Integration Toxicology/ Chemistry-AET Concept

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Threshold Concept

- Qualification Threshold (QT):
  - 5 µg/day for an individual organic leachable
- Safety Concern Threshold (SCT):
  - 0.15 µg/day for an individual organic leachable
- Analytical Evaluation Threshold (AET):
  - Derived directly from SCT

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Definition of AET

"The AET is defined as the threshold at or above which an OINDP pharmaceutical development team should identify and quantify a particular extractable and/or leachable and report it for potential toxicological assessment."

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Example AET Calculation for a Metered Dose Inhaler

Consider an MDI with 120 labeled actuations per canister, a recommended dose of 8 actuations per day, and a critical component elastomer mass per valve of 250 mg. For an individual organic leachable derived from this elastomer, the estimated AET would be:

$$Estimated\ \ AET = \left(\frac{0.15\ \mu\text{g/day}}{8\ \text{actuations/day}} \times 120\ \textit{labeled}\ \text{actuations/canister} \right)$$

$$Estimated \quad AET \approx 2.25\ \mu\text{g/canister}$$

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Example AET Calculation for a Metered Dose Inhaler

Consider an MDI with 120 labeled actuations per canister, a recommended dose of 8 actuations per day, and a critical component elastomer mass per valve of 250 mg. For an individual organic leachable derived from this elastomer, the estimated AET would be:

$$Estimated\ AET = \left(\frac{2.25\ \mu\text{g/canister} \times 1\ \text{canister/ valve}}{0.25\ \text{g of elastomer/valve}} \right)$$

$$Estimated\quad AET \approx 9.00\ \mu\text{g/g of elastomer}$$

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Estimated AET vs. Final AET

The Estimated AET is based on the SCT (0.15 µg/day) and the recommended daily dose of the drug product.

The Final AET takes the Estimated AET and includes the level of uncertainty in the analytical technique or method.

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Response Factor Database

Analyte	RRF (vs. 2-Fluorobiphenyl)	RRF (vs. p-Terphenyl-d_{14})
Palmitic acid	0.377	0.274
1,3-diacetylbenzene	0.383	0.231
Stearic acid	0.385	0.274
2,2'-methylene bis(6-tert-butyl-4-methyl phenol)	0.519	0.666
Docosane	0.568	0.402
4-tert-butylphenol	0.574	0.372
2,2'-methylene bis(6-tert-butyl-4 ethyl-phenol)	0.574	0.639
Tetracosane	0.584	0.424
2,4-diphenyl-4-methyl-1-pentene	0.824	0.527
Bis-2-ethylhexyl phthalate	0.870	0.654
BHT	1.062	0.694
Mean	0.611	0.469
Standard Deviation	0.221	0.175
% Relative Standard Deviation	36.1	37.2

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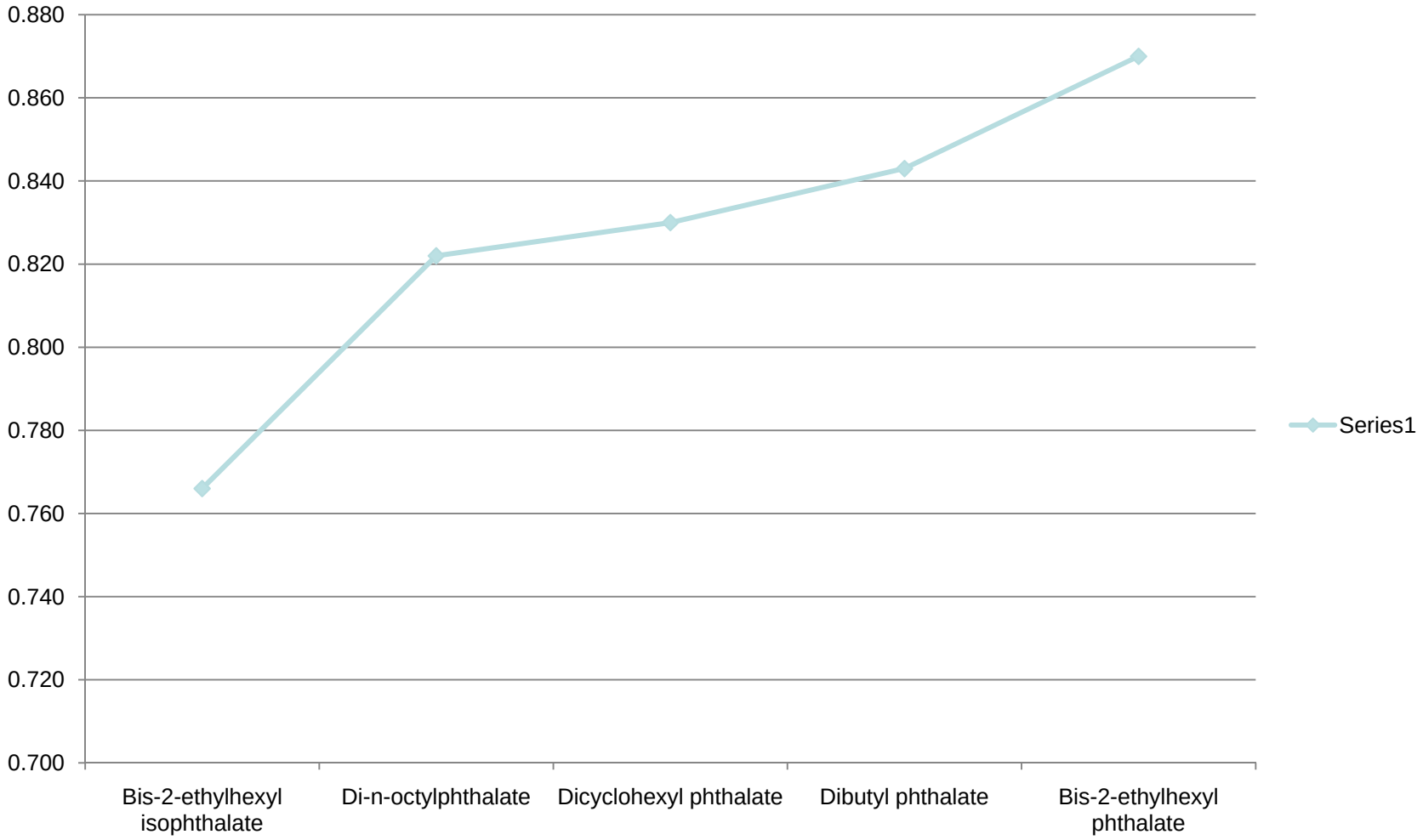
Response Factor Database (continued)



