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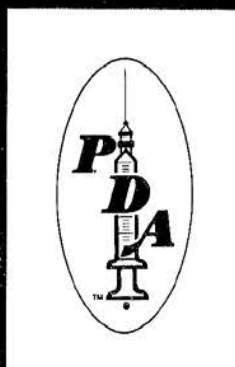
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Siliconization of Parenteral Drug Packaging Components

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Siliconization of Parenteral Drug Packaging Components

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Siliconization of Parenteral Drug Packaging Components

Lubrication of Packaging Components Task Force

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I. Scope

Most parenteral packaging components require the use of some form of lubrication in order to improve their processability and functionality. The Task Force on Lubrication of Packaging Components was formed because of an increasing number of questions about the use, measurement, and toxicity of lubricants.

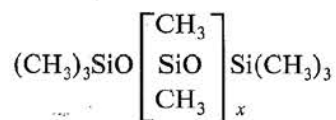
The purpose for this publication is to present information. The publication reviews the common lubricants, the reasons for their use, methods of application and analytical measurement.

It is not the intent of this Task Force to recommend specific materials, methods of application, or analytical procedures, but rather to provide a source of information concerning the use of lubrication on pharmaceutical packaging components.

II. Introduction

One of the most commonly used lubricants for pharmaceutical packaging is polydimethylsiloxane fluid often referred to as silicone fluid. Siliconization of packaging components such as glass, elastomeric closures, plastic, and metal, places an invisible water repellant film on the surface of the components. This film can aid in the free-draining characteristics, processing and machinability of vials and elastomeric closures (1, 2). Silicone fluid is commonly applied to plastic syringe barrels and glass cartridges used as plunger barrels to facilitate easy movement of the plunger within the barrel (3). The application of a silicone film to hypodermic needles reduces the frictional drag and thus the pain associated with this drag as the coated needle passes through body tissue (4).

The term silicone was first used in the early 1900's in England as a generic designation for a family of polymers based on the element silicon. Siloxane is an acronym derived from silicon, oxygen, and methane (5). Commercially, the siloxanes which are most often used are the polydimethylsiloxanes. These materials are a class of chemical compounds composed of alternating silicon and oxygen atoms in a linear arrangement with two methyl (CH_3) groups attached to each silicon atom. The polymers can be end-blocked by a variety of chemical structures. When the trimethylsiloxy [$(\text{CH}_3)_3\text{SiO}-$] group is used, a series of linear silicone fluids is produced which possess the following general structure:



The above formula represents molecules whose structures differ only in x , the number of dimethylsiloxane units; thus, as x increases the molecular weight and viscosity of the fluid increases. The relationship between the degree of polymerization (x), the molecular weight, and the viscosity of typical polydimethylsiloxane fluids appear in an article by S. Braley (6). A 350 centistoke polydimethylsiloxane fluid would have an approximate x value of 130 and an average molecular weight of 9780.

III. Reasons for Lubrication

A. Machinability

Machinability is greatly improved through the use of lubricated packaging components. Siliconization of rubber products reduces the friction present between the rubber closure and the metallic machinery. Lubrication helps eliminate clumping of parts as they are smoothly fed from hoppers to machine paths. These lubricated components then easily transverse down machine guides, reducing any possible problems, which are ultimately very costly in terms of lost production time.

B. Reduction of Insertion Force—Seating

After closures have been successfully transported to the vials, they must be inserted. Siliconization lowers the friction between the vial and the closure. This decrease in friction reduces the force necessary to insert vial stoppers properly.

C. Sealability

It has been observed in industrial manufacturing processes that the integrity of the closure/vial seal is improved by the siliconization of the closure.

D. Minimize Breakloose and Extrusion Force

As with stoppers, lubrication of syringe plungers through siliconization reduces the coefficient of friction on the surface of the plunger. This reduced friction minimizes the energy required to overcome the static force between the plunger and the barrel. Lubrication of the plunger also lowers the extrusion or dynamic forces needed to smoothly expel the drug product from the syringe. In order to keep potential functional problems to a minimum, breakloose and extrusion values should be low.

E. Syringe Barrel Lubrication

Syringe barrel lubrication is closely related to breakloose and extrusion values for plungers. Any lubricant present on the plunger or the barrel will greatly reduce the amount of friction between the two. The decrease in the friction will result in a reduction of force necessary to assure the proper operation. Siliconization of syringes will also aid in the initial insertion of the plunger into the syringe barrel during assembly.

F. Hypodermic Needle Lubrication

By utilizing a process of lubricating needles, a small residual amount of silicone is left on the surface. This silicone film on a hypodermic needle reduces frictional drag resulting in less pain during skin and muscle penetration (7). Lubrication of the needle surface also minimizes the force needed to pierce a rubber closure. In addition to enhanced penetration characteristics, siliconizing needles also improves the process of needle insertion into the protective sheath.

G. Drainage of Vial Contents

Siliconization of vials results in a thin water repellent film being applied to the inner surface of the vial. Aqueous

solutions tend to bead up on these surfaces since they do not wet the silicone film. This leads to characteristic improvements of the drainage of the vial (8). Siliconization of glass is also used to improve the handling of suspension products and to facilitate resuspension following storage.

