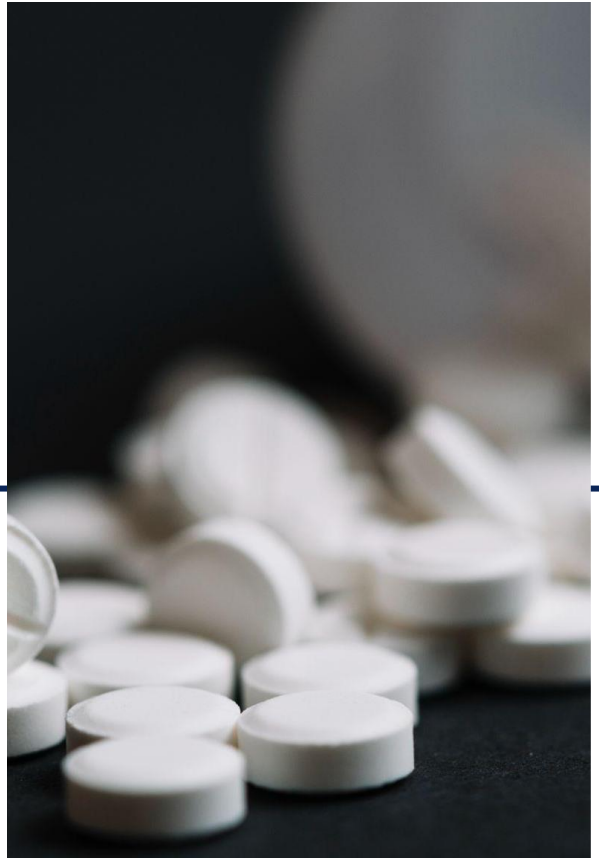
Analytical Method Development for Pharmaceutical Products



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National Center for Genetic Engineering and Biotechnology

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Outline

Quality by Design (QbD)

Analytical Quality by Design (AQbD)

Example: AQbD for LC-MS/MS method

Analytical Procedure Life Cycle (APLC)

ICH Q14/Q2(R2) USP <1220>, and (ISO/IEC) 17025:2017

Quality by Design (QbD)

A systematic approach to product and process development that builds quality into products from the initial design stage, based on sound scientific knowledge and quality risk management

Key Principle

- **Predefined objectives**
- **Product and process understanding**
- **Risk assessment**
- **Process control**
- **Continuous improvement**

International Council for Harmonization (ICH) Guideline Q8

QbD Workflow

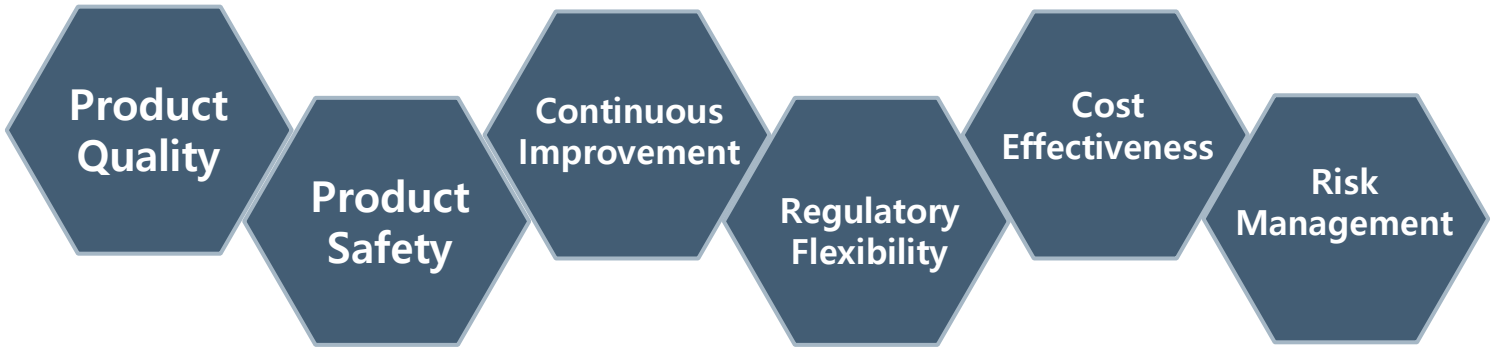
Quality by Design (QbD)

In Pharmaceutical Industries

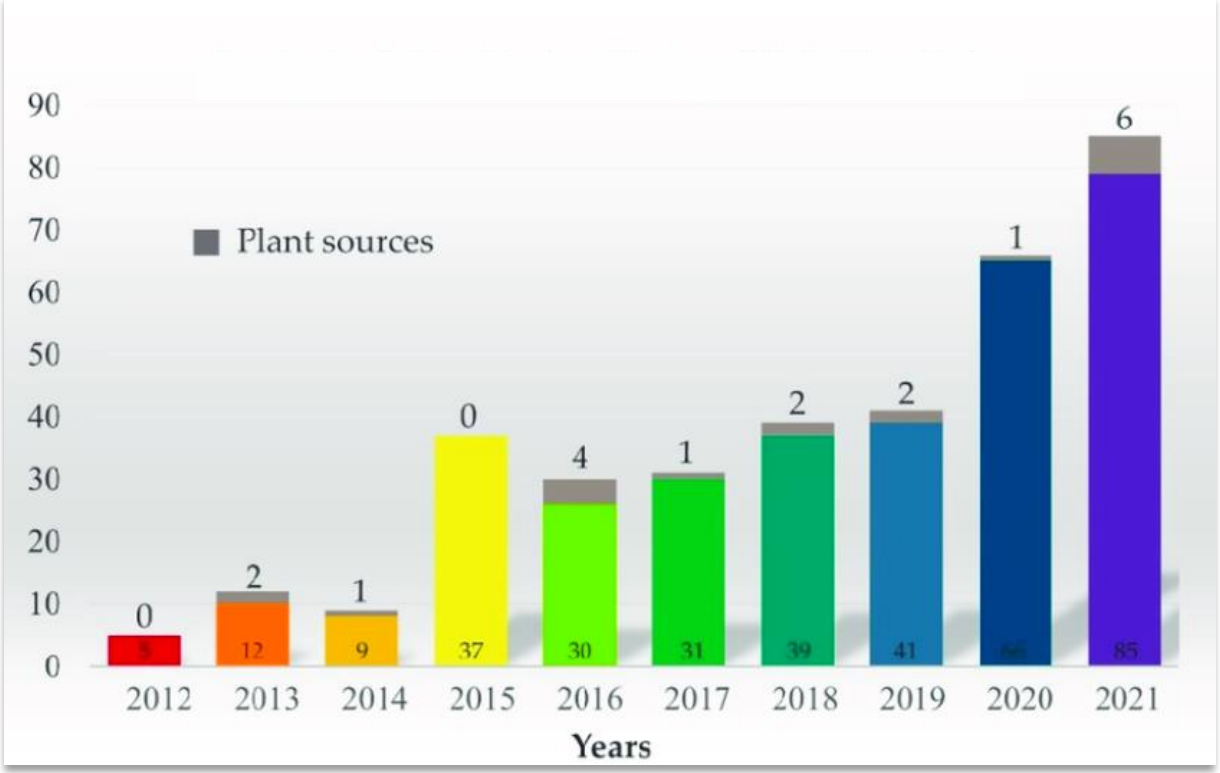
A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches.

Defined by Dr. Janet Woodcock



Analytical Quality by Design (AQbD)



https://www.mdpi.com/2223-7747/11/21/2960

Analytical Quality by Design (AQbD)

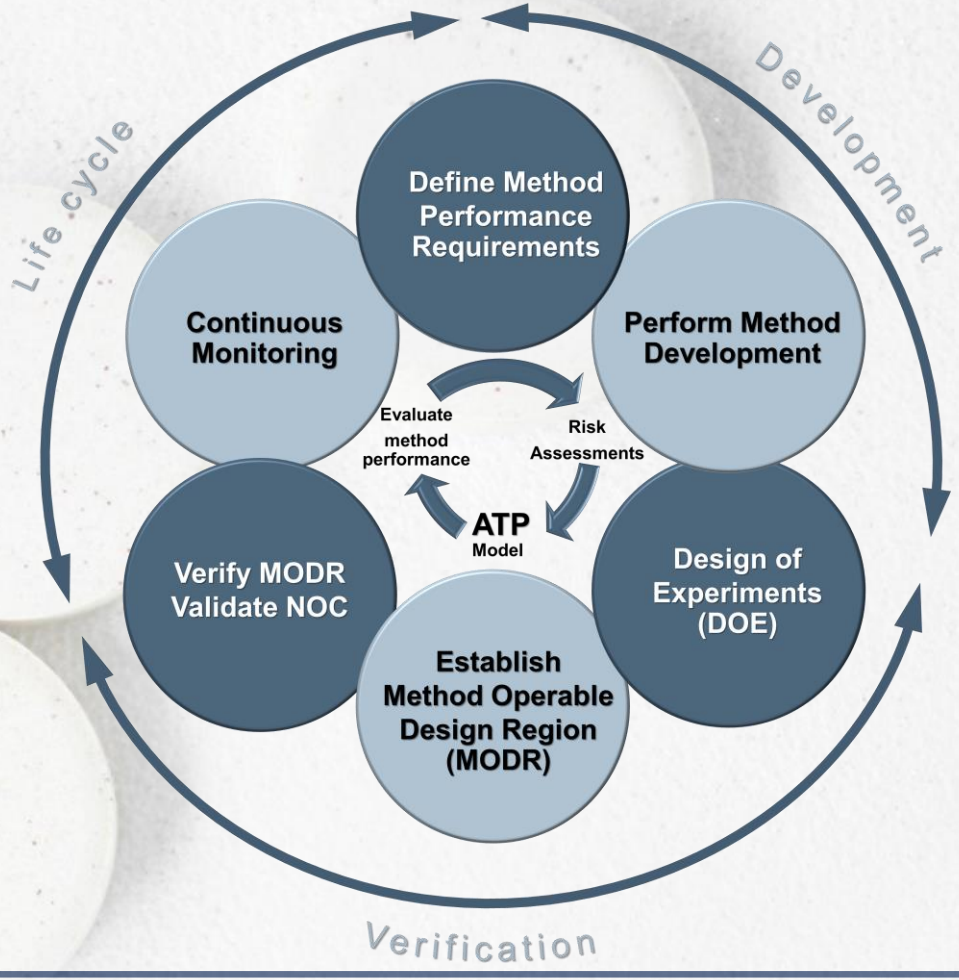
A systematic approach applied in analytical method development and optimization to ensure the reliability, robustness, and quality of analytical methods used in pharmaceutical analysis (and other fields)

