Introduction to Analytical Quality by Design (AQbD) principles

Amanda Guiraldelli, Ph.D.
Scientific Affairs Manager
US Pharmacopeia
awg@usp.org

Agenda

- Evolution of QbD and AQbD approaches
- Introduction to AQbD principles and key AQbD elements
  - Quality Risk Management
  - Chemometric tools
  - Method Operable Design Region
- AQbD Benefits

Analytical Quality by Design (AQbD)

AQbD Concept

AQbD is an enhanced approach to develop analytical procedures using QbD principles

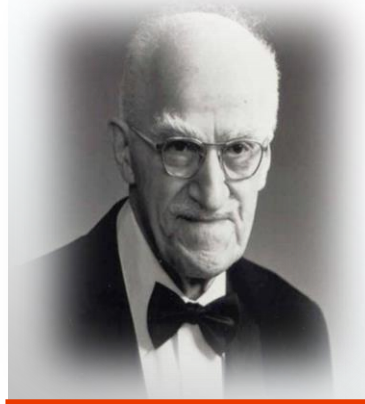
QbD concept:
"A systematic approach to development that begins with predefined objectives and emphasizes product and **process understanding** and **process control**, based on sound **science and quality risk management**" *(ICH Guideline Q8: Pharmaceutical Development)*

USP General Chapters – Analytical Procedure Environment:
<1225> Validation of Compendial Procedures
<1226> Verification of Compendial Procedures
<1224> Transfer of Analytical Procedures
<1210> Statistical tools for procedure validation
<1220> Analytical Procedure Lifecycle*
**still not official*

Stimuli Articles published in the PF
PF 39(5) Lifecycle Management of Analytical Procedures
PF 42(2) Fitness for Use
PF 42(5) Analytical target profile (ATP)
PF 42(5) Analytical control strategy

"Knowledge management and quality risk management are two of the primary enablers of QbD." (Patil, 2013)

Evolution of QbD and AQbD



Dr. Joseph M. Juran
1990
developed the QbD concept:
"quality should be designed into a product, and most of quality problems relate to the way in which a product was designed in the first place"

ICH guidelines which outline QbD concepts
2004: Q8 Pharmaceutical development
2005: Q9 Quality risk managment
2007: Q10 Pharmaceutical quality system
2012: Q11 Development and Manufacture of Drug Substance

ICH guideline Q14: Analytical Procedure Development: new guideline is proposed to harmonise the scientific approaches of Analytical Procedure Development

Aug2020 - MHRA: Response and Strategy for the application of AQbD concepts to pharmacopoeial standards for medicines

ICH Q14: Public consultation 2022

1970

*QSRRs - innovative approach for the prediction of chromatographic retention from the molecular structure

Numerous applications for:
- description of retention mechanisms,
- optimization of chromatographic methods,
- prediction of elution order, and column selection

Linear Free Energy Relationships (LFERs), Kaliszan QSRR-model, Hydrophobic Subtraction Model (HSM) etc

**QSRR: Quantitative Structure Retention Relationship*

1990

2002

FDA encourages risk-based approaches and the adoption of QbD principles in drug product development, manufacturing, and regulation.

"increased testing does not necessarily improve product quality. Quality must be built into the product."

2004 - 2012

2011

EMA-FDA pilot program for parallel assessment of QbD applications and

2017

Survey of pharmaceutical companies on implementation of AQbD concepts

International Consortium For Innovation and Quality - AQbD WG

2018

2020

GC <1220> Analytical Procedure Lifecycle Sep2020
**published in PF46(5)*

2021

USP & BP Workshop on AQbD & APLC Feb2021

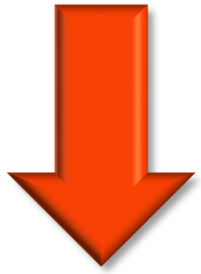
BP supplementary chapter The application of AQbD to pharmacopoeial methods April 21

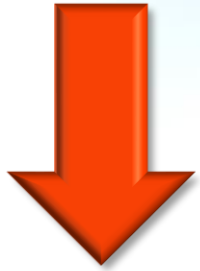
Quality Paradigm Shifts in an Evolving Global Environment

Compliance driven approach

Quality by Testing and Inspection

Static / Reactive





Integrated Risk-based Approaches

Quality by Design

Proactive Continuous Improvement

"The shift toward QbD and a culture of quality is already underway, and new compendial and regulatory approaches are needed that can support and help advance this transformation."

