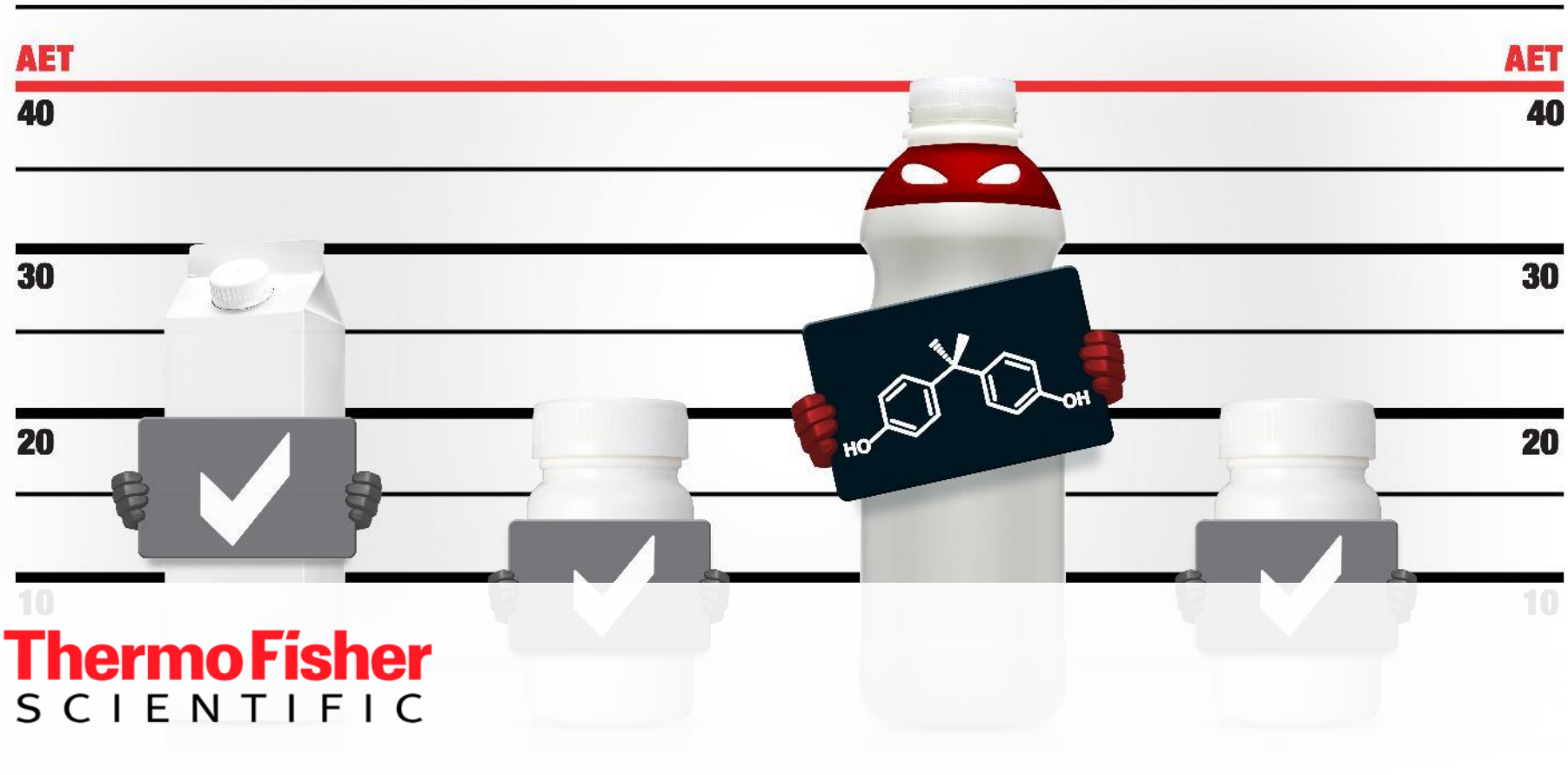
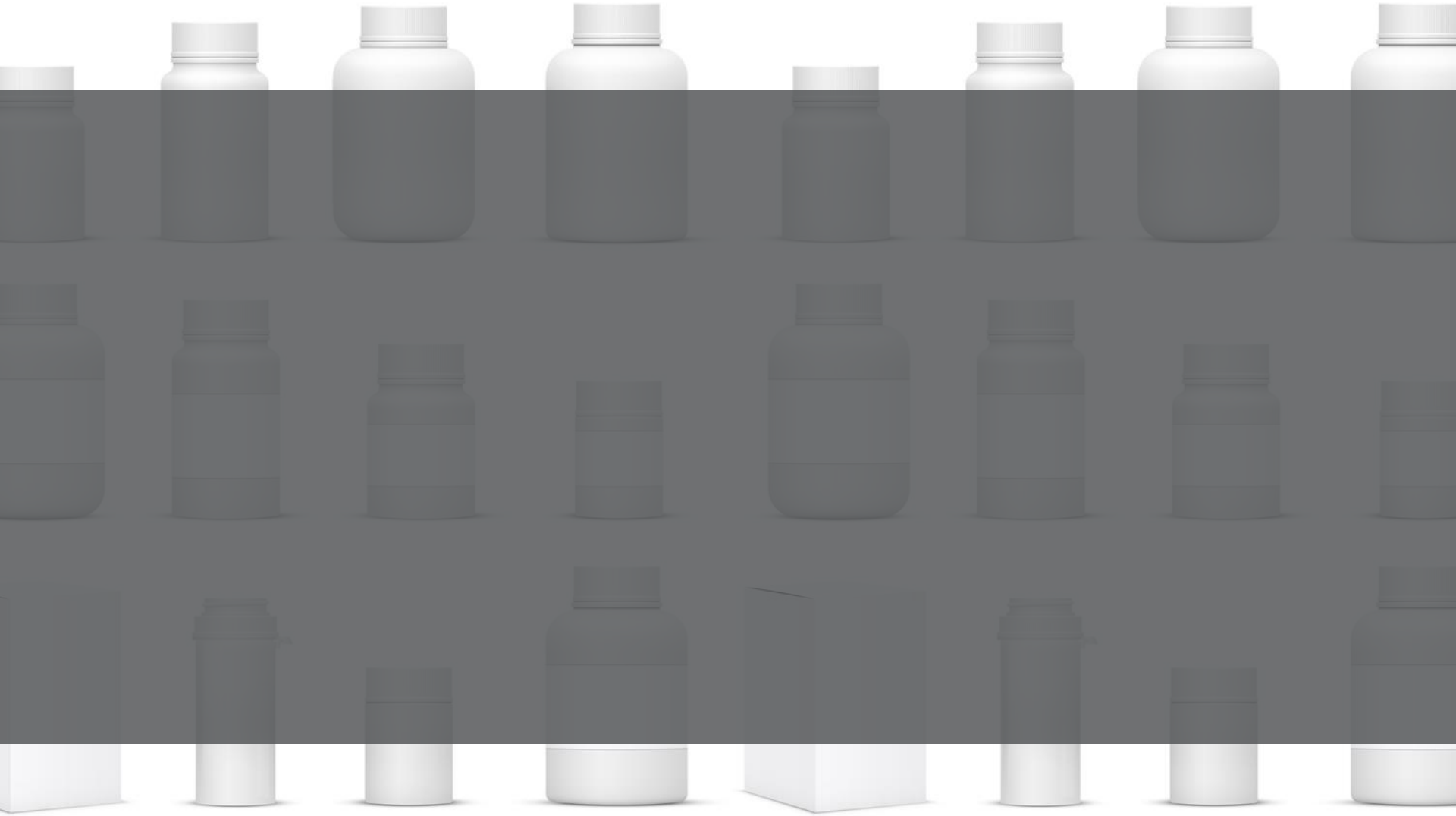


ThermoFisher SCIENTIFIC

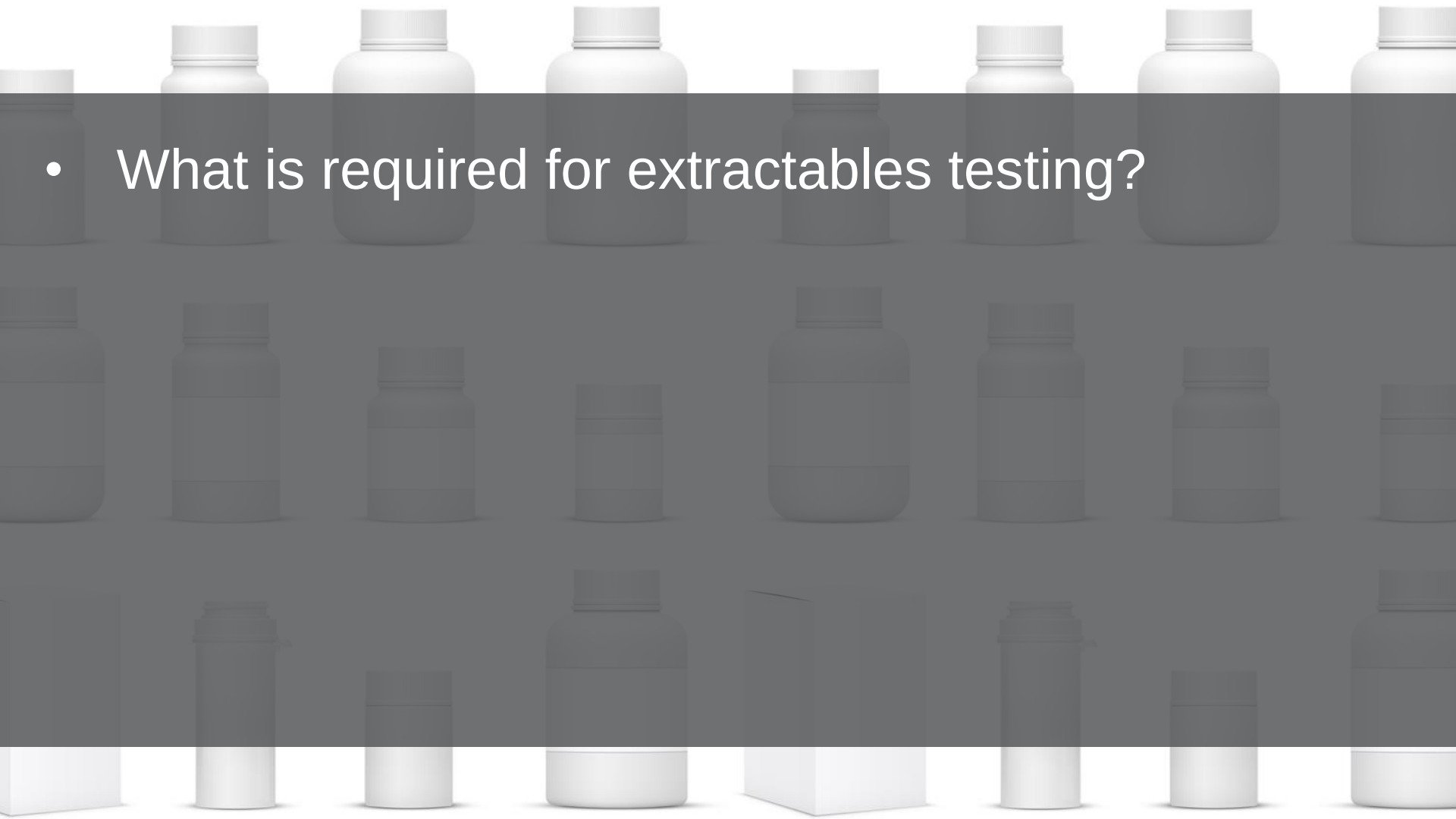
Analytical Workflows for Extractable and Leachable Impurities

Pharma & Biopharma Tours | 2016

Introduction

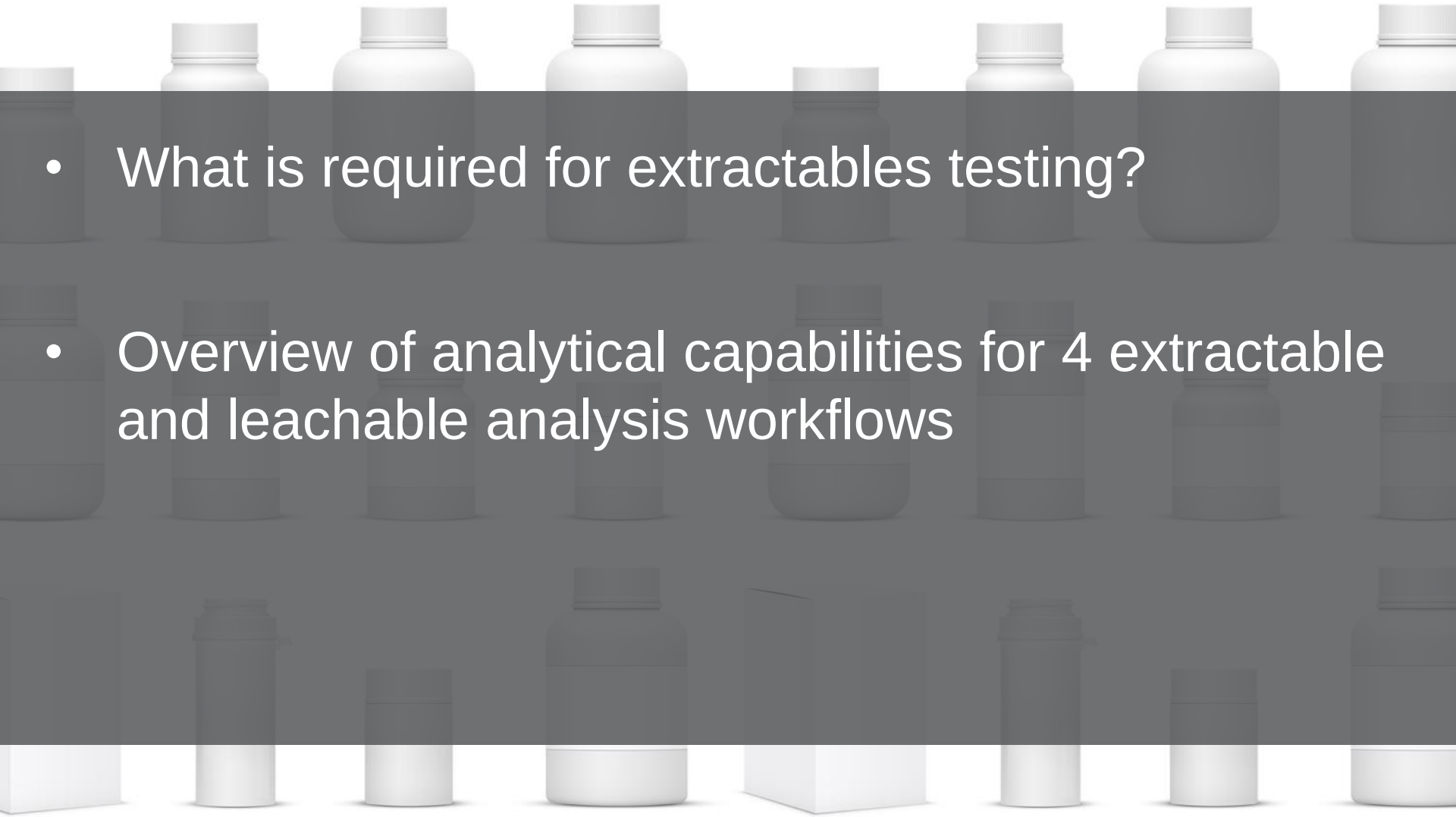


Introduction



- What is required for extractables testing?

Introduction



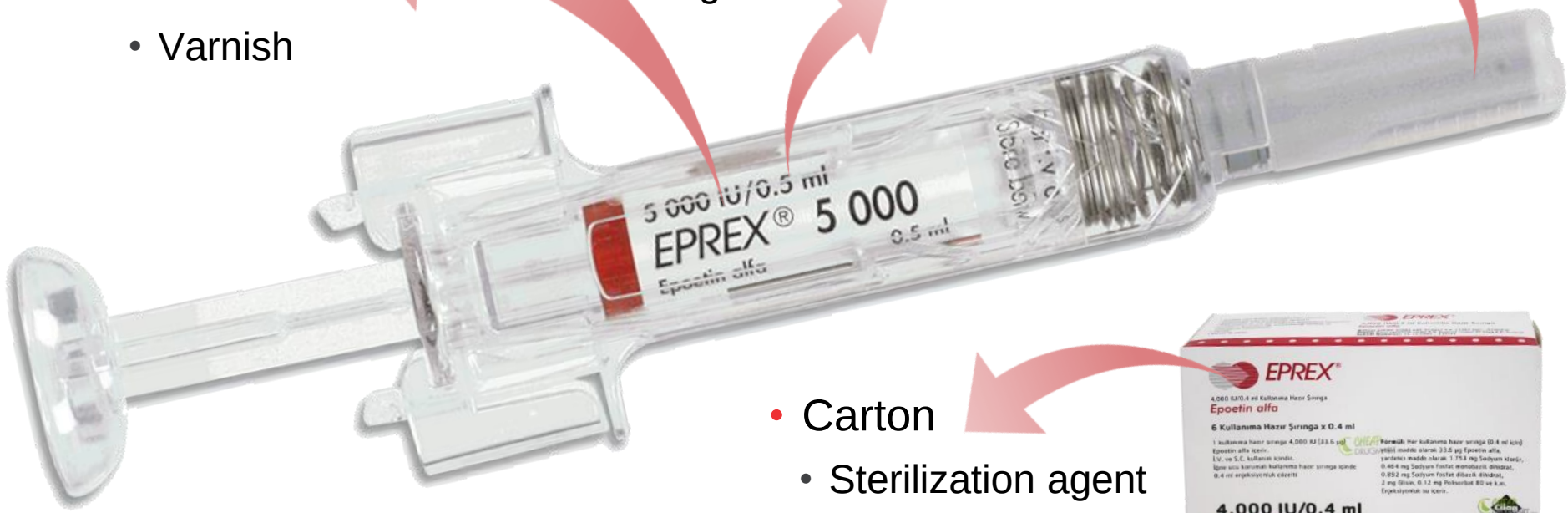
- What is required for extractables testing?
- Overview of analytical capabilities for 4 extractable and leachable analysis workflows

Introduction

- What is required for extractables testing?
- Overview of analytical capabilities for 4 extractable and leachable analysis workflows
- Introduce NEW technology for identification and quantification of unknown impurities

What is there to leach?

