Healthcare Solutions

DUPONT™

Silicone tubing for pharmaceutical processing

LIVEO™

Abstract

This article gives those involved in the manufacturing of pharmaceuticals a short, but scientific overview about tubing (in particular, silicone tubing) currently used for fluid transfer, peristaltic pumping and filling operations. The article presents the benefits and limitations of such tubing and discusses the variables that need to be taken into consideration.

Introduction

This article is about pharmaceutical processing and flexible tubing; that is, tubing made from various polymeric materials, and in particular, silicone polymers. Stainless steel and glass are also widely used in this application, but as they lie outside this definition will not be considered further, despite their outstanding and unique mechanical properties and inertness.[1]

Flexible tubing has gained more acceptance in recent years as it offers low costs and simplicity, particularly for single-use applications where one can reduce costs associated with validation, cleaning-in-place (CIP) or sterilization-in-place (SIP) and disposal of contaminated waste waters.

Many of the articles about flexible tubing for pharmaceutical processing are generated by suppliers, each one promoting their own attributes and advantages. Specifiers are then left to build their experience and search through a maze of data to make a final selection. Selecting suitable tubing is no simple task: suppliers may not openly provide the composition of their tubing (fluoroelastomer, polyurethane, polyvinylchloride, silicone, polyolefin or other), but rather, provide their opinion of what it is designed for.

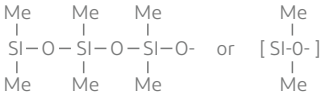
It is interesting to note that Billmeyer's textbook seems to offer few insights into the general properties of silicones, other than citing their weather resistance.[2] Indeed, silicone elastomers have limited mechanical strength and only represent a fraction of the polymers used around us, yet some of their properties make them unique in pharmaceutical applications. The approach of this article is to provide an exhaustive list of relevant parameters for silicone tubing, including what they can or cannot offer, to those who specify tubing.

The first mention of silicone tubing appeared in 1948 when butyl rubber was shown to have lower permeability to gases than a comparable silicone material.[3] It is astonishing that silicone tubing was already considered at that time, since silicones in general were not introduced to the market until around 1943. Today silicone tubing is used in many operations to assist in the production of pharmaceuticals, including fluid transfer, peristaltic pumping and filling operations.[4,5]

Silicone Properties

Silicones have many interesting properties that make them suitable for tubing applications, some of which are listed below.[6]

Silicone Polymers. Silicone is a commercial name describing many products, but most are made from polydimethylsiloxanes or PDMS of the structure:



These polymers are characterized by strong covalent bonds resistant to hemolytic scission (silicones are UV stable; they are also thermally and chemically stable and so easy to sterilize). The polar backbone can be susceptible to heterolytic scission, but the methyl groups along the chain provide shielding (Figure 1).

Silicones are therefore hydrophobic, and the contact angle of water on a PDMS model surface is high, 108°.[7] Because of this hydrophobicity, reactions between silicones and aqueous media are not favored in the absence of surfactants, and then only in the presence of very strong bases or acids.

Because of the low methyl-to-methyl intermolecular interactions between PDMS chains:

- PDMS displays very low Tg (146 K), a property critical for silicones to be elastomers (see below).
- PDMS is "compatible" with hydrocarbons (polymers dissolve in such nonpolar solvents, while elastomers absorb and swell in these solvents).
- PDMS is highly permeable to many low molecular weight species/nonpolar substances, such as hydrocarbons as described above or gases (Table 1). The latter property is useful for the oxygenation of cell cultures, for example, as used in the Corning® E-Cube™ Culture System (Figure 2).[8]

Silicone polymer synthesis has been reviewed elsewhere.[6] With respect to the application discussed here, and specifically regarding impurities, it is worth noting that the synthesis of silicone polymers starts from distilled ingredients and does not involve solvents or heavy metals. Impurities are essentially short linear or cyclic silicone oligomers of some volatility and of the general formula $-(SiMe2O)_n-$. Such species are either used as the starting oligomers or are generated during the polymerization reaction.

