September 7th, 2022

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Characteristics of Pharmacetuical Elastomers in Container Closure Systems

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Agenda

- **Introduction to Container Closure Systems**
  - Vials, PFS, Cartridges with a focus on elastomeric components
- **Introduction to Pharmaceutical Elastomers**
  - Selection criteria and key considerations
  - Physical and chemical properties
  - Applications, variations, and functionalities
  - E/L profiles
  - Common Concerns & Industry Trends
- **Pharmaceutical Elastomer Manufacturing Process**
- **Processing of Elastomeric Components**
  - Fundamentals of RFS and RTU components
  - **Importance of siliconization** and selection criteria
  - Basics of camera inspection
  - Sterilization choices and elastomer packaging selection
- **Importance of Manufacturing environment**

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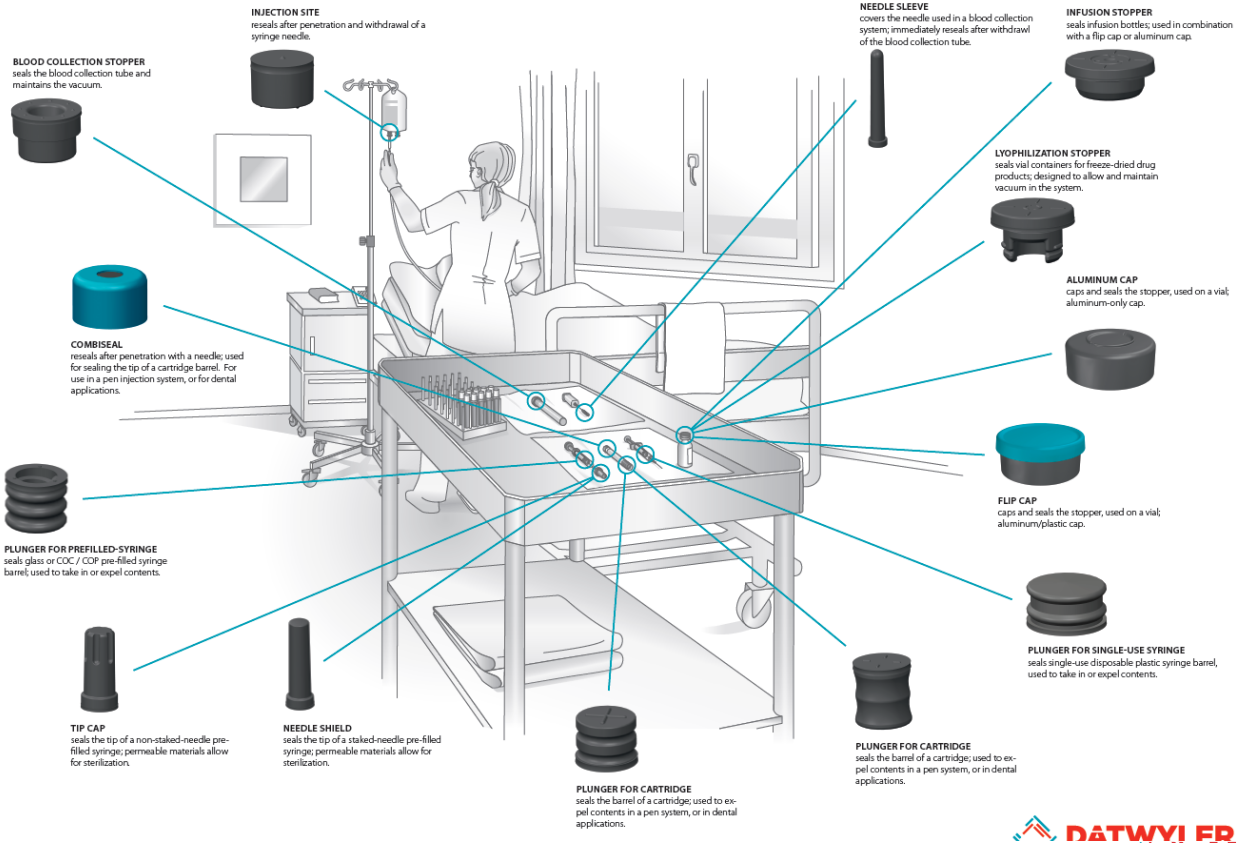
Pharmaceutical Elastomers & Seals



Pharmaceutical Elastomers

Customers dealing with different type of primary containers:

- Stoppers and aluminum seals **for Vial applications**
- Plungers and Combiseals **for Cartridge applications**
- Plungers, Tip Caps and Needle Shields **for Prefilled Syringe applications**
- Custom designs for **auto-injectors, drug delivery devices**

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Sealing solutions for Vials

Small volume parenteral (SVP)

Large volume parenteral (LVP)

VIAL STOPPERS

13 mm

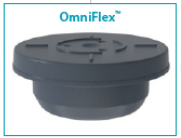
	SERUM		LYO			
			IGLOO		2-LEG	
						
Coated	–	Yes	–	Yes	–	Yes
Design	V9024	V9401	V9250	V9402	HPP002	HPP079
Compound	FM140 FM257 FM457	FM457	FM140 FM257 FM457 FM460	FM457	FM140 FM257 FM457 FM460	FM457

20 mm

	SERUM		LYO			
			IGLOO		2-LEG	
						
Coated	–	Yes	–	Yes	–	Yes
Design	V9025	V9407	V9172	V9397	V9154	V9396
Compound	FM140 FM257 FM457	FM457	FM140 FM257 FM457 FM460	FM457	FM140 FM257 FM457 FM460	FM457

29 mm

32 mm

	INFUSION	INFUSION			LYO
		DIN	ISO		4-LEG
					
Coated	–	–	–	Yes	–
Design	5294	V9003	V9240	V9240	V9262
Compound	FM140 FM257 FM457	FM140 FM257 FM457	FM140 FM257 FM457	FM259	FM140 FM257 FM457 FM460

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Sealing solutions for Vials

Key take-away messages:

Stopper types – serum, lyophilization, infusion

Typical sizes – 13, 20, 28, 29, 32 mm or custom designs

Elastomer formulations – typically halobutyls

Blowback – European or American or no blowback

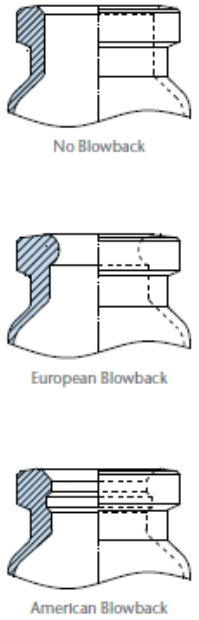

Image courtesy: Schott

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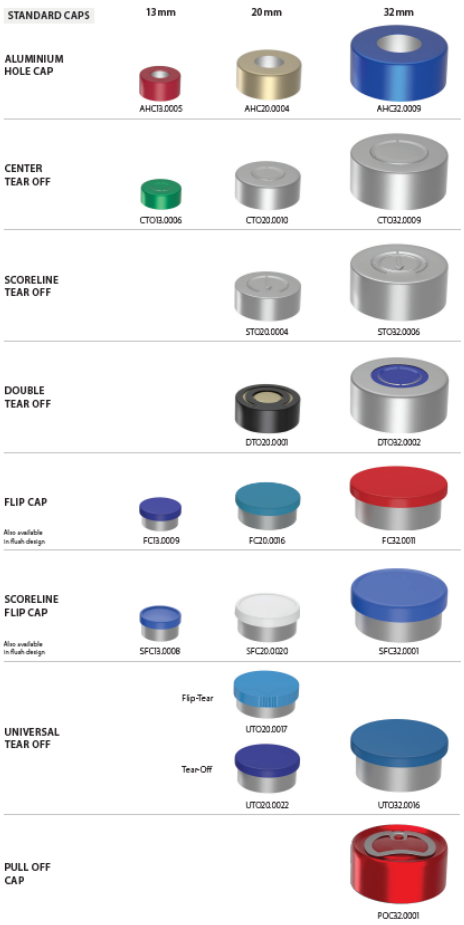
Sealing solutions for Vials

Aluminum seals

Flip Caps
(plastic caps and
aluminum seals)



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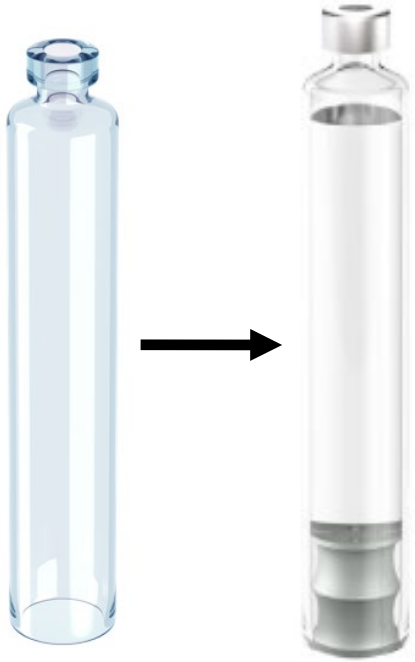
Sealing solutions for Cartridges



