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OMICS Group is an amalgamation of Open Access Publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 700+ online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 1000+ International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

# OMICS International Conferences

OMICS International is a pioneer and leading science event organizer, which publishes around 700+ open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 1000+ conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

# The value of the "simulated study" as a tool to predict actual leachables in parenteral drug products

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# Agenda

1. Relationship between extractables and leachables
2. The value of the simulated study
3. Optimal prediction tool for leachables in parenterals
4. Case study: two simulated studies for PFS
5. Conclusion

# Definition

- Leachables

  ”Compounds that *migrate* from the container/closure system of the drug product under normal in-use storage conditions and which a patient can be exposed to during intake of the drug”

- Extractables

  ”Compounds which can be *extracted* from individual components of the container/closure system (CCS) under appropriate solvent and temperature conditions - thereby simulating a ‘worst case’ leachable situation”

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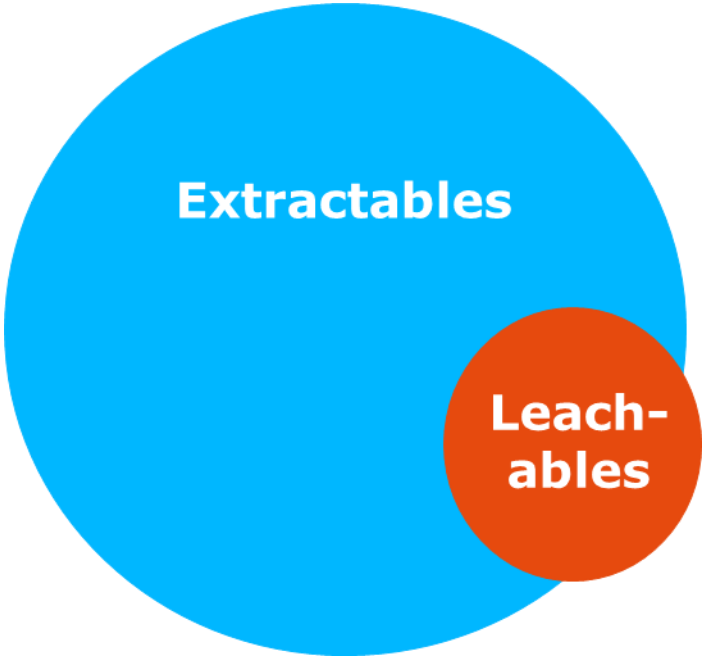
# Extractables and Leachable relationship

- Leachables (L) is a subset of the extractables (E)
- Reaction chemistry should be remembered

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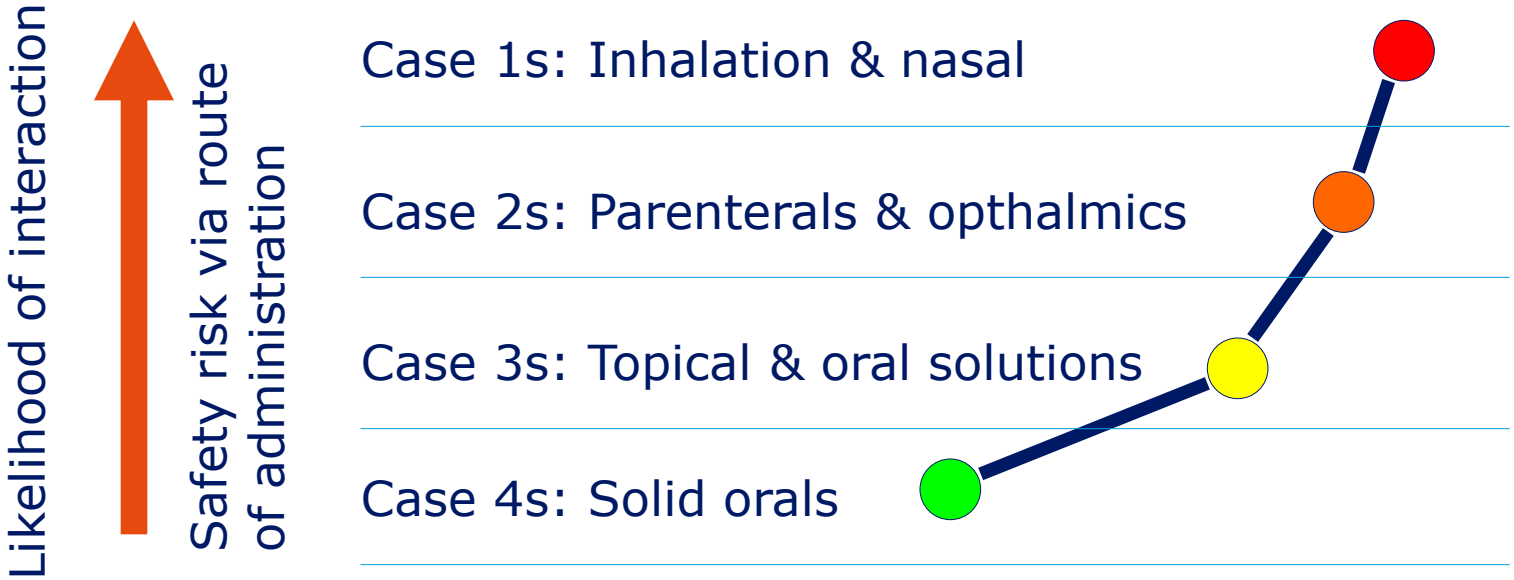
# Safety risk for leachables - FDA guideline