- Label
  - Ink
  - Solvent
  - Adhesive
  - Varnish
- Container-Closure
  - Plasticizer
  - Lubricant
  - Pigment
  - Stabilizer
  - Antioxidant
  - Monomers
  - Slip agent
  - Flame retardant



- Carton
  - Sterilization agent
  - Preservatives
  - Sealant & Ink

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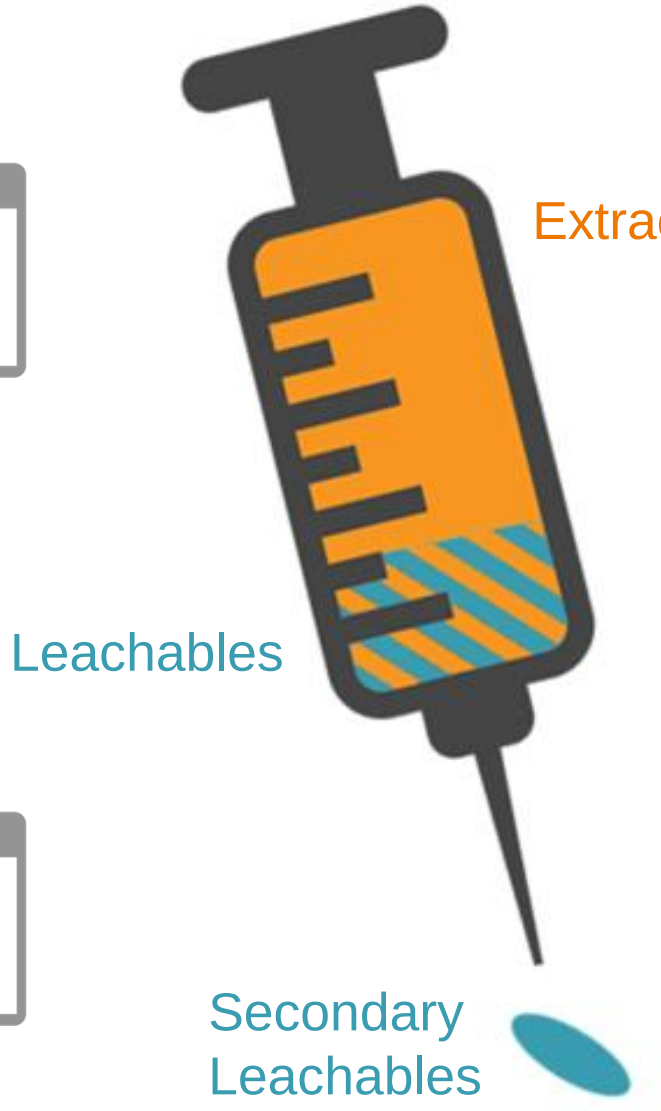
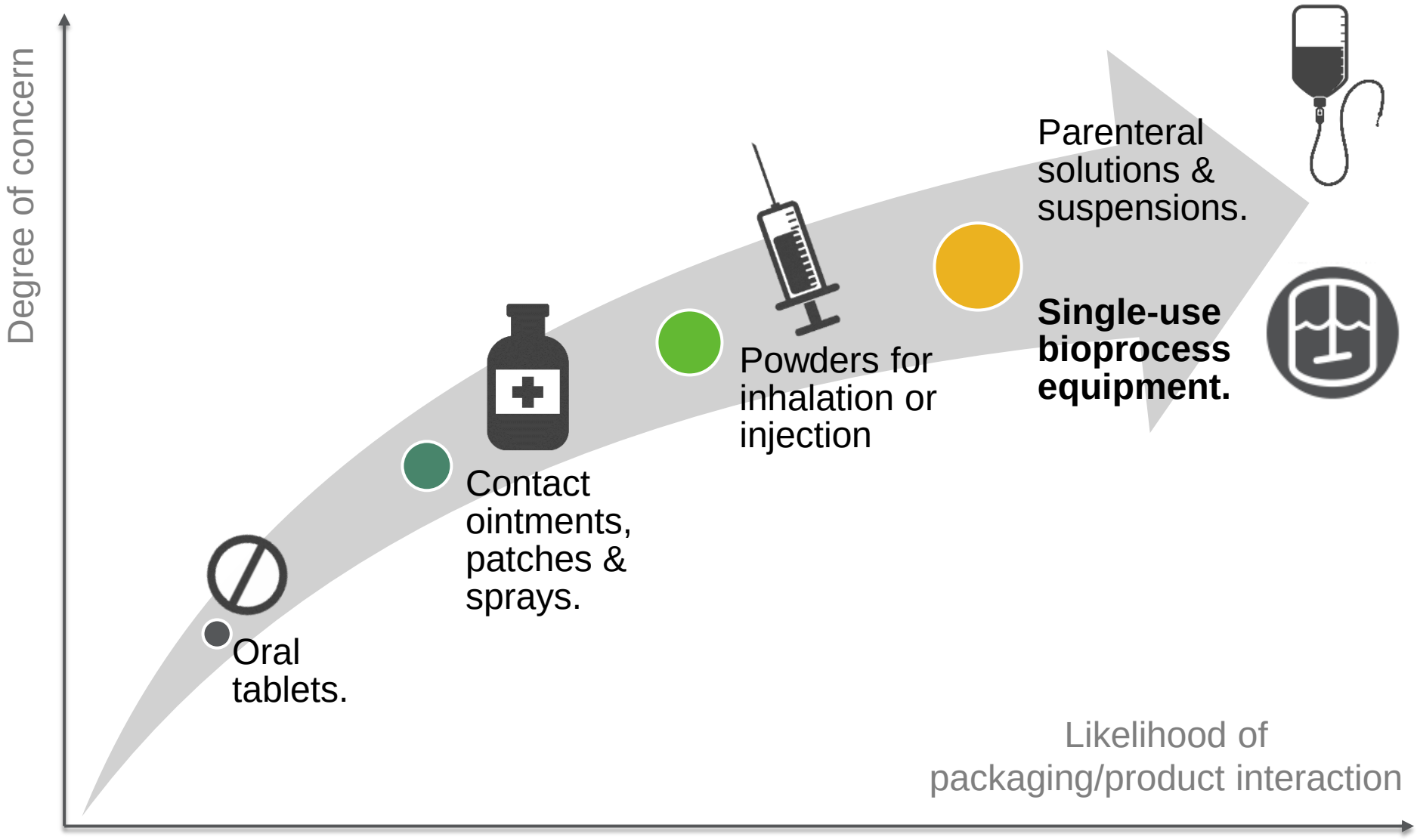
Extractables & Leachables

- **EXTRACTABLE**
  - Chemical released from process equipment, packaging or delivery system; **under laboratory extraction conditions**.

- **LEACHABLE**
  - Chemical that **migrates** from process equipment, packaging or delivery system; into drug formulation **under normal usage conditions**.



Where are is the greatest concern for leachables?



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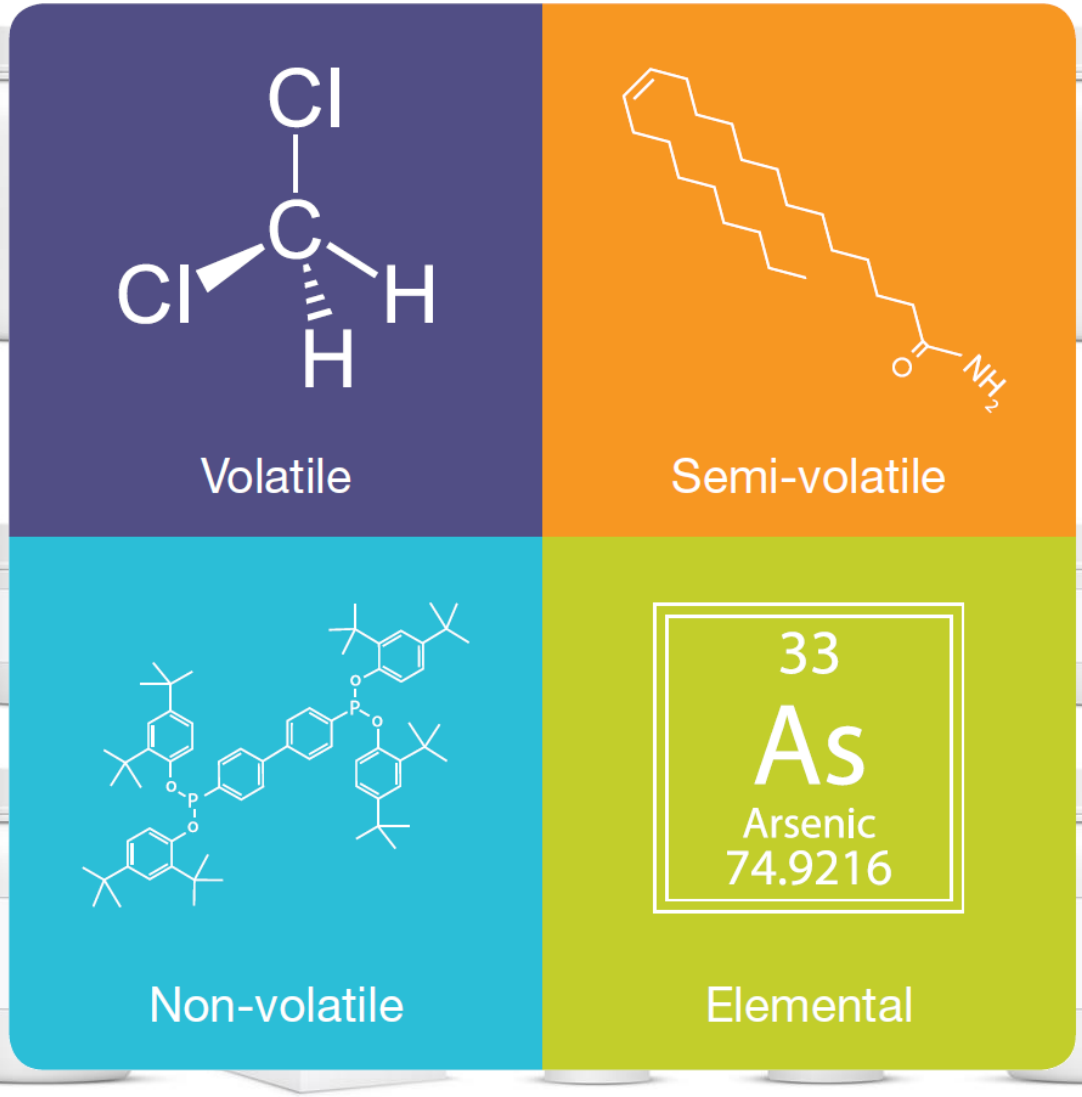
Analysis of Extractables & Leachables

Unknowns come in all shapes and sizes



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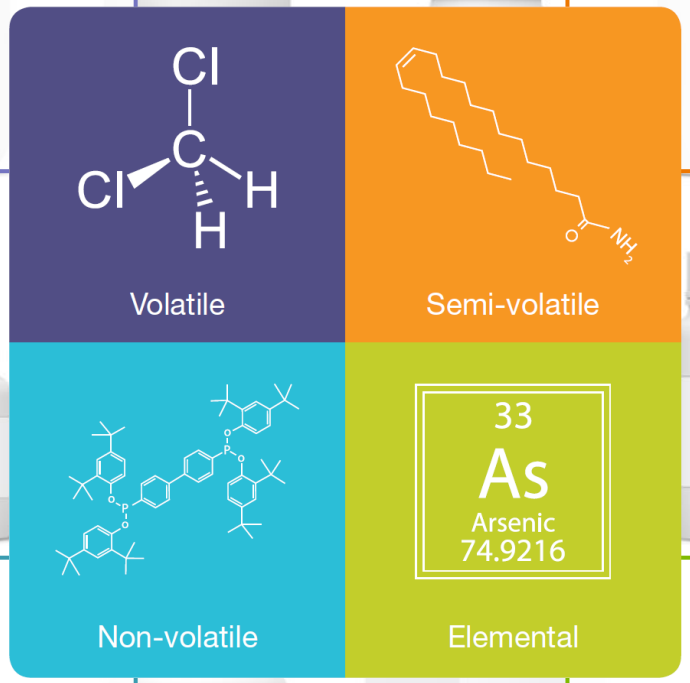
Analysis of Extractables & Leachables

- GC-MS
- GC-HRMS
- Headspace
- EI & CI
- Library

- GC-MS
- GC-MS/MS HRAM
- EI & CI
- Library



- ESI & APCI
- LC-UV or CAD
- LC-MS/MS HRAM
- IC-MS
- Library

- LC-ICP-MS
- IC-ICP-MS
- ICP-MS
- ICP-OES

Complete solution for Extractables & Leachables

Preparation	Consumables	Volatiles	Semi-volatiles	Non-Volatiles	Elemental
					
Accelerated solvent extraction technology	MS certified vials, columns and ultra-pure solvents	Headspace sampling and compliant GC-MS	Advanced Orbitrap-based HRAM GC-MS/MS	Advanced Orbitrap-based HRAM LC-MS/MS	Robust, compliant ICP-MS

EXTRACTION → **ANALYSIS AND REPORTING**

Sample preparation

Principle and Best Practices Recommended

Regulatory guidelines:

- USP Chapter <1663> & <1664>
- Product Quality Research Institute (PQRI)
- BioPhorum Operations Group (BPOG)

"Controlled extraction studies should;

- ***Employ vigorous extraction with multiple solvents of varying polarity***
- ***Incorporate multiple extraction techniques"***

Heated agitation
(2-30 days)

Sonication
(2-5 days)

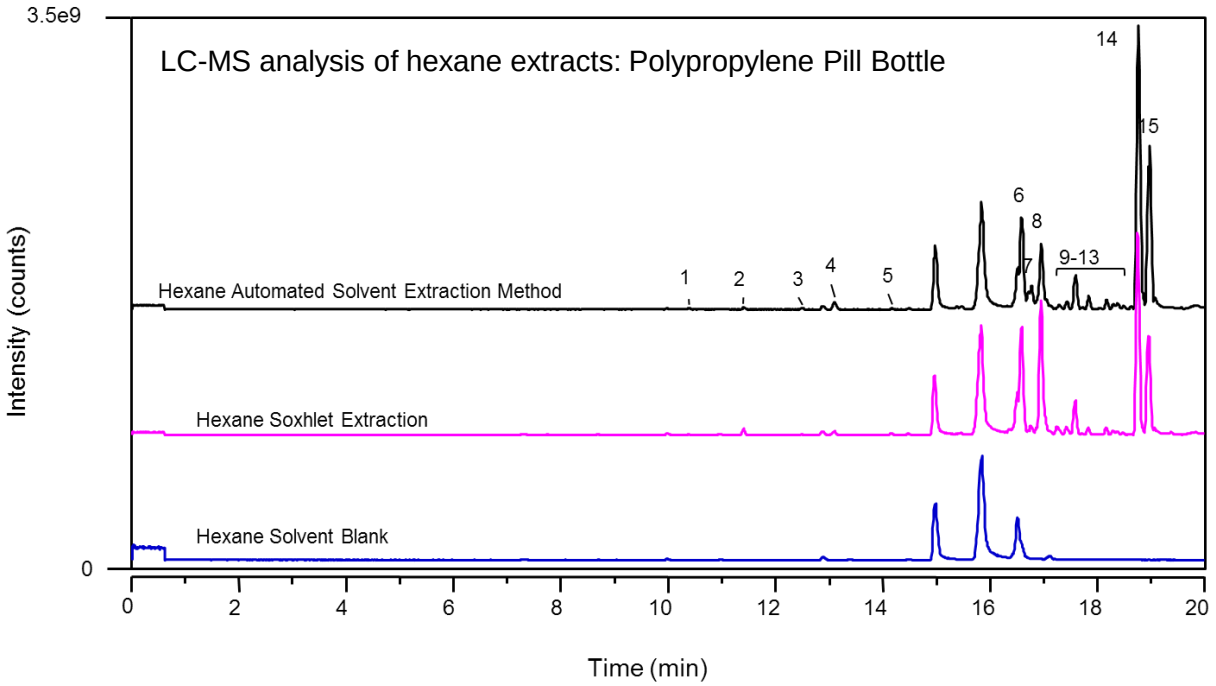
Soxhlet
(24 Hours)

Accelerated solvent extraction technique
(30 minutes)

Accelerated Solvent Extraction Technique

- Automates sample preparation for solid and semi-solid samples
- Extracts above the boiling point of solvent using elevated pressure
- Extraction time <30 min/sample
- Compliant Chromeleon software control

Thermo Scientific™ Dionex™ ASE™ 350
Accelerated Solvent Extractor System



Accelerated Solvent Extraction Technique

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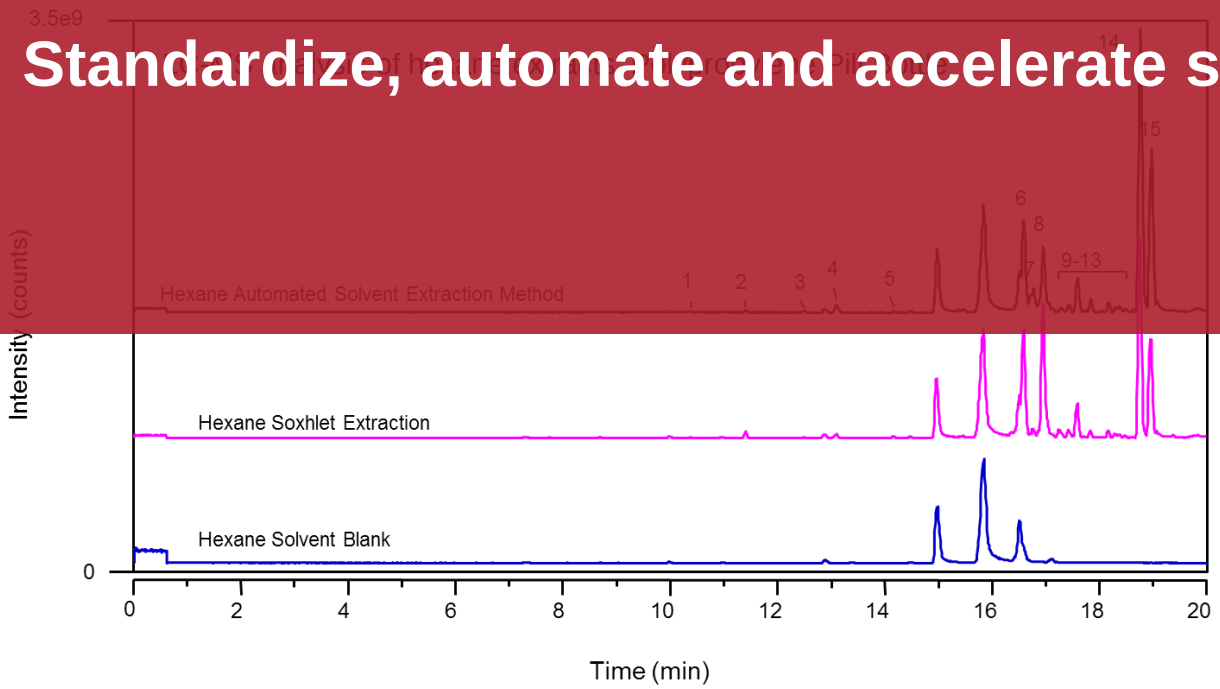
Thermo Scientific™ Dionex™ ASE™ 350
Accelerated Solvent Extractor System

Standardize, automate and accelerate sample preparation



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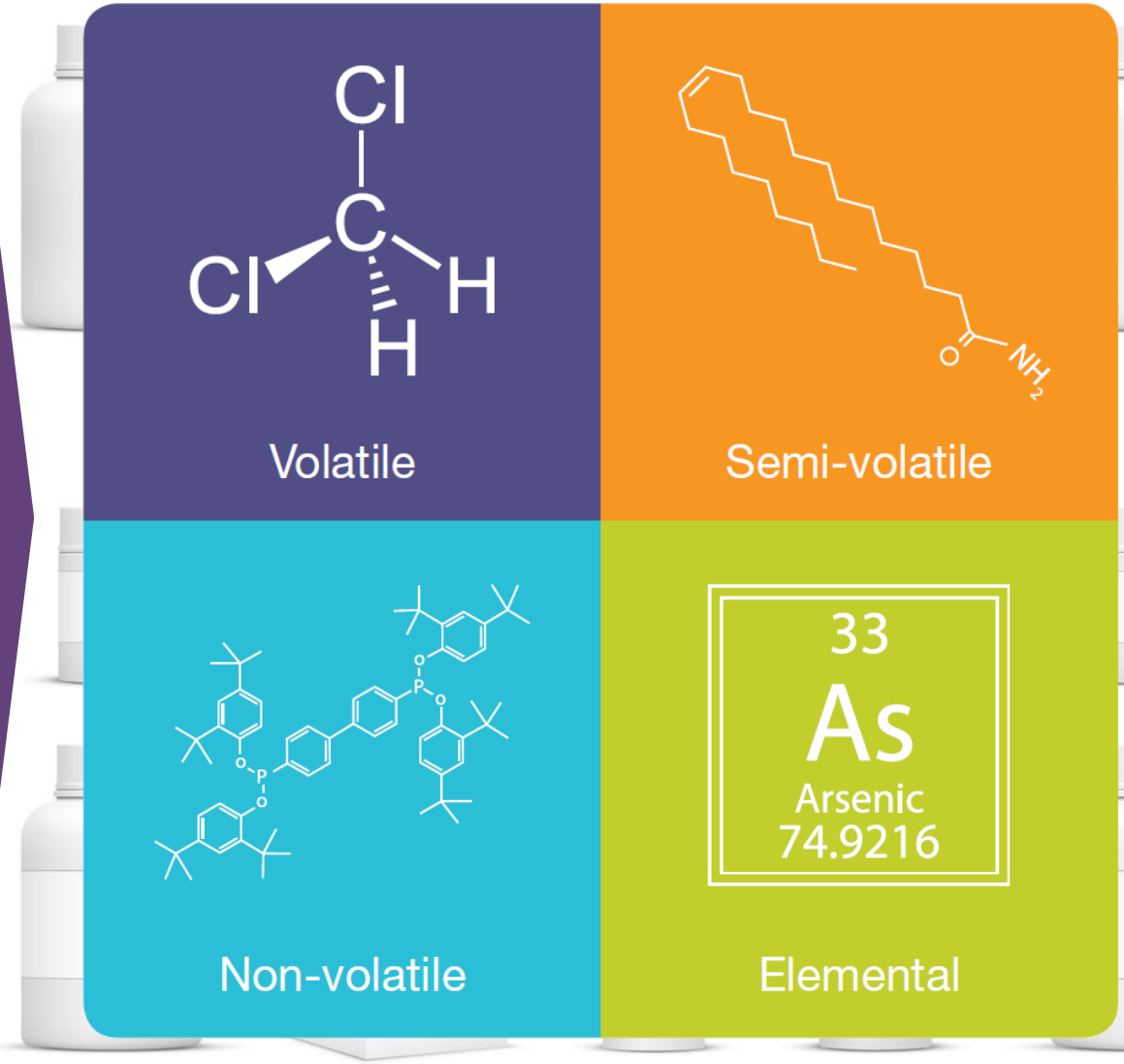
Comparison of Soxhlet vs. Dionex ASE 350 System

