Extractable & Leachable Considerations for Small Volume Parenteral Applications

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Overview

1. Regulatory expectations (brief recap)
    - US & EU
2. Typical materials of construction (MoC)
    - Rubbers
    - Glass (related) issues
    - Other Materials
3. Container closure systems (CCS)
    - Vials
    - Prefilled syringes
    - Cartridges

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1. Regulatory Expectations for Small Volume Parenterals – Brief Recap

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1.1. Regulatory Expectations - US

LIQUID SVP's

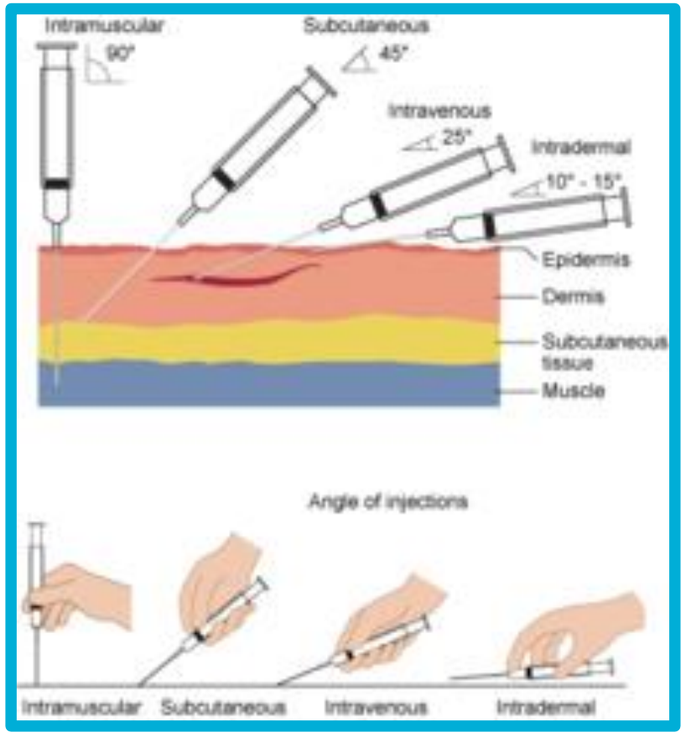
LYO

Ranking the Packaging Concerns

Parenteral:

*100% **Absorption/Bioavailability** in Human Body*

***Distribution** via Systemic Circulation, Blood*



Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Components – Dosage Form Interactions		
	High	Medium	Low
Highest	Inhalation Aerosols and Sprays	- Injections and Injectable Suspensions - Inhalation Solutions	- Sterile Powders and Powders for Injection - Inhalation Powders
High	Transdermal Ointments and Patches	- Ophthalmic Solutions and Suspensions - Nasal Aerosols and Sprays	-
Low	- Topical Solutions and Suspensions - Topical and Lingual Aerosols - Oral Suspensions and Solutions	-	- Oral Tablets and Oral (Hard and Soft Gelatin) Capsules - Topical Powders - Oral Powders

Adaped from USP <1664>, items in red shows revisions from original table from FDA 1999 packaging guideline

1.1. Regulatory Expectations - US

LIQUID SVP's

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Remarks:

1. "Medium" likelihood of interaction for liquid SVP:
   - Based upon the observation that most Parenteral DP are aqueous based.
   - For non-aqueous based drug products: more caution is needed!

2. "Low" likelihood of Interaction for lyo SVP:
   - Mainly based upon the observation that
     - The interaction between a solid (lyo cake) and a material (eg rubber) is limited
     - Limited direct contact between lyo cake and rubber closure

   → However interaction for a lyo cake and material may not need always a direct contact.

   → BE CAREFUL when "rationalizing" a lyo application as being non critical!!!

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1.1. Regulatory Expectations - US

Recent “Informal” Communications from the FDA

Video of **Dan Mellon** (FDA - CDER)

https://www.youtube.com/watch?v=mol_X2zQeig

1. Identify leachable compounds above the Qualification Threshold (QT)
2. The use of inappropriate threshold levels
3. Inadequate sensitivity of the detection methods for leachables (AET>LOQ)
4. Inadequate stability data to examine trends in leachables
5. Inadequate toxicology justification to support a Permitted Daily Exposure (PDE)
6. Inadequate descriptions of how extractables data were used to design leachables assessments
7. Inadequate correlations between extractables & leachables