IV. Compendial References

A. Medical Grade Silicone

The widely used term, Medical Grade Silicone, has no official compendial or regulatory status. The term Medical Grade was introduced by one manufacturer of silicone products. That producer, Dow Corning, attaches the following criteria to these products:

The biocompatibility of the material has been evaluated and a profile established. This profile is based on a series of tests performed by this manufacturer. Results of these tests are a part of the product information.

Medical Grade by this definition does not imply that the material has absolute biocompatibility or lack of toxicity—only that the level has been established by the tests. Further testing of the material by the user may be necessary to establish safety and efficiency for many specific uses.

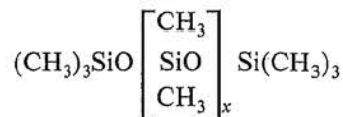
B. USP XXI, NF XVI

The United States Pharmacopeia (USP) contains no monograph on polydimethylsiloxane fluids. However, the USP furnishes a Reference Standard Polydimethylsiloxane, catalog number 54630. This reference standard is referred to in the National Formulary (NF) Monograph on Dimethicone. The original NF monograph on Dimethicone has been supplemented more than once and the most current version is listed in the 5th Supplement of The United States Pharmacopeia Volume XXI and The National Formulary Volume XVI (9).

The NF has as its goal to provide monographs for those pharmaceutical ingredients, which are not included in the USP, as a means of characterizing their composition by providing tests and stating testing limits. While some polydimethylsiloxane manufacturers perform tests necessary to document their adherence to NF specifications, it is necessary for the pharmaceutical end-user of untested fluid to perform the necessary analyses.

C. Cosmetic, Toiletry, and Fragrance Association (CTFA)

The term "Dimethicone" is defined (10) as a mixture of fully methylated linear siloxane polymers containing repeating units of the formula $[(CH_3)_2SiO-]$, units. These fluids possess the following general structure:



This definition is used by both the Cosmetic, Toiletry and Fragrance Association (CTFA) and by the National Formulary (NF). There is however, a different intent associated with these two systems of nomenclature.

The CTFA has adopted names for cosmetic ingredients, many taken from the USP or NF nomenclature system, to assist this industry in standardizing the labeling of these ingredients. The CTFA names do not, however, imply standards or grades of purity, strict chemical equality, or interchangeability of ingredients.

The difference between the CTFA and NF nomenclature concepts is one of compositional testing and stated testing limits. When the designation NF is used in conjunction with an official name, such as "Dimethicone, NF," it indicates that the product is in compliance with the NF standards. No such compliance testing or testing limits are associated with a CTFA product name, such as "Dimethicone."

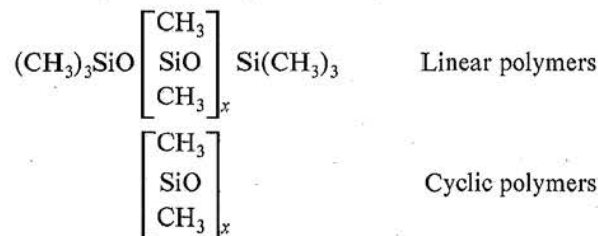
D. Code of Federal Regulations (CFR)

Polydimethylsiloxane fluids are listed in the Code of Federal Regulations, Title 21—Food and Drugs in 178.3570—Lubricants with Incidental Food Contact (a) (3). The specific listing is Dimethylsiloxane (viscosity greater than 300 cst).

V. Toxicity of Polydimethylsiloxane Fluids

A. Introduction

The linear and cyclic polydimethylsiloxanes (PDMS) are materials which are frequently used in cosmetic and pharmaceutical applications because of their stability, hydrophobicity, lubricity, and low toxicity. They are represented by the following structural formulas.



The value of x in the linear polymers can be 2 to several thousand while x for the cyclic species can be 3 to 14, with 4 and 5 being used most frequently. The materials are clear, colorless, oily liquids that are odorless, tasteless, and insoluble in water and highly water repellent. They are also stable at high and low temperatures and are highly resistant to changes due to heat or oxidation. The viscosity of these linear polymers can vary from 0.65 to 1,000,000 centistokes depending on the average chain length (11).

Selected polydimethylsiloxane compounds have been extensively studied to assess their suitability for use in cosmetic, pharmaceutical, and related applications. It is generally believed that data gathered from these selected polymers can be applied to all of the materials except for certain compounds of very low molecular weight.

There is no indication that toxicity would be related to molecular weight or viscosity of these fluids. Calandra et al. have summarized their review of the health and environmental aspects of polydimethylsiloxane fluids by stating: "The polydimethylsiloxanes, in a very extensive bat-

tery of studies, have been shown to be remarkably devoid of toxicologic problems (12). No effects have been demonstrated, even at exposure levels massively exaggerated, over any conceivable use except for transient eye irritation (13)."

Specific references concerning the toxicity of linear polydimethylsiloxane fluids are summarized in this document.

B. Skin

Polydimethylsiloxane (PDMS) was successfully substituted for the liquid petroleum and oil bases of liniments. These compounds were found to be pharmacologically similar to the original formulas with the added benefit of being odorless, having their wide viscosity range contribute to variety in liniment viscosity, and not being subject to rancidity (11). Human-repeated insult tests conducted with PDMS showed no indication that the materials are skin sensitizers (13).

