Controlled Extraction Studies

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AAPS

PQRI Leachables and Extractables Workshop
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Outline

- Overview
- Scope
- Recommendations & Examples
- Conclusions

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Overview

What?

PQRI Leachables and Extractables Working Group conducted **Controlled Extraction Studies** on specially created rubber and plastic test articles

“Best Practice” recommendations for the conduct of Controlled Extraction Studies are proposed.

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When?

- After evaluation of the available information
  - component formulation
  - fabrication processes

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Controlled Extraction Study

Definition:
A laboratory investigation into the qualitative and quantitative nature of extractables profiles from critical components of an OINDP container/closure system

Purpose:
To systematically and rationally identify and quantify potential leachables, i.e. extractables, to the extent practicable, and within certain defined analytical threshold parameters

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Outcomes

1. Establish a basis for the development and validation of routine quality control methods and acceptance criteria for critical component extractables profiles.
2. Establish a basis for the development and validation of leachables methods suitable for use in drug product leachables studies as well as for potential use as routine quality control methods for drug product leachables (should such be required by regulatory authorities).
3. Allow for “correlation” of extractables and leachables.

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Trace Organic Analysis

Two Directives (D. Jenke)

1. Extraction should be vigorous, but not so aggressive as to alter the qualitative and/or quantitative nature of the extractables profile
2. Must be technically justified and optimized to produce extractables profiles at least equivalent to leachables profiles obtained under worst case conditions

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Scope

Scope

Controlled Extraction Studies should be accomplished on all critical components incorporated into the container/closure systems of every type of OINDP

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Metered Dose Inhalers (MDIs)

- Dose metering valve elastomeric and plastic components
- Inner surface of the metal canister (coated)
- Actuator/mouthpiece

Note:
Surface extraction studies are necessary to identify and quantify any oily processing residues on uncoated metal canisters and certain metallic valve components.

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Dry Powder Inhalers (DPIs)

All elastomeric and plastic components which

- Direct contact with patient's mouth
- Direct contact with patient's nasal mucosa
- Direct contact with the drug product
- Direct contact with drug product stream

Notes:
Includes any container/closure system for the drug product unit doses, e.g. plastic or foil blisters, laminates.

Controlled Extraction studies on non-contact components may be beneficial. Consult the regulatory authorities regarding the identification of critical components early in the development process

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Inhalation Solutions and Sprays

All elastomeric and plastic components which

- Direct contact with patient's mouth
- Direct contact with patient's nasal mucosa
- Direct contact with the drug product (includes containers, dip tubes, etc.)

Notes:

Migration through semi-permeable plastic containers is of particular concern.

Direct contact sources include labels, inks, adhesives, etc.

Indirect sources include cardboard shipping containers, plastic coatings on the inner surface of a foil overwrap, etc.

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Process

Component fabrication and processing can potentially add extractables beyond what is expected from the known component formulation.

These could include:

- Mould release agents
- Antislip agents
- Antistatic agents
- Lubricants, and others

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Test Articles

Extractables profiles were obtained from four custom made test articles:

- Sulfur-cured elastomer
- Peroxide-cured elastomer
- Peroxide-cured elastomer
- Polypropylene

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Recommendations

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Recommendation #1

- ***Controlled Extraction Studies should employ vigorous extraction with multiple solvents of varying polarity.***