- Safety risk for leachables based on ”Container Closure Systems for Packaging Human Drug and Biologics: Chemistry, Manufacturing and Controls Determination” FDA guideline

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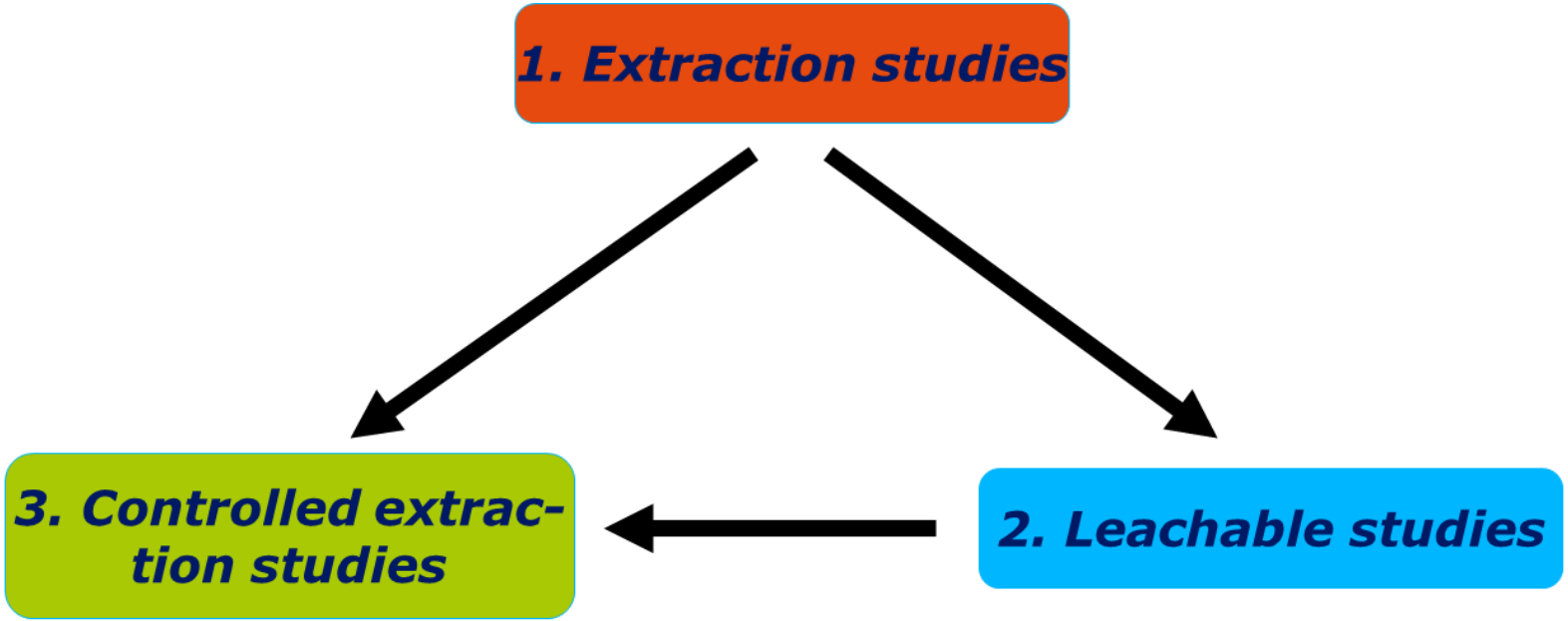
# E&L consortia