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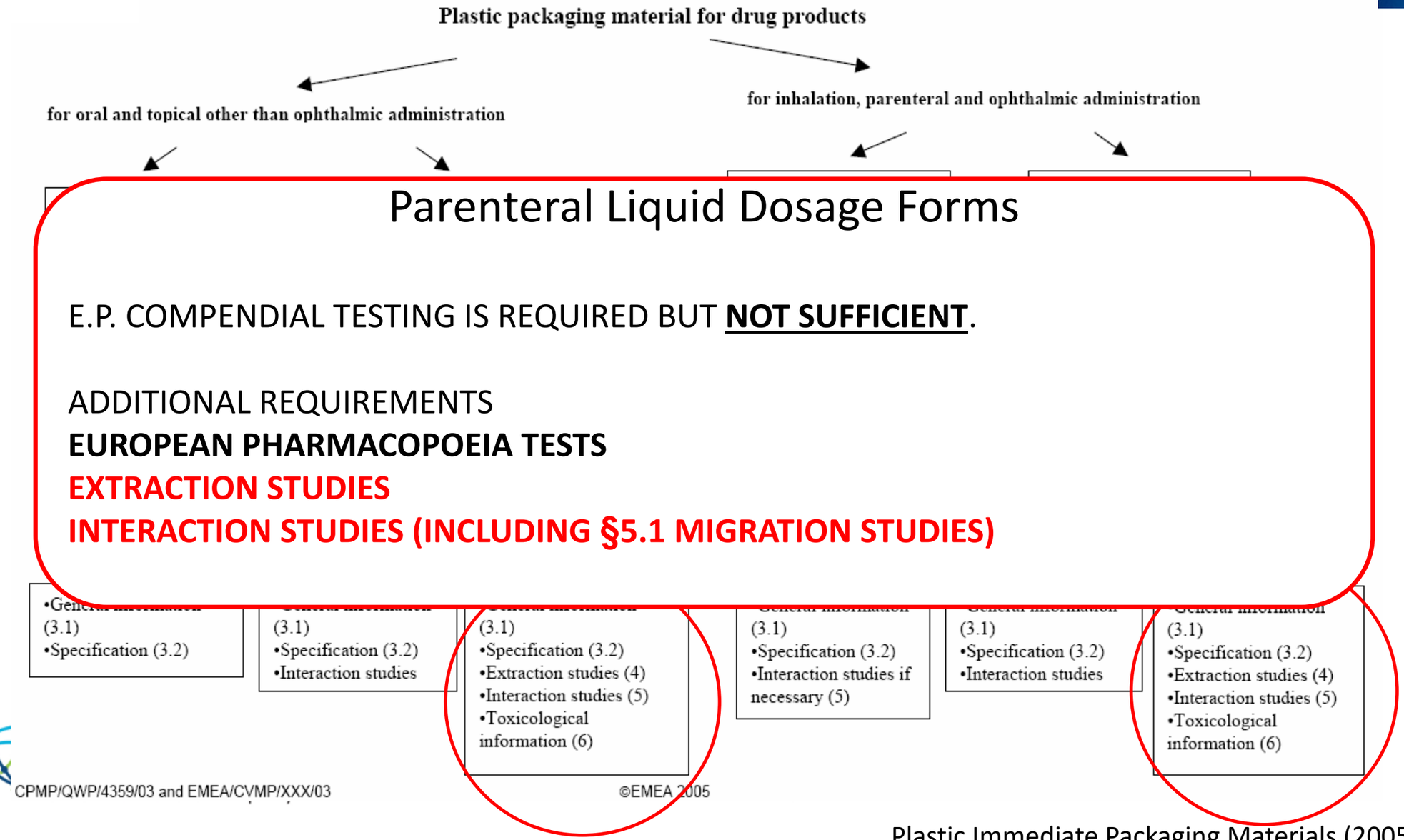
1.2. Regulatory expectations – EU

- Going through the decision tree: **liquid dosage forms – high requirements**



Parenteral Liquid Dosage Forms

E.P. COMPENDIAL TESTING IS REQUIRED BUT **NOT SUFFICIENT**.

ADDITIONAL REQUIREMENTS

EUROPEAN PHARMACOPOEIA TESTS

EXTRACTION STUDIES

INTERACTION STUDIES (INCLUDING §5.1 MIGRATION STUDIES)

Plastic Immediate Packaging Materials (2005)

2. Materials of Construction (MoC) for SVP Containers, and their associated Extractable & Leachable Profiles

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2.1. Materials of Construction: Rubbers

Composition of rubbers can be very complex!!

1. Initial ingredients of the rubber formulation
2. Impurities of these ingredients
   (e.g. residual solvents, oligomers in elastomer, halides in halobutyl rubber, et cet.)
3. Reaction / degradation products during rubber production

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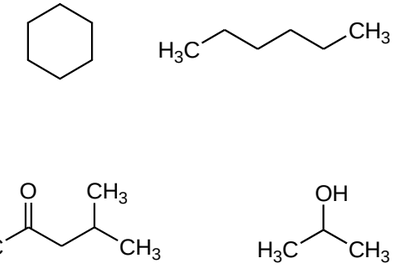
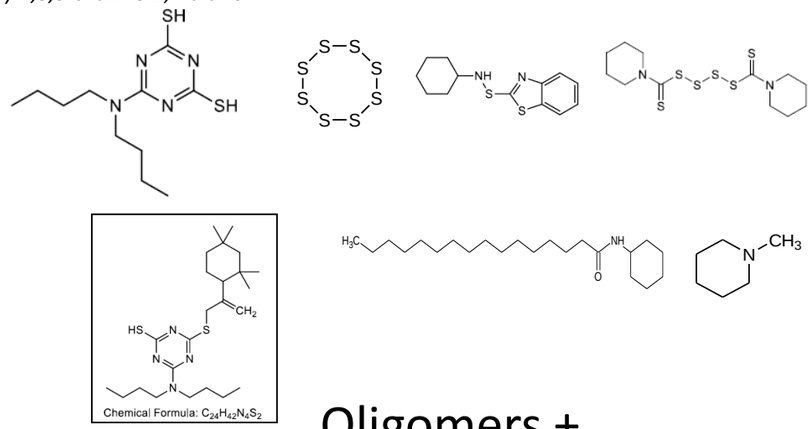
2.1. Materials of Construction: Rubbers – Examples of E/L