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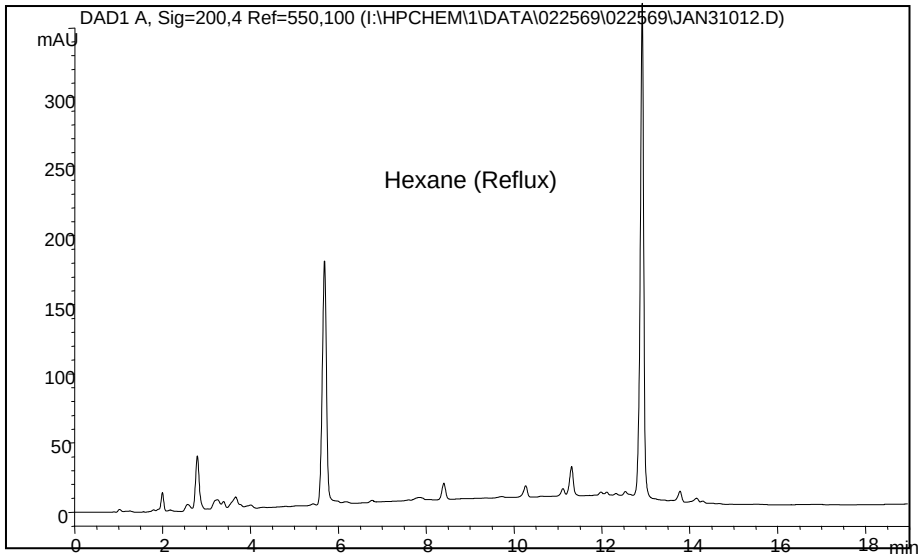
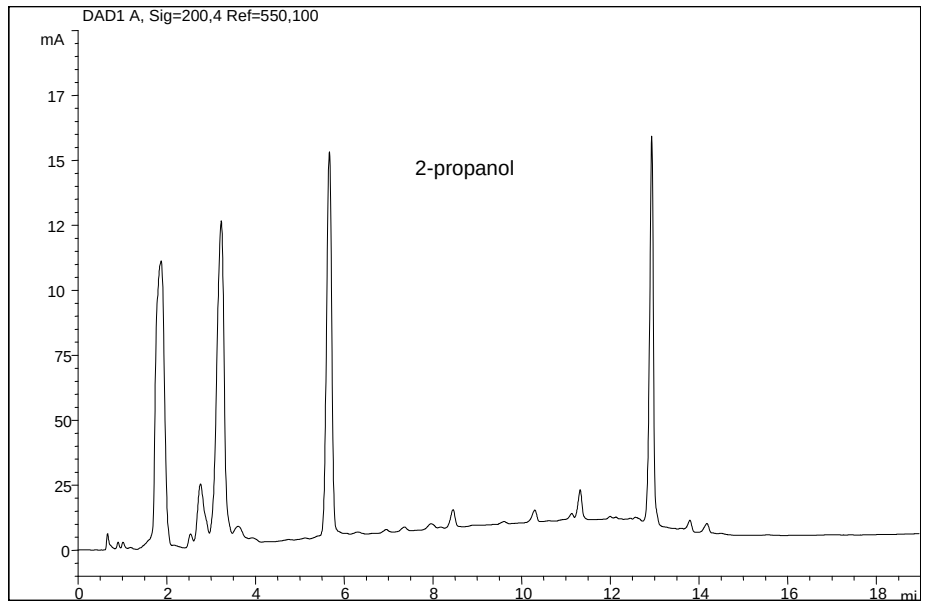
Recommendation #1-Polypropylene



Hexane Reflux



2-Propanol Reflux

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Recommendation #2

- ***Controlled Extraction Studies should incorporate multiple extraction techniques.***