- Product Quality Research Institute (www.pqri.org)
  - **2000** E&L group for Orally Inhaled Nasal Drug Products (OINDP) formed with the purpose to suggest best practises and guidance for E&L test and documentation
  - **2001** OINDP: Leachables and Extractables: Point to Consider
  - **2002** OINDP: Development of Scientifically Justifiable Thresholds for Leachables and Extractables
  - **2006** OINDP: Safety Thresholds and Best Practices for Leachables and Extractables in Orally Inhaled and Nasal Drug Products

# E&L consortia

- Product Quality Research Institute (www.pqri.org)
  - **2008** PQRI E&L group for Parenteral and Ophalmic Drug Products (PODP) formed with the purpose to suggest best practises and guidance for E&L test and documentation
  - **2013** PQRI work for OINDP's and PODP's intended to be captured in the USP
  - **2015** USP <1663> extractables and <1664> leachables expected

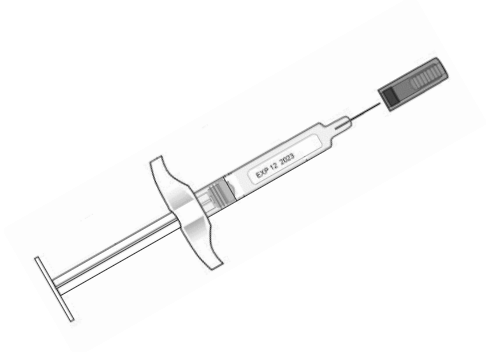
# PQRI OINDP suggestion



# Prefilled syringes volume and dosing frequency

Metered Dose Inhaler

Prefilled Syringe



Large Volume Parenteral

Volume

Number of doses

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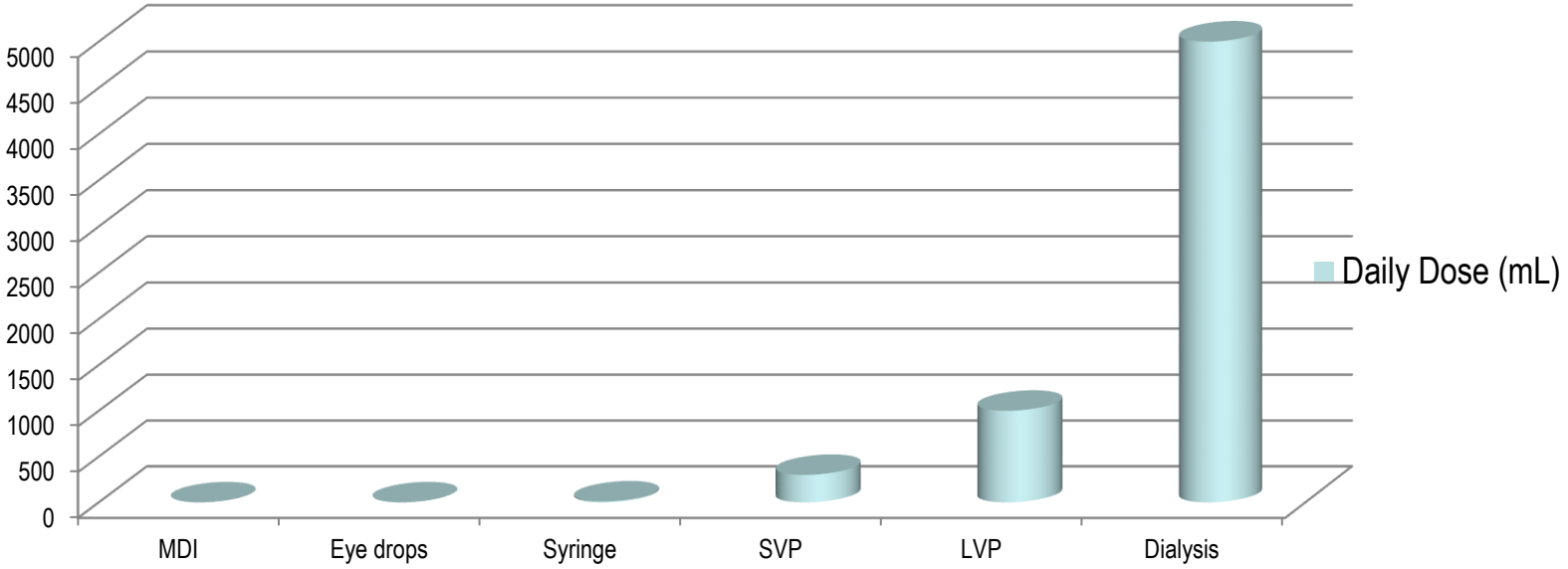
# Daily dose volumes PODP's




