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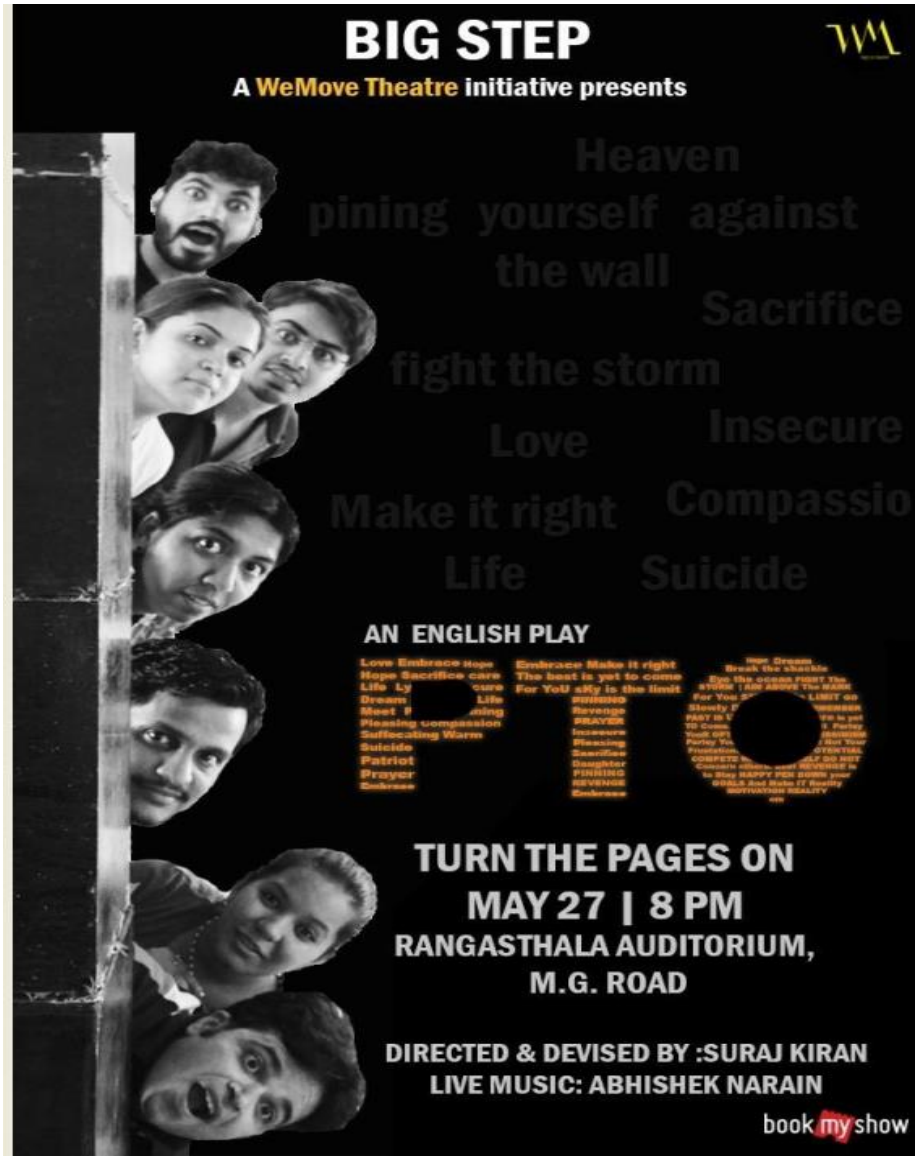
Risk Assessment For Analytical Methods

Manu Grover

Product Manager, Pharmaceuticals

Waters India

What is Risk ?



Why Risk Assessment?

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Why do we have queries from agencies?

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Incomplete data

Impurity profiling
Mass balance Studies
Understanding Innovators
Incomplete specs
Solution Stability

Method Concerns

Justification of analytical /Dissolution conditions
Use of filters etc.
Incomplete validations
In-appropriate LOD/LOQ

Human Concerns

Lack of experience
Lack of awareness
Work Pressure/Timelines
Lack of Training

Sample Concerns

Grade of Material-DMF source-Diff Specs
Input Materials related concerns like P.size, etc.
Solid State Characterization

Areas where "Risk Assessment" is required

Definitions

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A systematic process of evaluating the potential risks that may be involved in a projected activity or undertaking.

Risk assessment is the process where you:

- Identify Weak Parameters/process
- Analyze or evaluate the risk associated with that weak parameter
- Determine appropriate ways to eliminate or control the weak parameter.

A risk assessment is a thorough look at your analytical methods to identify those process/parameters etc that may cause analytical issues like ir-reproducibility, non-compliance, loss of resolution etc .

Evaluation of how likely and severe the risk is, and then decide what measures should be in place to effectively prevent or control the harm.

Regulations Reference

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ICH Q9 Quality Risk Management – Regulatory Perspective

- Integrated quality management
- Regulatory operations
- Development
- Facilities, equipment, utilities
- Materials management
- Production
- Laboratory control and stability studies
- Packaging and labeling

- System Risk (facility & people)
  - e.g., interfaces, operators risk, environment, components such as equipment, IT, design elements
- System Risk (organisation)
  - e.g., Quality systems, controls, measurements, documentation, regulatory compliance
- Process Risk
  - e.g., process operations and quality parameters
- Product Risk (safety & efficacy)
  - e.g., quality attributes: measured data according to specifications

Regulations Reference

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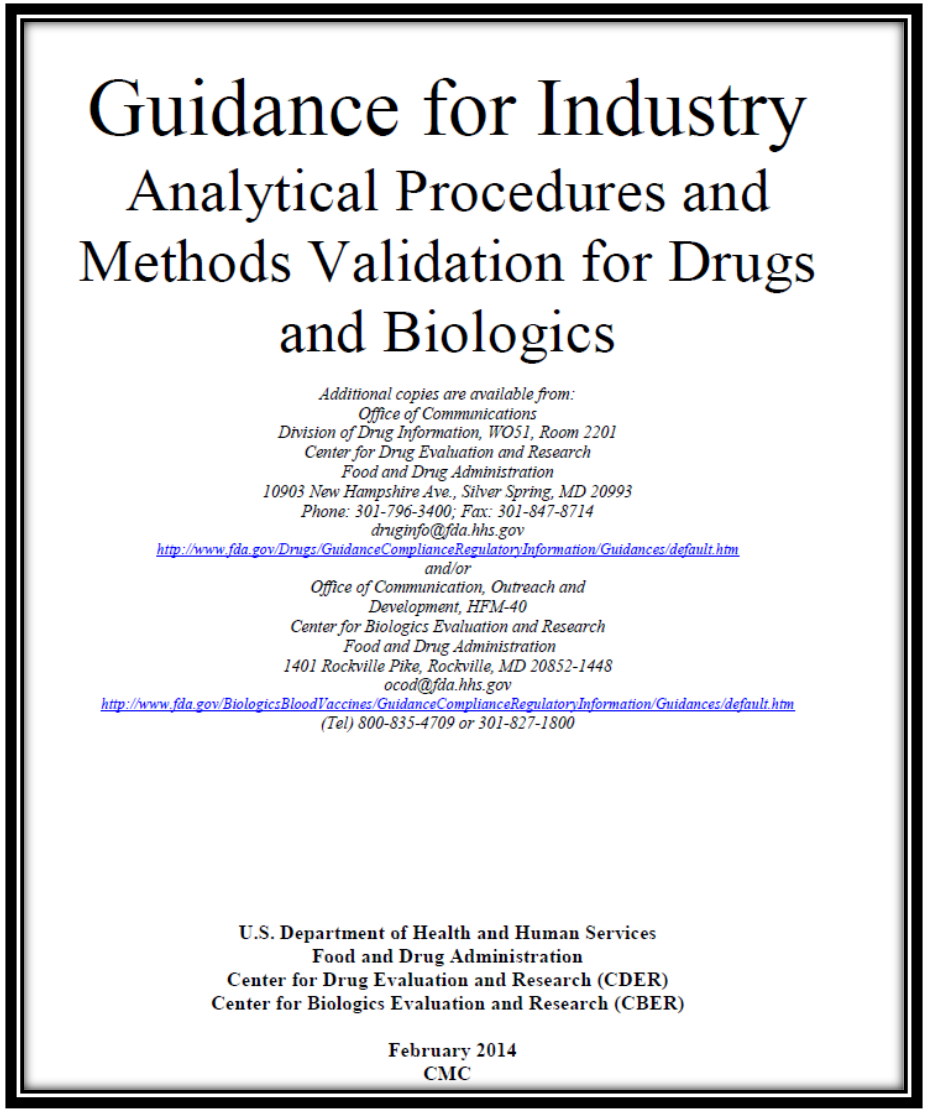

Guidance for Industry

Analytical Procedures and Methods Validation for Drugs and Biologics

Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or
Office of Communication, Outreach and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
(Tel) 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2014
CMC

Regulations Reference

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Analytical procedures verification or validation data should be submitted in the corresponding sections of the application in the ICH *M2 eCTD: Electronic Common Technical Document Specification*.[11]

When an analytical procedure is approved/licensed as part of the NDA, ANDA, or BLA, it becomes the FDA-approved analytical procedure for the approved product. This analytical procedure may originate from FDA recognized sources (e.g., a compendial procedure from the *United States Pharmacopeia/National Formulary* (USP/NF)) or a validated procedure you submitted that was determined to be acceptable by FDA. To apply an analytical method to a different drug product, appropriate validation or verification studies for compendial procedures with the matrix of the new product should be considered.

III. ANALYTICAL METHODS DEVELOPMENT

An analytical procedure is developed to test a defined characteristic of the drug substance or drug product against established acceptance criteria for that characteristic. Early in the development of a new analytical procedure, the choice of analytical instrumentation and methodology should be selected based on the intended purpose and scope of the analytical method. Parameters that may be evaluated during method development are specificity, linearity, limits of detection (LOD) and limits of quantitation (LOQ), range, accuracy, and precision.

During early stages of method development, the robustness of methods should be evaluated because this characteristic can help you decide which method you will submit for approval. Analytical procedures in the early stages of development are initially developed based on a combination of mechanistic understanding of the basic methodology and prior experience. Experimental data from early procedures can be used to guide further development. You should submit development data within the method validation section if they support the validation of the method.

To fully understand the effect of changes in method parameters on an analytical procedure, you should adopt a systematic approach for a method robustness study (e.g., a design of experiments with method parameters). You should begin with an initial risk assessment and follow with multivariate experiments. Such approaches allow you to understand factorial parameter effects on method performance. Evaluation of a method's performance may include analyses of samples obtained from various stages of the manufacturing process from in-process to the finished product. Knowledge gained during these studies on the sources of method variation can help you assess the method performance.