Solvent residues

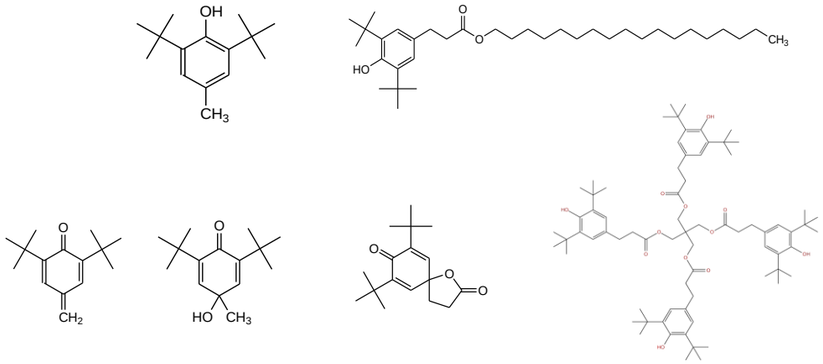


Curing agents + Reaction/degradation products

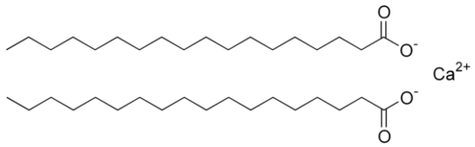
6-(Dibutylamino)-1,3,5-triazine-2,4-dithiol

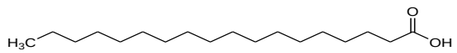


Anti-oxidants & Degradation products

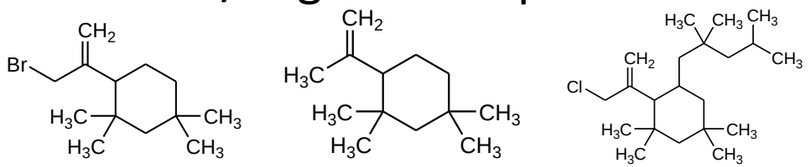


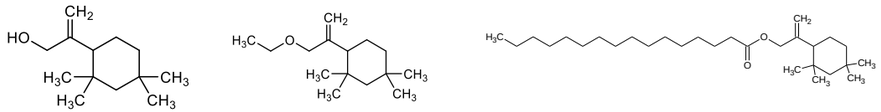
Acid scavengers



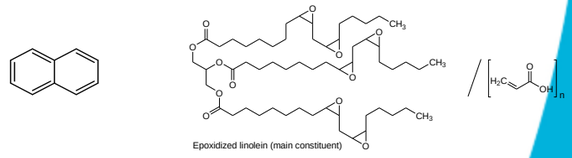


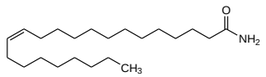
Oligomers + Reaction/degradation products





Other E/L Compounds





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2.1. Materials of Construction: Rubbers

Smart selection of ingredients can tune a rubber compound!

But in general too many ingredients should be avoided

→ negative impact on extractables profile:

“What you don’t put in, can’t come out”

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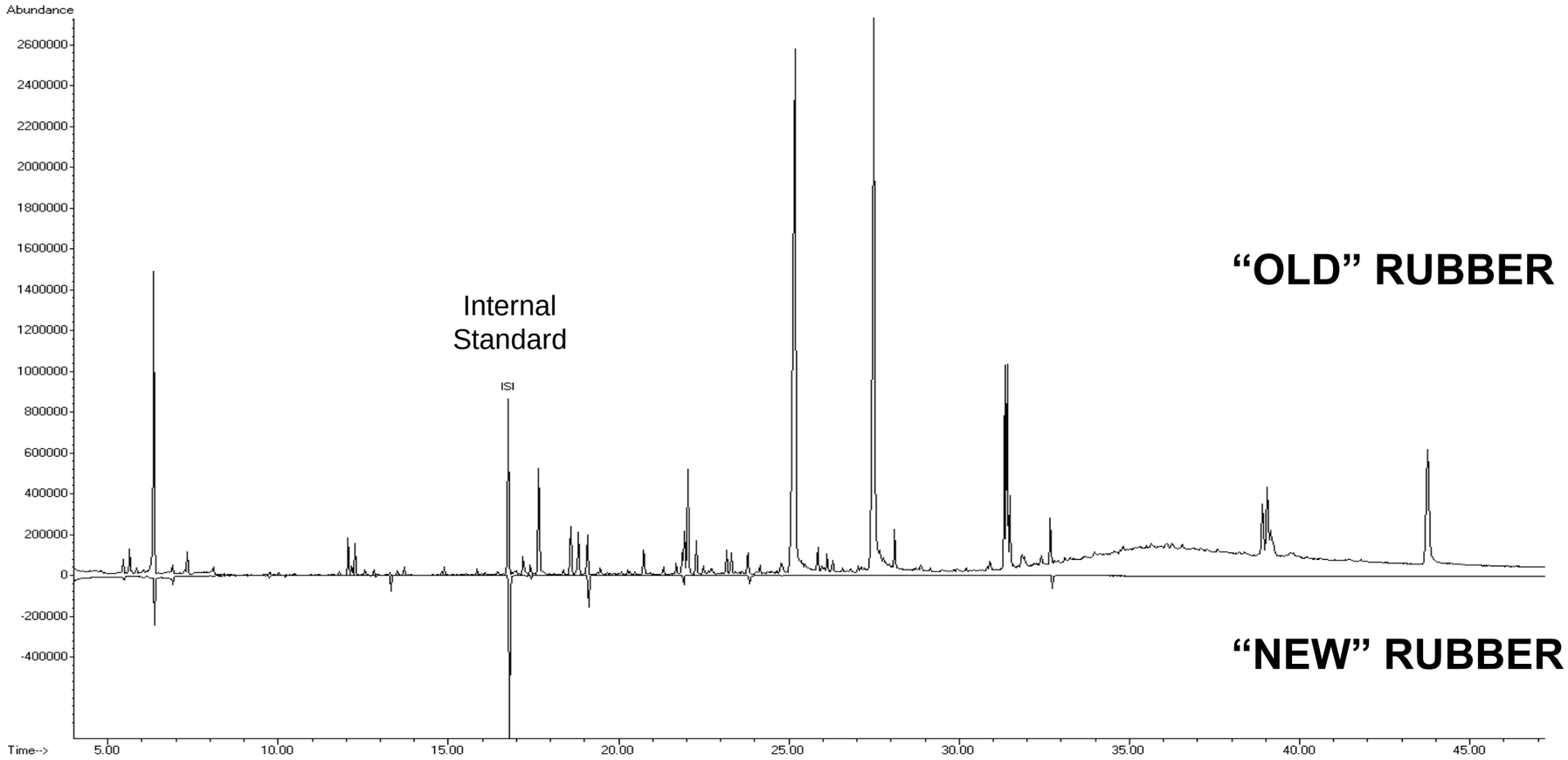
2.1. Materials of Construction: Rubbers