Taken from presentation by Dennis Jenke, Baxter Healthcare presented at the PQRI PODP E&L workshop Feb 2011.

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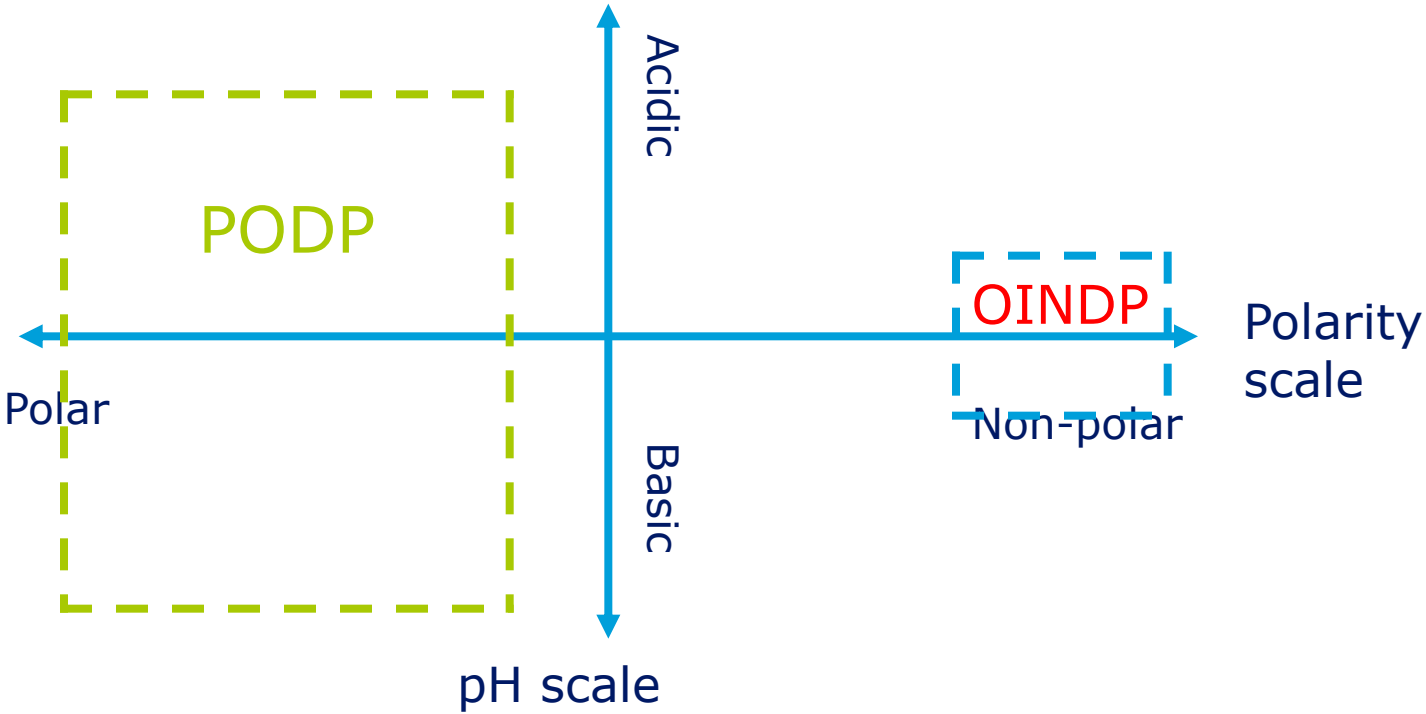
# OINDP's vs. PODP's formulations



