DOW CORNING Healthcare Solutions

Advancing healthcare through material innovations

Drug Delivery Systems

GInAS:

Industry perspective on polymer specifications/registration

Katherine Ulman
Associate Scientist & Global Regulatory Compliance Manager
Dow Corning Healthcare
Katherine.l.ulman@dowcorning.com

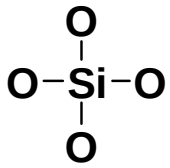
DOW CORNING

We help you invent the future.™

GInAS: Global Ingredient Archival system

Silicone
nomenclature

SILICA



Silica or SiO2 , an oxide
A common mineral: sand, quartz, ...
Only natural source of silicon is as silica or silicates in the magma and in minerals

SILICON

Si

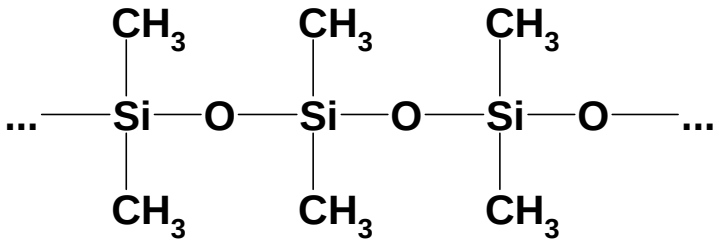
Silicon or Si, a metal
Second most common element on earth after oxygen

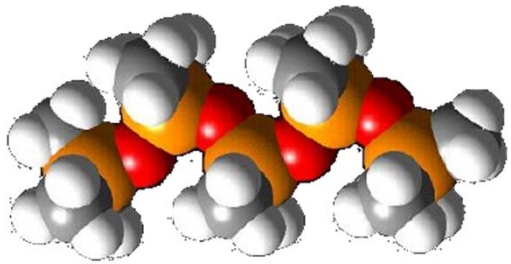
Element	*Rank*	*Abundance (%)*
Oxygen	1	49.2
Silicon	2	25.7
…		
Carbon	14	0.1

Silicones

nomenclature

- The name of **Silic**…….
  - **Silica** -Sand, naturally occurring, oxide of silicon (SiO_2)
  - **Silicate** -Si & O and other metals, inorganic material
  - **Silicon** -The pure element Si, made by reduction of sand with carbon
  - **Silicone** -A wide range of polymeric materials containing Si-O-Si bond
- Described by Kipping in 1908 as "**Me_2SiO**" where Me = CH_3
- Today, **Commercial Name** for numerous products
- Actually, **Polymers**: polydimethylsiloxanes ***(PDMS)***

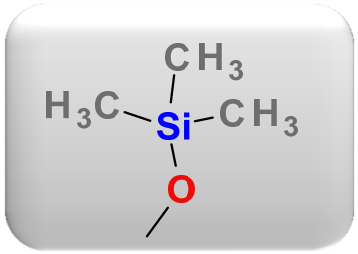
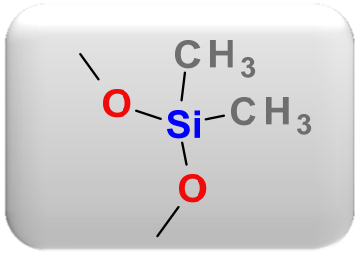
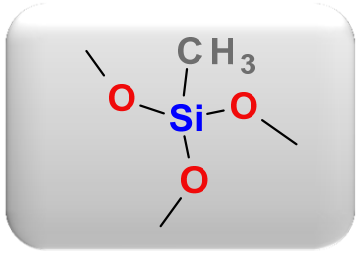
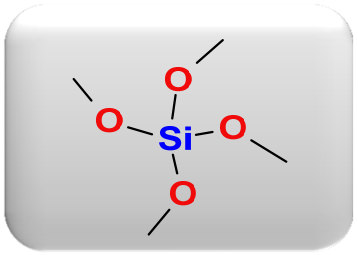




$Me_3SiO(SiMe_2O)_3SiMe_3$

Silicone

building blocks

M	D	T	Q
			
$Me_3SiO_{1/2}$	$Me_2SiO_{2/2}$	$MeSiO_{3/2}$	$SiO_{4/2}$
3	2	1	0
End block	Siloxane polymer	Silicone resins	Silica

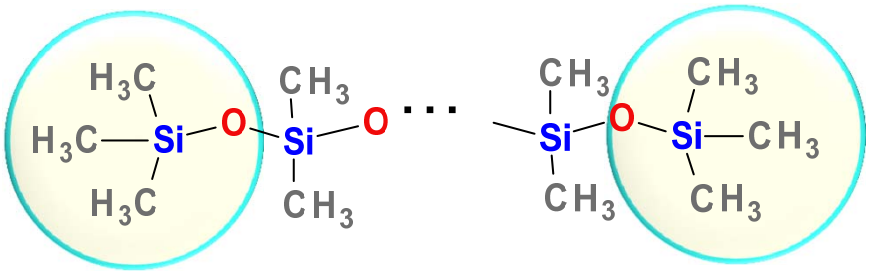
Organic ⟶ Inorganic

Soft & Flexible ⟶ *Hard & Brittle*

Siloxane

most common … PDMS

Trimethylsilyloxy endblocked polydimethylsiloxane!



or $Me_3SiO(SiMe_2O)_nSiMe_3$

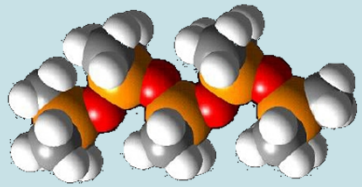
Other names:

Dimethicone

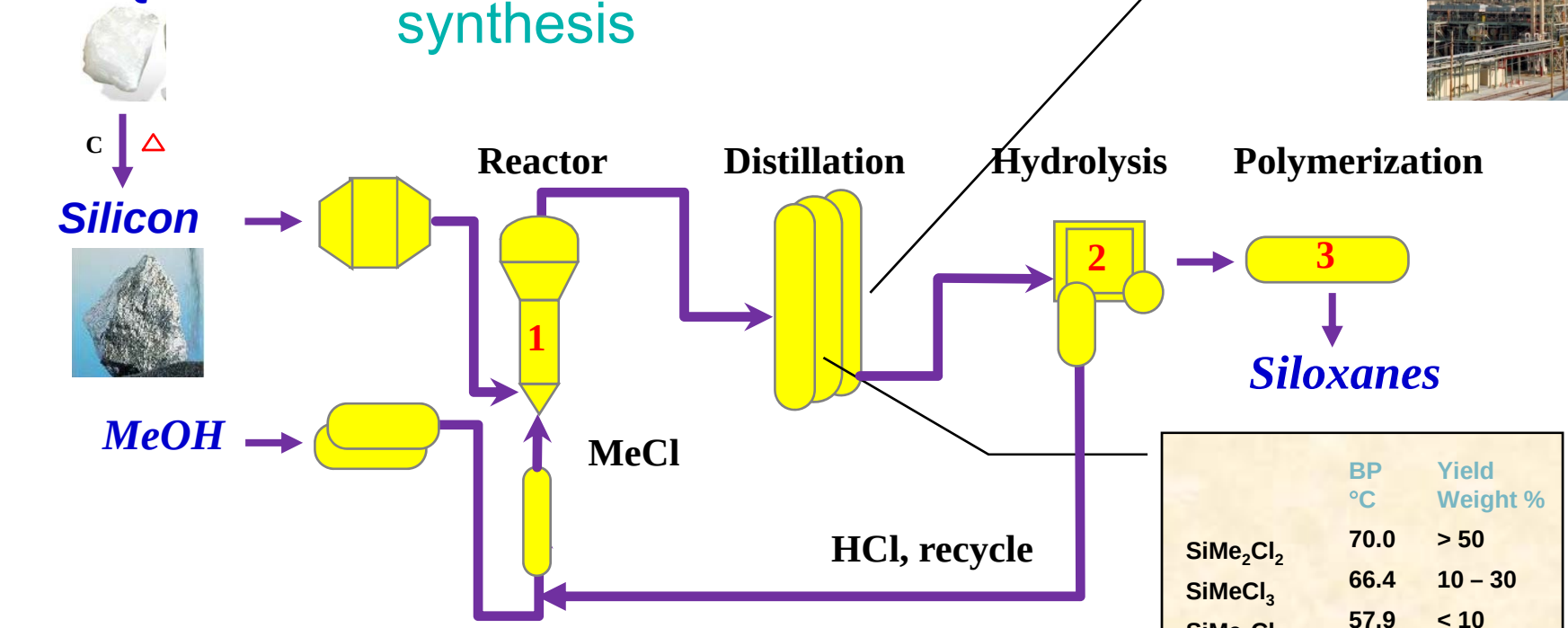
α-(Trimethylsilyl)-ω-methylpoly[oxy(dimethylsilylene)] [9006-65-9]