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Example AET Calculation for a Metered Dose Inhaler Component

Using the uncertainty as determined from the previous database the following is defined as how low one may go for this analysis:

$$\text{Final AET} = 2.25\mu\text{g/canister of elastomer} - 0.361(2.25\mu\text{g/canister})$$

$$\text{Final AET} = 1.44\mu\text{g/canister}$$

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Example AET Calculation for a Metered Dose Inhaler Component

But this is not good enough!!! As recommended by PQRI L&E Working Group–

"…..that the analytical uncertainty in the Estimated AET be defined as (1) %RSD in an appropriately constituted and acquired Response Factor database OR 50% of the Estimated AET, whichever is greater."

In this case the answer would be 1.13 µg/canister

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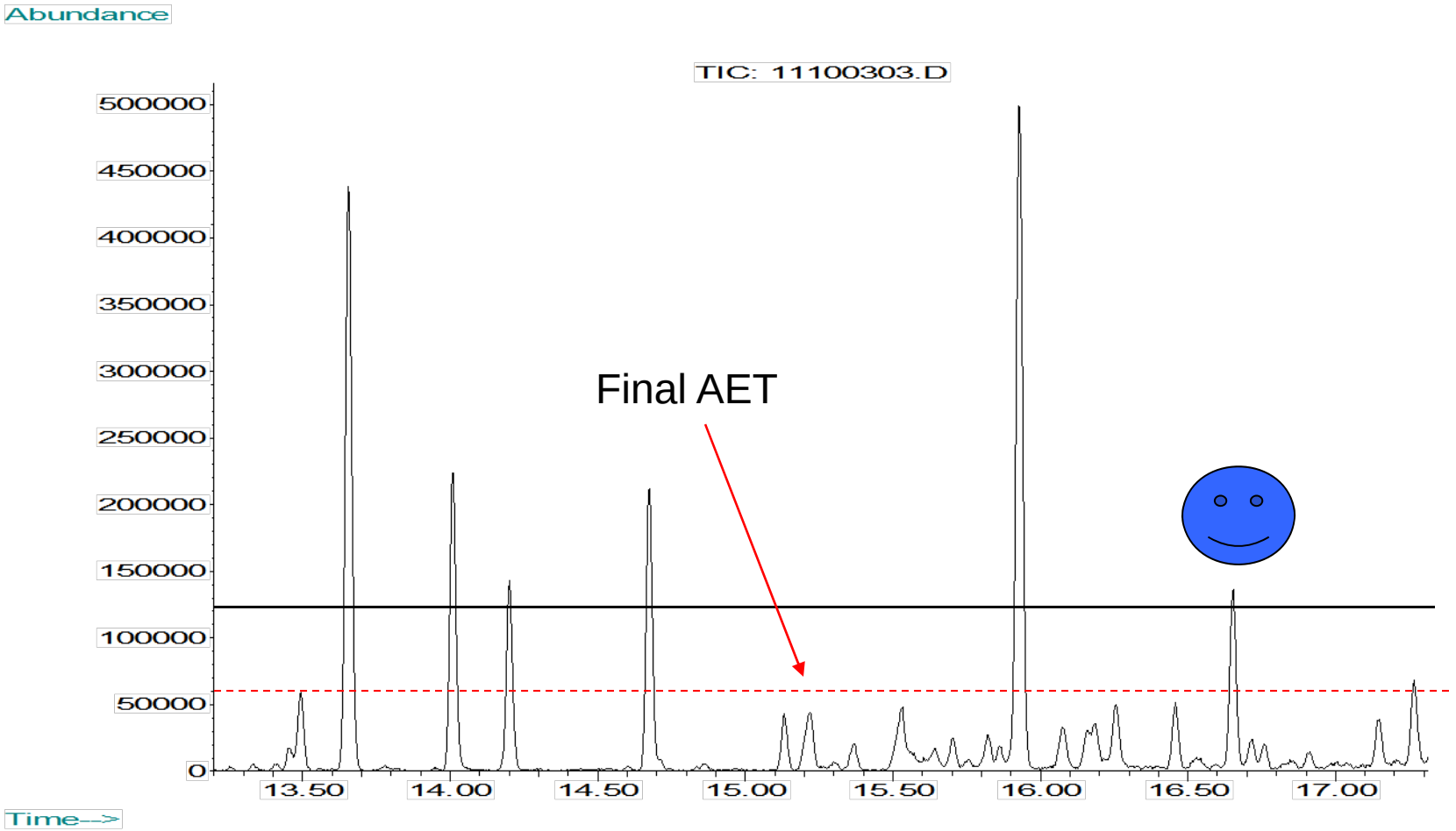
Final AET Profile