Key Principle

- Define Analytical Target Profile (ATP)
- Identify Critical Method Attributes (CMAs)
- Identify Critical Method Parameters (CMPs)
- Perform Risk Assessment
- Design of Experiments (DoE)
- Establish Method Operable Design Region (MODR)
- Control Strategy
- Continuous Method Monitoring

International Council for Harmonisation (ICH) guideline Q14

AQbD Workflow



Traditional Approach

One-factor-at time experiments

OFAT

- *Single-variable experiments*
- *Trial-and-error approach*
- *One factor-at-time (OFAT) investigation*
- *Fixed to a consistent method with associated performing criteria*

PROS

- Simplicity
- Isolation of Effects
- Ease of Interpretation

CONS

- Inefficient Use of Resources
- Failure to Capture Interactions
- Risk of Misinterpretation
- Limited Insight into Optimal Conditions

Enhanced Approach

Analytical Quality by Design

AQbD

- *QbD implementation*
- *Holistic understanding*
- *Control strategy to ensure the reliability robustness, and quality*

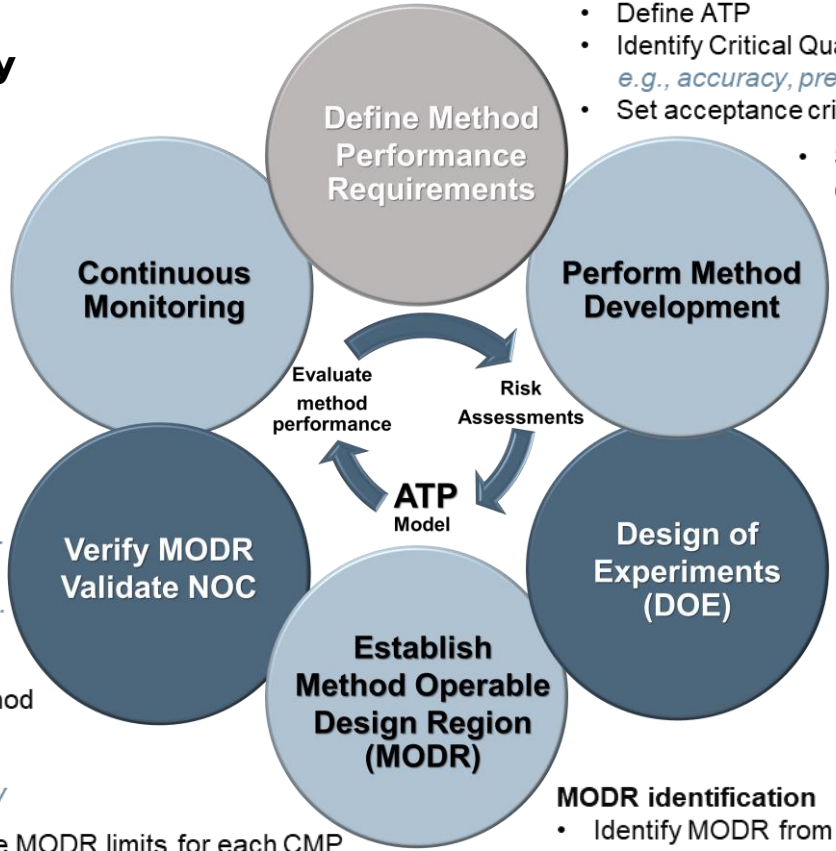
PROS

- Comprehensive Optimization
- Risk-Based Approach
- Efficient Resource Utilization
- Continuous Improvement

CONS

- Complexity
- Initial Investment
- Regulatory considerations

AQbD workflow
LC-Mass Spectrometry



- Define ATP
- Identify Critical Quality Attributes (CQAs)
  e.g., accuracy, precision, specificity, sensitivity, range
- Set acceptance criteria for CQAs

- Select UHPLC-MS technique and initial conditions
  - Identify Critical Method Parameters (CMPs) *e.g., column temperature, flow rate, ionization voltage parameters (voltages, gas flows)*

DOE process
- Systematic approach to study effects of multiple factors simultaneously
- Select experimental design *e.g. factorial, central composite*
- Conduct DOE by varying CMPs levels
- Identify CMPs that CQAs
- Develop mathematical models describing CMP-CQA relationships
- Predict optimal CMP settings for desired CQA values
- Identify CMP interactions and curvature effects
- Estimate MODR - the region of operability

MODR identification
- Identify MODR from models
- Perform experiments at conditions within MODR
- Confirm CQAs meet acceptance criteria within MODR
- Identify MODR boundaries from model predictions.

NOC Validation
- NOC is a specific set of CMP values within the proven acceptable MODR
- Validates the selected NOC for routine use
- Following guidelines (e.g. ICH, FDA) as applicable
- Evaluate all relevant CQAs and performance characteristics *e.g. specificity, accuracy, precision, linearity, range, ruggedness etc.*

For example:
MODR limits for a UHPLC-MS method
- *Column temperature: 35 - 45°C*
- *Flow rate: 0.25 - 0.35 mL/min*
- *Ionization voltage: 3000 - 4000 V*

- Use model equations to calculate MODR limits for each CMP
- Ensure MODR limits provide CQA results within set acceptance ranges
- Verify model predictions match experimental results at MODR limits
- Confirm models are accurate for determining MODR

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Quality by Design as a risk-based strategy in pharmaceutical analysis: Development of a liquid chromatography-tandem mass spectrometry method for the determination of nintedanib and its impurities

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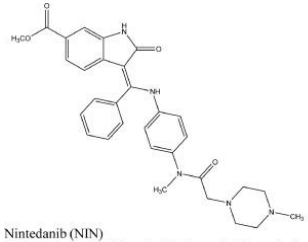
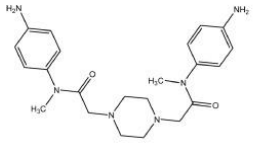
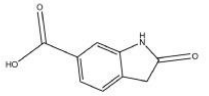


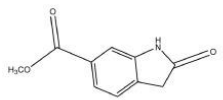
Nintedanib (NIN)
Methyl (Z)-3-(((4-(N-methyl-2-(4-methylpiperazin-1-yl) acetamido)phenyl)amino)(phenyl)methylene)-2-oxoindoline-6-carboxylate
CAS: 656247-17-5
MF: $C_{31}H_{33}N_5O_4$
MW: 539.64



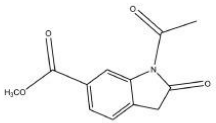
Impurity 1 (I_1)
2,2'-(Piperazine-1,4-diyl)bis (N-(4-aminophenyl)-N-methylacetamide)
CAS: N.A.
MF: $C_{22}H_{30}N_6O_2$
MW: 410.52



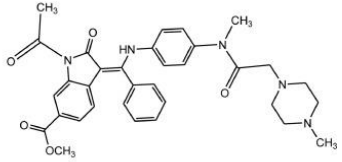
Impurity 2 (I_2)
2-Oxoindoline-6-carboxylic acid
CAS: 334952-09-9
MF: $C_9H_7NO_3$
MW: 177.16



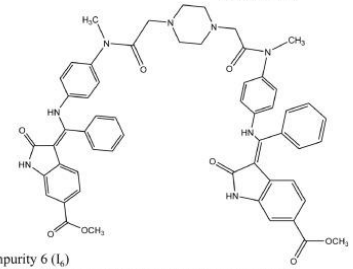
Impurity 3 (I_3)
Methyl 2-oxoindoline-6-carboxylate
CAS: 14192-26-8
MF: $C_{10}H_9NO_3$
MW: 191.19