e.g. $Me_3SiO(SiMe_2O)_4SiMe_3$

The siloxane chain is polar, but shielded by hydrophobic low interacting methyl groups.



Siloxane
synthesis



	BP °C	Yield Weight %
$SiMe_2Cl_2$	70.0	> 50
$SiMeCl_3$	66.4	10 – 30
$SiMe_3Cl$	57.9	< 10
$SiMeHCl_2$	41.0	< 5
Other silanes…	-	5

3 Steps

1. ***Chlorosilanes synthesis:***
   $Si + 2\ MeCl \rightarrow SiMe_2Cl_2$
2. ***Chlorosilanes hydrolysis:***
   $SiMe_2Cl_2 \rightarrow$ "$SiMe_2(OH)_2$" $\rightarrow HO(SiMe_2O)_nH + (SiMe_2O)_n$
3. ***Polymerization:***
   $Me_3SiOSiMe_3 + (SiMe_2O)_4 \rightarrow Me_3SiO(SiMe_2O)_nSiMe_3$

PDMS polymer synthesis

2. Chlorosilanes hydrolysis:

$$Me_2SiCl_2 \xrightarrow{+H_2O\,/\,-HCl} \text{“}Me_2Si(OH)_2\text{”} \xrightarrow{-H_2O} \underset{\textit{linear oligomers}}{HO(Me_2SiO)_xH} + \underset{\textit{cyclics}}{(Me_2SiO)_y}$$

di-silanol

3. Polymerization:

Condensation Polymerization:

$$y\ HO(SiMe_2O)_xH \xrightarrow{Cat./\,-H_2O} HO(SiMe_2O)_nH$$

linear oligomers — ***PDMS polymer***

Ring Opening Polymerization:

$$Me_3SiOSiMe_3 + z\ (Me_2SiO)_4 \xrightarrow{Cat.} Me_3SiO(SiMe_2O)_nSiMe_3$$

endblocker — ***cyclics*** — ***PDMS polymer***

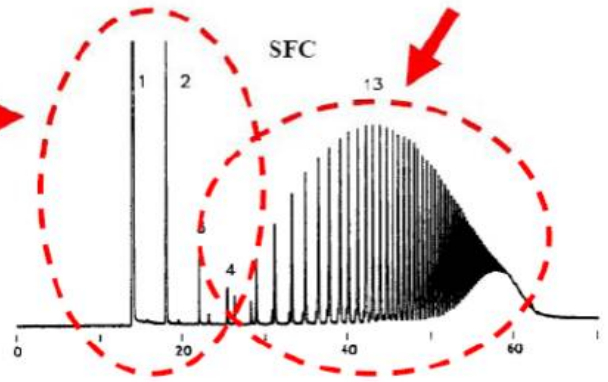
Silicone polymer

Physico-chemistry - polydispersity

PDMS is comprised of polydispersed polymers containing some low MW species which are typically reduced during manufacturing

Super Critical Fluid Chromatogram of a PDMS polymer before stripping

Volatiles / extractables can be reduced by evaporation



Picture courtesy A. Lee Smith, Dow Corning

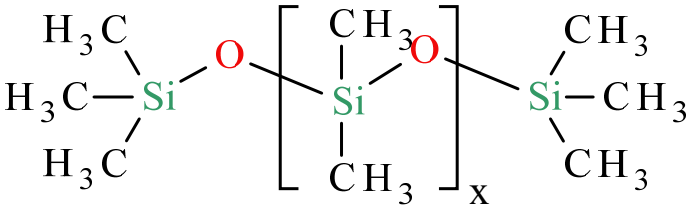
The presence of low MW species is part of the pharmacopoeia monograph test requirements

	Dimethicone NF	*Dimeticone EP*	*Silicone oil EP*
Gravimetric loss	< 2 % *15 g / 4 h / 200 °C*	< 0.3 % *1 g / 2h / 150 °C*	< 2 % *2 g / 24 h /150 °C*

Typical Physical Properties

DOW CORNING 360 Medical Fluids
DOW CORNING Q7-9120 Silicone Fluids

USP NF Dimethicone
Ph.Eur. - Dimeticone
Ph. Eur. – Silicone Oil used as lubricant



Physical Form @ 25°C	Liquid
Color @ 25°C	Colorless

Viscosity (cSt)	Specific Gravity	Refractive Index (RI)	GPC Mn	$Me_3SiO[Me_2SiO]_xSiMe_3$ Value for "x"
20	0.951	1.4018	2310	24
100	0.967	1.4032	6530	72
350	0.972	1.4042	11600	146
500	0.972	1.4043	13300	174
1000	0.972	1.4046	15500	208
12500	0.972	1.4047	28700	487

Pharmacopeia Specifications	Dimethicone USP NF	Dimeticone Ph.Eur.
	20, 100, 350, 1000 cSt	20, 100, 350, 1000 cSt
Refractive Index	X	---
Viscosity, capillary (cSt)	X	X
Specific Gravity	X	---
Acid No., BPB (mg KOH/g)	X	X
UV Spec. For phenyl	---	X
IR Identification	X	X
Volatile Content, %	X	---
PDMS Spectrum 368	X	---
Bacterial Endotoxins, LAL, < 10 EU/mL	X	---
Mineral Oil – no Fluorescence	---	X
Heavy metals, Dithizone =/< 5 ppm of the standard	X	X
Colorimetric, Silicone Present	---	X
Silicate, Silicone present	---	X

defining properties

product specifications

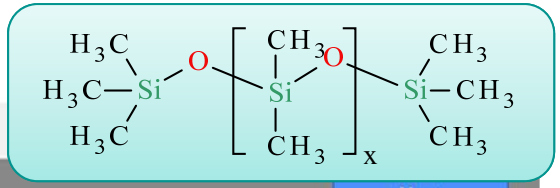
Dimethicone Fluids

US FDA IID Listings for Dimethicone

Ingredient	Route of Delivery	Form	CAS #	UNII code	Max use	unit
DIMETHICONE 1000	ORAL	CAPSULE, ENTERIC COATED PELLETS	9006659	MCU2324216	2.5	MG
DIMETHICONE 350	ORAL	CAPSULE	9006659	2Y53S6ATLU	3.7	MG
DIMETHICONE 350	ORAL	CAPSULE, SUSTAINED ACTION	9006659	2Y53S6ATLU	0.114	MG
DIMETHICONE 350	TOPICAL	EMULSION, CREAM	9006659	2Y53S6ATLU	1	%
DIMETHICONE 350	TOPICAL	SOLUTION	9006659	2Y53S6ATLU	0.5	%
DIMETHICONE MEDICAL FLUID 360	DENTAL	INJECTION		92RU3N3Y1O		
DIMETHICONE MEDICAL FLUID 360	INTRAVENOUS	INJECTABLE		92RU3N3Y1O		
DIMETHICONE MEDICAL FLUID 360	TOPICAL	EMULSION, CREAM		92RU3N3Y1O	5	%
DIMETHICONE MEDICAL FLUID 360	TOPICAL	LOTION		92RU3N3Y1O	1	%
DIMETHICONE MEDICAL FLUID 360	TRANSDERMAL	FILM, CONTROLLED RELEASE		92RU3N3Y1O	564	MG