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AET Key Points

- Know the daily dose parameters so the Estimated AET can be determined accurately
- For a robust Final AET
  - Select as many compounds as appropriate for the RRF database
  - Choose a suitable internal standard
  - Note a wide variety of compounds will potentially increase the %RSD for the database

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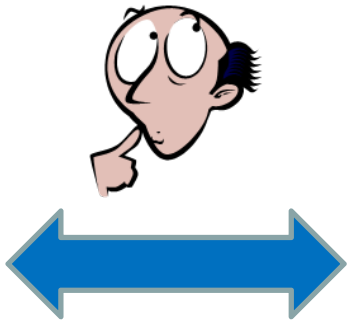
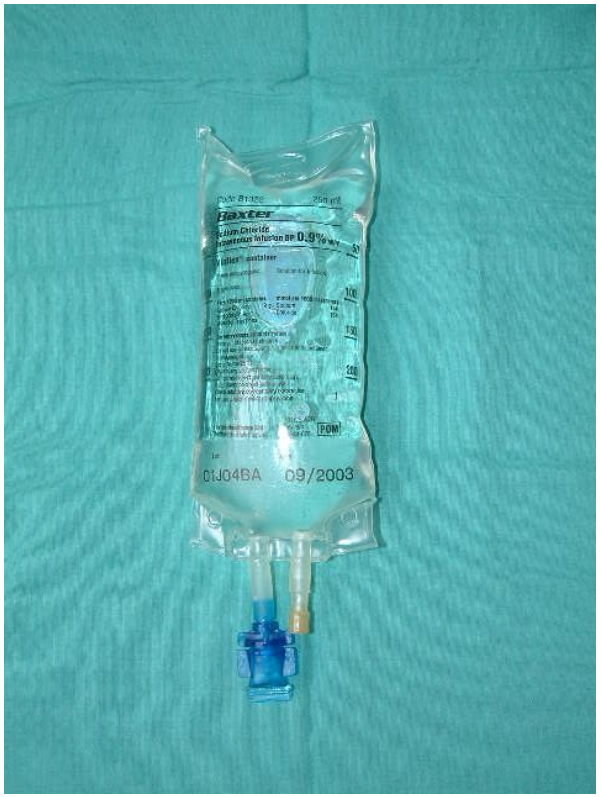
“The Dilemma”

Metered Dose Inhaler
(small volume/large number of doses)



Large Volume Parenteral
(large volume/small number of doses)



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“The Dilemma” (continued)

This dilemma was recognized by the OINDP Leachables and Extractables Working Group:

Consider an Inhalation Solution with 3 mL of drug product contained in a low density polyethylene (LDPE) container (1 g total weight LDPE), with a recommended dose of 3 containers per day. For an individual organic leachable the estimated AET would be:

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“The Dilemma” (continued)

$$Estimated\ AET = \left(\frac{0.15\ \mu g/day}{3\ doses/day} \times 1\ dose/container \right)$$

$$Estimated\ AET \approx 0.05\ \mu g/container$$

$$Estimated\ AET = \left(\frac{0.05\ \mu g/container}{3\ mL/container} \right)$$

$$Estimated\ AET \approx 0.017\ \mu g/mL$$ ➡

This is 17 ug/L which is at environmental trace analysis levels.

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“The Dilemma” (continued)

