Analytical Challenges Presented by Leachables from Sample Container Closure Systems in Drug Products AAPS Discussion Group

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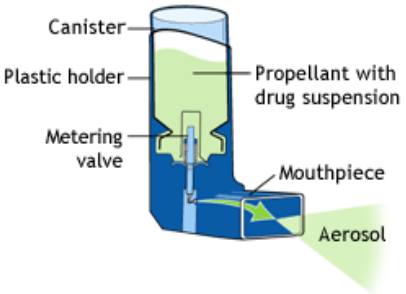
Sources of Leachables

- Leachables are compounds that migrate into a drug product from the sample container closure system (SCC) under normal storage condition
- Both the primary SCC in direct contact with the drug product (Metered dose inhalers, prefilled syringes, eye dropper, IV bag, etc.) and the secondary SCC which does not the contact drug product (printed labels, boxes, foil pouches, environmental exposure, etc.) can be sources of leachables
- Leachables present safety and efficacy risk



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Analytical Challenge for Leachables

- Leachables are unknowns (materials used in SCC not controlled like drug product)
- Leachables are not related to drug so analytical methods for drug product may not detect leachables
- Leachables often at levels orders of magnitude lower than drug degradation products or related substances

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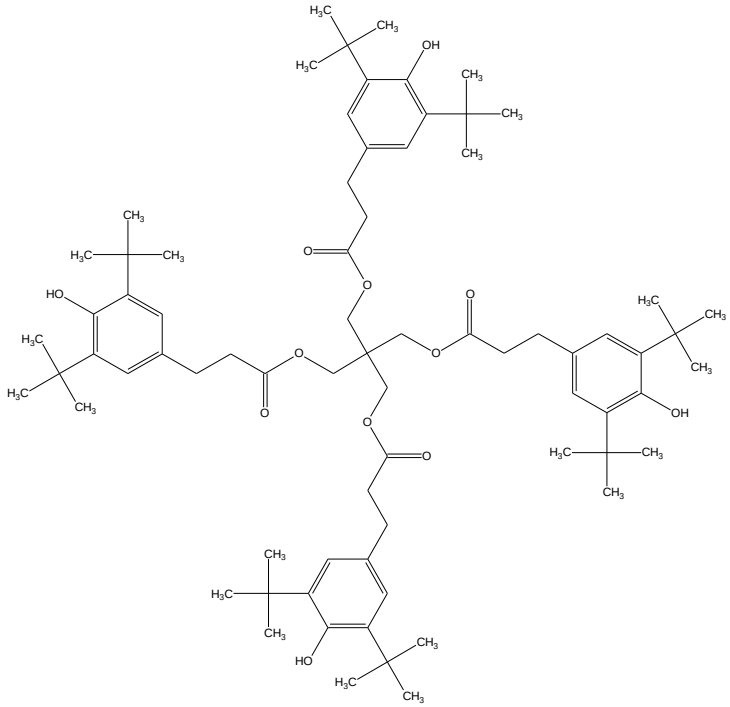
Examples of Leachables From Polymers and Elastomers

- Alkanes, alcohols and aldehydes
- Fatty Acids and Fatty Amides
- Phthalates
- Bisphenol A
- BHT
- Metals

- Antioxidants like Irganox 1010



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Product Quality Research Institute (PQRI) Guidances

- “Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products”, (OINDP) September 8, 2006.
- Held workshop in February 2011 to discuss Parenteral and Opthamalic drug products.