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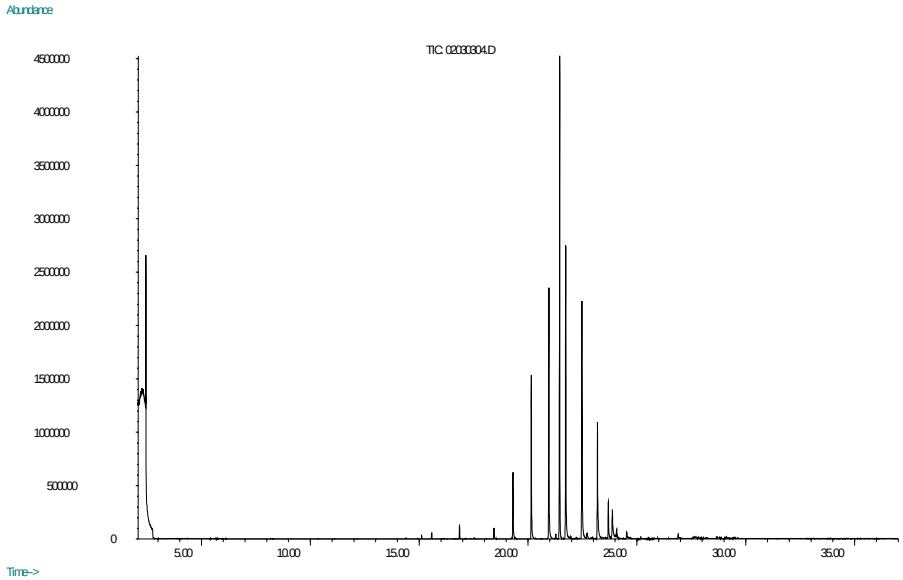
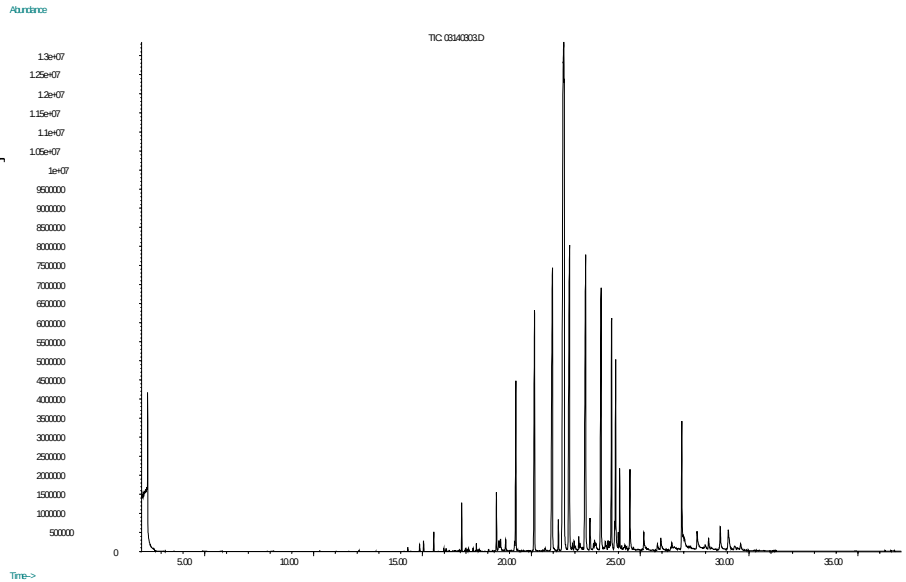
Recommendation #2-Sulfur Cured Elastomer



2-Propanol Sonication

2-Propanol Soxhlet



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Recommendation #3

- ***Controlled Extraction Studies should include careful sample preparation based on knowledge of analytical techniques to be used.***