Converting to an *Estimated AET for individual extractables in an extractables profile of this* particular LDPE:

$$Estimated\ \ AET = \left(\frac{0.05\ \mu \text{g/containe r}}{1\ \text{g material/c ontainer}} \right)$$

$$Estimated\ \ AET \approx 0.05\ \mu \text{g/g container material}$$

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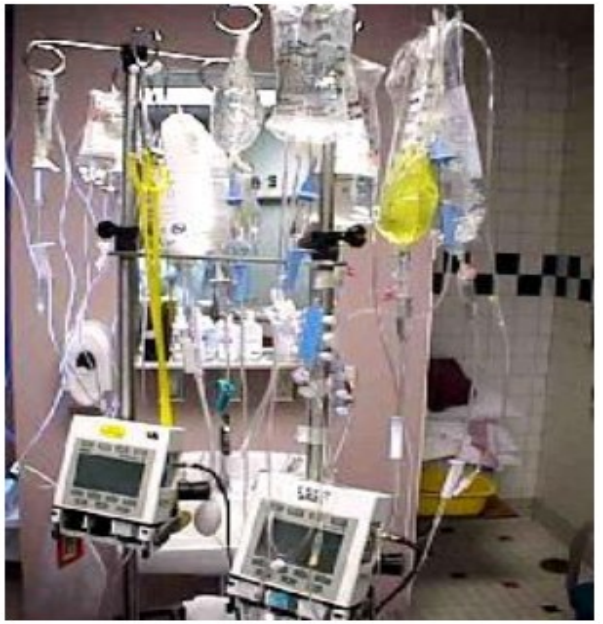
Large Volume Parenterals (LVPs)



Consider an LVP with 1L of drug product packaged in a container/bag (20 g total weight of appropriate polymeric material), with a recommended dose of 1 container per day. For an individual organic leachable the estimated AET would be:

$$Estimated\ \ AET = \left(\frac{0.15\ \mu\text{g/day}}{1\,\text{bag/day}} \times 1\text{dose/bag} \right)$$

$$Estimated \quad AET \approx 0.15\ \mu\text{g/bag}$$

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LVPs (continued)

$$Estimated\ \ AET = \left(\frac{0.15\ \mu\text{g/bag}}{1\,\text{L/bag}} \right) = 0.15\,\mu\text{g/L} = 0.00015\,\mu\text{g/mL}$$

Then, for an extractable:

$$Estimated\ \ AET = \left(\frac{0.15\ \mu\text{g/bag}}{20\ \text{g of material/bag}} \right) = 0.0075\,\mu\text{g/g}$$

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OINDP Recommendations – Inhalation Solutions

The Working Group recommends that if it can be scientifically demonstrated that:

1. ***Aqueous and/or drug product formulation extracts of Inhalation Solution direct formulation contact container closure system material yield no extractables at Final AET levels, or no extractables above final AET levels with safety concern; AND***
2. ***There is no evidence for migration of organic chemical entites through the unit dose container into the drug product formulation; THEN***

Drug product leachables studies are not required.

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OINDP Recommendations – Inhalation Solutions (continued)

This recommendation implies:

1. Careful and comprehensive Controlled Extraction Studies using water as well as stronger solvents such as methylene chloride or 2-propanol to identify any potential leachables, i.e., extractables, of potential safety concern.

2. A well designed drug product without paper labels and other sources of organic chemical migration into the drug product, either from the environment or from secondary protective packaging.

3. Comprehensive and fully validated Routine Extractables Testing methods, capable of detecting any significant change in the unit dose container material extractables profile.

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Controlled Extraction Studies

- A Controlled Extraction Study is a laboratory investigation into the qualitative and quantitative nature of extractables profiles of critical components of an OINDP container/closure system.
- The purpose of a Controlled Extraction Study is 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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Controlled Extraction Studies

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 the “correlation” of extractables and leachables.

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Best Practice Recommendations for Controlled Extraction Studies

- Controlled Extraction Studies should employ vigorous extraction with multiple solvents of varying polarity.
- Controlled Extraction Studies should incorporate multiple extraction techniques.
- Controlled Extraction Studies should include careful sample preparation based on knowledge of analytical techniques to be used.
- Controlled Extraction Studies should employ multiple analytical techniques.
- Controlled Extraction Studies should include a defined and systematic process for identification of individual extractables.
- Controlled Extraction Study "definitive" extraction techniques/methods should be optimized.
- During the Controlled Extraction Study process, sponsors should revisit supplier information describing component formulation.