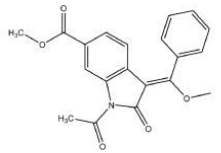
Impurity 4 (I_4)
Methyl 1-acetyl-2-oxoindoline-6-carboxylate
CAS: 676326-36-6
MF: $C_{12}H_{11}NO_4$
MW: 233.22



Impurity 5 (I_5)
Methyl (Z)-1-acetyl-3-(((4-(N-methyl-2-(4-methylpiperazin-1-yl)acetamido)phenyl)amino) (phenyl)methylene)-2-oxoindoline-6-carboxylate
CAS: N.A.
MF: $C_{33}H_{35}N_5O_5$
MW: 581



Impurity 6 (I_6)
Dimethyl 3,3'- (((((2,2'-(piperazine-1,4-diyl)bis(acetyl)) bis(methylazanediyl))bis(4,1- phenylene))bis(azanediyl))bis (phenylmethaneylylidene))(3Z,3'Z)-bis(2-oxoindoline-6-carboxylate)
CAS: N.A.
MF: $C_{56}H_{52}N_8O_8$
MW: 965.09



Impurity 7 (I_7)
Methyl (E)-1-acetyl-3-(methoxy(phenyl) methylene)-2-oxoindoline-6-carboxylate
CAS : 1168152-07-5
MF: $C_{20}H_{17}NO_5$
MW: 351.35

AQbD workflow for method development

NIN soft capsules containing 150 mg NIN esylate salt and soft capsules excipients (medium-chain triglycerides, hard fat, soya lecithin (E322))

Quantitative MS methods

- Frequently employed in drug analysis
- Provides quantitation for the impurities and elucidation of their structure
- MS detection provides both high selectivity for its ability to monitor selected ions
- Provides high sensitivity due to the high S/N ratio.

Challenging

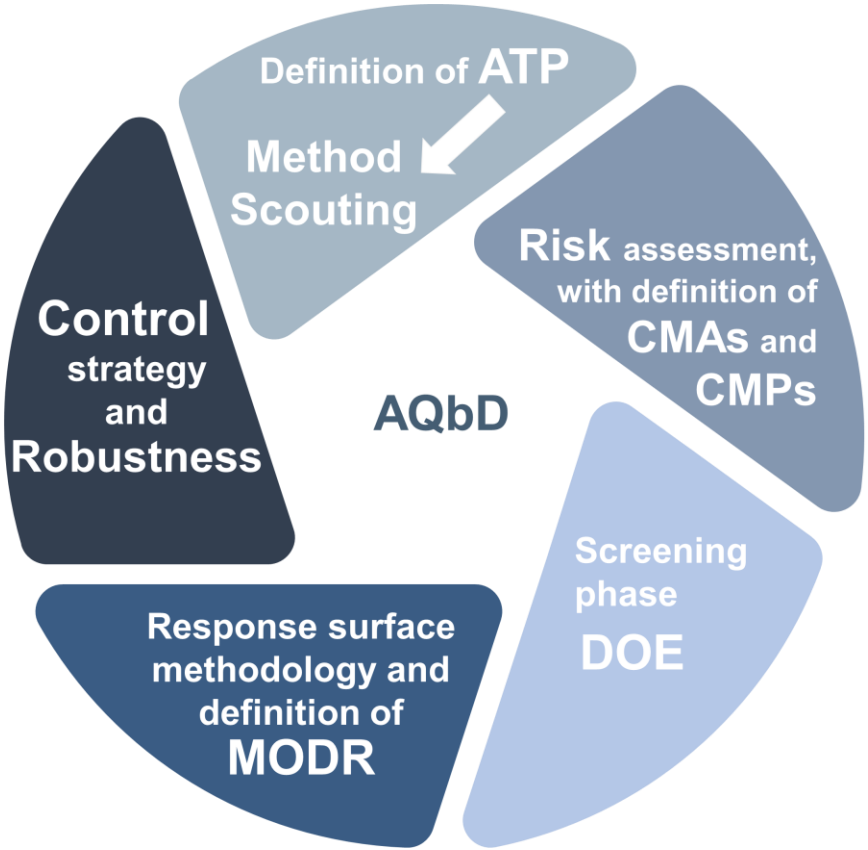
- Matrix effects may occur leading to interference problems
- Ion suppression caused by different processes
- Poor ionization for less- or non-volatile solutes
- Co-elution in the chromatographic separation
- Impurity profiling carried out by LC-MS
- Charge competition in the drop originated by the spray
- Impurities often have molecular structures close to the API with a similar chromatographic behavior.
- High concentration level of api in comparison with impurities could lead to peak overlapping problems.

Need

A systematic approach to LC-MS method development to obtain a robust optimum experimental zone where the impurities reach a sufficient chromatographic separation from the API.

AQbD Workflow for LC-MS/MS method

NIN soft capsules containing 150 mg NIN esylate salt and soft capsules excipients (medium-chain triglycerides, hard fat, soya lecithin (E322))



Analytical target profile and method scouting

Analytical target profile (ATP)

defined as the ***accurate simultaneous determination*** of the main compound NIN and its seven potential impurities in ***a short analysis time*** and was based on the achievement of ***an adequate selectivity between the API and the adjacent impurity peaks***.

ICH guideline Q2(R1)

- measure the active API within the typical content range of 80 –120%
- demonstrate selectivity towards target analytes with a mean bias of ≤ 2% across the range and RSD ≤ 2%
- RSD for impurities ≤ 5.0%
- LOQ for impurities ≤ 0.05% with respect to the normal impurity level (NIN) to ensure safety (considering a maximum daily dose of < 1 g)

Critical method attributes (CMAs)

The ***selectivity*** between the main compound NIN and the adjacent peaks.

to overcome problems of interferences and ion suppression due to their possible co-elution, and by ***analysis time***

Critical method parameters (CMPs)

Instrumental parameters

Composition of the ***mobile phase***

Analytical target profile and method scouting

Suspension

- ACN:H_2O (20:80 v/v) containing 0.1% v/v HCOOH. The final test [NIN] was about 1 mg mL^{-1}

Chromatographic columns

- ***Restek Ultra AQ C18 (100 × 2.1 mm, 2.7 µm) core-shell (Restek Corporation, Bellefonte, PA, USA)***
- Waters XTerra C18 (150 × 3.0 mm, 5 µm) fully porous (Waters Corporation, Milford, MA, USA)
- Phenomenex Luna C8 (150 × 4.6 mm, 5 µm) fully porous
- PFP (pentafluorophenyl propyl) Kinetex (100 × 2.1 mm, 2.6 µm) core-shell (Phenomenex, Torrance, CA, USA)

Standard conditions for scouting phase

- Sample injection volume: ***10 µL***
- Organic solvent in eluent B: ***ACN***
- HCOOH percentage in eluent A: ***0.10% v/v***
- Flow rate: ***0.33 mL min^{-1}***
- Oven temperature: ***25 °C***
- The elution started with 100% eluent A (***0.10% v/v HCOOH***)
- ***Linear gradient of eluent B (ACN)*** with a gradient slope of ***12.60%B min^{-1} to reach 95% of eluent B***

Analytical target profile and method scouting

LC-MS condition and parameters

- ***Alliance 2695 HPLC*** (Waters Corporation, Manchester, UK), equipped with ***a low-pressure binary pump***
- UV–Vis 2996 photodiode array (Waters Corporation)
- ***Quattro microTM triple quadrupole mass spectrometer*** (Waters Corporation), equipped with ***Z-spray ESI source***
- The autosampler temperature was set at 22 °C
- Full scan positive ionization mode from ***110 to 1000 m/z scan rate*** (0.8 s scan time).
- Z-spray interface parameters: capillary voltage, 3.2 kV; extractor and RF (Rear Focusing) lens, 3 and 0 V, respectively
- Source and desolvation temperatures were 130 °C and 380 °C, respectively
- Gas flows were 350 L/h for desolvation gas and 20 L/h for cone gas.
- ***Quadrupole resolution was set at 0.7 FWHM*** (Full Width at Half Maximum).
- Spectra were recorded in centroid mode.
- Compound dependent parameters for MS/MS analysis were optimized by directly infusing a solution of each standard at 20 µg/mL in MeOH:H_2O (50:50 v/v) containing 0.1% v/v HCOOH into the ESI interface.
- ***Multiple Reaction Monitoring (MRM)*** was selected as acquisition mode in the optimized conditions.
- ***MassLynx v. 4.1 software*** (Waters Corporation) was used for data processing and acquisition
- The chromatographic plots were realized using ***R software environment***

AQbD workflow for method development

NIN soft capsules containing 150 mg NIN esylate salt and soft capsules excipients (medium-chain triglycerides, hard fat, soya lecithin (E322)