QbD based development

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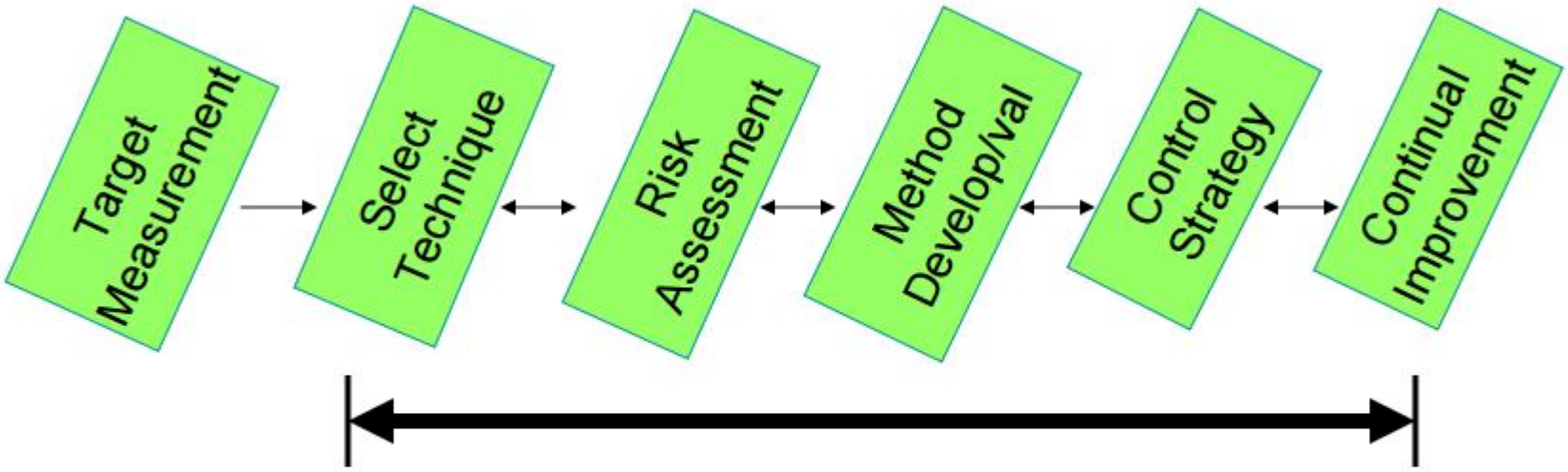
QbD Approach to Analytical Methods



- Allow continual feedback and feed-forward interactions among all steps.
- Meet and maintain method performance criteria

Define Risk Factor

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Analytical Method and Risk Management

Risk Factor = Severity x Occurrence x Detectability

- Severity = Effect on Patient
  - Related to safety or efficacy (CQAs)
  - Different than impact of a manufacturing failure
- Likelihood of Occurrence = Chance of Failure
  - Related to product and process knowledge and controls
  - Includes uncertainty for new processes or process changes
- Detectability = Ability to Detect a Failure
  - Appropriateness and capability of analytical method
  - Sampling considerations

Risk Assessment tools-Analytical

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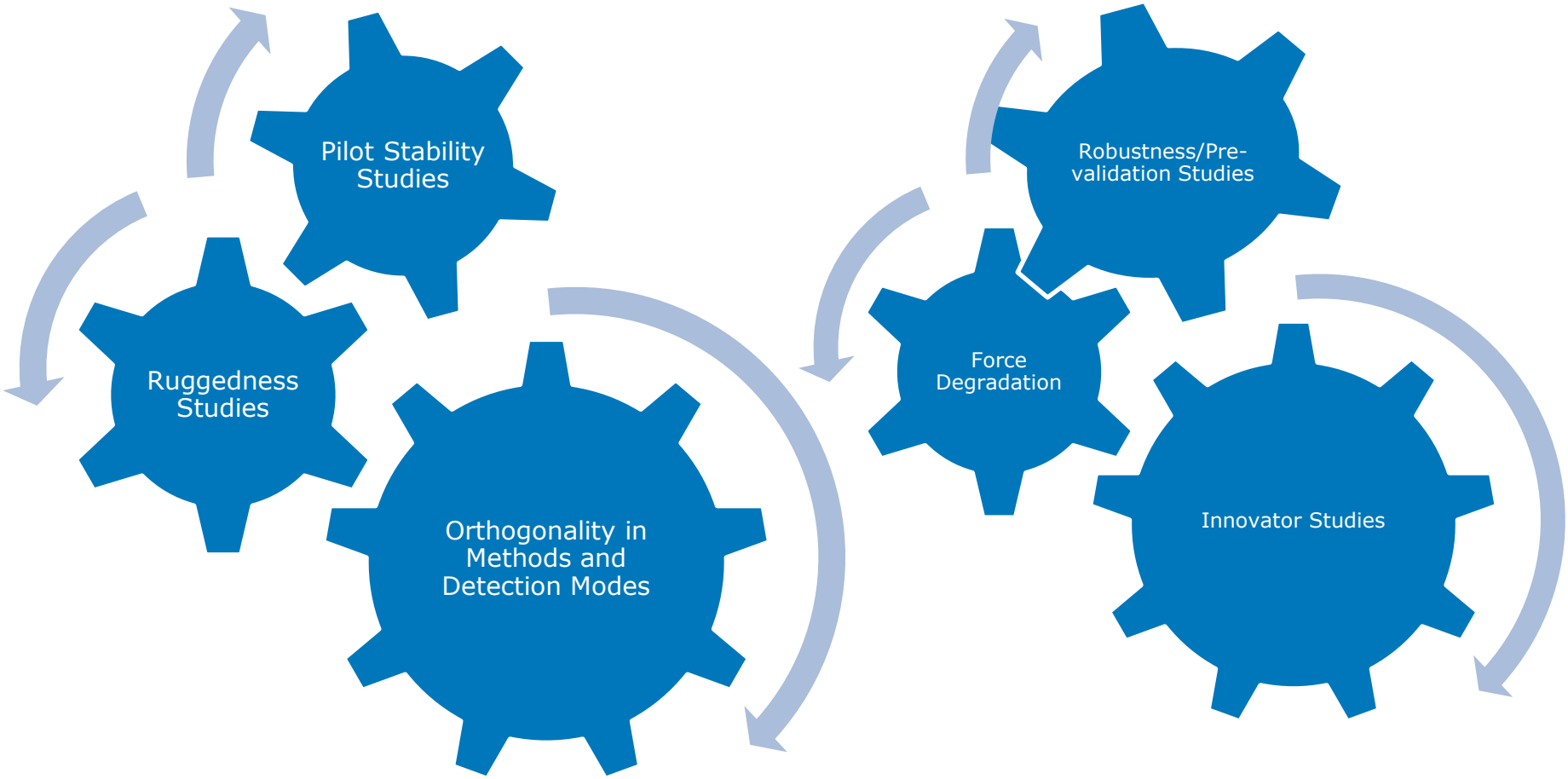

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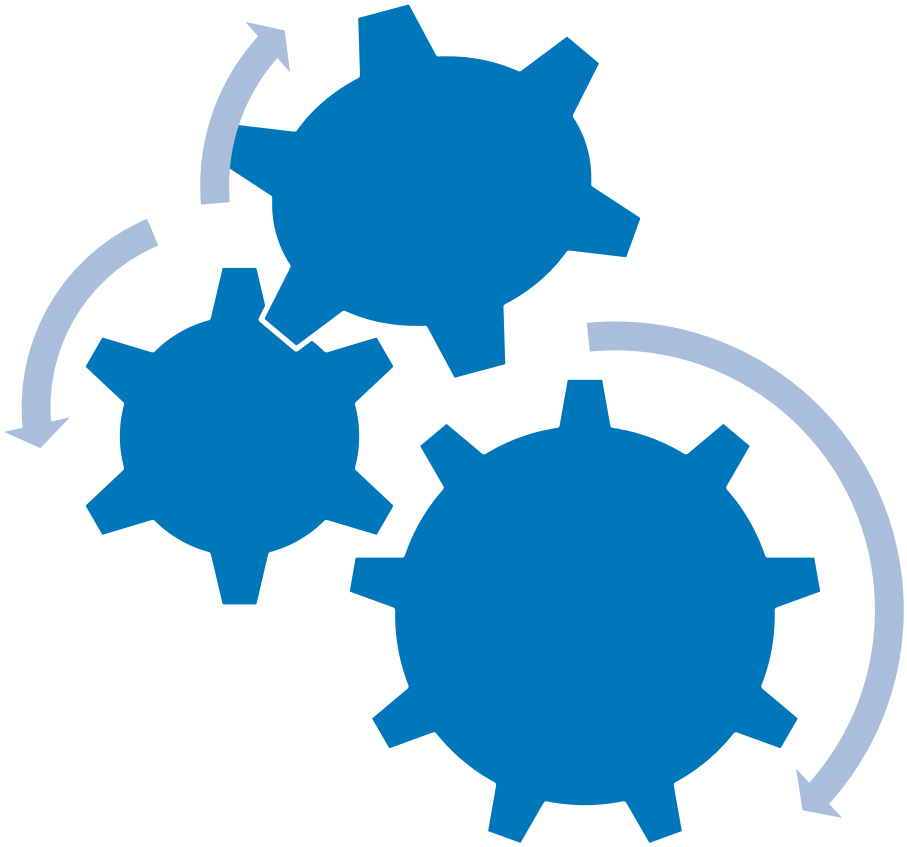