From 1–3 ml

DuraCoat™

Type	BI-LAYER	MONO-LAYER	BI-LAYER	MONO-LAYER	BI-LAYER
Design	ACS0001	ACS0002	ACS0003	ACS0004	ACS0006
Compound	FM257 + H1-7-207 FM457 + H1-7-207	FM257 FM457	FM257 + H1-7-207 FM457 + H1-7-207	FM257 FM457	H5-23-5 + H1-7-207 FM257 + H1-7-207 FM457 + H1-7-207

	ø 6.85 mm	ø 8.65 mm	ø 9.65–9.7 mm		
					NeoFlex™
Coated	–	–	–	–	Yes
Design	V4528	V9321	V9336	V9478	V9520
Compound	FM257 FM457	FM257 FM457	FM257 FM457	FM257 FM457	FM457

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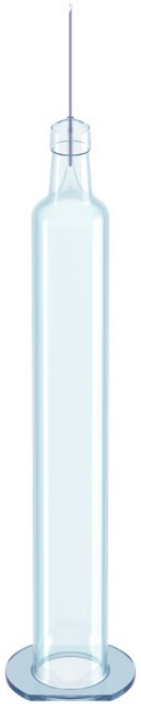
Sealing solutions for Prefilled Syringes



	SOFT NEEDLE SHIELD	RIGID NEEDLE SHIELD	TIP CAPS	
	½"	½"	RIBBED	MUSHROOM
				
Coated	–	–	–	–
Design	V6544	V9812	V9406	V9257
Compound	FM27 FM30	FM27 FM30	FM27 FM30 FM257	FM27 FM30 FM257

PLUNGERS	0.5 ml		1 ml long		1–3 ml		5 ml	10 ml
								
Coated	–	Yes	–	Yes	–	Yes	–	–
Design	V9315	V9503	V9283	V9519	V9258	V9517	V9319	V9344
Compound	FM257 FM457	FM457	FM257 FM457	FM457	FM257 FM457	FM457	FM257 FM457	FM257 FM457

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Introduction to Pharmaceutical Elastomers

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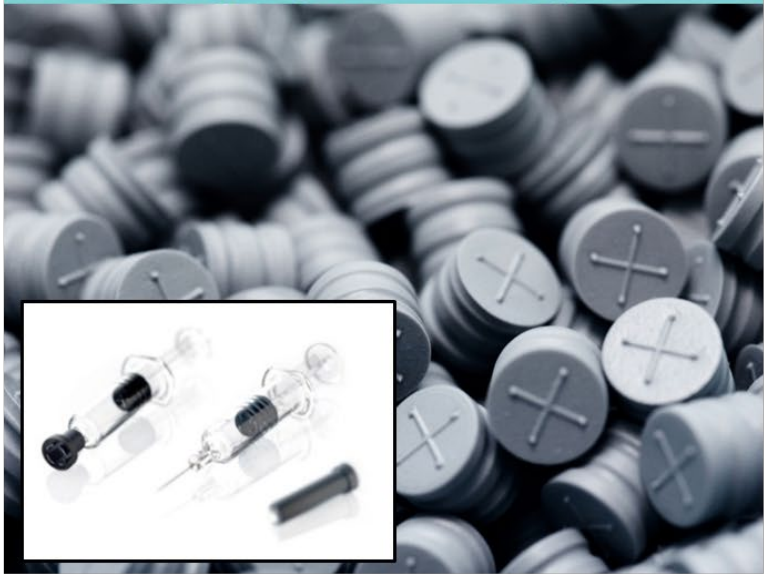
Elastomers in Pharmaceutical Applications

Vials

- Primary & secondary packaging components for small and large volume parenterals
- Fluoropolymer coated option

Prefilled syringes & cartridges



- High-precision components for injection systems and lined seals
- Fluoropolymer coated option

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Elastomers in Pharmaceutical Applications

Blood Collection

- Sealing components and needle sleeves for blood collection applications
- Tailor-made designs

Single-use Syringe

- Sealing components, not made with natural rubber, for single-use syringes

IV Systems

- Various components, not made with natural rubber, for IV systems

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Key Considerations for Pharmaceutical Elastomers

- Is the API or formulation absorbed by the elastomer?
- API and formulation stability
- Does the rubber react with the API and leach out impurities? (E/L profile)
- Temperature range at which closure and product are stable?
- Long term effects of storage
- Effects of sterilization on closures
- Seal integrity over the course of shelf life; CCI..?

Common Concerns
Drug Sensitivity

Drug products (especially biotech) are more sensitive to yesterday's packaging solutions:

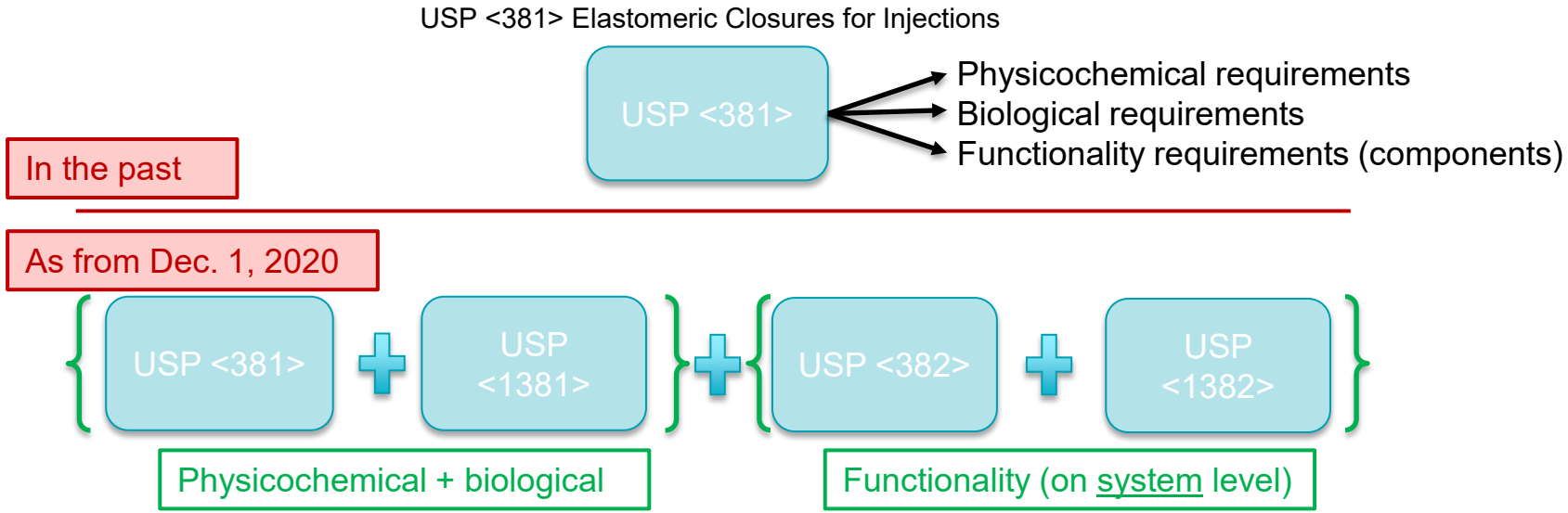
- Extractables and leachables
- Silicone fluid
- Particles

Common Concerns
Component Functionality

- Stoppers
  - Coring/ fragmentation
  - Needle penetration forces
  - Nedle self-sealing capacity
  - Machinability challenges
  - CCI
- Alu Seals
  - Pull-off forces
- Plungers in PFS systems
  - Break loose/ gliding behavior
  - CCI

USP <381> guidance is available for component functionality

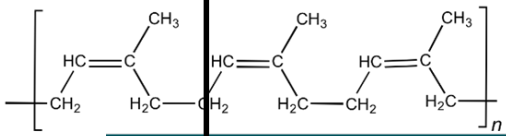
Revision of USP <381>



- USP <381> Elastomeric Components in Injectable Pharmaceutical Product Packaging/Delivery Systems
- USP <1381> Assessment of Elastomeric Components Used in Injectable Pharmaceutical Product Packaging/Delivery Systems
- USP <382> Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems
- USP <1382> Assessment of Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems

Evolution of Pharmaceutical Elastomers

Natural Rubber (latex)

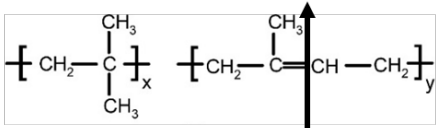


- Excellent physical properties, but poor gas barrier
- Application for short-term contact - disposable syringes, dropper bulbs

Synthetic Isoprene

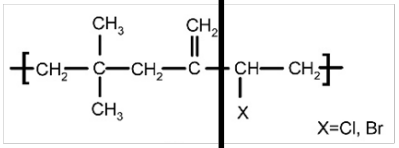
- Developed in 1909 at Bayer, Germany.
- Due to rising demand for natural rubber