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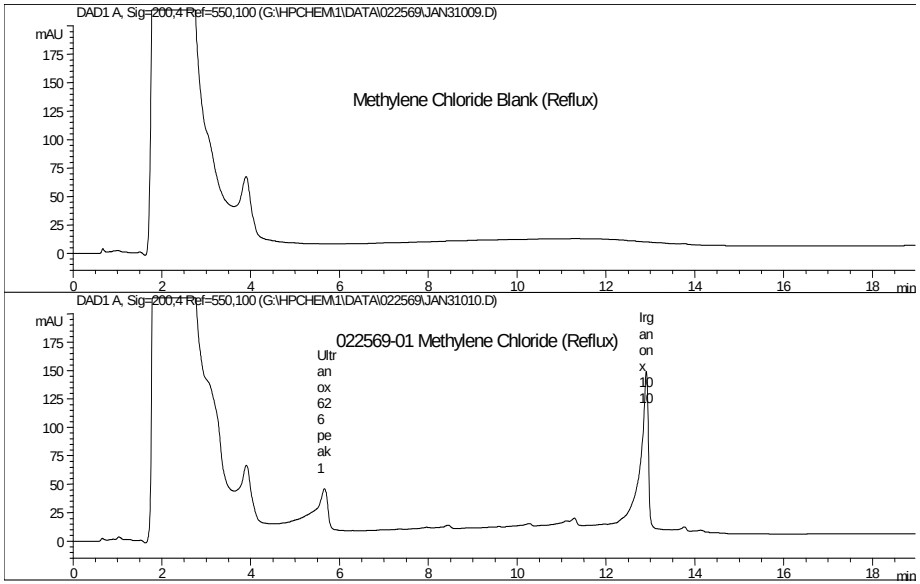
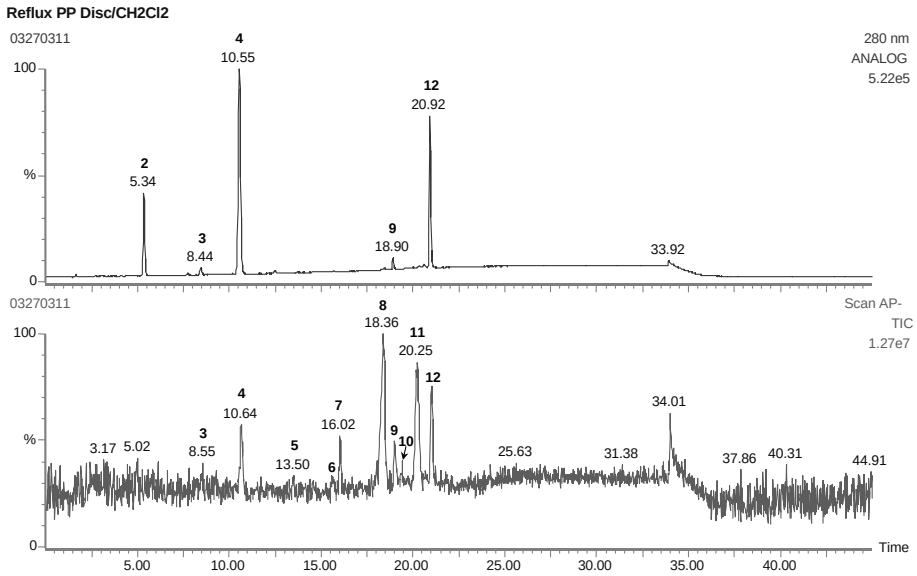
Recommendation #3-Polypropylene



2-Propanol Sonication

2-Propanol Soxhlet



Recommendation #4

- ***Controlled Extraction Studies should employ multiple analytical techniques***