Generating Chemical Equivalency data

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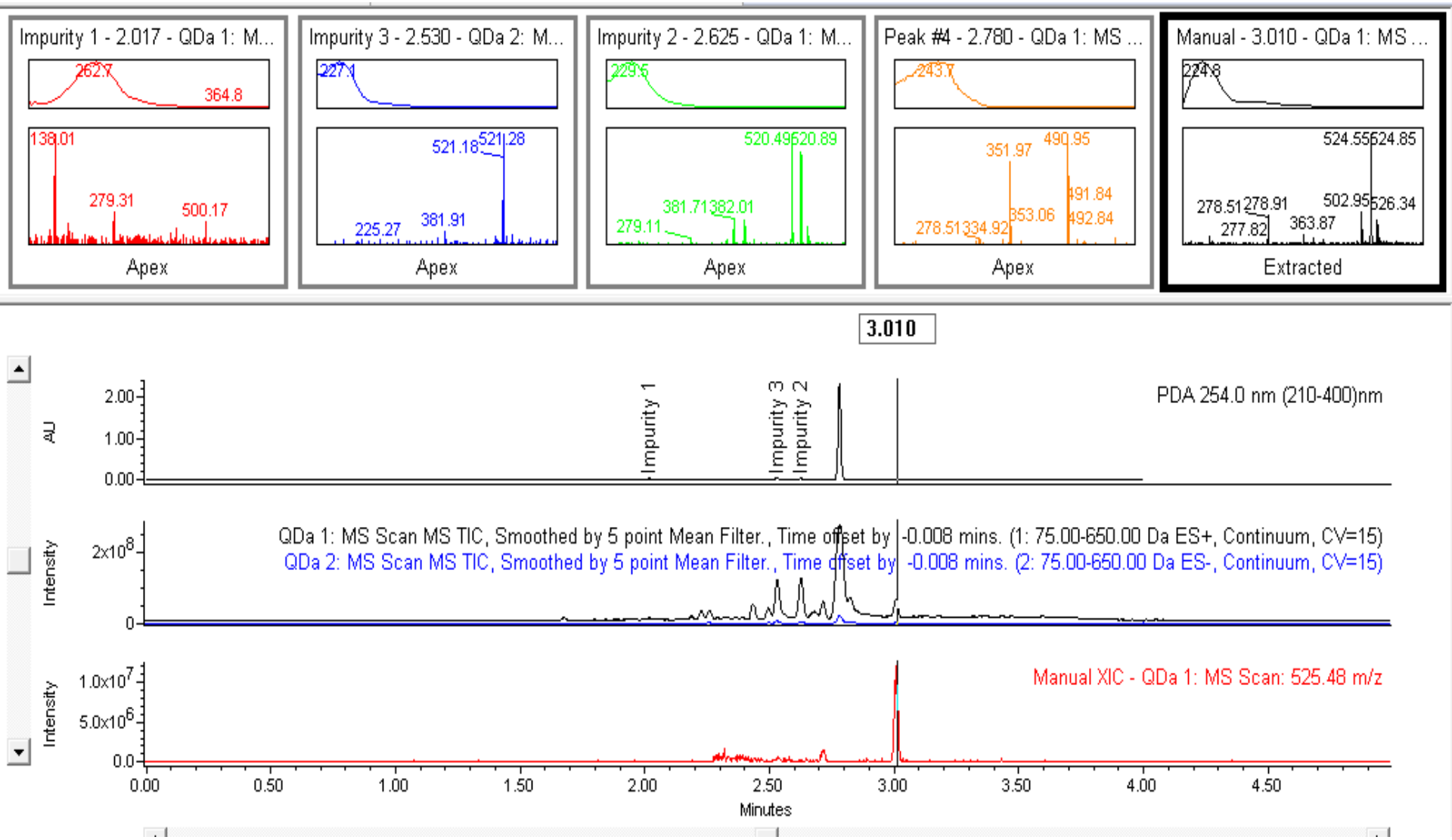

Finger Printing the Product

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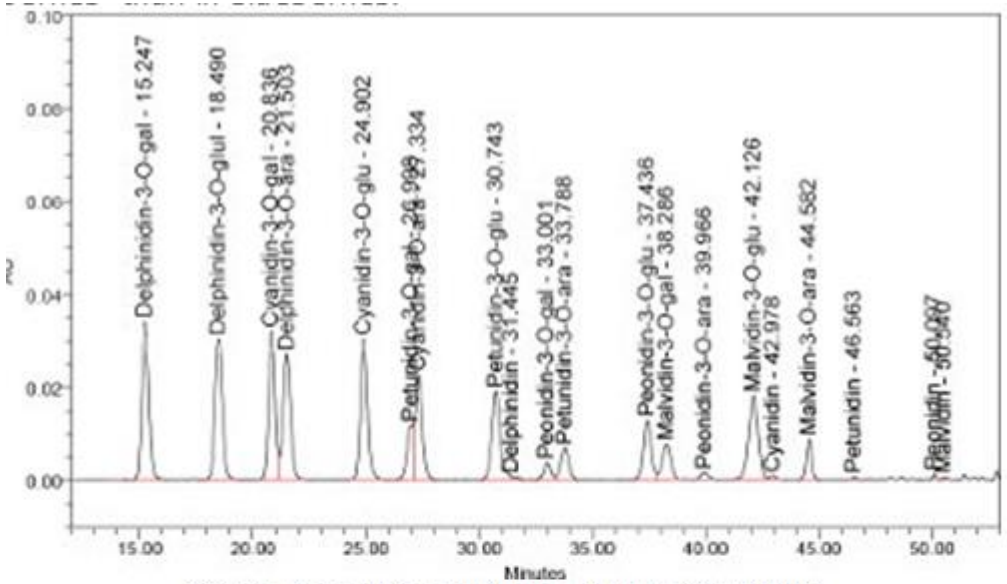
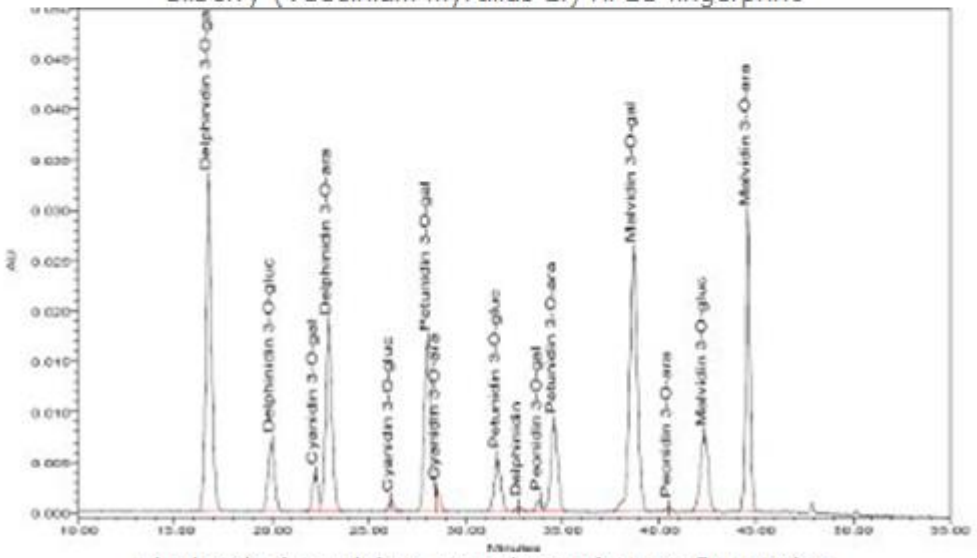


Bilberry (Vaccinium myrtillus L.) HPLC fingerprint



Blueberriy (Vaccinium corymbosum) HPLC fingerprint

COM

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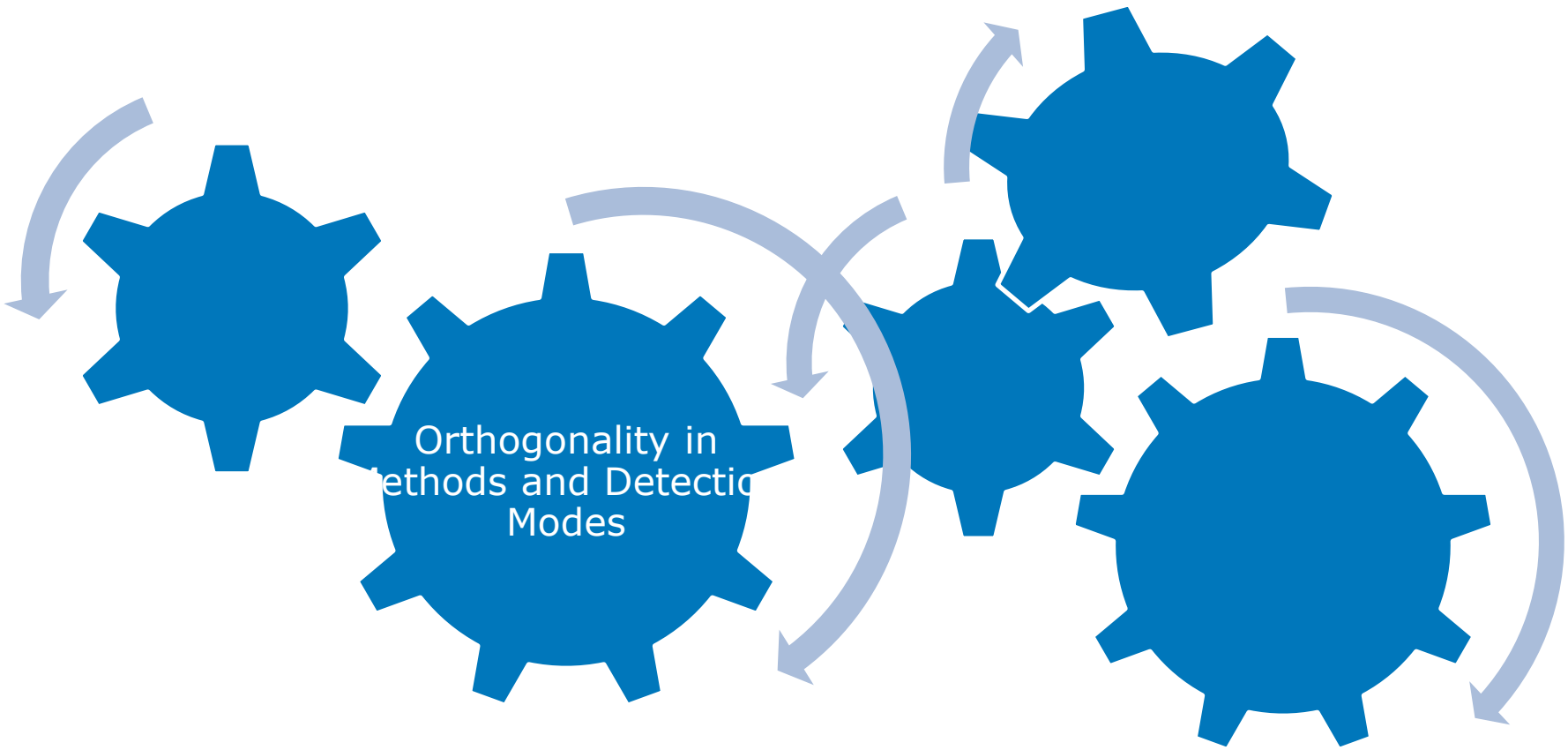

