Choosing LC Columns and Sample Prep Options for Biological Matrices

Jason Link, PhD

Overview of Biological Matrices

- **Samples include:**
  - Small molecule analytes
- **Matrices are biological fluids**
  - Plasma
  - Blood
  - Urine
  - Oral Fluids

- **Fast analyses, high-throughput sample processing**
  - Minimize column plugging to increase column lifetime
  - Reduce re-runs and repeat samples
  - Get the answer right, the first time, every time
  - Consistent performance, day in and day out

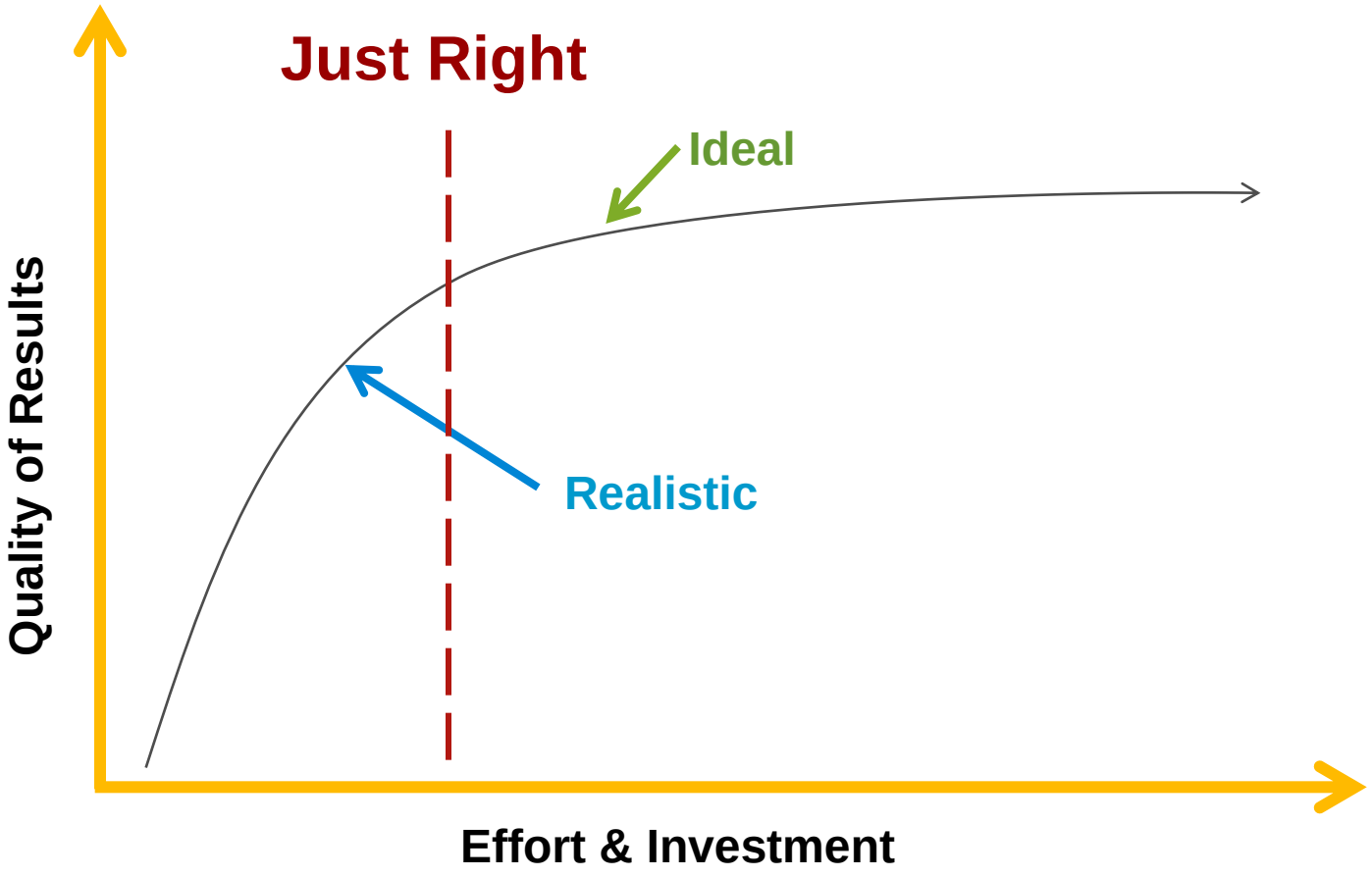
LC and Sample Prep Method Development for Biological Matrices

What's different in LC analysis with biological matrices?

- Sample matrix complexity
- Multiple components of interest
- Utilized along with MS detection

Modern column and sample prep technologies can make these analyses faster, while minimizing workflow interruptions!

Striking the Right Balance in Sample Preparation



Agilent Sample Preparation Products

Bond Elut Solid Phase Extraction

- ✓ Bond Elut Plexa Polymeric SPE
- ✓ Bond Elut Certify SPE
- ✓ SPEC disc SPE
- ✓ Bond Elut QuEChERS

Chem Elut SLE

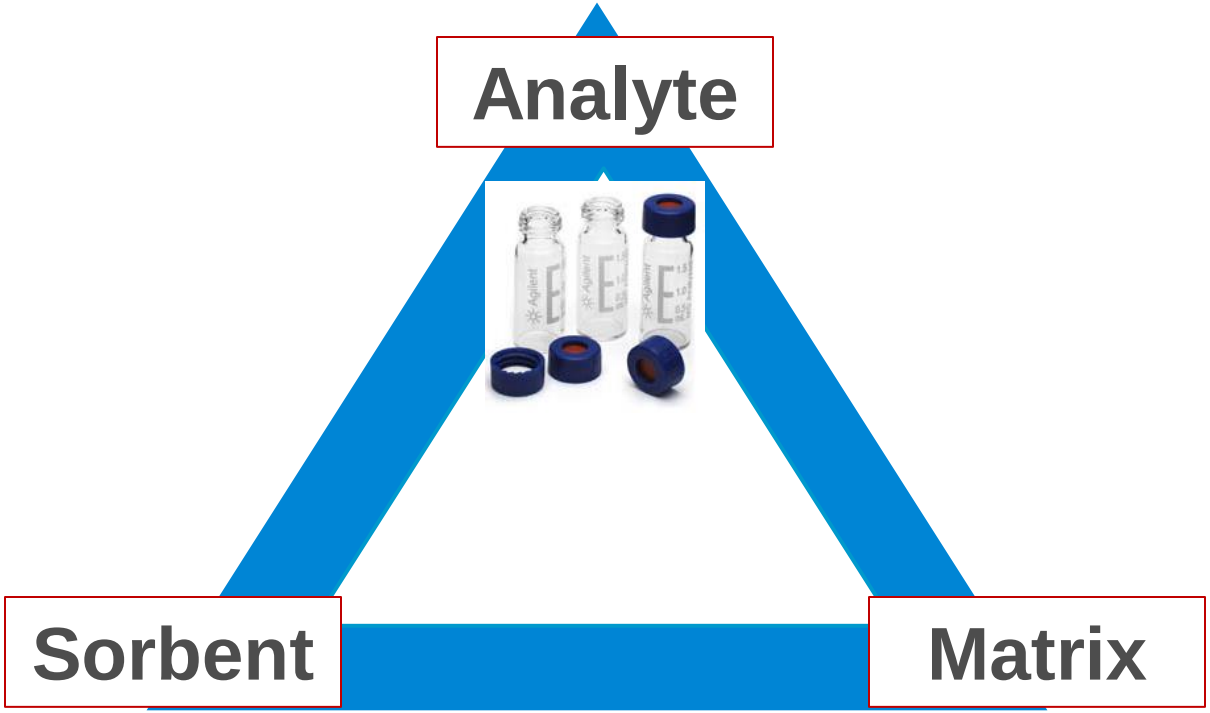
- ✓ Chem Elut SLE
- ✓ Tox Elut SLE
- ✓ Chem Elut Plus SLE
- ✓ Combilute SLE
- ✓ Hydromatrix

Captiva Filtration

- ✓ Captiva Syringe Filters, cartridges, and plates
- ✓ Captiva Non-Drip and ND Lipids cartridges and plates

Sample Preparation Considerations

We often talk about a “triangle” – but the questions about sample prep and SPE are more complex than this simple model



Other Sample Prep Considerations

- ✓ Analytical goals
- ✓ Published methods
- ✓ Instrument availability
- ✓ Skill and expertise
- ✓ Regulations
- ✓ Sample Size
- ✓ Detection limits
- ✓ Cost per sample
- ✓ Lab setup and supplies – investment
- ✓ Automation needs

Practical Approaches to Selecting a Sample Preparation Method


Interferences to Remove


Application Type


Matrix or Sample


Format for Automation

C18
Current Product Alternative


Journal Article, Application Note, or Book


Interactive Selection Guides

Sample Preparation Selection: Interference Removal Needs

	More Specific ←			Instrument Separation and Detection Specificity			← *Less Specific*	
	Less Specific →			*Sample Preparation Specificity*			→ *More Specific*	
Sample Prep Technique / Interference Removed	**Dilute & Shoot**	**Filtration**	**Liquid/Liquid Extractions**	**Supported Liquid Extractions (SLE)**	**Precipitation filtration**	**QuEChERS**	**Precipitation-Lipid Removal 'Hybrid' Filtration**	**Solid Phase Extraction**
Lipids	No	No	No	Some	No	Yes	Yes	Yes
Oligomeric Surfactants	No	No	No	No	No	No	Yes	Yes
Particulates	No	Yes	No	Some	Yes	Yes	Yes	Yes
Pigments	No	No	No	Some	No	Yes	No	Yes
Polar Organic Acids	No	No	Yes	Yes	No	Yes	No	
Proteins	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Salts	No	No	Yes	Yes	No	No	No	Yes

Filtration is suggested with any LC or GC method of sample preparation

Column Technologies for Method Development

Columns for high resolution and high speed analysis

- Sub-2 µm columns for ultra-high pressure operation
- Sub-3 µm superficially porous columns

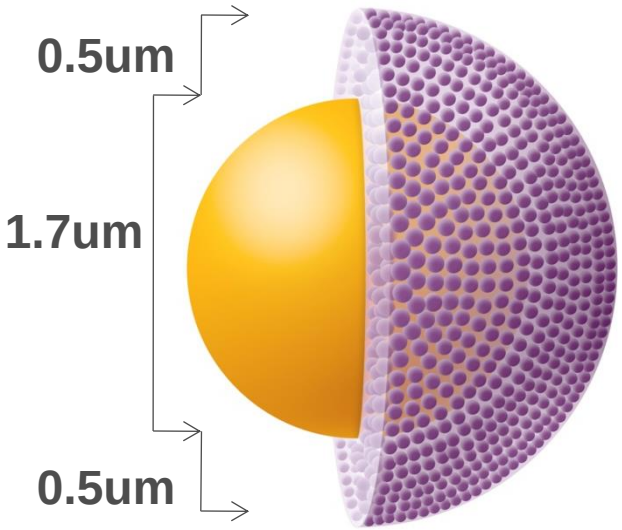
Considerations when developing methods on new column technologies

- Particle size < 3 µm
- Column pressure limits >400 bar (600-1200 bar typical)
- Other factors remain same as for legacy, 5 µm columns

Superficially Porous Column Technologies

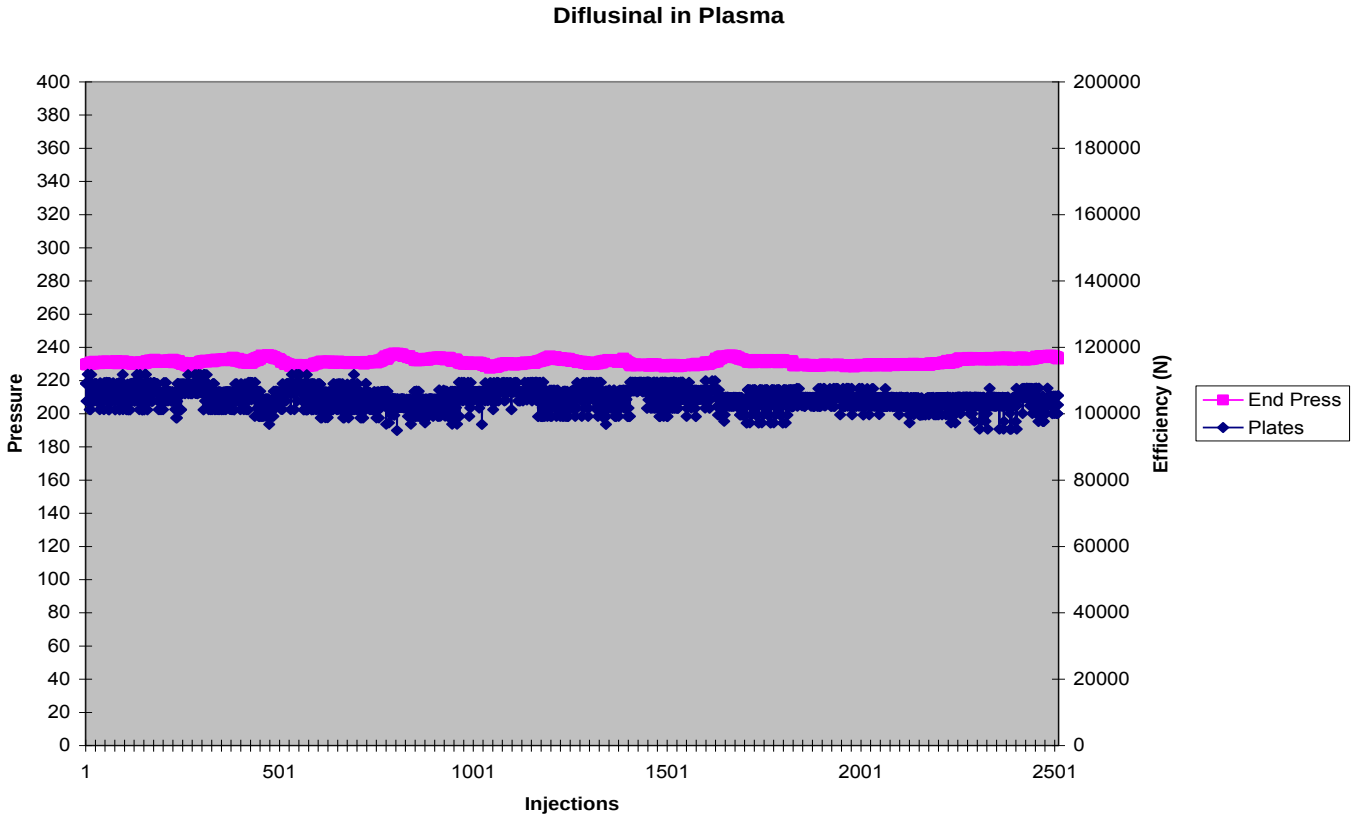
Poroshell 120 columns:

- **Efficiency ≈ 90% of sub-2 µm**
- **Pressure ≈ 40-50% of sub-2 µm**
- **N ≈ 2X 3.5 µm (totally porous)**
- **d_p = 2.7µm**
- **2 µm frit to reduce clogging**
- **P_{limit} = 600 bar for HPLC or UHPLC**
- **Particles**
  - **1.7 µm solid core**
  - **0.5 µm diffusion path**
  - **2.7 µm total diameter**



Poroshell 120 Resists Plugging with 2 µm Frit Challenging Plasma Sample

Column: Poroshell 120 EC-C18, 3.0 x 50mm, 2.7um LC: Agilent 1200 RRLC (SL)
Sample: Precipitated Plasma: 2 parts Plasma: 7 Parts 20/80 Water-MeCN w/0.1 % Formic Acid with 1 Part Diflusinal in 50/50 Water-MeCN 10 ug/ml (Final concentration Diflusinal 1 ug/ml) Shaken and allowed to settle 10 minutes
Not Centrifuged/ Not Filtered
Injection Volume: 1ul injections



Solvent A: Water w/0.1 % TFA
Solvent B: MeCN w/0.08 % TFA
Flow Rate 1 ml/min 1 ul injection

Time	% B
0	20
0.5	90
0.6	90
1.1	20
2.5	20

Poroshell 120 Column Chemistries

Poroshell 120 EC-C18 and C8

- Robust endcapped C18 for best peak shape at pH 2-9

Poroshell 120 Stablebond C18 and C8

- Robust chemistries for pH<2

Poroshell 120 Phenyl-Hexyl

- Same Eclipse Plus bonding process as ZORBAX Eclipse Plus Phenyl-Hexyl
- Excellent choice for pi-pi interactions
- Alternative selectivity to EC-C18 or SB-C18
- Selectivity similar to phenyl, diphenyl, or other phenyl-hexyl columns

10 phases!

Poroshell 120 SB-Aq

- Proprietary bonding phase is an excellent choice for polar analytes

Poroshell 120 Bonus-RP

- Embedded polar group provides unique selectivity for polar compounds

Poroshell 120 EC-CN

- Flexible endcapped CN chemistry with Normal and Reversed Phase character

Poroshell 120 HILIC

- Bare silica HILIC for use in Hydrophilic interaction chromatography of polar molecules

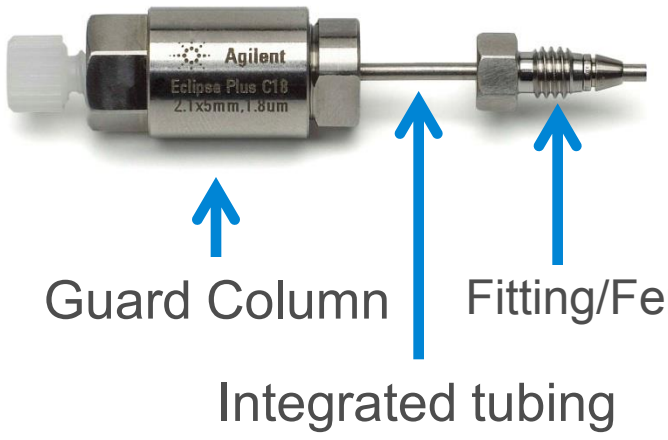
Poroshell 120 PFP

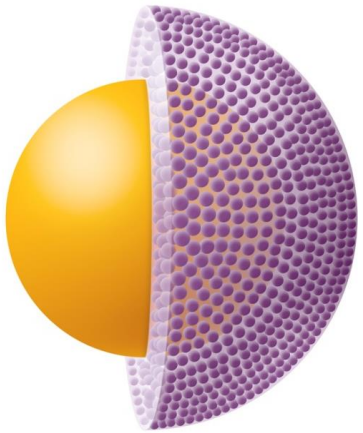
- Perfluoropehnyl chemistry for orthogonal selectivity relative to C18

Use of Guard Columns and Inline Filters

- Inline filters and guard columns extend the life of HPLC columns by preventing particulates and impurities from clogging and potentially irreversibly sticking to the analytical column
- Column lifetime is extended
- $$$ savings from fewer analytical columns purchased
- Minimal, if any, impact to the chromatography!

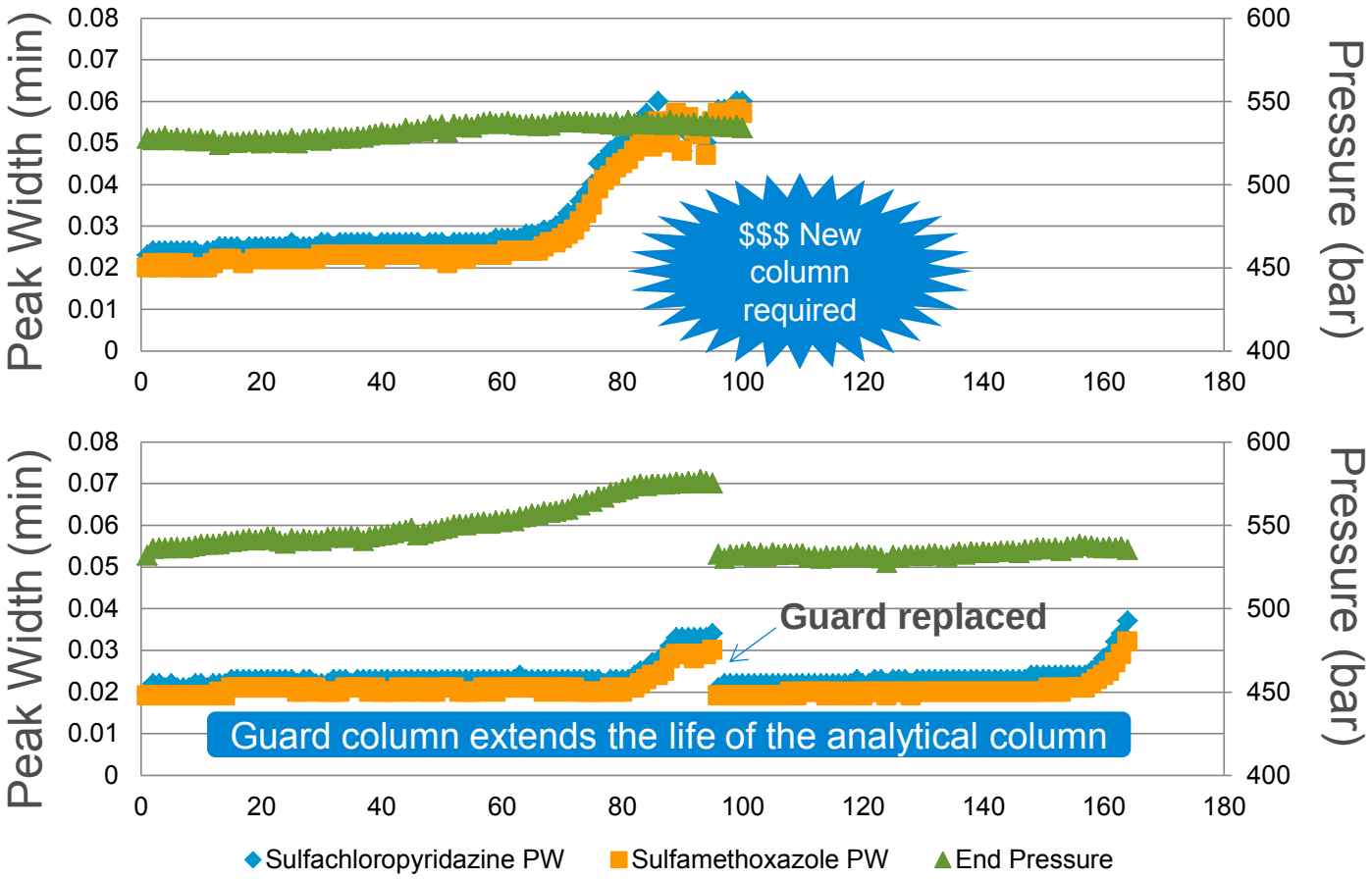
Poroshell 120
Fast Guard for UHPLC





Benefits of Installing a Fast Guard for UHPLC

Method: **Accelerated Lifetime Test** - Similac sample (milk substitute diluted 300:1) containing 2 sulfa drugs; Peak width change indicating column failure