Difference in extractable results for an **OLD** vs **NEW** rubber



(*IPA extract; GC/MS analysis*)

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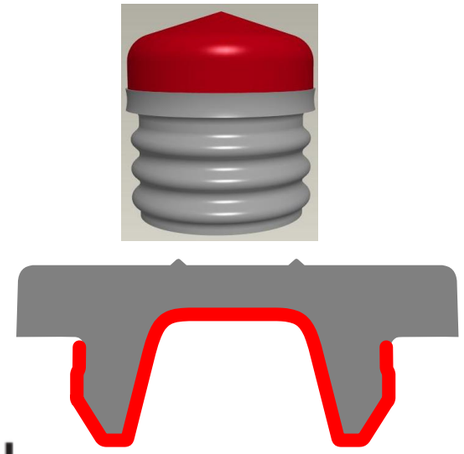
2.1. Materials of Construction: Rubbers

- Coated closures: barrier effect from the fluoropolymer!
  - Simplified extractables profile
  - Improved drug / excepients compatibility

- Different technologies:

Film coating technology



Spray coating technology

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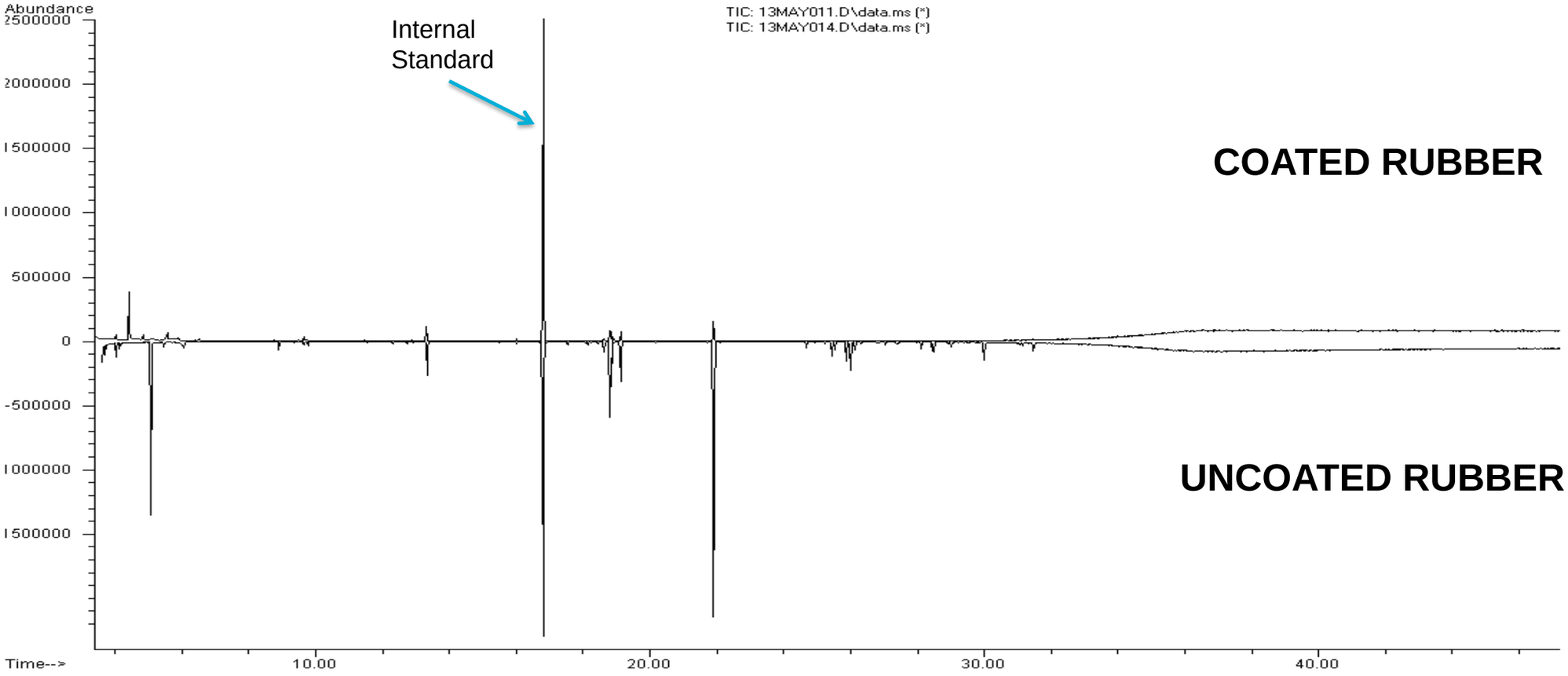
2.1. Materials of Construction: Rubbers

Difference in extractable results for an **COATED** vs **UNCOATED** rubber (same rubber grade)



(*IPA extract; GC/MS analysis*)

2.1. Materials of Construction: Rubbers

Number of leachables from rubbers in SVPs is determined by:

- The type of rubber formulation
- The number of ingredients in the rubber
- Type of ingredients (e.g. type of vulcanisation, type of AO, stabilizer….)
- Coated/non-coated rubbers
- The composition of the drug product
- The type of contact between the rubber and the drug product (e.g. exposed surface area)
- The storage temperature
- The storage time (expiration date)