Orthogonality in detection modes

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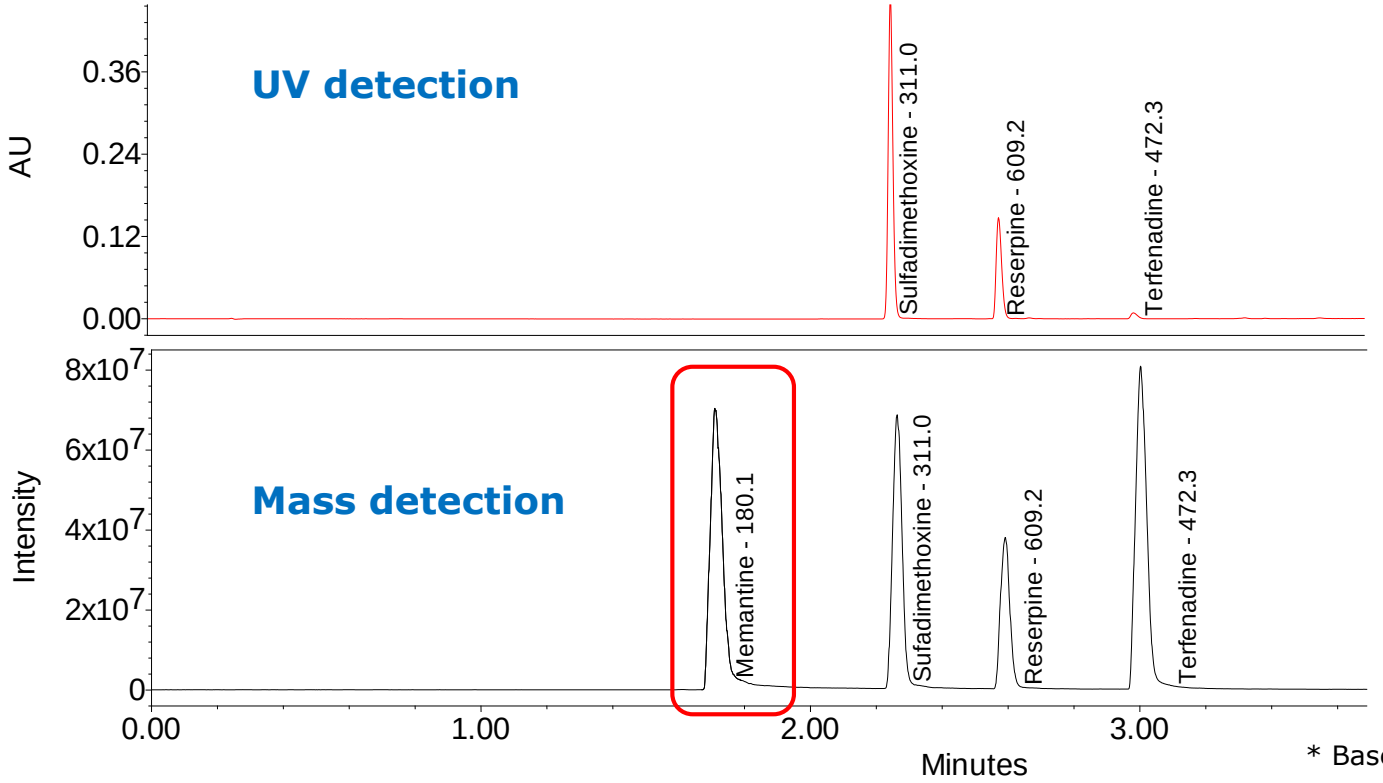
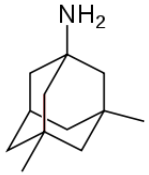


Don't miss anything - use complementary detection techniques (UV and MS)

* Base-peak mass annotation



Memantine has no chromophore and requires alternate detection techniques to UV

Detection, What can analytical scientists do !

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- **UV** – good sensitivity, precision, limited selectivity and qualitative, good diagnostic tool.
- **PDA** – good sensitivity, precision, qualitative information, peak purity, diagnostic tool.
- **ELSD** – universal response, complimentary to PDA or UV, high throughput, no qualitative.
- **QDa** – excellent selectivity, lead time, sensitivity, qualitatively superior, higher cost, highly versatile with detection options and info acquired.

High confident data in one injection !

Bringing in Next level of PDA detection

Sensitivity of Mass and Simplicity of UV/PDA detector

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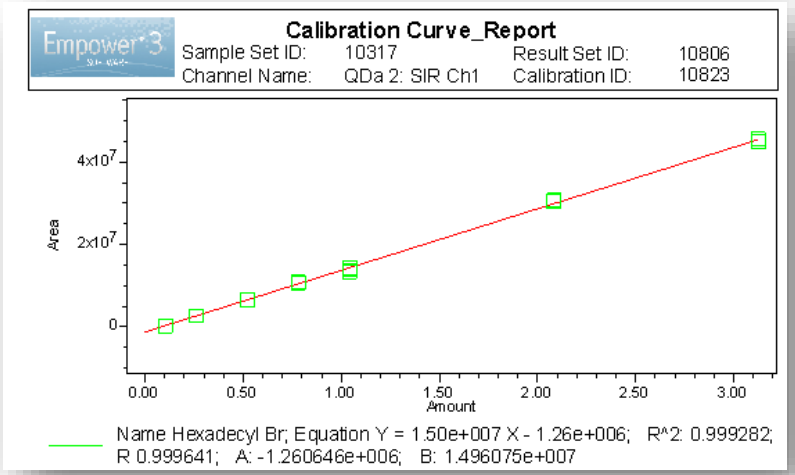

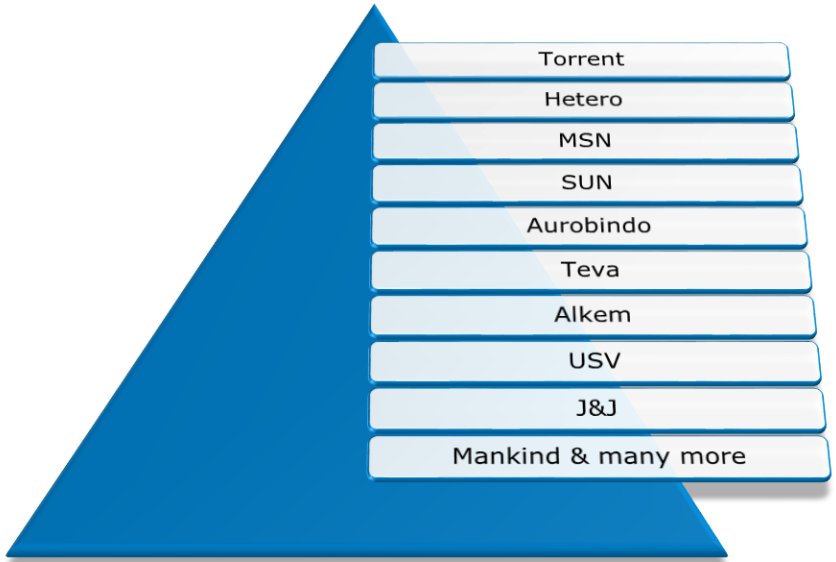

Data: PDA/ELSD/QDa

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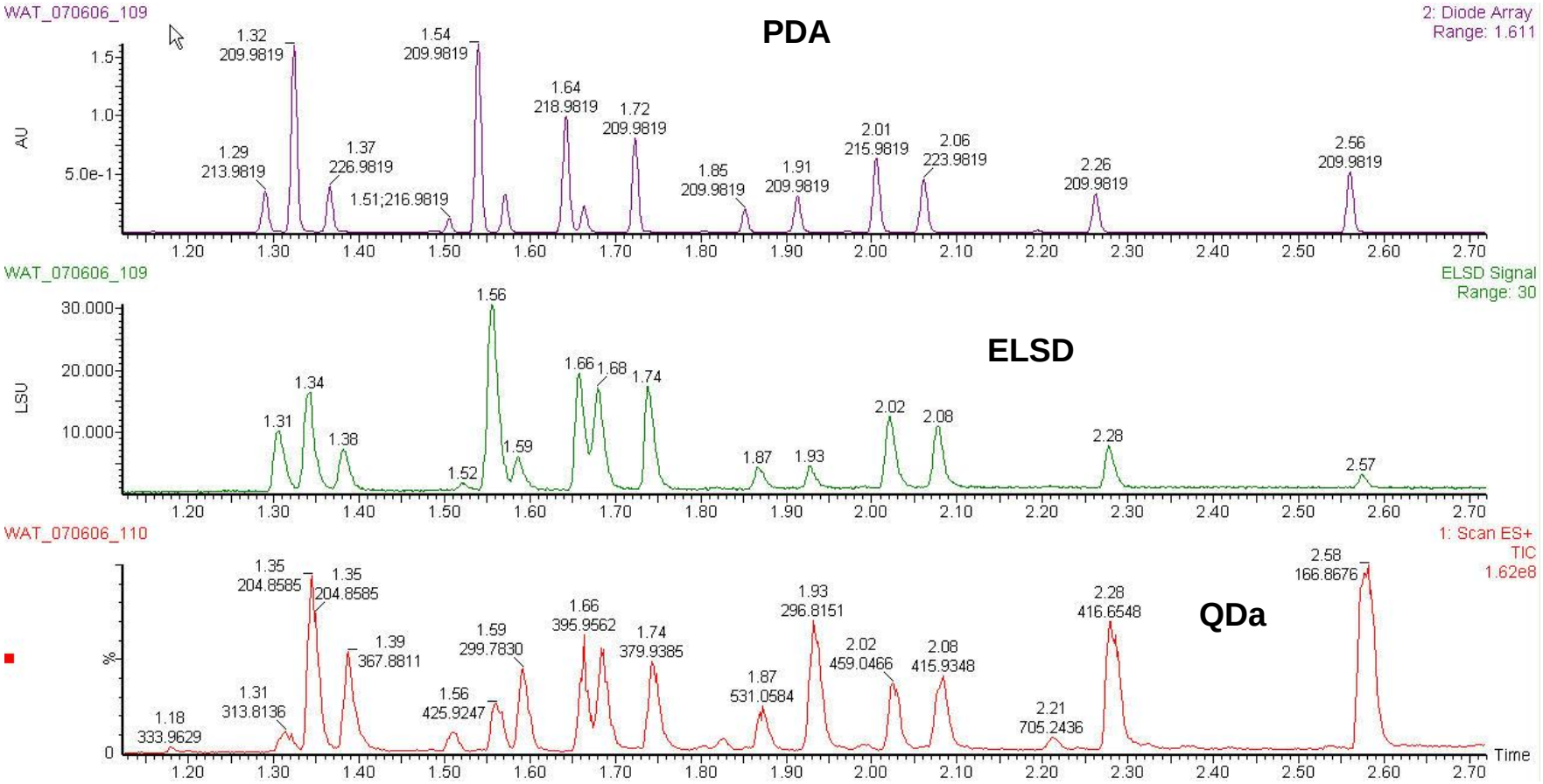

High confident data in one injection !

Those who can use PDA can use QDa

Profile and quantify more analytes....

