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Experimental Design Considerations for Extractable and Leachable Studies

Mike Ludlow

BCF 3rd Annual Extractables and Leachables Hybrid Conference

1st-2nd December 2022

Berlin, Germany

Email: mludlow@alliancepharmaco.com

Worldwide Resources

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Experienced scientific and management teams at significant scale

Malvern

Bioanalytical

Cambridge & Sandwich

- Bioanalytical
- Analytical and Materials Science

China

Lab evaluation in process

Brisbane

Bioanalytical

Drug Development Solutions - UK business units

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Bioanalytical Solutions

Cambridge, UK

1

2387m² ~300 people – one of the largest bioanalytical sites

>20 LC-MS instruments and extensive platforms for Immunoassay Bioanalysis

Analytical and Materials Science Solutions

2

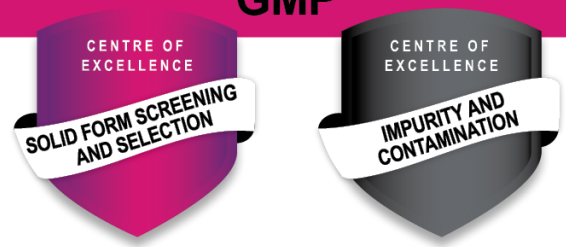
Cambridge, UK & Sandwich, UK

960m² ~50 people

Wide range of technology to support Organic and Inorganic Impurity testing, E&L, Foreign particulate and Materials testing

Bioanalytical Solutions (BAS)
Discovery, GLP, GCP

Analytical and Materials Science Solutions (AMS)
GMP



LC-MS Bioanalysis
- Fast turn-around supporting Clinical SAD/MAD studies
- Discovery, preclinical and tissues
- Small molecules, ADCs, Peptides, and Proteins
- Biomarkers
- High resolution LC-MS

Immunoassay Bioanalysis
- Biopharmaceutical modalities (PK)
- Immunogenicity (ADA/nAbs)
- Cell based assays and ELISpot
- Biomarkers
- Flow cytometry

Complementary Solutions
- Customised Method Development and Validation
- Pharmacokinetics and toxicokinetic parameter analysis
- Sample collection kits and logistics
- Data management
- Microsampling

Analytical Science
- Trace Impurities:
  - Organic analysis
  - Inorganic analysis
- Nitrosamine testing
- Extractables and leachables
- Structural elucidation

Materials Science
- Physical properties testing
- Solid form:
  - Characterisation
  - Screening and selection
- Foreign particulate matter

Testing Solutions
- Method Development and Validation
- Characterisation and QC testing
- Stability testing
- Troubleshooting

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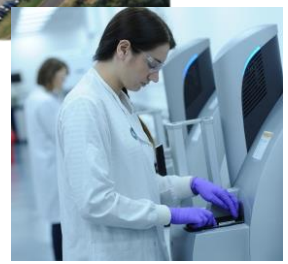
Expertise dedicated to solve your challenges.

Our scientists partner with you to provide a consultative, flexible and dependable solution for the development, validation, and application of testing methods



Analytical & Materials Science Solutions

	ANALYTICAL SCIENCE	MATERIALS SCIENCE
1 Experience	Small Molecule Pharmaceuticals, Consumer Products & Healthcare Raw Materials, Excipients, Active, Formulated Product, Packaging, Devices	
2 Capability	Analytical Chemistry, Impurity ID, Elemental Impurities, Extractables and Leachables	Materials Characterisation, Foreign Matter Analysis, Solid Form Screening
	Development & Validation of Testing Methods, Sample Analysis	
3 Solutions	Product Discovery, Development, Characterisation, Quality Control, Stability, Troubleshooting	
4 Excellence	CENTRE OF EXCELLENCE IMPURITY AND CONTAMINATION CENTRE OF EXCELLENCE SOLID FORM SCREENING AND SELECTION	Specific Centres of Excellence are focused on being at the forefront of scientific and industry developments, requirements, and solutions

Agenda

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- E&L objectives / key considerations
- Sample preparation
- Use of screening methods
- Validation requirements
- Summary and conclusion

Objectives – E & L Studies

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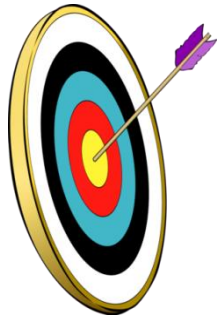
- Identification of potential leachables
- Quantitation of leachables in final drug product
- Enable toxicological safety assessment
- Define requirements for ongoing stability testing
- Product submission



Patient safety

E & L Relationship

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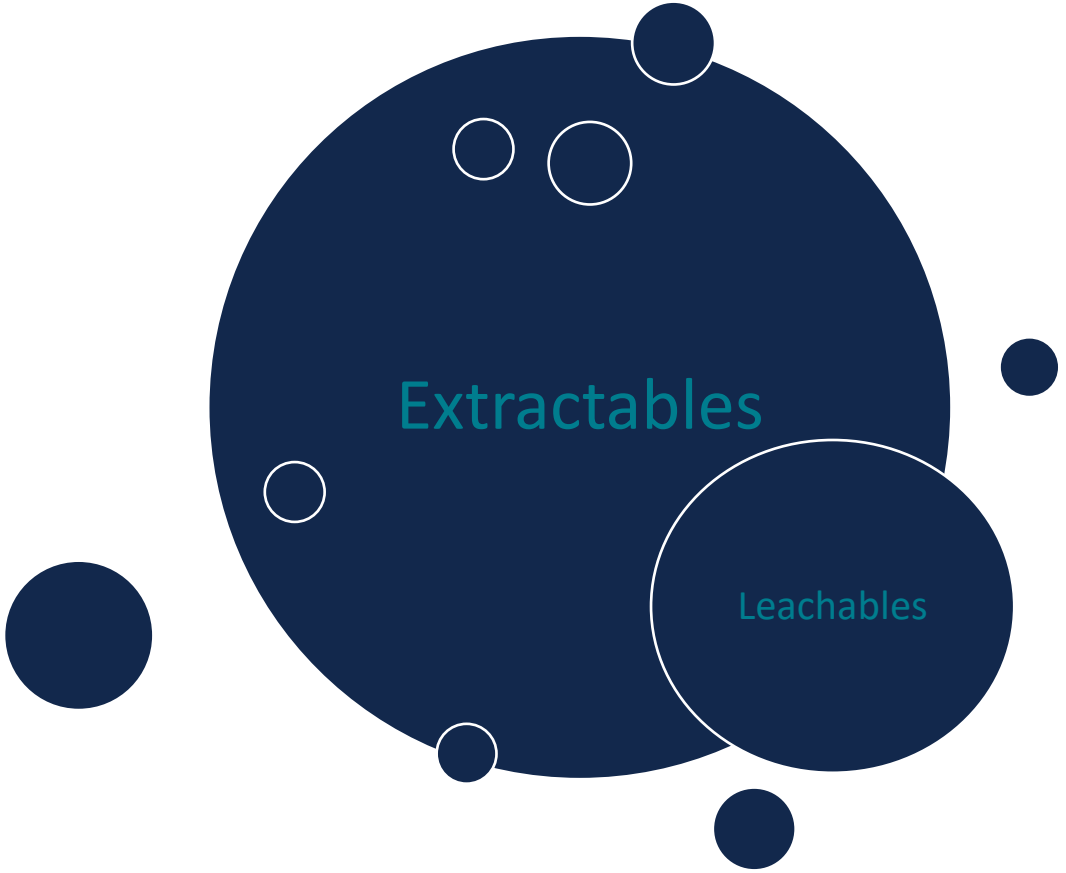