Parameter	Soxhlet	Dionex ASE 350 System
Extract solvent used per sample (mL)	160	<30
Total extraction time per sample (min)	1440	<30
Extracted compounds	Same	Same
Extracts peak Intensity Ratio Accelerated Solvent Extraction/Soxhlet		**1.4x to 90x**

Dionex ASE 350 system delivers faster extractions using less solvent

Volatiles



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Volatile impurities workflow

Sample with valve & loop headspace

Robustly separate

Identify and quantify using MS

Compliant data processing

- Analogous to **USP 467** Residual solvents workflow
- Molecules are generally known, or simple to identify
- **Routine compliant quantification**

ThermoFisher SCIENTIFIC

Complete technologies for volatile impurities

Thermo Scientific™ TriPlus™ 300 headspace sampler

Thermo Scientific™ Trace 1310 GC

Thermo Scientific™ TraceGOLD TG-624SilMS GC Columns

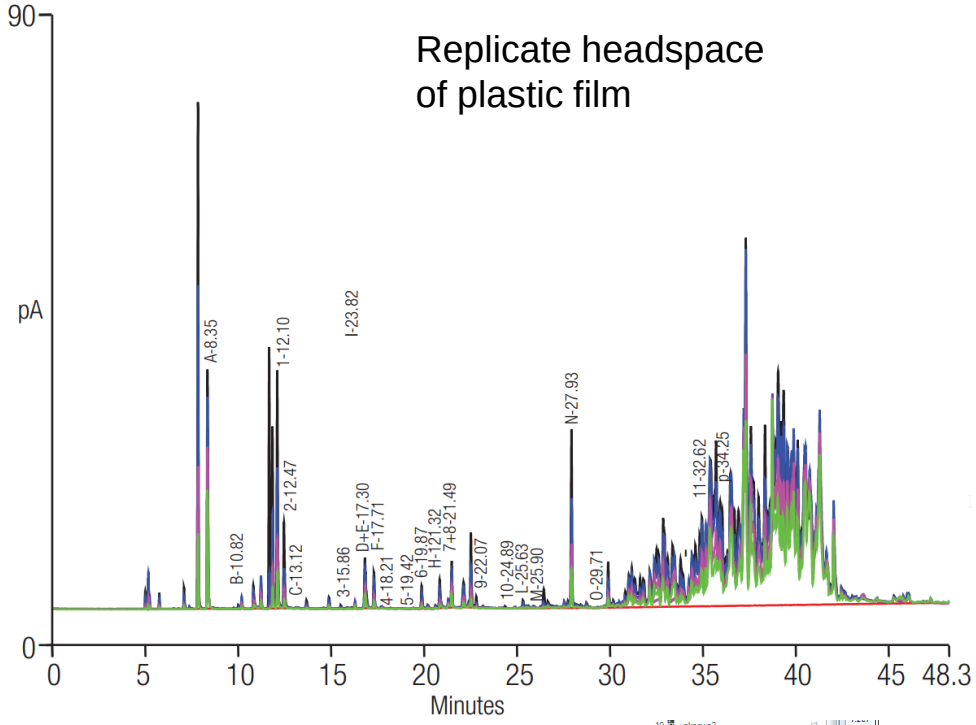
Thermo Scientific™ ISQ™ Series GC-MS

Thermo Scientific™ Dionex™ Chromeleon™ CDS

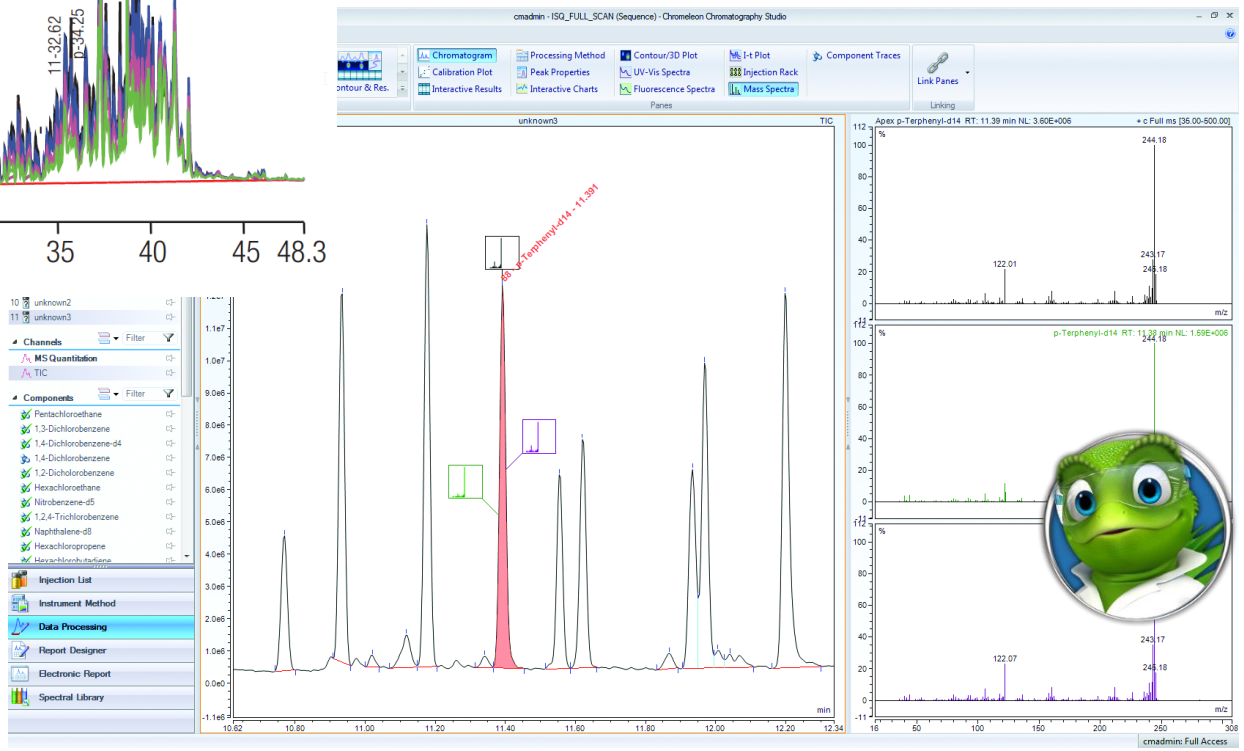
Thermo Scientific™ AppsLab Library™

ThermoFisher SCIENTIFIC

Volatiles headspace analysis



- Methods available on AppsLab
- One click Chromeleon eWorkflow
- Full **quantitative** and **qualitative** mass spectral analysis



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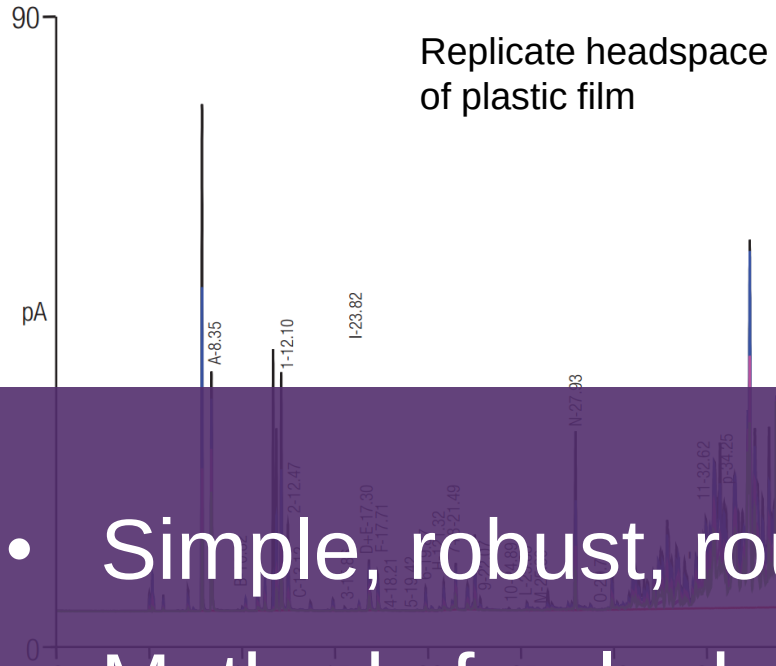
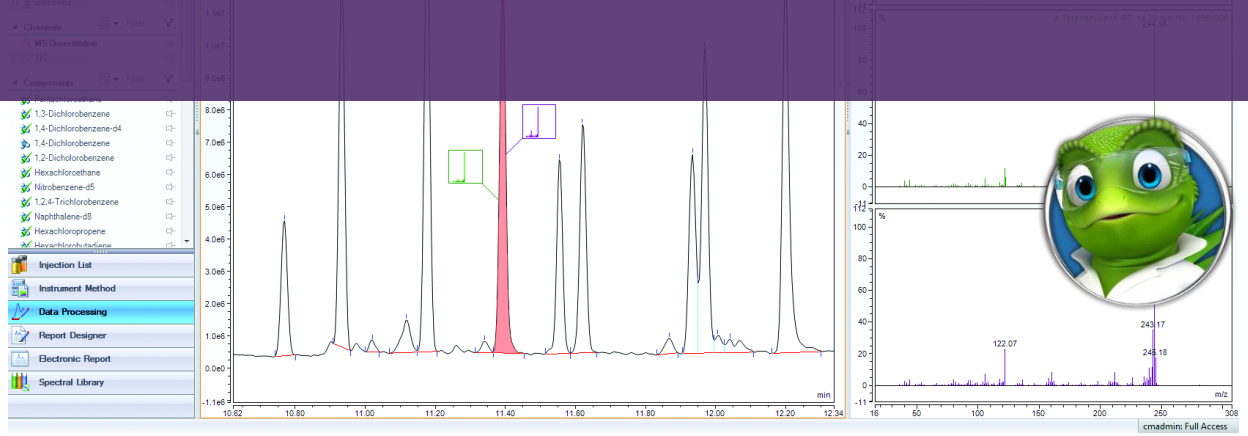
Volatiles headspace analysis



Replicate headspace of plastic film

- Methods available on AppsLab
- One click Chromeleon eWorkflow
- Full **quantitative** and **qualitative** mass spectral analysis

- Simple, robust, routine, compliant analysis
- Methods freely downloadable



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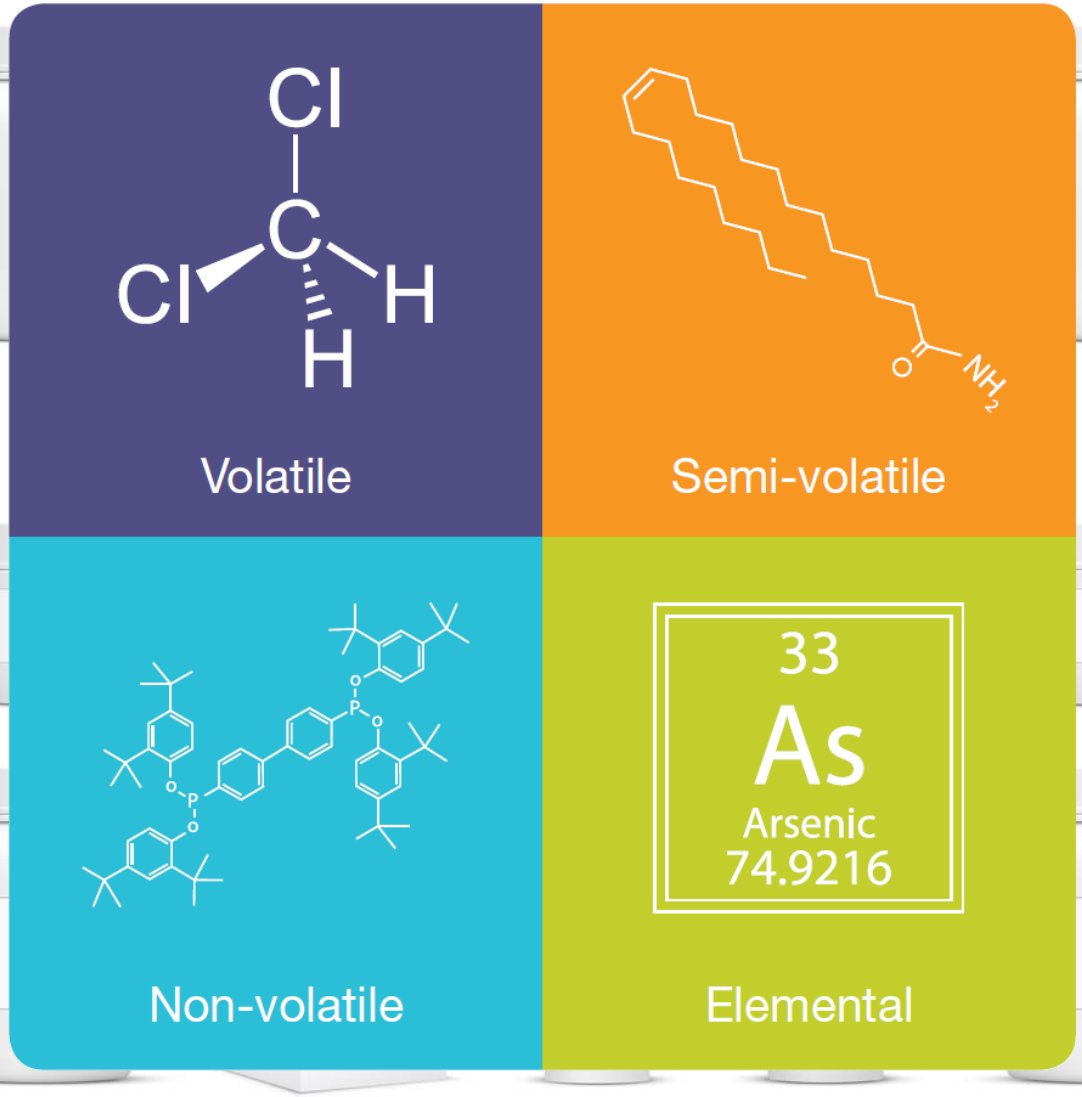
Non-Volatiles



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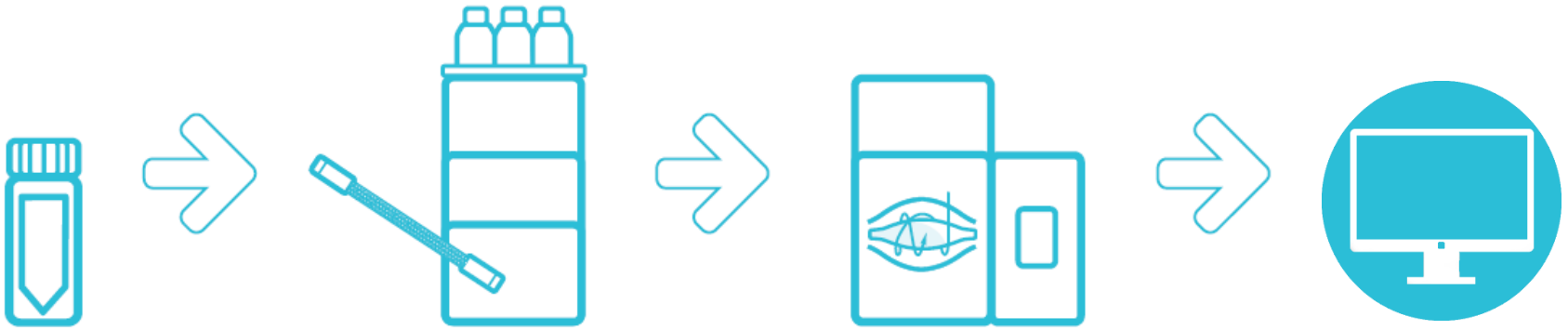
Non-volatiles unknown identification workflow



Extract

Separate and detect everything

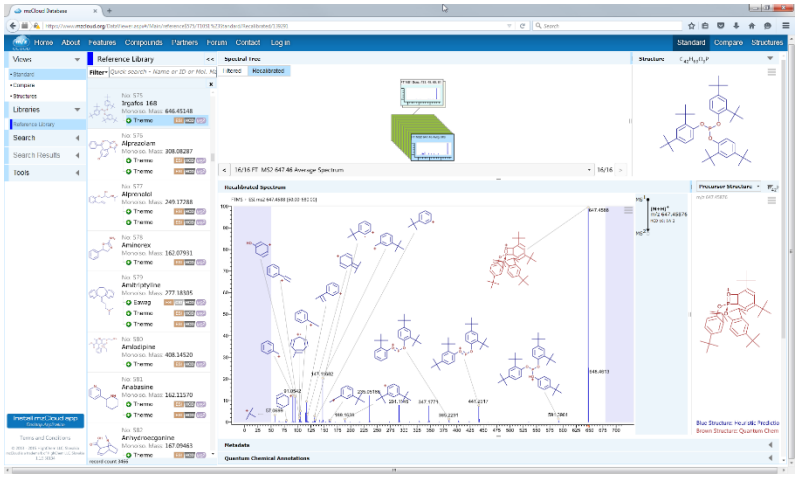
Identify with confidence of HRAM MS/MS

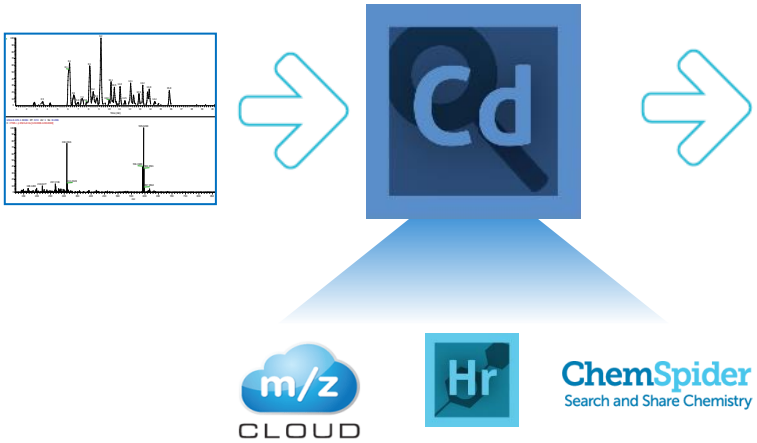
Software to search, elucidate & confirm

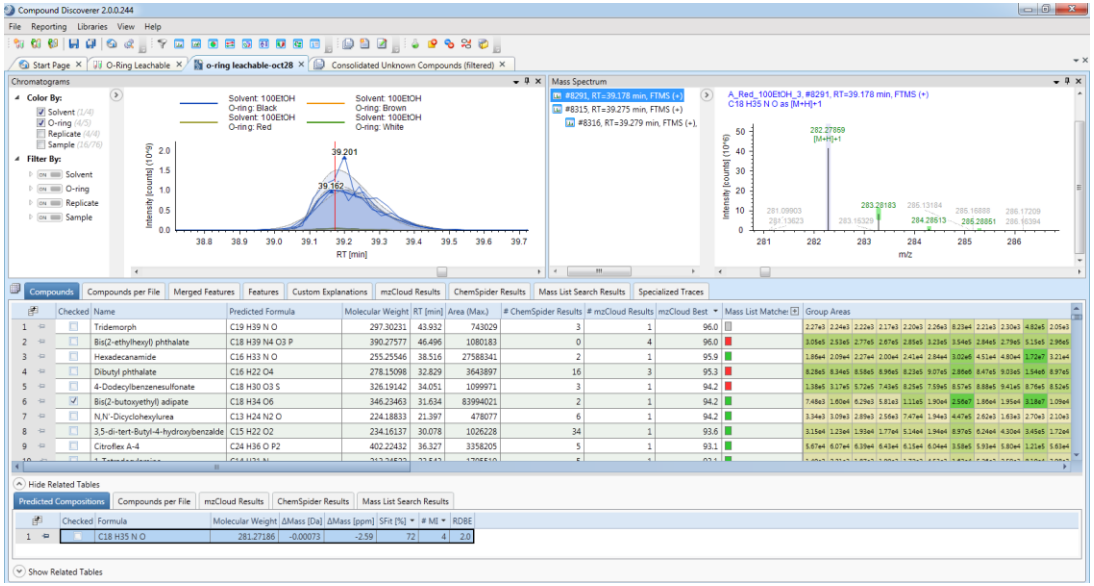
- Catch everything with orthogonal detection
- Detect in both positive and negative ion mode
- Have absolute confidence in elemental composition
- Get full sub-structural information
- Search wide variety of data sources in parallel