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2.2. Materials of Construction: Glass

GLASS COMPOSITION FOR DIFFERENT GLASS TYPES

Component	Type I (Borosilicate)	Type II, III, NP (Soda-Lime)
SiO_2	70 - 73%	69 - 73%
B_2O_3	10%	0 - 1%
Na_2O	2 - 9%	13 - 14%
Al_2O_3	6 - 7%	2 - 4%
BaO	0,1 - 2,0%	0 - 2%
K_2O	1 - 2%	0 - 3%
CaO	0,7 - 1,0%	5 - 7%
MgO	0 - 0,5%	3 - 4%
ZnO	0 - 0,5%	-

"Soda – Lime"

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2.2. Materials of Construction: Glass

RISK OF GLASS LEACHABLES

Major extractables from glass

- Alkali release (Na_2O)
- Silica release (Si_2O)

Minor extractables from glass

- K (K_2O), B (B_2O_3), Ca (CaO), Al (Al_2O_3) (more in alkaline environment!)
- Traces of Fe
- As (glass can contain arsenic oxide (III) as a fining agent to improve glass tranparency)

Possible risks:

- Al can accumulate in patients with reduced renal function, causing e.g. neurological diseases
- As is toxic
- Alkali release: pH shift of unbuffered solutions
- Release of metals can cause precipitation with some salts present in the DP

eg: Ba => $BaSO_4$, Al => $Al(OH)_3$

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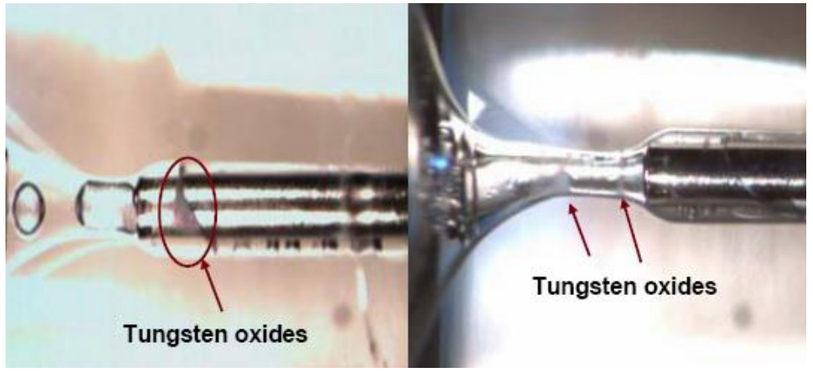
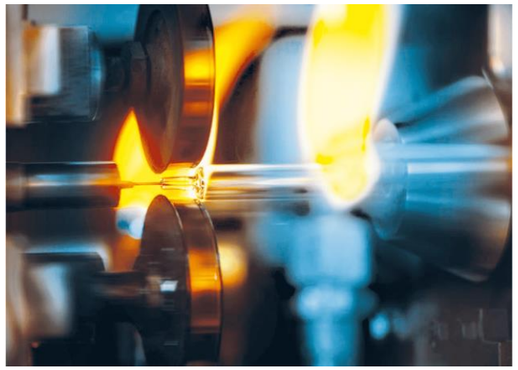
2.2.1. Materials of Construction: Glass Related Issues

TUNGSTEN RESIDUES – PREFILLED SYRINGES

- Tungsten pin used in the production of glass pre-filled syringes to open the syringe hub (cavity where staked needle is glued in)

→ Tungsten oxide residues are known to cause protein degradation (protein oxidation causing aggregation)





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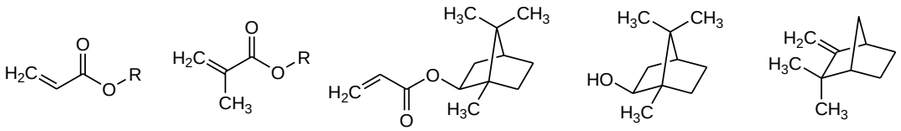
2.2.2. Materials of Construction: Glass Related Issues

GLUE RESIDUES – PREFILLED SYRINGES

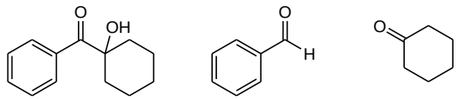
- Glue is used to glue in the staked needle into the PFS-system
- Prolonged contact with a drug product may release glue components
- Target compounds may depend upon the glue used (through UV Curing)

Base Polymer



Acrylate | Methacrylate | Isobornyl acrylate | Isoborneol | Camphene

UV curing / activation



Irgacure 184 | Benzaldehyde | Cyclohexanone

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2.2.3. Materials of Construction: Glass Related Issues

SILICONE OIL RESIDUES

- Silicone oil residues may denaturate proteins or form aggregates
- Glass surfaces are siliconized a.o. to reduce potential interactions with aqueous contact solutions
  - Hydrophobic surface / reduced wettability
  - Reduced alkali release
  - Silicone oil remainders become leachables

Less of an issue with Baked Silicone

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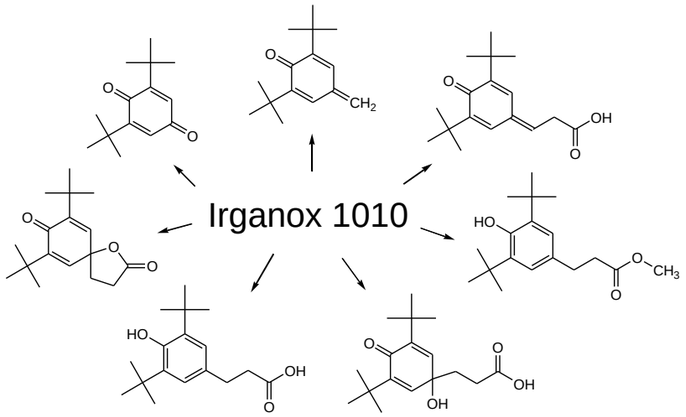
2.3. Materials of Construction: Polymers for Containers