No Guard

Column failure; new column required

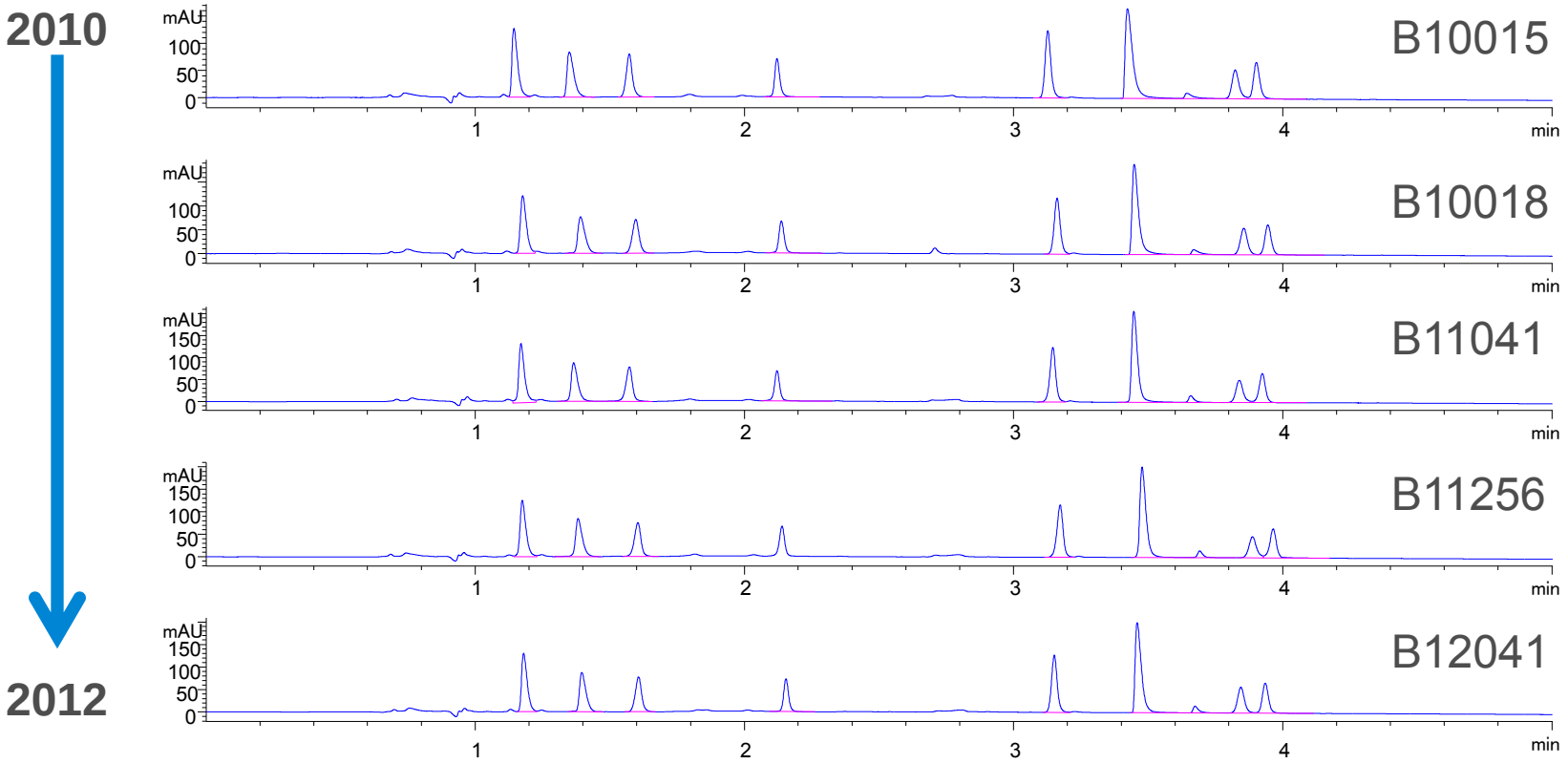
With Guard

Guard failure; guard replaced; same column used throughout analysis

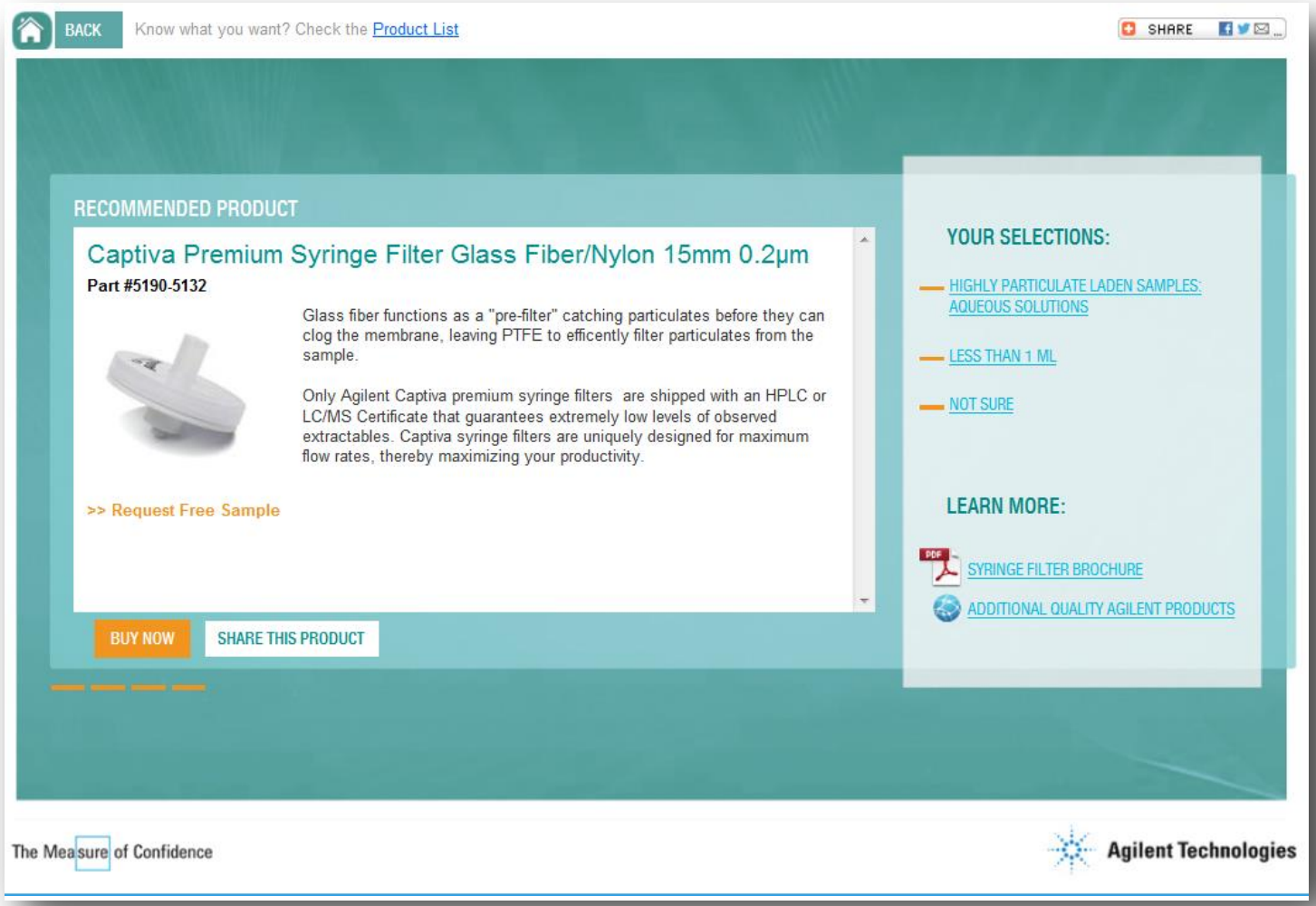
By installing a guard column when using dirtier samples, one can extend the life of their column, and utilize more inexpensive guard columns rather than column replacements

Other Considerations when Selecting a Column

- **Robustness and batch-to-batch reproducibility of Poroshell 120 columns**



Agilent Syringe Filter Selection Tool



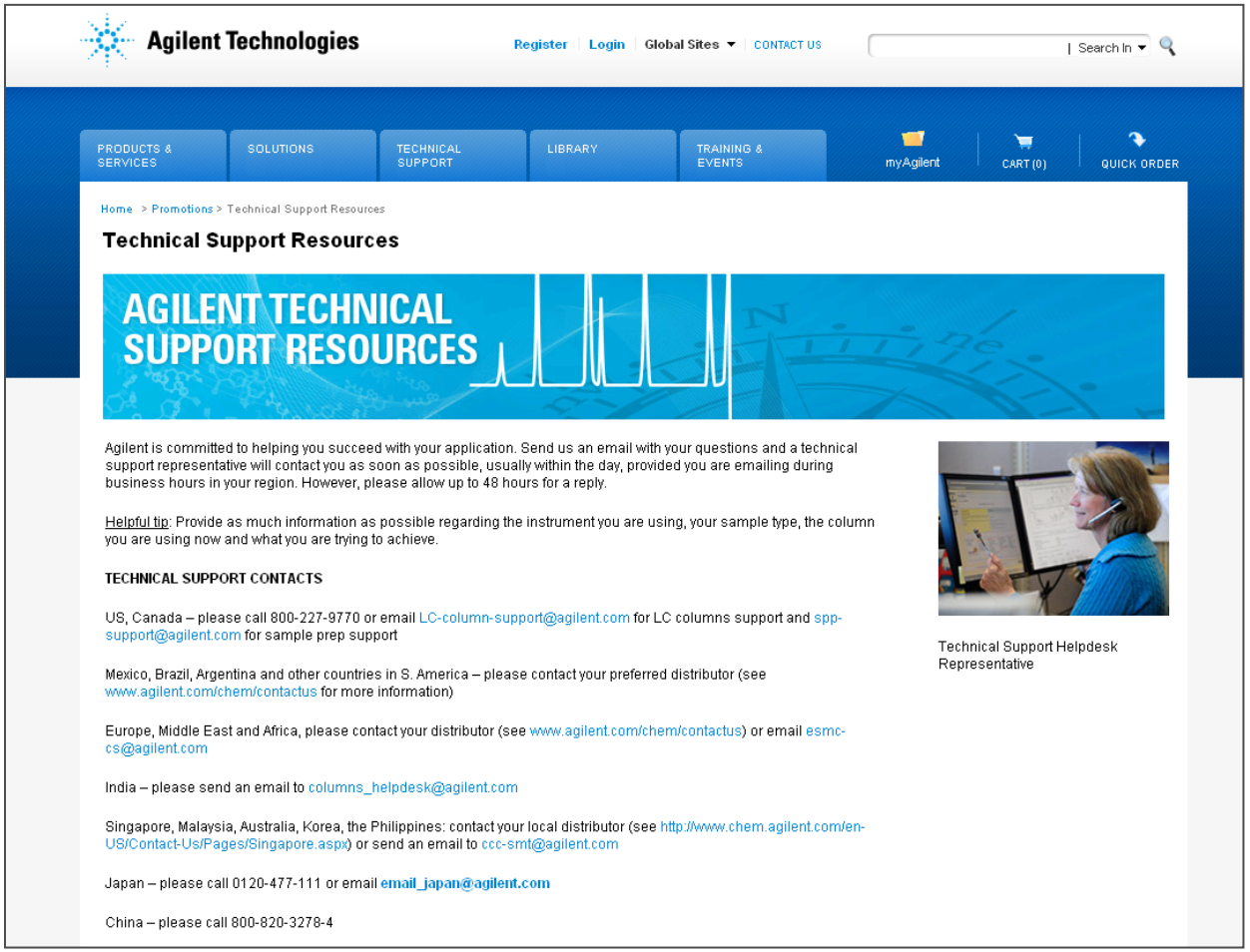
www.agilent.com/chem/SelectFilters

Agilent LC Column and Sample Preparation Navigator Tool

www.agilent.com/chem/navigator

Agilent is Here to Help

See www.agilent.com/chem/cstechsupport



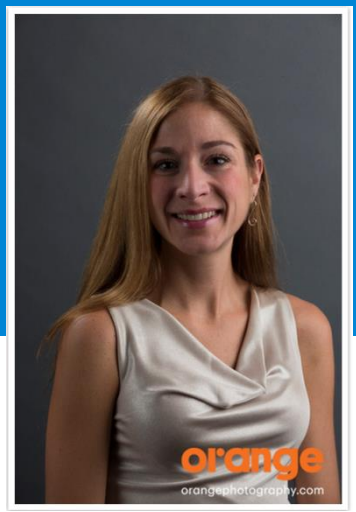
Opiates, Opioids and Benzodiazepines, Amphetamines & Illicit Drug Forensic Analysis by LC/MS