Factors to Consider

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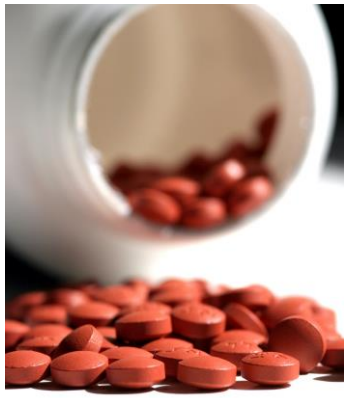
- Active ingredient (API)
- Excipients
- By-products and degradants
- Process related impurities
- Device / packaging related extractables

Wide range of;

- Chemical functionality
- Volatility
- Levels



Typical E & L Study Protocol

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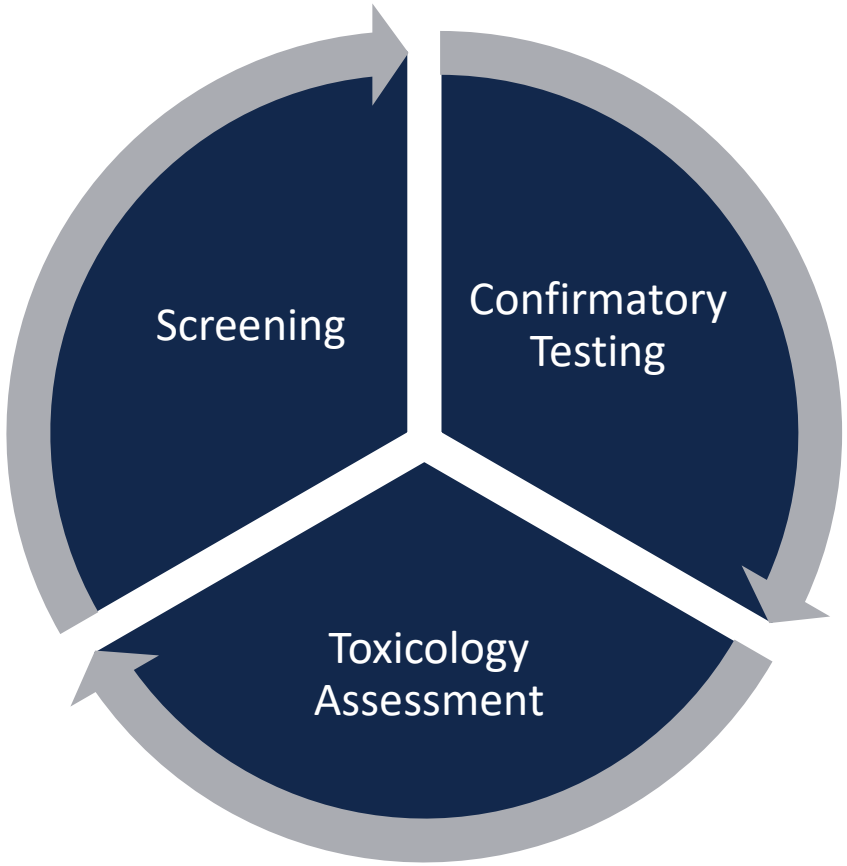
- Extraction study
  - Forced / simulated use
- Leachable analysis
  - Final drug product
- Stability testing
- Batch release

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Sample
Preparation
Considerations
for E&L

Factors to Consider

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- Sample homogeneity
  - SUS components
  - Wound dressings
- Extraction efficiency
- Impact of sample preparation
- Detection technique
  - Sample compatibility

Extraction Conditions

- Choice of solvent(s)
- Choice of extraction technique(s)
- Selection of extraction parameters
  - Time
  - Temperature / pressure
- Product use
- Relevant regulatory guidelines

Extraction Mode

- Exhaustive
  - Gravimetric vs chromatographic assay
- Exaggerated / accelerated
  - Multiple solvents of varying polarity
- Simulated use
  - Actual product formulation
  - Simulant solvent(s)
- Combined approach

Extraction Ratio

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Standard surface areas and extract liquid volumes – ISO 10993-12		
Thickness mm	**Extraction ratio** (surface area or mass/volume) ±10 %	**Examples of forms of materials**
<0,5	6 cm^2/ml	Film, sheet, tubing wall
0.5 to 1.0	3 cm^2/ml	Tubing wall, slab, small moulded items
>1.0	3 cm^2/ml	Larger moulded items
>1.0	1,25 cm^2/ml	Elastomeric closures
Irregularly shaped solid devices	0.2 g/ml	Powder, pellets, foam, non-absorbent moulded items
Irregularly shaped porous devices (low-density materials)	0.1 g/ml	Membranes, textiles
NOTE While there are no standardized methods available at present for testing absorbents and hydrocolloids, a suggested protocol is as follows: — determine the volume of extraction vehicle that each 0.1 g or 1.0 cm^2 of material absorbs; — then, in performing the material extraction, add this additional volume to each 0.1 g or 1.0 cm^2 in an extraction mixture.		