Cyclic Olefin Polymers = COP
Cyclic Olefin Copolymers = COC
Polypropylene = PP

Typical composition of commercial polymers for barrel manufacture

- Additives (BHT, Irganox 1010, stearates, pigments, clarifiers)
- Residues (monomers, solvent residues, processing residues)
- Oligomers (especially for PP)
- Degradation products from above compounds
  (organic acids, aldehydes, ketons, alcohols, chain scission fragments)



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2.4. Associated Concerns for Polymers Containers: Secondary Packaging

Regulatory Requirements for Secondary Packaging

FDA guidance document: 'Container Closure systems for Packaging Human Drugs and Biologics', 1999:

> "If the packaging system is relatively permeable, the possibility increases that the dosage form could be contaminated by the migration of an ink or adhesive component…In such case the secondary packaging component should be considered a potential source of contamination and the safety of its materials of construction should be taken into consideration…"

EMA: 'Guideline on Plastic Immediate Packaging Materials', 2005*:*

> "It should be scientifically demonstrated that no components of ink or adhesives, applied to the outer surface of the container closure system, will migrate into the medicinal product."

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2.4.1. Associated Concerns for Polymers Containers: Secondary Packaging

Label

= paper + ink + varnish + adhesive

Typical extractable compounds:

- Curing agents (e.g. benzophenone, Irgacure 184,...)
- Solvent residues (e.g. toluene, acetone)
- Adhesive residues (e.g. acrylates)
- Paper residues (e.g. (dehydro)abietic acids, abietates)

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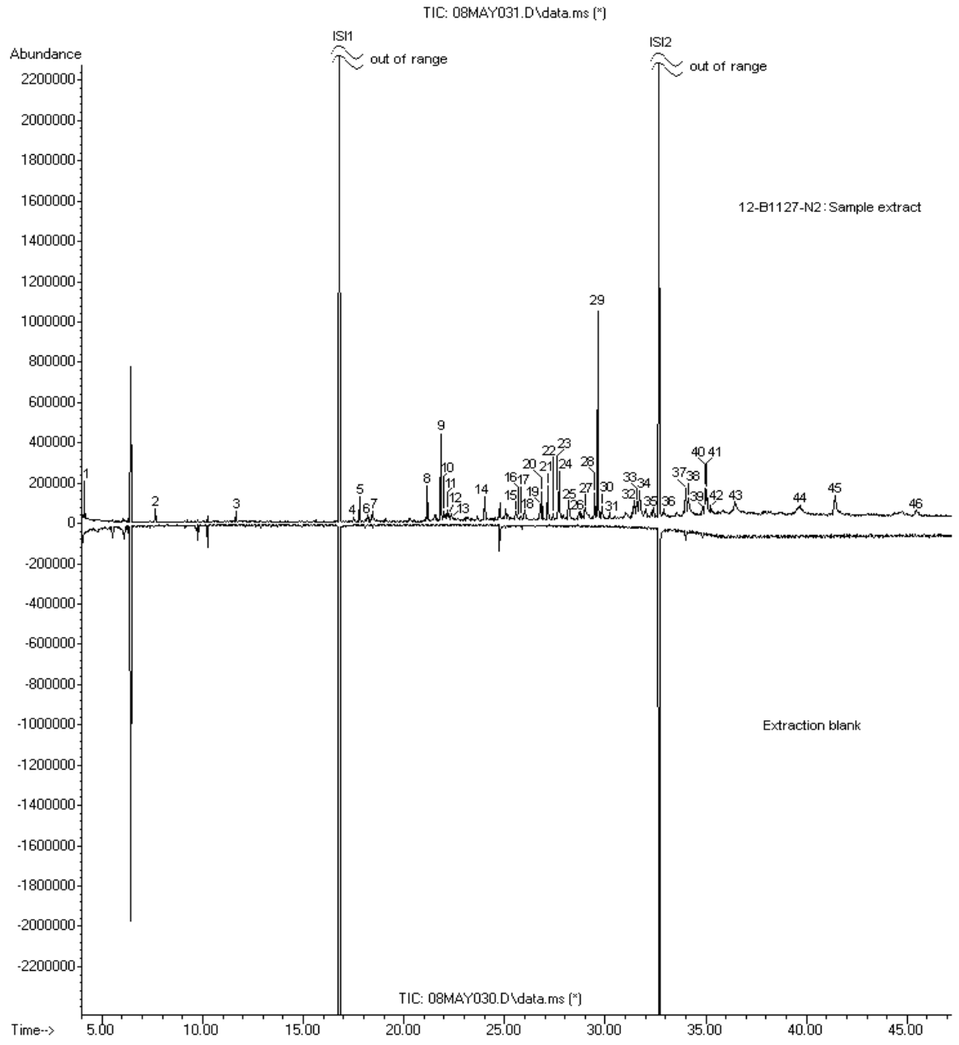
2.4.1. Associated Concerns for Polymers Containers: Secondary Packaging