Julie Cichelli, PhD

Agilent Technologies

Application Engineer

April 29, 2014

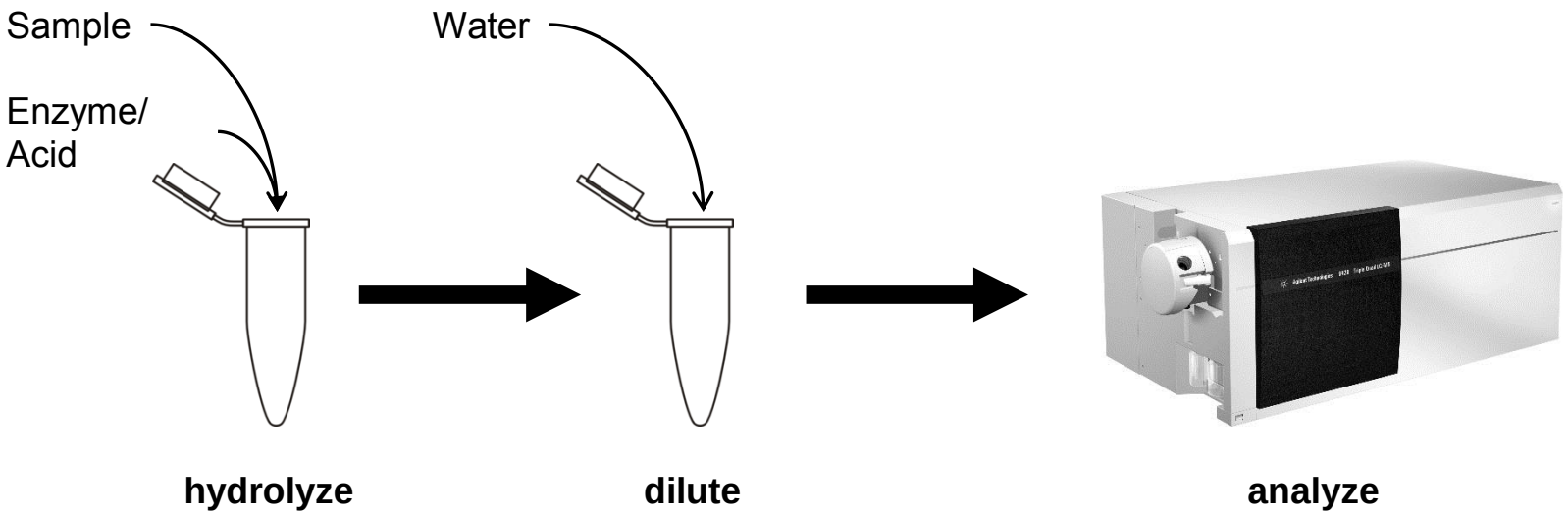


Agenda

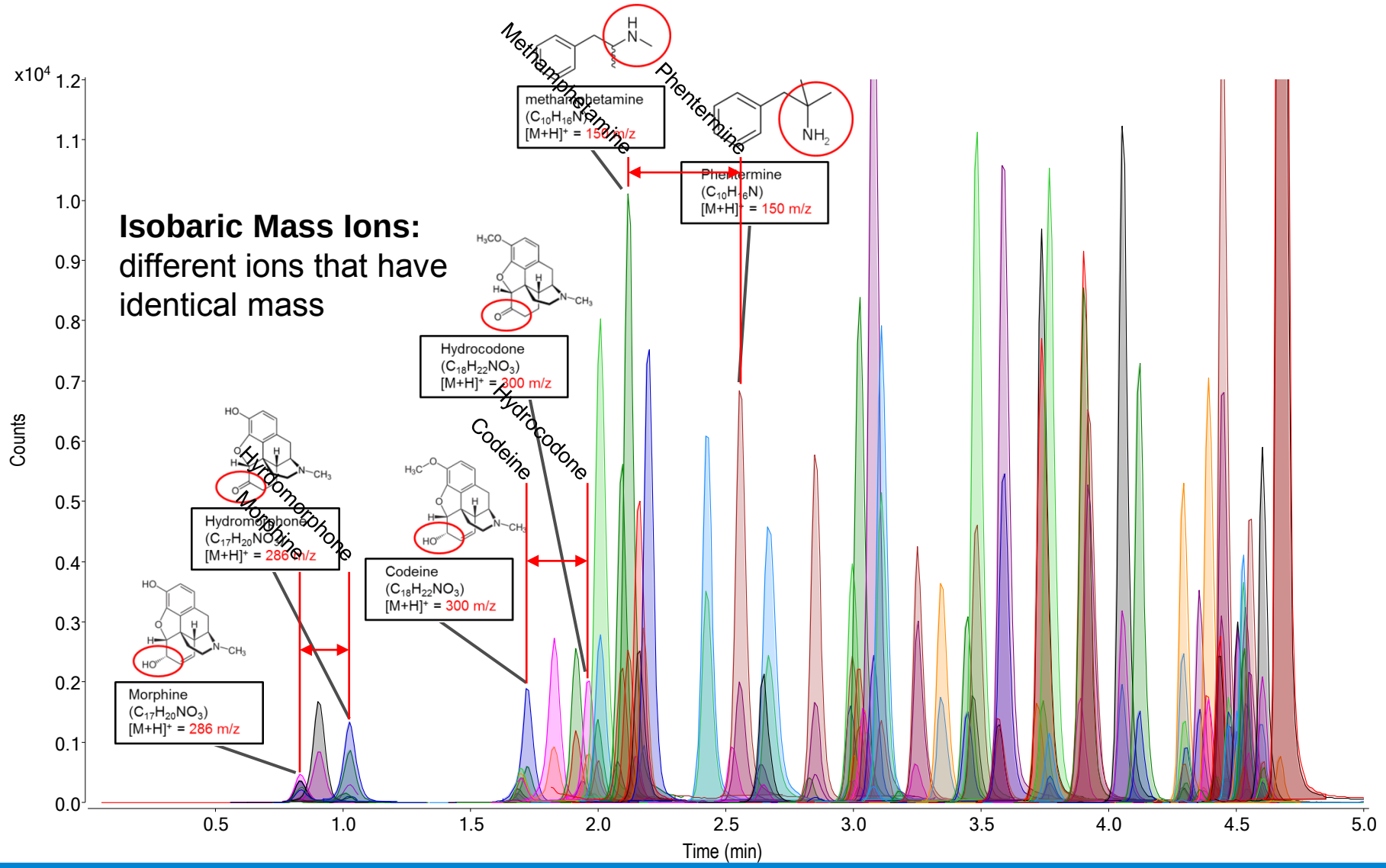
- A method for the rapid analysis of over 65 analytes in a single LC/MS analysis run
- Simplified method development through the use of Dynamic MRM (dMRM) and databases
- Qualitative and Quantitative data analysis
- Customized Reporting

Targeted Analysis of Over 65 Analytes for Forensic Toxicology

- An extensive screen and quantification in 5 to 6 minutes
- Internal standard corrected quantification
- Multi-point calibration curve covering a wide dynamic range
- Secondary qualifier ion for each analyte
- Simple sample preparation:



Chromatographic Separation of Over 65 Analytes



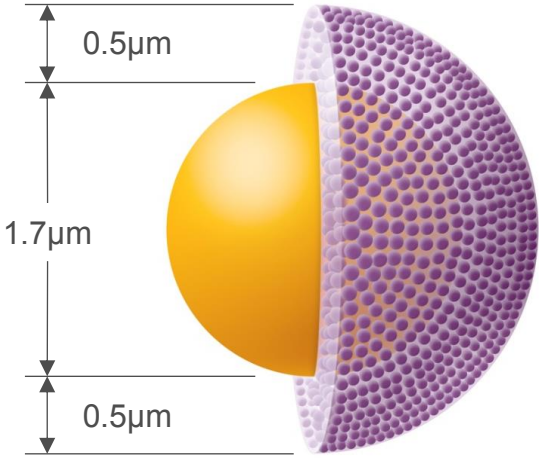
Poroshell 120 Columns for HPLC and UHPLC

Poroshell 120 is a high efficiency, high resolution column choice for enhancing productivity in LC and LC/MS

Poroshell 120 Columns have:

- 80-90% efficiency of sub-2µm columns
- ~40-50% lower pressure
- 2x efficiency of 3.5µm (totally porous)
- A 2µm frit to reduce clogging
- A 600 bar pressure limit for HPLC or UHPLC

- The superficially porous particle is 2.7um with a solid core (1.7um) and porous outer layer with a 0.5um diffusion path



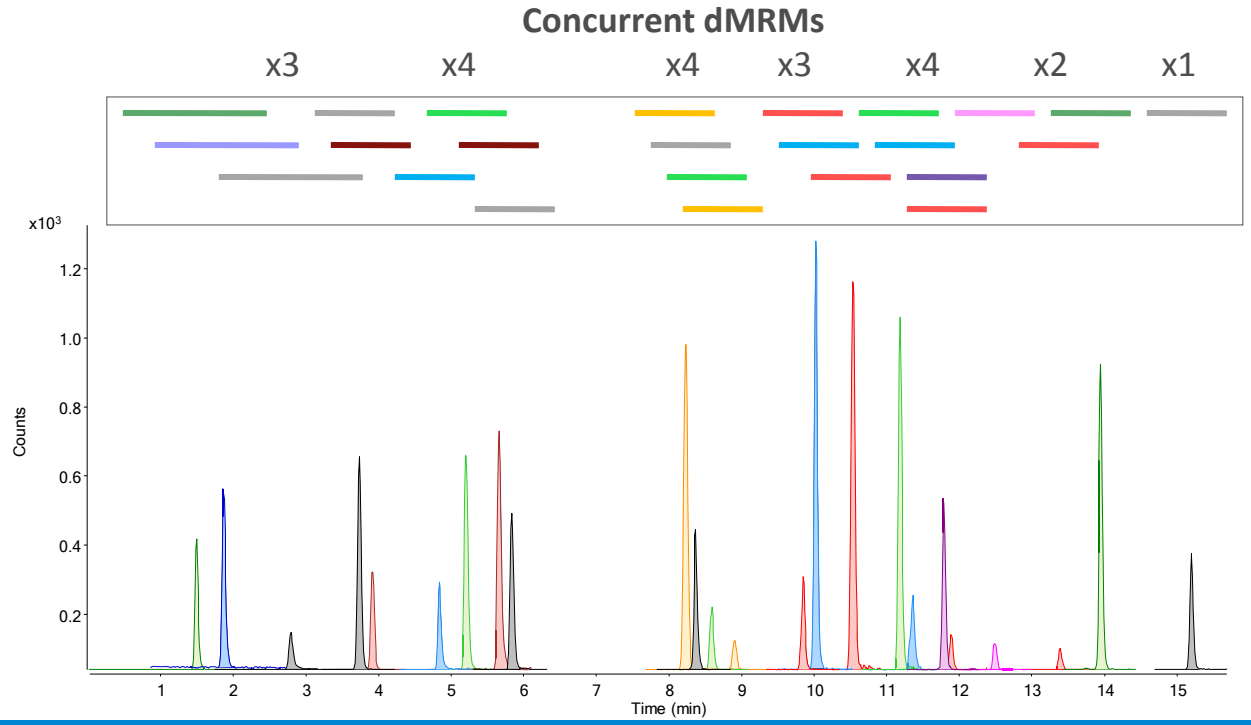
Poroshell 120 Performance After 3000 Injections

- Dilute and shoot sample preparation
- Analytes covering a wide range of retention times show excellent reproducibility

Analyte	%RSD (RT)	Analyte	%RSD (RT)	Analyte	%RSD (RT)
Morphine	0.7	Meperidine	0.4	Triazolam	0
Codeine	0.4	zolpidem	0.3	Naltrexone	0.1
hydrocodone	0.4	Fentanyl	0.1	chlordiazepoxide	0.1
MDMA	0.3	EDDP	0.1	Desmethyl diazepam	0.1
norFentanyl	0.2	Nitrazepam	0.1	Buprenorphine	0.3
Heroin	0.2	Propoxephine	0.1	Cocaethylene	0.2
Methyl Phenidate	0.2	Buprenorphine	0.3	11-nor-9-carboxy-delta9-thc	0

The Need for Dynamic MRM (dMRM)

- Nearly 200 MRM transitions for analytes, qualifier ions, and internal standards
- Monitoring all MRM transitions over the entire run results in poor quantification due to short dwell times and long cycle times
- dMRM only monitors each transition during the appropriate retention time window

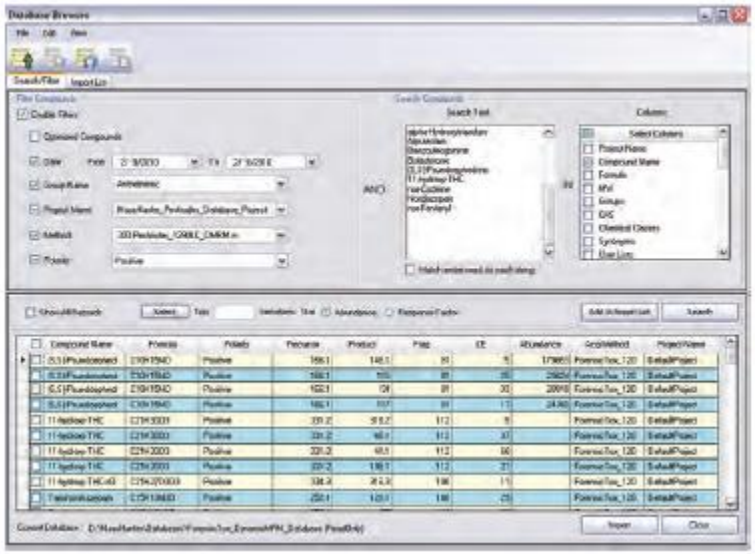


Easy LC/MS Method Creation and Customization

Agilent Analyzers and Application Kits

Triple Quadrupole LC/MS Forensic Toxicology Application Kit

Quickly and efficiently implement target screening methods



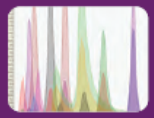
A Database containing over 2500x compounds each with multiple MRM transitions ensures fast method creation for development

Quickly establish screening methods for complex matrices using these leading-edge technologies

A Dynamic MRM database with more than 200 compounds, plus **Agilent MassHunter Data Acquisition and Analysis software,** let you quickly generate acquisition and analysis methods, which can be modified to meet your future needs.

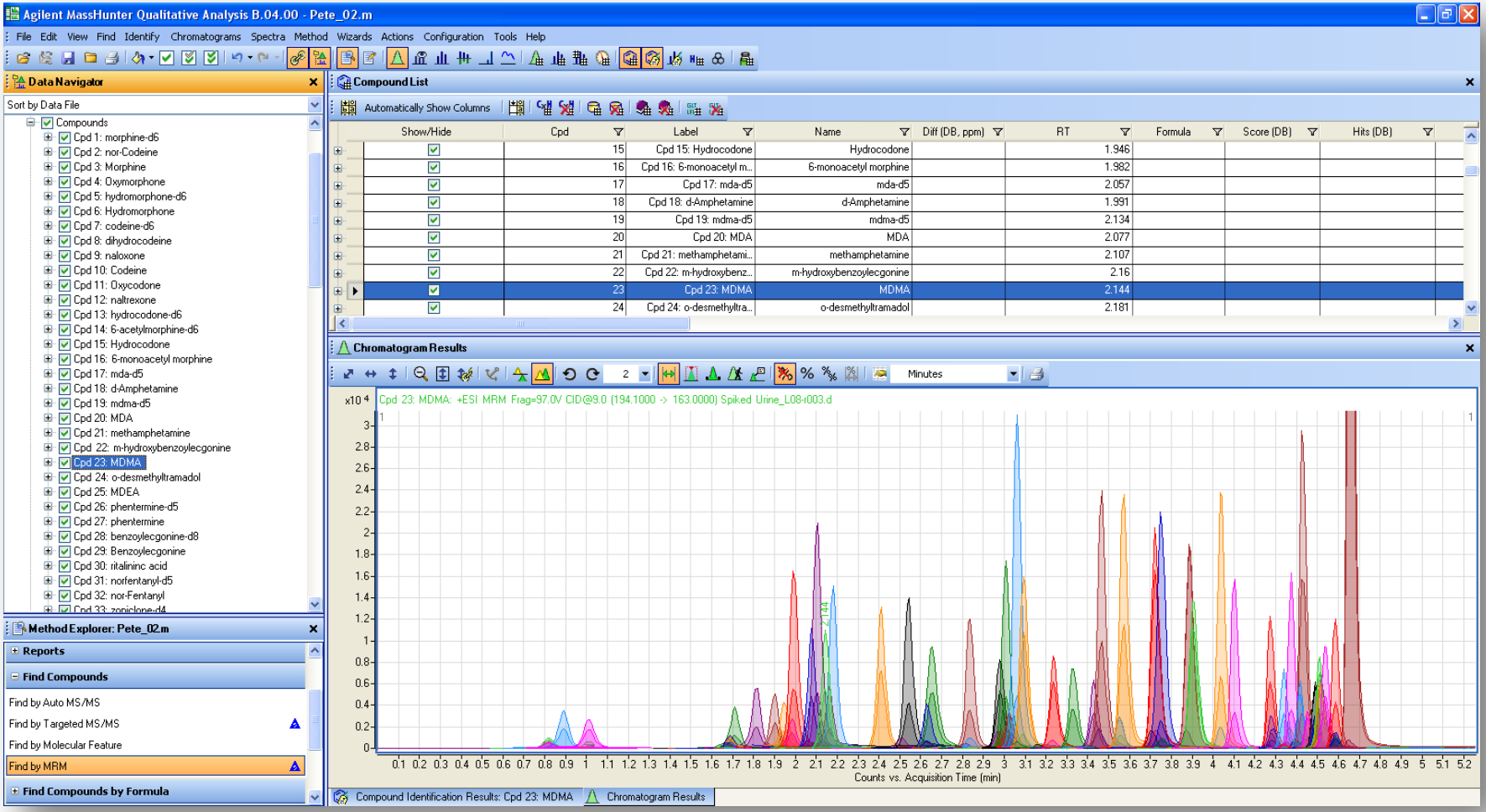
The Agilent 1200 Series SL Rapid Resolution LC, interfaced with Agilent's 6400 Series Triple Quadrupole LC/MS System delivers fast, high-resolution LC/MS/MS analysis.