NOTE: IID shows a “generic” UNII for dimethicone, however, the intent is for GInAS not to include this “generic” UNII code

GInAS Names (domain, language, jurisdiction) and References



Names | Physical Properties | Monomers | Polymer Structure | Physical Properties | Review

Cancel | Export | Next

Legend: This name resolves to a structure

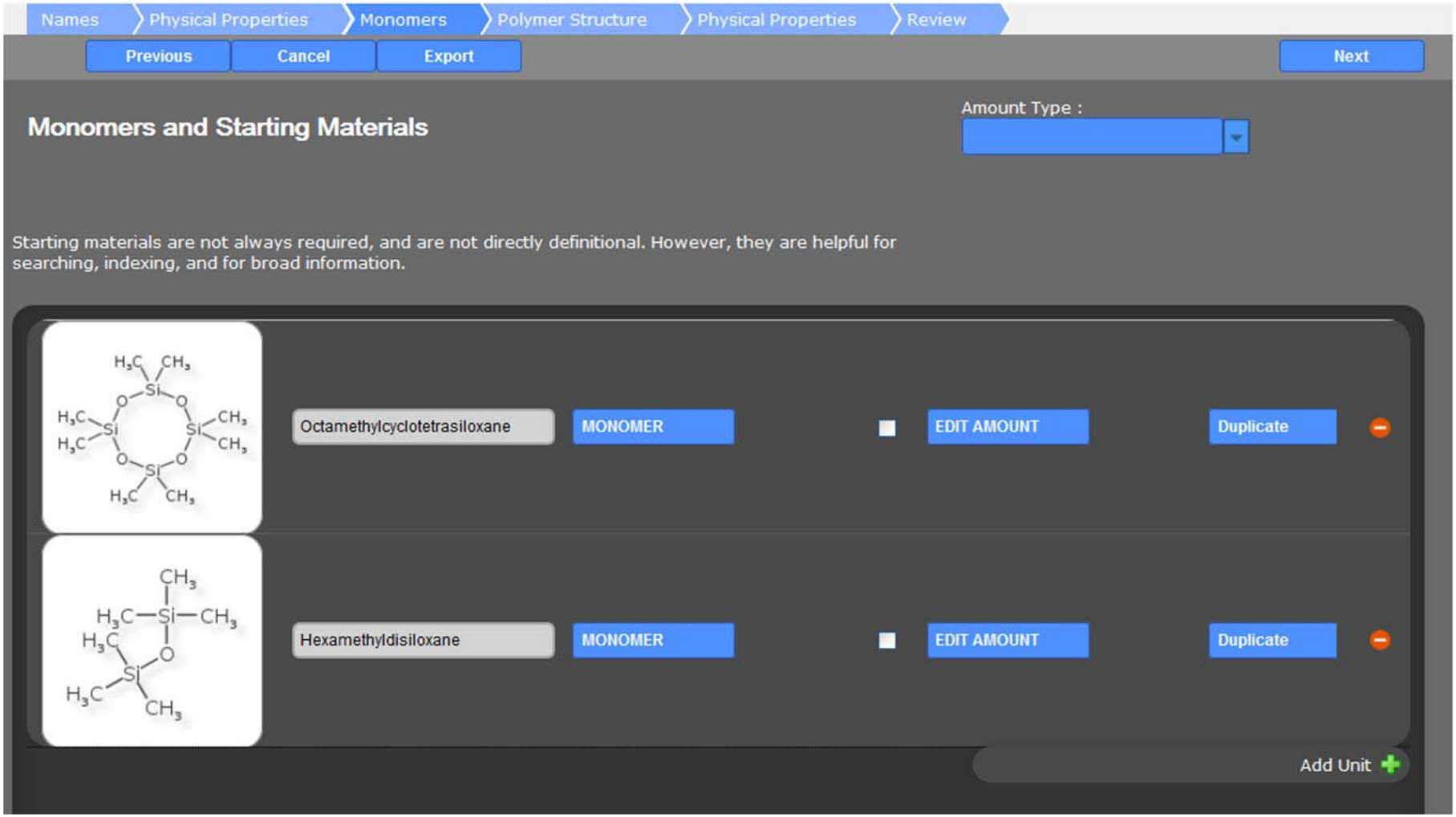
DIMETHICONE 350	Official Name	English	☑
DIMETICONE 350	Official Name	English	☐
DIMETHICONE (350 CST)	Common Name	English	☐
DOW CORNING 360 MEDICAL FLUID (350 CST)	Brand Name	English	☐
DOW CORNING Q7-9120 SILICONE FLUID (350 CST)	Brand Name	English	☐

Add Name List | Add Name

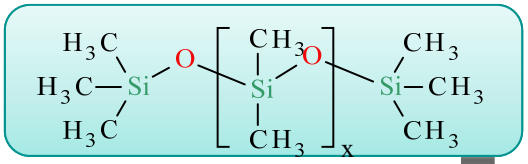
Monomers
(not defining)

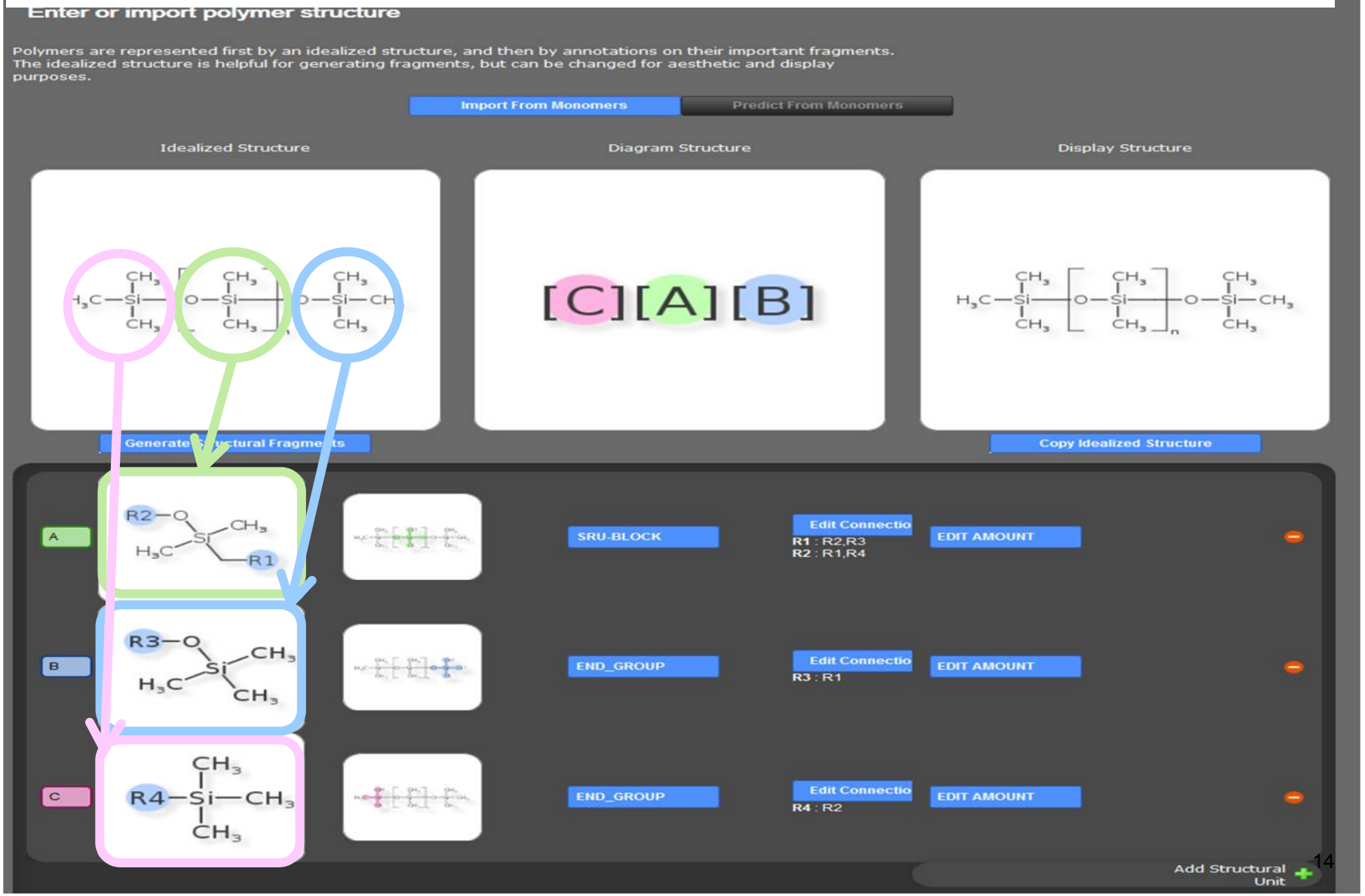
$Me_3SiOSiMe_3$ + z $(Me_2SiO)_4$ $\xrightarrow{Cat.}$ $Me_3SiO(SiMe_2O)_nSiMe_3$