C. Oral

Rowe et al. studied the effect of repeated oral administration of PDMS upon rats. They utilized DC 200 (viscosity = 350 cst) in 20 doses in 28 days with dose groups consisting of 1.0, 2.0, 5.0, 10.0, and 20.0 g/kg. The following results were noted when the experimental group was compared with a control group dosed with correlated amounts of olive oil (14):

Growth—no difference.

Bone marrow—total and nucleated cell counts within standard deviation.

Organ weights at autopsy—within normal limits.

Blood urea nitrogen—within normal limits.

Histopathology—microscopic examination showed no pathologic changes in the heart, spleen, liver, kidney, adrenals, pancreas, bone marrow, stomach, and intestine.

McDonald et al. corroborated these findings in their studies utilizing polydimethylsiloxane (various viscosity) as 1 percent of a rat's diet over a 90-day period (15). They noted no changes in organ weights, body weights, hematocrit, hemoglobin, white blood cell count, and differential. However, they did see some pneumonitis and consolidation with formation of caseous-centered abscesses in the lungs in many of the different groups, including the five control animals.

D. Intraperitoneal

Rowe et al. investigated a single intraperitoneal injection of PDMS in rats. They utilized 0.1, 0.3, 1.0, 3.0, and 10.0 mL/kg dose of varying silicone fluids. The only deaths noted were in the use of hexamethyldisiloxane in the three higher doses. This substance produced a considerable amount of local irritation and extensive visceral adhesions. In the subjects utilizing PDMS, the reaction noted was that of a nonirritating foreign body. Also found at autopsy were body fluid containing nodules on omental tissue and surfaces of the liver, spleen, and diaphragm. However, no inflammation was noted (14).

Hawthorne et al. showed that with subcutaneous or

intraperitoneal injections, the silicone fluid deposition was subjected to phagocytosis and systemic deposition into the reticuloendothelial system. In mice receiving subcutaneous or intraperitoneal injections greater than 7 mL/mouse, Hawthorne noted an accumulation of histocytes containing ingested silicone in the regional lymph nodes. Also clusters of macrophages with vacuolated cytoplasm were seen in distant organs, i.e., liver, spleen, kidney, pancreas, and ovary (16).

Rees et al. demonstrated that PDMS fluid introduced intraperitoneal or subcutaneous injection produced a generalized alteration of abdominal and epicardial adipose tissue. The fat cells appeared smaller and the cytoplasm contained vacuoles. There was macrophage clustering as noted above. The liver showed lesions in all parts of the hepatic lobule, and the kidney demonstrated interstitial renal lesions in which the glomerular capillaries were dilated by a clear, unidentified material (17).

Bischoff noted that, in rabbits, PDMS fluid (viscosity = 360 cs) could augment postoperative pelvic adhesions evaluated 2–4 weeks post-silicone administrations. Bischoff also demonstrated, utilizing male and female rats and mice, that 8/34 of the silicone-dosed females showed reticulum cell sarcoma in the lung or peritoneal cavity during the 17-month study. His doses were 2.0 mL for male rats, and 0.4 mL for female mice. This trend was not seen in the males which was comparable to control. He also noted in the female rat and the male mouse an increase in lung and peritoneal lymphoid tumors (18).

E. Eye

The effects of various types of silicones upon the eye were investigated by Rowe et al., utilizing rabbits. They observed the eyes immediately upon exposure and at 1, 4, 8, 14, and 48 hours post-exposure. The irritation produced was transitory and was eliminated within 24–48 hours. Fluorescein staining failed to show any corneal damage. According to Rowe the human response to these compounds is similar to that of rabbits. The human response demonstrated erythema of conjunctival membranes and edema of the lids is frequently seen (14).

F. Subcutaneous Administration

Andrews noted, in his albino mice studies of the injection site and underlying tissue following a 5 mL subcutaneous injection of DC 360 fluid, a tissue reaction at 1–3 days. This consisted of the mild exudative phase of the inflammatory process with polymorphonuclear cell infiltration and plasma cells and macrophages surrounding the silicone fluid. During 4–10 days, polymorphonuclear cells decreased in number and a predominance of lymphocytes, fibroblasts, and plasma cells were seen. Macrophages with clear vacuoles formed a capsule around the encountered cyst. Deposition of collagen fibers around fibroblasts was also noted after 18 months at the injection site, or in the lung, kidney, intestine, and spleen as well. Andrews also noted neutrophils containing vacuoles due to their phagocytizing the silicone (19).

Hawthorne et al. also noted a similar progression of tissue reaction. He noted that the silicone appeared un-

changed. This group also reported a mild degree of fibrosis present around the cyst with an occasional giant cell seen. This was noted at six months post-injection. However, Hawthorne only noted this cyst formation with massive doses of silicone fluid (16).

Hawthorne also reported that, in rats, small multiple vacuoles at the periphery of the cytoplasm of the red blood cells caused no toxic effects on blood values. This vacuolated red blood cell was seen at 9 months in the groups that had received 14, 21, and 24 mL of silicone fluid subcutaneously. No effect was seen on the white blood cells or the differential count (16). Hawthorne was also unable to prove Andrews' statement that PDMS is transported in the leukocytes in the blood (16, 19).