Analytical target profile and method scouting

Calculations and Softwares

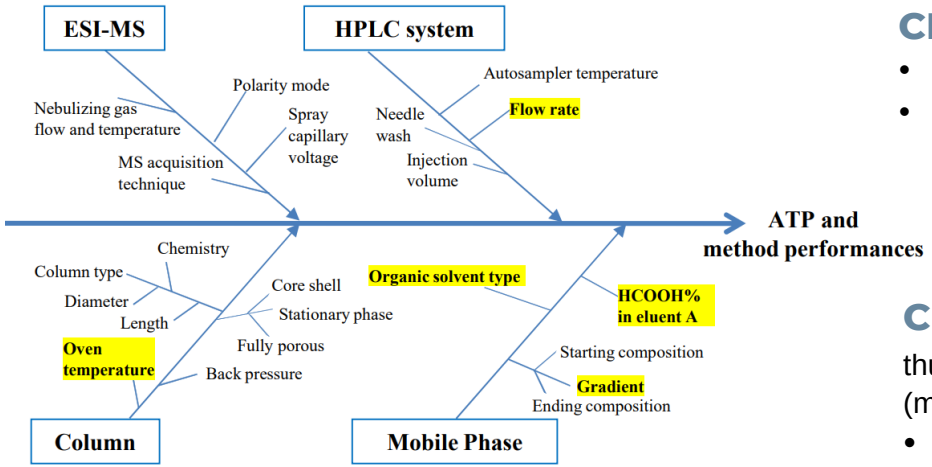
- ***Nemrod-W software*** for generating the symmetric ***screening matrix for investigating the knowledge space***
- ***Plackett-Burman design*** for testing ***robustness***
- ***Modde® 10 software*** for generating ***Box-Behnken design*** for ***response surface methodology (RSM) experimental design*** and for identifying the ***MODR*** by means of probability maps calculated by Monte-Carlo simulations

- The ***calibration curves***: 5 concentration values of the considered compounds (two samples for each concentration level)
- The ***[NIN] regression curve***: range 0.6–1.2 mg mL^{-1}
- The [NIN] chosen to enable to obtain a ***LOQ for all the impurities ≤ the reporting threshold of 0.05%***
- The ***regression curves for the impurities*** were from the respective LOQ to 1% with respect to [NIN]

I1 = 0.40 – 10.00 µg mL^{-1} I2 = 0.45 – 10.00 µg mL^{-1}, I3 = 0.38 – 10.00 µg mL^{-1}, I4 = 0.38 – 10.00 µg mL^{-1}, I5 = 0.50 – 10.00 µg mL^{-1}, I6 = 0.38 – 10.00 µg mL^{-1}, I7 = 0.50 – 10.00 µg mL^{-1}

Risk assessment, CMAs, and CMPs

CMAs are directly connected with the **ATP** and are response variables, giving information on the quality of the chromatogram



CMAs were selected as the **analysis time (t) ≤ 11 min**

- The retention time of I7 (the last eluting peak)
- Chromatographic selectivity between NIN and the adjacent peaks, set as
  - **α1: I4/NIN selectivity ≥1.03**
  - **α2: NIN/I5 selectivity ≥1.03**

CMPs which could potentially influence the selected CMAs and thus needed to be in depth investigated by means of **DoE** (multivariate optimization)

- **Flow rate**
- **Oven temperature**
- **HCOOH % in eluent A**
- **Type of organic solvent in the mobile phase**
- **Gradient slope of organic eluent**

Screening phase

3 CMAs
5 CMPs

$3^5 = 243$ exps

Free-Wilson model

$y = A_0 + A_1A + A^2A + B_1B + B^2B + C_1C + C_2C + D_1D + D_2D + E_1E + E_2E$

3^5//16 screening symmetric matrix

A high number of CMPs to be simultaneously studied keeping low the number of experiments.

16 exps (x2)

32 exps

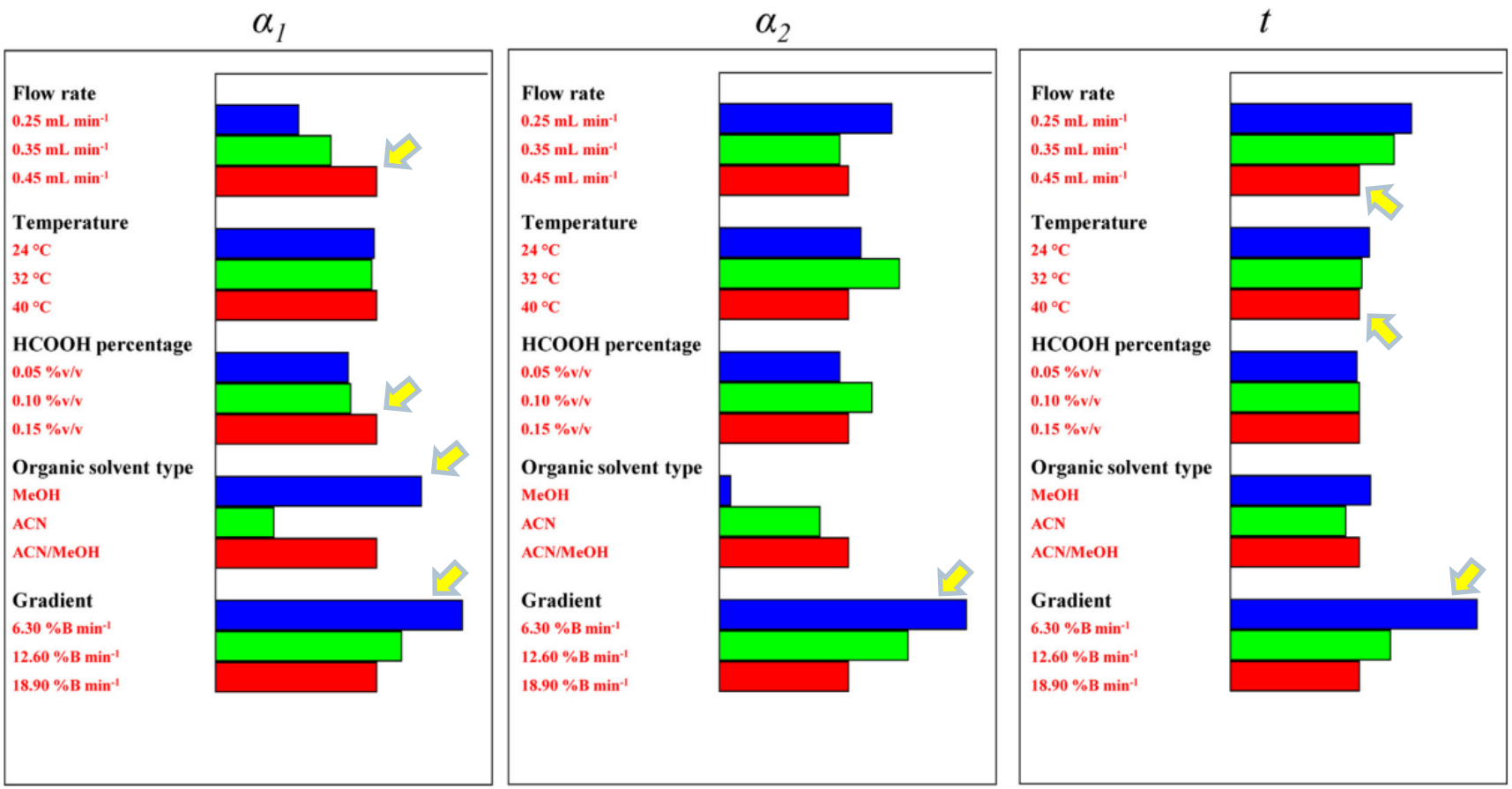
CMAs

- t (min) ≤11 min
- I4/NIN selectivity α1 ≥ 1.03
- NIN/I5 selectivity α2 ≥ 1.03

CMPs

- Flow rate: 0.25 – 0.45 mL min^{-1}
- Oven temp: 24 – 40 °C
- HCOOH: 0.05 – 0.15% (v/v)
- Gradient: 6.30 – 18.90% B min^{-1}
- Type of organic solvent:
  MeOH, ACN and ACN/MeOH 1:1

Exp. no.	Flow rate (mL min^{-1})	Temperature (°C)	Formic acid percentage (%v/v)	Organic solvent type	Gradient (%B min^{-1})	α_1	α_2	t (min)
1	0.25	32	0.10	ACN/MeOH	12.60	0.952	1.223	13.78
2	0.25	32	0.10	ACN/MeOH	12.60	0.978	1.094	12.86
3	0.45	24	0.10	ACN	18.90	0.932	1.086	8.02
4	0.45	24	0.10	ACN	18.90	0.928	1.098	8.00
5	0.45	40	0.05	ACN	12.60	0.947	1.110	9.40
6	0.45	40	0.05	ACN	12.60	0.991	1.060	9.43
7	0.30	40	0.15	MeOH	12.60	1.038	1.065	12.46
8	0.30	40	0.15	MeOH	12.60	1.038	1.069	12.47
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮



Stat. analysis by ANOVA

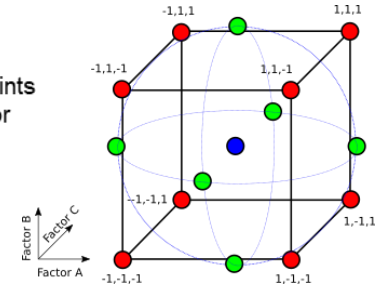
Response Surface Methodology and Method Operable Design Region