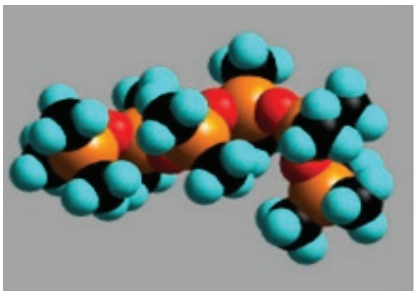


Figure 1. Three-dimensional view of a short PDMS oligomer, $Me_3SiO(SiMe_2O)_4SiMe_3$, showing the shielding of the polysiloxane backbone by the methyl groups (structural representation courtesy of S. Grigoras, DuPont).

Figure 2. Silicone tubing is used to oxygenate the Corning® E-Cube™ culture system (photograph courtesy of Corning Inc.).

Table 1: Comparison of the Permeability of Polydimethylsiloxane with Other Polymers[9]

	Permeability to O_2 $(cm^3.cm)/(s.cm^2.kPa) \times 10^{-7}$	Permeability to CO_2 $(cm^3.cm)/(s.cm^2.kPa) \times 10^{-7}$
Polydimethylsiloxane (PDMS)	79	405
Polyethylene (PE)	0.002	0.007
Polytetrafluoroethylene (PTFE)	0.001	0.003

Silicone Elastomers. Silicone polymers are easily converted into three dimensional networks or elastomers using a cross-linking reaction (cure). For making tubing, two reactions are preferred.[6]

1. Peroxide initiated, where a peroxide is used to produce radicals $R^{\cdot}$ and initiate bonds between chains. This works best when the siloxane chains carry some vinyl groups:

$$\equiv Si\text{-}CH{=}CH_2 + CH_3\text{-}Si\equiv \xrightarrow{R^{\cdot}} \equiv Si\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}Si\equiv$$

where ≡ represents the remaining valences of the Si (Me groups and backbone chain).

The peroxide of choice for extrusion, and to minimize air inhibition, is bis (2,4- dichlorobenzoyl) peroxide. But, this peroxide gives rise to the formation of byproducts such as 2,4-dichlorobenzoic acid10 or various polychlorobiphenyl congeners (PCBs).[11] These byproducts can affect the stability of the tubing, diffuse and concentrate at the surface or "bloom" and/or lead to toxicological concerns. After extrusion of such tubing, and prior to use, these byproducts must be eliminated by careful post-curing, which may require several hours in ventilated ovens at elevated temperatures.

2. Platinum catalyzed where an organometallic Pt complex catalyses the addition of a SiH group to a vinyl group:

$$\equiv Si\text{-}CH{=}CH_2 + H\text{-}Si\equiv \xrightarrow{Pt\ cat.} \equiv Si\text{-}CH_2\text{-}CH_2\text{-}Si\equiv$$

The advantages of this reaction are that there are no byproducts (addition reaction), only a low level of catalyst (10 ppm of Pt) is used, and there is no need for post-curing.

As the cross-linking points are few and the polymer chains long, cross-linked silicone networks retain the low Tg displayed by silicone polymers. So, silicones are elastomeric at ambient temperature without the need for platicisers.[12] This property also allows them to maintain their purity.

Note that as the chain-to-chain interactions are weak, silicone networks have low mechanical properties in the absence of fillers, such as fumed/amorphous silica. To ease the compounding of such filler, various silica surface treating agents are used. In particular, these include hydroxy-endblocked short chain siloxane oligomers such as $HO(SiMe_2O)_nH$, or silazanes such as $(Me_3Si)_2NH$, which bond to the silica surface and render the silica more easy to disperse in the silicone polymer.[13]

Silicone Tubing. Silicone tubing is made by extrusion of the above compounded elastomers, known as high consistency silicone rubbers (HCR). These thermoset materials are available as two-part products:

Base plus a peroxide, usually in the form of a paste (or "masterbatch") for the peroxide initiated products, or

- Part A and part B for the Pt catalyzed products.

In both cases, the two components are mixed at the point of use, for example using a two-roll mill, before extrusion at room temperature followed by continuous curing in high temperature ovens. Different dies and mandrels are used to produce single-lumen tubing of various size and wall thickness (defined by their outside diameter/inside diameter, or OD/ID, with specific tolerances). Other tubing designs are also available (e.g., multilumen, side-by-side), but these are generally for use in more specific applications such as medical devices. Levels of remaining oligomers (see above) depend on cure conditions or further processing steps, such as postcuring for the peroxide products, and storage. Tubing is packaged and provided as extruded, usually in 50-foot coils, and double-bagged in separately sealed polyethylene bags.