Confidently go from spectra to structure

- Thermo Scientific™ Compound Discoverer™ Software
  - HRAM MS/MS spectra
  - Compare batches and replicates
  - Search multiple databases in parallel including mzCloud.org
  - Deliver one unified report





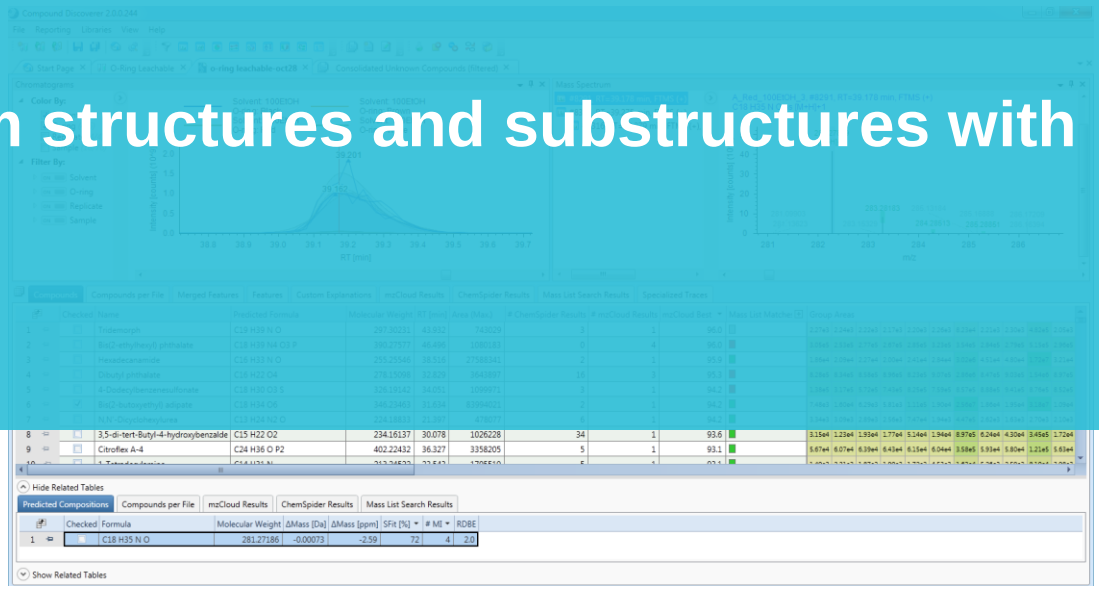


ThermoFisher SCIENTIFIC

Confidently go from spectra to structure

- Thermo Scientific™ Compound Discoverer™ Software
  - HRAM MS/MS spectra
  - Compare batches and replicates
  - Search multiple databases in parallel including mzCloud.org
  - Deliver one unified report

- **Unambiguously confirm structures and substructures with absolute confidence**



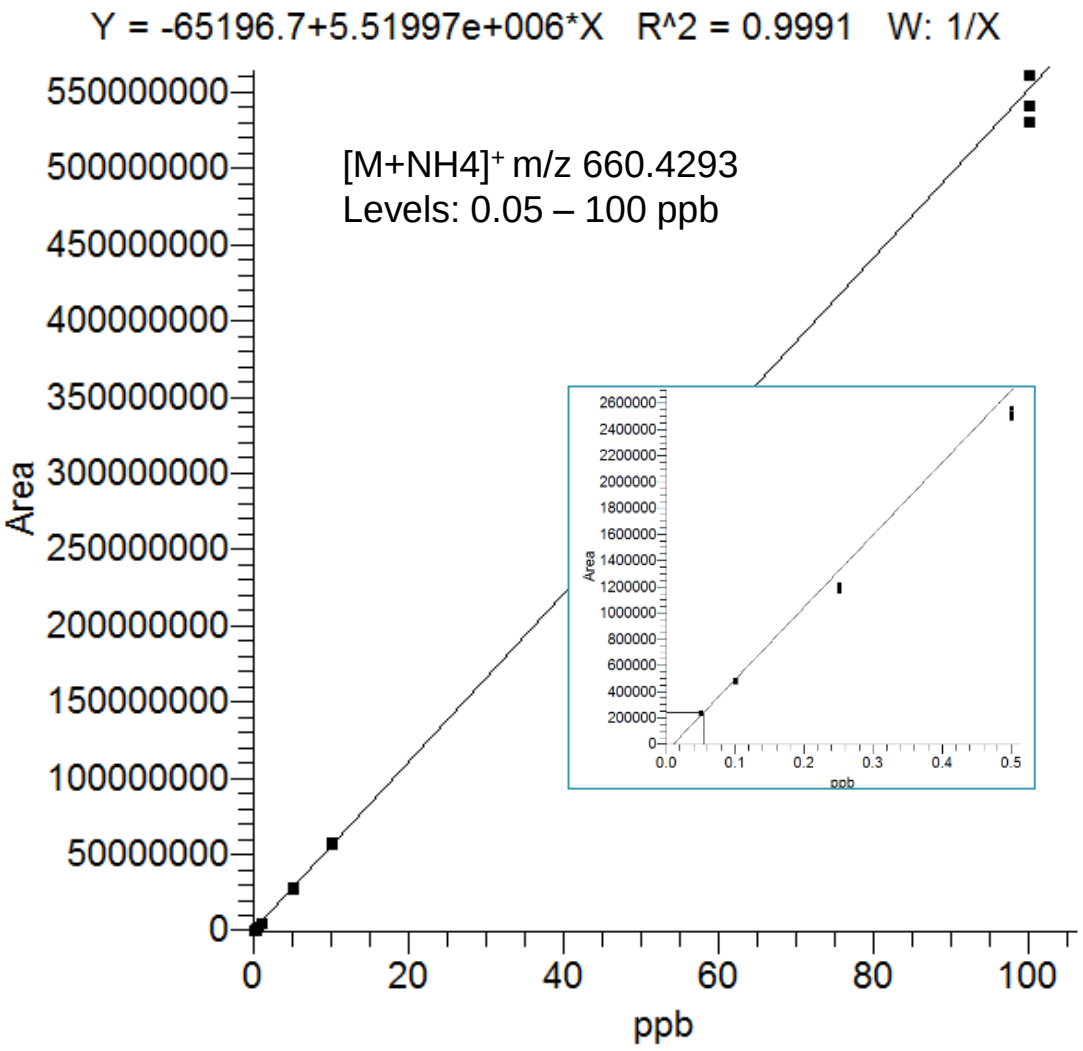
mzCloud

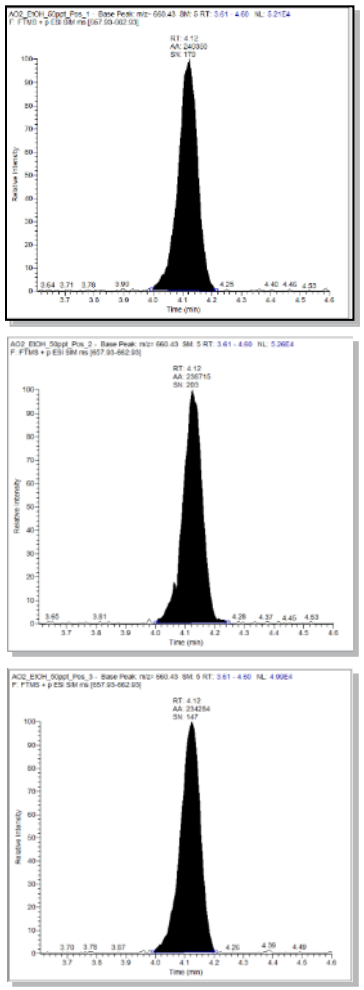
HighResNP

ChemSpider Search and Share Chemistry

ThermoFisher SCIENTIFIC

Quantify non-volatile extractables – Irganox1035





+VE

50 ppt
(Triple Injections)

Detect in positive and negative ion mode in the same run

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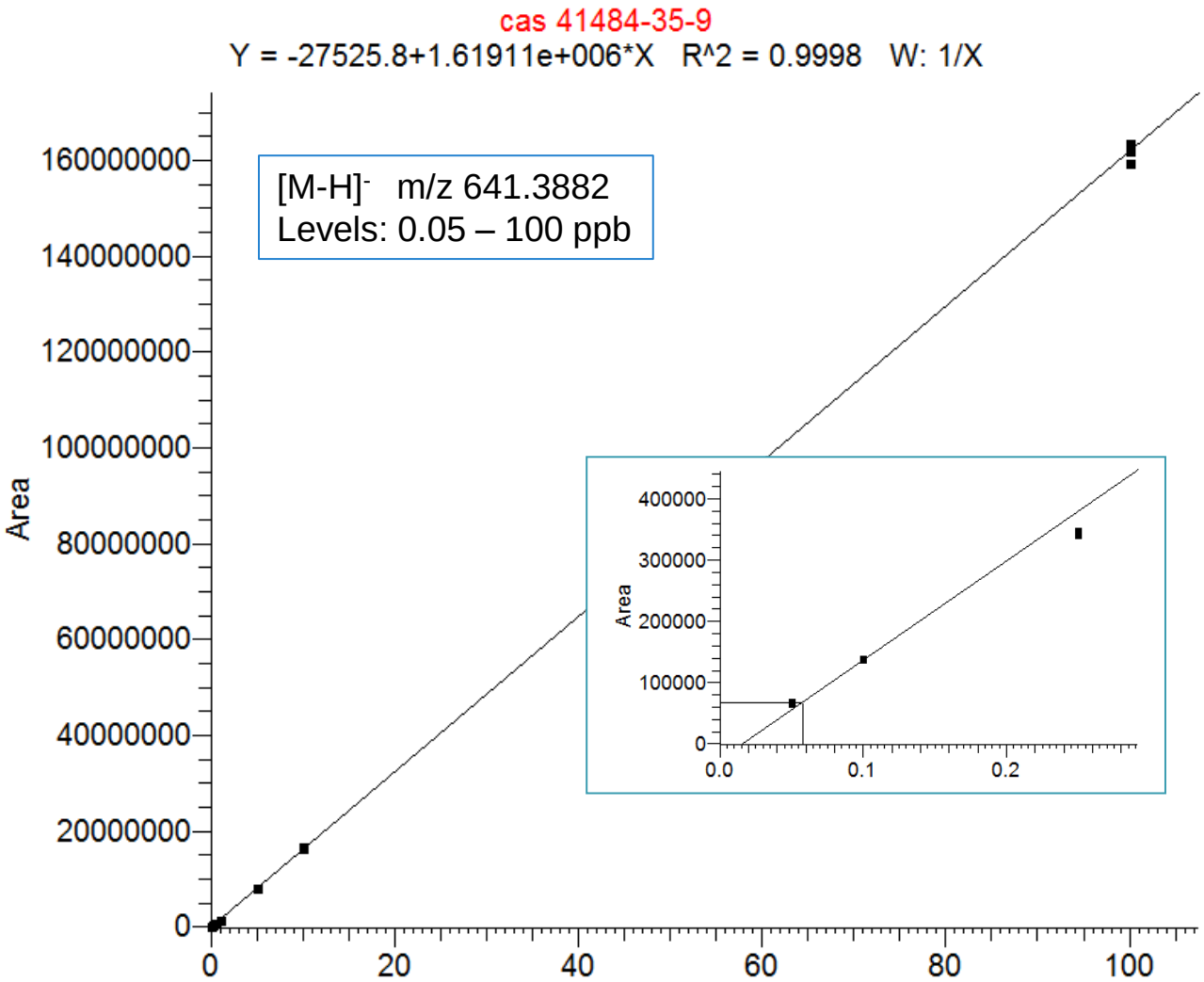
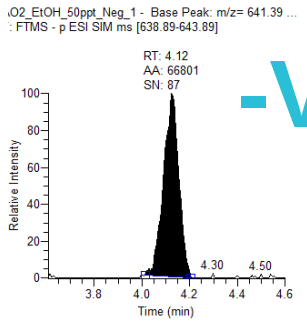
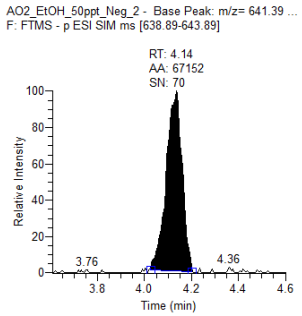
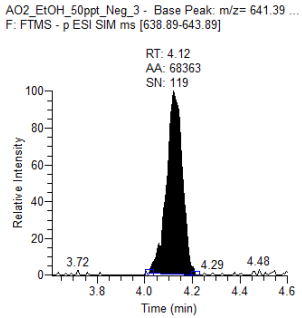
Quantify non-volatile extractables – example Irganox1035





-VE





50 ppt
(Triple Injections)

Full sensitivity in negative ion mode

ThermoFisher SCIENTIFIC

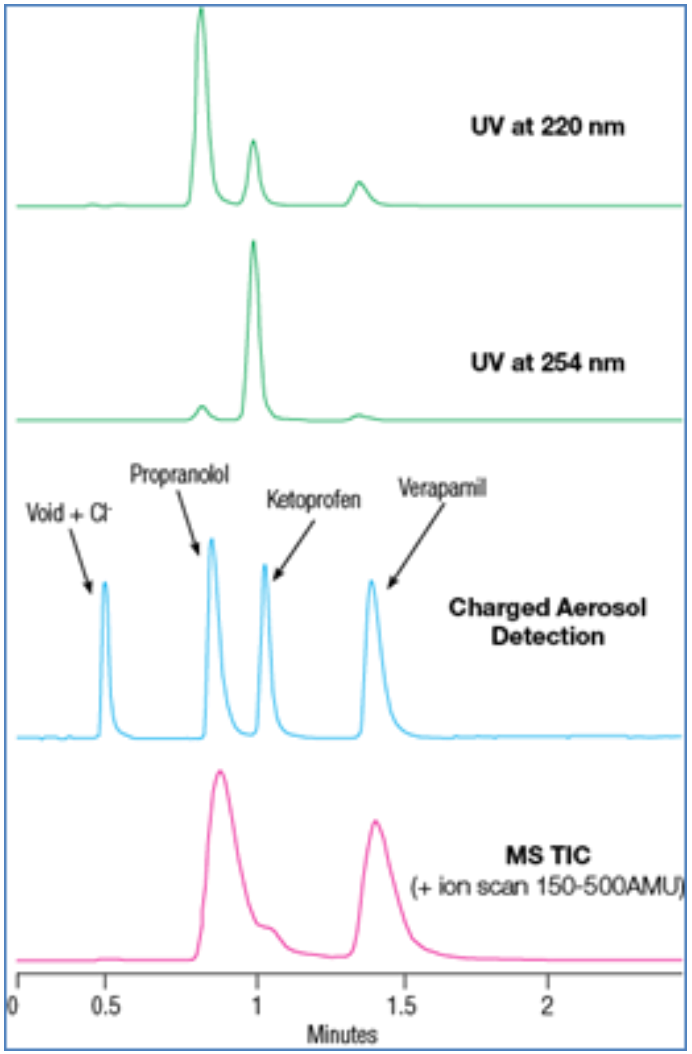
See what you're missing with Charged Aerosol Detection

- Detection without chromophore
- Quantify without exact standards
  - Relative quantification due to consistent response
  - Use virtually any standard for simplified AET calculations
- Consistent analyte response
- Four orders dynamic range

Released 2015

Thermo Scientific™ Vanquish™ Charged Aerosol Detector — Full integration with Thermo Scientific™ Vanquish™ UHPLC platform, slide-in module design, reduced flow path for optimum operation

Comparison of Charged Aerosol Detection to UV and MS



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CAD for extractables and leachables

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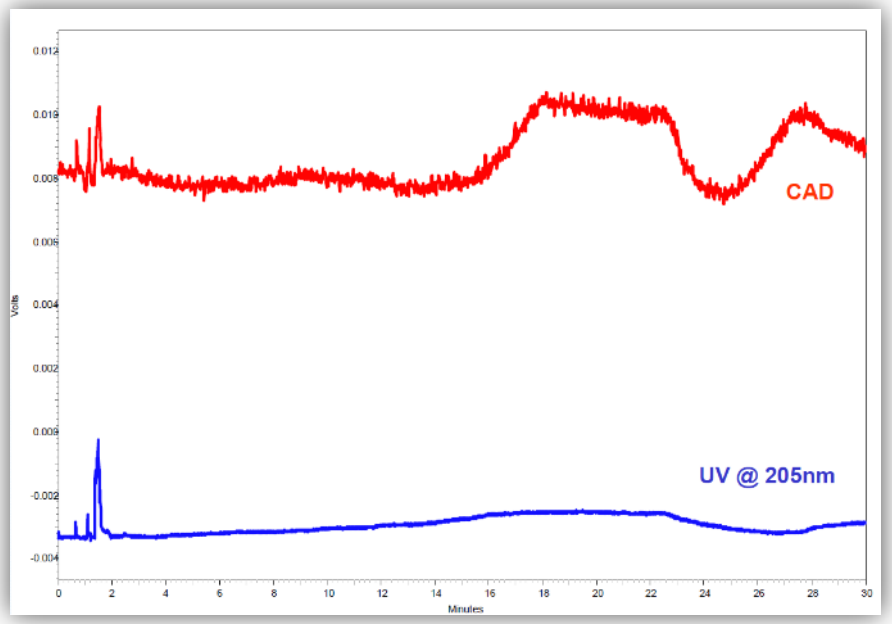