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- Easy to use, robust mass detection allows quick and reproducible analysis
- Affordable and low running cost
- Readily deployable in QC environment-Easy and Compliant

System Suitability Report 2

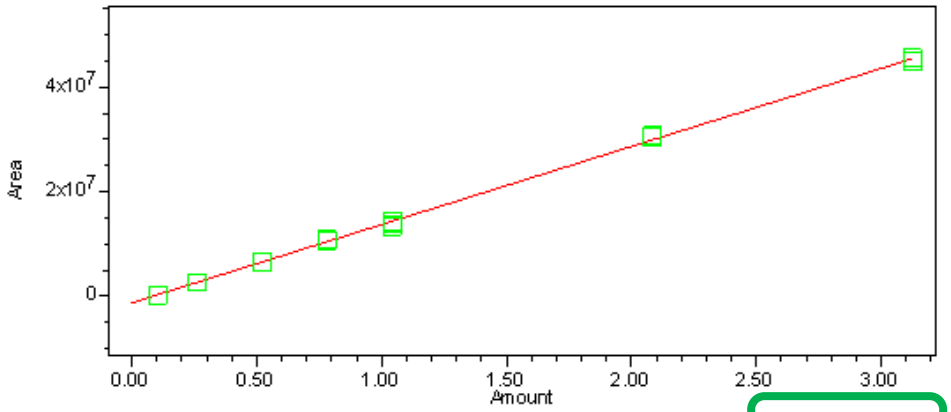
Sample Set ID: 2565
Result Set ID: 6781
Channel Name: QDa 2: SIR Ch1

Name: Cetrimonium Br

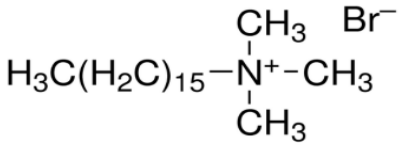
	Name	Inj	RT	Area	USP Tailing	K Prime
1	Cetrimonium Br	1	1.086	132801434	1.1	3.3
2	Cetrimonium Br	2	1.085	132176370	1.1	3.3
3	Cetrimonium Br	3	1.084	133458598	1.1	3.3
4	Cetrimonium Br	4	1.084	133265613	1.1	3.3
5	Cetrimonium Br	5	1.082	130749136	1.1	3.3
6	Cetrimonium Br	6	1.082	130945752	1.1	3.3
Mean			1.084	132232817	1.1	3.3
Std. Dev.			0.002	1162201.831		
% RSD			0.16	0.88		

Calibration Curve_Report

Sample Set ID: 10317 Result Set ID: 10806
Channel Name: QDa 2: SIR Ch1 Calibration ID: 10823



Name Hexadecyl Br; Equation Y = 1.50e+007 X - 1.26e+006; R^2: 0.999282;
R 0.999641; A: -1.260646e+006; B: 1.496075e+007



Risk Assessment tools-Analytical

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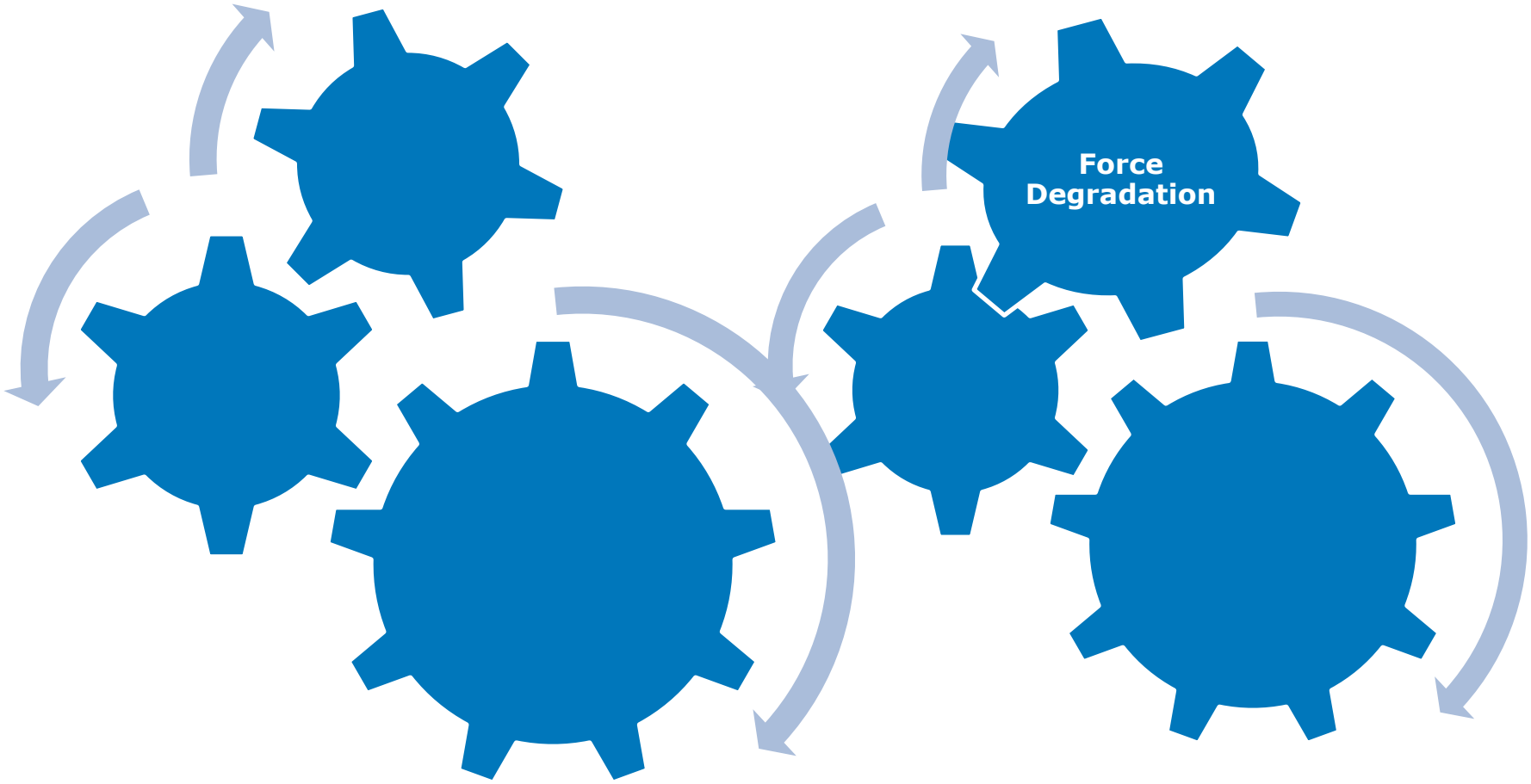

Reporting Force degradation studies

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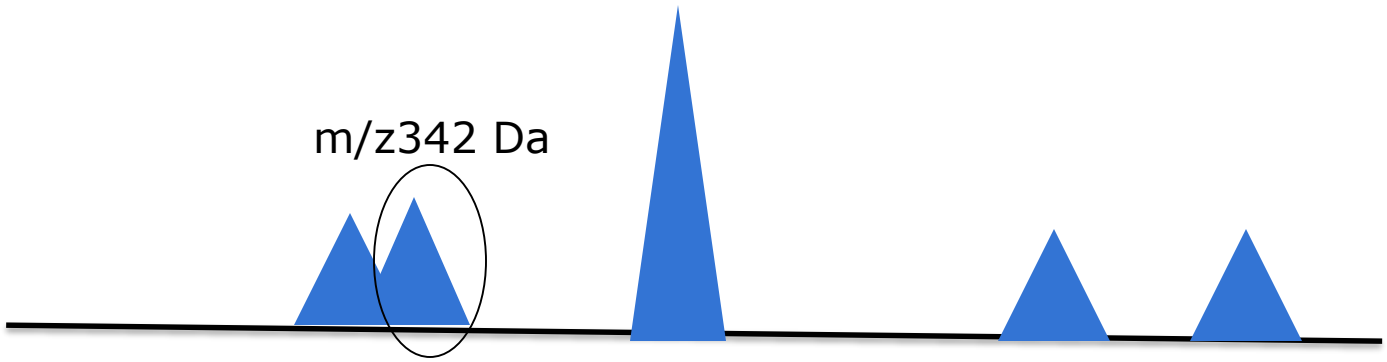
Degradation type: Stressed 60°C/0.1NHCl		
RRT	λmax/Mass	Type
0.6	298nm/324Da	Process
0.65	285nm/342Da	Degradation
1.2	280nm/392Da	Degradation
1.8	278nm/442Da	Process
2.2	269nm/452Da	Degradation
2.25	289nm/469Da	Process

Degradation type: Stressed 60°C/0.1N NaOH		
RRT	λmax/Mass	Type
0.6	298nm/324Da	Process
0.7	285nm/347Da	Degradation
0.8	289nm/356Da	Degradation
1.2	280nm/392Da	Degradation
1.8	278nm/442Da	Process
2.25	289nm/469Da	Process

Stability 40°C/75%RH 12 Months, HDPE Bottle



ACQUITY QDa for mass balance studies....

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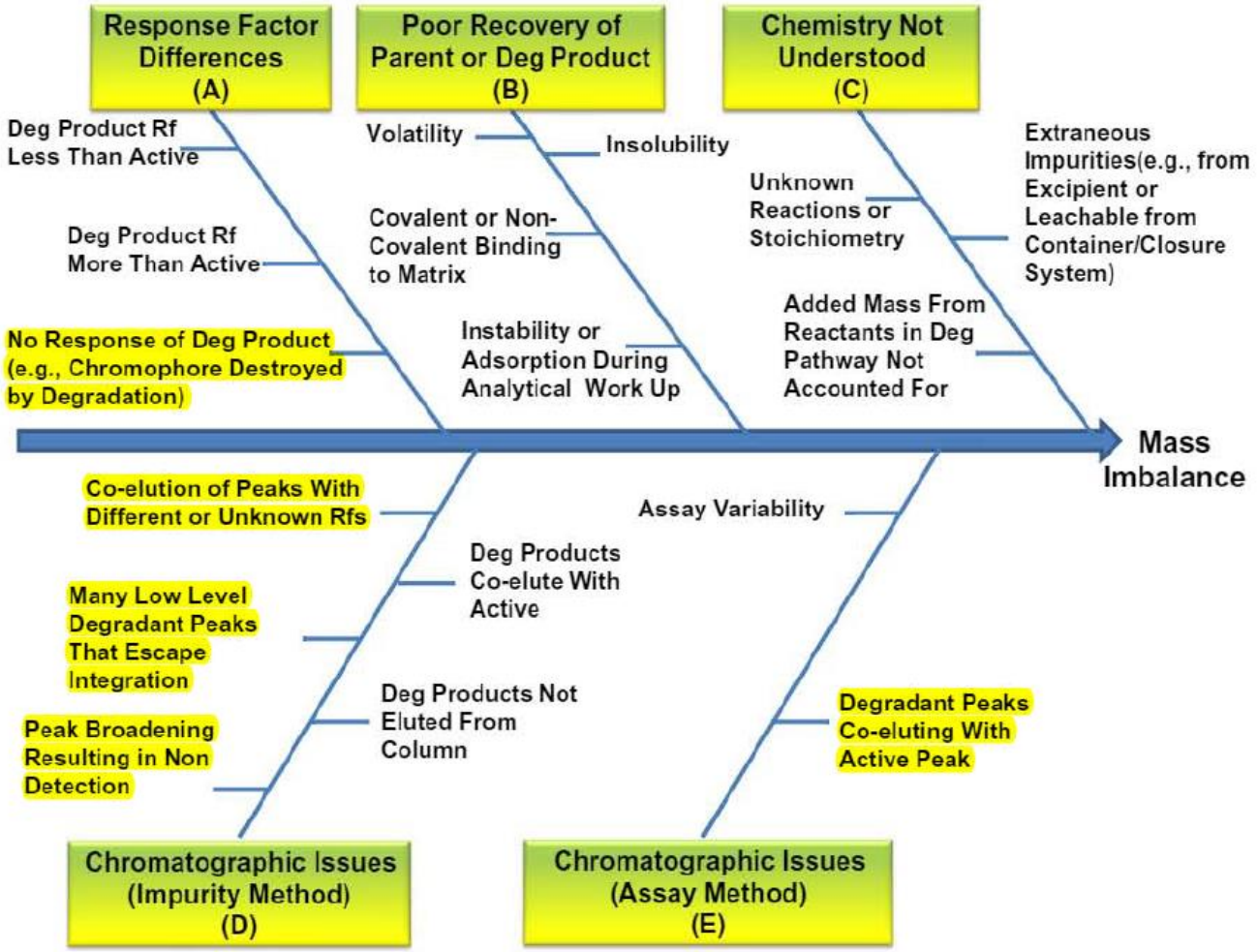

Sources of mass imbalance and where mass detection via QDa can help...