It is worth mentioning that, as silicones are thermoset, they cannot be reprocessed as thermoplastics. For the same reason, they cannot be heat sealed; therefore, to make connections, silicone tubing is stretched over a hose barb connector and secured with two cable ties attached in opposite directions to hold the tubing in place.[5] Overmolding is possible and sometimes used in the medical device area.

Several considerations are important in the selection of tubing. The next sections address them by comparing the properties of various tubing materials as well as their performance in transfer pumping operations.

Tubing Performance

Brand. Although branding is not really a property, it is still worthy of some consideration as it occurs in literature and can be confusing. What exactly a brand is intended to represent in terms of performance is somewhat of a mystery, especially when one single brand name encompasses materials with very different compositions. Of special concern to DuPont is the use of their silicone elastomer brand, Liveo™, which is often used to mean "any silicone" used in a medical application. A practical approach would be to understand the owner and meaning of a brand before relying on it.

Appearance and Mechanical Properties. Silicone clarity is at best described as "translucent" when compared to some organic thermoplastics. This results because silicone elastomer, from which the tubing is made, comprises silicone polymers and amorphous silica (see above). Since these two materials have different refractive indices, and as there is no specific compounding to match them, silicone tubing is translucent.

After cure, silicone elastomers display interesting mechanical properties (Table 2). These include medium hardness and high elongation at break, although with lower tensile strength than polyurethane (PU). They have a tacky surface and a high coefficient of friction when compared to polytetrafluoroethylene (PTFE), yet they are far less rigid. Being hydrophobic and excellent electrical insulators, they can attract dust. Their operating temperature range is wider than PVC.

For silicone tubing, various defects may exist, including:

- Extrusion lines or gels (probably resulting from premature cure in the extruder)

- Bubbles (evolution of water vapor during cure from moisture that may have been absorbed onto the cooled cylinders of the two-roll mill or hydrogen evolution from a side reaction between H-Si≡ and hydroxyl species in Pt cured product)[6]
- Particulate contamination

Establishing limits for such defects is not an easy task, yet they should be detailed in a supplier's sales specifications. Some visual tests are even referenced in ISO standards related to silicone elastomers used for tubing extrusion.[17]

Other issues associated with mechanical properties relate to floor space and handling. Concerns here are "managing" the tubing in the production of pharmaceuticals, utilizing the smallest possible floor space, while avoiding problems such as kinking. Variables to consider include bend radius (the radius of a bent section of tubing measured to the innermost surface of the curved portion) and force to bend (the amount of stress required to bend to a specified radius).[18]

Table 2. Typical Mechanical Properties of Materials Used for Flexible Tubing[2,14-16]

Property	Unit	PTFE	Silicone	PVC	PU
Tensile strength	MPa	21–35	6.8–8.7	14	56
	psi	3000–5000	990–1265	2000	8000
Elongation at break	%	200–400	570–795	400	550
Hardness	Shore	D: 50–65	A: 50–80	A: 68	A: 85
Brittle temperature	°C	-240	-80	-40	-68
Max. operating temperature	°C	+260	+215	+79	+80
Color	-	Opaque	Translucent	Clear	Clear

Silicone tubing can by marked by external printing but, because of its low surface energy, inks do not adhere well and can be removed during cleaning with solvents, which are sometimes used. Silicone is also pigmentable. Barium sulphate has long been used as white filler for bulk pigmentation or in co-extrusion stripes for medical devices where X-ray radiopacity is important.

Service Temperatures. Because of their low Tg and high thermal stability, silicones can operate over a wide range of temperatures. Perhaps not relevant to manufacturers of pharmaceutical or biotechnology products, silicones are quoted with a temperature operating range from -80°C to +215°C, the widest operating range for any commercial elastomer.[2]

Chemical Resistance. Although they are unlikely to be present in pharmaceutical processing such as fermentations or filling operations, two factors limit the chemical resistance of silicones: swelling by certain organic solvents and chemical degradation by strong bases or acids.

Swelling of silicones occurs in hydrocarbon nonpolar organic solvents such as toluene. Up to 200% w/w gain can occur, resulting in a mechanically weaker elastomer where bonds are not actually broken but where the elastomer is "diluted." Swelling is dependent on both time and molecular weight because it is diffusion controlled. Silicone tubing swells quickly in low molecular weight silicones but less in high molecular weight silicones (Table 3).