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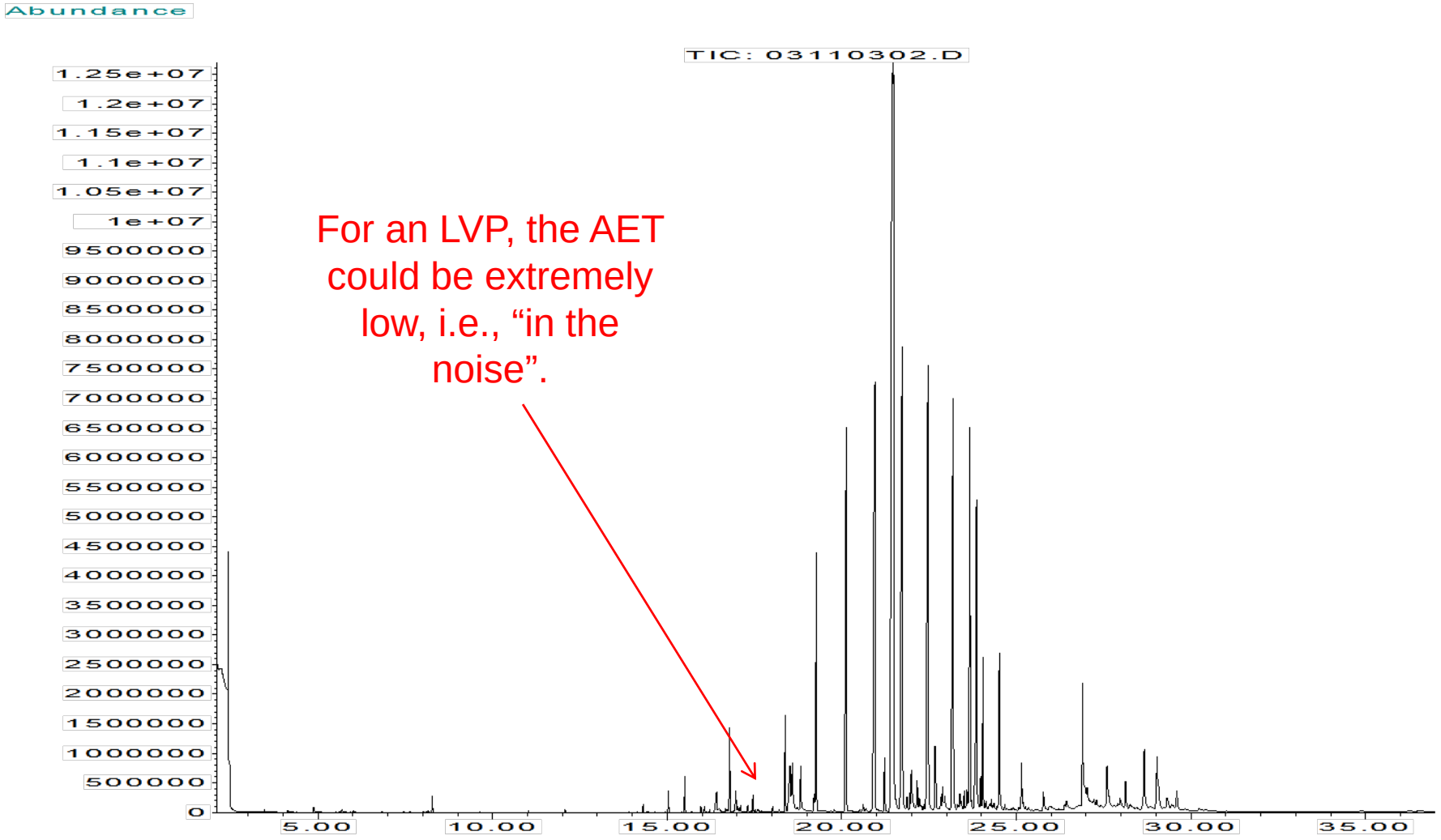
GC/MS Total Ion Chromatogram
(Soxhlet extraction in hexane for 16 hours, injected neat)



For an LVP, the AET could be extremely low, i.e., “in the noise”.

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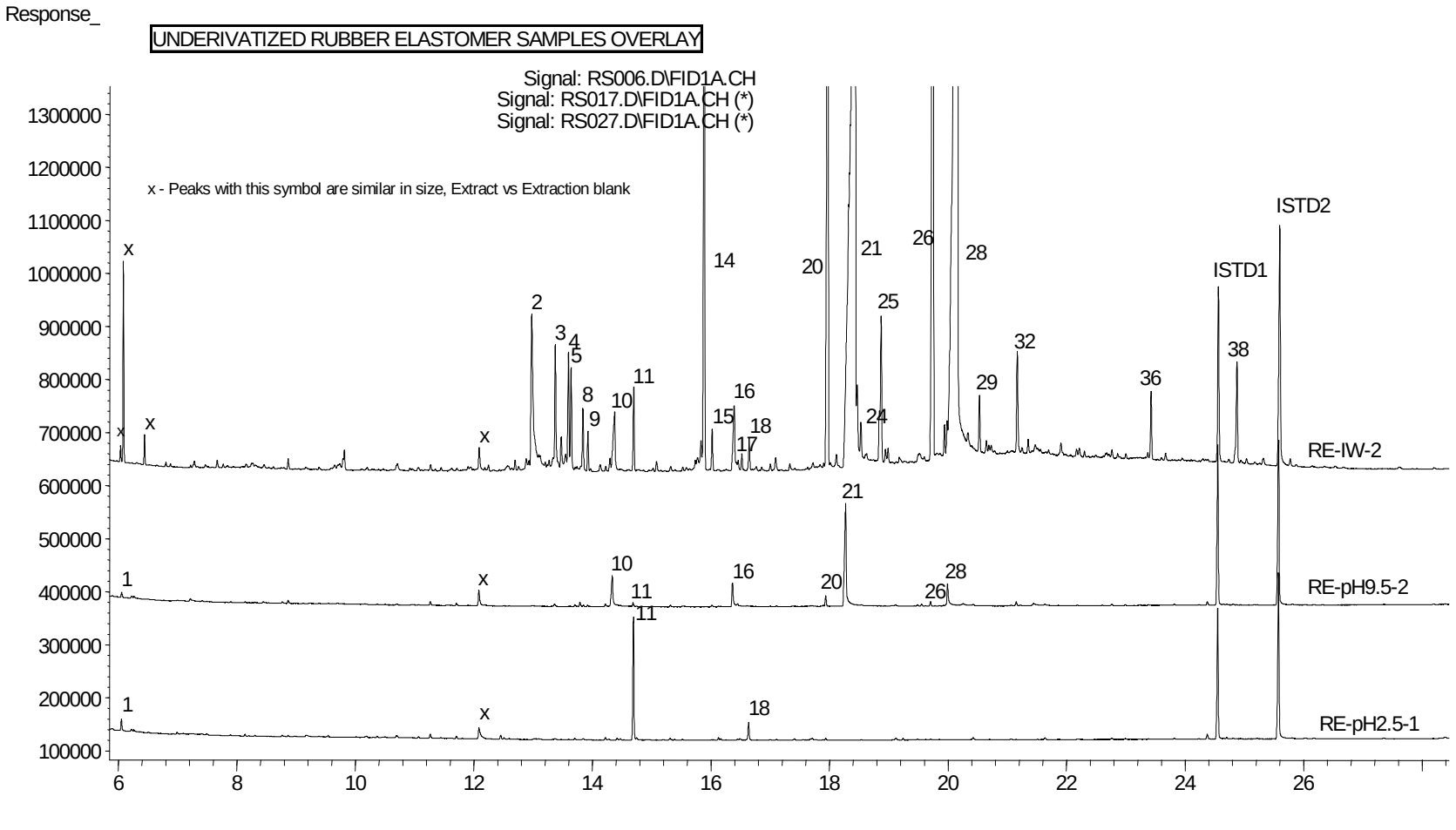
PODP – Potential Leachables