Butyl Rubber



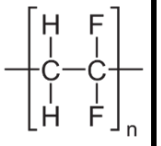
- Developed by standard Oil in 1937 in Linden, NJ; Copolymer of isoprene and iso-butylene
- Chlorinated and brominated versions used in pharmaceutical applications
- Excellent gas and moisture barrier properties

Halo Butyl rubber



- Developed in 1950s and 1960s,
- provide significantly higher curing rates
- Co-vulcanization with other rubbers is now possible such as isoprene and styrene-butadiene rubber

Fluoropolymer Coatings



- Inert barrier coatings with low coefficient of friction
- Teflon was discovered in 1938, NJ, DuPont; but use over pharmaceutical rubber was in the 90s

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Key Considerations for Pharmaceutical Elastomers

Relevant Physical Properties:

- Elastomer hardness *(ISO 48-4)*
- Density *(ISO 2781)*
- Ash Content *(Ph.Eur. 2.4.16)*
- Compression Set *(ISO 815-1)*
- Tensile Strength, Elongation, Modulus (*ISO 37*)
- Water vapor transmission rate (ASTM F-1249)
- Oxygen transmission rate (ASTM D-3985)

Relevant Chemical Properties and Regulatory Compliance

- Ph. Eur. 3.2.9, ISO 8871-1, USP <381> <382>, JP 7.03
- E/L profile – tested in WFI (basic, neural, acidic), hexane, isopropyl alcohol

Important to have data packages with physical, chemical and regulatory information for pharmaceutical elastomers

**Aforementioned testing is not a comprehensive list of tests that are needed or performed.*

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Pharmaceutical Elastomers

Pharmaceutical elastomers are thermoset rubbers as opposed to thermoplastic materials. Examples of thermoset rubbers:

- Natural rubber (NR)
- Polyisoprene (IR)
- Polychloroprene (CR)
- Styrene butadiene (SBR)
- Nitrile butadiene rubber (NBR)
- Ethylene propylene diene monomer (EPDM)
- Butyl rubber (IIR)
- Silicone rubber (Q)

Pharmaceutical Elastomers

Natural rubber / Polyisoprene

- Natural rubber: latex allergy discussions
- Historically the oldest elastomer type
- Need complex curing systems
- Good elastic properties
- Polyisoprene (synthetic) replaces Natural rubber

SBR (styrene-butadiene rubber)

- Intermediate permeability
- Typically used for pre-assembled EtO sterilized components (e.g. Needle Shields)

Pharmaceutical Elastomers, cont.

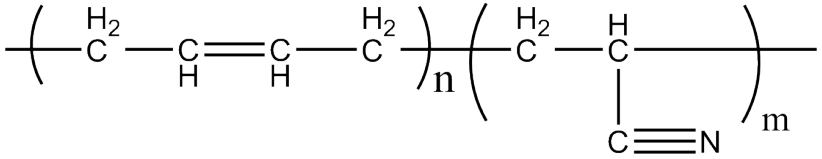
Halobutyl (**BromoButyl, ChloroButyl**)

- Cleanest curing system
- Lowest permeability
- High resistance to ageing
- Regular **butyl** still on the market, and also newer types like **BIMS** (Brominated isobutylene para-methylstyrene)

Pharmaceutical Elastomers, cont.

Nitrile rubber

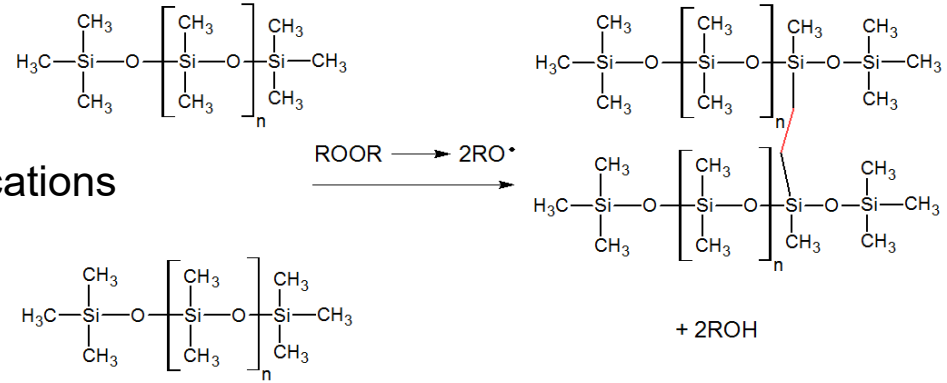
Typically used for mineral oil based drugs



Silicone rubber

High permeability

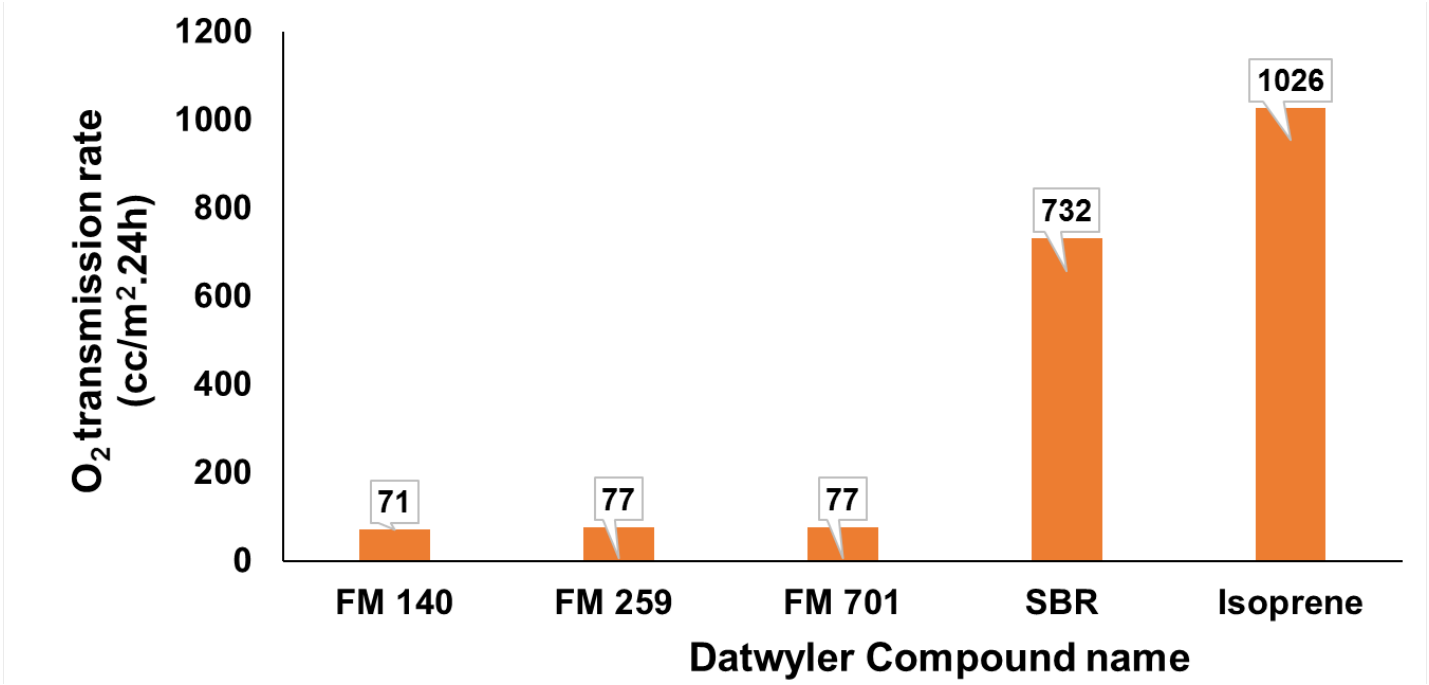
Typically not used for parenteral applications