Data from ESA Biosciences, Inc., Chelmsford, MA

CAD for extractables and leachables

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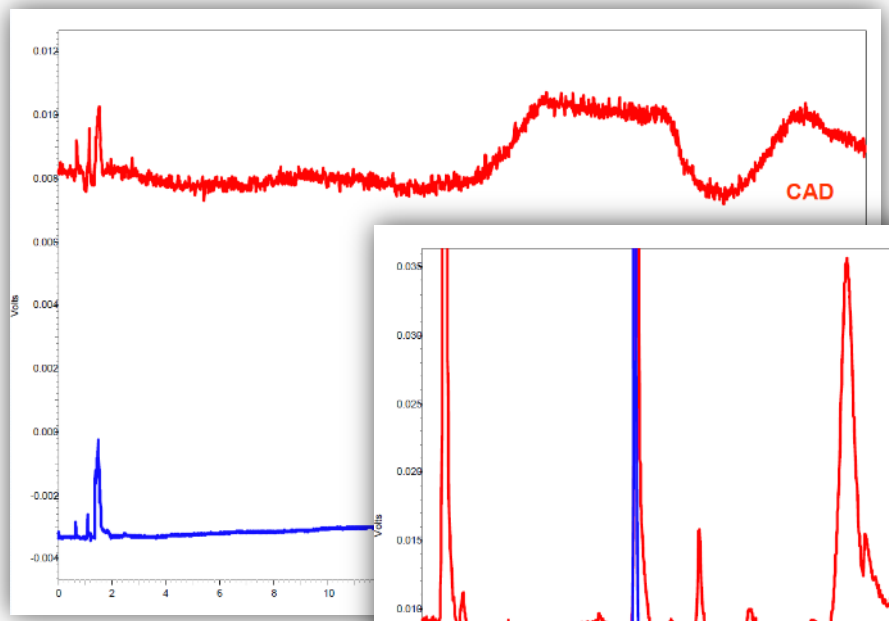

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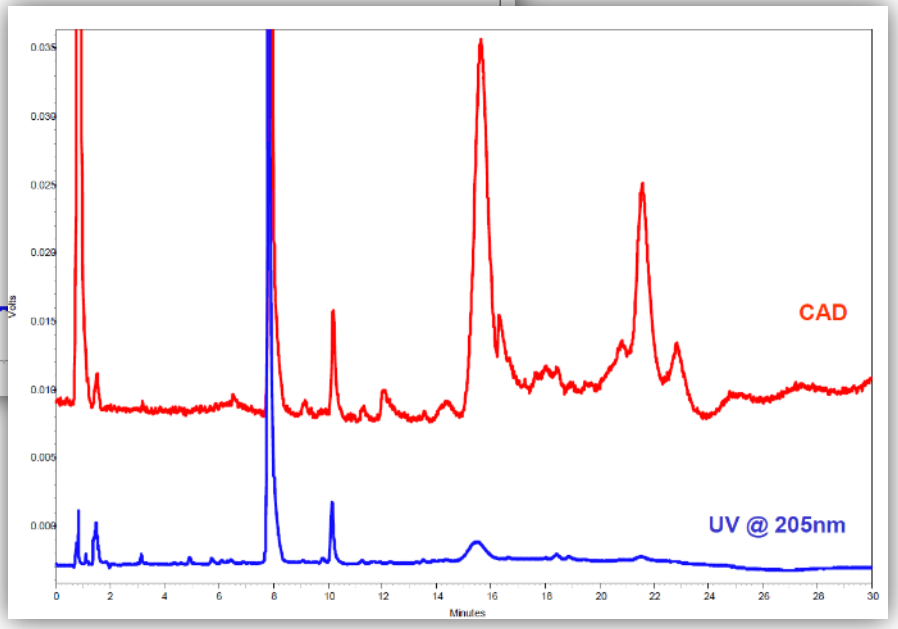

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CAD for extractables and leachables

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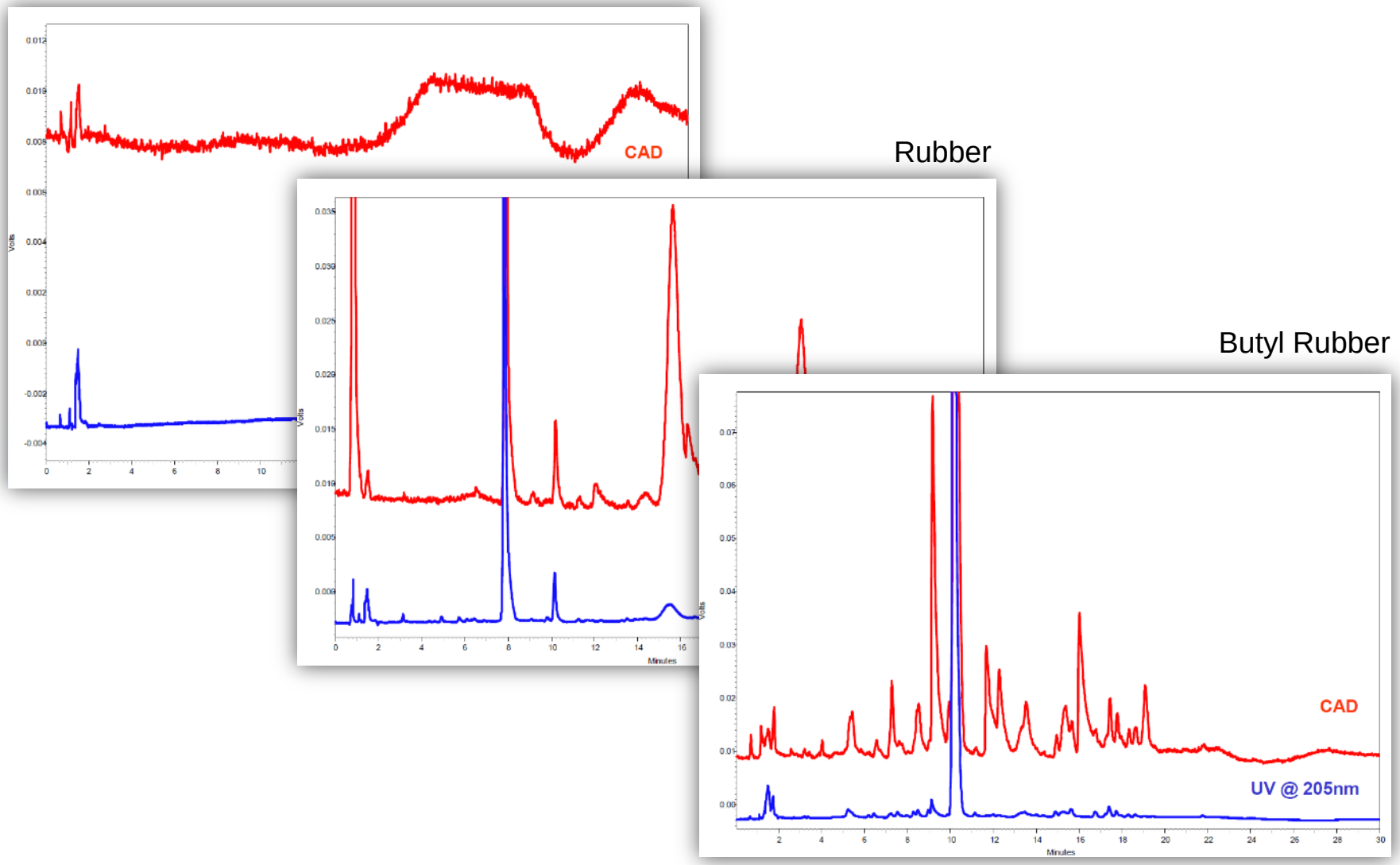
Rubber

Butyl Rubber



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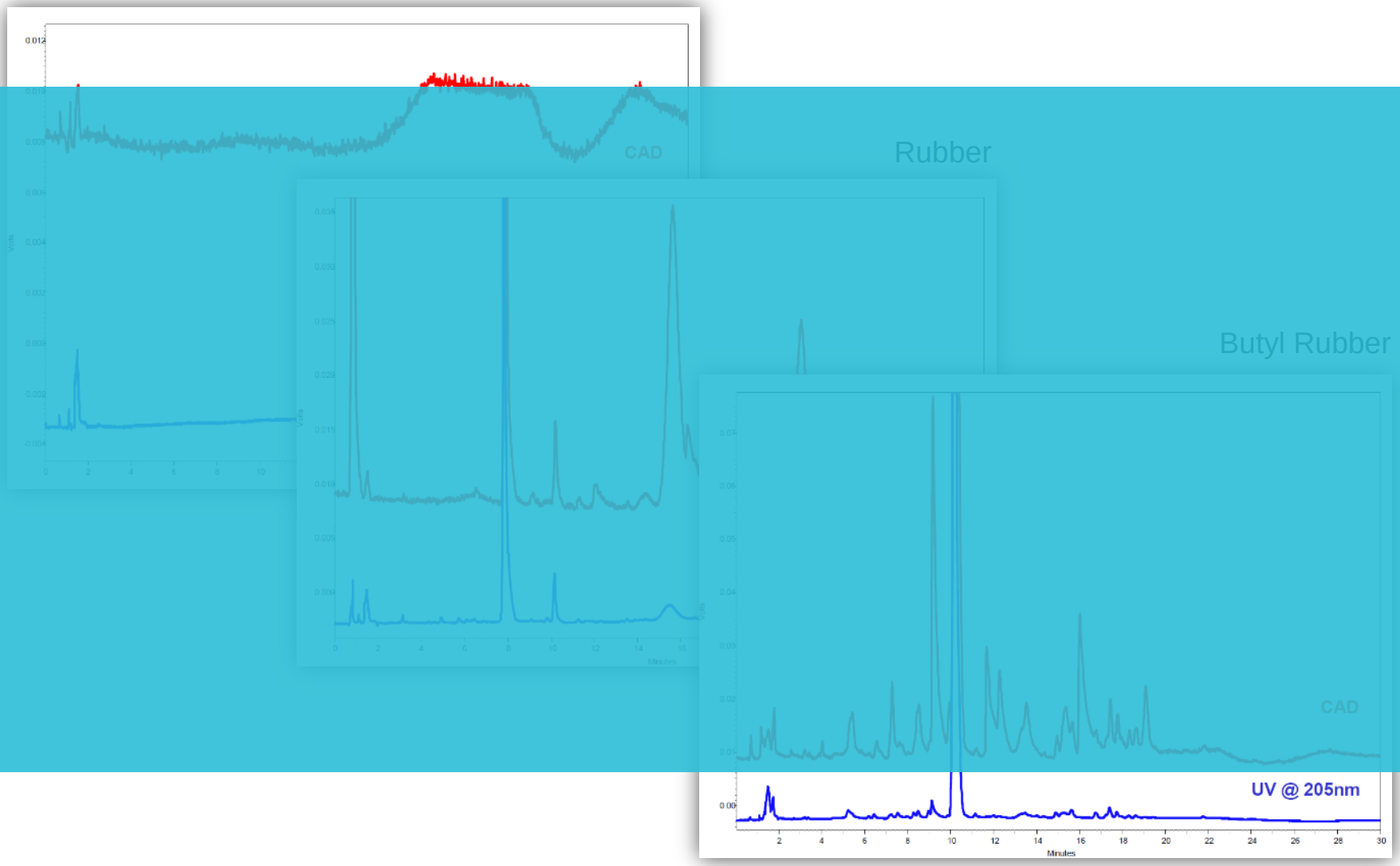
CAD for extractables and leachables



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CAD for extractables and leachables

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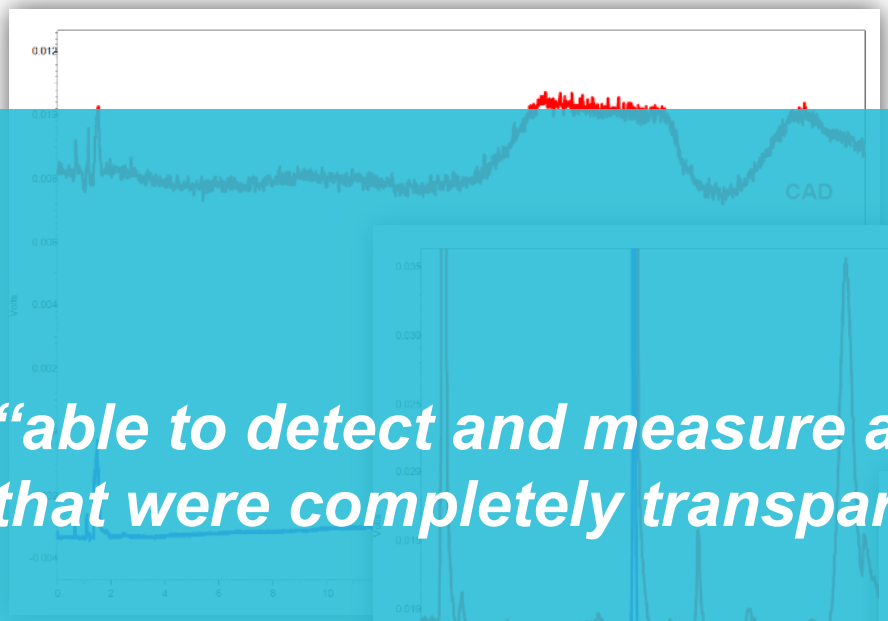

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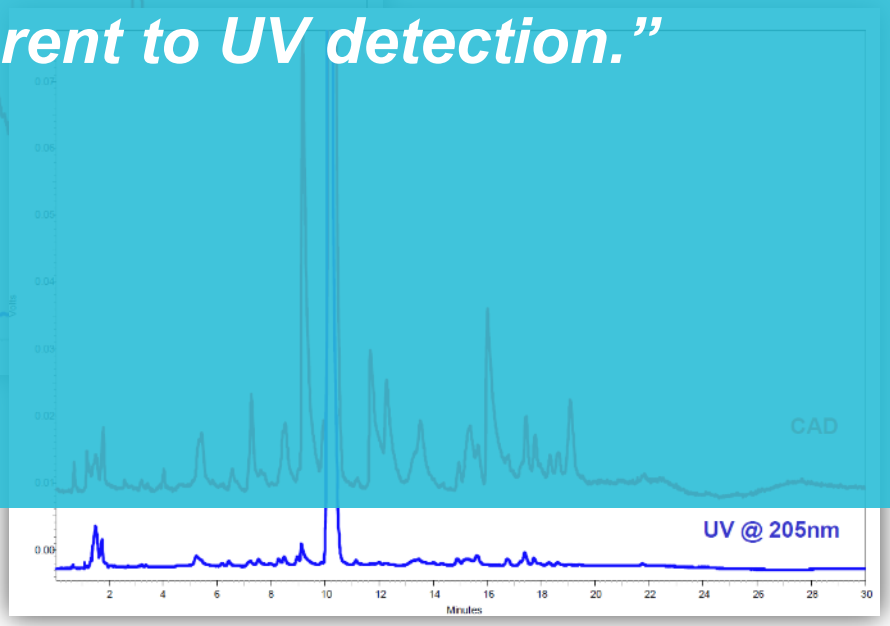

- ***"able to detect and measure a large number of compounds that were completely transparent to UV detection."***

Data from ESA Biosciences, Inc., Chelmsford, MA

CAD for extractables and leachables

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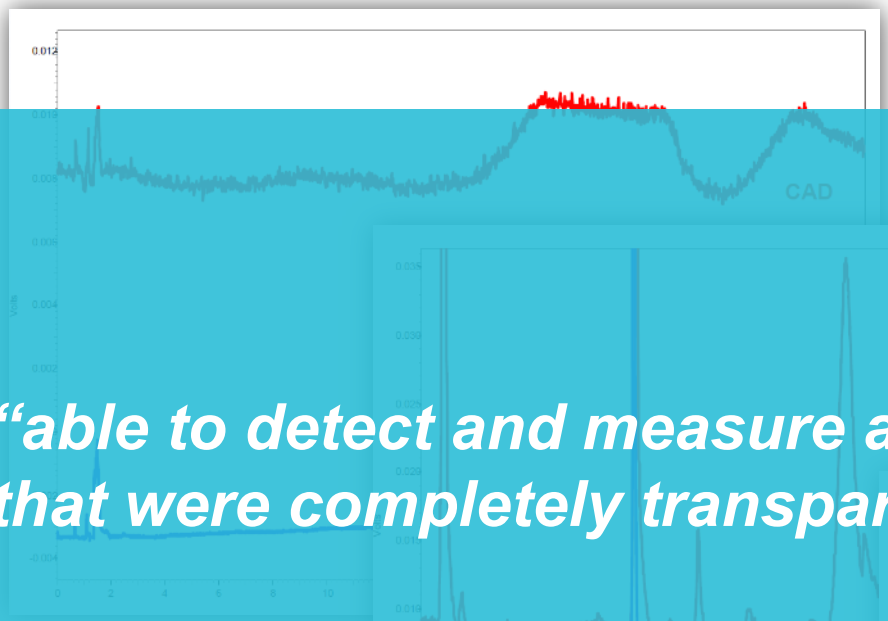

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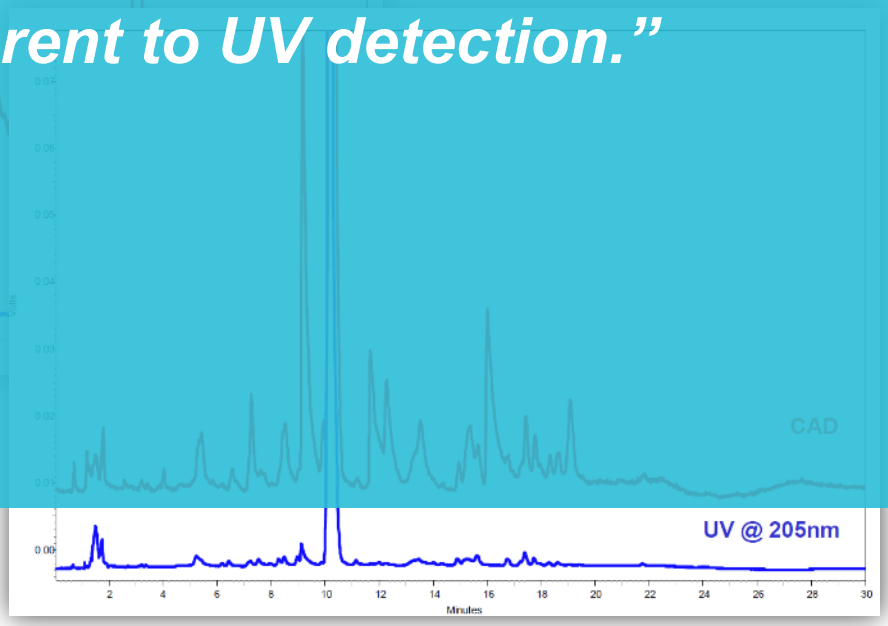

- ***"able to detect and measure a large number of compounds that were completely transparent to UV detection."***