Review

Assessing mass balance in pharmaceutical drug products: New insights into an old topic

Steven W. Baertschi [a,*], Brian W. Pack [a], Cherokee S. Hoaglund Hyzer [a], Mark A. Nussbaum [b]

[a] Small Molecule Design and Development, Eli Lilly and Company, Indianapolis, IN 46285, USA
[b] Department of Chemistry, Hillsdale College, 33 East College St. Hillsdale, MI 49242, USA

Risk Assessment tools-Analytical

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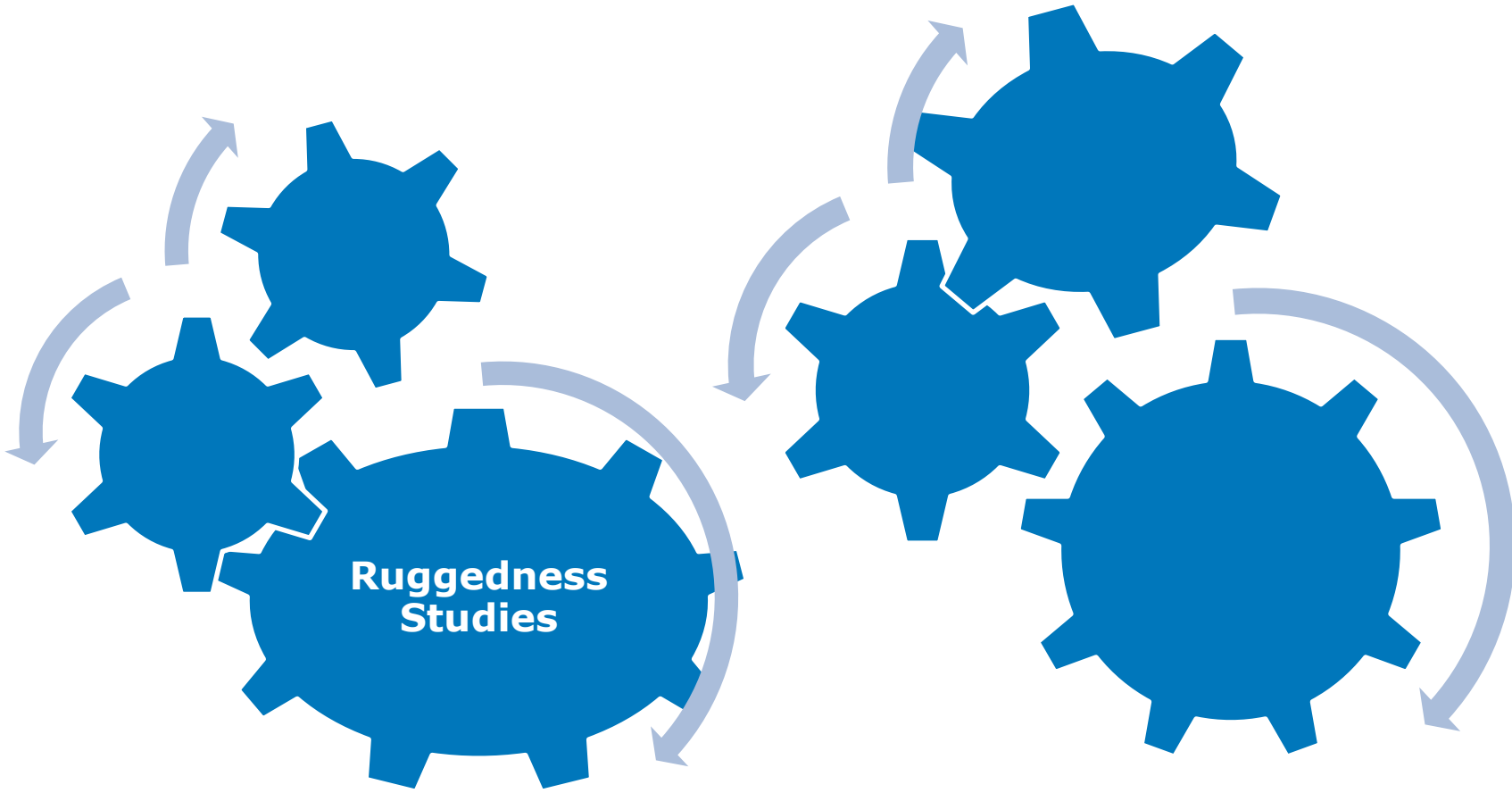

Robustness & Ruggedness

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- Degree of reproducibility of test results under a variety of conditions
  - Different Laboratories
  - Different Analysts
  - Different Instruments
  - Different Reagents
  - Different Days
  - Etc.
- Expressed as %RSD

Typical variations in LC

- ❑ Variations of pH
- ❑ Variations in mobile phase
- ❑ Different columns
- ❑ Temperature
- ❑ Flow rate

Robustness: Variations in pH

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Quaternary Solvent Manager-R — Auto•Blend Plus™

General | Solvents | Misc | Data

Buffer system: * pH2.9-3.8 Formic Acid Ammonia 25mM Incl. Organic

Concentration to deliver: 25 mM

Recommended pH range: 2.95 to 3.79

Acid: 125mM Formic Acid — 125 mM
Base: 125mM Ammonium Hydroxide — 125 mM
Organic: Acetonitrile — 100 %
Aqueous: Water

	Time	Flow (mL/min)	pH	pH Curve	Organic (%)	Organic Curve
1	Initial	1.000	2.95	Initial	5.00	Initial
2	5.00	1.000	2.95	6	40.00	6
3	5.50	1.000	2.95	6	80.00	6
4	6.00	1.000	2.95	6	80.00	6
5	6.50	1.000	2.95	6	5.00	6
6	10.00	1.000	2.95	6	5.00	6
7	30.00	0.100	2.95	6	50.00	11

Quaternary Solvent Manager-R — Auto•Blend Plus™

General | Solvents | Misc | Data

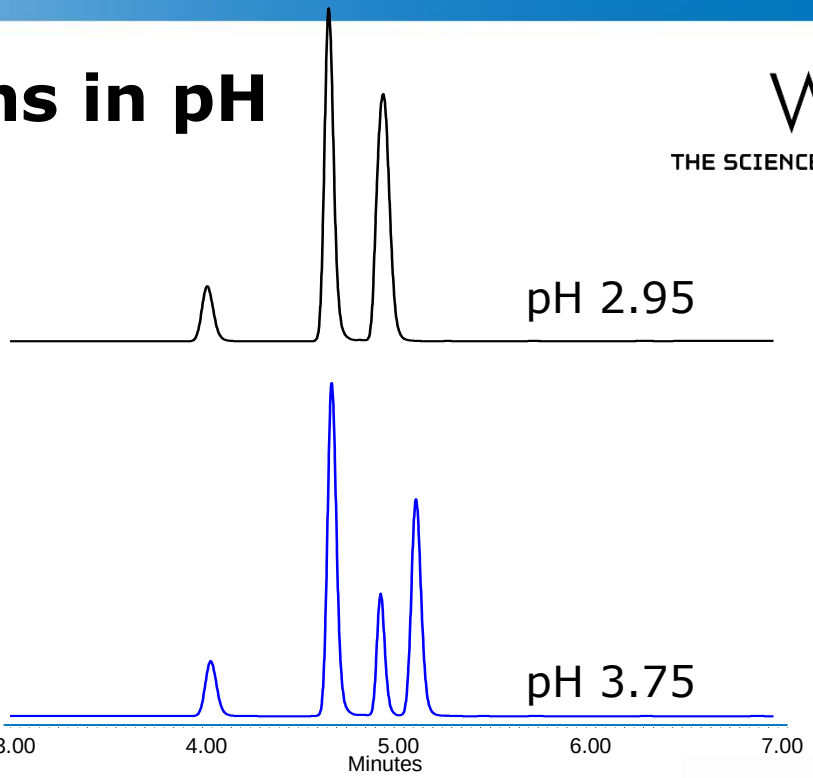
Buffer system: * pH2.9-3.8 Formic Acid Ammonia 25mM Incl. Organic

Concentration to deliver: 25 mM

Recommended pH range: 2.95 to 3.79

Acid: 125mM Formic Acid — 125 mM
Base: 125mM Ammonium Hydroxide — 125 mM
Organic: Acetonitrile — 100 %
Aqueous: Water

	Time	Flow (mL/min)	pH	pH Curve	Organic (%)	Organic Curve
1	Initial	1.000	3.75	Initial	5.00	Initial
2	5.00	1.000	3.75	6	40.00	6
3	5.50	1.000	3.75	6	80.00	6
4	6.00	1.000	3.75	6	80.00	6
5	6.50	1.000	3.75	6	5.00	6
6	7.00	1.000	3.75	6	5.00	6
7	10.00	1.000	3.75	6	5.00	6



ACQUITY Arc™

Risk Assessment
Dissolution Studies

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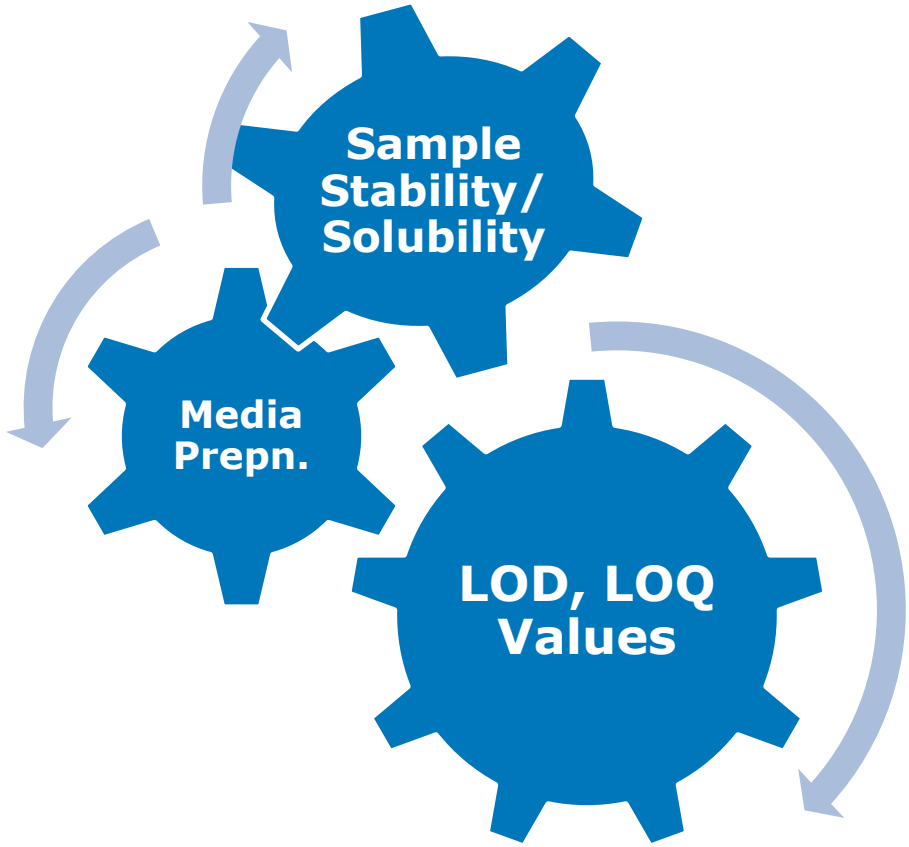