Extraction Conditions

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- Standardised extraction conditions (ISO 10993-12)

  a) (37 ± 1) °C for (72 ± 2) hr

  b) (50 ± 2) °C for (72 ± 2) hr

  c) (70 ± 2) °C for (24 ± 2) hr

  d) (121 ± 2) °C for (1 ± 0,1) hr

Analytical Evaluation Threshold (AET)

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$$AET = \frac{DBT \times \frac{A}{BC}}{UF}$$

Where:

AET in µg/mL
DBT (Dose Base Threshold)
A = number of devices used to generate the extract
B = volume of solvent used to generate the extract (mL)
C = number of devices a patient will be in contact with per day
UF is the uncertainty factor of the analytical method(s)

Source: ISO 10993-18 Biological Evaluation of Medical Devices – Chemical Characterisation of Medical Device Materials within a Risk Management Process

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Use of Screening Methods for E&L

Analytical Techniques for E & L

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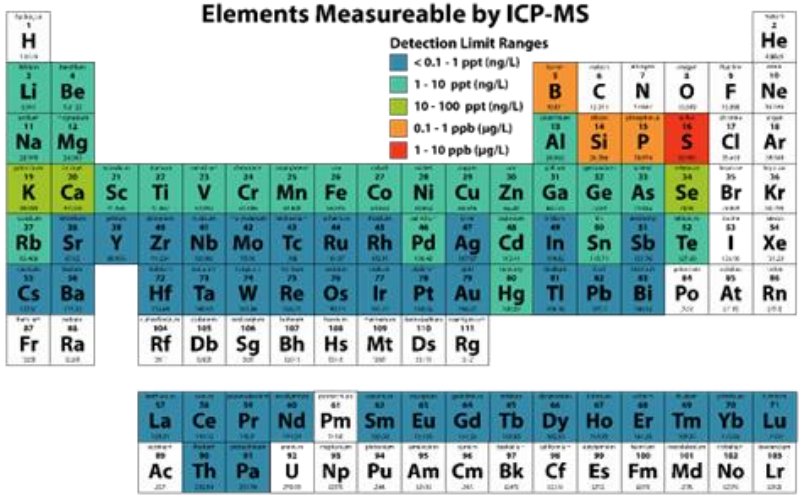
- Organics
  - LC-UV
  - LC-MS^n
  - GC-FID
  - HS-GC-MS
  - GC-MS
- Elemental impurities
  - ICP-OES
  - ICP-MS

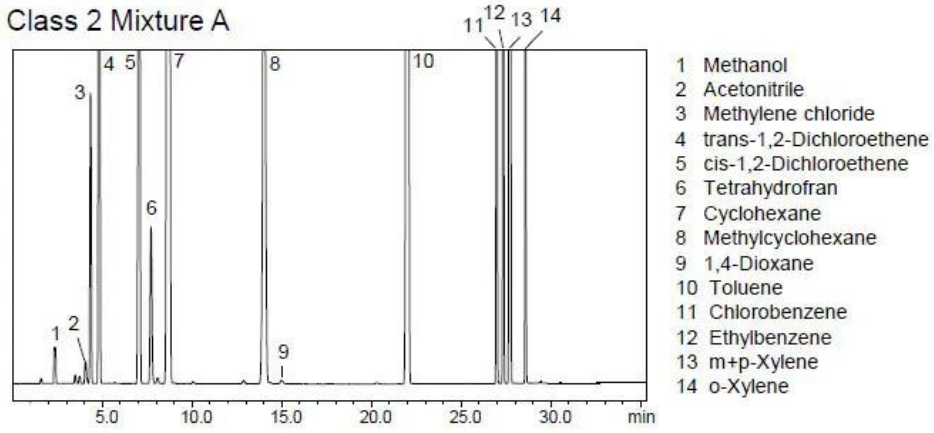
ICP-MS

- Specificity
  - Targeted screening
  - ICH Q3D
- Sensitivity
- Self-validating limit test
- Semi-quantitative / quantitative results



GC-FID

- Non-specific
- Sensitive
  - Targeted screening
    - Residual solvents e.g. USP<467>
- Limit test / proof of absence
- Batch-to-batch variation



GC-MS

- Specific
  - Extensive databases available
    - NIST 20
    - Wiley
- Sensitive
- Variable RRF

GC-MS – additive test mixture

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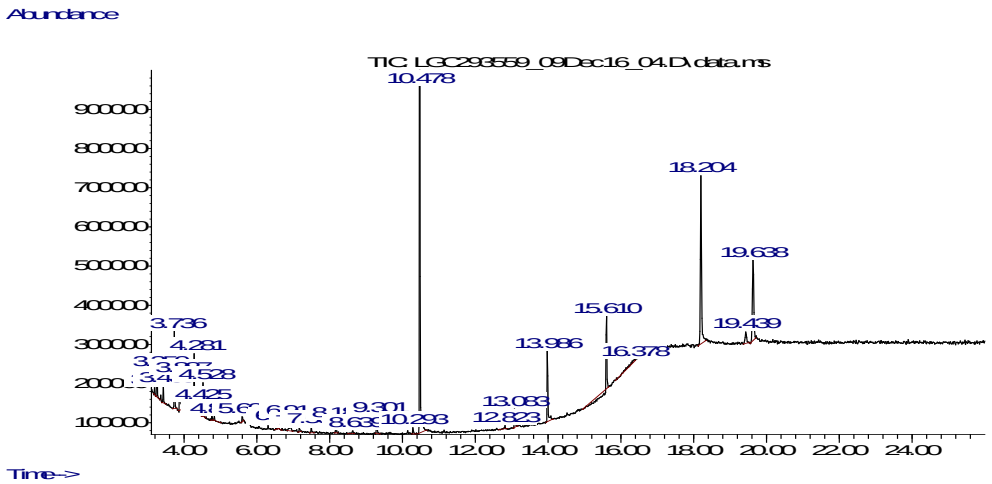