Agilent's Jet Stream Electrospray lowers detection levels of analytes in complex matrices.

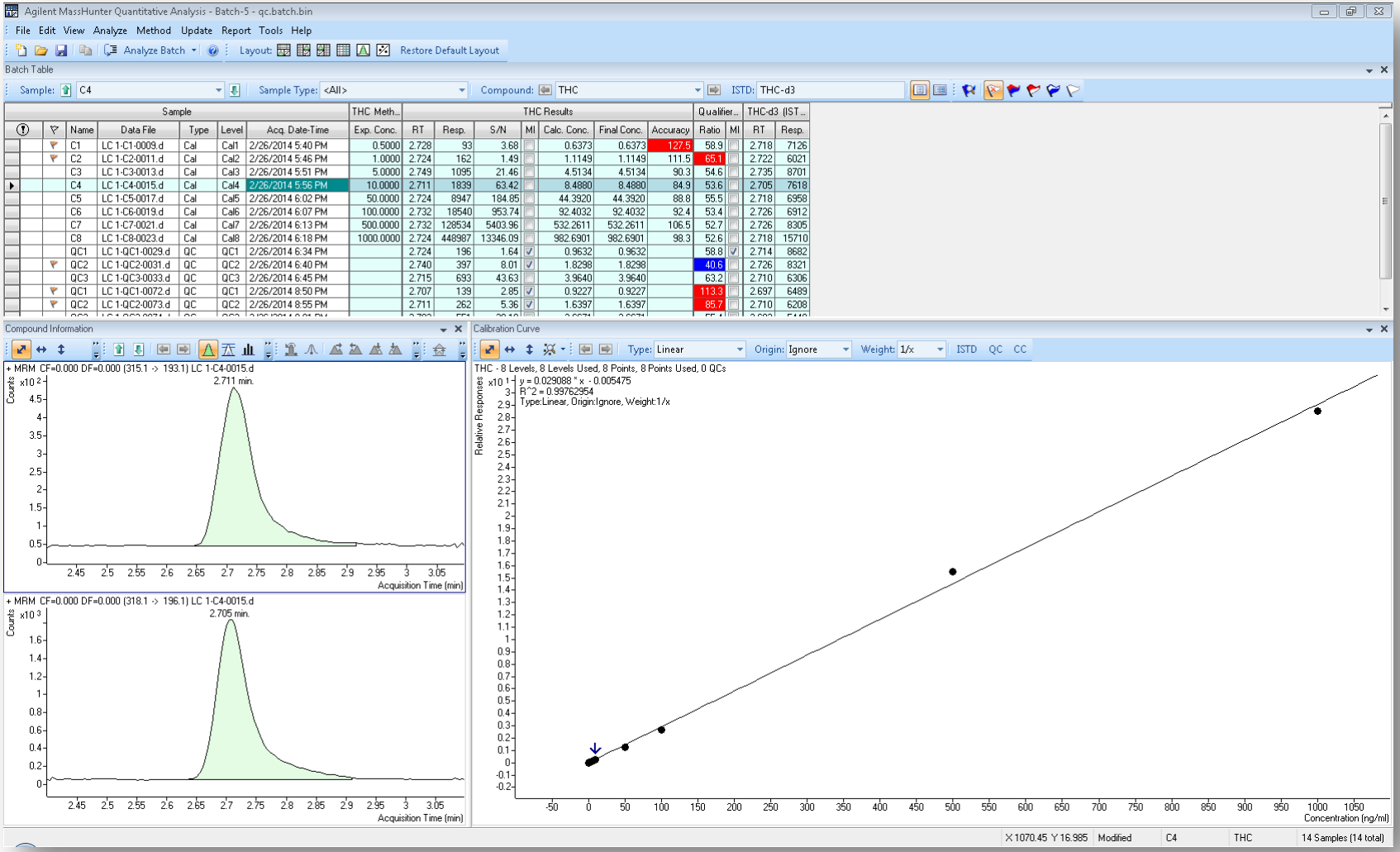


Dynamic MRM maximizes the Quadrupole's detection capability – without sacrificing sensitivity – when a large number of compounds are being analyzed at femtomole concentrations.