On the other hand, degradation can occur in the presence of strong bases or strong acids, which hydrolyze the siloxane bonds and cause depolymerization of the siloxane backbone.

This leads to various "trade" tables (Table 3), which sometimes contain conflicting information since test conditions and ratings are not always comparable. Moreover, combinations of ingredients may prove to be much more potent than single ingredients. For example, silicone can be "cleaned" from laboratory glassware with a mixture of water, alcohol and strong base, while none of the ingredients alone will affect it.

Not surprisingly, therefore, compatibility must be assessed on a case-by-case basis.

Purity and Extractables. Those involved in pharmaceutical validation now divide the issue of material migration from tubings and containers into "leachables" and "extractables." The former are materials that migrate under normal use conditions, while the latter require exaggerated temperatures or rigorous solvents ("worst case"). Extractables are expected to include leachables, and this term will be used here for further discussion.

In either case, tubings made with plasticizers might be expected to produce more extractables than those without additives. Silicones inherently do not require plasticizers, stabilizers, UV absorbers or antioxidants. Due to the manner in which they are manufactured, silicones often contain very low levels of heavy metals, usually less than 10 ppm.

Table 3. Silicone Tubing/Elastomer Resistance to Various Ingredients and Conditions

		Change in mechanical properties[20]				
Ingredient	**Overall rating[19]**	**Conditions**	**Hardness Change, Shore A**	**Tensile Strength % change**	**Elongation at Break % change**	**Volume* % change**
Water	C – Fair moderate effect	7d/24°C	Nil			nil
		7d/70°C	Nil	-5	+10	nil
Steam		7d/5 psi	-5	-15	+5	+5
		1d/50 psi	-5	-25	-10	+5
NaOH 50%	A1 – Excellent	7d/24°C	-5			nil
KOH	C – Fair	1d/150°C (sat.)	-20	-40	-10	-10
Toluene	D – Severe effect	7d/24°C				+205
Acetone	D – Severe effect	7d/24°C	-10			+15
Ethanol	B – Good	7d/24°C	-5			+5
Silicone	C - Fair	7d/24°C (10 cSt)	-15	-45	-55	+95
		7d/24°C (60,000 cSt)	-5	-10	Nil	+10

*Negative figures are linked to degradation or, more precisely, depolymerization.

Pt complexes are used as catalyst for cross-linking but at low levels (10 ppm Pt); once cured, quantifiable levels of platinum are not found in extractables, even when rigorous solvents are employed.[21]

For silicones, extractables consist in large part of short chain oligomers,[6] -$(SiMe_2O)_n$-, for which acceptable residual levels may be defined by risk assessment.

A recent article reviewed how best to analyze for extractables from silicone elastomers.[21] The article focuses on obtaining the maximum potential extractables in one single extraction test. "Exaggerated" conditions are described with precautions taken not to lose significant volatiles, as could occur during storage or sterilization, and to minimize degradation of the elastomer.

The recommended conditions allow separation of extracts from the product and minimize swelling, which could impact data interpretation due to poor solvent recovery and the entrapment of extractables in the swollen elastomer network. The observations were as follows:

- Among the solvents used, the highest levels of extractables were observed with acetone (around 2% w/w), while low levels of extractables were obtained with ethanol, water or other aqueous media. Acetone may be an ideal solvent for "exaggerated" studies per the purpose of this study.
- Sample configuration is critical, as extraction yields decrease with thicker samples.
- Extractables, as expected, decrease upon storage or after sterilization.

Understanding tubing composition is therefore a consideration in selecting the best way to study extractables. Ultimately, the goal is to detect and assay specific impurities and correlate them to toxicological studies (see below).

Cleaning and Sterilization. Tubing is packaged "as extruded." The importance of cleaning prior to use is mentioned in an article comparing silicone with other tubing, with regards to incubation of natural plankton:[22] silicone exerted no significant effect, while some other tubing decreased the phytoplankton growth rate, an effect that in some cases was removed after washing. Prior to use, cleaning with water for injection (WFI), followed by compressed air drying in controlled-atmosphere rooms is practiced by some, though few details are available.