“The Dilemma” - Summary

- For large volume/small number of doses aqueous based PODP (i.e., LVPs) Controlled Extraction Studies with organic solvents can be used for:
  - Materials selection, including initial safety evaluation of extractables.
  - Developing routine extractables control analytical methods.
  - Developing drug product leachables methods
- Controlled Extraction Studies with aqueous solvent systems can be used for detecting/identifying potential leachables at AET levels.
- Leachables analytical methods can then be developed (if necessary) as high sensitivity target compound assays, at AET levels.

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Additional AET Issue for Consideration

- Analytical techniques and response factors, i.e., how to set an AET for an analytical technique/method with widely varying RFs/RRFs, such as LC/UV and LC/MS?

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GC/MS and GC/FID

GC/MS
(Controlled Extraction Studies)

GC/FID
(Routine Extractables Testing)

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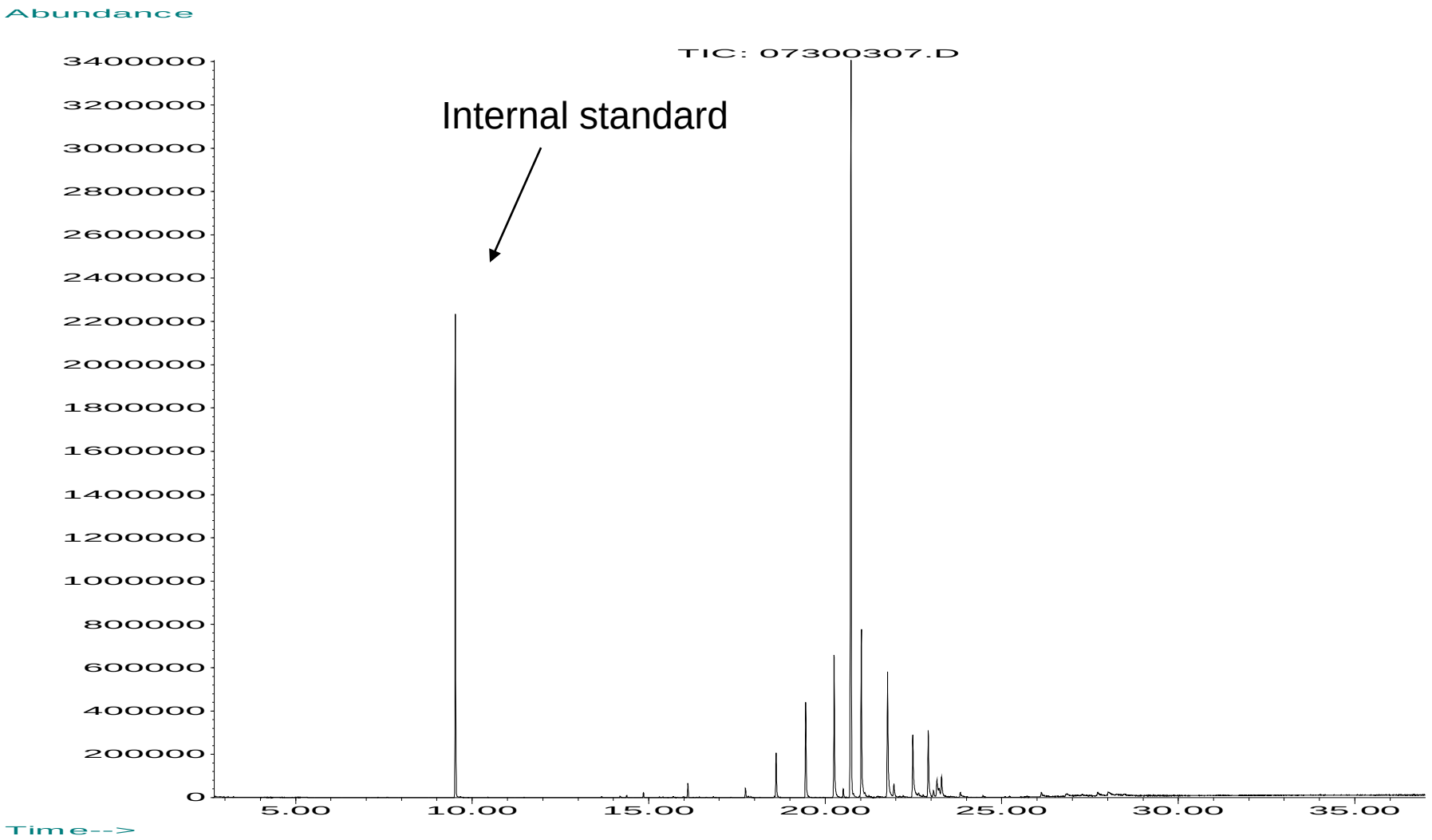
GC/MS Extractables Profile of an Elastomer