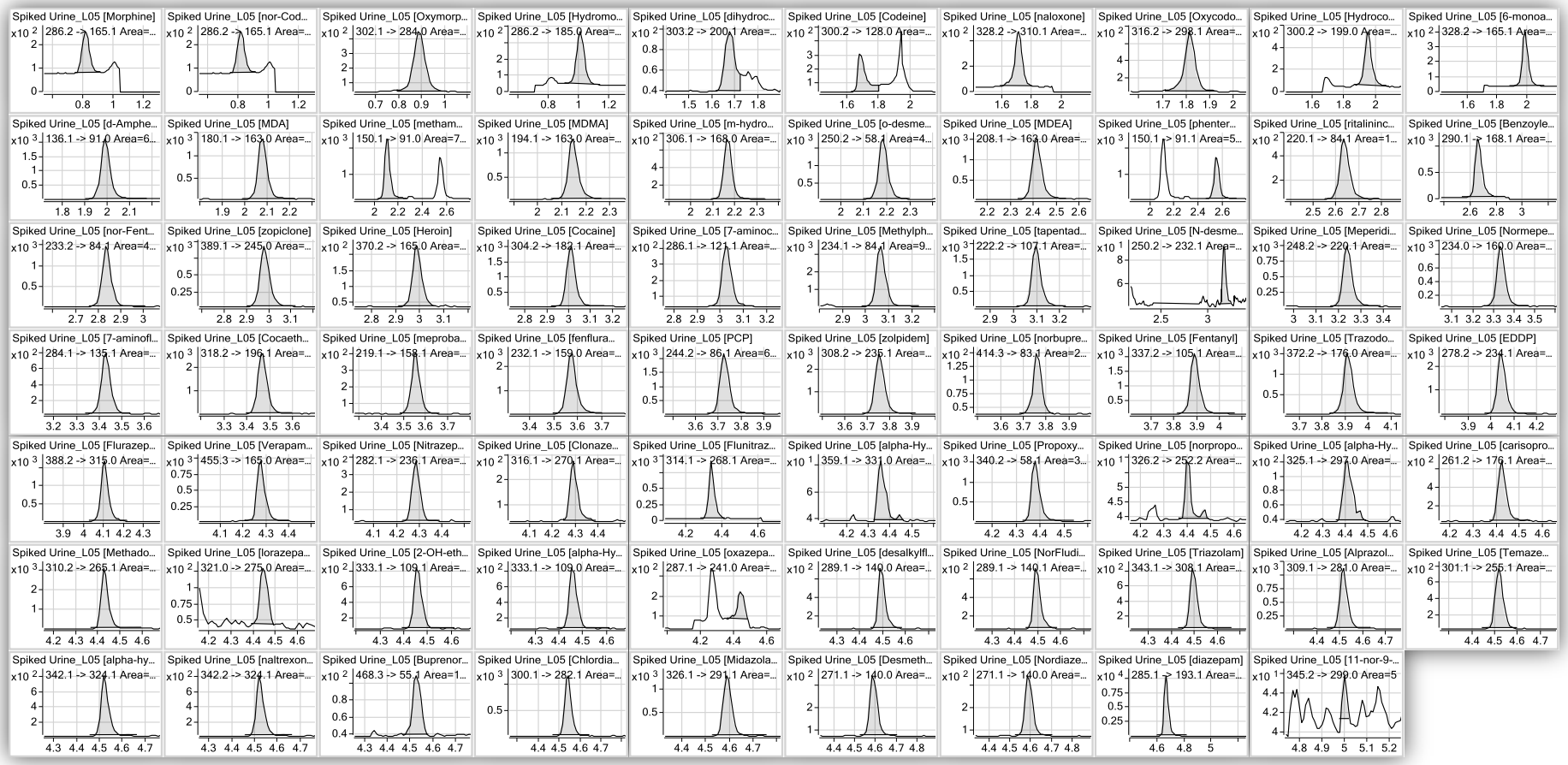
Qualitative Screening
Find By MRM



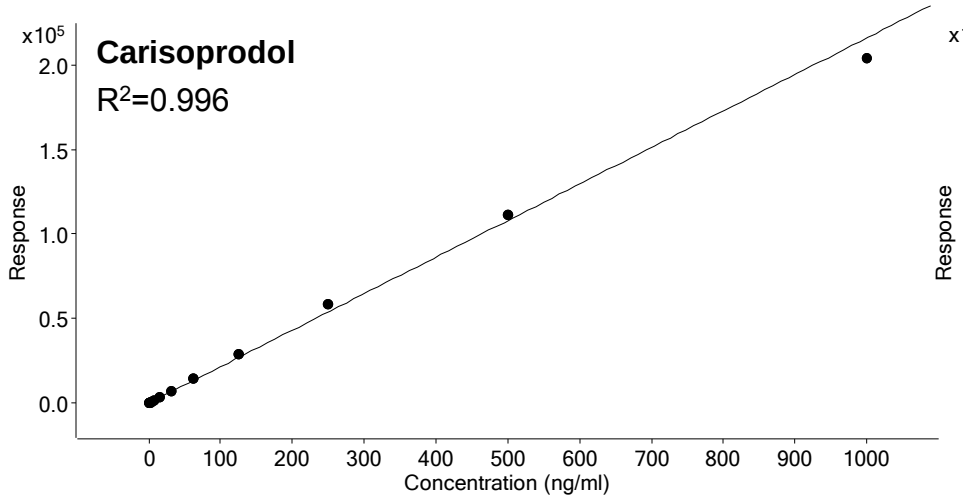
Quantitative Analysis
Batch at a Glance

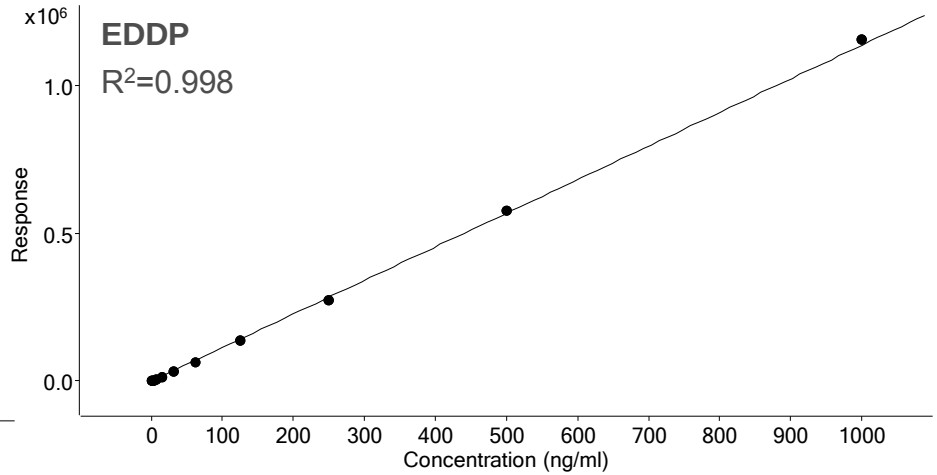


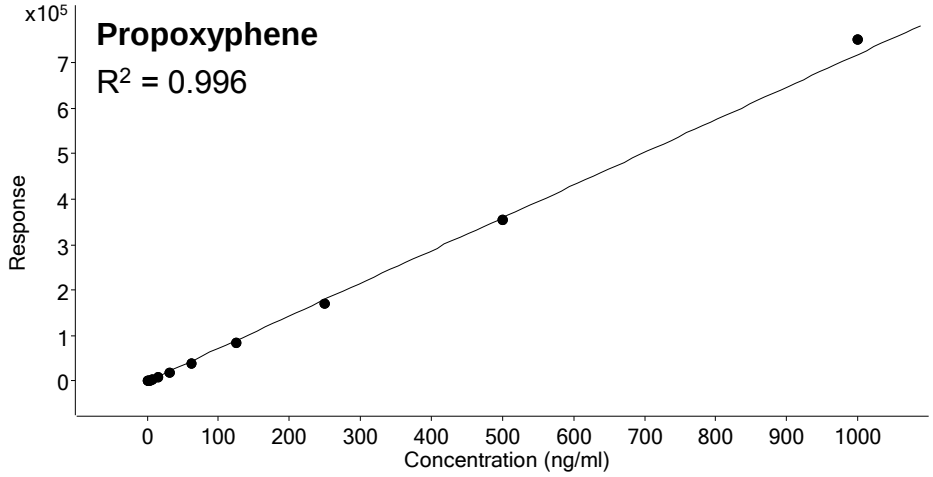
Data Review with Compounds at a Glance

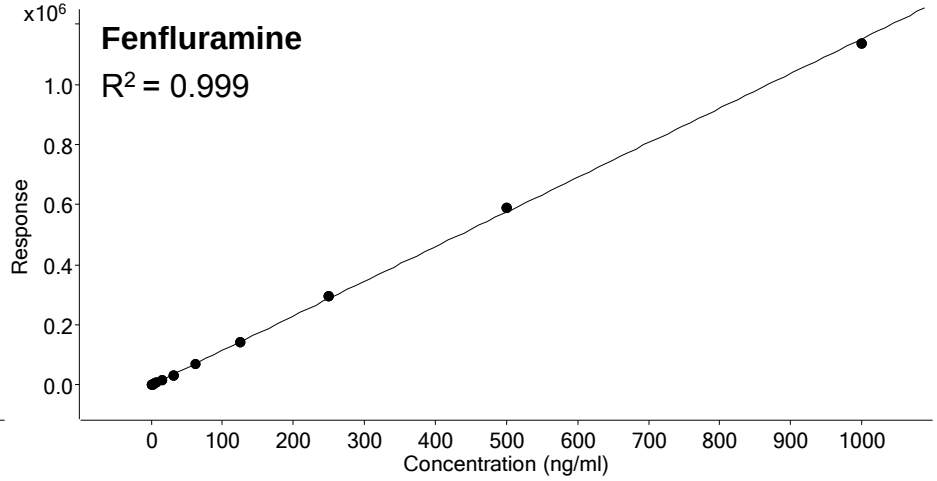


Quantative Analysis
Calibration Curves









Customizable Reporting

Quantitative Analysis Sample Report

Batch Info

Batch Data Path	C:\Demo Data[redacted]
Analysis Time	##########
Report Time	##########
Last Calib Update	##########

Instrument	6430	**Sample Name**	PM_MIx_50ppb
Operator	[redacted]	**Data File**	PMSeqA_056.d
Sample Type	Calibration	**Acq Method File**	[redacted]Optimized_dMRM_ESI_Methanol_01.m
Dilution	1	**Acq Time**	2010-10-09 00:24
Position	P2-E9	**Sample Info**	
Injector Vol.	5	**Comment**	

Compound	Test Outcome	Measured Result	Cutoff	RT	Area
Morphine	Positive	50.3	40.0 ng/ml	0.863	15955
Oxymorphone	Positive	51.4	40.0 ng/ml	0.948	68076
Hydromorphone	Positive	49.4	40.0 ng/ml	1.090	37464
Codeine	Negative	50.4	60.0 ng/ml	1.817	22263
Naloxone	Positive	51.6	40.0 ng/ml	1.881	71272
Oxycodone	Positive	50.8	40.0 ng/ml	1.959	144027
Naltrexone	Positive	50.9	40.0 ng/ml	2.039	73330
Hydrocodone	Positive	49.8	35.0 ng/ml	2.085	85546
6-monoacetyl morphine	Positive	52.6	40.0 ng/ml	2.133	35081
d-Amphetamine	Positive	50.8	40.0 ng/ml	2.230	128641
methamphetamine	Negative	50.1	80.0 ng/ml	2.318	184766
MDMA	Positive	49.8	40.0 ng/ml	2.332	123486
Strychnine	Negative	49.3	80.0 ng/ml	2.492	26033
MDEA	Negative	50.1	80.0 ng/ml	2.587	138131
nor-Fentanyl	Positive	51.1	8.0 ng/ml	2.976	152310
Heroin	Positive	51.4	25.0 ng/ml	3.097	2098
Tramadol	Negative	49.3	75.0 ng/ml	3.122	252341
Cocaine	Positive	50.0	50.0 ng/ml	3.136	117743
7-Aminoclonazepam	Positive	50.0	40.0 ng/ml	3.154	38927
Meperidine	Negative	50.4	60.0 ng/ml	3.364	252158
Normeperidine	Positive	50.0	40.0 ng/ml	3.451	97713
Meprobamate	Positive	50.1	40.0 ng/ml	3.747	18383
PCP	Positive	50.0	40.0 ng/ml	3.779	210618
Norbuprenorphine	Positive	51.0	40.0 ng/ml	3.831	2172
MDA	Negative	7.6	40.0 ng/ml	3.890	81000
Fentanyl	Positive	4.9	2.0 ng/ml	3.975	20177
Trazodone	Positive	49.6	40.0 ng/ml	4.067	136292
EDDP	Positive	48.5	25.0 ng/ml	4.075	312209
Verapamil	Positive	46.6	40.0 ng/ml	4.310	61548
Nitrazepam	Positive	50.1	40.0 ng/ml	4.391	21352
Propoxyphene	Positive	48.2	40.0 ng/ml	4.425	160040
Norpropoxyphene	Negative	29.6	40.0 ng/ml	4.442	898
Methadone	Positive	49.7	40.0 ng/ml	4.454	595919
alpha-Hydroxyalprazolam	Negative	49.5	50.0 ng/ml	4.485	4798
Lorazepam	Positive	49.2	40.0 ng/ml	4.538	2106
Oxazepam	Negative	48.4	55.0 ng/ml	4.545	3204
Alprazolam	Negative	49.9	50.0 ng/ml	4.566	78443
Temazepam	Positive	49.4	40.0 ng/ml	4.610	31380
Buprenorphine	Positive	50.2	50.0 ng/ml	4.638	9526
Nordiazepam	Negative	51.2	65.0 ng/ml	4.692	8293
Proadifen	Positive	48.3	40.0 ng/ml	4.688	109420
Diazepam	Positive	50.1	35.0 ng/ml	4.756	48262

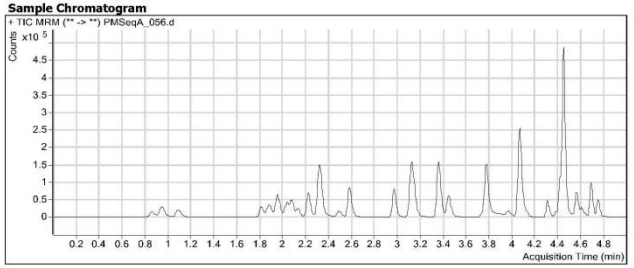
Quantitative Analysis Sample Report

Batch Info

Batch Data Path	C:\Demo Data\ACME_Toxicology_Inc
Analysis Time	##########
Report Time	2/15/2014 5:43 PM
Last Calib Update	##########

Instrument	6430	**Sample Name**	MIx_50ppb
Operator	P. John Doe	**Data File**	SeqA_056.d
Sample Type	Calibration	**Acq Method File**	Optimized_dMRM_ESI_Methanol_01.m
Dilution	1	**Acq Time**	10/9/2013 0:24
Position	P2-E9	**Sample Info**	
Injector Vol.	5	**Comment**	

Sample Chromatogram



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Cocaine	Positive	50.0	50.0 ng/ml	3.136	117743
7-Aminoclonazepam	Positive	50.0	40.0 ng/ml	3.154	38927
Meperidine	Negative	50.4	60.0 ng/ml	3.364	252158
Normeperidine	Positive	50.0	40.0 ng/ml	3.451	97713
Meprobamate	Positive	50.1	40.0 ng/ml	3.747	18383
PCP	Positive	50.0	40.0 ng/ml	3.779	210618
Norbuprenorphine	Positive	51.0	40.0 ng/ml	3.831	2172

Conclusions

- Agilent makes it easy to create custom analytical panels for the measurement of Opiates, Opioids, Benzodiazepines, Amphetamines & Illicits
- Panels can be comprehensive or focused to suit your needs
- Dynamic MRM functionality, automatic optimization and MRM transition Database help make analytical method development straightforward
- Results can be achieved with a simple Dilute & Shoot sample preparation
- Agilent's MassHunter software is optimized for your data review and reporting workflow

Ultrafast SPE/MS Analysis of TCAs in Serum

Vaughn Miller

RapidFire Applications Manager

Today's Agenda

RapidFire/MS features and benefits

Demonstration data

- Tricyclic antidepressants in serum in clinical research

Summary

Follow-up information

What is RapidFire/MS?

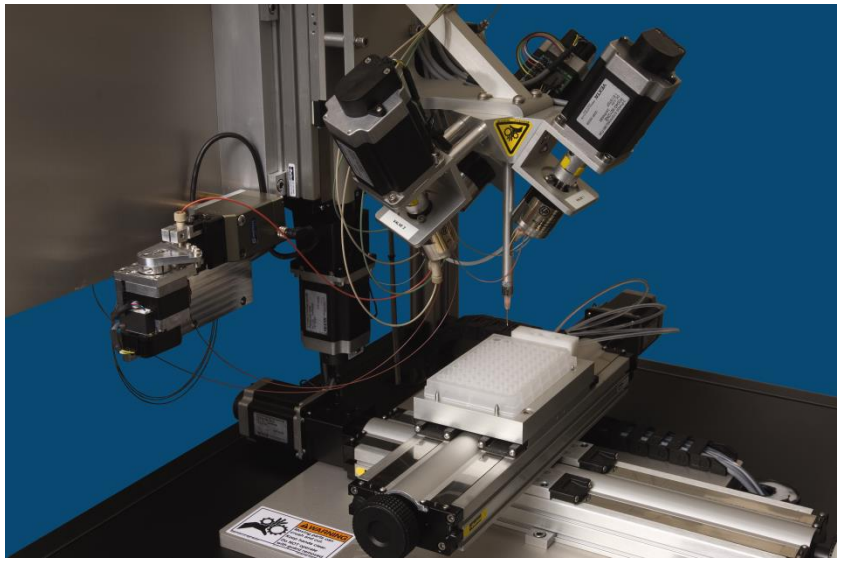
Ultrafast autosampler &

online SPE system

- Replaces LC in LC/MS
- Reusable SPE cartridge
- Integrates with standard ESI MS instruments (QQQ & TOF)
- **Cycle time = 8-15 s/sample**

Compatible with biological matrices

- Microsomal incubations
- Cell culture media
- Serum, plasma or whole blood
- Urine