RT (Min)	Standard Name	CAS no
10.478	Benzophenone	000119-61-9
13.083	Stearic acid (Octadecanoic acid)	000057-11-4
13.986	Oleamide (9-Octadecenamide, (Z)-)	000301-02-0
15.610	Erucamide (13-Docosenamide, (Z)-)	000112-84-5
18.204	Irgafos 168	031570-04-4
19.638	Irganox 1076	002082-79-3

GC-MS – alkane test mixture

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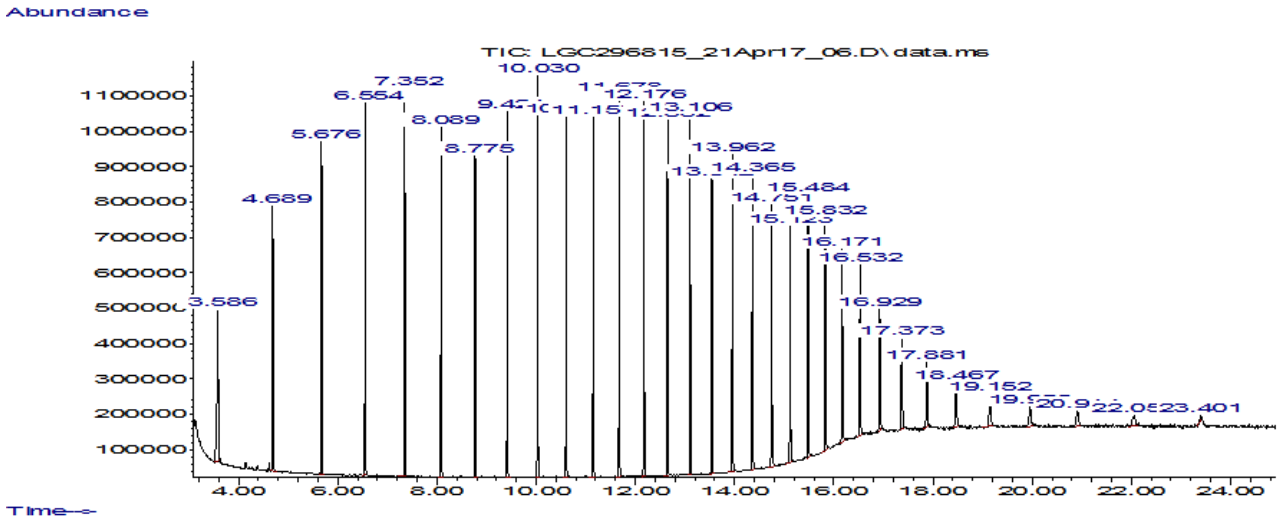

RT (Min)	Standard Name	CAS no
3.698	Octane	000111-65-9
4.826	Nonane	000111-84-2
5.821	Decane	000124-18-5
6.700	Undecane	001120-21-4
7.500	Dodecane	000112-40-3
8.240	Tridecane	000629-50-5
8.929	Tetradecane	000629-59-4
9.574	Pentadecane	000629-62-9
10.190	Hexadecane	000544-76-3
10.764	Heptadecane	000629-78-7
11.319	Octadecane	000593-45-3
11.837	Nonadecane	000629-92-5
12.337	Eicosane	000112-95-8

HPLC-UV

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- Non-specific / prone to interference
- Variable sensitivity
- Standard method of choice for assay and related substances
- Variable RRF

HPLC-UV

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- Monograph methods are usually designed for the determination of multiple impurities
- Methods use a single selected wavelength
- Impurities and drug substance often have very different UV spectra
- Impurities are present at low concentrations

??? How accurate / robust is the use of RRF ???

HPLC-UV - RRF Study

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- Use a range of selected impurities and the chosen drug substance (Ibuprofen) to calculate the “actual” RRF using established HPLC-UV methodology
- Assess the variance in RRF under changing analytical conditions

  e.g. wavelength, slit width, detector accuracy, column manufacturer, impurity concentration

HPLC-UV – Ibuprofen + related substances

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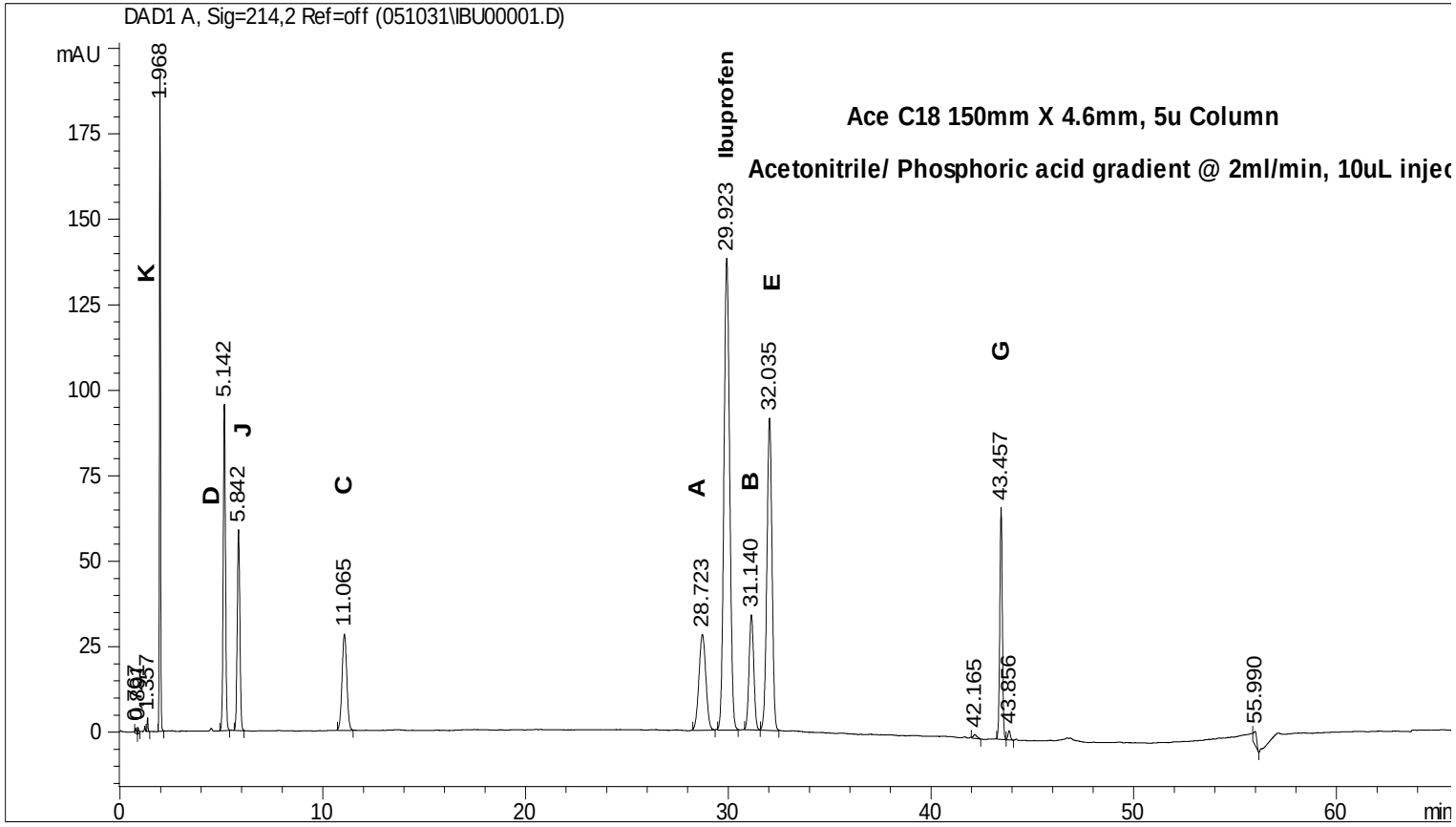