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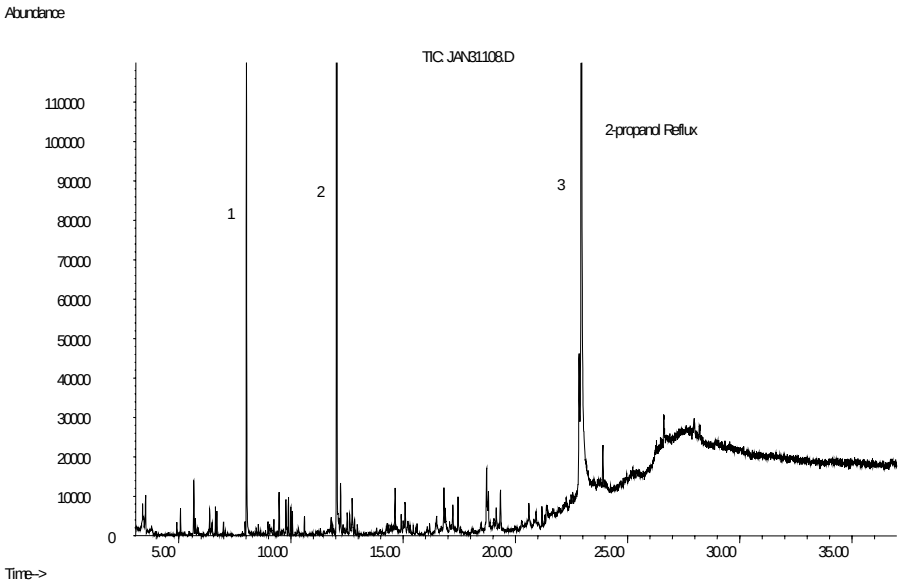
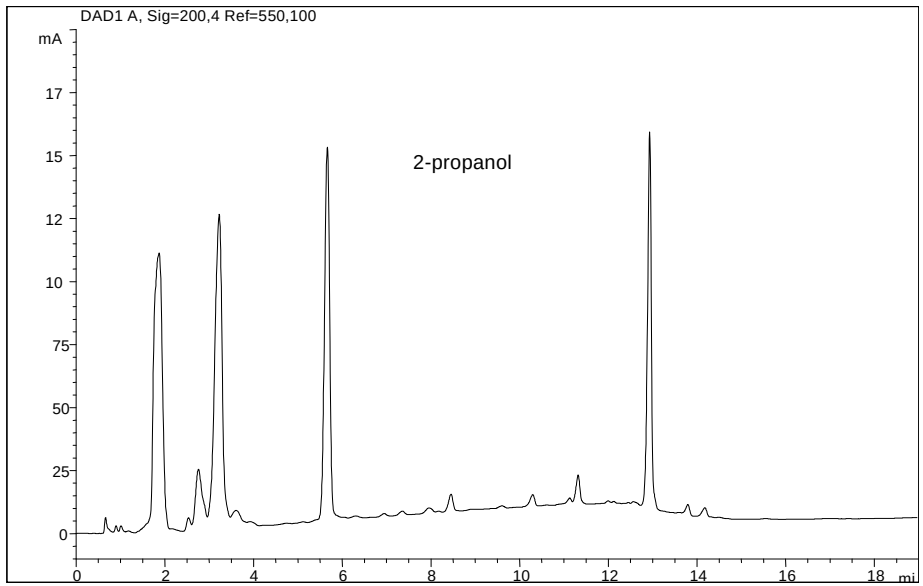
Recommendation #4-Polypropylene



GC-MS
2-Propanol Reflux



HPLC-DAD
2-Propanol Reflux

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Recommendation #5

- ***Controlled Extraction Studies should include a defined and systematic process for identification of individual extractables***

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Example Categories

Identification Categories for Structure Elucidation of Extractables and Leachables by GC/MS and LC/MS	
Category	**Identification Data**
A	Mass spectrometric fragmentation behavior
B	Confirmation of molecular weight
C	Confirmation of elemental composition
D	Mass spectrum matches automated library or literature spectrum
E	Mass spectrum and chromatographic retention index match authentic specimen