Agilent Web Link

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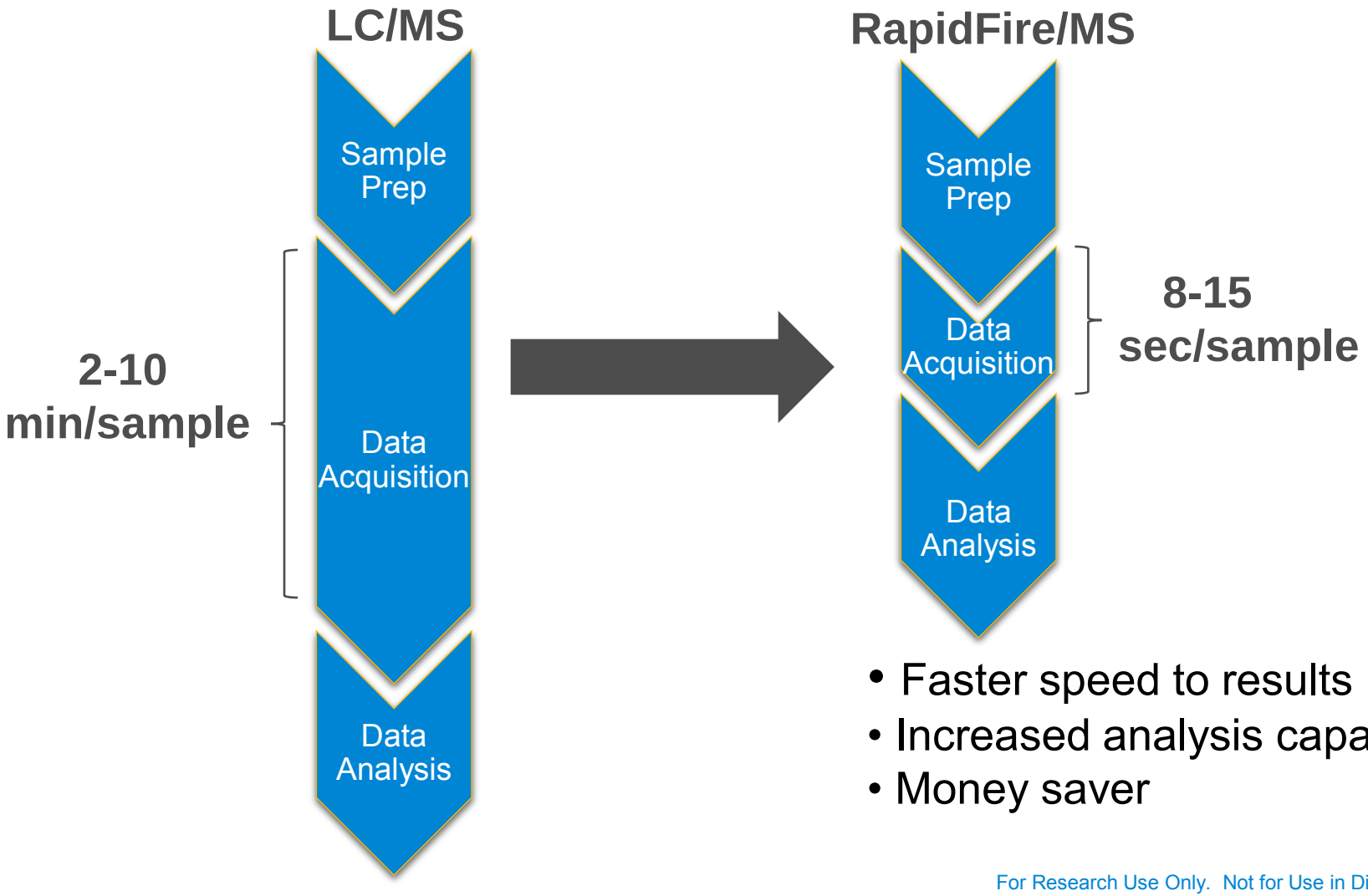
RapidFire Decreases Data Acquisition Time



- Faster speed to results
- Increased analysis capacity
- Money saver

Demonstration Data

Tricyclic Antidepressant (TCA) Research Drug Panel in Serum

Tricyclic Antidepressant Drug Panel in Serum

8 Analytes, 20 MRMs

Sample preparation

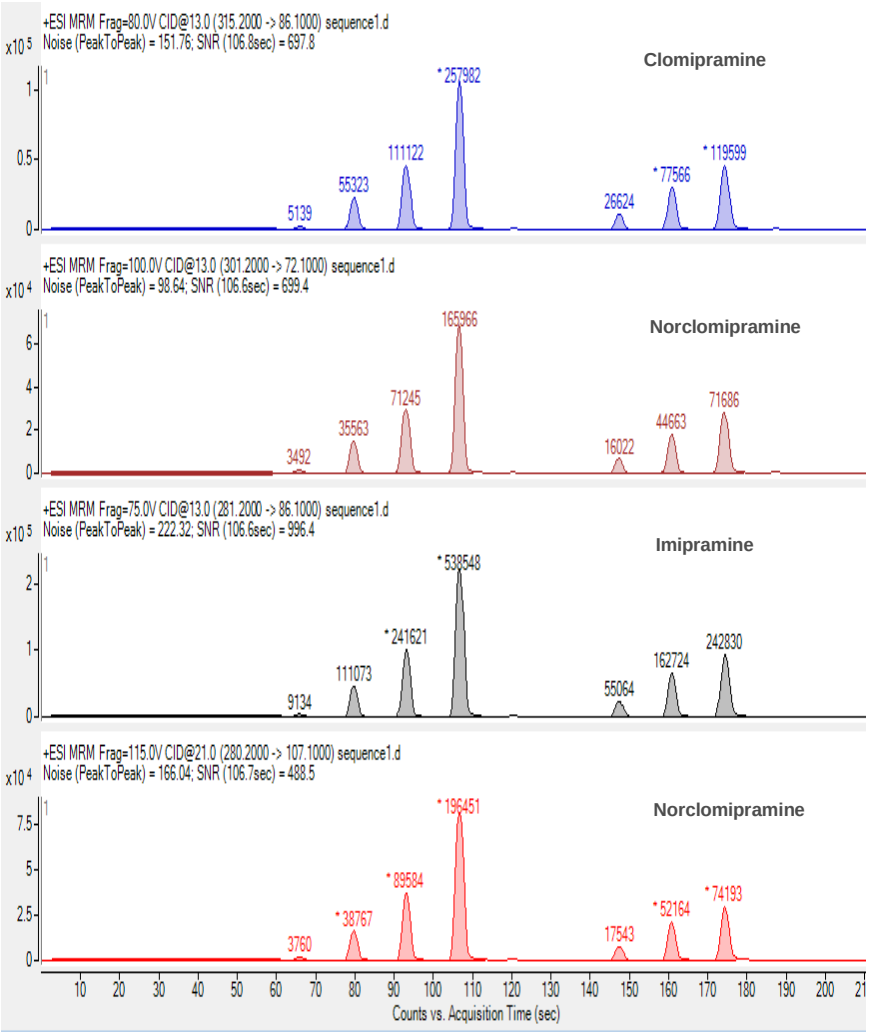
- MeOH/$ZnSO_4$ crash
- 1:10 dilution (water)

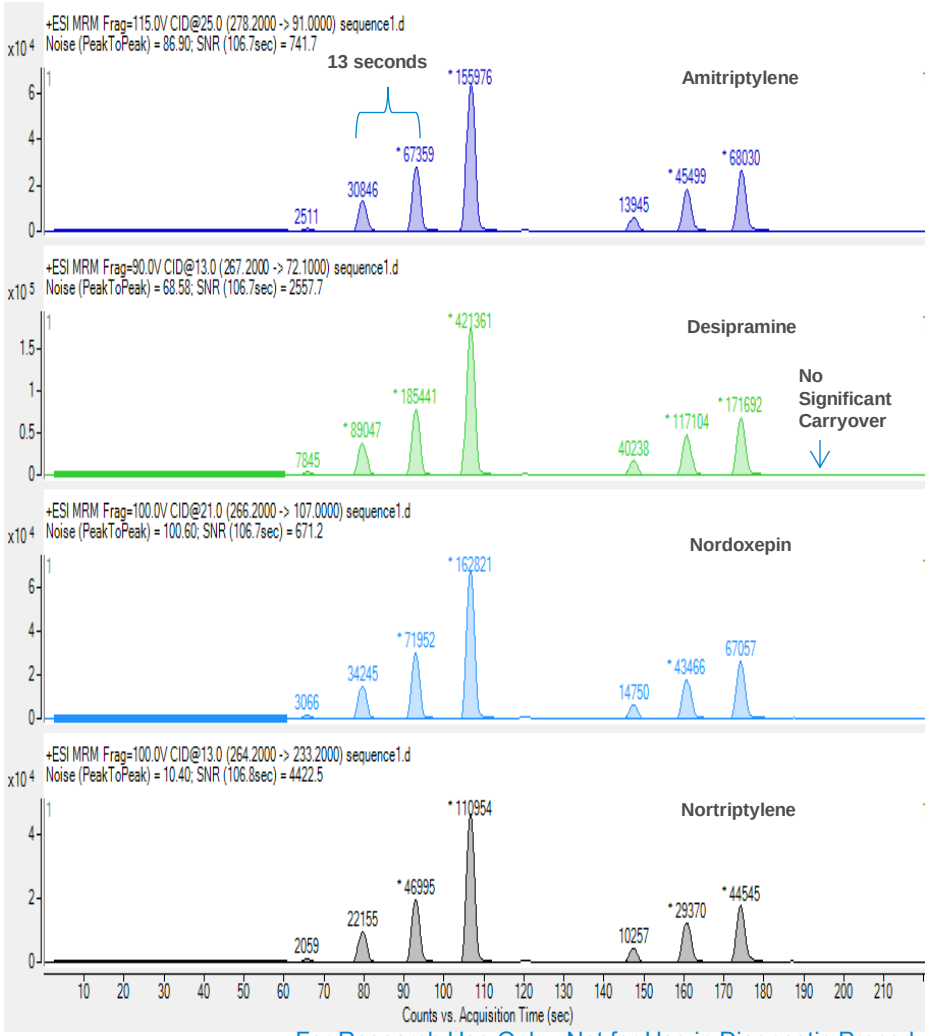
RapidFire analysis

- RapidFire 300 + Agilent 6460 Triple quad
  - Solvent A: 0.1% formic acid in water; 1.5 mL/min
- Solvent B + C: 0.1 % formic acid in methanol; 1.25 and 0.8 mL/min
- C18
- Total sample cycle time = 13 sec
- LOQ = 10 ng/ml

Compound Name	Precursor Ion	Product Ion
Clomipramine_d3	318.2	89.1
Clomipramine Q	315.2	86.1
Clomipramine	315.2	58.1
Norclomipramine Q	301.2	72.1
Norclomipramine	301.2	44.1
Imipramine-d3	284.2	89.1
Doxepin_d3	283.2	107.1
Amitriptylene-d3	281.2	91.1
Imipramine Q	281.2	86.1
Imipramine	281.2	58.1
Doxepin	280.2	115
Doxepin Q	280.2	107.1
Amitriptylene	278.2	117.1
Amitriptylene Q	278.2	91
Desipramine Q	267.2	72.1
Desipramine	267.2	44.1
Nordoxipin	266.2	235.1
Nordoxipin Q	266.2	107
Nortriptylene Q	264.2	233.2
Nortriptylene	264.2	91.1

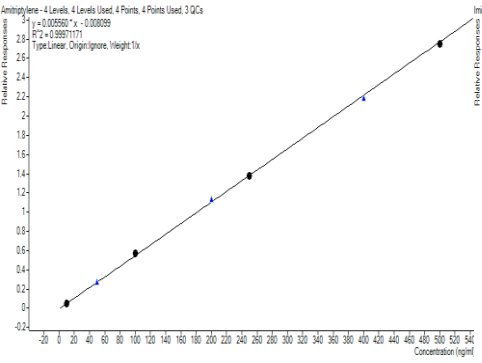
Analysis Speed and Carryover



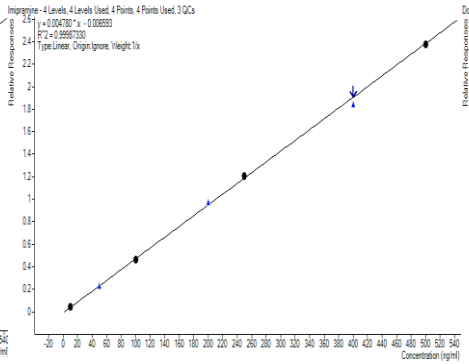


Calibration Curves

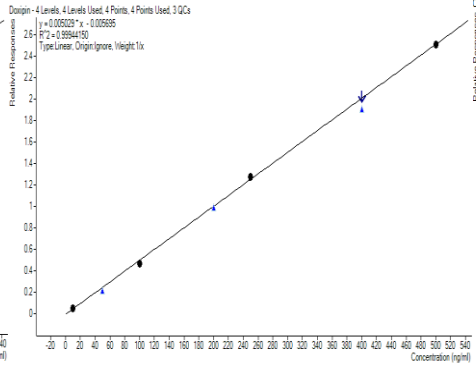
Linear Range from 10-500 ng/mL



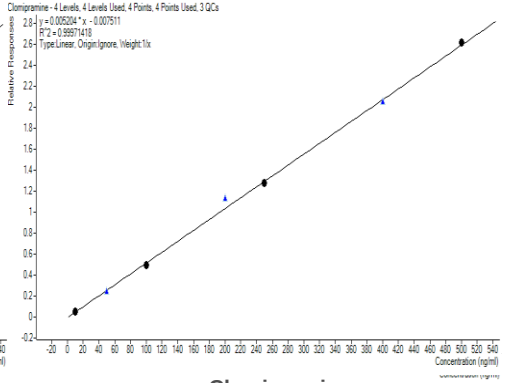
Amitriptylene



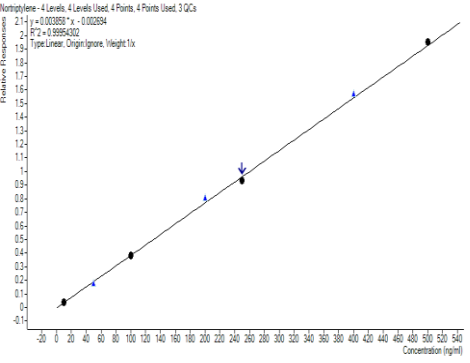
Imipramine



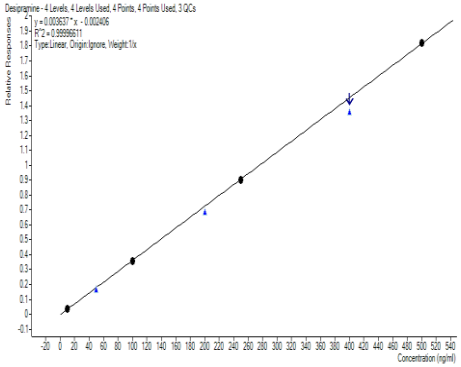
Doxepin



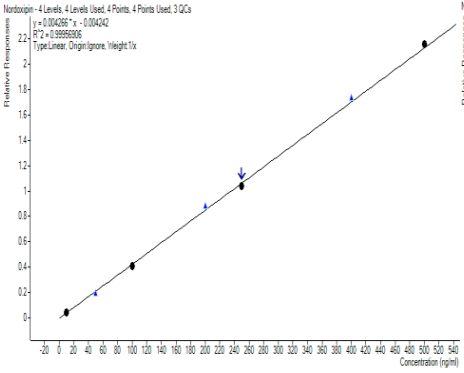
Clomipramine



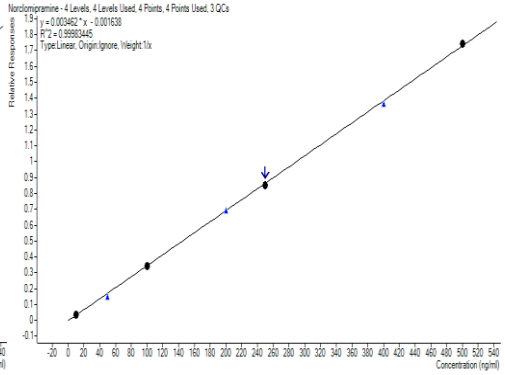
Nortriptylene



Desipramine



Nordoxepin



Norclomipramine

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Inter and Intraday Accuracy & Precision