Understanding Quality Paradigm Shifts in the Evolving Pharmaceutical Landscape

Vincent Antonucci, Amy R Barker, Narendra Chirmule, Joseph DeFeo, Jennifer Devine, Taha Kass Hout, Michael S. Levy, Gugu N. Mahlangu, Horacio Pappa, Barbara Rellahan, Dan Snider, Jaap Venema, Jane Weitzel, Wesley Workman

Analytical Procedure Development

- Approaches used for analytical procedures development

“Traditional approach”
One-factor-at time experiments (OFAT)
testing of factors and their effects
one at a time instead of multiple factors
simultaneously.

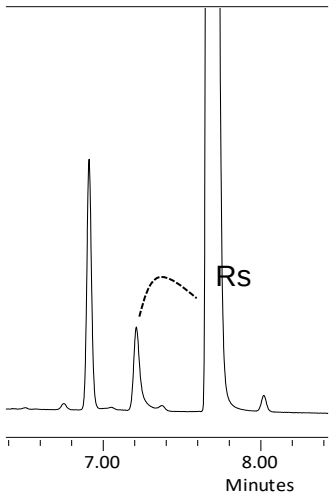
“Enhanced approach”
e.g.: Analytical Quality by Design (AQbD)
systematic approach which studies
multiple factors simultaneously to evaluate
the impact on method performance

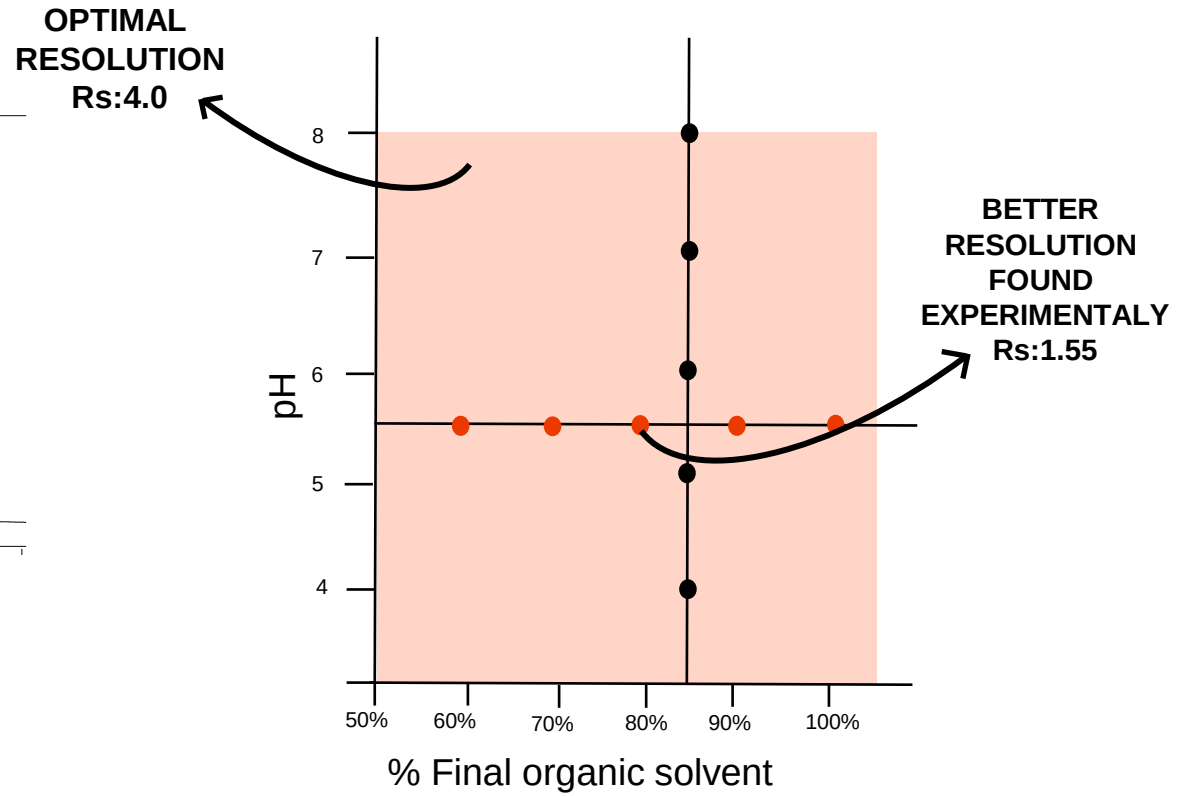
Analytical Procedure Development

Traditional approach - Changing “one factor at a time” (OFAT)