Dissolution Method Development

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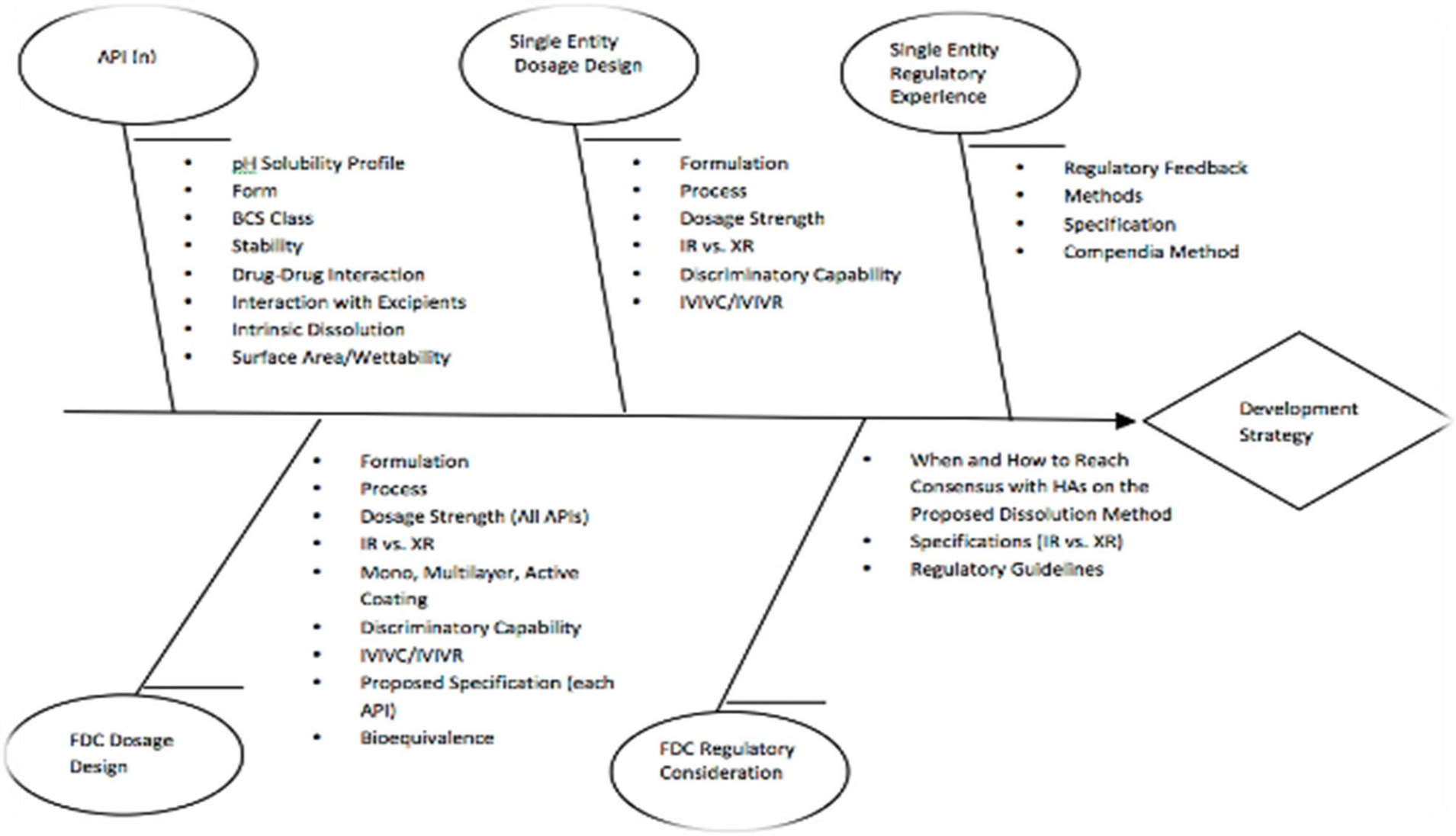

Understanding Dissolution Process

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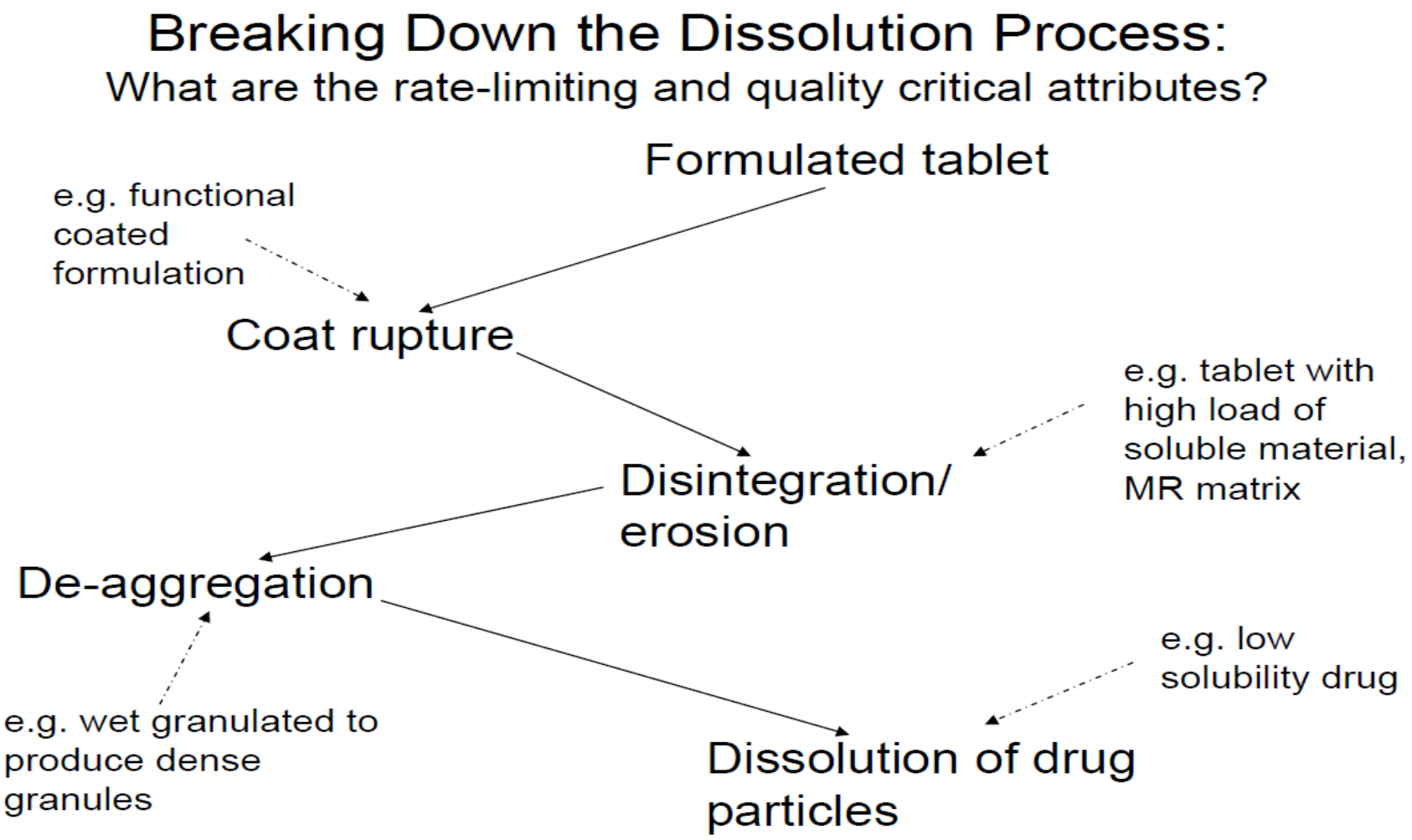

Risk Assessment Dissolution Studies

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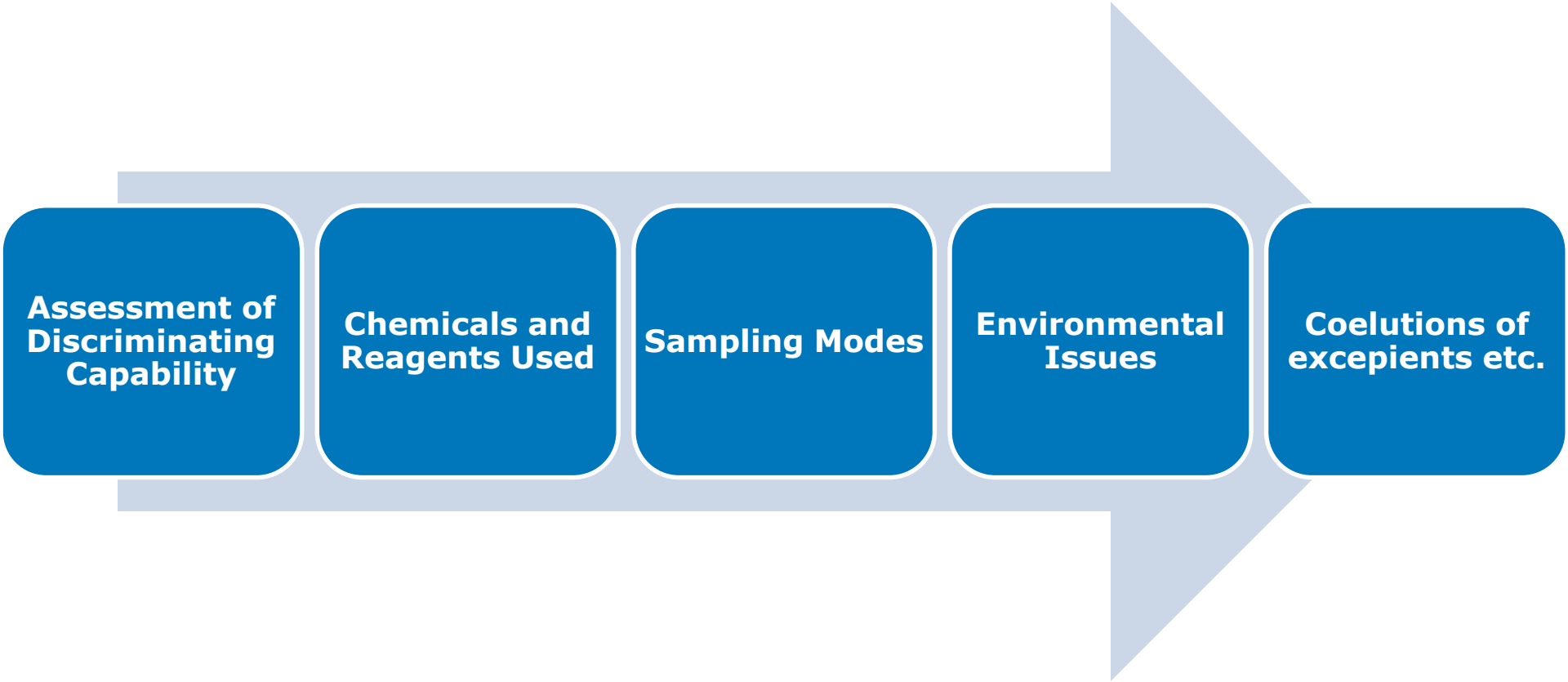

