma silicone tubing to produce a single component. The process chemically bonds the LSR and tubing, thereby eliminating the need for tie wraps or other cumbersome clamping devices. This approach reduces the chance of injuries, such as cuts, which could affect the manufacturing environment or compromise product sterility.
For better assurance of reduced bioburden, the assemblies are often irradiated with a cobalt-60 gamma source and supplied ready to use in the intended application, again reducing the risk for product contamination and simplifying the drug manufacturer’s processing operations.

With the general trend toward greater use of disposable devices, silicone tubing requirements have changed and the tubing is increasingly specified for single-use applications. The broad temperature stability of the tubing allows it to be sterilized by autoclave and to withstand both high and low temperatures typically necessary for biopharmaceutical processing (2). Flexibility, resilience, kink resistance, pressure resistance, and a low level of extractables are also critical qualities of silicone tubing for these applications. The platinum-catalyzed silicone tubing, which is one of the major components of FTAs, is available in 50, 65, or 80 Shore A durometer. In addition, Pharma Advanced Pump Tubing (APT), a special 50-durometer elastomer that provides approximately four to six times longer life in peristaltic pumps compared to standard 50-durometer tubing, is available.

**Flexibility in Design and Components**

Today’s biopharmaceutical and pharmaceutical applications require flexibility and versatility for tubing and connective components. Many types of connections exist with some of the most common being a wye, tee or sanitary flange, while other customer-specific configurations are also available. Dow Corning can partner with customers to provide custom component configurations and characterization data targeted to meet their specific application needs. For example, Pharma APT might be used in sections of an assembly exposed to peristaltic pump operations while tubing with a higher durometer is used downstream where more durability and resistance to burst pressure is required.

**Silicone: The Material of Choice for Purity**

Emerging global regulatory requirements have shown an increased concern for biocompatibility of materials that have body contact or that may leach into parenteral drug products. As a result, suppliers of silicone tubing often receive questions related to whether silicone materials contain genetically-modified organisms (GMOs), animal-derived ingredients, natural rubber, latex, organic impurities, preservative impurities or phthalates. Therefore, it is critical that biopharmaceutical manufacturers work with suppliers that fully understand and manage their supply chain to ensure they produce materials in compliance with current regulatory standards and guidelines. In this regard, Dow Corning Pharma Fabricated Tubing Assemblies (like Dow Corning Pharma Tubing) have been specifically developed and designed for the transport of critical fluids, taking into account that the purity of those fluids is paramount.

The silicone elastomers used to produce the fabricated tubing assemblies comprise a silicone (polydimethylsiloxane polymer) base, silica, silicone cross-linker, inhibitor and a catalyst (3). No other additives or organic plasticizers, GMOs, vegetable-derived or animal-derived products are added to the silicone formulation. In addition, silicone elastomers do not contain latex.

Silicone is probably the most extensively tested material used in health care applications (4). With its documented biocompatibility, long history of use and established performance knowledge base, silicone products often stand out as the materials of choice in applications that use tubing. Because silicones do not support microbial growth and because they have low extractables content, they are adapted to a wide range of applications.

With its integrated supply chain, Dow Corning controls each process, from synthesizing the silicone polymer, to formulating the elastomer, to extruding and fabricating the components and finally to
delivering the completed FTA. Dow Corning’s FTAs are thoroughly tested, fully traceable, comprehensively documented and thoroughly managed for contamination and change control, including customer notification of significant change. With these safeguards and the low extractables content of silicone when compared to other organic materials, the risk of contamination is greatly minimized.

Dow Corning’s FDA-registered Healthcare Industries Materials Site in Hemlock, MI is dedicated to the production of silicone materials for healthcare applications and is registered with the FDA as a Drug Establishment. The quality system for the production of tubing and FTAs is based on principles of current Good Manufacturing Practices (cGMPs) for both Bulk Pharmaceutical Products and Medical Devices, and the site is ISO 9001:2000 registered. Dow Corning also maintains its own in-house toxicology and expertise center at the company’s Midland, MI headquarters.

**Biocompatibility**
The emerging regulatory environment has caused users of single-use components to fully characterize materials coming in contact with their solution; therefore, Dow Corning has extensively studied the silicone components of Dow Corning Pharma Fabricated Tubing Assemblies per relevant monographs such as USP Class VI (<87>, <88>, <661>, <381>, European Pharmacopeia 3.1.9., and 21 CFR 177.2600. When partnering with Dow Corning, information related to tests such as those referenced and much more can be available.

**Effects of Sterilization Methods**
Silicones remain stable when exposed to a range of sterilization techniques and can be readily sterilized by both autoclave and irradiation.

*Physical performance – dimension, tensile strength, elongation and modulus.* Figure 1 illustrates the stability of silicone tubing when exposed to several autoclave cycles.

![Figure 1. Physical property data following autoclave for Dow Corning® Pharma 50 Tubing (fast exhaust, 132°C, 30 min.).](image)

Gamma irradiation using a cobalt-60 source is a relatively simple method that is gaining widespread use because sterilization can be performed after packaging the final product. Although it is a common means of controlling microorganisms in single-use components, gamma irradiation ionizes and excites polymer molecules, which can result in physical property changes to many polymer formulations (5). However, silicone tubing generally withstands gamma irradiation of up to 50 kiloGray (kGy) without significant degradation or change in physical characteristics.
To demonstrate the impact of gamma irradiation on Dow Corning FTAs and their subcomponents, analysis was performed on several samples of silicone tubing (6) before and after irradiation. Results in Figure 2 were generated on four different tubing products. They were prepared from formulations containing polydimethylsiloxane polymer with different cross-link densities and loaded with varying levels of reinforcing filler and other compositional components. The tubing properties ranged in hardness from Shore A durometer 50 to Shore A durometer 80. As shown in Figure 2, there were no statistically significant changes in the inside diameter of the four tubing products (regardless of tubing durometer) after exposure to 50 kGy of gamma radiation.