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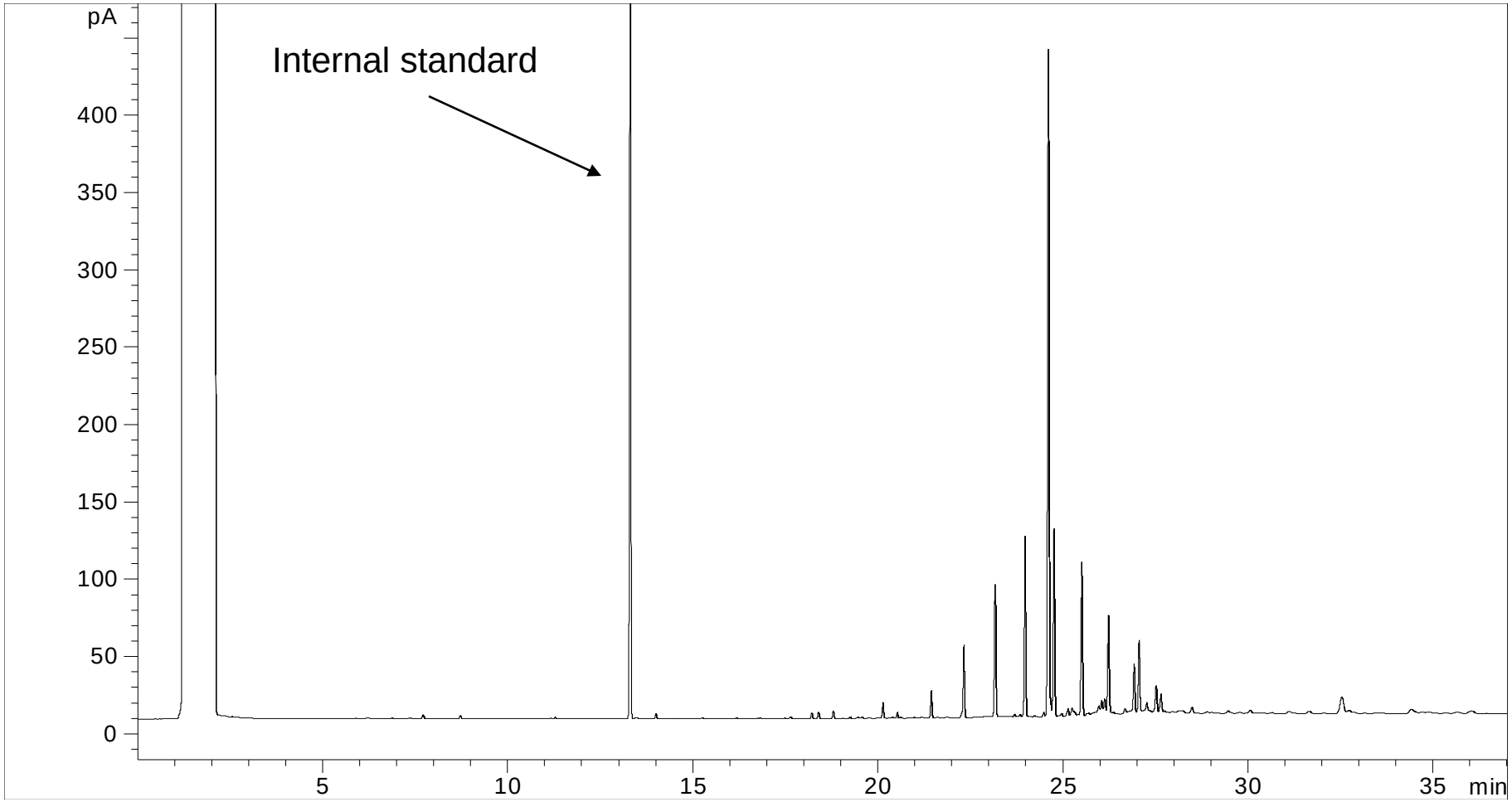
Potential Routine Extractables Control Method – GC/FID