HPLC-UV – Ibuprofen RRF Summary

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Prod.Nr.	Impurity.	m (mg)	Area (abs)	Area (rel)	RRF	Impurity Type
02.00	Ibuprofen	1.002	836236	166913	1.00	Drug Substance
02.13+.33	A+O	1,002+1,018	249869	121768	0.73	Byproduct of Synthesis
02.01	B	1.178	139326	118273	0.71	Byproduct of Synthesis
02.10	C	1.002	123074	122828	0.74	Intermediate
02.11	D	1.071	145838	136170	0.82	Byproduct of Synthesis
02.04	E	1.132	158918	140389	0.84	Degradation product
02.28	F	1.061	139326	131069	0.79	Byproduct of Synthesis
02.38	G	0.990	122549	123787	0.74	Byproduct of Synthesis
02.30	H	1.125	146650	130356	0.78	Byproduct of Synthesis
02.31	I	1.017	58323	57348	0.34	Byproduct of Synthesis
02.02	J	1.154	98309	85190	0.51	Degradation product
02.26	K	1.035	119590	115546	0.69	Degradation product
02.24	L	1.010	117993	116824	0.70	Degradation product
02.34	M	0.951	159398	167611	1.00	Intermediate
02.35	N	1.048	142022	135517	0.81	Byproduct of Synthesis
02.19	P	1.079	167505	155241	0.93	Byproduct of Synthesis
02.36	Q	1.125	146984	130652	0.78	Byproduct of Synthesis
02.37	R	1.196	163622	136808	0.82	Intermediate
02.03	-	0.995	52215	52477	0.31	Degradation product
02.08	-	1.011	35471	35085	0.21	Degradation product
02.09	-	0.969	142022	146566	0.88	Degradation product

HPLC-UV Spectra - Ibuprofen

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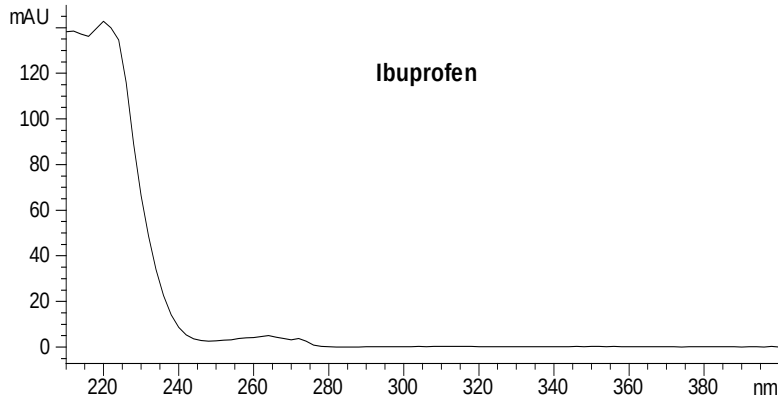
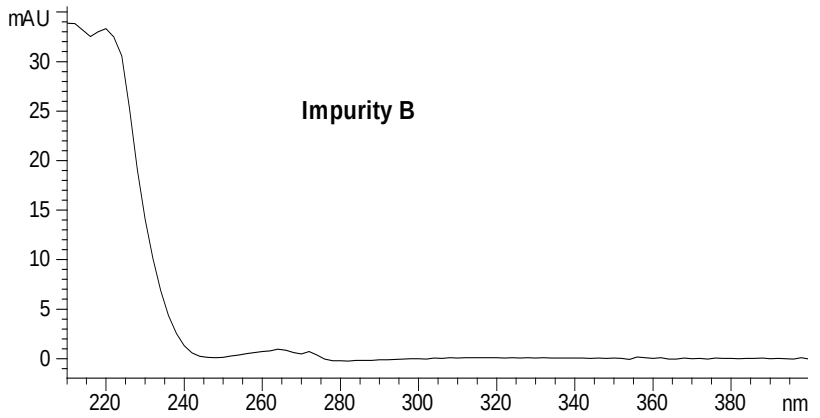
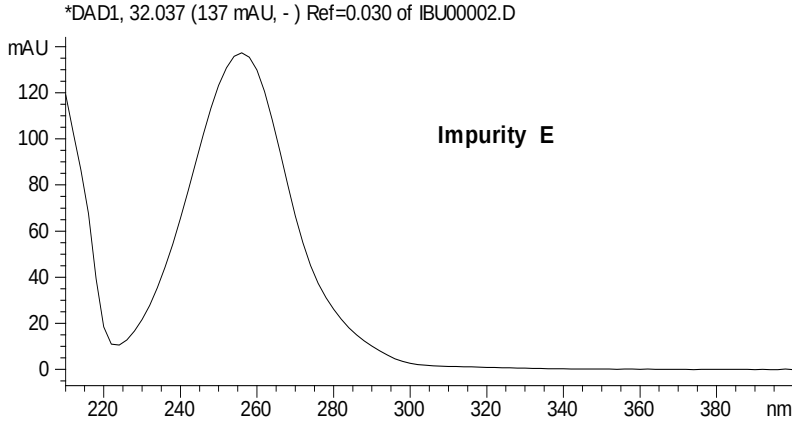
*DAD1, 29.924 (143 mAU, -) Ref=0.030 of IBU00002.D