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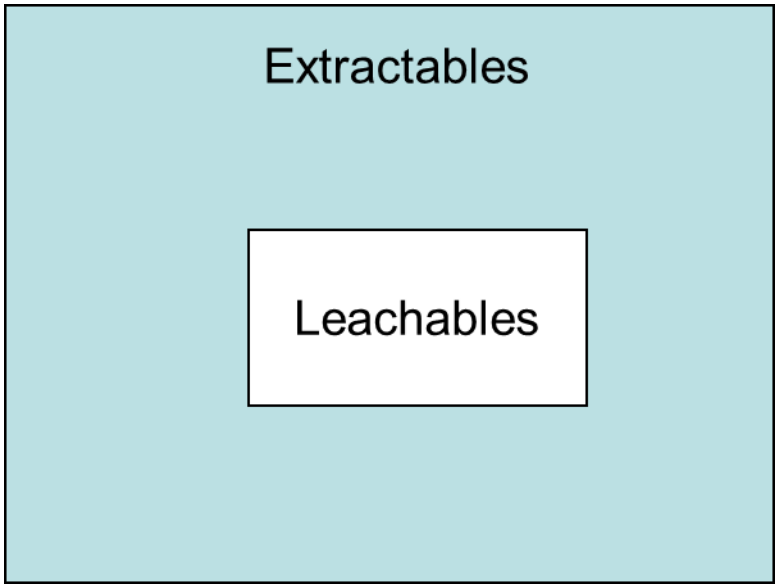
Perform Extraction Studies

- Extraction Studies are performed on SCC under exaggerated conditions with the goal of extracting all possible leachables

- Extractables are compounds that can be extracted from the SCC under exaggerated conditions that might become leachables



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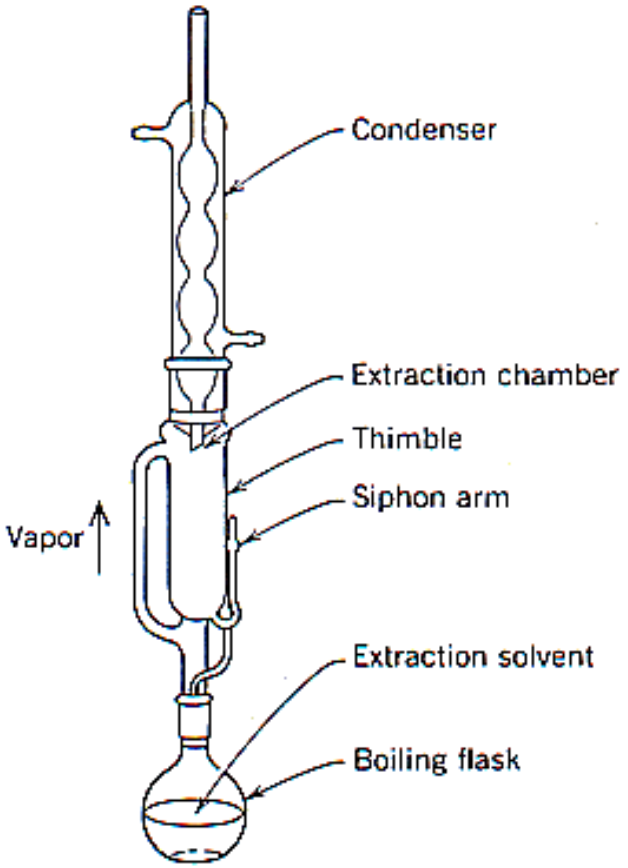
Forced Extraction Studies

- Forced Extraction
  - Components of SCC are extracted separately
  - Solvents selected to mimic drug product and a “worse case” scenario
    - 2-3 solvents based on drug product
    - Buffer, 50/50 EtOH/H2O and Hexane are common examples
  - Extract by reflux, Soxhlett, oven incubation, etc.
- Required for OINDP, recommended for “simple” or “clean” SCC



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Simulated Use Extraction

- Simulated Use Extraction
  - Use placebo (or model of drug product) as solvent
  - Exaggerate exposure of placebo to SCC component (increase ratio of material to volume, orient for direct contact, etc.)
  - Store at elevated temperature for extended time (4-13 weeks)
- Recommended for large volume parenterals and complicated SCC for non-OINDP
- Can be done in addition to forced extractions

Analyze Sample Extracts

- Analyze sample extracts using screening methods
  - Volatile organic extractables by headspace GC-MS
  - Semi-volatile organic extractables by direct inject GC-MS
  - Non-volatile organic extractables by LC-MS
  - Inorganic extractables by ICP-MS
- Methods are not validated but performance is verified
  - at least determine sensitivity and accuracy/precision of representative compounds