Box-Behnken Design *estimating the second order polynomial equation representing the CMPs-CMAs relationship*

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x2 + \beta_3 x_3 + \beta_{11} x_1\,2 + \beta_{22} x_2{}^2 + \beta_{33} x_3{}^2 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 + \varepsilon$$

N = 2k(k-1) + cp
N = experimental points
k = numbers of factor
cp = center points

3 factors 15 points
4 factors 27 points
5 factors 46 points



3 levels per factor (CMP), Total = 3 CMPs

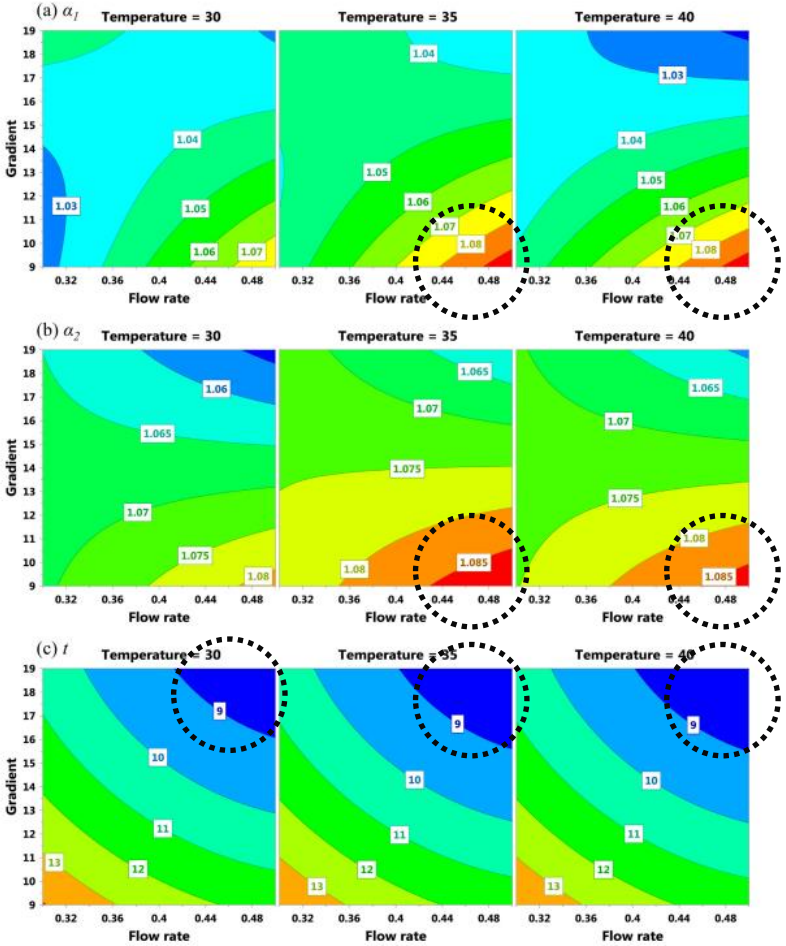
13 experimental plan (each CMA) , x2 = 26 exps

Box-Behnken design for response surface methodology with two replicates for each run.

Exp. no.	*Flow rate* (mL min^{-1})	*Temperature* (°C)	*Gradient* (%B min)	α_1	α_2	*T* (min)
1	0.30	30	14.00	1.028	1.063	11.87
2	0.50	30	14.00	1.053	1.070	9.64
3	0.30	40	14.00	1.019	1.073	11.78
4	0.50	40	14.00	1.058	1.080	9.49
5	0.30	35	9.00	1.050	1.077	14.02
6	0.50	35	9.00	1.089	1.085	11.59
7	0.30	35	19.00	1.096	1.093	10.51
8	0.50	35	19.00	1.019	1.053	8.27
9	0.40	30	9.00	1.036	1.072	12.53
10	0.40	40	9.00	1.073	1.080	12.41
11	0.40	30	19.00	1.036	1.052	9.14
12	0.40	40	19.00	1.030	1.057	9.05
13	0.40	35	14.00	1.044	1.074	10.30
⋮	⋮	⋮	⋮	⋮	⋮	⋮

CMPs

- **Flow rate:** 0.30 0.40 0.50 mL min^{-1}
- **Oven temp:** 30 35 40 °C
- **HCOOH:** 0.15% (v/v)
- **Gradient:** 9 14 19 %B min^{-1}
- **Type of organic solvent:** MeOH



Response contour plots

Relationship between gradient and flow rate at different temperature

Flow rate: high levels
Gradient : low levels

→ High selectivity between NIN and adjacent peaks

- **α1: I4/NIN**

Flow rate: high levels
Gradient : low levels

→ High selectivity between NIN and adjacent peaks

- **α2: NIN/I5**

High flow rate
High gradient

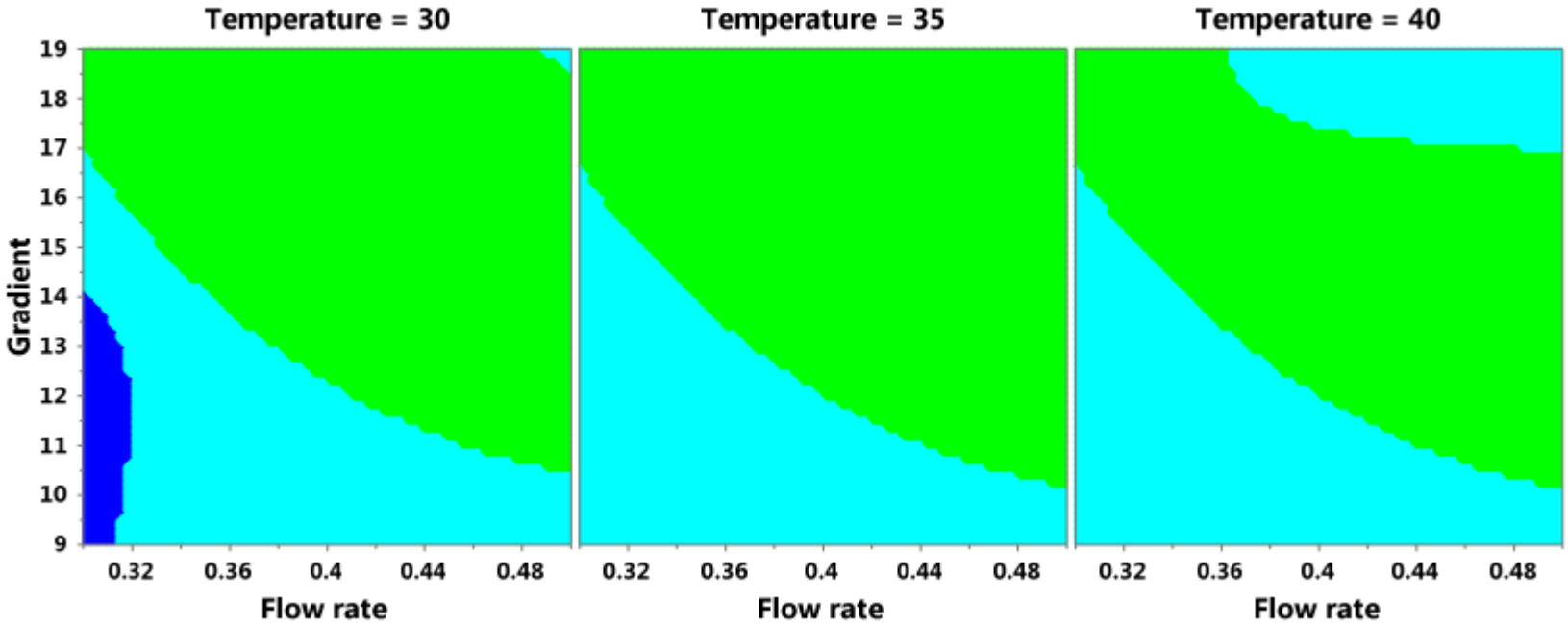
→ Minimization of the analysis time

- **t ≤11 min**

Sweet spot plots

describes ideal location or condition that maximizes performance or achieves desired outcomes

CMAs were satisfied according to their predicted values



Define MODR

The MODR was calculated by **Monte-Carlo simulations** with the **threshold for the risk of failure was set to 10%**

Flow rate: 0.37 – 0.43 mL min^{-1}
Temperature: 38 – 40 °C
Gradient: 12.85 – 15.15 %B min^{-1}