Rees et al. noted in studies using massive subcutaneous doses of PDMS, an alteration of the tissue structure of the subcutis. Fat cells showed varying degrees of atrophy with cytoplasmic vacuoles. A large number of clear cells was seen throughout the injection site. These were phagocytes with eccentric nuclei. Rees also noted that administration of 7 mL or greater subcutaneously showed a greater than 50 percent mortality rate of mice at 3 months (17).

G. Intravenous Administration

The Dow Chemical Company has placed the intravenous LD50 for the DC 200 (350 cst) fluid in rabbits at about 0.5 g/kg. Cause of death appeared to be the accumulation of silicone fluid in the lungs. It was possible to inject 0.1 g/kg daily for 25 days without obvious ill effects (20).

H. Inhalation

Calandra et al. reported that rats, dogs, and guinea pigs exposed to 300 centiskokes PDMS fluid at a concentration of 2.1 mg/L for 6 hours demonstrated no ill effects (12).

I. Reproduction

Kennedy et al. showed in studies utilizing 20 mg/kg, 200 mg/kg, and 1,000 mg/kg PDMS subcutaneously (DC 360 fluid) in rats that there was no alteration of weight gain, food consumption, or genital development in male rats. In female studies during gestation, the average length of gestation, as well as the mean body weight of the pups, was comparable to the control. No abnormal patterns of behavior nor gross abnormality of dams and pups were noted at 21 days when sacrificed (13).

He also noted a slightly greater number of fetuses derived from dams tested with either 200 or 1,000 mg/kg DC 360 fluid with incompletely developed sternebrae, than fetuses from the control group of the low-dose group. They also noted a slight increase in lack of cranial closure in the 1,000 mg/kg group. He showed that there was an increased incidence of in utero mortality at the 200 and 1,000 mg/kg dose groups during the third trimester as compared to control. They also noted that there was no evidence of teratogenic activity in either rats or rabbits.

Kennedy et al. also noted there was no evidence of fetotoxicity in rats caused by DC 360 fluid when administered during the third trimester of pregnancy. There were no adverse effects on reproductive performance, or on

weights, numbers, or survival of the progeny. Kennedy also stated that they noted no teratogenic effects in rabbits using DC 225 fluid (13).

J. Human

Rees et al. noted that liquid or solid silicone conforms fairly well to the perfect implant material. Elastomeric silicone rubber can be used to replace bone or cartilage in the chin, nose, ear, and related soft tissue reconstruction. Liquid silicone is injected subcutaneously to restore lost tissue contours. They note that there are virtually no complications. Tissue tolerance is high and infection and exposure only occur with solid implants in areas of high tension or gross contamination (21).

Selmanowitz and Orentreich note that in patients followed after having PDMS injected subcutaneously for cosmesis, no alterations were noted in complete blood count with differential, blood chemistry (glucose, BUN, urate, cholesterol, total protein, albumin, bilirubin, alkaline phosphatase, SGOT, LDH, calcium and phosphorus), and urinalysis (22).

Bischoff also noted some interaction with products containing PDMS and the body's response to these silicones. In humans ingesting oils containing PDMS caused a decreased effectiveness on anticoagulants such as warfarin or phenindione (18).

VI. Types of Silicone Lubricants

A. Polydimethylsiloxane Fluid ("Silicone oil")

There are three separate types of silicone products available for use as a lubrication aid for packaging components. The most widely used silicone fluid is a clear, colorless, polydimethylsiloxane fluid, commonly referred to as "Silicone oil." Some major suppliers of polydimethylsiloxane fluid are listed below:

Supplier	Trade Name	Viscosity Range
Bayer Chemical Co.	Baysilon M	Full
Dow Corning	360 Fluid	Full
	200 Fluid	Full
General Electric	SF18 (350)	350 cst only
Rhone-Poulenc, Inc.	Rhodorsil	
	70047 Fluid	Full
Union Carbide Corp.	L-45FG	350 cst only
Wacker-Chemie GmbH	AK Silicone	Full
	Fluids	

Dow Corning differentiates an industrial grade PDMS fluid (DC 200) from "Medical Grade" fluid (DC 360) on the basis of biocompatibility testing profiles. Rhone-Poulenc, Inc. will also supply biocompatibility data on their Rhodorsil® 70047 line.

Fluid polysiloxane can be applied to glass, metal, plastic, and elastomeric surfaces either straight or in a diluted form as a temporary PDMS fluid in water emulsion. When coated on glass or ceramic surfaces, the fluid can be "cured" or converted to a highly durable film by heating the treated surface at temperatures up to 350 °C. More

specific application details can be found in the application section of this paper.

B. Silicone Emulsions

Another form of silicone product used for lubrication of packaging components is a water dilutable emulsion containing approximately 35 percent polymethylsiloxane fluid. The emulsion may be used as received or it may be diluted with water to any desired silicone fluid concentration. The major suppliers of silicone fluids have emulsions available. Specific product information can be obtained from each supplier. Dilution of emulsions with water may result in the need for a bacteriostat or fungistat to counteract possible microbial activity. The emulsifying agents used in silicone emulsions may support bacterial growth.