# OINDP's vs. PODP's formulations

- OINDP
  - Small differences in polarity and pH
  - Low risk for secondary leachables
    - Interactions/reactions between leachables and formulation components or drug product
- PODP
  - Large variation in polarity and pH
  - Medium to high risk for secondary leachables

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# PQRI extractables recommendation

- Extraction solvents and techniques suggested by the PQRI is identical for both OINDP and PODP

| | Thermal | n-Hexane | Iso-propanol | Isopropan-ol/Water | Aqueous pH 2.5 | Aqueous pH 9.5 |
|---|---|---|---|---|---|---|
| **Headspace** | X | --- | --- | --- | --- | --- |
| **Reflux** | --- | X | X | PC/PVC only | --- | --- |
| **Soxhlet** | --- | X | X | --- | --- | -- |
| **Sealed Vessel** | --- | --- | --- | 55°C/3d | (121°C/ 1hr)[2] | (121°C/ 1hr)[2] |
| **Sonication** | --- | --- | --- | --- | x | x |

[1]: All test articles (materials) were extracted following this scheme if not indicated otherwise

[2]: autoclave conditions: (121°C/1hr)

Taken from presentation by Dennis Jenke, Baxter Healthcare presented at the PQRI PODP E&L workshop Feb 2011.

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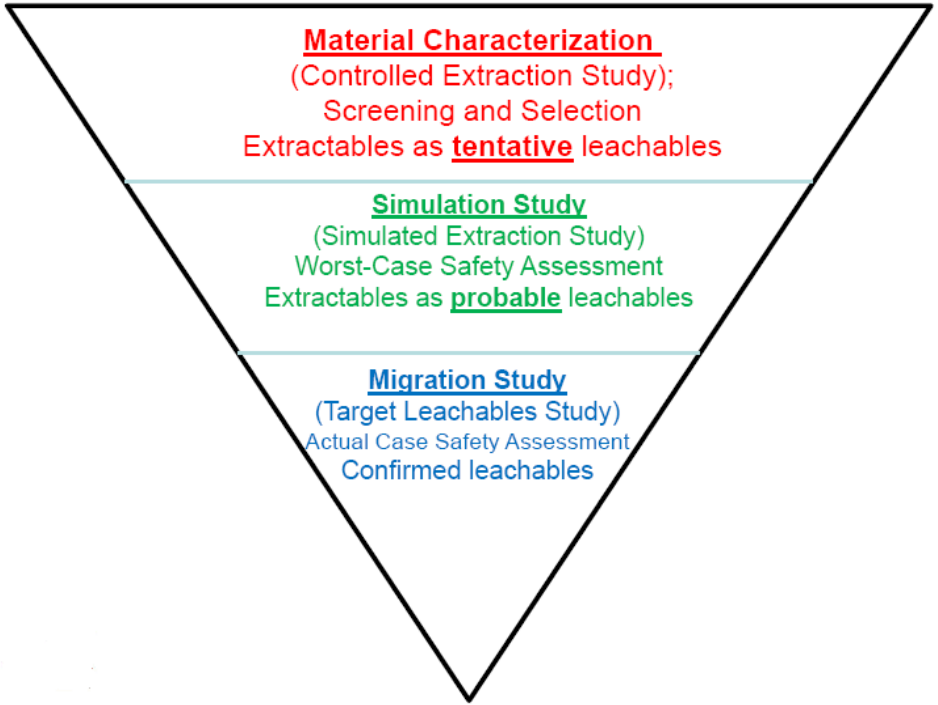
# Reaction chemistry/Secondary leachables

- Soluble parenteral drug product formulations can be very complex
  - Several possibilities for reaction chemistry
- High focus on secondary leachables in biologics from health authorities
  - E.g. presentation by Ingrid Markovich, FDA at the PQRI PODP E&L workshop Feb. 2011
- Extraction techniques and solvents can not mimic secondary leachables
  - Extraction techniques rarely comparable drug product formulations

# Safety Assesment Triad




Taken from presentation by Dennis Jenke, Baxter Healthcare presented at the PQRI PODP E&L workshop Feb 2011.