Label

Example chromatogram for GC/MS analysis of IPA extract



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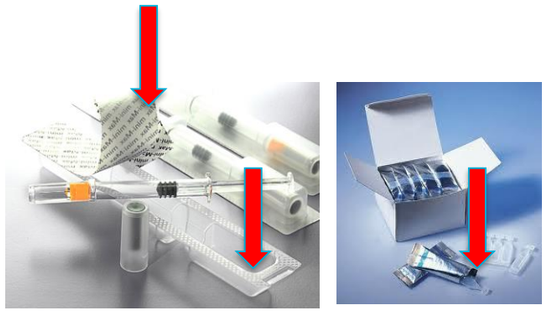
2.4.2. Associated Concerns for Polymers Containers: Secondary Packaging

Overwrap / overpouch / blister



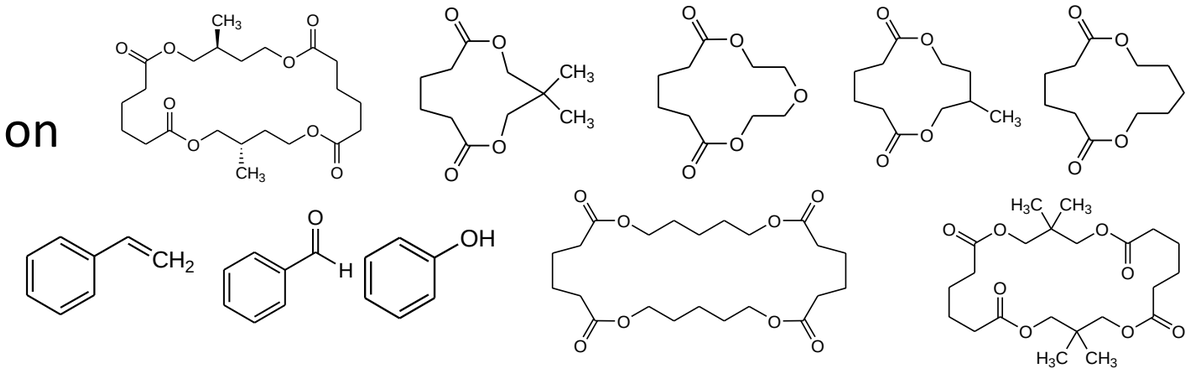
(to compensate for potential lower barrier properties of the polymer)

- Multilayer system
- Aluminum as barrier layer
- Tie-layers to keep the different layers together

Typical extractable compounds:

- Bislactone compounds from Tie-layer
- Residues from other layers (depends largely on selected materials of the multilayer)

bislactones



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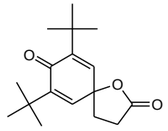

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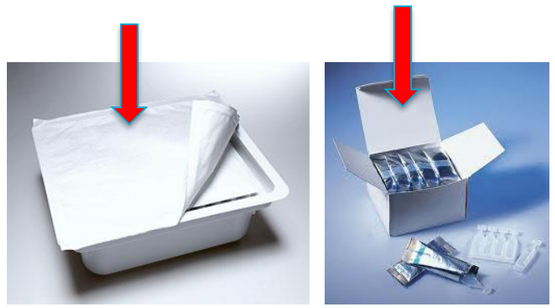
2.4.3. Associated Concerns for Polymers Containers: Secondary Packaging

Tubs

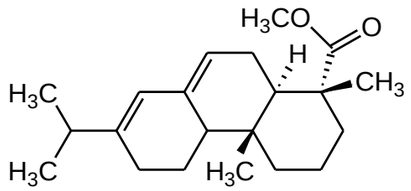
Carton / paper

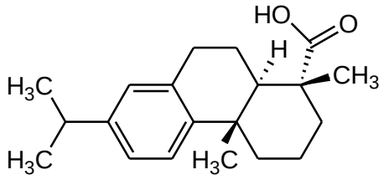
for nested syringes (eg Tyvek)

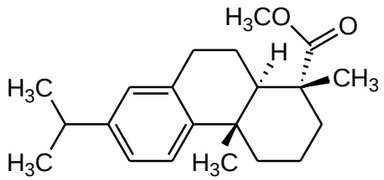
also from label

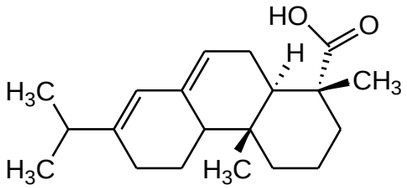


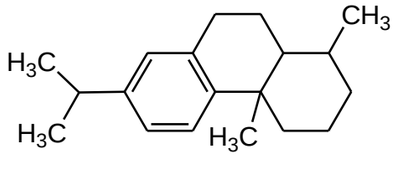
Example structures of abietic acids, abietates and vanillin

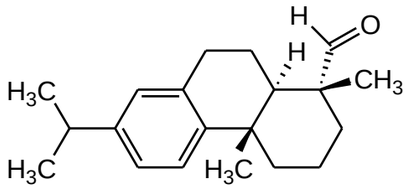


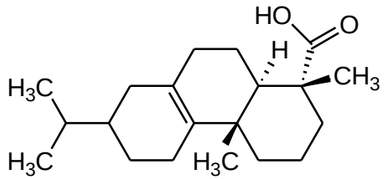


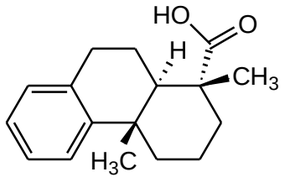


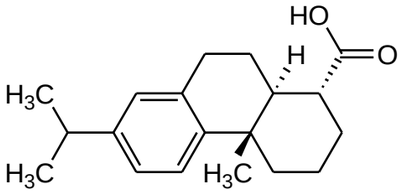


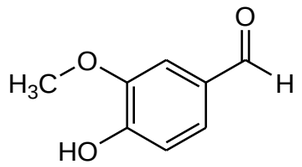












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3. What Does it mean for the different SVP- Container Closure Systems?