endblocker ***cyclics*** ***PDMS polymer***

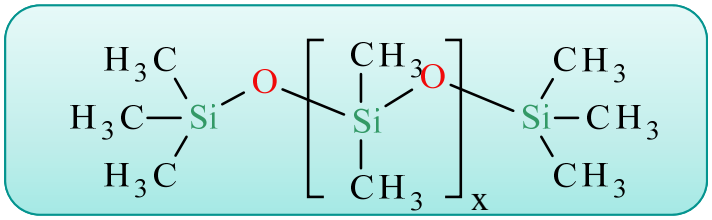


Polymer topology: fragments and connections

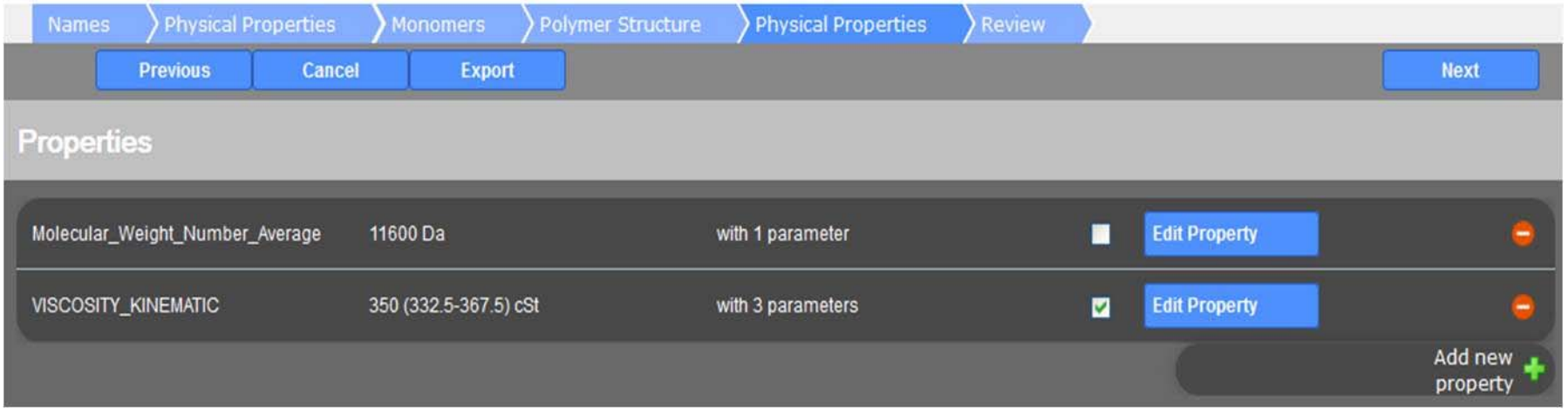




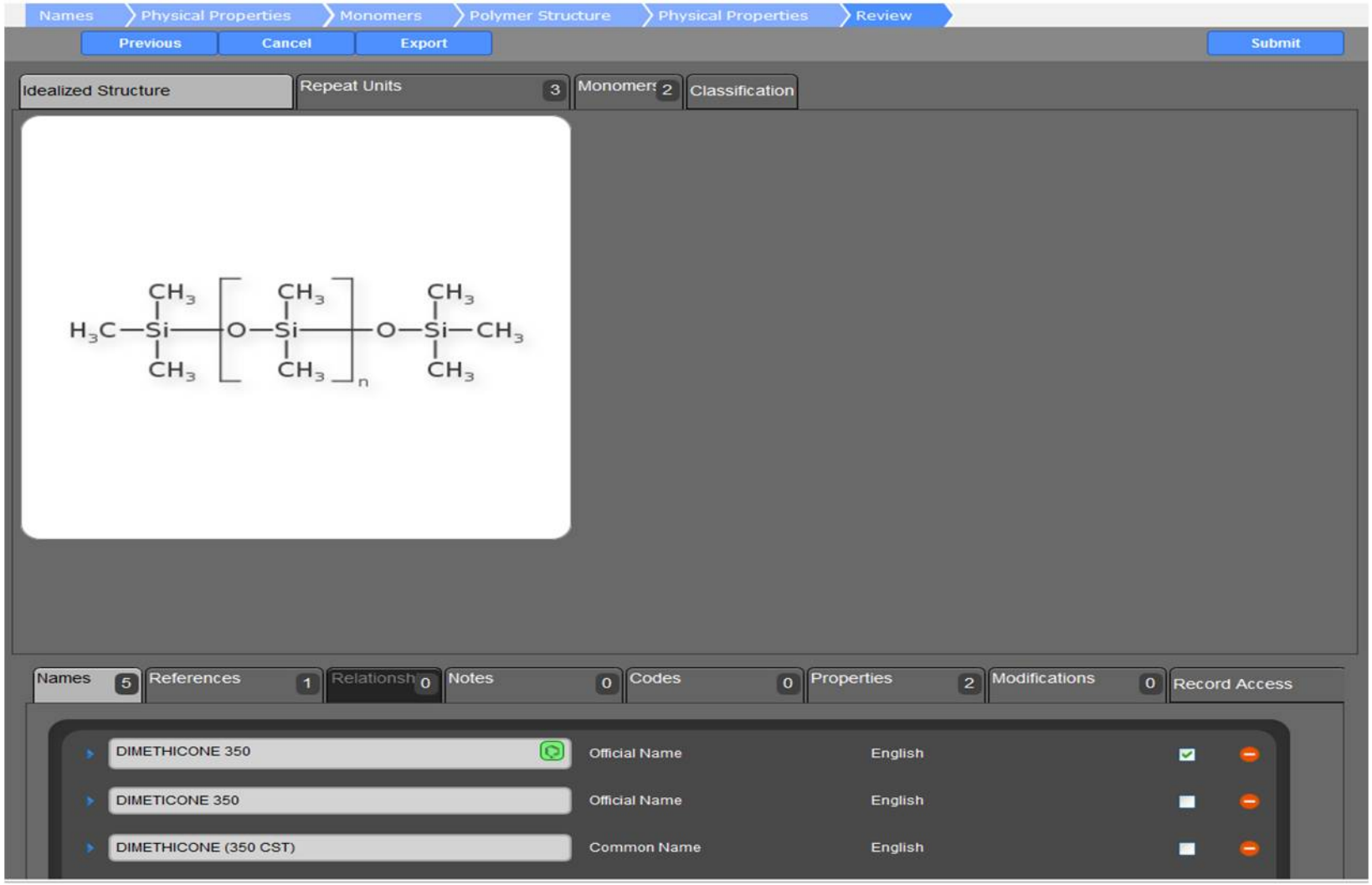
Annotate defining properties



defining properties
Refractive Index
Viscosity, capillary (cSt)
Specific Gravity



Review and submit



Silicone Fluids vs Silicone Elastomers

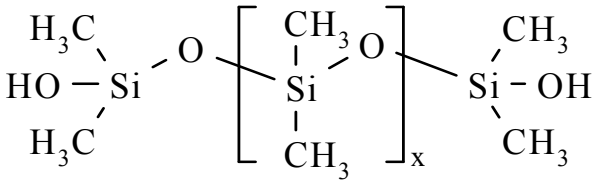
- Silicone polymers are easily converted into elastomers by creating covalent bonds between adjacent macromolecules to form three-dimensional networks
- Silicone elastomers differ from linear silicone fluids in three ways

Linear Polymers	Elastomers
Physical properties determined by chain length	Physical properties determined by degree of crosslinking