C. Air Curable Silicones

There is a silicone product, currently available, which cures at room temperature. Not much field experience has been generated with this product use on pharmaceutical packaging. It is listed here as a potential alternative to silicone fluids which require higher temperature to "cure."

The product is available from Dow Corning as MDX-4159 fluid. It is a solution containing 50 percent polydimethylsiloxane which contains an amino functional group mixed with aliphatic solvents. The fluid is not soluble in water. Organic solvents, including aliphatic and aromatic hydrocarbon solvents such as isobutanol and lower molecular weight alcohols, can be used to dilute the fluid to a 2 to 5 percent active silicone level. Since many polymers, both plastic and elastomeric, can be adversely affected by organic solvents, care should be taken in the selection of the diluent. Lower molecular weight alcohols are recommended for elastomeric closures.

VII. Method of Application of Silicones

A. Introduction

The methods of application described in this publication will be limited to those involving polydimethylsiloxane preparations. Other materials such as plastic and resin coatings are sometimes used to impart lubricity to parenteral package components. However, the application of such materials is impractical for the general user as a process step.

One should consider the use of dedicated equipment for all operations involving the preparation and application of PDMS fluid lubricants. It is very difficult to remove all residuals of PDMS fluid during cleaning operations.

B. Preparations

Essentially all treatments utilized for the lubrication of parenteral components are based on the use of PDMS fluid (Silicone Oil). Four main types of preparations and their typical silicone oil concentrations are listed below.

Preparation	Typical PDMS Concentration, %
PDMS Fluid	100
Water dispersion	0.008-10
PDMS fluid in water Emulsion	0.1-25
PDMS fluid in solvent	0.1

Dispersions are prepared by the user, prior to use, with the aid of high-shear apparatus such as rotor/stator dispersers or commercial blenders. One should assess the uniformity of such as rotor/stator dispersers or commercial blenders. One should assess the uniformity of such preparations and be aware that separation may occur during processing.

Emulsions can be prepared by the dilution of commercially available products or by preparing in situ emulsions. Commercial preparations are easily diluted and remain uniformly distributed with the aid of gentle mixing. The user should be aware that emulsifying agents are present in these preparations and residuals of these may remain after treatment. If incompatibilities are found between these emulsifiers and the packaged product, consideration should be given to developing an emulsification process using other agents.

Solutions can be prepared by dissolving PDMS in solvent/carrier systems such as Freon, (1,1,1-Trichlorotrifluoroethane) or Chlorothene (1,1,1-Trichloroethane). Both solvents are volatile and can be dissipated during processing to leave a residual silicone coating. Caution should be used in handling these solvents. Both have potentially adverse effects on the environment. In addition, Chlorothene requires special handling for operator safety.

C. Applications to Elastomeric Materials

Rubber parts, such as vial stoppers, syringe plungers, tip caps, and needle guards, are the most frequently lubricated components used in parenteral manufacture. Lubrication is usually accomplished by direct application of PDMS fluid to the components. Tablet coating pans are often used to distribute the fluid onto the parts. The amount of silicone applied can be controlled by sprayers or atomizers which are usually calibrated on the basis of performance (amount delivered per unit time).

Commercial washing equipment is available which automatically performs a silicone application. Care should be taken in establishing rotation speeds and length of duration of these distribution operations so as not to cause abrasion of the parts. When the same vessel is used for washing and silconing, cleaning procedures must be established which will assure that particulate matter is not left in the equipment following the silicone cycle. PDMS fluid tends to trap particulates and interfere with efficient cleaning between cycles. A mild caustic detergent or an organic solvent can facilitate cleaning of the processing equipment. Validation of cleaning agent removal is part of the process development.

Rubber components can also be lubricated using emulsions or dispersions. This is accomplished through rinsing, or more often, direct immersion of parts in the preparation. Typical contact times range from instantaneous up

Plastic	Results
Nylon	No effect
Polystyrene	No effect
Methacrylics	No effect
Modified methacrylics	No effect
Polycarbonates	No effect
Phenolics	No effect
Cellulose acetate butyrate	Stiffened
Polyacetal (Delrin®)	Stiffened and crazed
Linear polyethylene	Some stress cracking
Linear polypropylene	Some stress cracking
Polyvinyl chloride	Shrinks and hardens
PTFE (Teflon®)	No effect
Polyethylene	Some stress cracking

Figure 1—Effect on plastic after 30 day immersion, PDMS 350 cst.

to 30 minutes. Subsequent to these procedures, parts are drained and sterilized. Drying steps may be used before and/or after sterilization. Again, the effects of interaction between product and possible residual emulsifiers should be considered.

D. Application to Glass

PDMS fluid can be applied to syringe barrels, glass vials, and other glass parts by rinsing with emulsions or dispersions. Typical concentrations used for this purpose are in the range of 0.5 to 1 percent. Carrier/solvent systems are also used for this application.

This operation is usually carried out in a commercial vial washer. It may be incorporated into a standard wash cycle; for example, as a final rinse. Some believe this operation to be more successful when glass is washed and dried prior to performing the silicone application.

Following application of silicone to glass parts, silicone is "cured" by means of dry heat. Temperatures up to 350 °C are used to effect a chemical bonding (cure) between the silicone and the glass (23).

Caution should be taken to minimize silicone residuals on the outside of the glass. The presence of silicone will interfere with adherence of labels to the glass vials.