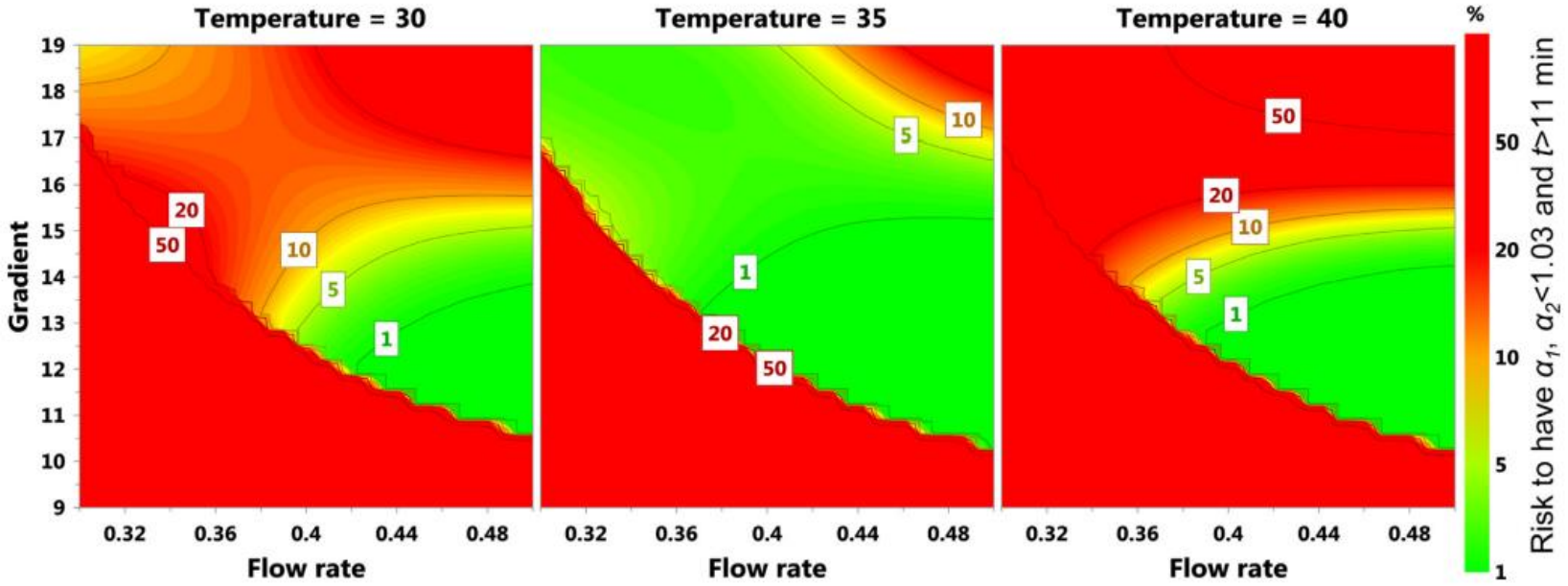


Fig. 4. Risk of failure maps obtained by plotting flow rate *vs.* gradient at different values of temperature: 30 °C, 35 °C and 40 °C. The MODR is the zone bounded by the line corresponding to 10% risk of failure.

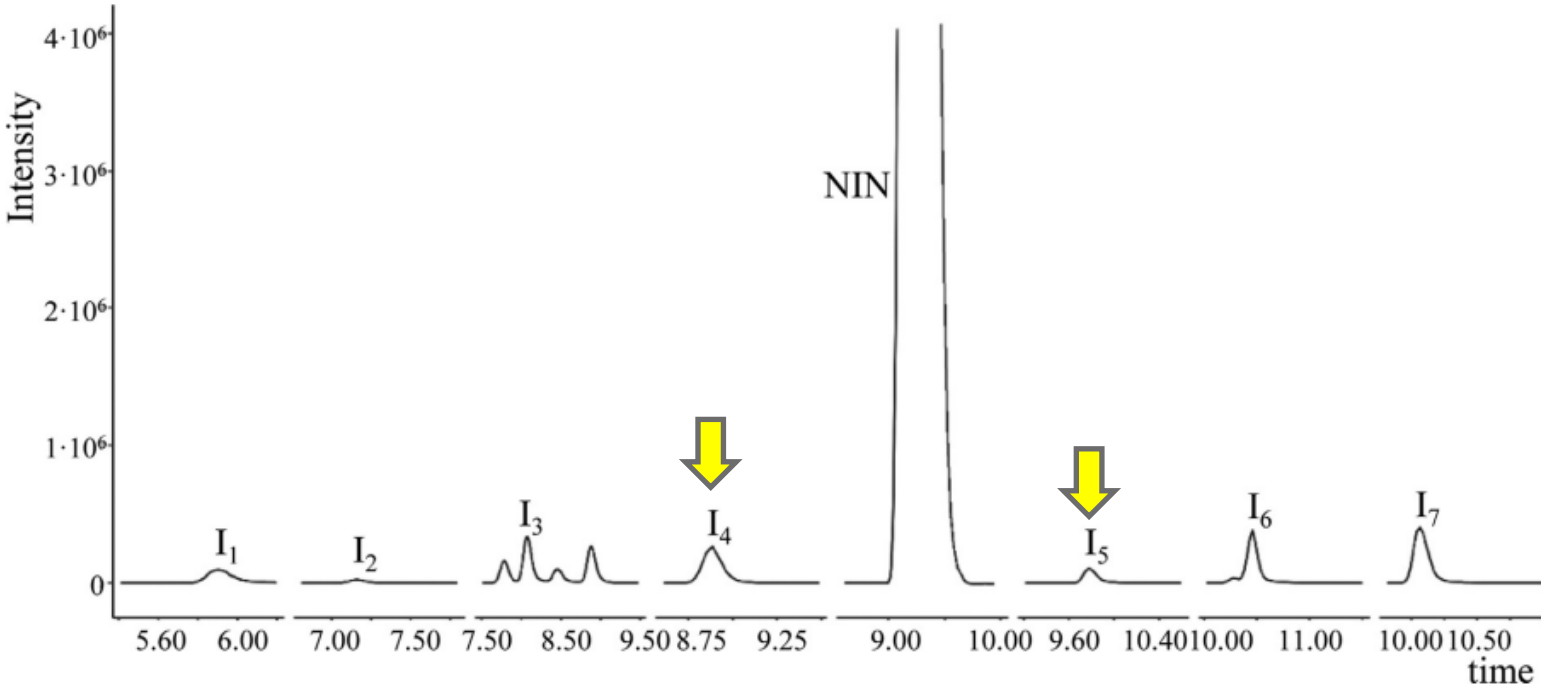
Experimental domain/optimized values for the CMPs

Critical method parameter	Screening levels
Flow rate	0.25-0.35-0.45 mL min^{-1}
Temperature	24-32-40 °C
Formic acid percentage	0.05-0.10-0.15% v/v
Organic solvent type	MeOH-ACN-ACN/MeOH
Gradient	6.30-12.60-18.90 %B min^{-1}

Validation of the MODR and validation of the calculated models

LC-MS/MS chromatogram

A standard solution: NIN 1 mg mL^{-1} and NIN impurities 0.01 mg mL^{-1})



Robustness testing and control strategy

Robustness testing

- Multivariate approach
- Plackett–Burman design

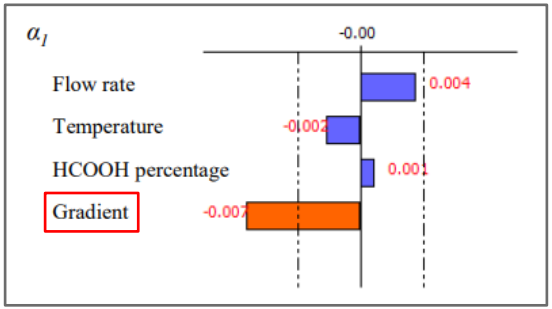
CMPs

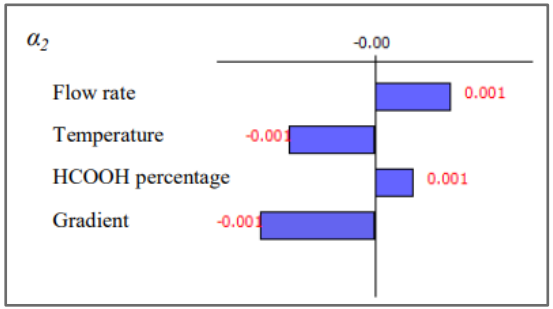
- **Flow rate:** 0.38 and 0.42 mL min^{-1}
- **Oven temp:** 39 and 41 °C
- **HCOOH:** 0.14 and 0.16 % (v/v)
- **Gradient:** 13.50 and 14.50 %B min^{-1}
- **Type of organic solvent:** MeOH

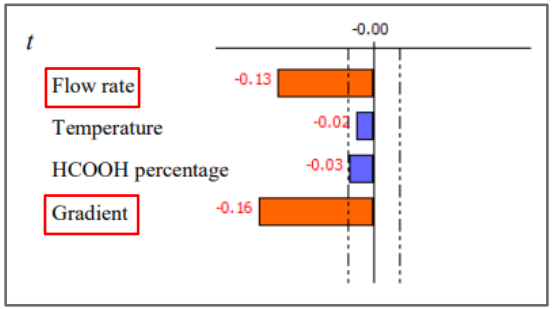
Plackett-Burman design for robustness testing with two replicates for each run.