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# Extraction and leachable studies

Material characterization and understanding

Individual part, material or system

Extraction solvent and technique often worst case

Extraction study

Measurement of probable leachables

Individual design depending on application

Can use drug product or placebo as solvent

Simulated study

Mesurement of actual leachables

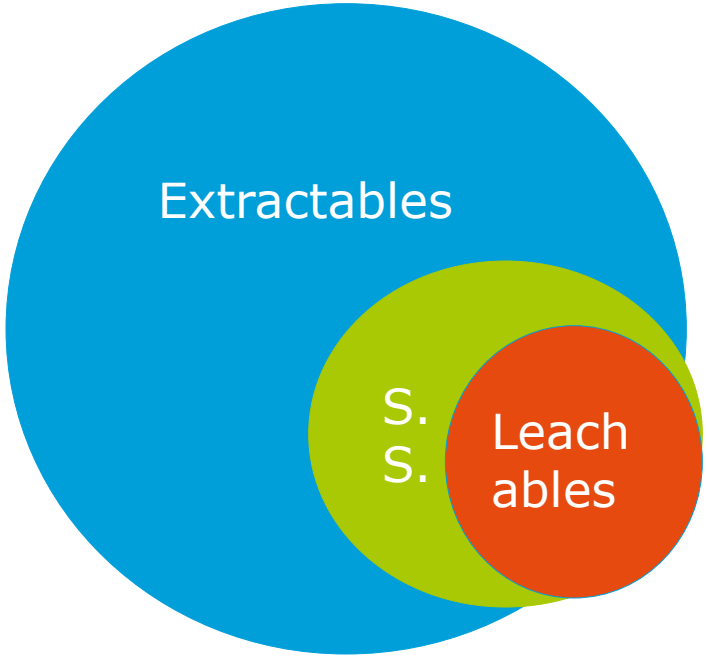
Final drug product formulation and packaging

Full product life time (shelf life + in-use)

Leachable study

# Simulated study

- Secondary leachables = reaction products of leachables with formulation components or drug product
- Secondary leachables observed by S. S. and leachables study – not observed as extractables




S.S. = Simulated study

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# Optimal prediction tool for leachables in parenterals DP

- Parenterals being **lyophilised** and **soluble** drug products for injection or infusion

- Migration process for **lyophilised** drug products (vials etc.)
  - Evaporation of volatile leachables from CCS into the gas phase of the vial during the lyophilisation procedure
  - Adsorption into the lyophilised drug product

- Optimal prediction tool for leachables in **lyophilised** drug products
  - **Volatile extractables testing** (GC-MS and GC-HS-MS)

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# Optimal prediction tool for leachables in parenterals DP

- Migration process for **soluble** drug products (cart., PFS, vial etc.)
  - Migration of leachables from CCS to DP solution ("like dissolves like", polarity, pH, surface tension etc.)
  - Equilibrium between CCS and DP solution

- Optimal prediction tool for leachables in **soluble** drug products
  - **Simulated study**