EPDM rubber

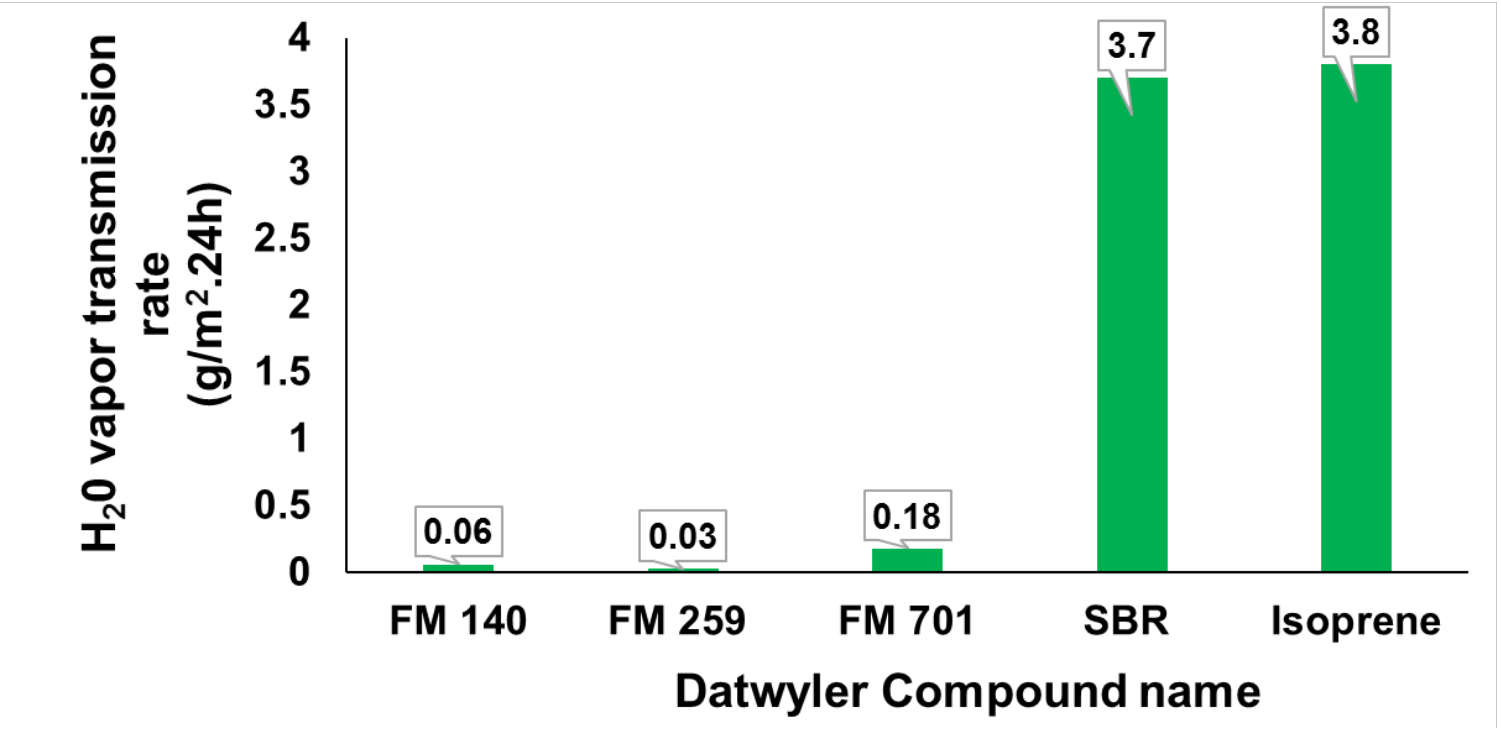
For niche applications

Oxygen Transmission Rate



- Data shown for typical SBR (styrene-butadiene) and isoprene compounds
- FM 259 is a fluoropolymer coated compound

Water Vapor Transmission Rate



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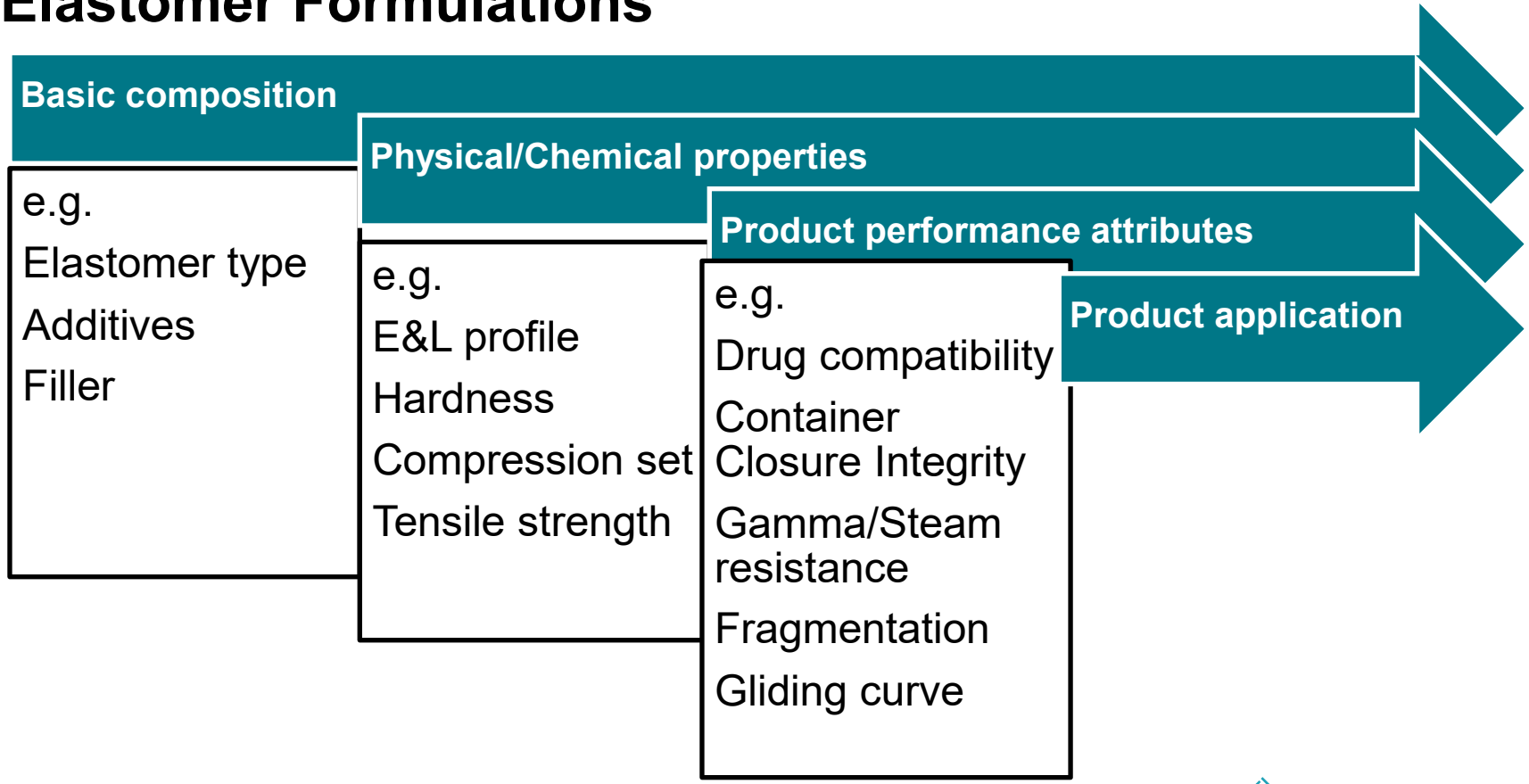
Elastomer Formulations



Elastomer Formulations

Typical ingredients in elastomers (a summary):

- **Elastomer base** – Halobutyl, SBR, Isoprene
- **Fillers** – Clays, mineral powders; provide structure
- **Plasticizers** – processing aids, provide flexibility
- **Curing System**
  - Crosslinking agent – introduce elasticity; co-determine strength and hardness
  - Accelerator – no longer used in modern formulations due to increased E/L
  - Activators – activate crosslinking sites, increase vulcanization efficiency
- **Pigment** – Impart color
- **Antioxidant** – prevent rubber degradation
- **Wax** – processing aids

Elastomer Formulations

Fillers give mechanical strength (stiffness) to a rubber

Attributes physical properties to a rubber compound

- More filler = Harder compound
  →Better for gliding profile plungers
  →Better against stickiness in bulk
  →Worse for stopper piercing (coring!)

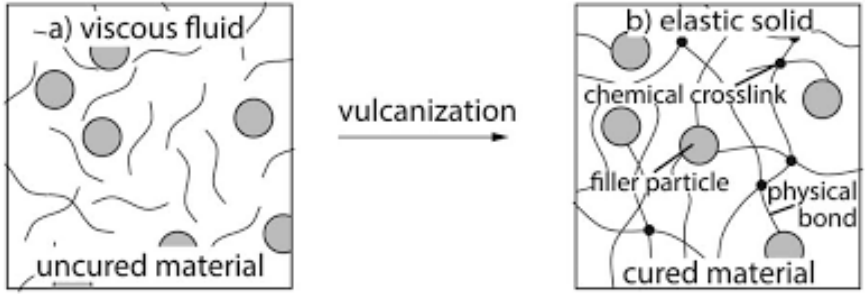
Inorganic fillers (‘white compounds’)

- Aluminum silicate (clay)
- Magnesium silicate (talc)
- Silicate
- [Calcium carbonate]

Carbon black (‘black compounds’)

- Undesired for cleanliness reasons
- May be associated with polynuclear aromatic hydrocarbons (PAHs)

Elastomer Formulations



- **Cure systems:**
  - Crosslinking agents
    - Activator: gives the onset of vulcanization
    - Accelerator: speeds up the vulcanization, easily extractable organic molecules such as thiurams, sulfenamides, thiazoles, ...
- **Modern cure systems**
  - Aim at giving less extractables
- **Historic cure systems**
  - Used easily extractable organic accelerators