Linear polymers are liquids, viscosity increases with increases in molecular weight	Elastomers are solids with indefinite molecular weight
Soluble in solvents	Swell in solvents

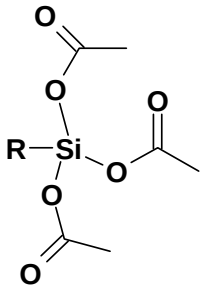
SILASTIC® Medical Adhesive Silicone, Type A

Formulation

Polymer (SiOH terminated PDMS)

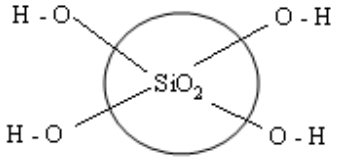


Crosslinker (triacetoxysilane)



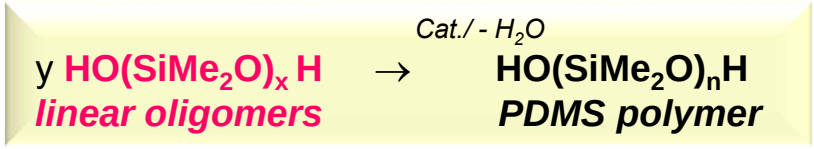
R = Me and Et

Filler (SiO_2)



= Silica

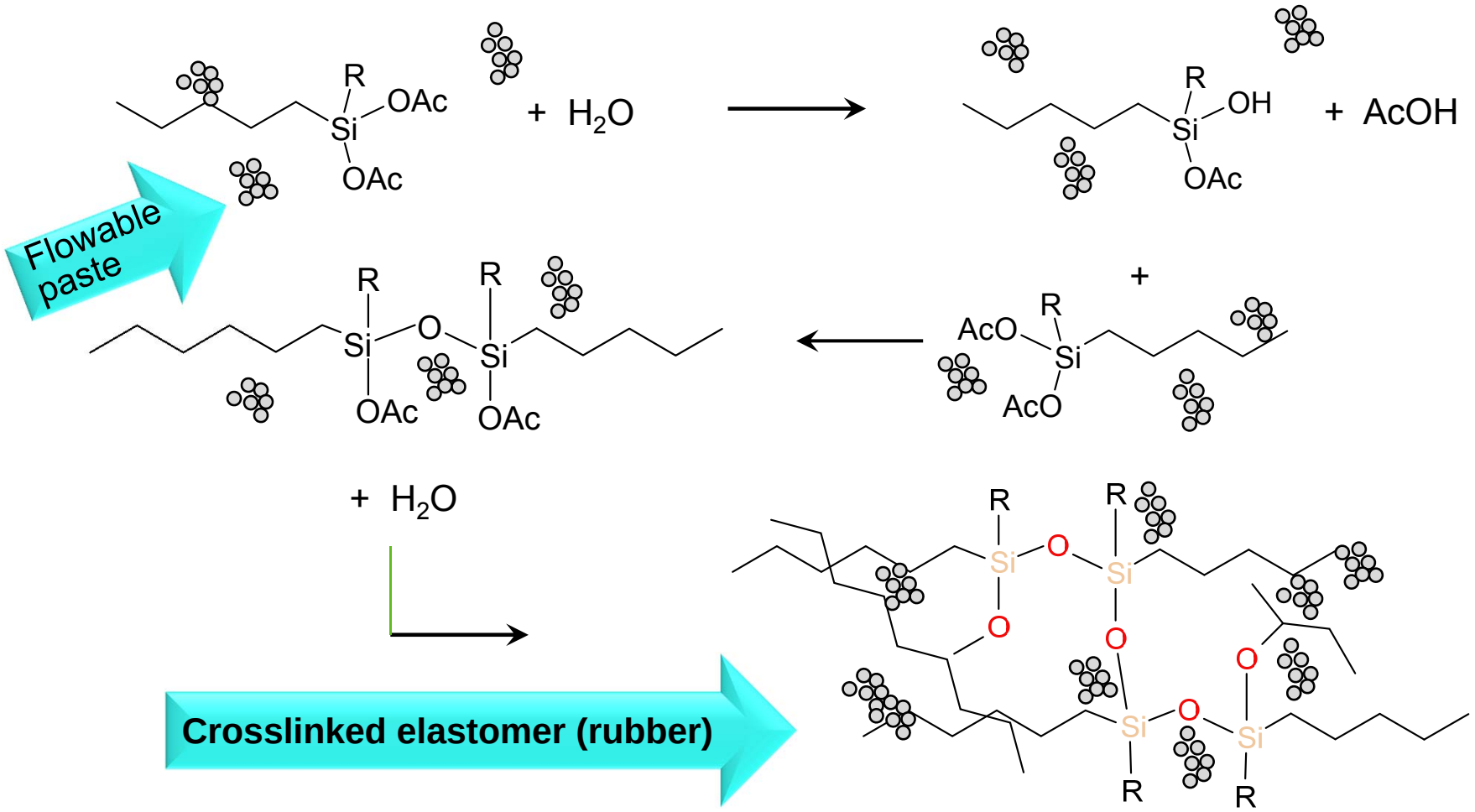
Catalyst (Sn)



Note: Sn catalyst used for Medical Adhesive Silicone, Type A is bovine free

SILASTIC® Medical Adhesive Silicone, Type A

Vulcanization of Acetoxy Elastomer



SILASTIC® Medical Adhesive Silicone, Type A

US FDA IID Listing

Ingredient	Route of Delivery	Form	CAS #	UNII code	Max use	unit
SILASTIC MEDICAL ADHESIVE, SILICONE TYPE A	IMPLANTATION	PELLET, IMPLANT		PENDING	13	MG