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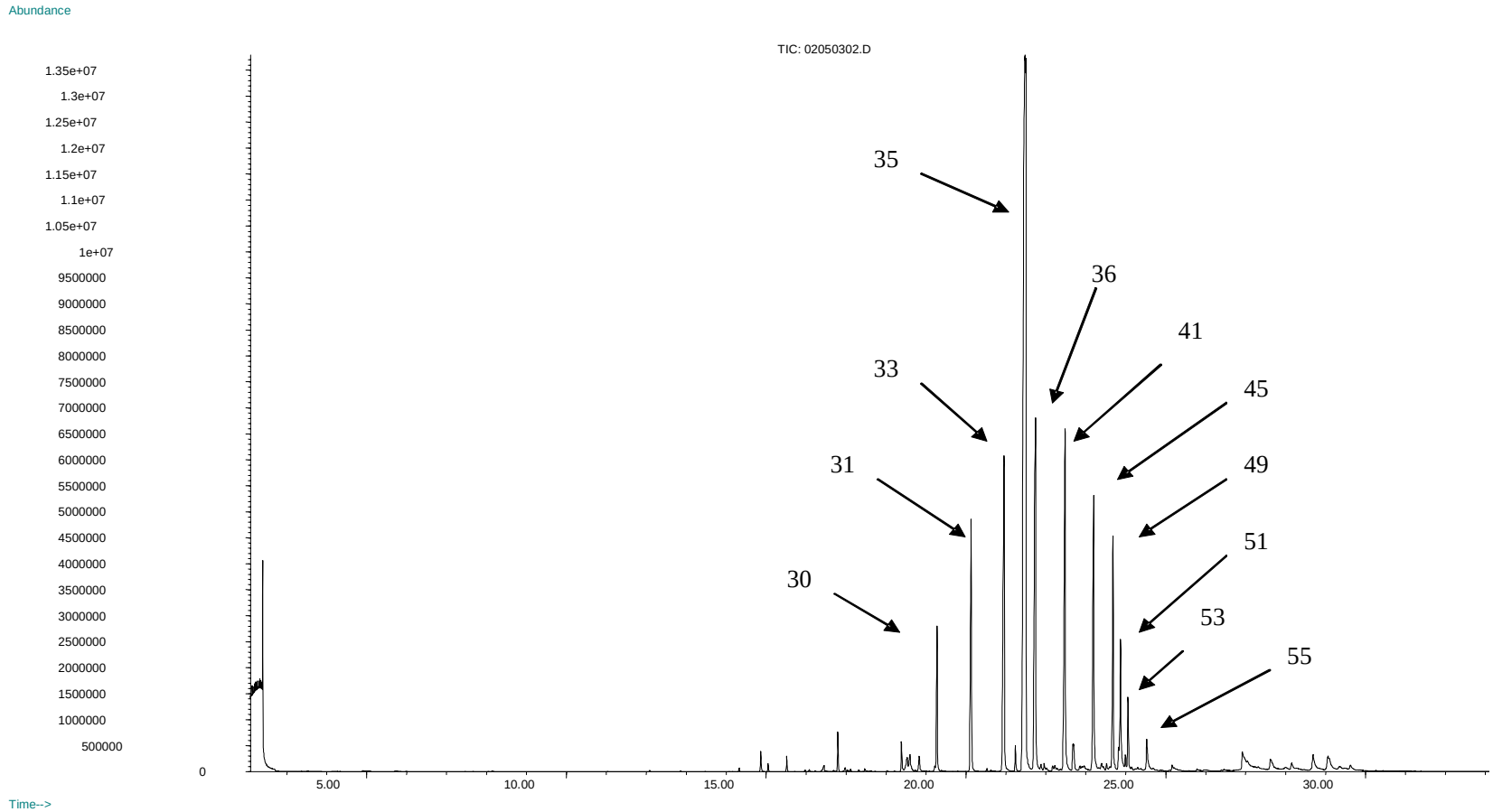
Recommendation #5-Sulfur Cured Elastomer



Recommendation #6

- ***Controlled Extraction Study "definitive" extraction techniques/methods should be optimized.***

