Workshop #1: Leachables & Extractables

Case Study: A Problematic Extractable for a Pulmonary Delivery Device System

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Extractables – A Window of Opportunity

- Extractable data are generated before determining the leachable profile
- From a toxicology perspective, formal regulatory reportable risk assessments are typically not performed on extractables, but instead are developed for what actually migrates into the final product (i.e. the leachables)
- Since, however, the leachables are typically a subset of the extractables, a review of pertinent toxicology data for the extractables is beneficial and highly recommended
- Identifying and mitigating a potential toxicology issue at the extractable stage greatly increases the probability you will successfully develop a safety position for your leachables

Case Study - Background

- A device was being developed to deliver pharmaceutical products via the pulmonary route
- During the material selection phase, various components were subjected to an extractables screen by Thermal Desorption GC-MS
  - Enabled rapid development and characterization of the extractable profiles from the various components of the device
- A toxicological assessment paradigm developed for extractables was utilized to determine the potential risk of these chemicals should they subsequently become leachables

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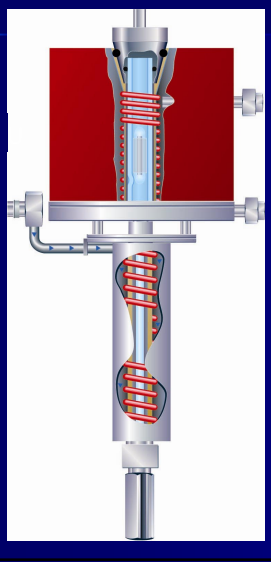
The Analytical Procedure

Thermal Desorption GC-MS



- The inlet of a standard GC/MS is modified to allow for direct thermal desorption of solid samples
- A solid sample is placed into a sample tube
- The tube is heated while the carrier gas sweeps over the sample
- As analytes volatilize, they are pulled away from the sample by the carrier gas.
- A cold trap is used to collect the analytes during desorption. This is then heated to introduce the analytes onto the GC column.

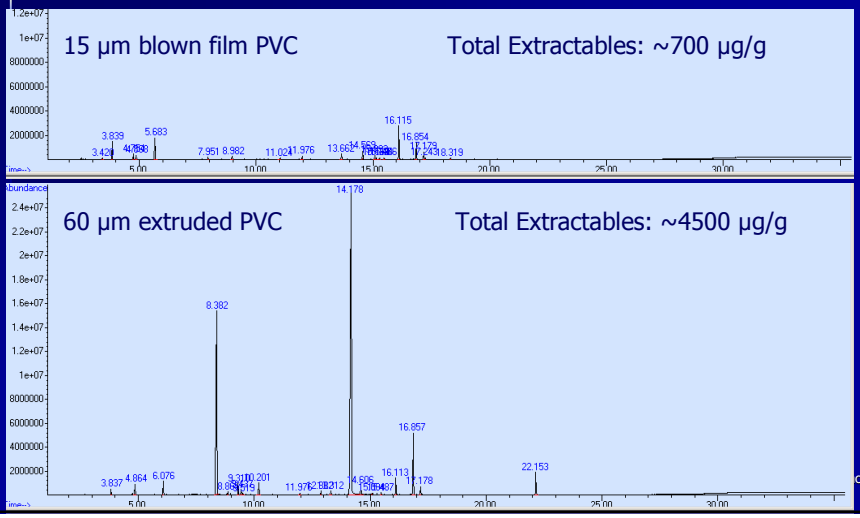
Benefits of TDGCMS

- Minimal sample preparation, highly sensitive
- Detects volatile and semi-volatile extractables
- Detects polar and non-polar extractables
  - Orthogonal to solvent extraction
- Efficient enough that multiple packaging options may be screened
  - Extractables data can be considered before packaging is finalized

Selection of a drug contact surface

- Product: A dry powder inhaler, which stores drug product in small unit doses
- Important properties of the drug contact surface include machinability into the appropriate shape to reduce the absorption of water. This requires a thinner layer.
- Thinner PVC can not be extruded, therefore blown film PVC was considered
- 15 and 30 µm blown film PVC samples were analyzed along side 60 µm extruded PVC

TDGCMS Chromatograms



PVC Analytes

60 µm extruded PVC	15 and 30 µm blown film PVC
2-ethylhexyl mercaptoacetate	**Maleic anhydride**
2-ethyl-1-hexanol	Methyl methacrylate
2-ethylhexyl ester acetic acid	hexadecane
n-butyl ether	1,1'oxybis-octane
Glycerin	BHT
hexadecane and docosane	
1,1'-oxybis-octane	
Total ~4500 µg/g	**Total ~700 µg/g**

- Different profiles suggest different stabilization systems
- Proposed blown film PVC has a "cleaner profile" but different analytes
- Questioned PVC supplier about presence of maleic anhydride
  - Related to a thermal stabilizer, dioctyl maleate

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The Toxicology Procedure

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For Extractable Risk Assessment - Consider the "Big Five"

Genetic Toxicology, Carcinogenicity, Reproductive Toxicology, Sensitization, and Irritation

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Qualitative Assessment (Pass/Fail/No Data)

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If Needed, Perform Quantitative Assessment Assuming Same Amount Will Occur in Leachable Study (Pass/Fail)

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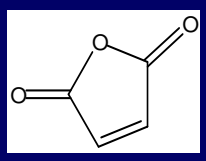
Final Assessment – Pass/Data Gaps May Require Some Testing/Fail

Maleic Anhydride



- **DSRD safety assessment:**
  - DEREK structural analysis yielded alert s for sensitization (skin and respiratory) and irritation
  - A confirmed irritant and sensitizer in animals models and humans
  - human nasal irritation occurs within 1 minute following exposure to 1.5 ppm maleic anhydride… same dose from exposure to maleic anhydride from the blisters (50 microgram / 50 kg).
  - As there is no safety margin from these calculations and the fact that people will be exposed day after day to the powder thus possibly increasing sensitization/irritation, it is recommended that maleic anhydride NOT be in the blisters.
- **Team cycled back in process to successfully select new options with negligible loss in development time**

Conclusions

- Early extractables screening and subsequent toxicological evaluation can provide detailed information on the composition and safety of the packaging material
  - Provides project teams with the information they need to select packaging that
    - meets the project needs and
    - minimizes E+L concerns
  - Raise "red flags" early
- Facilitates data-driven decisions in package selection

Acknowledgements

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