Data from ESA Biosciences, Inc., Chelmsford, MA

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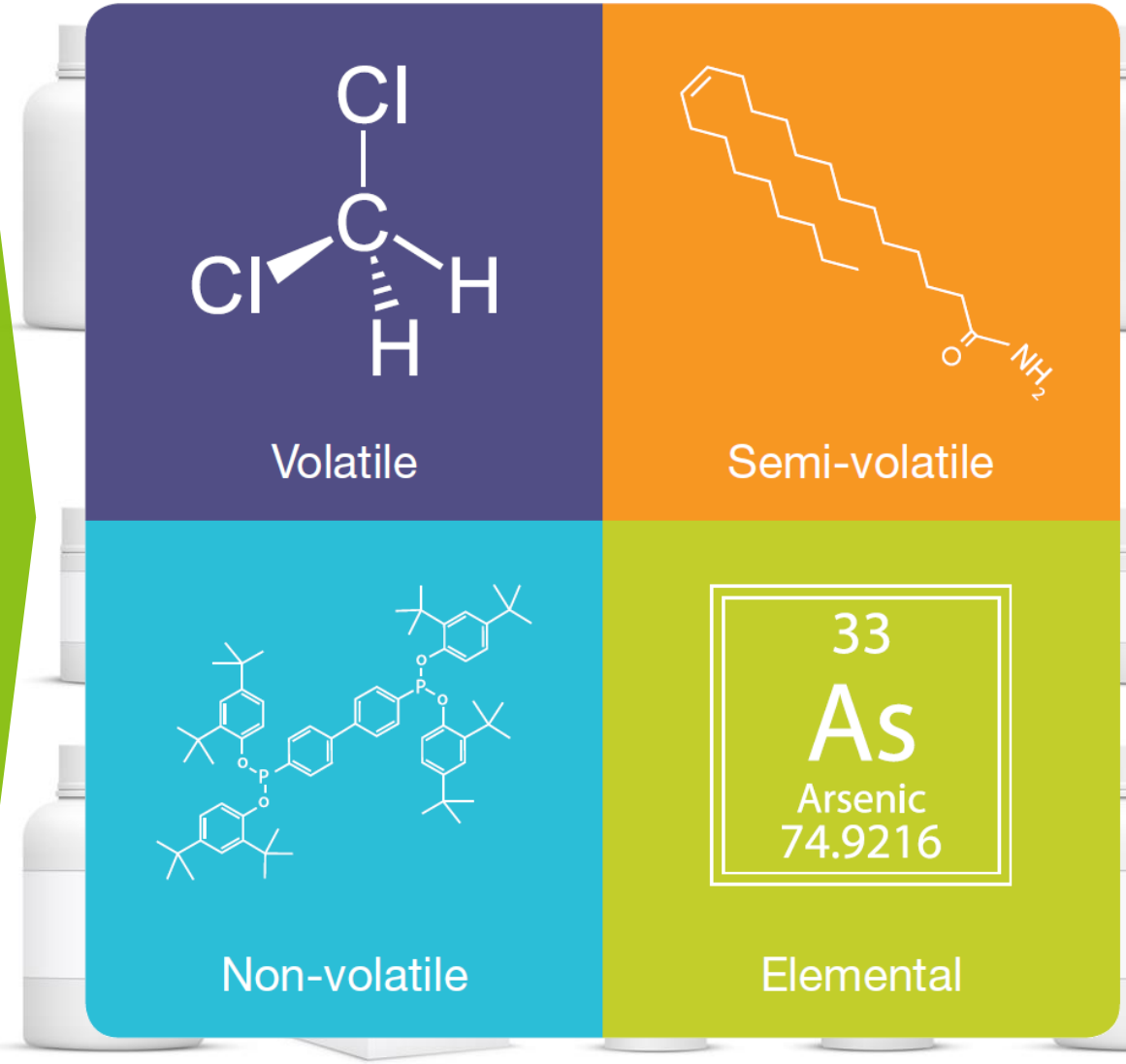
Elemental impurities



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Elemental impurity workflow

Extract

Automated dilution and standard preparation

Organic tolerant ICP-MS

Compliant data processing

- Workflow analogous to ICH Q3D and USP 232 & 233
- Demands organic tolerance and robust trace analysis
  - Polymer, extraction solvent and cell media

- Thermo Scientific™ iCAP™ RQ ICP-MS with prepFAST
- Thermo Scientific™ Qtegra™ ISDS software

ThermoFisher SCIENTIFIC

Analysis of pharmaceutical valve o-rings to USP 232/233

- Calibration Range: between 1000-fold and 10-fold dilution of lower limit
  - **R^2 better than 0.99**
- Sensitivity Verification: Analysis @ 0.5x lower limit
  - **±30% of prepared concentration**
- Accuracy Check: Spike recovery of a 0.2 mg/L solution after complete sample acidification routine
  - **±20% of expected concentration**
- Drift Check: Standard 2 (500x dilution) was analyzed every 10 samples
  - **±30% of prepared concentration**

SMITHERS RAPRA

ThermoFisher SCIENTIFIC

Analysis of pharmaceutical valve o-rings to USP 232/233

Qtegra - [Example Reporting Labbook]

Home Page | Example Reporting Labbook

Create | Column Filter

Content

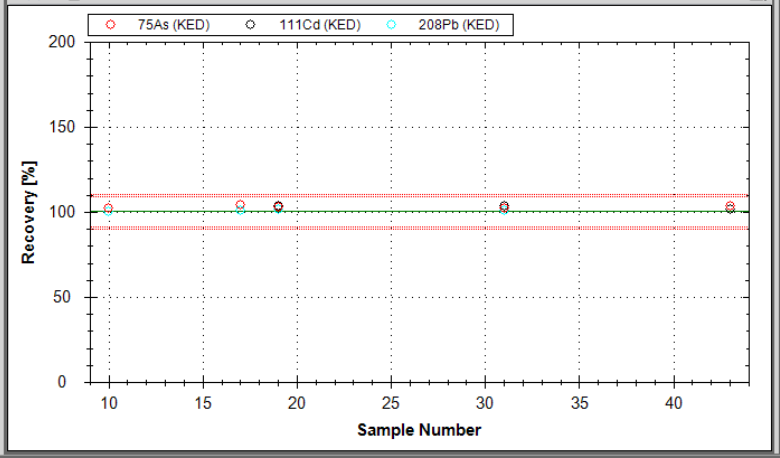
- Summary
- iCAP Q
  - Method Parameters
    - Analytes
    - Acquisition parameters
    - Monitor Analytes
    - Survey scan settings
    - Interference correction
    - Standards
    - Quantification
    - Ratios
    - Quality Control
  - Evaluation Results
    - Concentrations
    - Concentration Ratios
    - Intensities
    - Intensity Ratios
    - Survey Intensities
    - Survey Concentrations
    - Spectra View
  - Instrument State
- Cetac ASX-520
- Sample List
- Log Messages
- Signing
- Query
  - Query
- Reports

Concentrations

No	Time	Sample Type	Label	45Sc (KED)	72Ge (KED)	75As (KED) [ppb]	89Y (KED)	111Cd (KED) [pp	159Tb (KED)	208Pb (KED) [pp	232Th (KED)
21	6/17/2013 6:02:16 PM	UNKNOWN	CCB	110.3%	105.1%	0.014	103.5%	0.016	91.4%	0.017	88.0%
22	6/17/2013 6:06:04 PM	UNKNOWN	6020S MDL BLANK	86.9%	93.0%	0.017	94.7%	0.014	97.3%	0.036	99.1%
23	6/17/2013 6:09:53 PM	UNKNOWN	6020S MDL 1	86.9%	92.7%	0.532	94.8%	0.100	97.9%	0.153	101.0%
24	6/17/2013 6:13:41 PM	UNKNOWN	6020S MDL 2	87.9%	94.1%	0.517	94.8%	0.084	97.2%	0.132	99.2%
25	6/17/2013 6:17:30 PM	UNKNOWN	6020S MDL 3	88.0%	94.8%	0.561	97.0%	0.102	96.7%	0.143	100.4%
26	6/17/2013 6:21:18 PM	UNKNOWN	6020S MDL 4	86.9%	93.7%	0.508	94.7%	0.079	97.3%	0.155	98.6%
27	6/17/2013 6:25:08 PM	UNKNOWN	6020S MDL 5	87.8%	93.8%	0.502	94.6%	0.087	98.1%	0.134	99.4%
28	6/17/2013 6:28:57 PM	UNKNOWN	6020S MDL 6	85.5%	92.8%	0.511	93.5%	0.081	97.2%	0.123	100.5%
29	6/17/2013 6:32:45 PM	UNKNOWN	6020S MDL 7	86.7%	91.8%	0.554	94.0%	0.105	99.1%	0.144	100.1%
30	6/17/2013 6:36:34 PM	UNKNOWN	6020S MDL 8	84.8%	90.7%	0.509	94.8%	0.081	96.9%	0.132	100.2%
31	6/17/2013 6:40:23 PM	QC - CCV	CCV	91.0%	96.8%	204.956 (102.5%)	96.8%	206.580 (103.3%)	98.0%	201.981 (101.0%)	99.8%
32	6/17/2013 6:44:12 PM	UNKNOWN	CCB	94.5%	97.4%	0.058	96.0%	0.045	95.8%	0.046	95.4%
33	6/17/2013 6:48:00 PM	UNKNOWN	CCB	96.2%	98.6%	0.052	98.6%	0.053	94.5%	0.059	93.7%
34	6/17/2013 6:51:39 PM	UNKNOWN	6020S halfMDL BLAN	84.6%	90.1%	-0.004	92.2%	0.005	96.6%	0.022	100.3%
35	6/17/2013 6:55:28 PM	UNKNOWN	6020S halfMDL 1	82.6%	89.2%	0.267	91.9%	0.039	96.0%	0.068	99.3%
36	6/17/2013 6:59:16 PM	UNKNOWN	6020S halfMDL 2	82.7%	89.2%	0.258	92.3%	0.039	97.5%	0.065	99.3%
37	6/17/2013 7:03:05 PM	UNKNOWN	6020S halfMDL 3	82.3%	88.8%	0.254	92.2%	0.045	96.1%	0.070	98.6%
38	6/17/2013 7:06:53 PM	UNKNOWN	6020S halfMDL 4	82.4%	88.0%	0.280	90.0%	0.037	95.8%	0.063	98.0%
39	6/17/2013 7:10:42 PM	UNKNOWN	6020S halfMDL 5	82.0%	89.1%	0.267	89.4%	0.036	95.5%	0.064	98.7%
40	6/17/2013 7:14:31 PM	UNKNOWN	6020S halfMDL 6	82.5%	87.8%	0.253	90.4%	0.044	94.4%	0.068	99.5%
41	6/17/2013 7:18:19 PM	UNKNOWN	6020S halfMDL 7	82.6%	88.0%	0.251	92.2%	0.036	95.0%	0.062	98.9%
42	6/17/2013 7:22:08 PM	UNKNOWN	6020S halfMDL 8	82.5%	88.0%	0.256	92.7%	0.034	95.9%	0.062	98.6%
43	6/17/2013 7:25:57 PM	QC - CCV	CCV	89.1%	92.0%	207.303 (103.7%)	95.4%	203.082 (101.5%)	96.5%	203.752 (101.9%)	97.6%
44	6/17/2013 7:29:45 PM	UNKNOWN	CCB	92.5%	94.3%	0.078	93.9%	0.072	93.8%	0.085	93.9%
45	6/17/2013 7:33:33 PM	UNKNOWN	CCB	97.2%	96.4%	0.054	96.0%	0.054	95.6%	0.056	93.8%

Details

75As (KED) 111Cd (KED) 208Pb (KED)



Sample list line 43:

Add Comment

Status: Success
Creation: Added during runtime
Description:
Comment:
Start time: 6/17/2013 7:25:57 PM
Stop time: 6/17/2013 7:29:45 PM
User name: iCAPQ-PC\iCAPQ

Quality control

CCV test passed.

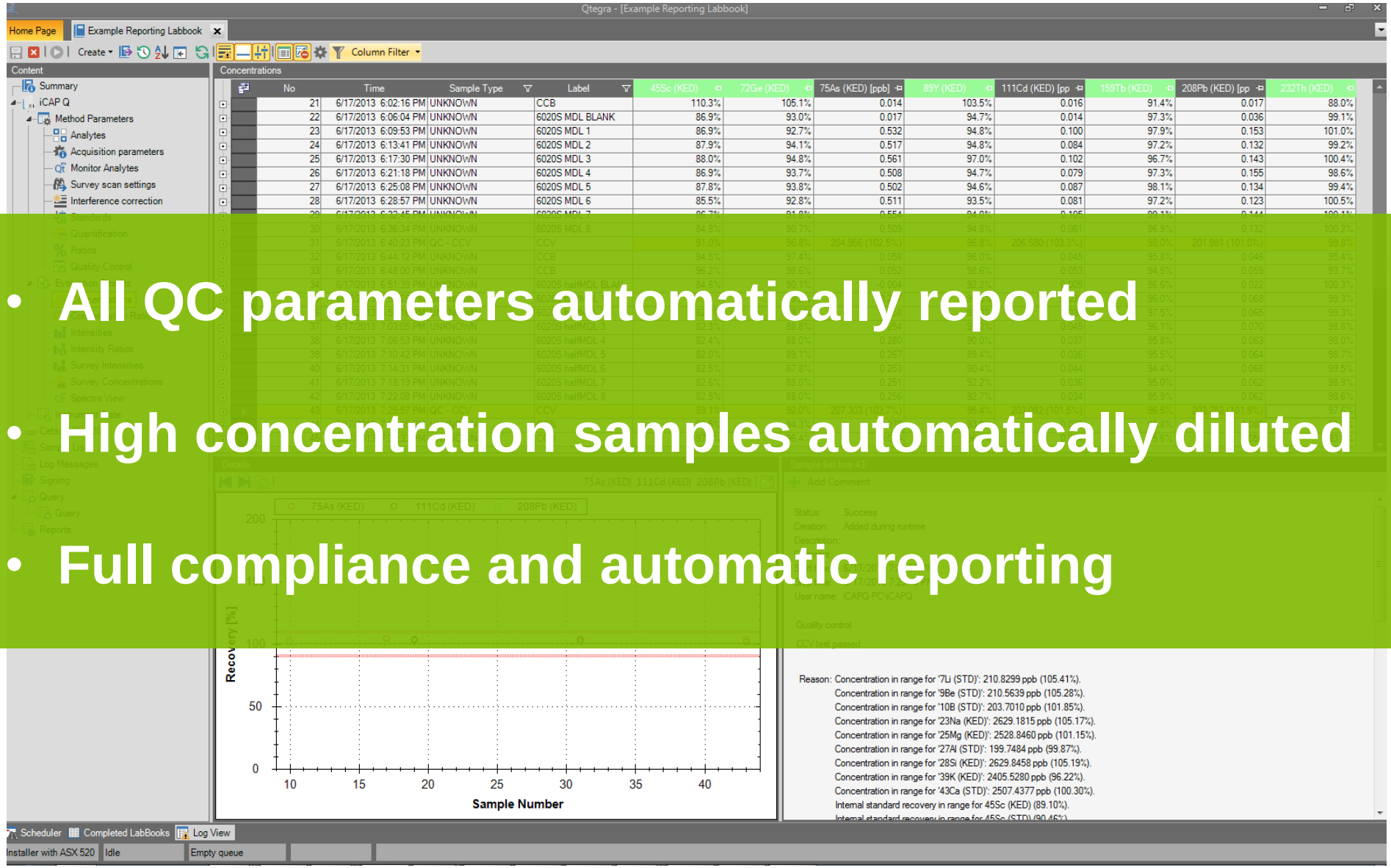
Reason: Concentration in range for '7Li (STD)': 210.8299 ppb (105.41%).
Concentration in range for '9Be (STD)': 210.5639 ppb (105.28%).
Concentration in range for '10B (STD)': 203.7010 ppb (101.85%).
Concentration in range for '23Na (KED)': 2629.1815 ppb (105.17%).
Concentration in range for '25Mg (KED)': 2528.8460 ppb (101.15%).
Concentration in range for '27Al (STD)': 199.7484 ppb (99.87%).
Concentration in range for '28Si (KED)': 2629.8458 ppb (105.19%).
Concentration in range for '39K (KED)': 2405.5280 ppb (96.22%).
Concentration in range for '43Ca (STD)': 2507.4377 ppb (100.30%).
Internal standard recovery in range for 45Sc (KED) (89.10%).

Scheduler | Completed LabBooks | Log View

Installer with ASX 520 | Idle | Empty queue

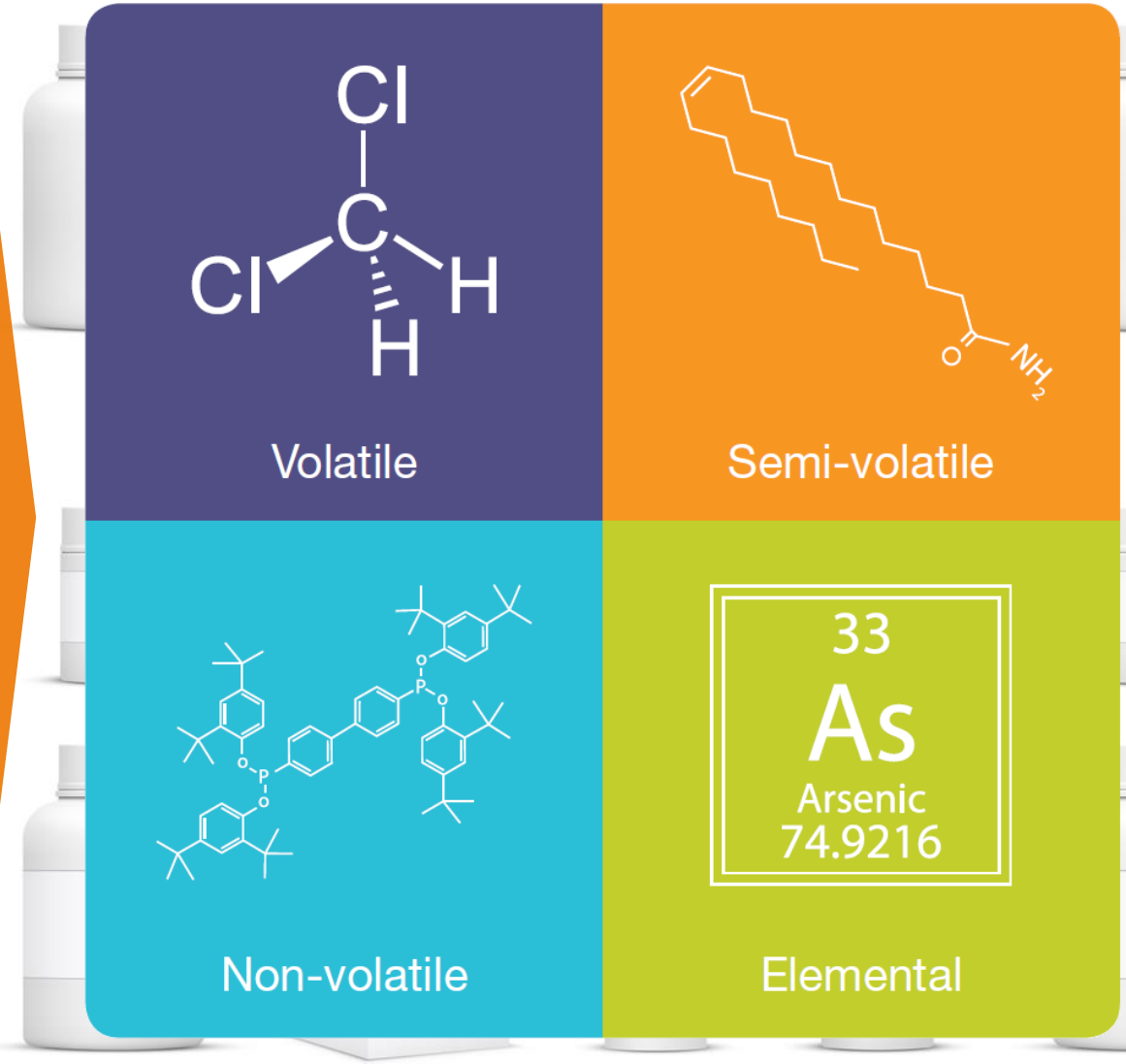
ThermoFisher SCIENTIFIC

Analysis of pharmaceutical valve o-rings to USP 232/233



- **All QC parameters automatically reported**
- **High concentration samples automatically diluted**
- **Full compliance and automatic reporting**