Elastomer Formulations

Inorganic pigments

- Titanium dioxide
- Traces of carbon black
- Oxides of iron

Organic pigments

- Avoided in modern compounds

Halobutyl polymer stabilizers

- Calcium stearate
- Epoxydized soybean oil

Anti-oxidants

- Already present in halobutyl elastomer
- Hindered phenol type anti-oxidants
- Additionally added to improve environmental stability (ageing)

Plasticizer, Waxes, Oils

- High polymeric weight plasticizers, Paraffinic oil
- To tune a formulation (e.g. reduce coring)

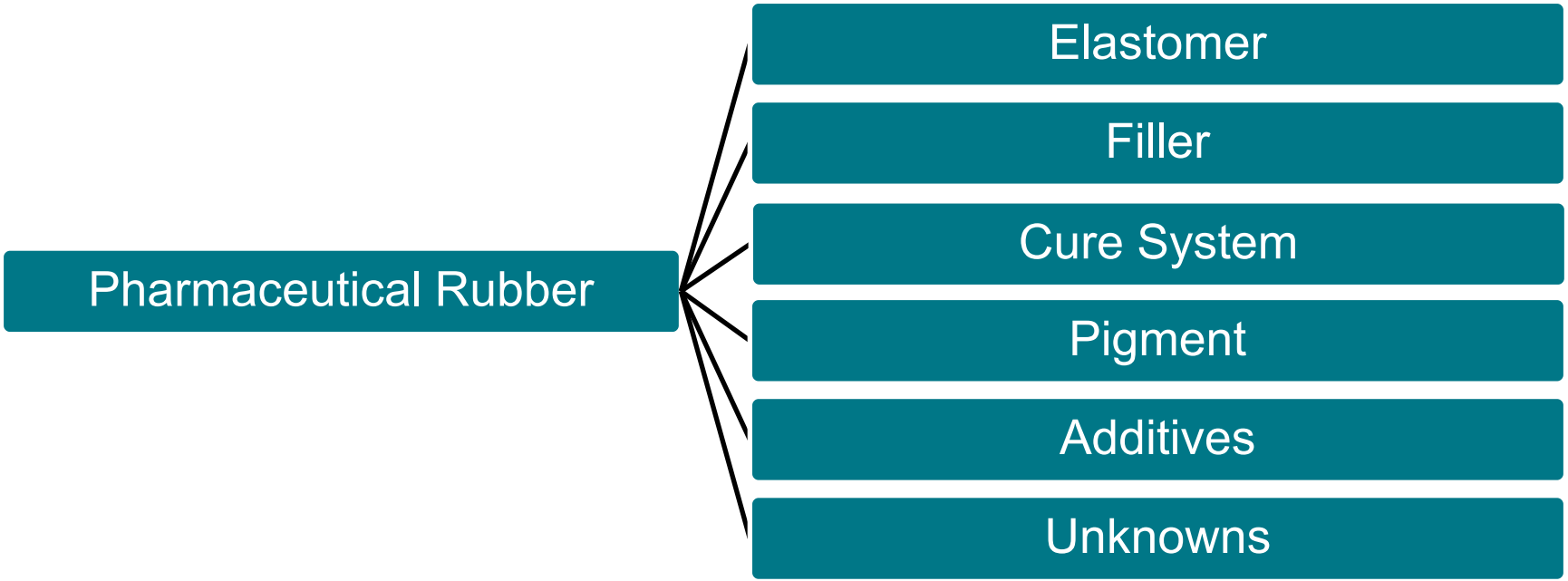
Extractables & Leachables

To understand the difference between leachables and extractables

- **Extractables** = The entire set of chemical species which “could” leach from the packaging over a wide pH, temperature, and solvent range.
- **Leachables** = Real time/game ready. Tested at the end of shelf life under normal conditions.

- Request available data packages from vendors which detail broad based analytical testing of packaging materials
- Understand toxicity and immunogenicity issues with identified leachables
- There are so many pathways to destabilize your drug product; if it’s not in there it can’t cause problems.

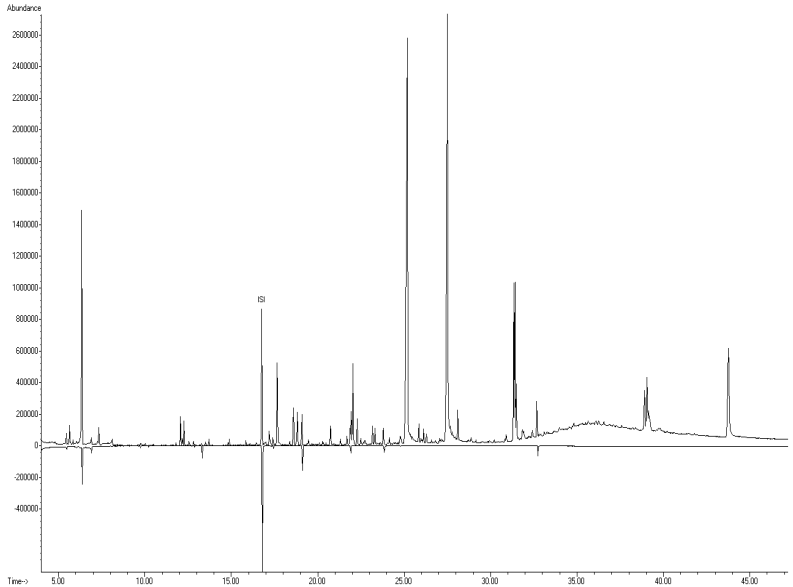
Extractables & Leachables



Extractables & Leachables

Difference in Extractable Results for an **OLD** vs **NEW** rubber

(*IPA Extract; GC/MS analysis*)