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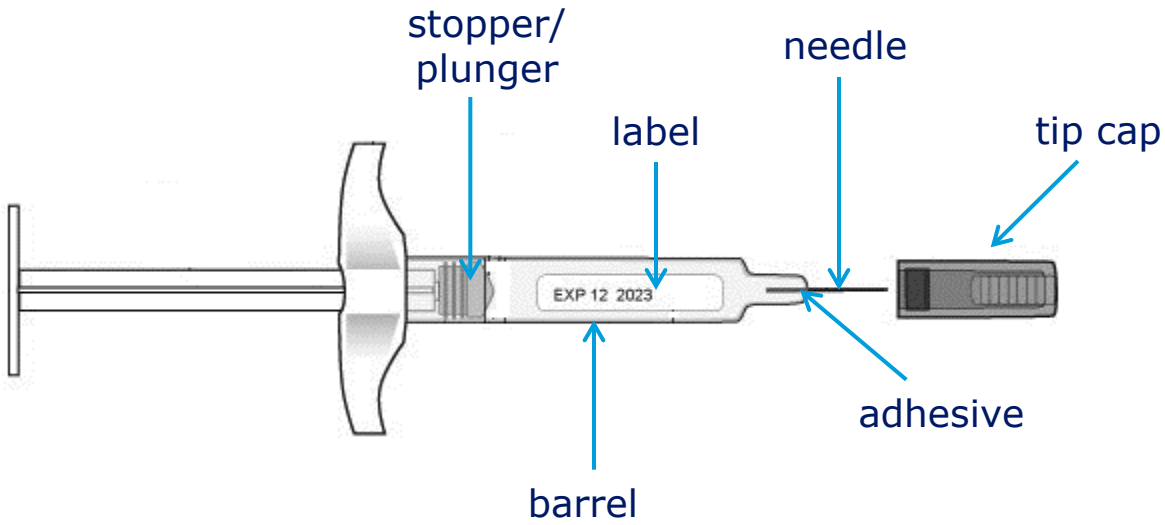
# Simulated leachable study Prefilled Syringe

- Several contact materials



# Processing of Prefilled Syringes - tungsten

- The syringe needle channel is formed using a tungsten pin at high temp. (up to approx. 1200 °C)
- The tungsten pin has to be replaced during the syringe manufacturing every few hours due to extensive abrasion and deterioration of the pin
- In the cone channel of the syringe tungsten deposits can be found (elemental/metallic or tungstates/oxides)
- Tungsten deposits can lead to protein aggregation and oxidation

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# Processing of Prefilled Syringes - siliconisation

- Glass, Cyclic Olefin Copolymer (COC) or Cyclic Olefin Polymer (COP) barrel are siliconised
  - Understanding and control curing process is key to reduce silicone leaching
- Silicone leaching can lead to protein aggregation
- High focus on toxicity of small siloxanes such as octamethyl-cyclotetrasiloxane (D4) carcinogenicity, adjuvants and immunomodulatory factors
  - Siloxanes are expected to be present in a silicone polymer as a result of partial polymerization and/or degradation of the polymer over time

# Processing of Prefilled Syringes - siliconisation

- Solubility of siloxanes in an aqueous solution is low

| Chemical name | Short name | Water solubility at 23 °C [ng/mL] | Henry's law constant at 25 °C [Pa x $m^3$/mol] |
|---|---|---|---|
| Octamethylcyclotetrasiloxane | D4 | 56 | 1.21 x $10^6$ |
| Decamethylcyclopentasiloxane | D5 | 17 | 3.34 x $10^6$ |
| Dodecamethylcyclohexasiloxane | D6 | 5 | 4.94 x $10^6$ |

- The high Henry's law constant combined with the low water solubility means that D4, D5 and D6 have strong tendencies to partition into a gas phase if such one is present

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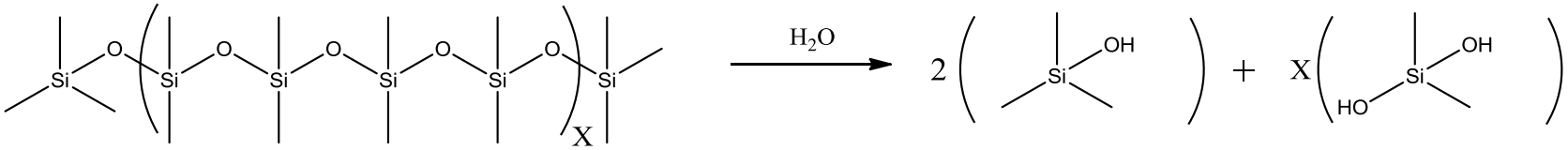
# Processing of Prefilled Syringes - siliconisation

- Hydrolytic degradation of silicone oil in aqueous drug product environment
  - Mapped degradation profile in the environment

Silicone oil (Polydimethylsiloxane;PDMS)




- Trimethylsilanol and dimethylsilanediol can be analysed by $^{29}Si$ and $^{1}H$ NMR spectroscopy and GC-HS-MS