Because of its stability, silicone is easy to sterilize. Common sterilization procedures include:[23]

- Autoclave (steam) in a standard gravity steam sterilization cycle (30 minutes at 15 psi and 121°C), or in a highspeed flash steam sterilization cycle (15 minutes at 30 psi and 132°C). Note that silicone materials are more difficult to heat than materials such as thermoplastics because they have thermal insulating properties and so may require more time to heat.
- Gamma irradiation studies on DuPont™ Liveo™ Pharma Tubing products have shown that doses of gamma irradiation up to 5 Mrad (50 kGy) minimally affect the physical properties (durometer, elongation, modulus, tensile, tear strength) and extractables profile of the tubing.
- Ethylene oxide (ETO) with sufficient time to allow for complete degassing of residual ETO. Residual levels of ETO after sterilization have been investigated with different tubing, and silicone was shown to absorb less and release ETO faster than PVC or polyester-polyurethane tubing.[24]
- Sterilization by e-beam also has been mentioned.[25]

Repeated sterilizations, up to 10 cycles for ETO[25] and 25 cycles with steam,[26] have shown no significant effect on the mechanical properties of silicone elastomers.

Tubing Performance in Transfer Operations

Surface Smoothness. Inner surface smoothness is sometimes promoted to reduce risk of particle entrapment and buildup.[27] Probably more important is poor wetting to improve drainage and limit biofilm adhesion. PTFE, despite a higher rugosity than electro-polished stainless steel,[1] has been shown to be amenable to biofilm removal.[28] This phenomenon has been linked to its hydrophobicity and high water contact angle.[1] Some authors interpret these results as lower reactivity and inherently better compatibility.[25] Note that similarly to PTFE, PDMS also yields a high water contact angle.[7] There are probably some limitations to such compatibility claims: a high water contact angle appears to be important, but this alone is not sufficient to make conclusions regarding low chemical reactivity, and for tubing selection, other criteria also need to be considered.

Another interesting aspect concerns rugosity. PTFE, despite its rugosity, results in a lower pressure drop than stainless steel tubing. This allows retrofitting with perfluoropolymers as pressure losses can be minimized and allows for lower diameter tubing.[1] Such a study does not yet seem to exist for silicone tubing.

Burst Resistance. Silicone tubing is highly flexible and expands with increased intraluminal pressure. For example, when pumping high viscosity fluids or when short-bend radii make kinking a concern, there is a risk that the tubing may "balloon" and ultimately burst. A recent study details burst resistance for both standard and braid-reinforced DuPont™ Liveo™ silicone elastomer tubing (the latter is made from silicone elastomer overlaid with a polyester braid and then another layer of silicone elastomer).[29] The results indicate:[30]

- Lot-to-lot variation appears greater with smaller dimension tubing, most probably because small defects are likely to be more critical here.
- For tubing of a given dimension, burst strength increases with increasing elastomer hardness (50 to 80 Shore A).
- Depending on dimensions, the burst strength (at room temperature) of standard silicone tubing lies in the range 30 to 250 psi, while that for reinforced/braided tubing can be five-fold greater for the corresponding dimensions.

Note that since silicone mechanical properties are strain rate-dependent, burst resistance may be affected by the rate of pressure change.[30] Some suppliers quote a maximum working pressure, often between 1/5 and 1/3 of the burst pressure, yet apparently without published data to support this or without explanations about the process variables to be considered. So, setting limits is left with the user.

Sorption. Over time, tubing can selectively absorb certain ingredients from the solution it comes into contact with, in particular low molecular weight substances. A recent study on the sorption of parabens shows that if filling lines are left idle for extended periods, perfluoro tubing performs better than many other tubing products, including silicone tubing, which can absorb up to 40% of the preservatives over a six-hour period (static condition, no flow).[31-34] Sorption of other substances has been reported (e.g., liposomal formulations).[35]

Tubing Performance in Pumping Operations

The advantages of peristaltic pumping are clear (closed system with no risk of outside contamination by air or lubricant from the pump). The technique is used not only for processing pharmaceuticals, but also for blood pumping in extracorporeal blood circulation in cardiopulmonary bypass surgery or hemodialysis. These are some of the most demanding tubing applications. They not only require resistance to "chemicals" but also resistance to distortion during use, which could reduce flow rates as the tubing flattens, and resistance to catastrophic failure/leakage (pump life). Pump life depends on many factors such as pump settings, the product being pumped, and the tubing material itself. Overall, certain organic thermoplastics seem to perform better than silicones when only considering pump life,[36] although there is much conflicting data.