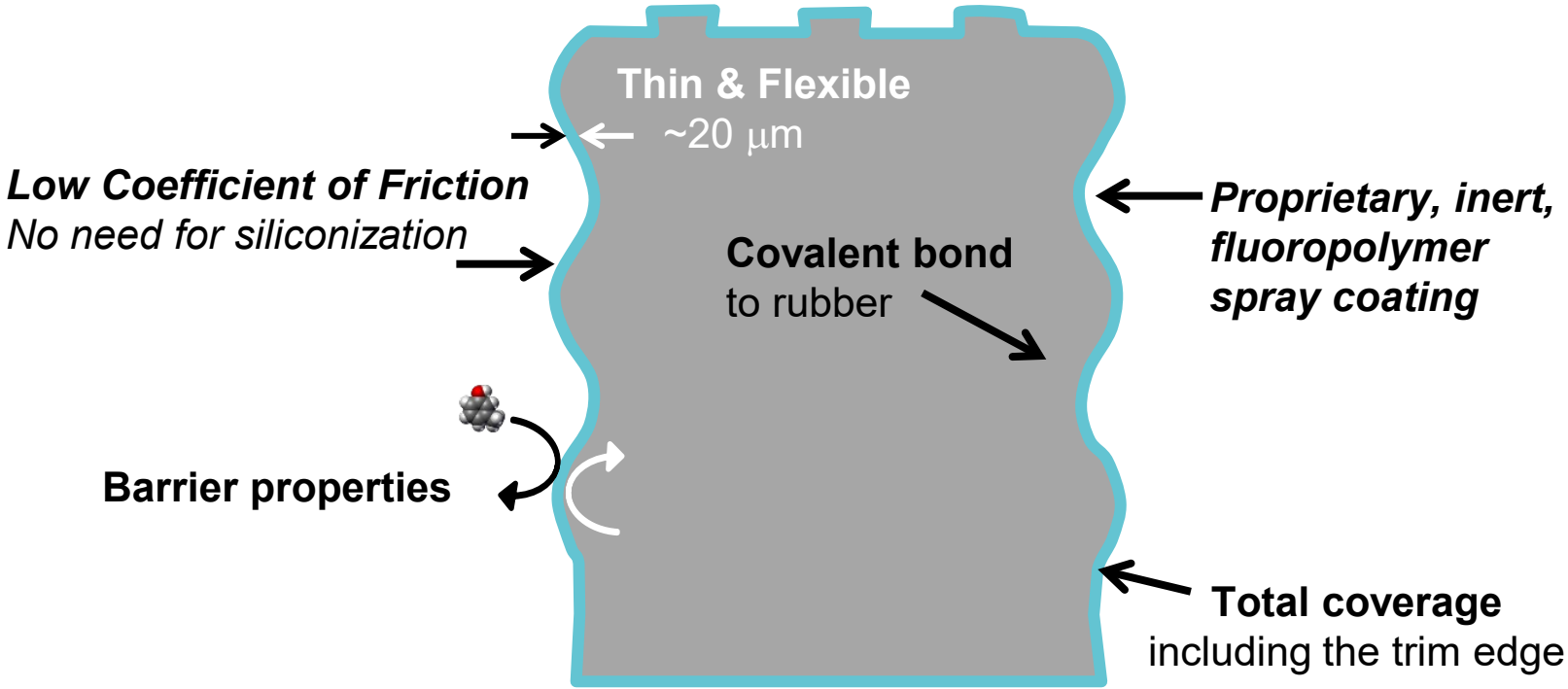
“OLD” Pharmaceutical RUBBER

“NEW” Pharmaceutical RUBBER

Common Concerns
Industry Trends

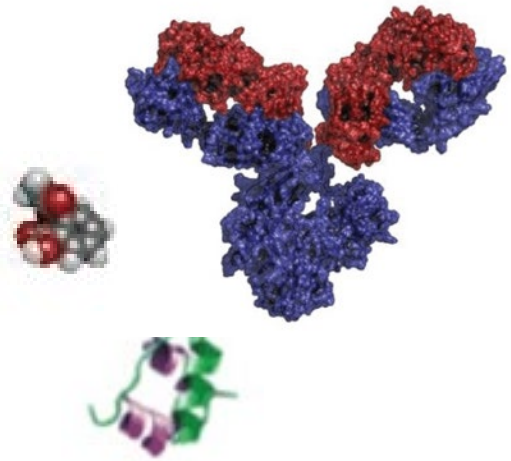
- Efficient filling/stoppering operations
- Less human intervention in the fill/finish process
- Need for zero defects
- Counterfeit products
- Smaller batch sizes/individualized medicine
- Lyophilization
- Cold chain storage issues
- Novel device requirements

Fluoropolymer Spray Coating Technology

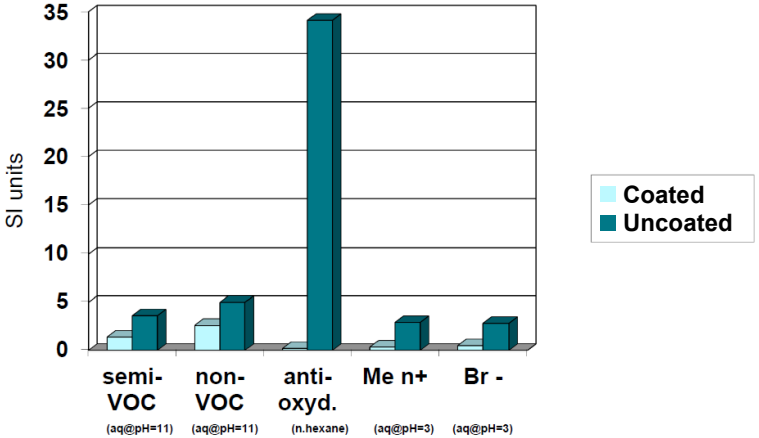


Fluoropolymer Spray Coating Properties

Ultra low extractable: spray coating acts a as a barrier to a wide range of chemical species



Spray coating components



Sensitive formulations, large molecules, biologics and (even with small molecules)

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Elastomer Manufacturing and Component Processing

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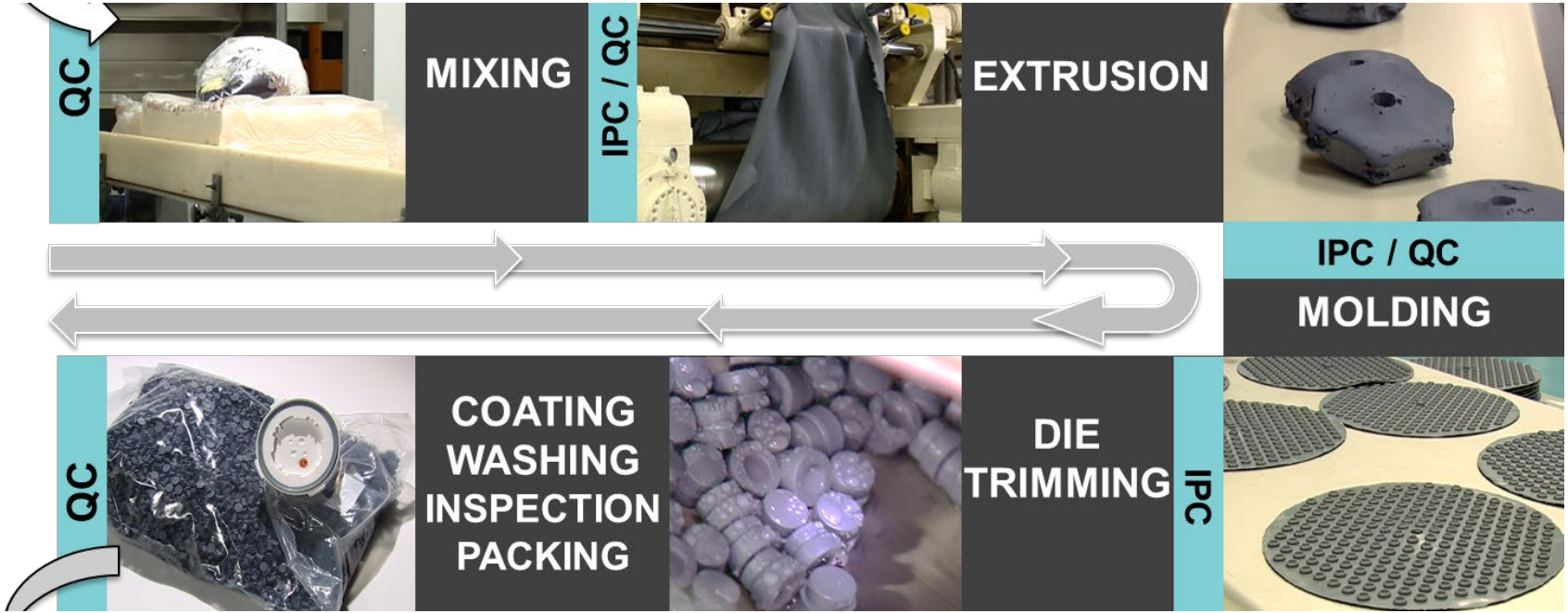
Elastomer Manufacturing Process



Component Processing

- Fundamentals of RfS and RTU components
- Importance of siliconization and selection criteria
- Basics of camera inspection
- Sterilization choices and elastomer packaging selection

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Product Options

	DATWYLER	Pharmaceutical User		
Bulk	Washed & siliconized closures in bags	Washing & siliconization	Sterilization	Filling
RfS	Washed & siliconized closures in RfS bags	Sterilization	Filling	
RTU	Washed & siliconized sterile closures in RTU bags	Filling		

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Ready for Sterilization (RfS)

Why are rubber components washed?

- Washing removes elastomeric debris, dirt and particles generated during molding and die-trimming
- Bring products in a controlled state of microbiological cleanliness (bioburden and endotoxins)
- Meet regulatory requirements:
  - FDA's guidance for industry – *Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice cGMP of 2004*
  - EMA guidance: *Note on quality of water for pharmaceutical use*

Why are components siliconized?

- Elastomers are inherently sticky
- To allow for functional properties, machinability and transportation

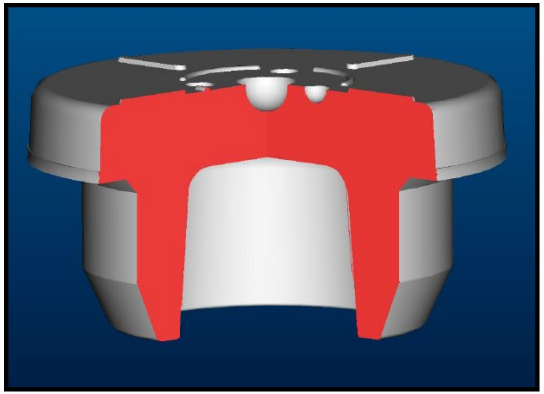
Ready for Sterilization (RfS)

What makes components RfS?