- One factor is varied at a time to evaluate the impact on the analytical response

E.g.: Response to be optimized: Resolution (Rs) between critical pair in liquid chromatography





STEP 1:
- Factor **pH**: vary
- Factor **column, organic solvent** and gradient program**:** constant

STEP 2:
- Second factor organic solvent: Vary
- Factor **columns** and **pH:** constant

OFAT DISADVANTAGES

- Interaction between factors can’t be estimated
- Limited understanding about the method
- It is not possible to predict the analytical response within a set of conditions which were not tested.
- The number of experiments and time needed is not known at the beginning of the method development

AQbD approach

Gather prior knowledge

QUALITY TARGET PRODUCT PROFILE (QTTP)
ANALYTICAL TARGET PROFILE (ATP)

Predefined objective that stipulates the performance requirements

Adapted from QbD Approaches to Analytical Methods - FDA Perspective, AAPS Annual Meeting, Washington DC, 2011 and USP GC <1220>

STAGE 1: PROCEDURE DESIGN

LIFECYCLE/ KNOWLEDGE/ QUALITY RISK MANAGEMENT

1. **CRITICAL QUALITY ATTRIBUTES (CQA)**
   CRITICAL PROCEDURE ATTRIBUTES (CPA)

   Analytical responses representing method quality

2. **CRITICAL PROCESS PARAMETERS (CPP)**
   CRITICAL PROCEDURE PARAMETERS (CPP)

   Analytical conditions which impact significantly on method performance
   Prior knowledge/Initial risk assessment

3. **MULTIVARIATE CHEMOMETRIC TOOLS**

   Data Generation (DOE: screening/optimization)
   Multivariate Data Analysis
   Predictive Modelling
   Prediction Models Validation

4. **KNOWLEDGE SPACE**
   ***In-silico* ROBUSTNESS TEST → MODR**
   MODR VALIDATION

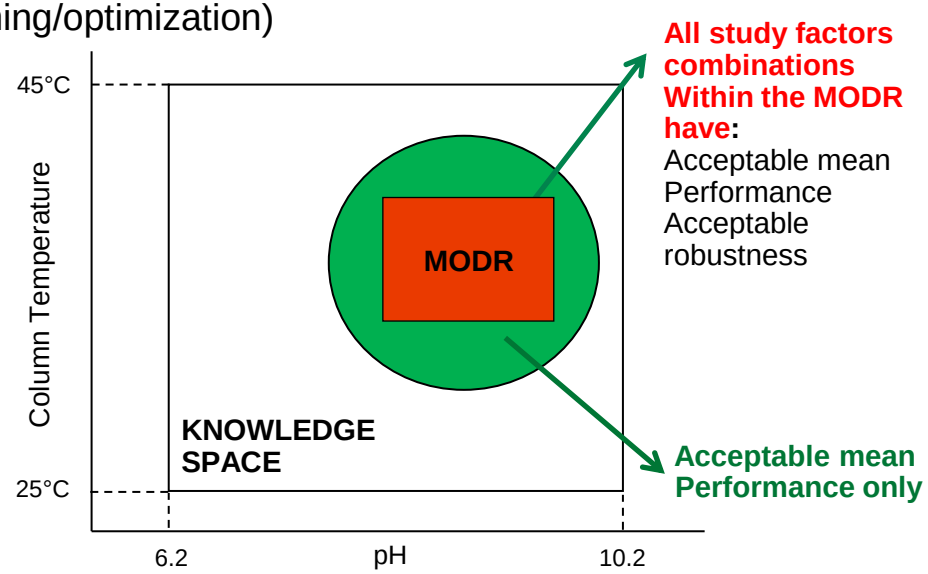
   Risk Assessment and Control

5. **ANALYTICAL CONTROL STRATEGY**

   e.g.: system suitability tests

STAGE 2: PROCEDURE PERFORMANCE QUALIFICATION

STAGE 3: CONTINUED PROCEDURE PERFORMANCE VERIFICATION



Quality Risk Management (QRM)