Typical Physical Properties
as supplied

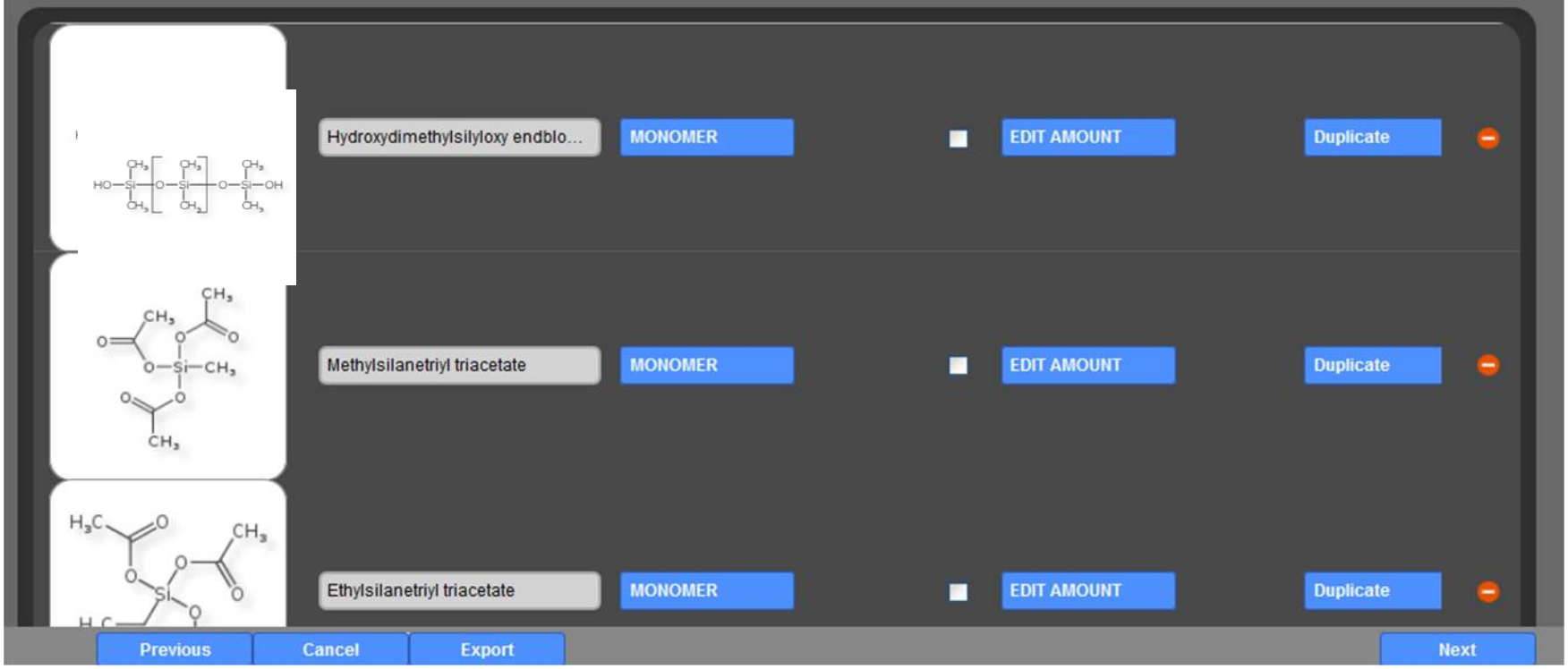
Property	SILASTIC Medical Adhesive, Type A
Appearance, uncured	Translucent paste
Skin-over time, @ 55% RH	7 – 8 minutes
Specific Gravity @ 25 °C	1.06
Durometer, hardness, Shore A	35
Tensile Strength	3.3 MPa / 480 psi
Elongation at break	450 %

defining properties

product specifications

SILASTIC® Medical Adhesive Silicone, Type A (Med A) Starting Materials

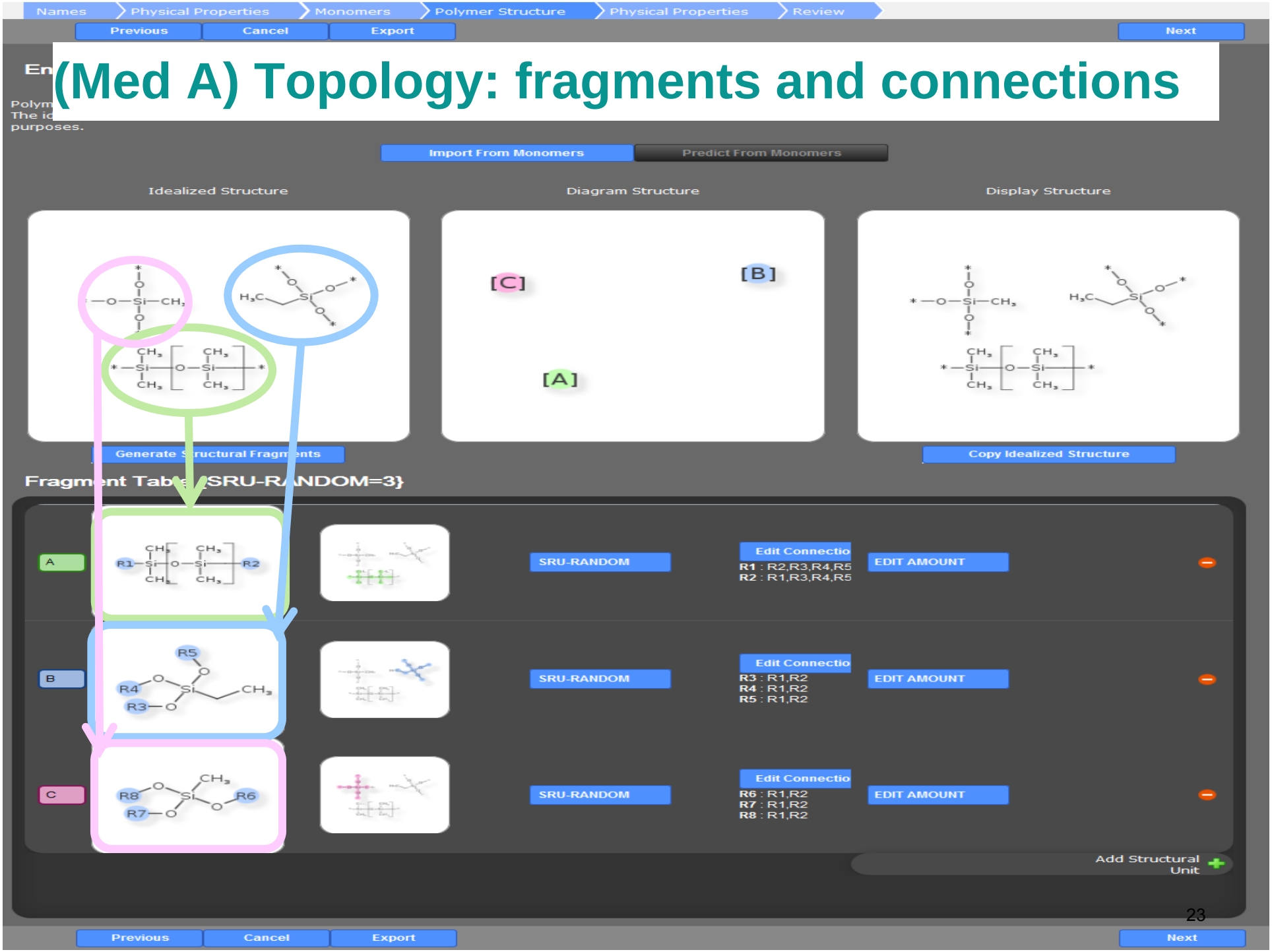
Starting materials are not always required, and are not directly definitional. However, they are helpful for searching, indexing, and for broad information.