Amitriptylene (ng/mL)	Interday % Accuracy (n=6)	Interday % Precision (n=6)	Intraday % Accuracy (n=6)	Intraday % Precision (n=6)
50	99.1	3.3	98.7	5.4
200	107.6	1.5	104.8	2.2
400	96.9	2.9	102.1	1.9

Doxepin (ng/mL)	Interday % Accuracy (n=6)	Interday % Precision (n=6)	Intraday % Accuracy (n=6)	Intraday % Precision (n=6)
50	92.2	2.0	99.8	3.3
200	102.6	2.2	100.4	1.5
400	97.2	2.3	96.4	1.5

Nortriptylene (ng/mL)	Interday % Accuracy (n=6)	Interday % Precision (n=6)	Intraday % Accuracy (n=6)	Intraday % Precision (n=6)
50	97.3	2.3	97.3	2.7
200	105.9	3.9	101.9	0.4
400	96.2	2.9	98.7	2.8

Nordoxepin (ng/mL)	Interday % Accuracy (n=6)	Interday % Precision (n=6)	Intraday % Accuracy (n=6)	Intraday % Precision (n=6)
50	97.4	4.8	99.4	4.9
200	102.9	2.9	103.1	1.7
400	97.6	1.3	101.7	1.4

Imipramine (ng/mL)	Interday % Accuracy (n=6)	Interday % Precision (n=6)	Intraday % Accuracy (n=6)	Intraday % Precision (n=6)
50	103.7	2.9	102.4	2.6
200	103.9	0.8	98.9	2.2
400	94.6	2.3	98.5	3.9

Clomipramine (ng/mL)	Interday % Accuracy (n=6)	Interday % Precision (n=6)	Intraday % Accuracy (n=6)	Intraday % Precision (n=6)
50	97.6	2.6	97.0	3.6
200	107.2	2.5	102.7	4.8
400	104.2	1.4	100.9	5.0

Desipramine (ng/mL)	Interday % Accuracy (n=6)	Interday % Precision (n=6)	Intraday % Accuracy (n=6)	Intraday % Precision (n=6)
50	98.1	1.6	97.3	2.3
200	97.6	1.4	96.6	0.8
400	91.8	1.5	92.9	1.5

Norclomipramine (ng/mL)	Interday % Accuracy (n=6)	Interday % Precision (n=6)	Intraday % Accuracy (n=6)	Intraday % Precision (n=6)
50	91.5	1.5	97.8	4.0
200	98.1	1.6	99.9	2.4
400	97.5	1.7	97.3	3.5

- Utak Laboratories QC standards
- Coefficient of variation values were all < 8%

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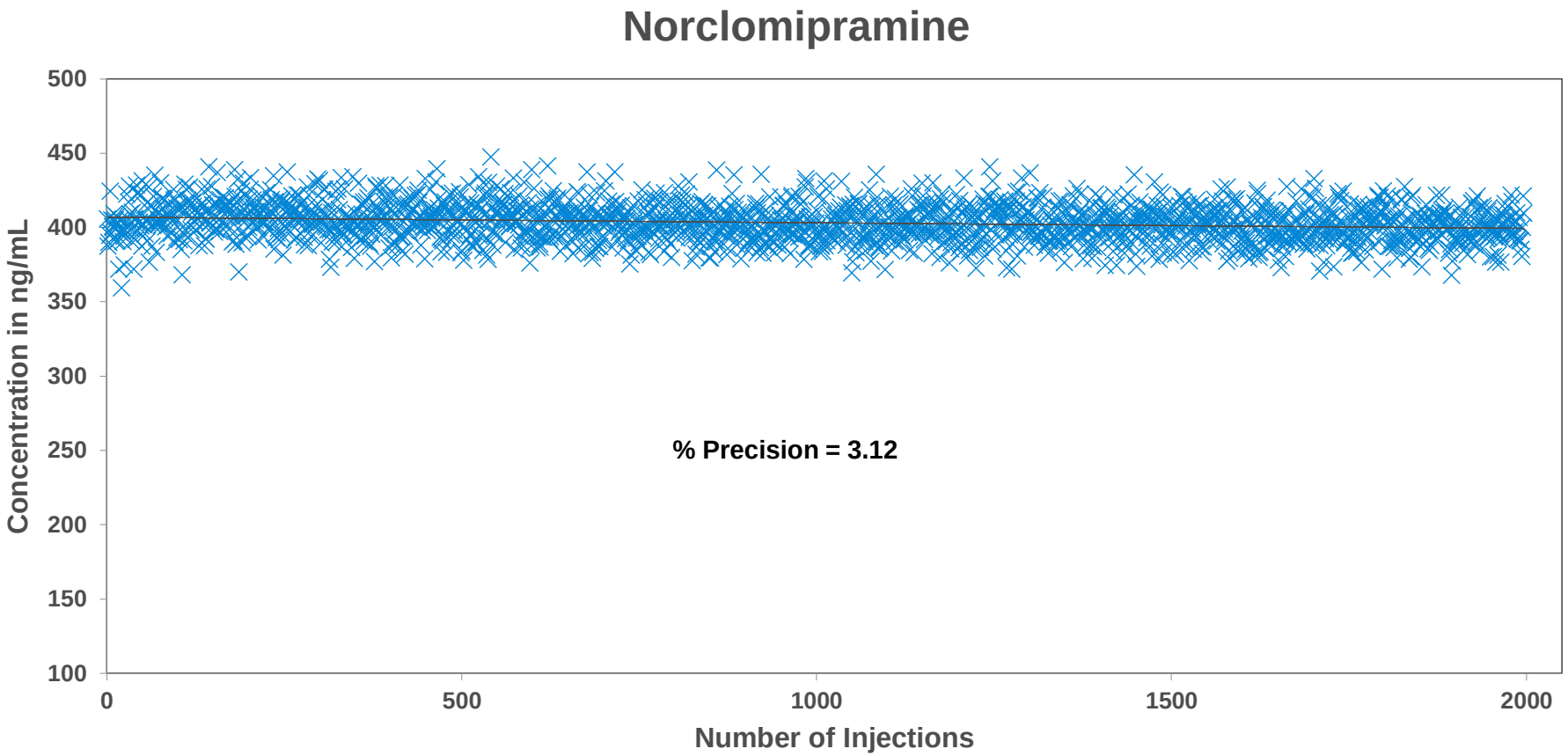
Reproducibility Study



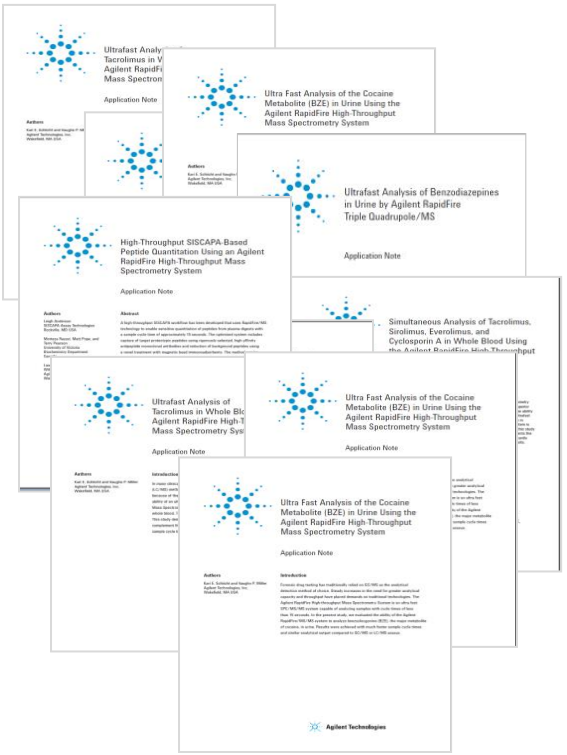
2000 injections of the same sample showing robustness of the RapidFire system, SPE cartridge lifetime and consistency in area counts and quantitation for the drugs in the panel.

RapidFire/MS Clinical Research Methods

Serum or whole blood matrix, <16 seconds/sample

Quantitative Analysis

- Antiepileptic panel
- Tricyclic antidepressant panel
- SSRI panel
- Clozapine/norclozapine
- Antifungal panel
- SISCAPA peptide analysis
- AssayMAP protein analysis



RapidFire/MS Forensic Toxicology Methods

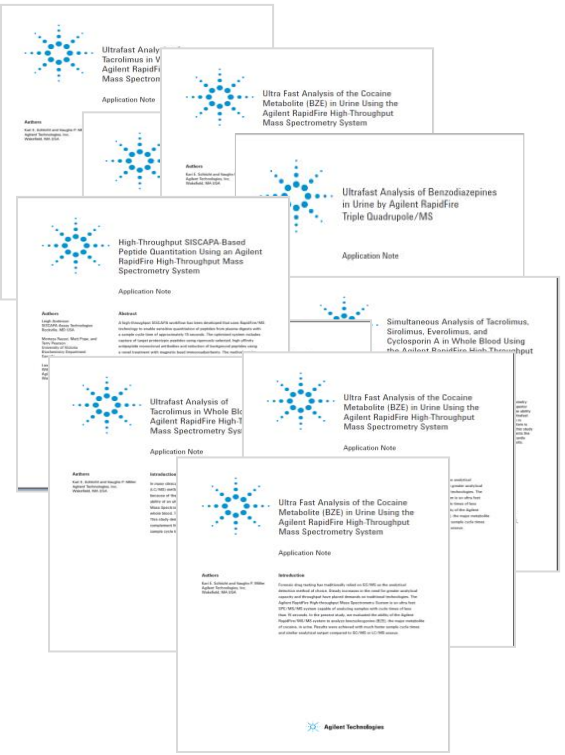
Urine matrix, <16 seconds/sample

Quantitative Analysis

- Methadone & EDDP
- Benzodiazepine panel
- THCCOOH
- BZE
- Z-drugs panel
- Buprenorphrine & Norbuprenorphrine
- Gabapentin & Pregabalin
- Cotinine in urine or serum

Qualitative Analysis

- Amphetamine panel
- Bath salts panel
- Synthetic cannabinoids panel
- Barbiturates panel
- TOF panels – coming soon



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The Value of RapidFire/MS

SPE/MS results are comparable to LC/MS for many applications

- Linearity
- Accuracy & precision
- Reproducibility

Advantages of RapidFire/MS

- **Fastest Time to Result**
  - < 20 seconds per sample
  - > 250 samples/hour
  - > 5,000 samples/day
- **Increased Capacity**
  - Able to analyze 1000's of samples per day on a single system
- **Cost efficient**
  - Lower operating cost and smaller lab footprint than multiple MS systems
  - Least expensive way of analyzing hundreds of samples (or more) per day
    - Direct cost < $0.1/sample
- **Excellent tool for development of new drug analyte panels**
  - More sensitivity and specificity without the interference found in traditional methods
  - Ability to create new panels quickly (i.e. designer drugs)

Questions?

RapidFire Applications Manager

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- 781-928-2758

Agilent Web Site

- RapidFire 365 home page (link)
- RapidFire clinical research video (link)
- Productivity calculator (link)
  - Compare LC/MS to RapidFire/MS: capital cost & turn around time
- Brochure
  - Pharma discovery focused, but specs of instrument (link)

Review article: SPE/MS technology

- Bioanalysis, 2012
  - SPE-MS analysis of absorption, distribution, metabolism and excretion assays: a tool to increase throughput and streamline workflow