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1.Vials:

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Glass Vials

Liquid Drug Products

Reconstitution Solution

- **Glass vial**: Metals (direct assessment in LEA study if glass composition is available)
- **Rubber closure**:
  - ✓ Inverted position → higher migration
  - ✓ Migration will be determined by:
    - Solubility of leachables in drug product solution
    - Potential diffusion of compounds through rubber, into solution
    - Temperature
    - Coated vs. non-coated
  - ✓ VOC, SVOC and NVOC, silicone oil and some metals may cause:
    - Safety issue
    - Reactive with drug product: also potential Performance & Quality Issue!
  - ✓ Also, ions (chloride, bromide and fluoride) may need to be “checked off”...

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Polymeric Vials

Liquid Drug Products

Reconstitution Solution

- **Polymer vial**:
  - ✓ VOC, SVOC and NVOC and some metals may cause:
    - Safety issue
    - Reactive e.g. with reconstituted DP: also potential Performance & Quality Issue!
  - ✓ Also, ions (eg. acetate and formate) may need to be “checked off”...

- **Rubber closure:** (see previous slide)

- **Secondary packaging:**
  - ✓ Label
  - ✓ Overwrap/overpouch/blister
  - ✓ Tubs
  - ✓ Carton/paper

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2. Pre-Filled Syringe:

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Glass Pre-Filled Syringes

- **Glass barrel**:
  - ✓ Metals
  - ✓ Silicone oil
  - ✓ In case of staked needle:
    - Tungsten residues
    - Needle glue

- **Rubber plunger** (very similar to rubber stopper for vial):
  - ✓ Horizontal position -> contact with all parts
  - ✓ Migration will be determined by:
    - Solubility of leachables in drug product solution
    - Potential diffusion of compounds through rubber, into solution
    - Temperature
    - Coated vs. non-coated
  - ✓ VOC, SVOC and NVOC, silicone oil and some metals may cause:
    - Safety issue
    - Reactive with drug product: also potential Performance & Quality Issue!
  - ✓ Also, ions (chloride, bromide and fluoride) may need to be “checked off”...

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Polymeric Pre-Filled Syringes

- **Polymeric barrel**:
  - ✓ VOC, SVOC and NVOC, silicone oil and some metals may cause:
    - Safety issue
    - Reactive e.g. with reconstituted DP: also potential Performance & Quality Issue!
  - ✓ Also, ions (eg. acetate and formate) may need to be “checked off”...

- **Rubber plunger** (see previous slide)

- **Secondary packaging:**
  - ✓ Label
  - ✓ Overwrap/overpouch/blister
  - ✓ Tubs
  - ✓ Carton/paper

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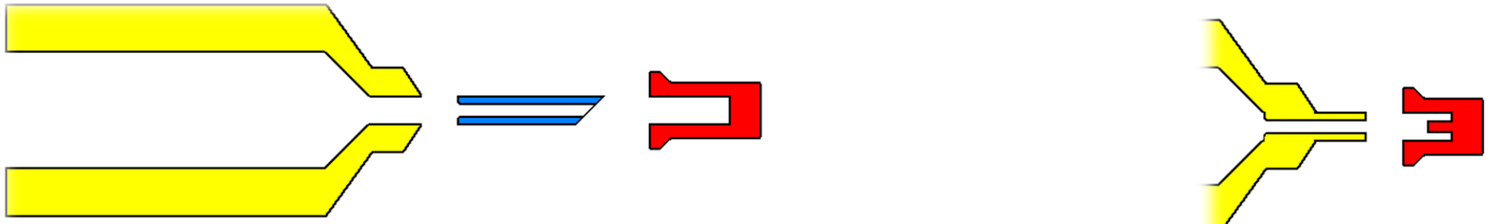
Pre-Filled Syringes

- **Needle shield**
  - ✓ No direct contact between drug product and needle shield
  - ✓ HOWEVER: Release of VOC and SVOC compounds from the needle shield into the content of the PFS is possible!
  - ✓ VOC and SVOC → potential Safety issue and Performance & Quality Issue
  - ✓ Typically no NVOC, metals and ions investigation is necessary

- **Tip Cap**
  - ✓ Direct contact between drug product and tip cap



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3. Cartridges

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Cartridges

- **Glass barrel**:
  - ✓ Metals
  - ✓ Silicone oil

- **Cartridge plunger** (very similar as for PFS):
  - ✓ Horizontal position -> contact with both rubber closures
  - ✓ Migration will be determined by:
    - Solubility of leachables in reconstitution Solution (typically inorganic aqueous solution (typically low solubility for most non-polar organic compounds))
    - Potential diffusion of compounds through rubber, into solution
    - Temperature
    - Coated vs. non-coated
  - ✓ VOC, SVOC and NVOC, silicone oil and some metals may cause:
    - Safety issue
    - Reactive with drug product: also potential Performance & Quality Issue!
  - ✓ Also, ions (chloride, bromide and fluoride) may need to be “checked off”...

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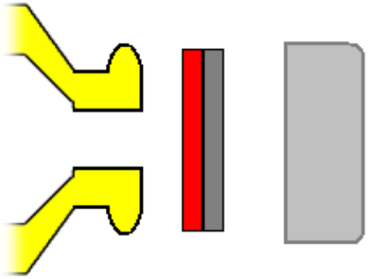
Cartridges



- **Sealing Disk:**
  - ✓ Typically, a sealing disk is a two-layered system
  - ✓ The inner layer has product contact (primary contact), should be the focus of the investigation
    - “One Sided” extraction mimics the product contact, avoids contribution of the outer layer
    - “Complete Extraction” of the 2 layered sealing disk can be considered as worst case
  - → Both approaches can be taken and have found regulatory acceptance

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Questions?

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Thank you

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