- Washed with a validated washing program
  - Purified water, and with Water-for-Injection (WFI) in last rinse
  - Defined specifications on low level of microbiological contamination
- Microbiological specifications apply:
  - for FirstLine™ → Bioburden: ≤ 0.05 CFU/cm²; Endotoxins: ≤ 0.02 EU/cm²
- Packaged in steam sterilizable (RfS) bags
  - Flexible packaging configurations including multiple Tyvek bags, RTP bags
- Visual inspection results with particulate analysis and silicone monitoring per batch

Ready for Sterilization (RfS)

‘Easy-to-wash’

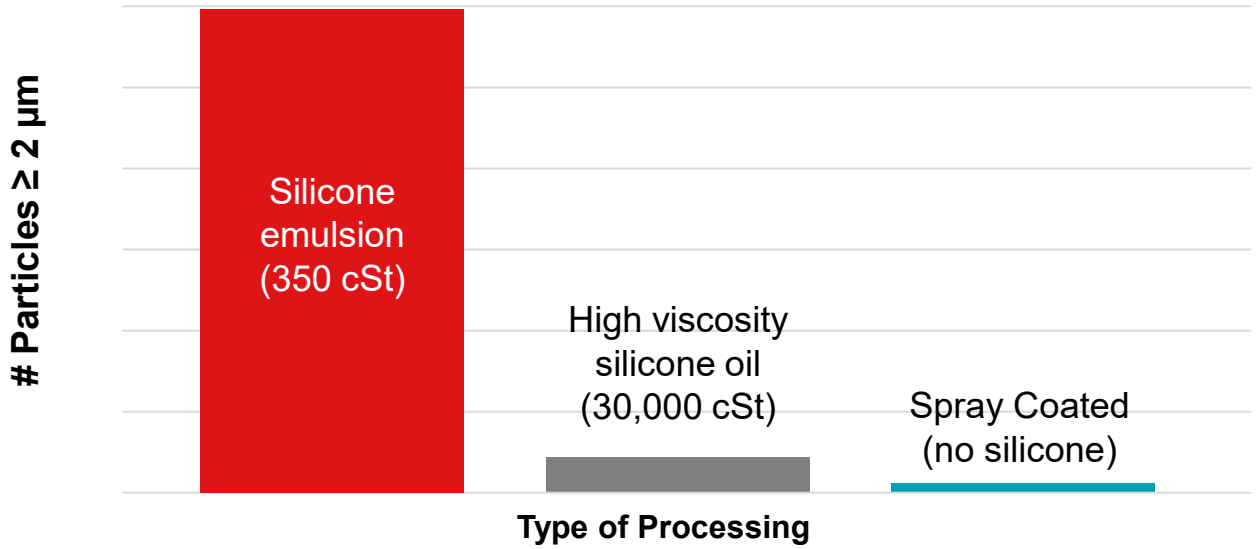


‘Difficult-to-wash’

Product Design: Impact of Silicone

Lubricious barrier coatings:
Siliconization of elastomeric components

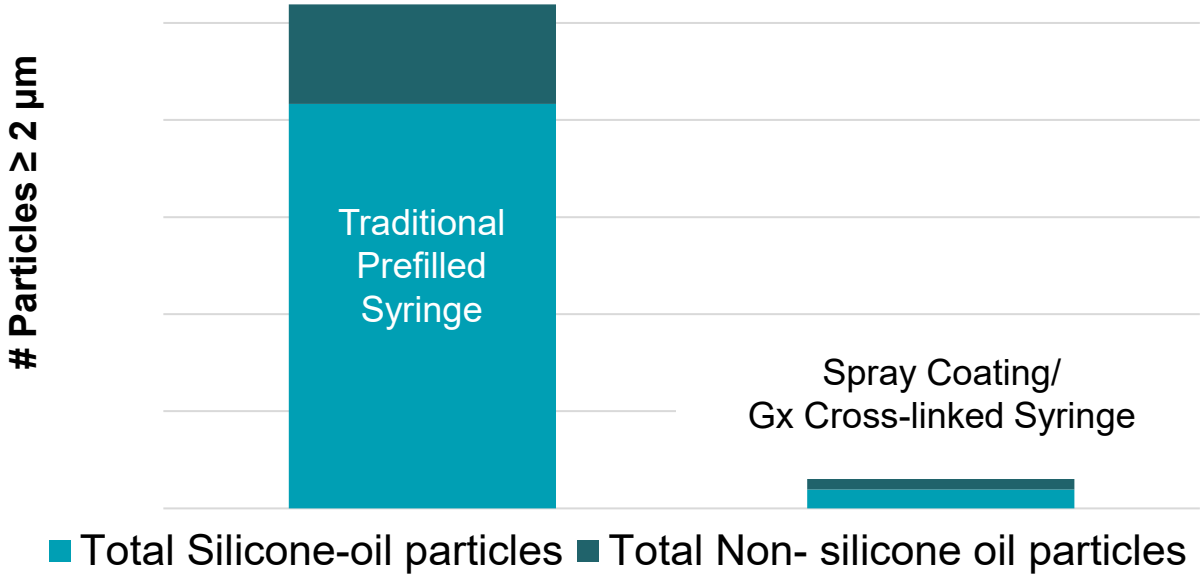
#particles per 10 cm^2 (ISO 8871-3)



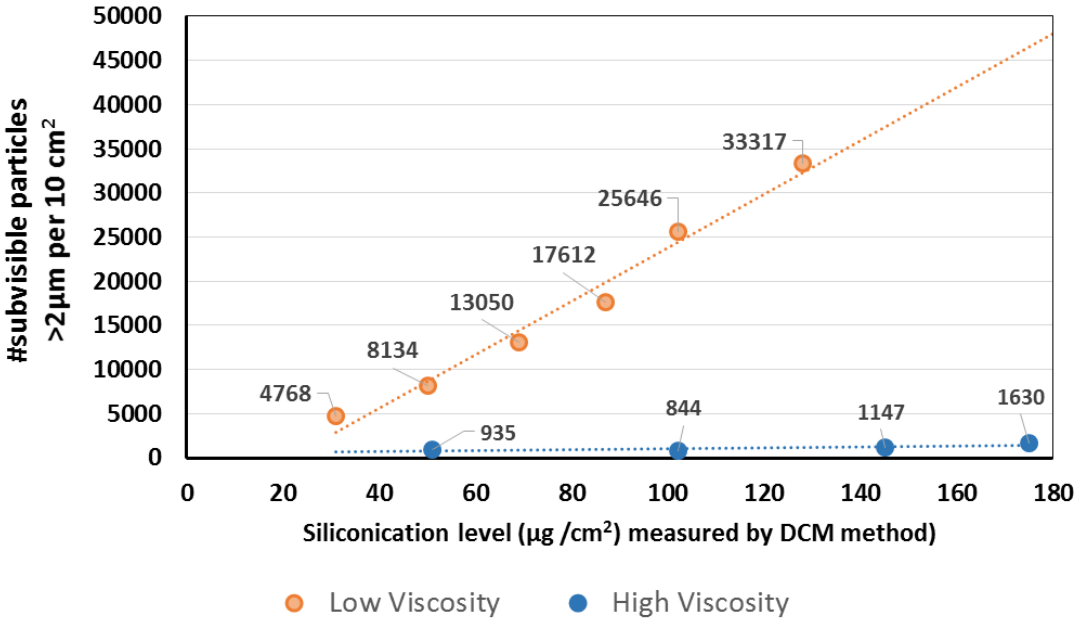
Datwyler provides both silicone options and in varied quantities to match the drug packaging needs.

Product Design: Impact of Silicone

Lubricious barrier coatings:
Ultra-low visible and subvisible particle levels



Product Design: Impact of Silicone



- High viscosity (30,000 cSt) and low viscosity (350 cSt)
- High viscosity silicone produces ~7 times less silicone particulate than low viscosity silicone
- Linear relationship between the quantity of silicone

Introduction to Camera Inspection

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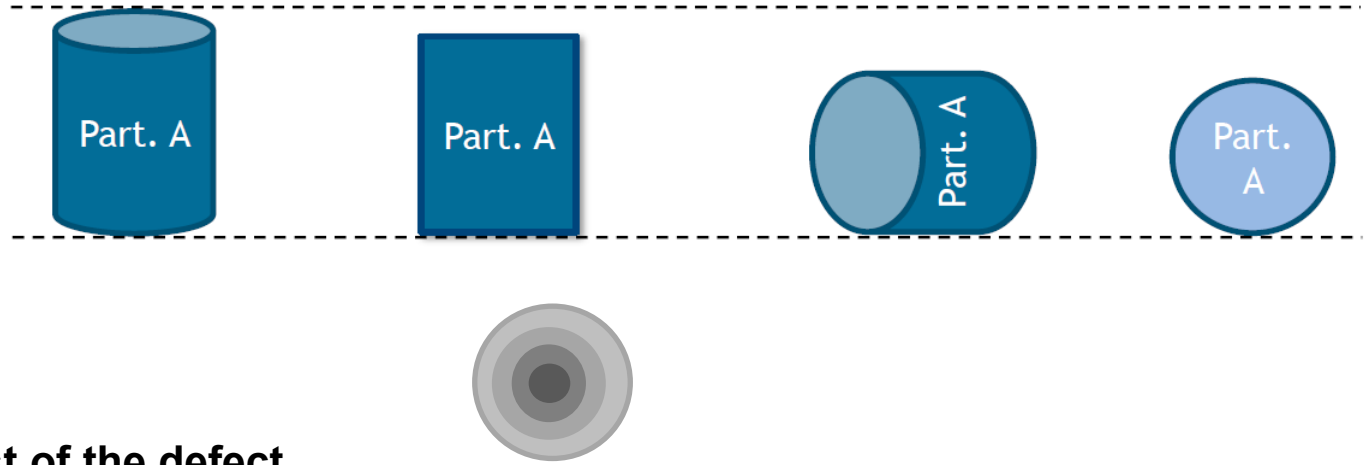
Chance of Detection

Perspective



Contrast of the defect

Detectability of the particle **x** Sensitivity of the vision machine → Detection level of the machine

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Camera Inspection

REJECTED DEFECTS:

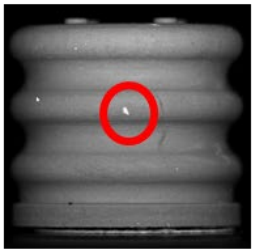
Capabilities: **What can we see and remove**?