The recovery capability or resilience of the elastomer is critical and can be measured by tests such as compression set (how much "memory" will remain in an elastomer after it has been subjected to a permanent compression) or hysteresis (how much energy is being dissipated between a "low stress and relax" cycle).

Regarding silicone, peroxide initiated elastomers perform better than those cured with platinum. An interesting correlation has been established between hysteresis, a simpler test to run than compression set, and tubing pump life. It has been found that the extended pump life of peroxide initiated silicone elastomers may be explained by their lower compression set and lower hysteresis when compared with platinum cured elastomers.[37] As a result of this observation, platinum cured elastomers with lower hysteresis have been developed for use in pumping applications.[38]

Table 4. Spallation Weight During Pumping (5 l/min with saline)[40]

	Particles total weight (µg)			
Time (hr)	Silicone Peroxide	Silicone Platinum standard grade	Silicone Platinum lower hysteresis grade	PVC
1	87	197	86	85
4	191	383	229	219

Spallation refers to degradation and the amount of particles generated and released from the tubing wall during peristaltic pumping but well before catastrophic failure or leakage. Spallation is dependent on the tubing composition: low spallation has been reported for fluoroelastomers,[30] and the issue has been much studied in blood pumping applications. In addition, pump settings have been shown to be critical. When occlusion forces were reduced, spallation from silicone tubing was largely reduced.[39] Interestingly enough, platinum cured silicone elastomer with lower hysteresis, as described above, once again appears to perform better than standard grades of platinum tubing (Table 4).

Standards

Relevant standards that should be considered when selecting tubing for pharmaceutical processing might include:

- FDA G95-1 Memorandum "Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices"
- International Standard ISO 10993: "Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing," and "idem, Part 11: Tests for Systemic Toxicity"
- United States Pharmacopeia: "Biological Reactivity Tests, In Vivo," Classification of Plastics: Class V and VI
- ASTM F748-98: "Standard Practice for Selecting Generic Biological Test Methods for Materials and Devices"
- FDA 21 CFR 177.2600: Rubber articles intended for repeated use
- 3-A Sanitary standards, Standards and practices for the sanitary design, fabrication, installation and cleanability of dairy and food equipment or systems used to handle, process and package consumable products where a high degree of sanitation is required
- National Sanitation Foundation (NSF51): "Materials and Components used in Food Equipment"
- European Pharmacopoeia 3.1.9: "Silicone elastomers for closures and tubing"

Each of these standards addresses different properties that could impact tubing selection, such as identification, presence of specific impurities, extractable or volatile substances, heavy metals, resistance to specific chemicals and some biological parameters.

It is interesting to note that tubing is sometimes promoted in the EU as carrying a "CE Mark." This is irrelevant for pharmaceutical applications, and even in medical device applications, as the tubing alone is only a "component," perhaps essential, but not yet a finished product requiring compliance with the Medical Device Directive (93/42/EEC) and CE Marking. However, the Directive does require that tubing users be responsible for establishing the quality and suitability of the tubing they select.

Toxicology, Impact on the Environment and Disposal

Interesting trade claims are made by some suppliers, such as "contains no toxic extractables (non-PVC, non-latex, non-silicone)".[36] Data from a recent study, based on clinical trials on tubing used in extracorporeal circulation during cardiopulmonary bypass, showed that platinum cured silicone tubing induced lower leukocyte adhesion than any other tubing.[41] Although it is not the purpose of this article to provide a detailed review of this topic, there is growing attention in this area, both at a product level and along the entire supply chain, from raw materials though product generation and disposal.

For raw materials, even process ingredients can be critical, especially if they are potentially toxic and/or hazardous. For example, there is currently much discussion about perfluorooctanoic acid (PFOA) or its salts, which are used as essential processing aids in the polymerization of fluoropolymers, even if the finished products are not expected to contain PFOA.[42] The material from which the tubing is made can also be important;

for example, in the case of polyvinylchloride (PVC), phthalate plasticizers may be present. Silicones too have been in the limelight following the breast implant controversy. As a result, manufacturer associations are coordinating efforts and sharing costs to address such issues. One example is the $35 million Siloxane Research Program, which, under DuPont's leadership, is further investigating the toxicology of six silicone model compounds.