Exp. no.	Flow rate (mL min^{-1})	Temperature (°C)	Formic acid percentage (%v/v)	Gradient (%B min^{-1})	α_1	α_2	t (min)
1	0.42	41	0.16	13.50	1.054	1.064	9.46
2	0.42	41	0.16	13.50	1.065	1.079	9.56
3	0.38	41	0.16	14.50	1.047	1.072	9.58
4	0.38	41	0.16	14.50	1.033	1.060	9.51
5	0.38	39	0.16	14.50	1.031	1.070	9.49
6	0.38	39	0.16	14.50	1.038	1.075	9.52
7	0.42	39	0.14	14.50	1.045	1.065	9.37
8	0.42	39	0.14	14.50	1.054	1.073	9.38
9	0.38	41	0.14	13.50	1.042	1.068	9.85
10	0.38	41	0.14	13.50	1.048	1.075	9.95
11	0.42	39	0.16	13.50	1.064	1.081	9.66
12	0.42	39	0.16	13.50	1.053	1.073	9.62
13	0.42	41	0.14	14.50	1.039	1.073	9.34
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮

Robustness testing and control strategy







Control strategy of the method

- **1.03 < α1 < 1.06**
- **1.06 < α2 < 1.08**
- **9.24 < t < 10.48 min**

Validation of the MODR and validation of the calculated models

Method validation
ICH guideline Q2(R1)

For routine quality control of pharmaceutical dosage forms

- Selective to the analytes of interest
- Typical content specification range of the API of 80 –120%
- Mean bias ≤2% of theoretical across the range
- Relative Standard Deviation (RSD) ≤ 2%.

For the analysis of impurities

- Higher RSD was accepted (≤5.0%)
- A limit of quantitation equal (LOQ) or lower than the reporting threshold of 0.05% with respect to NIN (as from maximum daily dose <1 g) was required

Validation
ICH guideline Q2(R1)

Test sample containing

- 1 mg mL^{-1} NIN + 0.01 mg mL^{-1} NIN impurities

Selectivity test

6 injections, 3 consecutive days

- Intra-day RSD values of AUC: 0.6-0.8% for NIN and 1.3-2.4% for the impurities
- Inter-day RSD values of AUC: 0.9% for NIN and 1.6-2.8% for the impurities.
- Intra-day RSD values for t : 0.12 to 0.15%,
- Inter-day RSD values for t : 0.17%.

Sensitivity test

- LOD/LOQ values (µg mL^{-1}): I1, 0.30/0.40; I2, 0.30/0.45; I3, 0.25/0.38; I4, 0.25/0.38; I5, 0.35/0.50; I6, 0.25/0.38; I7, 0.30/0.50

Linearity test

- Coefficient of determination (R^2) = 0.995 -0.999

Accuracy (%recovery)

- 95.9 ± 4.8 – 104.6 ± 8.1

Precision (% RSD)

- 0.8 – 4.6

Validation
ICH guideline Q2(R1)

Test sample containing

- Vargatef ® soft capsules containing 150 mg NIN
- 4 parallel replicates
- The observed CMA values were included in the control strategy interval (**α1 = 1.049 ± 0.015, α2 = 1.073 ± 0.012, t = 10.23 ± 0.05 min; α/2 = 0.025**)
- The determined content of NIN: 98.4 ± 1.6 %
- RSD 1.0 % showing evidence of good precision.
- All the impurities were below the LOQ concentration values and thus fell below the reporting threshold of 0.05% with respect to NIN.

Method validation
ICH guideline Q2(R1)

For routine quality control of pharmaceutical dosage forms

- Typical content specification range of the API of 80–120%,
- Selective to the analytes of interest
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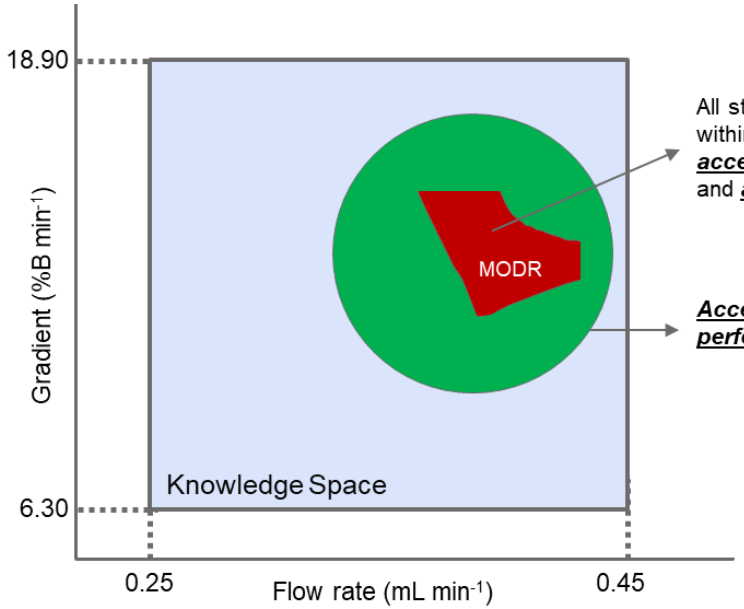
Analytical Quality by Design (AQbD)



MORD is a multidimensional combination and interaction of procedure parameters where all study factors combined have been demonstrated to

- provide ***acceptable mean performance***
- provide ***acceptable robustness***
- ensure ***ATP is fulfilled***

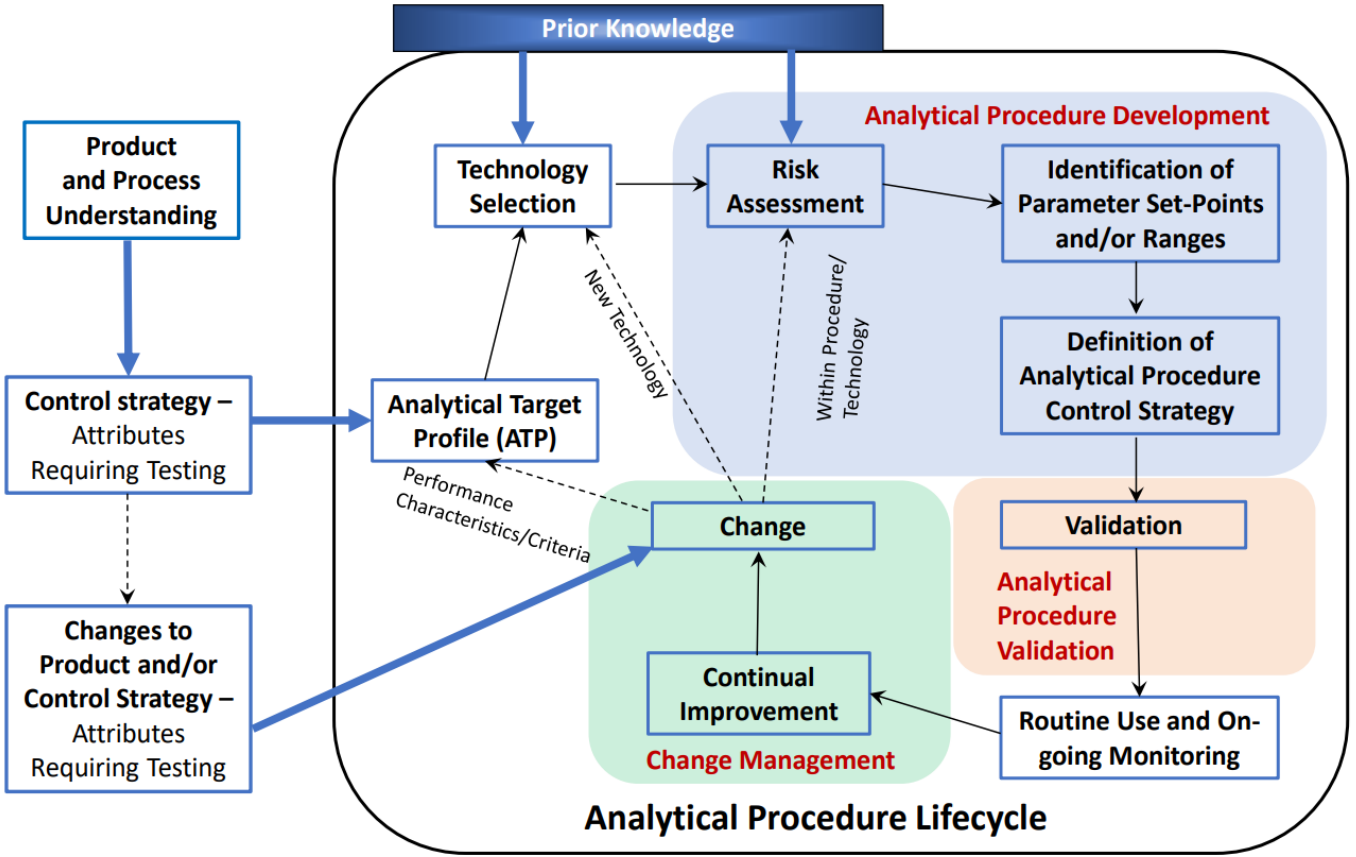
Robustness assessment plays an essential role