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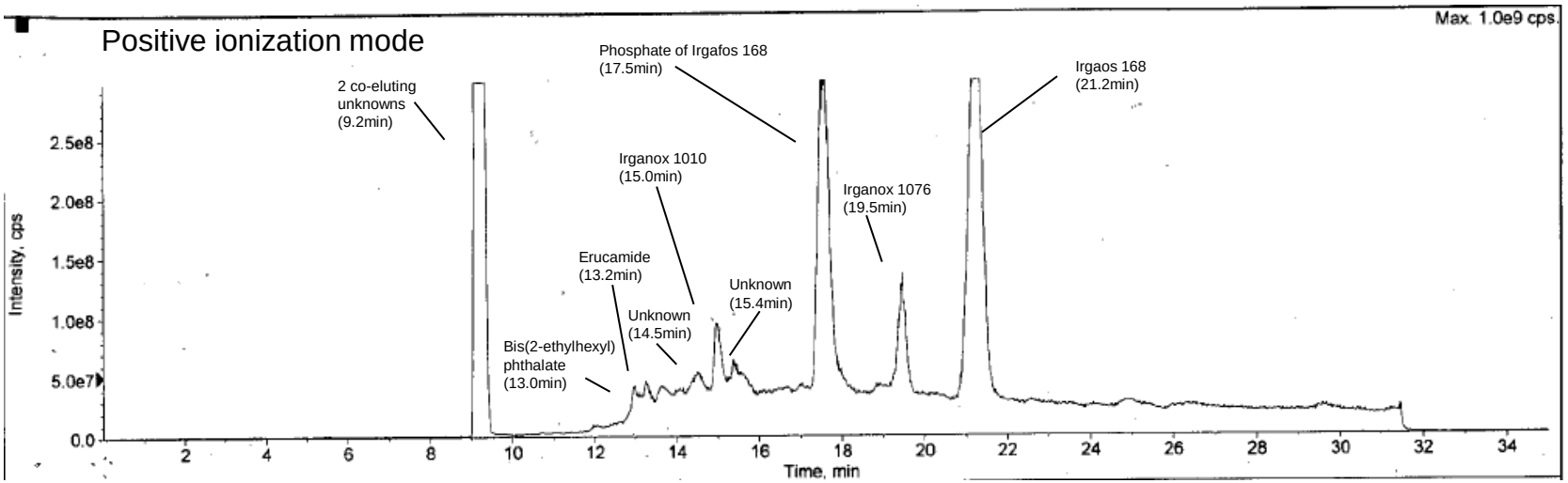
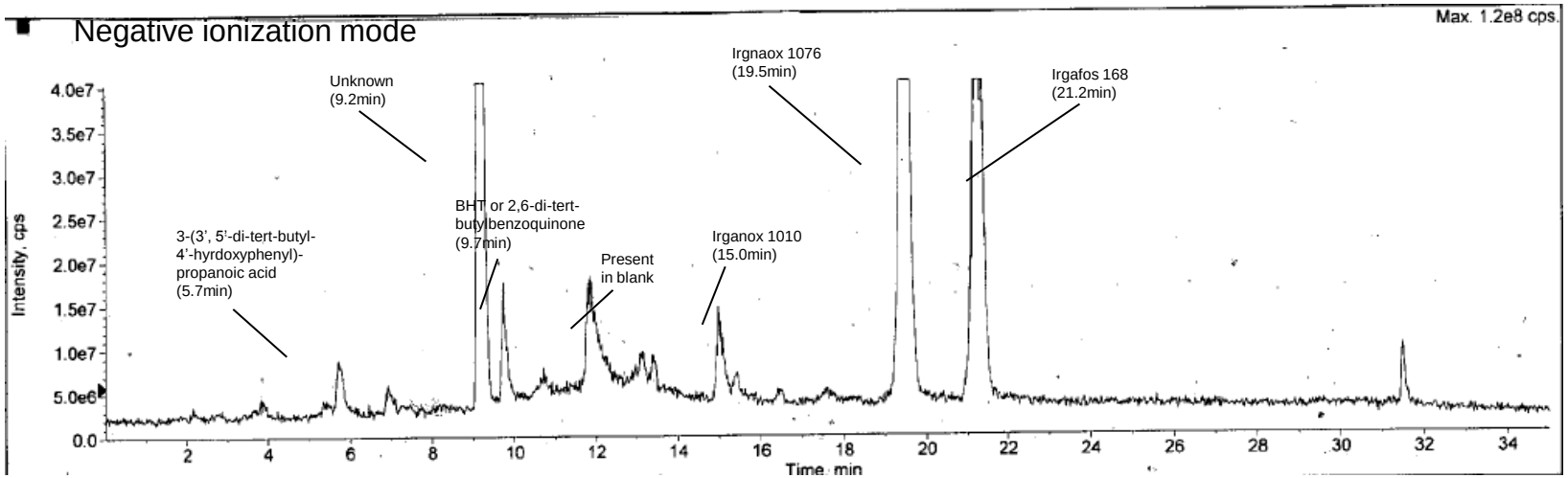
Example HPLC-MS Analysis of an IPA Extract of a Printed Plastic Film