Risk Assessment for Discriminating Capability

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Table 2. Example Risk Assessment of Dissolution Discriminating Capability

Risk	Impact	Risk Rating	Range Studied	Discriminating Results
API particle size	Large particle size may affect content uniformity and provide slow dissolution	Low	API particle sizes (D90): Compound A: 70 – 150 µm Compound B: 40 – 120 µm	Discriminating capability was demonstrated on the low and high end of the particle size for both compounds A and B.
Formulation composition	Operator error in material charging may alter the formulation significantly.	Medium	Disintegrant (intra-granule): 1.0% - 5.0% (Target: 3.0%)	Discriminating capability was demonstrated.
Lubrication process	Over lubrication may cause dissolution slow down	Medium	Lubricant: 0.5% - 1.5% (Target: 1.0%) Blending time: 2 - 6 minutes (Target: 4 minutes)	Discriminating capability was demonstrated.
Roller Compaction parameters	The parameters can impact the granule hardness and size and consequently may impact dissolution.	Medium	Within the control limit: Roll Pressure: 40 ± 10 Bar Roll Gap: 2.2 ± 0.4 mm	Discriminating capability was demonstrated at the edge of the control limits.
Tablet Compression	Tablet hardness may impact dissolution	Low	Within the control limit: Tablet Hardness: 30 ± 5 SCU	Discriminating capability was demonstrated at the edge of the control limits.

Risk assessment also includes identifying potential risk factors that could critically impact the robustness and discriminating capability of the method.

Failure Mode and Effect Analysis (FMEA) could be used as an effective tool in identifying potential critical factors, impact of failures and cause of failure, and ranking the risks so that poor method performance could be proactively prevented.

Rating Risks and Prioritization

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Category	Variable	Class
Measurement	UV Wavelength	X
Method	Media – acid concentration	X
Environment	Ambient laboratory conditions	N
Method	Add organic to dissolve std	C
Materials	Surfactant supplier	N
Method	Paddle rotation	
Method	UV recirculation	

Controlled (C)
Experimental (X)
Noise (N)

Experimental Parameter	Lin.	Acc.	Prec.	Score (sum)	Rank
Media Acid Conc.	7	9	5	21	H
Surfactant Conc.	3	7	3	13	M
Mobile Phase Org.	7	7	5	19	H
Column Temp.	5	3	5	13	M
Sample Volume	3	5	3	11	L
Paddle Speed	?	?	?	?	?

Creating Control Document

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Parameter	Impact on Method Performance	Rationale for Impact Assessment	Classification	Design Space	Suggested Action
HCl Concentration	Yes	Affects % dissolved and discrimination between batches	B	± 10% from nominal	Ensure HCl concentration is in range.
Tween Concentration	Yes	Affects % dissolved and discrimination between batches	B	± 5% from nominal	Ensure Tween concentration is in range.
Flowcell Pathlength	Yes	Variation in pathlength can result in inaccurate results. Use of 5 different apparatus in ruggedness exercise produced negligible variation in results.	B	± 2% from nominal	Ensure that flowcell pathlength is within range.
Standard Preparation Technique	Yes	Inadequate standard dissolution can produce inaccurate results.	D	Operator must ensure that all standard is dissolved before proceeding.	Method revised to include a different validated standard preparation technique.
Standard Weighing Technique	Yes	Standard solution degrades upon extended contact with aluminium weigh boat.	D	Operator must not immerse or store aluminium weight boat in standard solution.	Method revised to exclude extended storage of standard solutions containing aluminium weigh boats.
Multidose Apparatus	No	Use of 5 different apparatus in ruggedness exercise produced negligible variation in results.	C	Any	None
Tween Manufacturer, Grade, Lot	No	Sample preparation by 5 different operators at 3 sites in ruggedness exercise produced negligible variation in results.	E	Any	None
Environment	No	Use of 5 different apparatus at 3 sites in ruggedness exercise produced negligible variation in results.	C	Any	None
Operator	No	Use of 6 different operators in ruggedness exercise produced negligible variation in results.	C	Any	None[2]

Creating Control Document

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SCORING REPORT

Empower 3 SOFTWARE

Sample Set ID: 4001
Result Set ID: 6805
Processed Channel Descr.: PDA 270.0 nm (200-400)nm

Run Time: 7.0 Minutes
Injection Volume: 1.00 ul

	Sample	Column	Strong Solvent	pH	Total Peaks	Total Peaks Rs >=2.0	Total Peaks Tailing <=1.5	Lowest Rs	Min k*	RT of Last Peak
1	Low pH, MeOH	CSH C18	MeOH	Low pH	9	7	7	1.283	3.22	3.11
2	Low pH, ACN	CORTECS C18+	ACN	Low pH	9	7	5	0.769	1.98	2.15
3	Low pH, ACN	CSH C18	ACN	Low pH	9	5	7	2.308	2.15	2.30
4	Low pH, MeOH	CORTECS C18+	MeOH	Low pH	8	7	3	2.094	2.99	2.98
5	Low pH, MeOH	CSH Phenyl Hexyl	MeOH	Low pH	8	6	8	1.690	2.30	3.13
6	Low pH, ACN	CSH Phenyl Hexyl	ACN	Low pH	8	5	5	0.654	0.98	2.21
7	Low pH, MeOH	HSS PFP	MeOH	Low pH	8	2	2	1.870	6.86	3.44
8	Low pH, ACN	HSS PFP	ACN	Low pH	7	2	2	0.108	4.51	2.61

Risk Assessment for Coelutions

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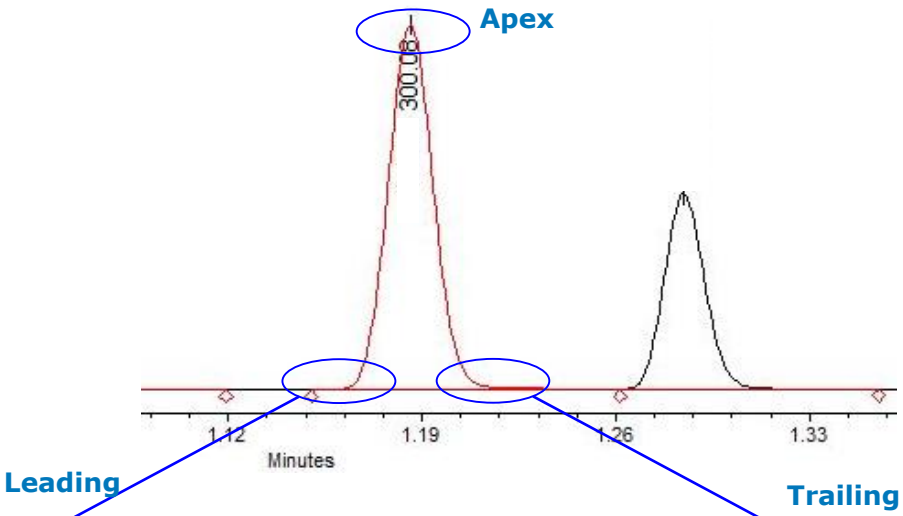
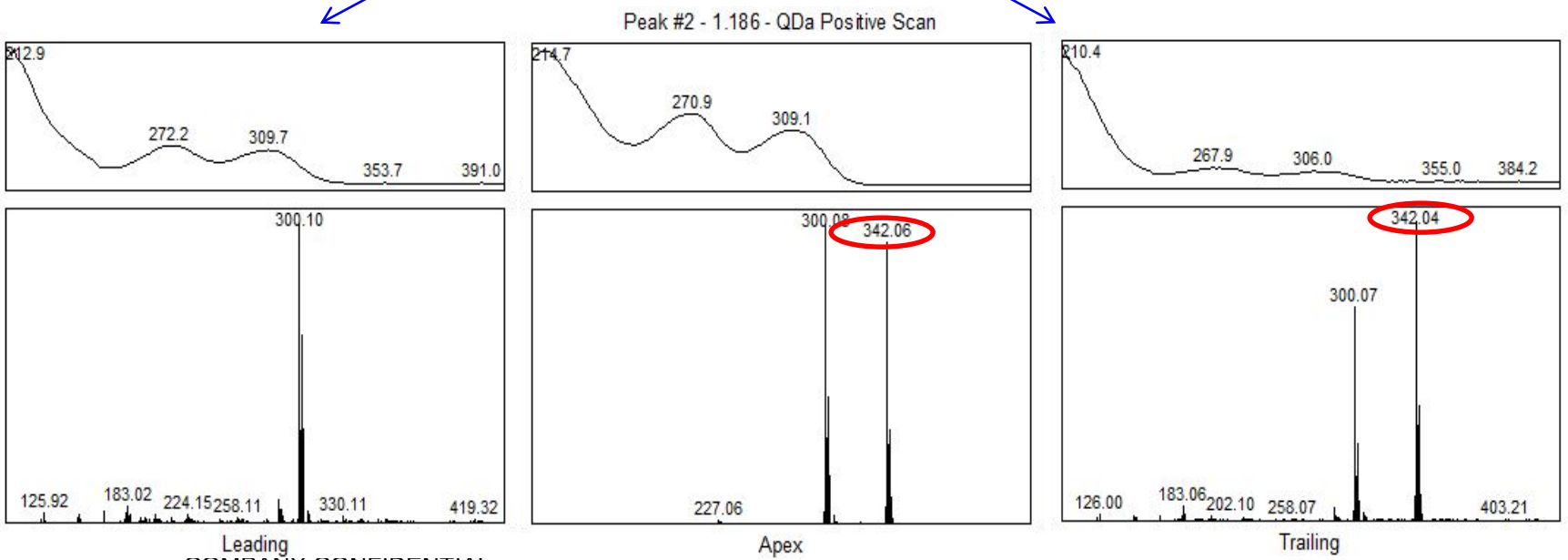


Check peak purity using both mass and PDA data in Empower®

Empower™ 3



And Finally….

Contact Details

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Or on Linkedin