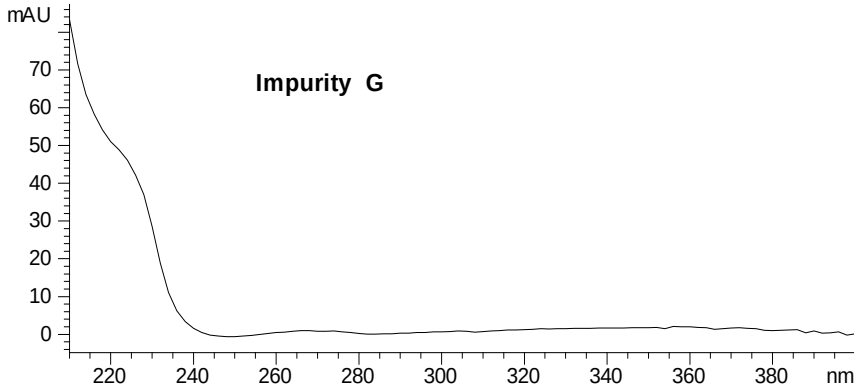
*DAD1, 31.144 (34.1 mAU, -) Ref=0.030 of IBU00002.D



*DAD1, 32.037 (137 mAU, -) Ref=0.030 of IBU00002.D



*DAD1, 43.457 (83.9 mAU, -) Ref=0.030 of IBU00002.D



HPLC-UV - Wavelength Selection

Impurity	% Variation in RRF 204nm	% Variation in RRF 224nm
A	+38%	-86%
B	-3%	-20%
C	+80%	-73%
D	+8%	+6%
E	+12%	-59%
G	-2%	-6%
J	+24%	-87%
K	+38%	-29%

HPLC-UV – Alternate Column Manufacturer

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Impurity	% Variation in RRF
A	-5%
B	-2%
C	-1%
D	-3%
E	-3%
G	-2%
J	-1%
K	-10%

Alternative Detectors - Omeprazole

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Impurity	MS(LCQ) *	MSD*	Corona CAD*
A	0.11	0.53	1.2
B	0.66	1.65	1.1
C	5.95	2.87	1.1
D	1.92	2.17	0.8
F+G	Co elute		
H	1.95	1.08	0.8
I	0.63	1.96	0.9

**Using Volatile Buffer*

Conclusions

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- Small changes in method parameters can result in large variations in RRF
- Variation in RRF increases with decrease of concentration
- RRF can both over and under estimate the levels of impurities
- All detectors show some variation in RRF
- *Extreme care is needed when using RRF*

LC-MS

- High specificity
  - High resolution MS
  - Targeted analysis
  - Limited commercial databases
  - Matrix interference
- High sensitivity
  - MRM
- Variable RRF

LC-MS – Mixed Standard @ 0.1µg/mL

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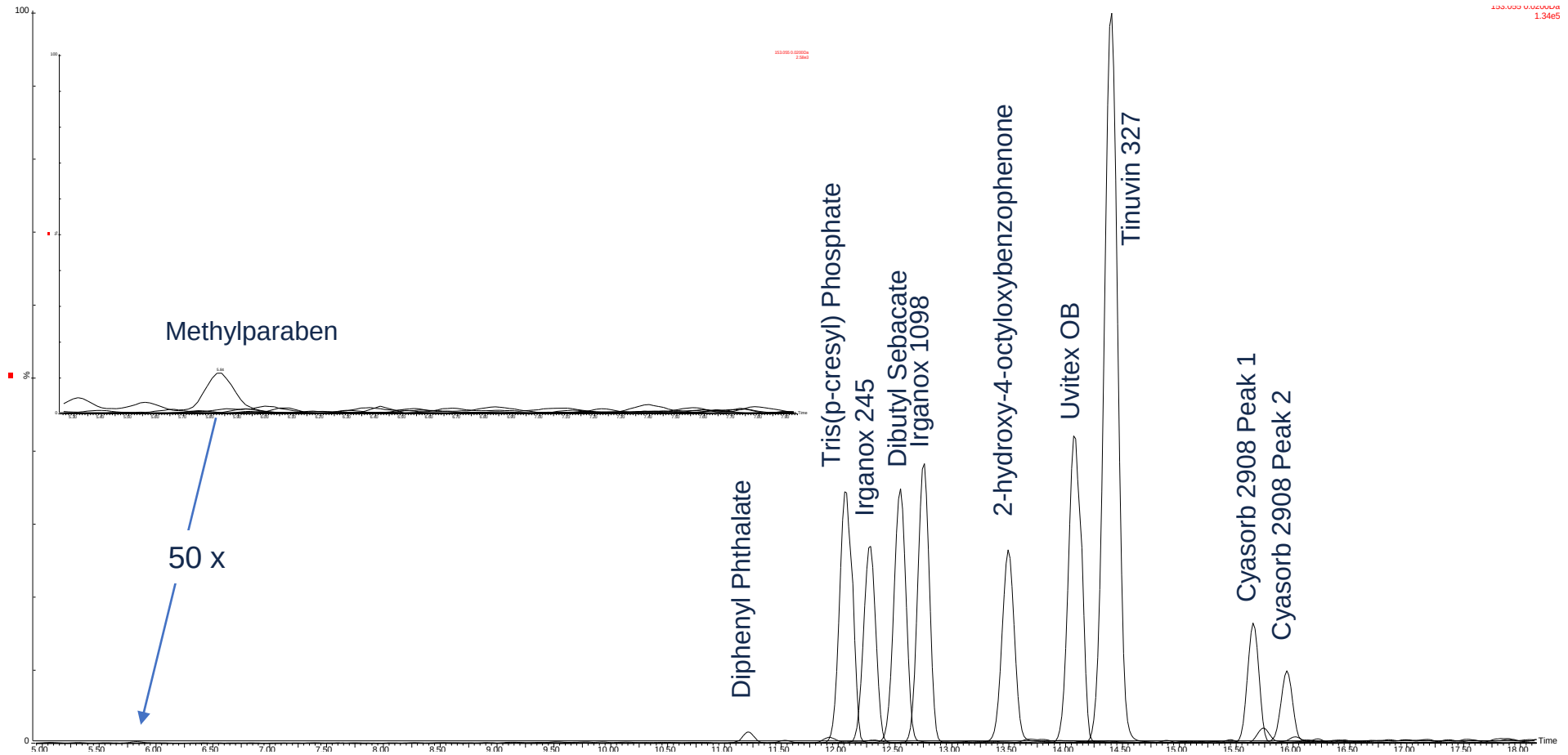