E. Application to Plastics

It is known that many plastic materials are not adversely affected by surface applications of silicone. General Electric conducted a study where many types of plastics were immersed in 350 centistokes silicone fluid for 30 days (24). Tensile and impact tests were performed to measure physical property changes in the plastics. Figure 1 summarizes the data generated. It is apparent that many plastics were not affected while others showed stiffening, stress cracking, and crazing.

VIII. Measuring Application Consistency

A. Functional Testing

The tests for siliconization on package components can be divided into two categories: functional and chemical or analytical. Functional testing is the most widely used

means of determining whether the amount of PDMS applied is effectively providing adequate lubrication. The most widely used functional testing is a trial run through the packaging equipment. This is commonly referred to as running machinability trials. In the case of vial stoppers, lubricated closures are fed into the hoppers or vibratory bowls and the progress of those closures down the track and into the vial neck is followed. It is advisable to start the machinery trials with a minimal amount of lubricant applied to the component. Subsequent runs with increasing levels of lubricant application can be run in order to determine the optimum amount necessary for the desired line speed.

There are two other functional tests that yield quantitative data which may be helpful. The first of these is the Static Coefficient of Friction (COF), defined as the ratio of the frictional force resisting the movement of the surface being tested to the force applied perpendicular to the surface. Using a Testing Machine, Inc., Coefficient of Friction Tester (26), a metal block containing one closure or plunger in each of four cavities is placed plug side down on an inclined plane. The plane angle at which the block begins to slide is recorded. The tangent of this angle is the COF. It is more convenient to compare to the angle itself during evaluations of parts with various silicone levels. In order for this COF data to be meaningful some confirmatory testing must be performed to determine what COF value will indicate successful machinability at desired line speeds.

The second quantitative test that may prove helpful is a measure of the Insertion Force. Insertion Force is defined as the pressure in grams necessary to seat a closure into the neck of a standard vial in preparation for capping. Insertion Forces of closures with and without lubricant can be compared using an Instron Universal Testing Instrument (27) to measure and record the Insertion Forces.

Syringe systems for drug packaging and delivery are common in the parenteral drug industry. The force needed to start a syringe plunger down the barrel portion of the syringe can be minimized by the use of PDMS on the elastomeric plunger tip as well as by the use of PDMS applied to the interior surface of the barrel. An Instron Universal Testing Instrument can be used to record this force, known as the Breakloose Force.

The force required to move the plunger down the length of the syringe barrel is referred to as the Extrusion Force. If the plunger travels smoothly down the barrel, with no chattering or irregularities, the Extrusion Force will be the same for the entire barrel length. Generally, the Breakloose Force is higher than the Extrusion Force because the force needed to start a stationary object (the plunger) is greater than the force needed to maintain the motion of that object. In addition, microscopic absorption of externally applied lubricant on the plunger tip can be a factor in high Breakloose Forces. If the barrel's lubricant is not cured onto the barrel surface, as in the case of plastic barrels, the insertion of the plunger tip into that barrel during the syringe assembly can reduce the amount of lubricant present at the plunger/barrel interface by mechanical sweeping effects. This also can contribute to a

high Breakloose Force. It is recommended that Breakloose and Extrusion Testing on lubricated assembled syringes be performed both immediately after syringe assembly, as well as after some real or artificially induced aging to measure the true effectiveness of a siliconization procedure. Specific details on Breakloose and Extrusion Testing can be found in the Parenteral Drug Association Technical Methods Bulletin, No. 2 (28).

The absorption of silicone fluid into elastomeric closure components can be affected by the type of polymer, the type and amount of filler material as well as the plasticizer type and amount in the elastomeric formulation. The amount of silicone absorbed can also be affected by the length of the sterilization cycle used. The storage period between siliconization of rubber components and their use, should be controlled. The amount of external silicone needed on an elastomeric plunger to yield an acceptable Breakloose value, initially and throughout the shelf life, should be individually determined for each specific elastomeric formulation.

B. Analytical Determinations

The following infrared method has been used by some manufacturers of elastomeric components to quantitate levels of silicone fluids on their products. It is presented for information and does not have compendial status (29). Atomic Absorption (AA) has been used to determine silicone levels. AA has been found to be tedious and difficult to reproduce in these analyses. Infrared analysis has thus far proven to be more practical.

Quantitative Determination of Surface Silicone Fluid Lubricant from Elastomeric Closures

Principle: The surface silicone fluid is dissolved off the closures using a fluorinated organic solvent. The extract residue is taken up into carbon tetrachloride and quantitative infrared determinations are performed.

Comments: Internal silicone used as a plasticizer in some elastomeric closures does not contribute to the silicone fluid extraction because of the short duration of the fluorinated hydrocarbon contact.

Instruments and Reagents:

1. Infrared spectrophotometer
2. Potassium bromide liquid cell (0.05)
3. Carbon tetrachloride (Reagent Grade)
4. 1,1,2-Trichloro-1,2,2-trifluoroethane (Reagent Grade) (Refrigerant 113)

Extraction: Place all appropriate number of whole closures (usually 5 pieces for 13 or 20 mm closures and 3 for 28 mm closures) into 200 mL Erlenmyer flask. Add 50 mL of 1,1,2-trichloro-1,2,2-trifluoroethane (Refrigerant 113) and immediately shake for 30 seconds. Remove solvent to a 100 mL beaker. Wash Erlenmyer flask with 10 mL Refrigerant 113 for 5 seconds and remove solvent to the same 100 mL beaker.