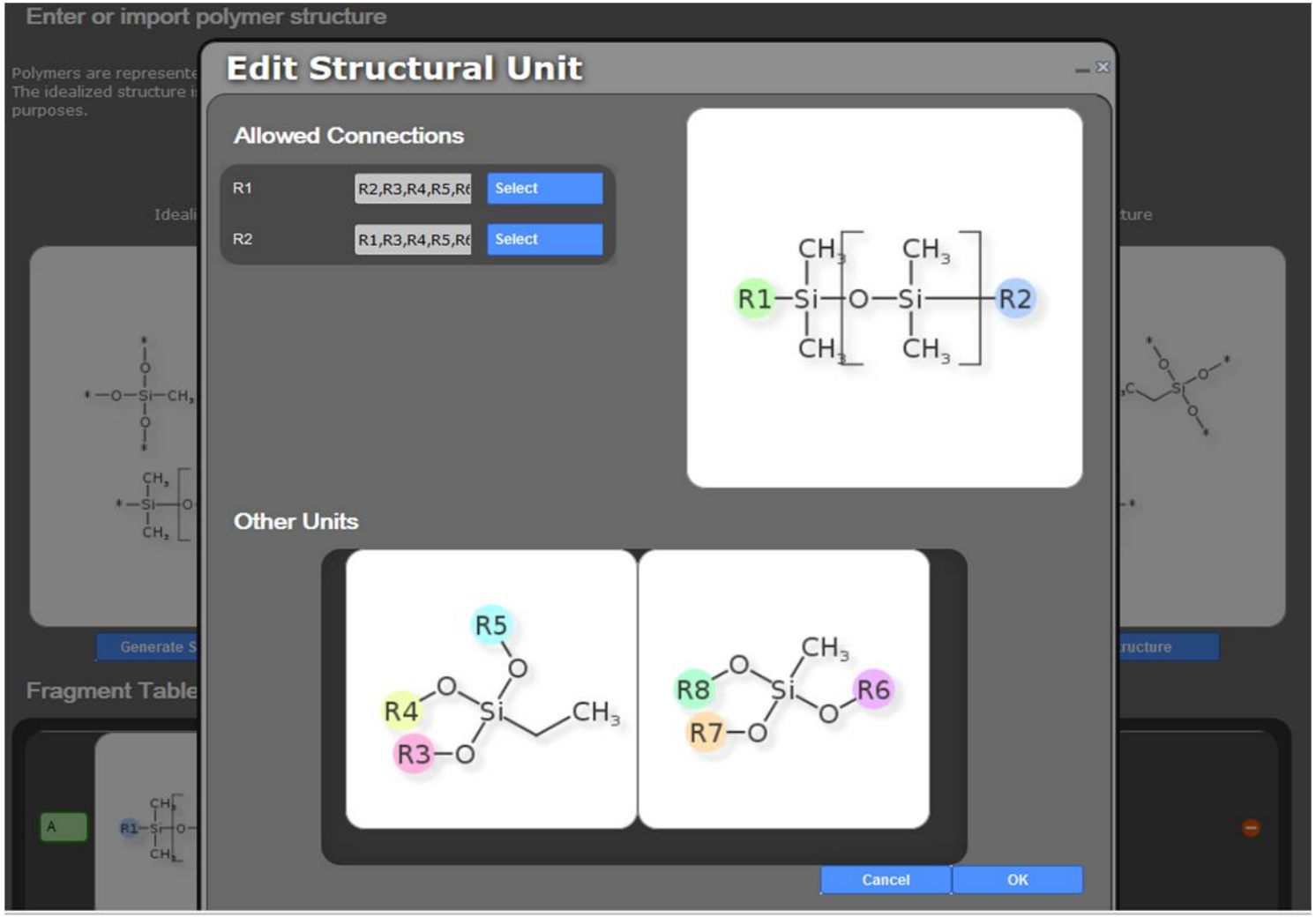
DOW CORNING

We help you invent the future.™

(Med A) Topology: fragments and connections

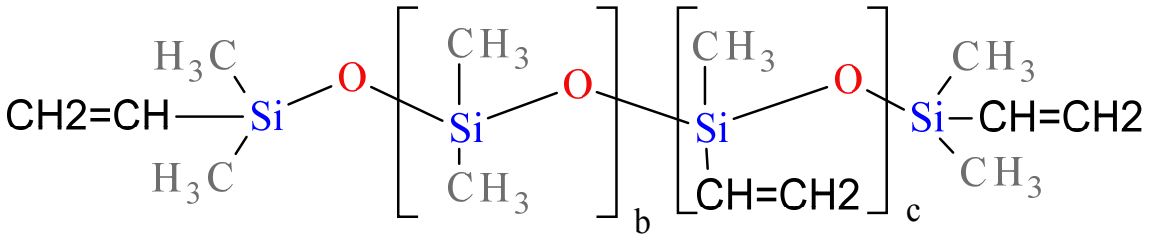


(Med A) Topology: fragments and connections



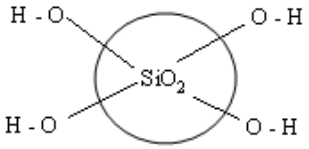
Example of dimethylsiloxane/ methylvinylsiloxane copolymer formulation

Polymer(s)

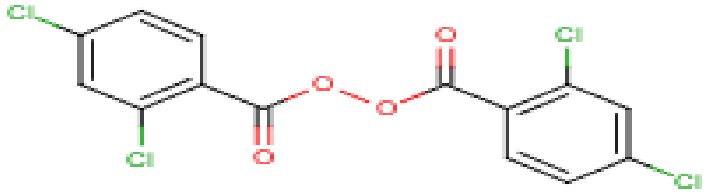


dimethyl, methylvinyl siloxane, dimethylvinylsiloxy-terminated

Filler (SiO_2)