Silicone and the environment are addressed in a recent book.[43] Regarding silicone tubing disposal, incineration is probably the most likely method. Incineration of silicone tubing leads to the formation of CO_2, SiO_2 and water; thus, there are no toxicity concerns with its degradation products. In addition, the toxicity of silicone elastomers is not a concern. In addition to their use in pharmaceutical processing, they are often used in many long-term medical devices such as hydrocephalic shunts or pacemaker leads.

Another environmental impact to consider is single- versus multiple-use tubing, the latter requiring a significant level of validation, WFI and disposal of CIP-contaminated streams.[5]

Cost

Cost to acquire tubing is only one element to consider, as there is a spectrum of options from a fixed "asset" made of a stainless steel and/or glass for multiple uses, to a simpler asset including reuseable or disposable tubing, to a single-use flexible approach made of both disposable bags and tubing. A recent article addresses the issue. It concludes that single-use options offer much capital savings as expected, and that they improve manufacturing flexibility. They also offer opportunities to offset higher raw material costs by immediate savings in validation costs and in recurring costs such as the amount of WFI needed for CIP operations,[44] or the costs of disposal of contaminated waste streams from such operations.[5]

Regulatory Aspects

Global emerging regulations are focusing on risk management[45] and integrated quality systems.[46-48] Integrated quality systems should include not only the ISO 9000 family of quality management standards, but also the appropriate levels of good manufacturing practices (GMPs) based on the criticality of the material being produced (tubing for implantation vs. tubing for external fluid processing), the chance that a significant event could occur, and the potential that the event could be catastrophic. Thus, the supply of raw materials, encompassing such "process aids" as tubing, could be required to follow critical GMPs principles for certain high risk applications.

Although tubing manufacturers are skillfully specialised at extruding, many of them process industrial elastomers for industrial applications. Although they may provide specific test results for pharmaceutical applications per the above standards, this approach often does not take into account other critical requirements, such as applicable GMPs.

Currently, in some countries, "process aids" such as tubing are treated as component articles of drug products and therefore come under the same control regulations as the drugs themselves. Traceability and change control are two important factors to consider. Today many extrusion houses rely on detailed documentation for raw materials, cleaning agents and packaging components as well as change control and notification of changes for materials produced upstream by their suppliers. Other critical variables that may be important include environmental control in the extrusion area, cross-contamination resulting from other materials produced on site, and rework practices. A recent publication highlights various requirements designed to ensure compliance and management for risk.[49]

Based on the above trends, DuPont is unique as a supplier of tubing because of its integrated supply chain and the fact that it produces both silicone elastomers and silicone tubing at sites registered and audited by the United States FDA. This provides complete traceability from polymer compounding through tubing manufacturing, and this under a quality system based on both ISO 9001:2000 and critical principles of GMPs.

Conclusions

First some trends:

- There is currently major growth in biotechnology, and a possible shortage of stainless steel reactor capacity. In addition, there is a move towards simpler/faster solutions from tubing with fittings, to fully equipped ready to use "rigs" with tubing, filter, adaptors and connections already in place. This allows raw materials and gas feeds, filtering, sample withdrawal or fluid transfer. Disposable bags with tubing "rigs" are now replacing some reactors (see above). It is also interesting to note that such assemblies are now being outsourced, which is likely to create a new niche market for suppliers.
- Emerging regulatory requirements also favour such assemblies as long as they use well-known materials.

Along with an appropriate understanding of the physicochemical properties of the material, tubing selection also requires knowledge of:

- Costs, not just cost to acquire, but cost in use.
- Risk management; for example, what level of quality or control, such as is provided by GMPs or other standards, is needed from the selected supplier in the application.
- Safety for the ultimate user, the patient, with an understanding of the purity and extractable profile, and links between these and toxicological studies.

In conclusion, silicones appear to be well suited to meet the above. In making a final tubing selection, one must consider their benefits as well as their limitations. It is important to remember that silicone tubing has now been used successfully for more than 30 years in various fluid transfer operations.

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