LC-MS – Impact of Cone Voltage

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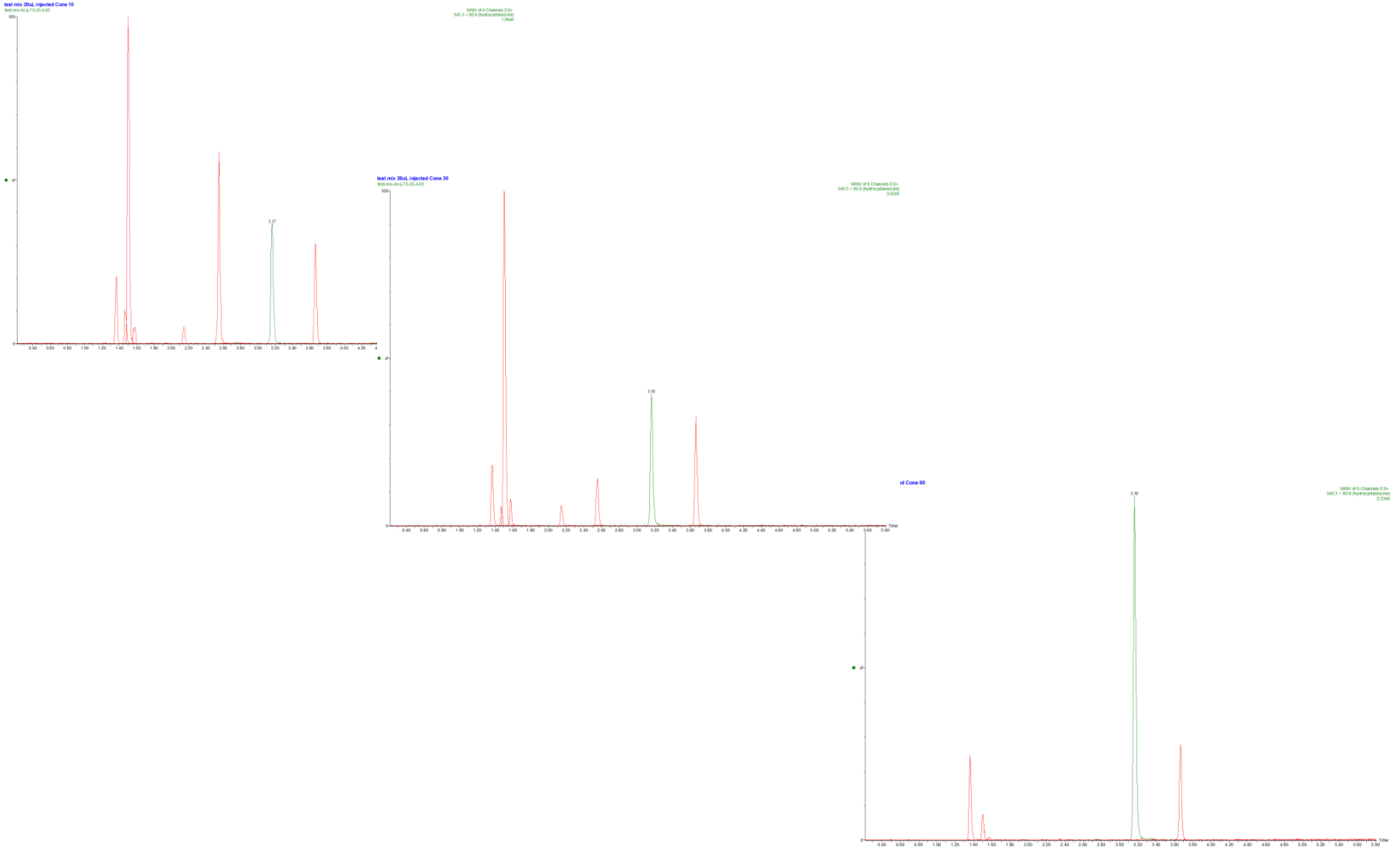