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Identification and Semi-Quantitication of Extractables

- Identify extractable based upon MS
  - Unknowns are unfortunately common
- When possible, use commercially available compounds (or close model compounds) to:
  - confirm identifications by matching retention time and MS
  - determine response factors for quantitation
- Report identifications and concentration in material (usually as ppm)

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Estimated Analytical Evaluation Threshold

- Analytical Evaluation Threshold (AET) is calculated from the toxicological Safety Concern Threshold (SCT)
- If SCT not determined for a given compound, use default value of 0.15 µg/day

$$Estimated\ AET = \left(\frac{SCT\ \left(\frac{ug}{day}\right)}{\#\ of\ Doses/day} \right) \times \frac{\#\ of\ Doses}{SCC}$$

$$Estimated\ AET = ug/SCC$$

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Example AET Calculation

- **Example Nasal Spray Component :**

  4 doses per day

  120 doses per container

  0.45g tube

- **Estimate AET:**
- **Convert SCT (0.15 µgTDI) to µg/container**

$$\frac{0.15\ \mu g/day}{4\ doses/day} \times 120\ doses/container = 4.5\ \mu g/tube$$

$$\frac{4.5 \mu g/tube}{0.45g\ tube} = 10 \mu g/g$$

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Final AET

- Final AET = Estimated AET X Uncertainty Factor
- Recommend Uncertainty Factor = 0.5
- Any extractable above Final AET should be selected as a target leachable

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Example Extractables Profile

Extractable	ppm
cyclohexane	5.02
BHT	16.03
2,6-bis(1,1-dimethylethyl phenol	1.84
Oleamide	3.75
Palmitic Acid	9.90
Bis(2-ethylhexyl)phthalate	9.06
Irganox 1010	10.02
Phosphate of Irgafos 168	102.22
Irgafos 168	57.75
Irganox 1076	20.67

AET = 10 ppm

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Leachables Methods

- Develop methods for targeted leachables in drug product.
  - GC-FID or GC-MS method for volatile organic leachables
  - HPLC-UV, HPLC-CAD or LC-MS for non-volatile organic leachables
  - ICP-MS
- Can convert final AET to drug product volume for use as a specification
- Method should have AET ≥ LOQ
  - Common challenge for parenterals
  - Sample concentration may be required

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Validation of Leachables Method

- Validate to the AET the same as for a related substances method
- Method performance may drive acceptance criteria
  - For example, a well-developed method for a challenging leachable has an AET = LOQ (S/N=10). Using “looser” validation acceptance criteria (e.g. 40% for accuracy) would be preferable to raising method LOQ.

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Use of Leachables Methods

- Used to analyze drug product samples from stability study (intended storage condition) or migration study.
- If possible, include controls of placebo in SCC and drug product in a different container (e.g. glass) to help identify drug degradation products.
- All leachables that were not included in validation must be identified.
  - Impact on validation assessed.
- Leachables can degrade or react with drug product to form compounds not seen during extraction studies.
  - The compounds will need to be identified and assessed for toxicity.

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Conclusions

- Leachables present risk and are a unique analytical challenge.
- Extraction Studies are designed to identify potential leachables so that appropriate analytical methods can be developed.
- Considering leachables when designing stability studies can simplify data interpretation.

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