Analytical Conditions Change Management

Change of analytical conditions

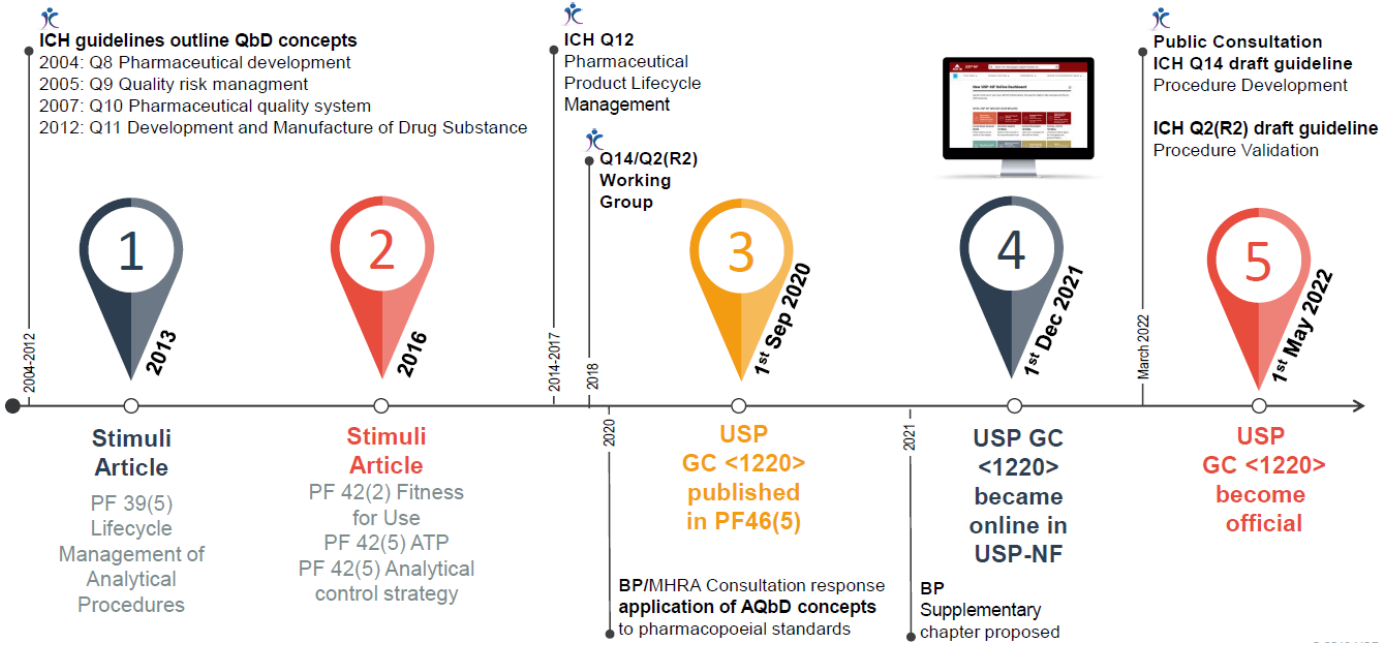
- within the range previously qualified may not require additional experimentation before implementation.
- outside the set point or range that was previously qualified would require a risk assessment.

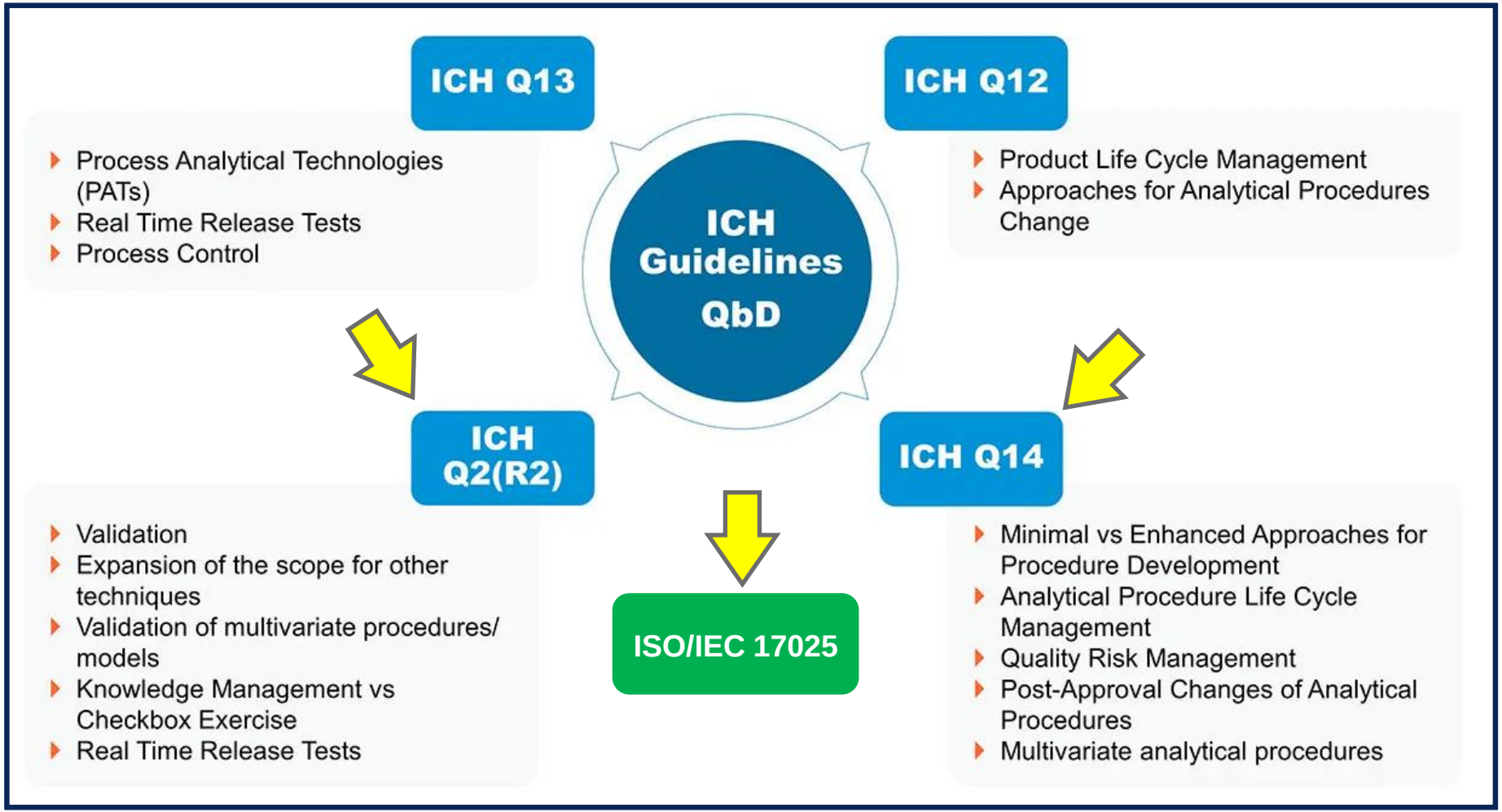
The Analytical Procedure Lifecycle



The Analytical Procedure Lifecycle

Framework for analytical procedures that holistically incorporates all the events that take place over the procedure life cycle that are designed to demonstrate that a procedure is, and remains, fit for the intended purpose




ICH Q13
Process Analytical Technologies (PATs)
Real Time Release Tests
Process Control
ICH Q12
Product Life Cycle Management
Approaches for Analytical Procedures Change
ICH Guidelines QbD
ICH Q2(R2)
Validation
Expansion of the scope for other techniques
Validation of multivariate procedures/ models
Knowledge Management vs Checkbox Exercise
Real Time Release Tests
ICH Q14
Minimal vs Enhanced Approaches for Procedure Development
Analytical Procedure Life Cycle Management
Quality Risk Management
Post-Approval Changes of Analytical Procedures
Multivariate analytical procedures
ISO/IEC 17025

ICH guideline Q14
Analytical Procedure Development

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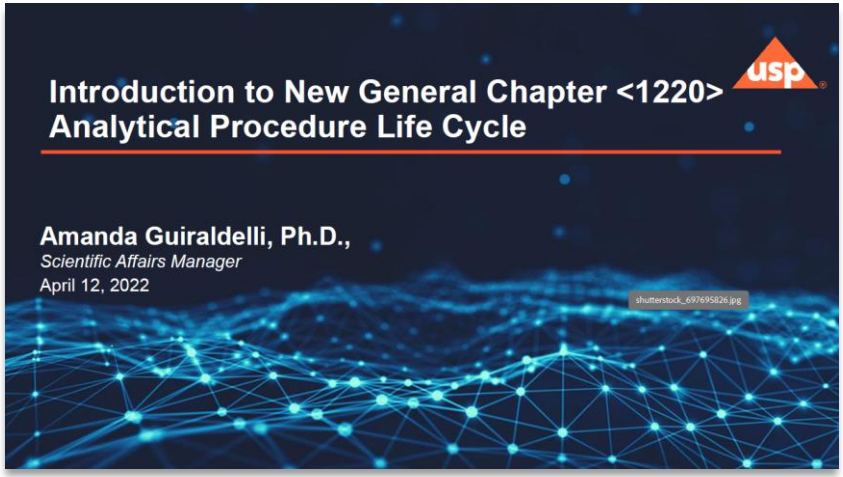

Thanks