Semi-volatiles



ThermoFisher SCIENTIFIC

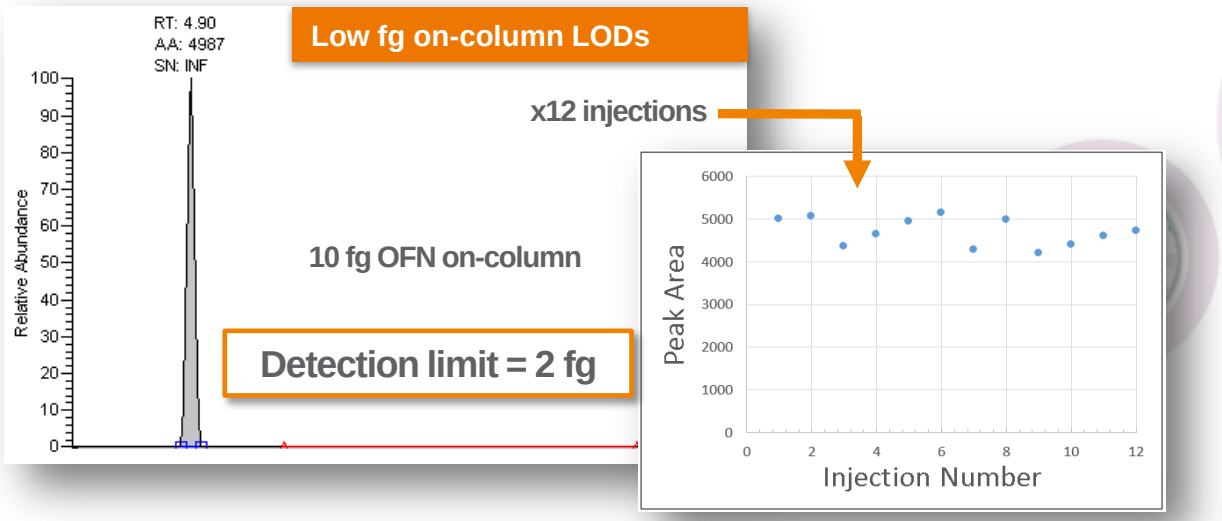
Semi-volatile impurity identification and quantification workflow

Extract | Separate | Identify with confidence of HRAM MS/MS | Software to search, elucidate & confirm

- Deconvolve, identify and quantify even the narrowest GC peaks
- Unambiguously calculate empirical formulae without needing to average scans
- Simplify data review and report

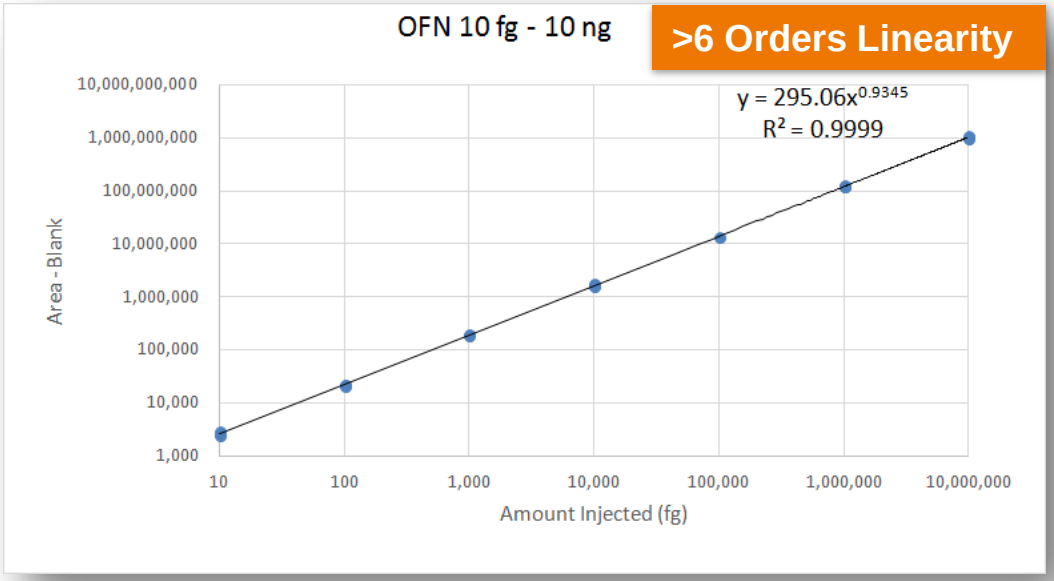
- Thermo Scientific™ Q Exactive™ GC system
- Thermo Scientific™ TraceFinder™ software

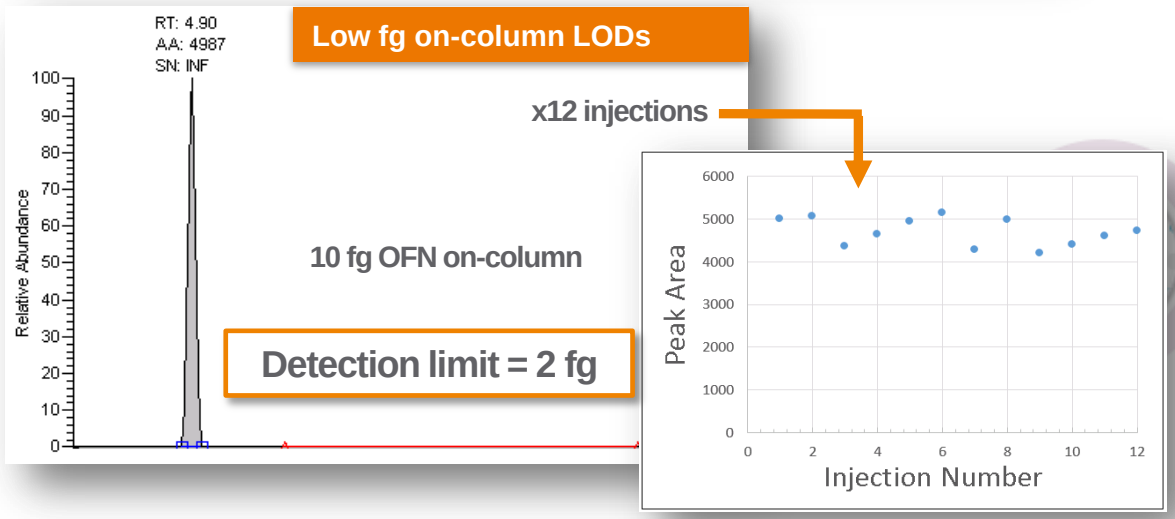
Detect, quantify and identify at any concentration



ThermoFisher SCIENTIFIC

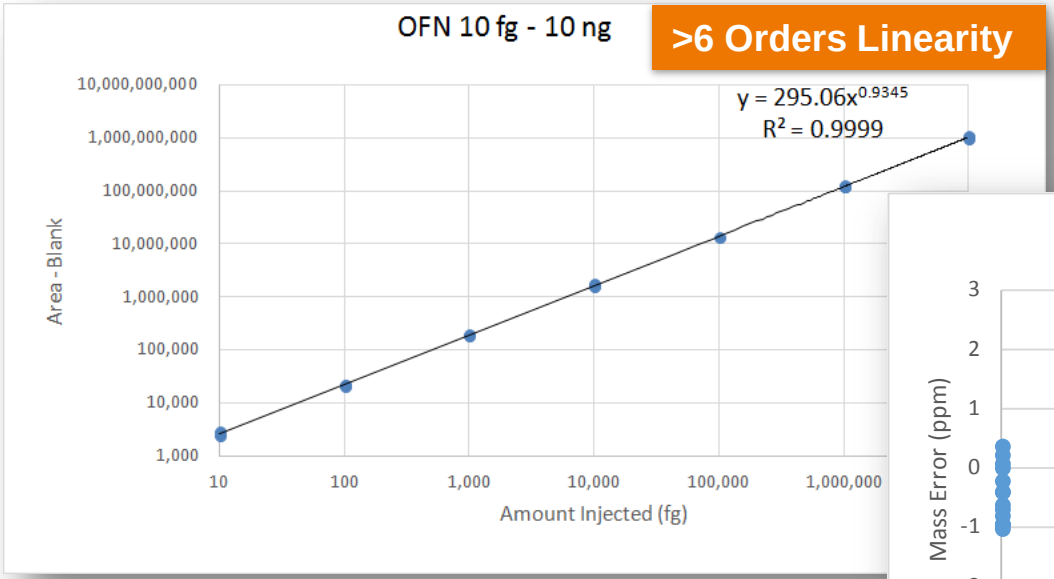
Detect, quantify and identify at any concentration

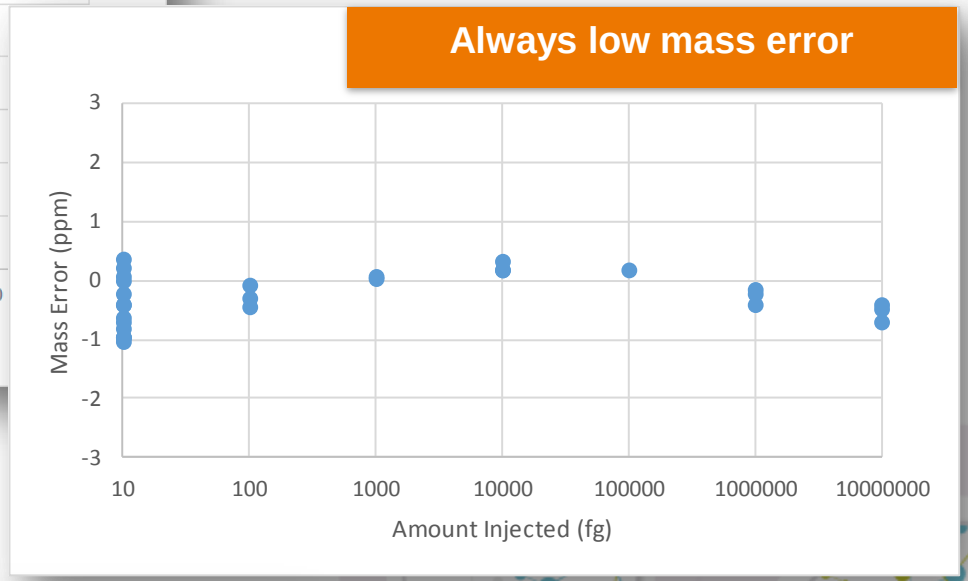


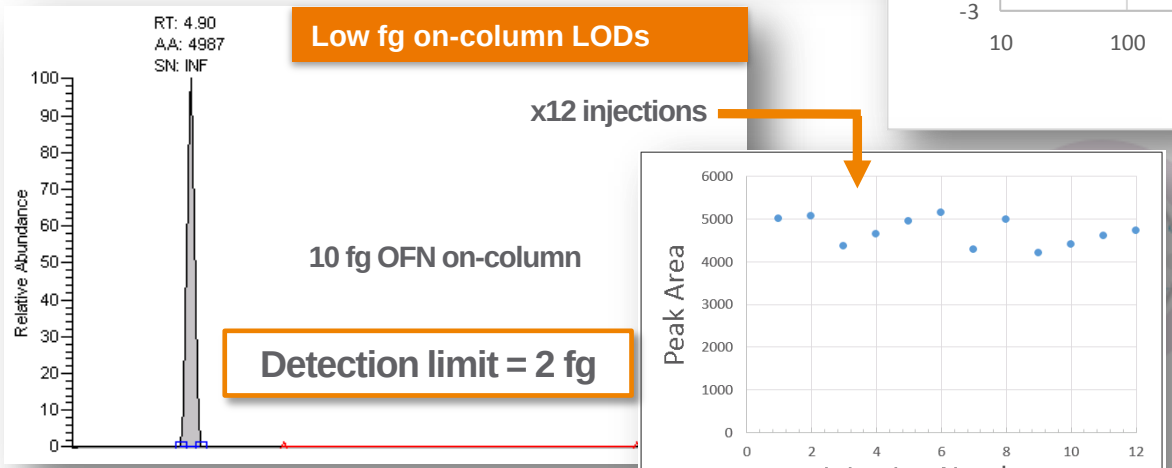


ThermoFisher SCIENTIFIC

Detect, quantify and identify at any concentration

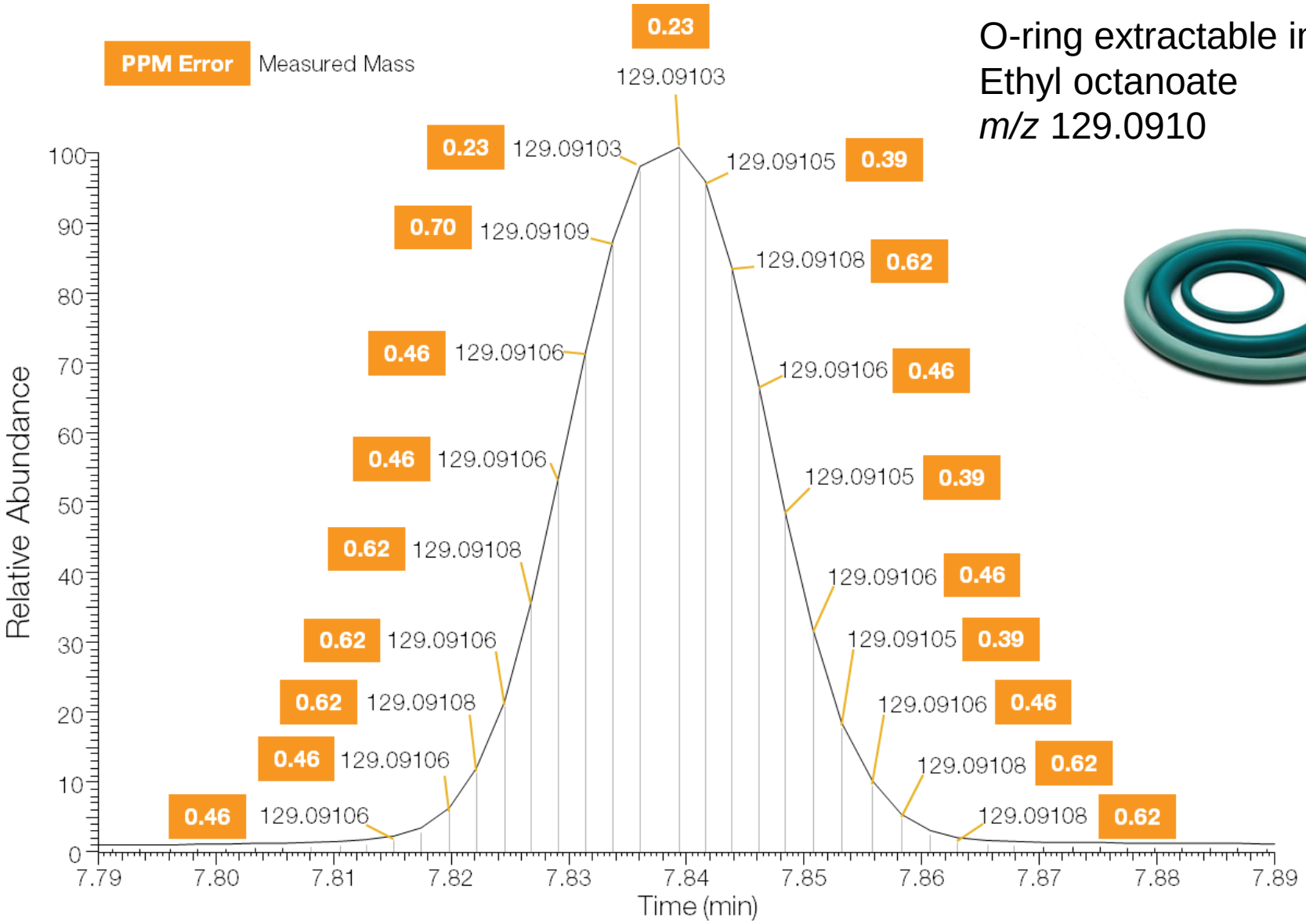






ThermoFisher SCIENTIFIC

Scan speed and accurate mass error across a peak



O-ring extractable impurity
Ethyl octanoate
m/z 129.0910

ThermoFisher SCIENTIFIC

Isolate peaks of interest, identify with confidence

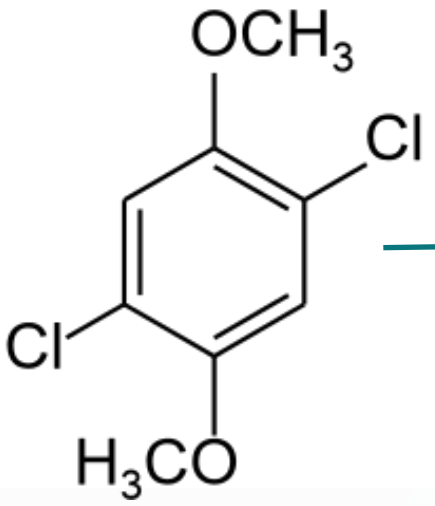
- Heat map shows peaks elevated in sample versus control

- Simple intuitive data interpretation
- Easily quantify

ThermoFisher SCIENTIFIC

High Resolution Filtering

Candidate Compounds



Subset formulae

$C_8H_8Cl_2O_2$

Acq m/z	Fragment ID	Theo m/z	Mass Error (ppm)
147.9477	$C_5Cl_2H_2O$	147.9477	0.20277
148.9369	$C_5Cl[37]ClHO$	148.9369	0.2679
149.9448	$C_5Cl[37]ClH_2O$	149.9448	0.06602
151.9419	$C_5[37]Cl_2\ H_2O$	151.9418	0.72528
154.9895	$C_7ClH_4O_2$	154.9894	0.38712
155.9974	$C_7ClH_5O_2$	155.9973	0.89745
157.9943	$C_7[37]ClH_5O_2$	157.9943	0.25381
159.9479	$C_6Cl_2H_2O$	159.9477	0.87529
161.9446	$C_6\ Cl[37]ClH_2O$	161.9448	0.80213
162.9711	$C6Cl_2H_5O$	162.9712	0.36816
163.9745	$C_5[13]CCl_2H_5O$	163.9745	0.3342
164.9682	$C_6Cl[37]ClH_5O$	164.9682	0.24186
165.9716	$C_5CCl[37]ClH_5O$	165.9716	0.02832

$$\text{HRF Score} = \frac{\sum (m/z * \text{Intensity})_{explained}}{\sum (m/z * \text{Intensity})_{observed}} \times 100\%$$

Confidently identify

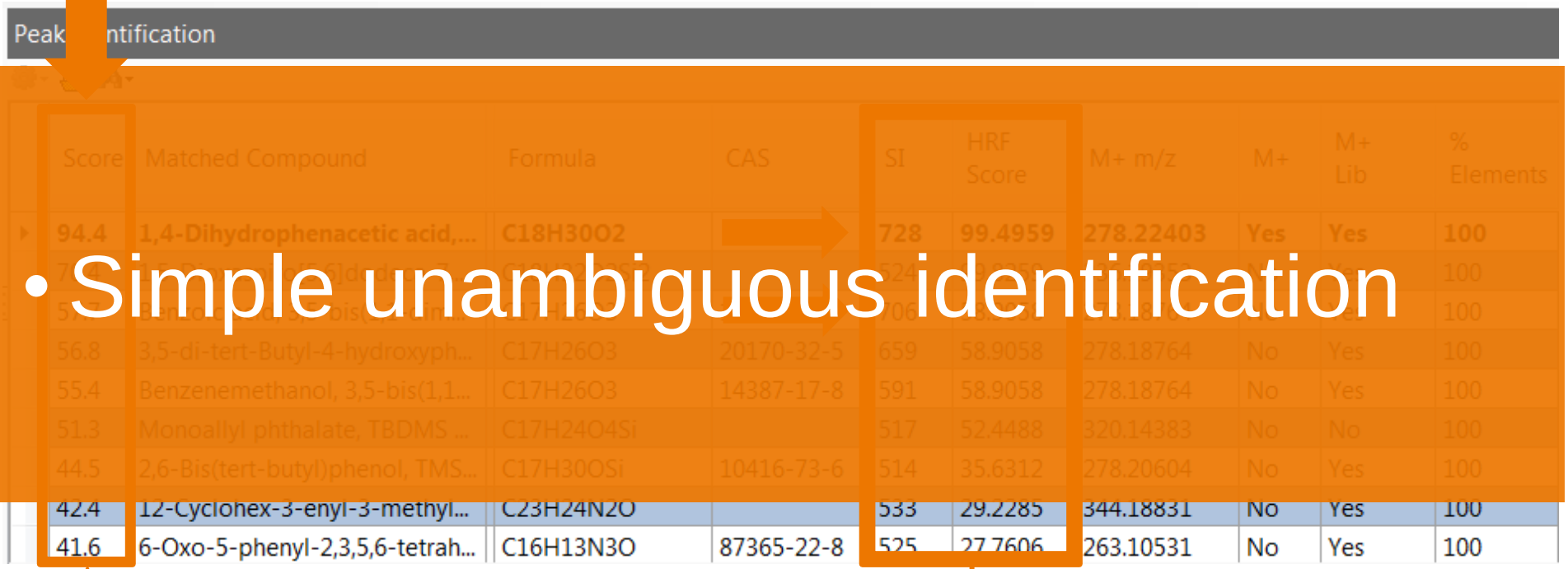
Combined SI and HRF values give an overall score (%) to quickly and confidently identify the compound. Eliminates other hits that would be valid if only SI used.