In another study, physical properties (tensile strength at break, percent elongation at break and modulus at 200%) were measured on Pharma 50 tubing samples before and after gamma irradiation. Physical property changes due to gamma irradiation were consistent with increased cross-linking of the polymer chains and resulted in increased tensile strength at break, increased modulus at 200% and decreased percent elongation at break (Figure 3).

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**Figure 2.** Average inside diameter of silicone tubing, before and after gamma irradiation at 50 kGy.

**Figure 3.** Physical property changes in tubing before and after gamma irradiation at 50 kGy (Dow Corning® Pharma 50 Tubing).
Extractables evaluations. Silicone formulations used in the production of tubing and molded assemblies for pharmaceutical or biopharmaceutical processing applications typically do not include plasticizers, stabilizers, UV absorbers or antioxidants. Extractables for these formulations consist of short chain silicone-based oligomers. To evaluate the effect of extreme gamma irradiation (50 kGy) (2) on extractables, both gamma irradiated and control samples of Pharma 50 tubing were subjected to various solvent extractions.

Gamma irradiation had statistically insignificant effects on the measured extractables content, regardless of tubing formulation (durometer). In addition, based on the requirements of USP Class VI testing, biocompatibility data on gamma-irradiated tubing showed that exposure did not compromise biocompatibility of these materials.

Performance Evaluations
Because FTAs may be exposed to high pressure during fluid transfer, resistance to leakage and burst were evaluated (6). To assess potential for leakage, an FTA sample was filled with water, pressurized, and observed for visible fluid loss. With water pressurized at 25-30 psi for five minutes, each FTA test group showed no fault in design that resulted in leakage. In actual use, pressure resistance will be product specific and will depend on factors such as wall thickness, inside diameter, formulation, and type of connection.

To evaluate burst pressure, an FTA component (molded silicone wye and tubing) was filled with water then pressurized until a leak occurred. As shown in Figure 5, the sterilized FTAs displayed better burst strength than the nonsterilized FTA, suggesting that FTA performance can be improved with exposure to common sterilization techniques.

![Figure 5](image)

Figure 5. Average burst pressure (psi) for molded silicone wye with 50 durometer, 3/8 inch ID x 5/8 inch OD tubing, following autoclaving (60 min, 121°C) and gamma irradiation (34 kGy).

FTAs that are connected to existing manufacturing equipment can be exposed to traction; therefore, pull-apart strength was evaluated. The test method was based on ASTM D 412. To execute the pull-apart test, the molded connection was placed between load cells on laboratory equipment capable of gathering stress/strain data (Instron® tensile testing equipment). For the results shown in Figure 6, tubing connections approaching 180 degrees from each other were connected in the jaws of the load cells then pulled apart at a specified rate. Results were recorded as force in pounds required to pull the molded
assembly or its components apart. The maximum value of pull-apart force was recorded in Figure 6 for the control, as well as for tubing sterilized by both autoclaving and gamma irradiation.

![Figure 6. Pull-apart (lb) for molded silicone wye with Pharma-50 3/8 inch ID x 5/8 inch OD tubing, following autoclaving (60 min, 121°C) and gamma irradiation (34 kGy).](image)

Other physical performance measures meaningful to users of products such as silicone tubing and fabricated tubing assemblies can correlate to the respective product formulation and/or physical dimensions. One such tubing dimension is called the hoop stress quotient (HSQ), which compares the inner diameter of tubing to its outer diameter.

One noticeable difference between the products used in the burst pressure test is their Shore A hardness (durometer). Durometer is an indication of the resistance of a product to compression, which often correlates to the burst pressure resistance of the material. Changing the cross-link density and/or concentration of reinforcing filler of the product can impact its strength.

The data in Figure 7 show an increase in burst pressure for a given size (HSQ) as durometer increases. The figure also shows that burst pressure can be influenced by changes to the dimension of the tubing. Together, these properties can be customized to target a specific process condition.

![Figure 7. Relationship between hoop stress quotient and burst pressure for Pt-catalyzed Pharma tubing.](image)
Silicone tubing can be formulated for high resilience, a property that is vital in applications such as peristaltic pumps, where the tubing is required to return to its original shape after compression with a roller. Because roller pumps may need to run at several hundred rotations per minute, the tubing experiences repeated flexing and releasing.

Performance of silicone tubing in peristaltic pump applications can be formulation dependent. While tubing products are prepared from similar polydimethylsiloxane formulations, their composition or physical profiles may differ in important aspects such as concentration of reinforcing filler and cross-link density. This formulation flexibility imparts significant performance differences, which illustrate the importance of identifying critical process needs to ensure selection of the most effective tubing formulation for the intended application (Figure 8).

![Figure 8. Pump life of tubing without back pressure (pump life results using water; 3/8 inch ID x 5/8 inch OD tubing was run at 600 rpm; 3/16 inch ID x 3/8 inch OD tubing was run at 650 rpm).](image)

**Conclusions**

Dow Corning’s Pharma Fabricated Tubing Assemblies provide a range of benefits in pharmaceutical and biopharmaceutical processing applications. The documented low level of extractables helps ensure purity of drug products. In addition, the fully-fabricated, single-use components offer faster and more efficient assembly and implementation, minimizing overall system cost. The overall result can be improved production with significantly reduced risk of product contamination.
References