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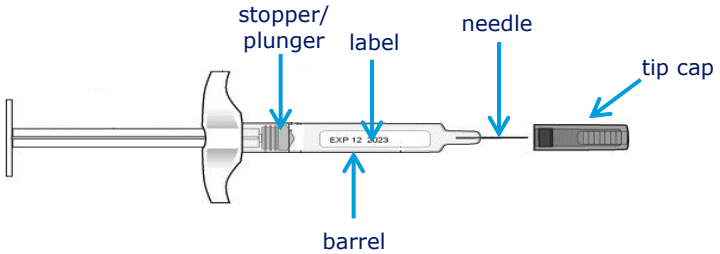
# Case study: aqueous diluent in prefilled syringe

- Standard prefilled syringe containing
  - Rubber plunger
  - Type I glass barrel
  - Label
  - Luer lock type needle




- Processing
  - Tungsten pin for needle channel in barrel
  - Siliconisation of barrel

- Aqueous diluent in prefilled syringe expected to be stored in prefilled syringe for more than 3 years

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# Case study: aqueous diluent in prefilled syringe

- Rubber plunger and tip cap
  - Extractable information in general available from supplier as PEL (Potential Extractable List) or extraction report using water and organic solvent
  - Experience with rubber plunger/tip caps is that few leachables in an aqueous drug product or diluent are either
    - not extracted using water
    - not described in a PEL list
    - not described in an extractable report
    - … and furthermore the huge number of extractables in an organic solvent that are rarely leachables

*Solution: perform a simulated study to simulate actual leachables in the diluent*

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# Simulated immersion study rubber plunger

- Using actual diluent
- Immersion of rubber plunger into diluent
- Stored at an accelerated temperature (3 months at 40 °C) compared to in-use and shelf life of diluent (3+ years at 5 °C and 3 days at 30 °C)
- Surface contact area to diluent solution 10 times higher than in prefilled syringe

*Only for visualisation – rubber plunger surface area to solution >> 10*

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# Simulated immersion study rubber plunger

- Observed simulated leachables were

Organic

- 4-methyl-benzaldehyde
- 4-methyl-benzoic acid
- 4'-methyl-acetophenone
- 2- and 3-hexanone
- 2- and 3-hexanal
- Methyl isobutyl ketone
- 4-tert-amylphenol
- 2-chloro-4-tert-amylphenol

Only two organic mentioned as extractables in PEL/extraction report

- Ethanol
- Propanol

- Inorganic
- Calcium
- Magnesium
- Zinc
- Bromide

All inorganics mentioned as extractables in PEL/extraction report

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# Simulated under filling study prefilled syringe

- Silicone composition received from supplier
- Simulated study by immersion difficult to performed
- Instead a simulated study in under filled prefilled syringes was used
  - Under filling solvent was aqueous diluent
  - Under filling volume approximately 4 times lower than actual filling volume of PFS
    - Concentration of tungsten leachables theoretically 4 times higher in under filled simulated study
  - Stored at an accelerated temperature (3 months at 40 °C) compared to in-use and shelf life of diluent (3+ years at 5 °C and 3 days at 30 °C)

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# Simulated under filling study prefilled syringe

- Rubber plunger
  - Same simulated leachables as in simulated study by immersion
  - Lower concentrations compared to simulated study by immersion
- Tungsten
  - Tungsten concentration 0.3 ppm (µg/mL)
- Silicone
  - Trimethylsilanol and dimethylsilanediol
  - No siloxanes detected by GC-MS
  - No indication for presence of silicone particles by Micro Flow Imaging (MFI)

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# Conclusion

- Simulated study can be used to simulate actual leachables in a complex soluble drug product solution or diluent

- Simulated study
  - Will ***predict*** actual leachables and interactions with DP and formulation components
  - Will ***omit*** the huge number of extractables to investigate
  - Will ***reduce*** the risk for having critical leachables at the end of product lifetime at an early development phase

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# Conclusion

- Each company needs to design their simulated study based on their specific application
  - Drug product formulation
  - Container closure system
  - Administration form
- Two simulated studies proposed for prefilled syringes
  - Immersion study
  - Under filling study

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