LC-MS – Impact of Cone Voltage

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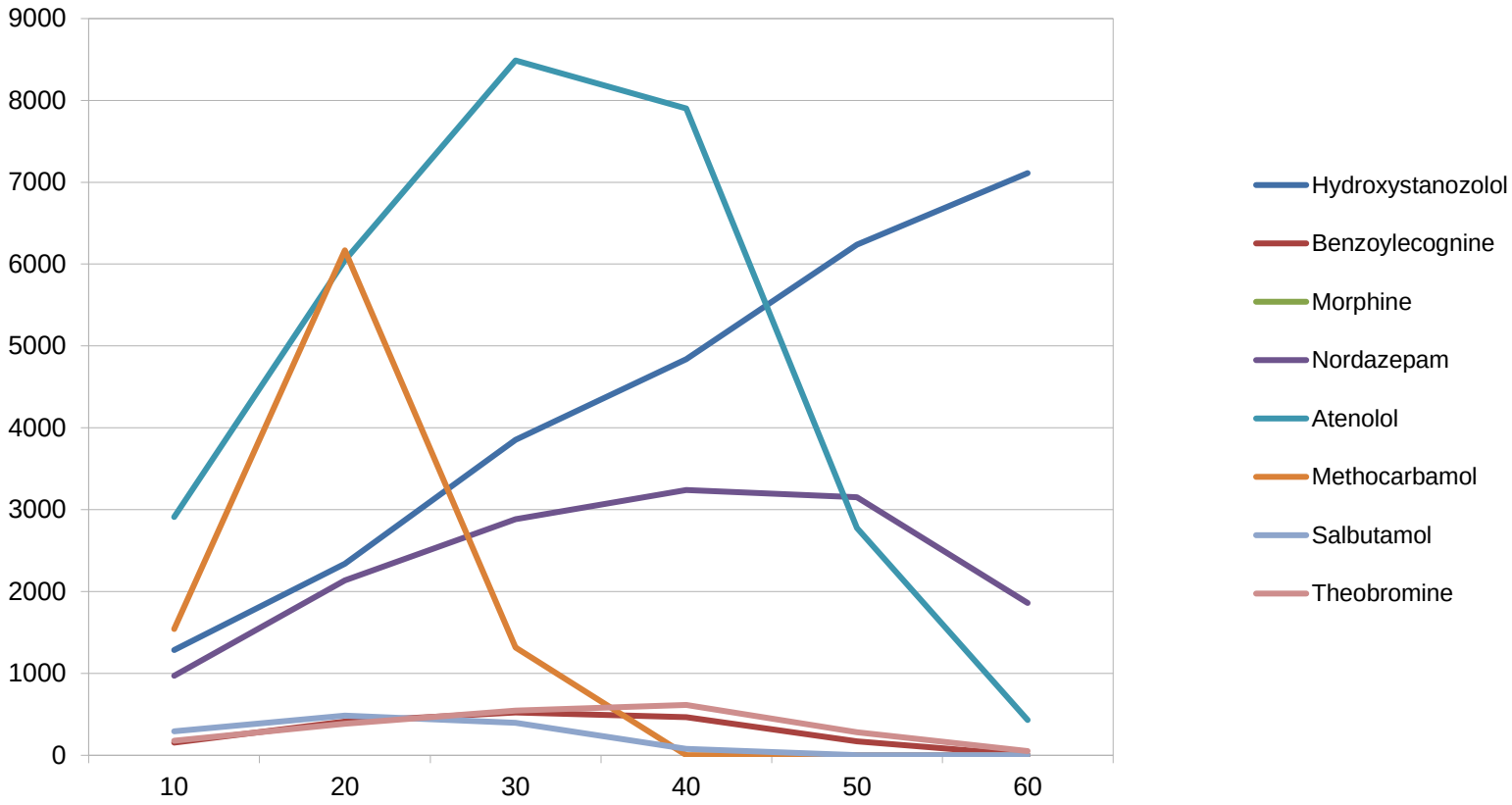

Choice of Reference Standard(s)

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- Matched (where available)
- Related (if possible)
- Low / bracketing RRF (where matched / related standard are not available)
- Threshold marker

Nitrosamines – a cautionary tale

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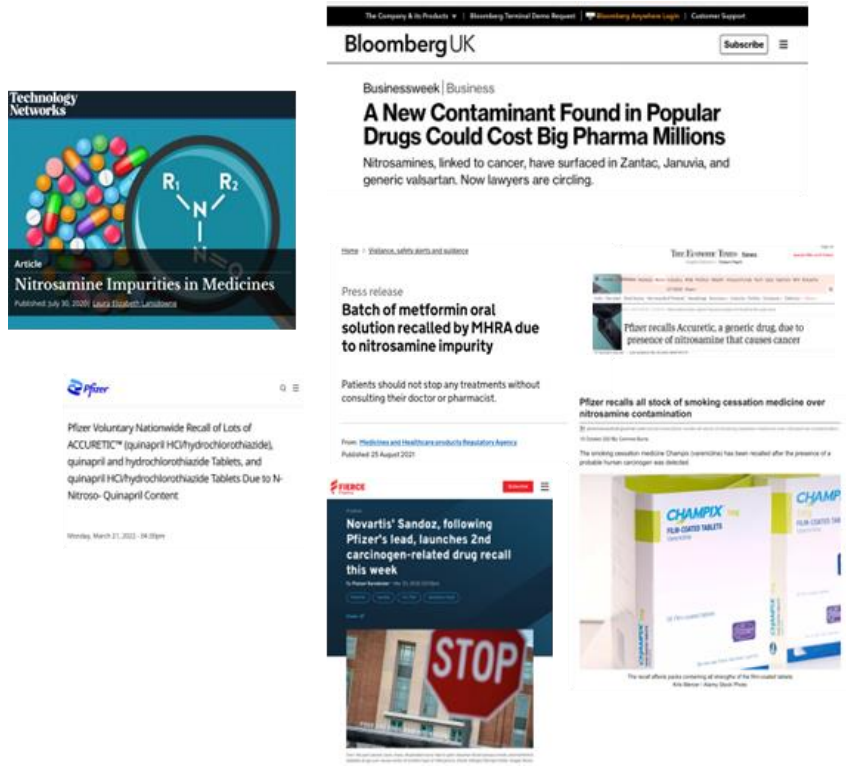
- Levels of N-Nitrosodimethylamine (NDMA) detected in Ranitidine batches
- Suspected carcinogen
- Target analysis required
  - LOD ~ppb
- Not detectable using conventional screening methods



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Validation of Methods for E&L

Method Validation

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- Screening methods
- Analyte specific
- Product specific
- Quantitative assay vs limit test procedure
- Validation parameters (ICH Q2)
  - Specificity; linearity; range; accuracy; precision; LOD; LOQ; robustness

Method Validation

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- Use of method
  - Product development
  - QC of packaging / drug delivery devices
  - Stability testing
  - Routine product QC
- Hybrid methods

Method Validation

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Type of Analytical Procedure	Identification	Testing for Impurities		Assay
		Quantitative	Limit	
Accuracy	-	+	-	+
Precision				
Repeatability	-	+	-	+
Intermediate precision	-	+	-	+
Specificity	+	+	+	+
Detection limit	-	+	+	-
Quantitation limit	-	-(+)	-	-
Linearity	-	+	-	-
Range	-	+	-	-

+ Typically evaluated - Typically not evaluated
Source: ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology

Summary

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- Screening method(s) have a key role in the analysis of E&L
  - Selection of technique(s) needs careful consideration
  - Awareness of the limitations of screening method(s) is required
- Correct choice of standard(s) is vital to validate results
- Good experimental design is vital to ensure cost effective, high quality, robust and reliable E&L data

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Thank you for your attention

Any questions?

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