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LC/MS and LC/UV

LC/MS
(Controlled Extraction Studies)

LC/UV
(Routine Extractables Control)

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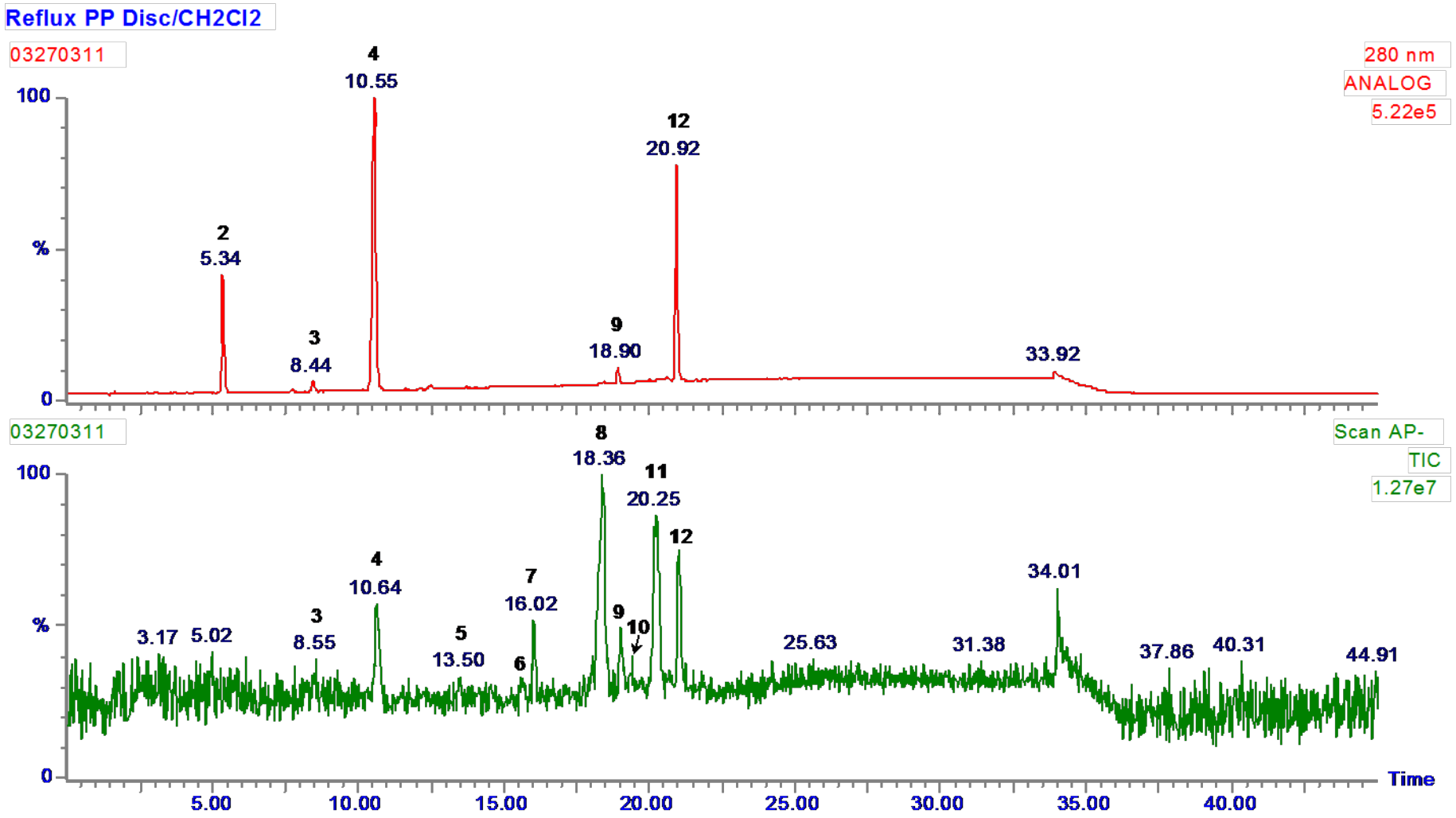
Polypropylene – Extractables Profile by LC/UV/MS



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Key References

- Safety Thresholds and Best Practices For Extractables and Leachables in Orally Inhaled and Nasal Drug Products, Submitted to the PQRI Drug Product Technical Committee, PQRI Steering Committee, and U.S. Food and Drug Administration by the PQRI Leachables and Extractables Working Group, Daniel L. Norwood (Chair), Product Quality Research Institute, September 2006, http://pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf (accessed 11/15/2006).
- "Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products: An Overview of the PQRI Recommendations", D. L. Norwood, D. Paskiet, M. Ruberto, T. Feinberg, A. Schroeder, G. Poochikian, Q. Wang, T. J. Deng, F. DeGrazio, M. K. Munos, and L. M. Nagao, *Pharmaceutical Research*, **25**(4), 727-739 (2008).
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