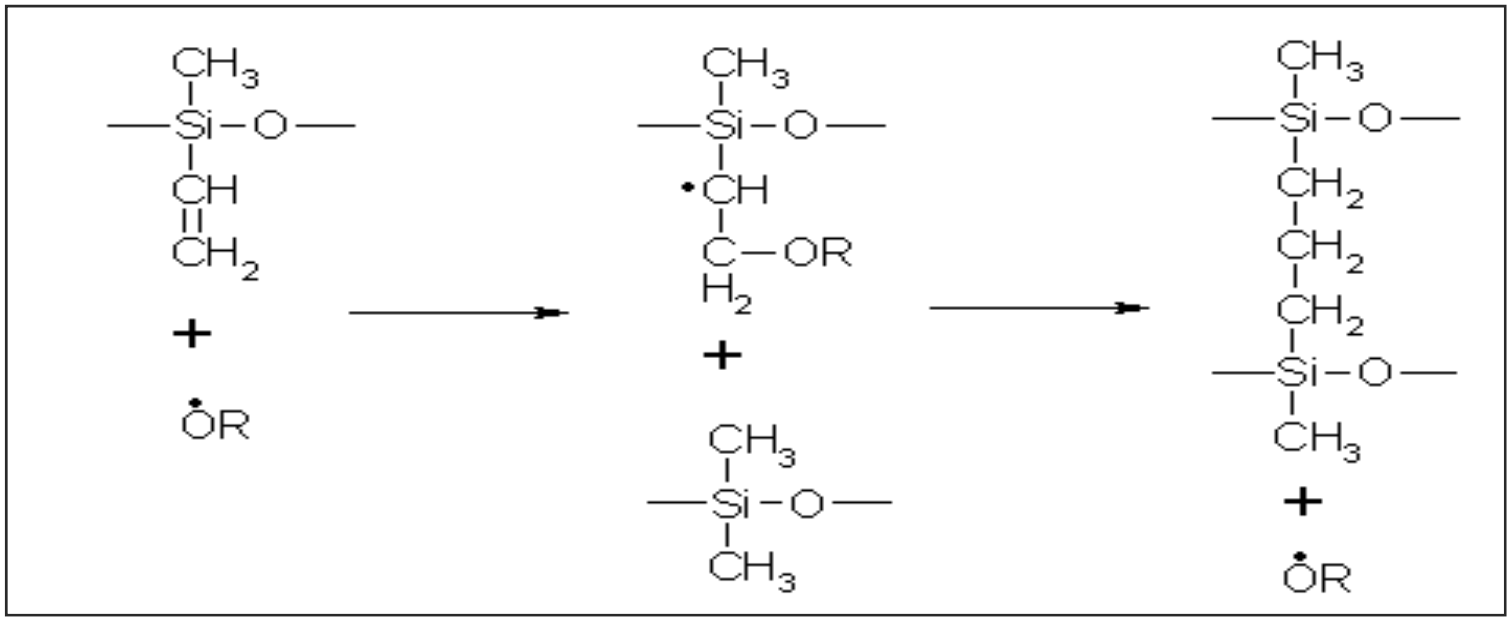


Catalyst

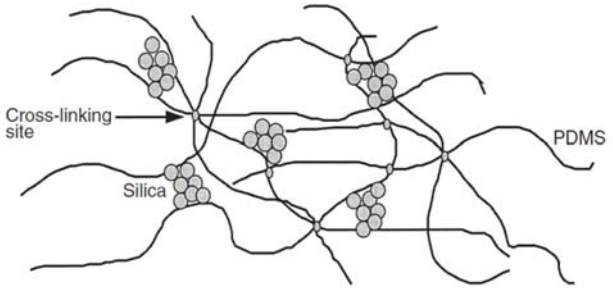


bis-(2, 4-dichlorobenzoyl) peroxide

Peroxide Cure (vinyl present)



Reactions continue to form crosslinked network



Ref. Severnyi and Weij cited in Siloxane Polymers, Clayson & Semlyn eds., 1993 Prentice Hall, pp. 572-577

Facts about peroxide cure HCRs

- Heat-activated cure
- Peroxide crosslinks organic groups via free-radical addition
- Physical properties vary with gum (polymer) type, filler level and peroxide type
- Cure rate can be varied by temperature, peroxide type and concentration
- Forms peroxide by-products which typically require post cure to remove

Dimethylsiloxane/methylvinylsiloxane copolymer

US FDA IID Listings

Ingredient	Route of Delivery	Form	CAS #	UNII code	Max use	unit
DIMETHYLSILOXANE/ METHYLVINYLSILOXANE COPOLYMER	IMPLANTATION	PELLET, IMPLANT		Pending	142	MG
DIMETHYLSILOXANE/ METHYLVINYLSILOXANE COPOLYMER	IMPLANTATION	ROD		Pending	142	MG
DIMETHYLSILOXANE/ METHYLVINYLSILOXANE COPOLYMER	INTRAUTERINE	INTRAUTERINE DEVICE		Pending	121	MG
POLY(DIMETHYLSILOXANE/ METHYLVINYLSILOXANE/ METHYLHYDROGENSILOXANE) DIMETHYLVINYL OR DIMETHYLHYDROXY OR TRIMETHYL ENDBLOCKED	VAGINAL	DRUG DELIVERY SYSTEM		Pending	9980	MG

Typical Physical Properties of Cured Silicone Elastomer

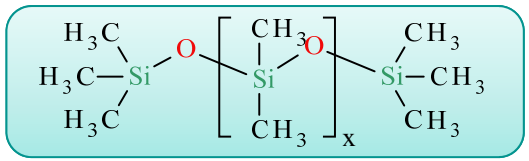
Property	Cured Elastomer
Physical Form	Rubber
Color	Color of the cured article (e.g. translucent gray)
Specific Gravity @ 25 °C	Ratio of the weight of a given volume of material to the weight of an equal volume of water.
Durometer, hardness, Shore A	Measure of cured elastomer (rubber) hardness.
Tensile Strength	Force required to extend a known dimension of a cured rubber article.
Elongation at break	Length a sample can be stretched before it breaks.

defining properties

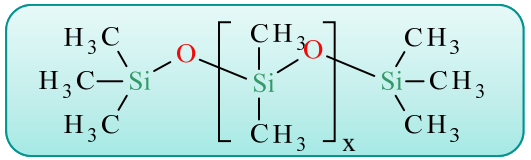
product specifications

Questions to consider pertaining to polymer specifications / registration

- Will the database differentiate between different “grades” of product based on some physical modification (e.g. fluid that has been depyrogenated)?



VS



  - If so, how?

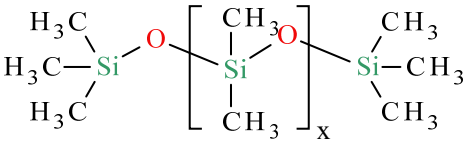
- How far back in the synthesis /chemistry will be necessary/appropriate ?
  - from sand? silicon? chlorosilanes? dimethyl cyclics and/or oligomers?

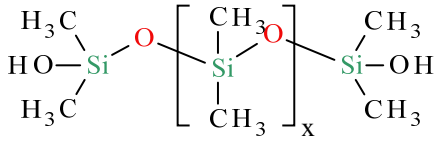
$SiMe_2Cl_2$
$SiMeCl_3$
$SiMe_3Cl$
$SiMeHCl_2$

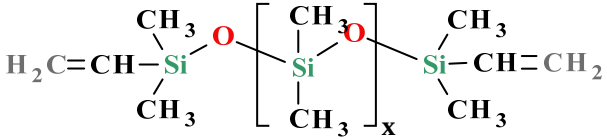
$HO(SiMe_2O)_nH$
$(SiMe_2O)_n$

Questions to consider pertaining to polymer specifications / registration

- What basis will be used to determine when a range for a defined polymer property (MW, degree of substitution, etc) is outside an established UNII?
  - How will different ratios of copolymers be handled?
  - What about different polymer end-groups or level of backbone functionality?



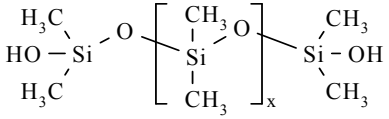


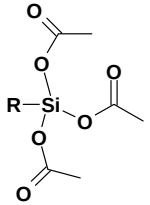


Viscosity (cSt)	$Me_3SiO[Me_2SiO]_xSiMe_3$ Value for "x"
20	24
100	72
350	146
500	174
1000	208
12500	487

Questions to consider pertaining to polymer specifications / registration

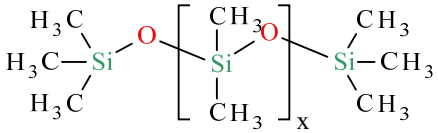
- How will “formulations” be handled
  - uncured elastomers





Sn

  - simethicone / simethicone emulsions



- What about when different ingredients and/or additives are used to produce the same monograph product?
  - simethicone / simethicone emulsions

- How will ingredients that are chemically modified during use be handled?
  - Cured elastomers / rubbers / adhesive
  - Acrylic pressure sensitive adhesives

Questions to consider pertaining to polymer specifications / registration

- What about substances that could be produced differently?
  - Fumed silica,
  - precipitated silica,
  - ground silica (quartz)?

- What about polymers sold in solvent where the solvent is removed during processing?

Your Questions

Bibliography:

Silicones chemistry and properties:

- Noll, W., "*Chemistry and technology of silicones*", Academic Press (1968)
- Owen, M.J., *"Why silicones behaves funny"*, Chemtech, 11, 288 (1981) (revised and reprinted in Chimie Nouvelle, 85, 27 (2004))
- Hardman, B. and Torkelson, A., "*Silicon compounds (Silicones)*", 20, 922, Encyclopedia of Chemical Technology, Kirk-Othmer, Wiley-Interscience publ. (1982)
- Colas, A. , *"Silicones: Preparation, Properties and Performance"*, Chimie Nouvelle, 8 (30), 847 (1990) (revised 2004)
- Silicones in Industrial Applications, *Inorganic Polymers*, Nova Publishers, Edited by Roger De Jaeger and Mario Gleria, 2007.