Evaporate solvent to dryness in a fume hood. Cool and dissolve residue in 5 mL Refrigerant 113. Transfer to 20

mL Erlenmyer, rinsing beaker twice with 2 mL solvent to assure complete transfer. Evaporate solvent to dryness.

Accurately add 1 mL carbon tetrachloride to dissolve the residue. This is the test sample. Caution should be taken to prevent evaporation of the solvent during period prior to infrared determination.

Standard Solutions: Prepare a stock solution of 1000 mg of Silicone fluid (same fluid and viscosity used to lubricate the closures) in 50 mL of carbon tetrachloride.

Prepared the following standard solutions using carbon tetrachloride to dilute to 10.0 mL in a volumetric flask having a neck that will accommodate a ground glass stopper.

	Stock Solution, mL	Concentration of Silicone Fluid, mg/mL
S_0	0	pure solvent
S_1	5	1
S_2	1	2
S_3	2	4
S_4	3	6
S_5	4	8
S_6	5	10
S_7	7	14
S_8	9	18
S_9	10	20

The Standard solutions can be kept refrigerated and in tightly sealed flasks for about 3 months.

Calibration Curve: The IR spectrum of the Standard solutions should be recorded using a liquid cell that provides a 0.05 mm layer of liquid to be scanned. The reference should be air. Silicone fluid exhibits a sharp absorbance peak at 1260 cm^{-1} . The absorbance value¹ at 1260 cm^{-1} should be recorded for all the standard solutions and a calibration curve generated with the mg/mL silicone fluid along the X axis and the absorbance values at 1260 cm^{-1} along the Y axis.

The solvent carbon tetrachloride exhibits a small absorbance value at 1260 cm^{-1} . Because of this fact, the calibration curve created from the absorbance values of the suggested standards will not pass through 0.

Once the calibration curve has been established, at least 3 standards should be run concurrently with test samples to confirm the validity of the curve.

Test Solutions: Generate an Infrared Spectrum for each test sample and record the absorbance value at 1260 cm^{-1} . The corresponding amount of silicone fluid in mg can be determined from the calibration curve. The amount in mg of silicone fluid per closure is determined by dividing the mg from X axis by the total number of closures used in the original extraction.

¹ If the infrared spectrophotometer being used scans only in % transmission, the readings must be converted to absorbance values before proceeding.

IX. Particulate Matter

A. Haze On Reconstitution

Upon reconstitution of dry products, the presence of haze in the solution has been observed. Investigations found that this can arise as a result of PDMS fluid adsorption on the product surface (30). The tendency to develop this haze depends on several factors; for instance:

1. the air pressure during freeze drying; the rate of silicone adsorption increases with decrease in air pressure,
2. the nature of the closure,
3. the chemical composition of the surface area and polymorphic form of drug product,
4. the concentration of the reconstituted product,
5. level of PDMS fluid on the surface.

In addition to PDMS fluid, certain rubber components such as sulfur and paraffin can contribute to haze on reconstitution (31). In the case of haze caused by PDMS fluid, the haze will usually decrease or disappear within an hour because of the separation of the PDMS fluid from the encapsulated solid particles of drug product.

B. PDMS Fluid Effect on Particle Counting Instrumentation

Most parenteral pharmaceuticals are aqueous vehicle preparations. PDMS fluid, being hydrophobic, will not mix with aqueous solutions. Heavy application of PDMS fluid to rubber closures or plastic and glass syringes could result in the formation of globules suspended in the drug vehicle. Even low application levels may result in suspended particles due to vial agitation or the frictional forces developed in a syringe system. In cases of silicone baked onto a surface such as in glass vials or syringe barrels, flaking of the lubricant can occur.

The HIAC-Royco counter will record silicone globules. The same is true for other immiscible liquids such as benzyl alcohol. PDMS fluid globules will be counted as solid particles by particle counters using a light scattering or light blockage principle for particle detection and sizing. This has created a controversy regarding the current USP method. The implied assumption, in these controversial discussions, is that silicone particles are less harmful than other particulate matter. Particulate counts obtained using a Coulter counter which uses resistance modulation for detection are also affected in the same manner.

C. Cleanability of Siliconized vs. Nonsiliconized Closures

Many factors affect the cleanability of closures. The type of elastomeric compound used has as great an effect on amount of particulate formation as the method of washing (30). On the other hand, closures can be overwashed; i.e., reach a state where abrasion generates more particles than washing removes.

While PDMS fluid lubrication reduces friction and thus decreases abrasion, it also tends to make particles adhere to the surfaces more readily or even entrap them. Since the siliconized surface is essentially hydrophobic, the removal of particles is difficult. Nonsiliconized clo-

sures are easier to clean providing optimal cycles have been determined. Once lubricated with PDMS fluid, closures must be protected from external particulate contamination and subjected to a minimum of mechanical forces.

Prelubricated closures may not benefit from further washing, provided they were adequately washed prior to siliconizing. Particulate removal from prelubricated closures is difficult to validate.