- Particulates (fiber, hair, dust, etc.)
- Discoloration -- Embedded metal
- Dimensional errors
- Incomplete features
- Damages or defects

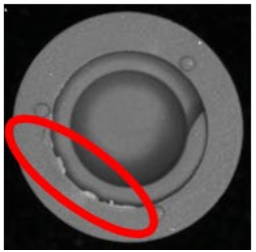
What are the limits?

- System will capture and remove particulates of area size <0.03mm^2 or ~175 x 175 microns in area (threshold)
- Minimum 10% contrast ratio difference in gray values (product color is important)

Deformed product



Foreign Matter



Damaged Coating

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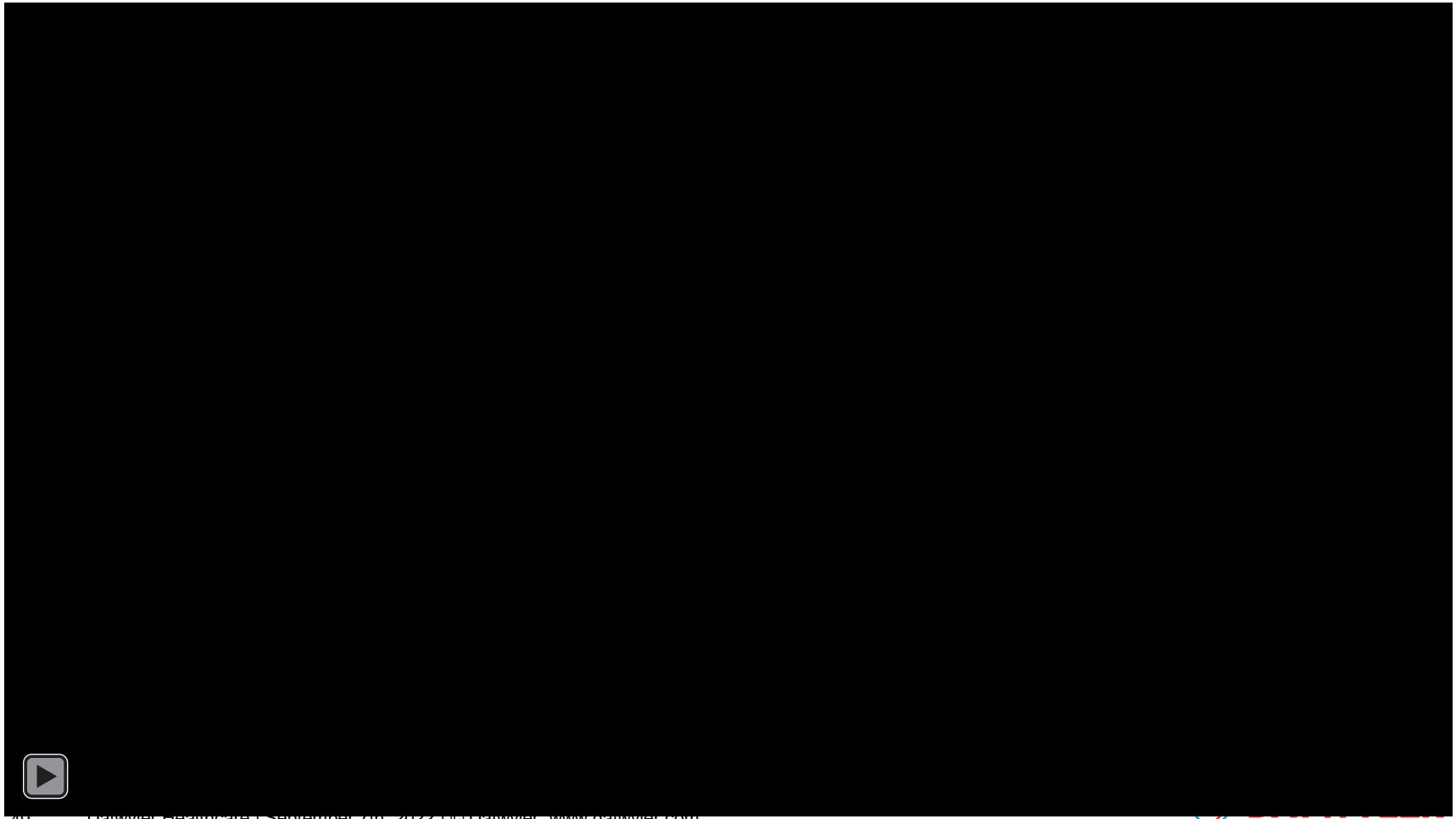

Introduction to Sterilization Methods

Gamma Sterilization

- An irradiation method where electromagnetic gamma rays are used to sterilize material
- Due to higher penetrability of gamma rays (relative to beta), frequently used to sterilize dense materials in the bulk
- Typical dosage is from 15-40 KGy, and is material dependent

Steam Sterilization

- A physical sterilization method where material to be sterilized must be in contact with steam at 121°C, 30 min.
- Typically, material is packaged in Tyvek bags to allow steam permeation

Ethylene Oxide (ETO) Sterilization

- A chemical sterilization method that is widely used for disposable medical devices and for sterilization of nested and tubbed empty prefilled syringes with assembled tip cap or needle shield

An Assessment – Gamma-RTU and Steam-RTU

Advantages

Gamma-RTU

- **Flexible packaging conditions** – due to high penetrability of gamma rays, dense materials packaged in bulk and stacked can be sterilized
- **Low cost solution that is easy to implement** – No isolators or clean rooms required for sterilization

Steam-RTU

- **No measurable effect on chemical/physical properties**
- **High compatibility** with elastomeric formulations

Disadvantages

- **Measurable effect on chemical/physical properties that is dependent on the elastomer formulation and irradiation dosage.** Elastomeric formulations need to be formulated that are compatible with gamma. – For eg. hardness, stickiness, fragmentation may be altered

- **Residual moisture content monitoring** in elastomer may not be desirable for certain applications – For eg. Lyophilization
- **Exposure to high temperature dry heat** – Subsequent drying step (from dry heat) may adversely affect elastomer or the outside packaging material
- **Tyvek bags** are a source of particulate contamination

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Importance of Manufacturing Environment

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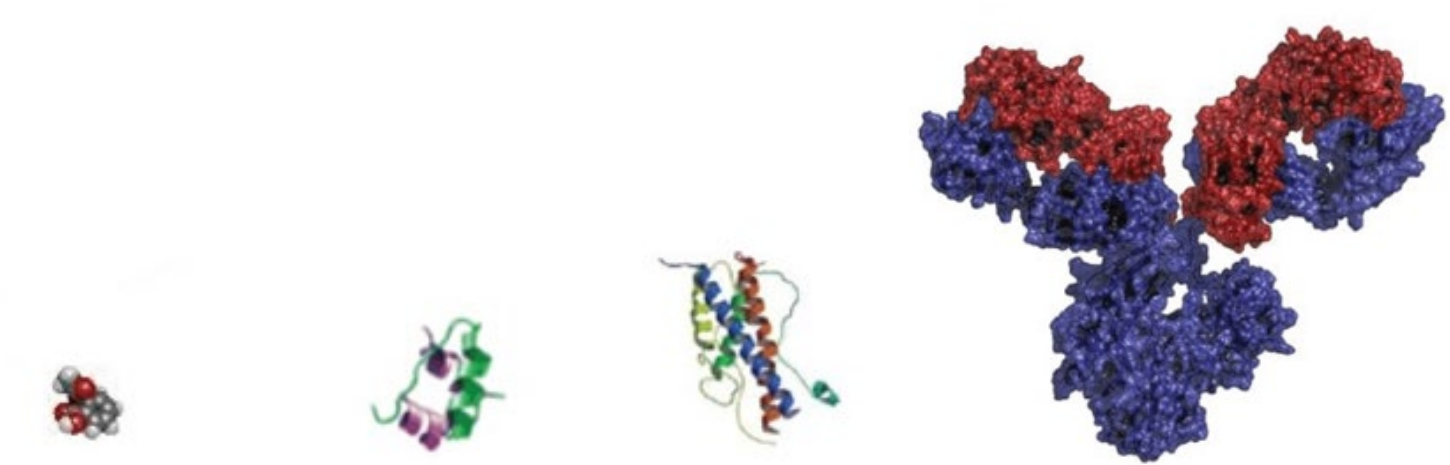
Pharmaceutical Trends



Molecular Mass

Small molecule
Low sensitivity

Large molecule
High sensitivity

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Should the component manufacturing environment be an extension of the API manufacturing environment?

Thank you!

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