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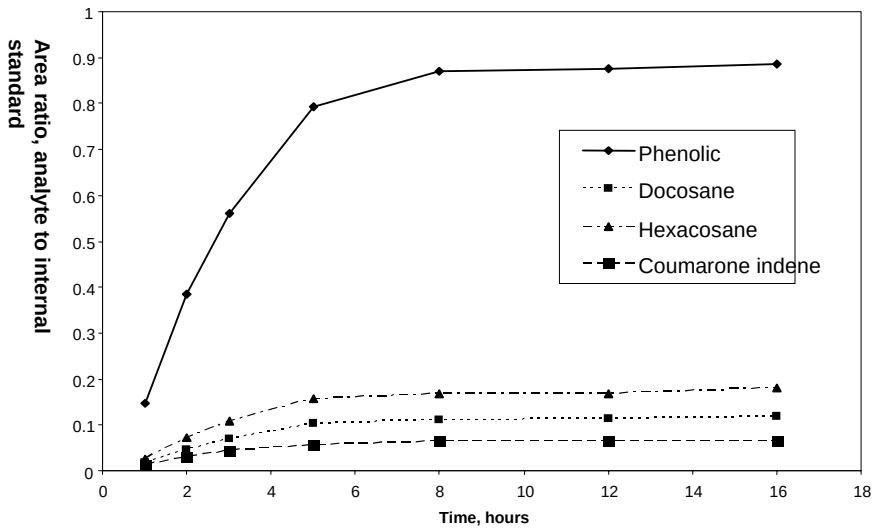
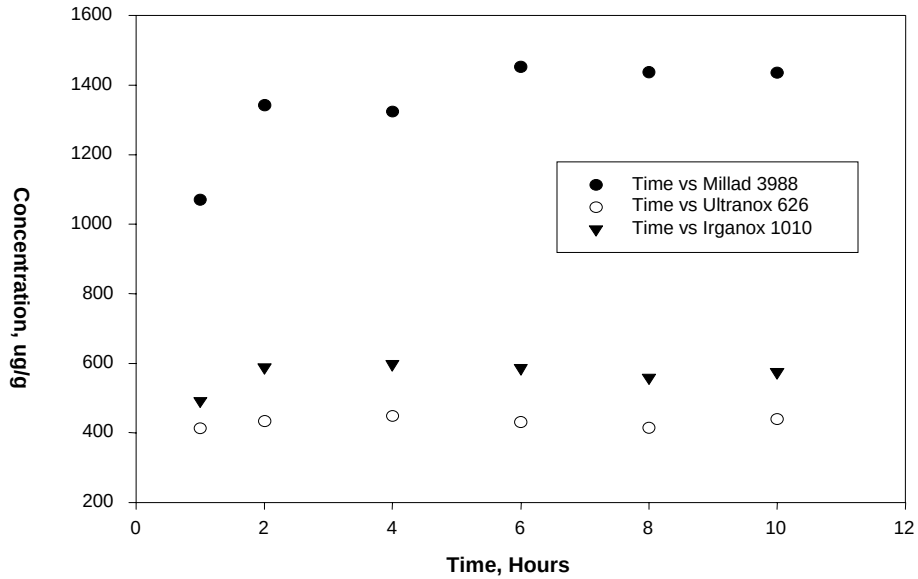
Recommendation #6-Optimization



2-Propanol Reflux Extraction of Polypropylene

Methylene Chloride Soxhlet Extraction of Sulfur-Cured Elastomer



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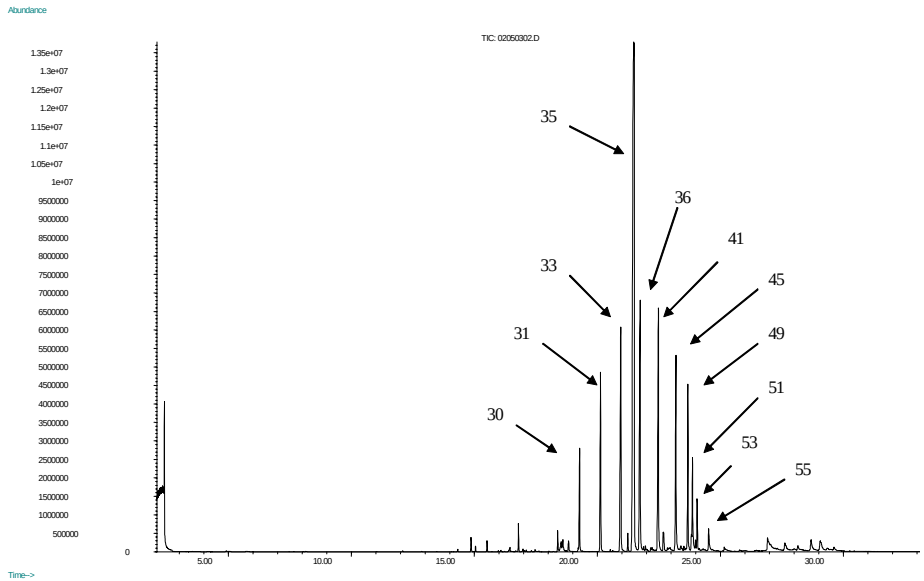
Recommendation #7