X. Nonsilicone Lubrication

Other methods of lubrication besides the application of polydimethylsiloxane fluid have also been employed for pharmaceutical elastomeric components. The alternate lubrication methods involve the addition of internal lubricants to the elastomeric compound, chlorination of the molded parts, application of coatings and films, and modification of fundamental rubber chemistry.

A. Internal Lubrication

Addition of internal lubricants is among the earliest methods applied to affect the lubrication of elastomeric components. Internal lubricants such as paraffin wax or polyethylene are mixed with the other ingredients of elastomeric compound and the compound is molded in the usual way. The lubricants migrate to the surface of the component in a phenomenon known as blooming. Blooming relies on the relative insolubility of the lubricant in the elastomeric compound; as a result the lubricant will always appear at the surface. The advantages of this technique are that it is not restricted to any one elastomer and that the lubricant is always available at the closure surface. The major disadvantage is that since the lubricant is not chemically bound to the rubber matrix, it may contribute to the particulate burden of the drug preparation.

B. Surface Chlorination

Chlorination was developed to circumvent the problems with internal lubrication. Elastomeric components are immersed in a solution which contain ionized chlorine. The chlorine atoms act on the surface of the part to remove "dangling rubber molecules." These molecular tails cause the tackiness seen in natural rubber compounds, especially gum compounds with low filler levels. The advantage of this technique is that it results in a smooth, tack-free surface which generally requires no additional lubrication. The disadvantages are that the method is generally only useful for natural rubber or certain synthetic elastomers. There may be inconsistency in application, and excessive application may cause discoloration of the elastomeric surface with the heat used in drying or sterilization cycles.

C. Films and Coatings

Films have been introduced as an alternate lubrication method. This method was an extension of lacquer coatings, which were applied to stoppers to prevent the release of extractables and particulate matter. Typically, the modern films are composed of an olefinic or fluorocarbon polymer laminated by a proprietary process to the elasto-

mer component. When films are applied, the level of lubricant required can be reduced. An additional advantage, not related to lubrication, is that the fluorocarbon coatings render the component inert to most drug preparations. Disadvantages are the expense of the components and the possibility that the coating does not cover the surface completely. If the coating covers the flange area of the closure, validation of the integrity of the seal must be performed.

D. Chemical Modification

A recent approach to a method of lubrication has been based on changing the fundamental properties of rubber through chemical modification. New elastomeric closure formulations have been marketed using this technique. The advantages are that the method is simple and inexpensive, it does not generate particulates and that it involves the entire rubber component. The disadvantage is that it is a new formulation which requires stability and compatibility studies.

XI. Survey Results

The Lubrication Task Force mailed survey forms to just over 120 persons on the PDA Membership List, in an attempt to determine current practices in lubrication. Twenty-six responses were received. Four of the respondents did not utilize lubrication, leaving 22 useful responses.

The results of this survey have been incorporated into the appropriate sections of this document. The raw data will be given to the PDA office, to be held as reference.

XII. Glossary

A lexicon of commonly used terms concerning silicone fluid and its relationship to all siloxanes follows:

Centistokes	A unit of kinematic viscosity abbreviated cst or cs. It is defined as the viscosity in centipoise (gm/cm—sec/100) divided by the density in gm/cc, when both are measured at the same temperature (30).
Dimethicone	This is a term which the Cosmetic, Toiletry and Fragrance Association Inc. (CTFA) defines as a mixture of fully methylated linear siloxane polymers endblocked with trimethylsiloxy units. There are no analytical requirements for compliance with this definition.
Dimethicone, NF	This is a National Formulary (NF) term. Its structural definition is the same as the CTFA definition. The fluid may have a nominal viscosity in a discreet range between 20 and 12,500 cst. The NF requires that a po-

Dimethylsiloxane	lydimethylsiloxane fluid must conform to a number of testing specifications before it can be called "Dimethicone, NF." The term, therefore, implies that the product possesses a certain minimum standard of quality.
Organosilicone polymer	A polymer which is composed of $(CH_3)_2SiO$ units.
Polydimethylsiloxane	Materials which are composed of silicon-oxygen-silicon bonds in which those silicon bonds not satisfied by an oxygen atom are bonded to an organic group.
Polysiloxane	A class of compounds composed of alternating silicon and oxygen atoms in a linear arrangement with two methyl groups attached to each silicon atom.
Silicon	A general term describing a silicon containing polymer whose silicon atoms are separated by oxygen atoms; thus they contain Si-O-Si bonds.
Silicone	The fourteenth element of the periodic table.
Silicone emulsion	A general term describing a solid or liquid polymer made up of silicon-oxygen-silicon bonds in which hydrocarbon groups are bonded directly to all or a portion of the silicon atoms.
Silicone fluid	A water-based dispersion of a silicone fluid. The dispersed silicone fluid particles are usually stabilized by one or more organic surfactants.
Silicone oil	A general term describing a liquid silicone which is commonly used to refer to polydimethylsiloxane.
Silicone polymer	See Silicone fluid.
Siloxane	A somewhat redundant term often used to refer to polymers which are composed of organosubstituted siloxane units.
	A material which is composed of silicon-oxygen-silicon bonds.

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