- **QRM**
  - systematic process for the assessment, control, communication, and review of risk to the quality of the reportable value across the lifecycle of the analytical procedure
- **Aim**
  - assess the proposed procedure conditions
  - identify appropriate controls on the analytical procedure parameters and material attributes that will ensure the procedure meets the ATP.
- **Risk Management Methodologies**
  - flowchart, process mapping, cause and effect diagrams, failure mode effects analysis (FMEA), failure mode effects and criticality analysis (FMECA) etc.

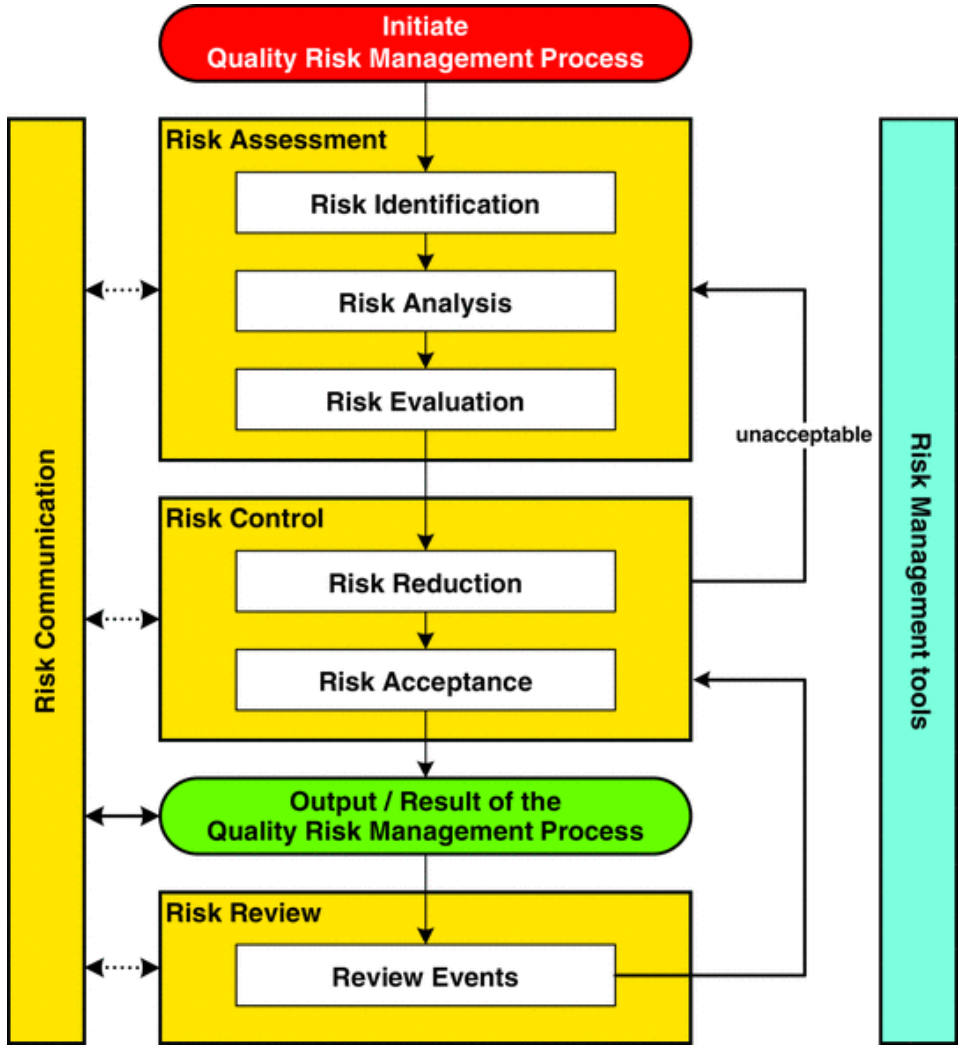


Figure 4. Overview of a typical QRM process (ICH Q9).