Peak ntification

Score	Matched Compound	Formula	CAS	SI	HRF Score	M+ m/z	M+	M+ Lib	% Elements
94.4	**1,4-Dihydrophenacetic acid,...**	**C18H30O2**		**728**	**99.4959**	**278.22403**	**Yes**	**Yes**	**100**
70.4	1,5-Dioxaspiro[5.6]dodeca-7,...	C18H32O2Si2		524	99.8259	336.19353	No	Yes	100
57.7	Benzoic acid, 3,5-bis(1,1-dim...	C17H26O3		706	58.9058	278.18764	No	Yes	100
56.8	3,5-di-tert-Butyl-4-hydroxyph...	C17H26O3	20170-32-5	659	58.9058	278.18764	No	Yes	100
55.4	Benzenemethanol, 3,5-bis(1,1...	C17H26O3	14387-17-8	591	58.9058	278.18764	No	Yes	100
51.3	Monoallyl phthalate, TBDMS ...	C17H24O4Si		517	52.4488	320.14383	No	No	100
44.5	2,6-Bis(tert-butyl)phenol, TMS...	C17H30OSi	10416-73-6	514	35.6312	278.20604	No	Yes	100
42.4	12-Cyclohex-3-enyl-3-methyl...	C23H24N2O		533	29.2285	344.18831	No	Yes	100
41.6	6-Oxo-5-phenyl-2,3,5,6-tetrah...	C16H13N3O	87365-22-8	525	27.7606	263.10531	No	Yes	100

Confidently identify

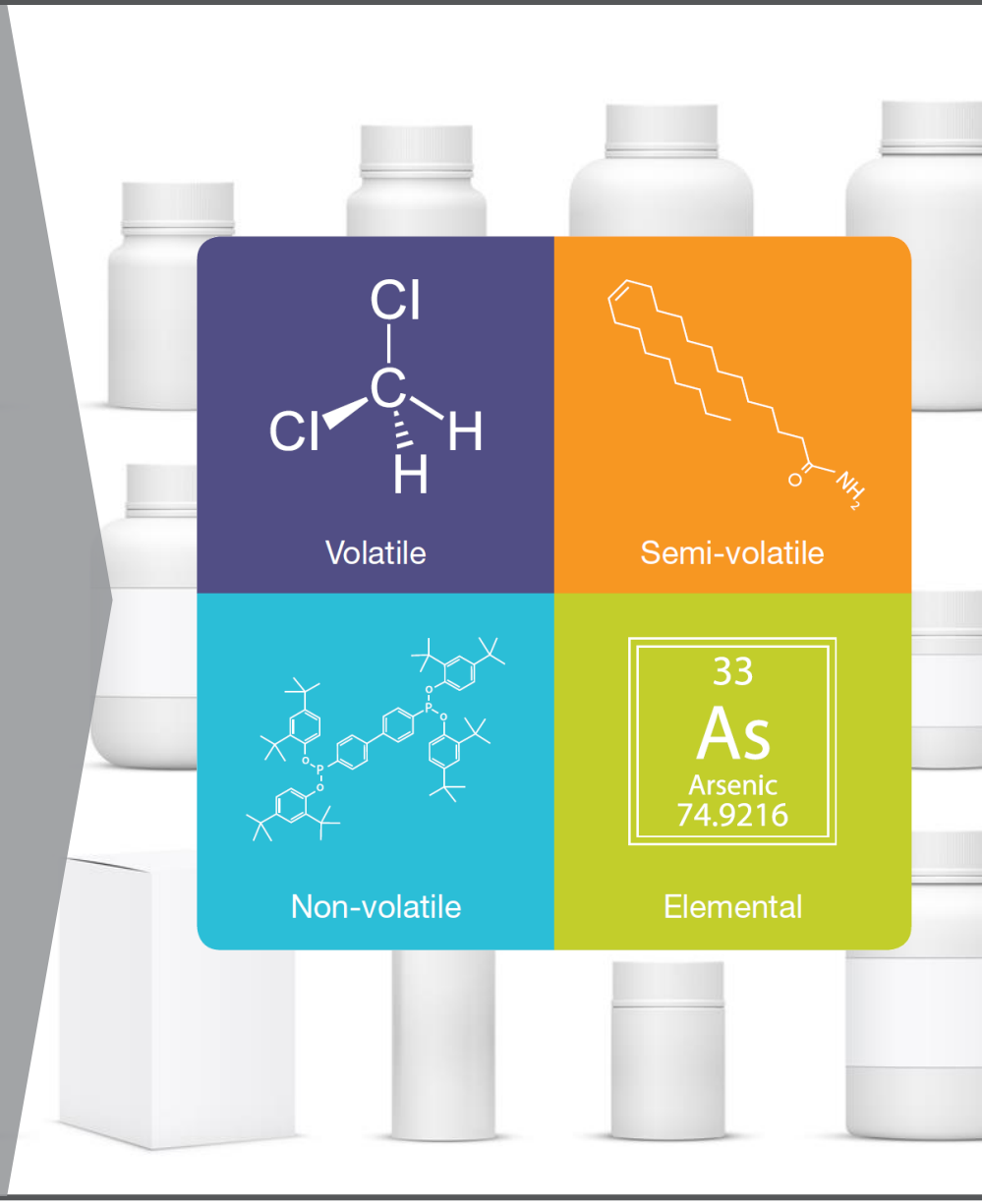
Combined SI and HRF values give an overall score (%) to quickly and confidently identify the compound. Eliminates other hits that would be valid if only SI used.



- Simple unambiguous identification

ThermoFisher SCIENTIFIC

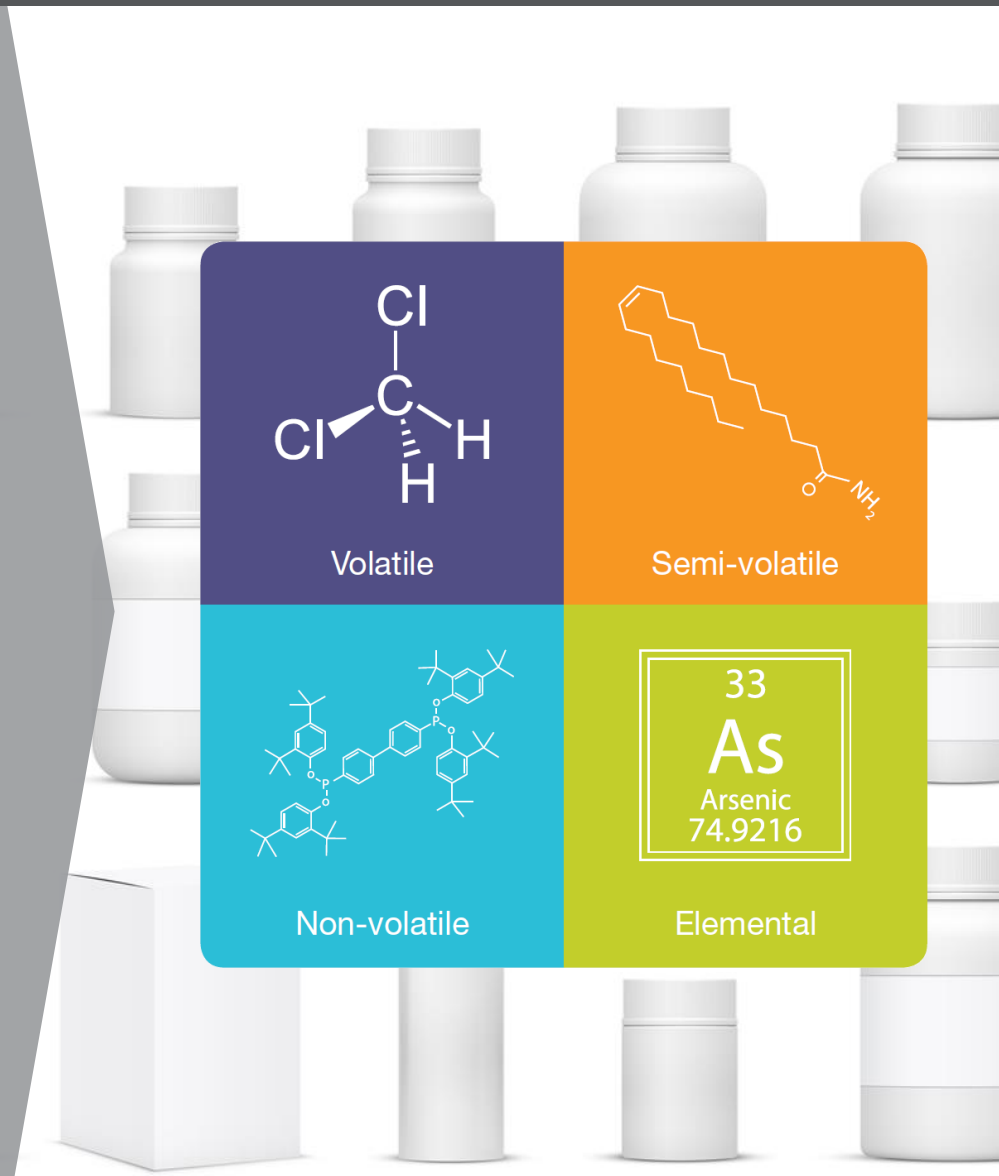
Complete capabilities for Extractables & Leachables



ThermoFisher SCIENTIFIC

Complete capabilities for Extractables & Leachables

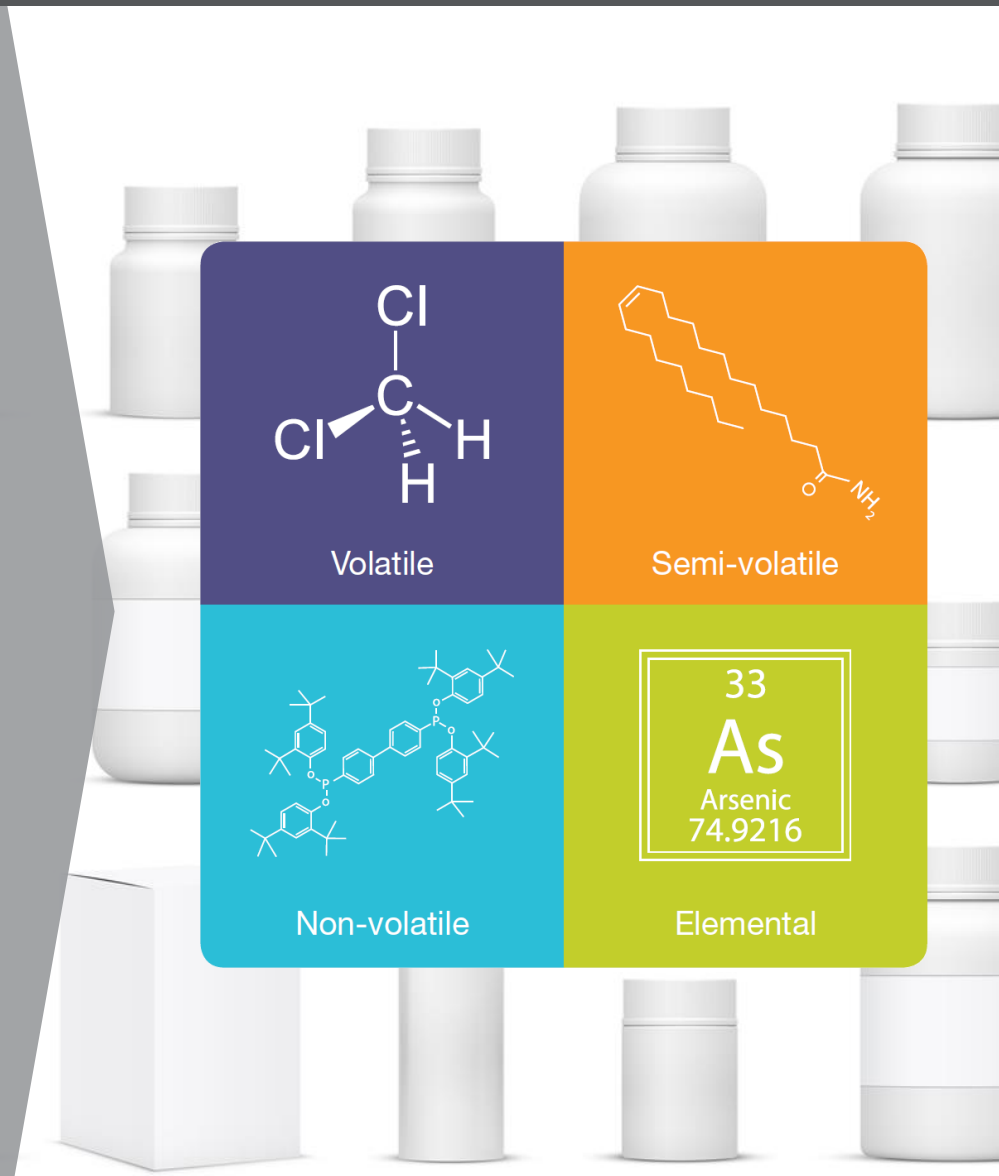
- **Confidently quantify**



ThermoFisher SCIENTIFIC

Complete capabilities for Extractables & Leachables

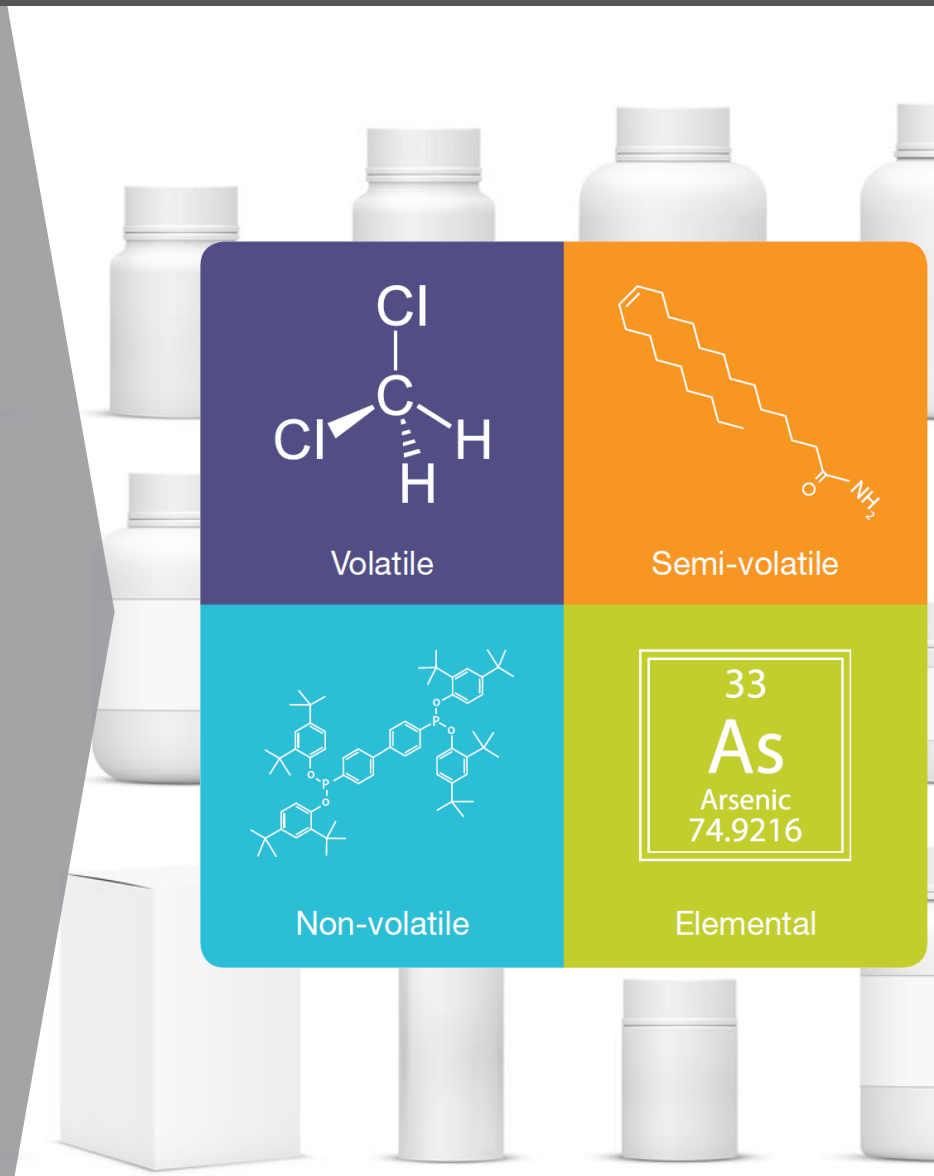
- **Confidently quantify**
- **Unambiguously identify**



ThermoFisher SCIENTIFIC

Complete capabilities for Extractables & Leachables

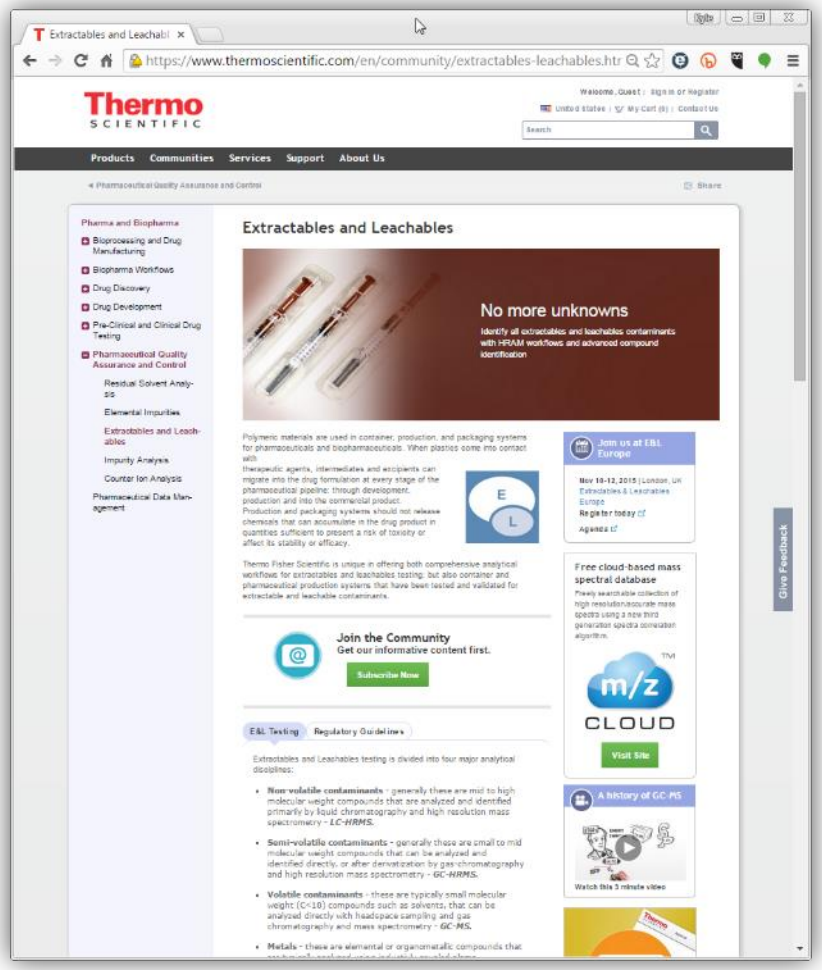
- **Confidently quantify**
- **Unambiguously identify**
- **Easily report**



ThermoFisher SCIENTIFIC

E&L Resources

- Webinars
- Applications
- Blogs
- Regulatory updates
- White papers
- And more…



www.thermoscientific.com/Leachables

ThermoFisher SCIENTIFIC

Thank you

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