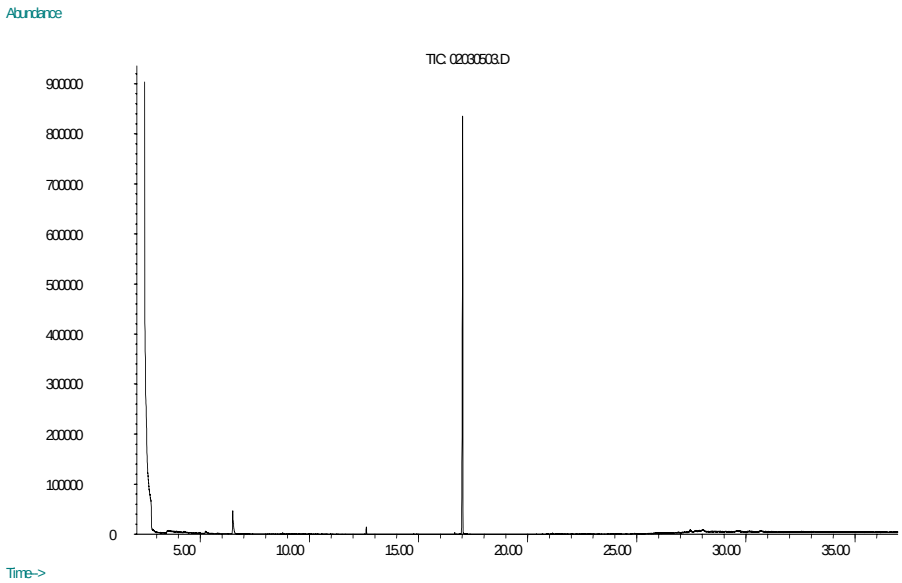
- ***During the Controlled Extraction Study process, sponsors should revisit supplier information describing component formulation.***

Recommendation #7-Sulfur Cured Elastomer



GC-MS of Tetramethylthiuram Monosulfide

GC-MS of Methylene Chloride Soxhlet Extract



Recommendation #8

- ***Controlled Extraction Studies should be guided by an Analytical Evaluation Threshold (AET) that is based on an accepted safety evaluation threshold***

-Dan Norwood Presentation, 11:15am

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Recommendation #9

- ***Polyaromatic Hydrocarbons (PAH's; or Polynuclear Aromatics, PNA's), N-nitrosamines, and 2-mercaptobenzothiazole (MBT) are considered to be "special case" compounds, requiring evaluation by specific analytical techniques and technology defined threshold***

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Recommendation #9

PAHs/PNAs		N-nitrosamines
Naphthalene	Chrysene	N-nitrosodimethylamine
Acenaphthylene	Benzo(b)fluoranthene	N-nitrosodiethylamine
Acenaphthene	Benzo(k)fluoranthene	N-nitrosodi-n-butylamine
Fluorene	Benzo(e)pyrene	N-nitrosomorpholine
Phenanthrene	Benzo(a)pyrene	N-nitrosopiperidine
Anthracene	Indeno(123-cd)pyrene	N-nitrosopyrrolidine
Fluoranthene	Dibenzo(ah)anthracene	
Pyrene	Benzo(ghi)perylene	
Benzo(a)anthracene		

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Recommendation #10

- ***Qualitative and quantitative extractables profiles should be discussed with and reviewed by pharmaceutical development team toxicologists so that any potential safety concerns regarding individual extractables,* i.e. *potential leachables, are identified early in the pharmaceutical development process***

  - **Day 1**

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Conclusions

Three Final Points

1. Not intended to be prescriptive
2. Scientifically justified alternatives are not precluded
3. Consult the appropriate regulatory authority

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Thank You

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