42(5) Stimuli Article: Analytical Control Strategy

Chemometrics

Concept

- Is a chemical discipline that uses mathematical, statistical, and other methods to accomplish two objectives:
  - to design or select optimal measurement procedures and experiments, and
  - to provide the maximum amount of relevant chemical information by analyzing chemical data

  USP General Chapter <1039> Chemometrics

- chemometrics aims to extract information from a certain type of data and draws upon multivariate methods to:
  - generate and
  - analyze data with many factors or variables,
  - while having large focus on knowledge generation

Chemometrics

Knowledge Generation

DATA GENERATION

- How to plan experiments?
  - Design of Experiments (DOE)
    - **Screening**
    - **Optimization**

DATA ANALYSIS

- How to explore multivariate datasets and gain knowledge?
  - Multivariate Data Analysis

Application of Knowledge

PREDICTIVE MODELLING

- How to predict quantitative properties?
  - Linear (MLR, PCR, PLS…)
  - Non-Linear (LS-SVM, ANN …)
- How to classify/discriminate samples?
  - Unsupervised classification (HCA, PCA…)
  - Supervised classification (PLS-DA, SIMCA, ANN, OPLS-DA…)

MODEL VALIDATION

- Generate evidences that the models are fit for use
- Statistical Analysis

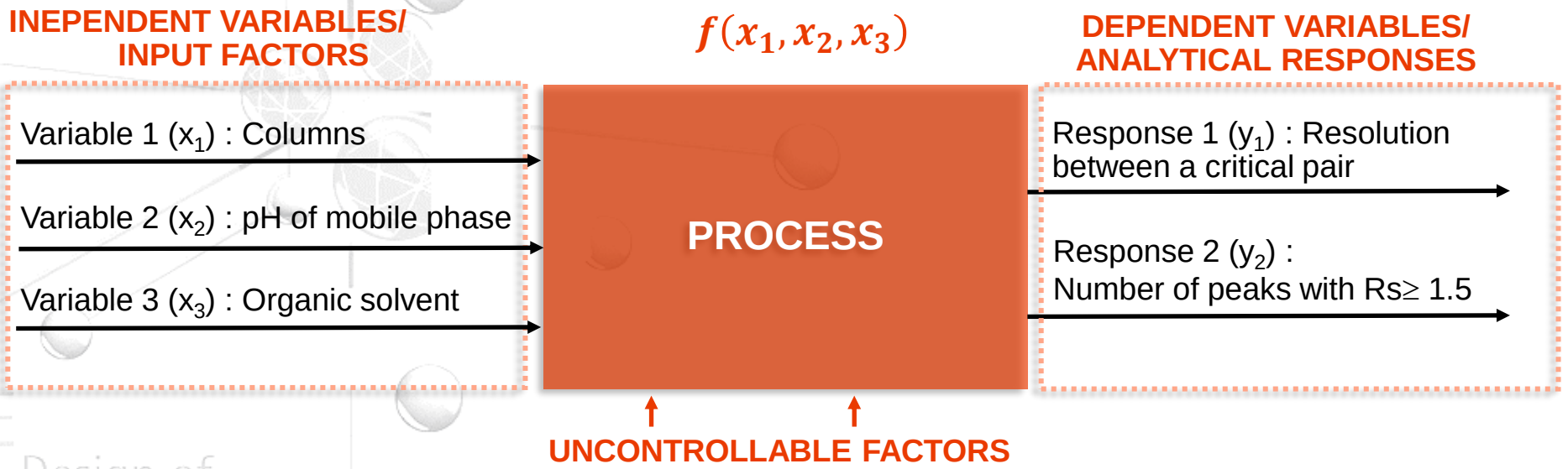
Illustration of chemometrics as a process to generate and apply knowledge using data-driven methods

Adapted from R. Sjögren, Synergies between Chemometrics and Machine Learning, 2021

Design of Experiments (DOE)

- DOE is defined as a branch of applied statistics that deals with:
  - planning, conducting, analyzing,
  - and interpreting controlled tests to evaluate the impact of the factors on the process parameters.

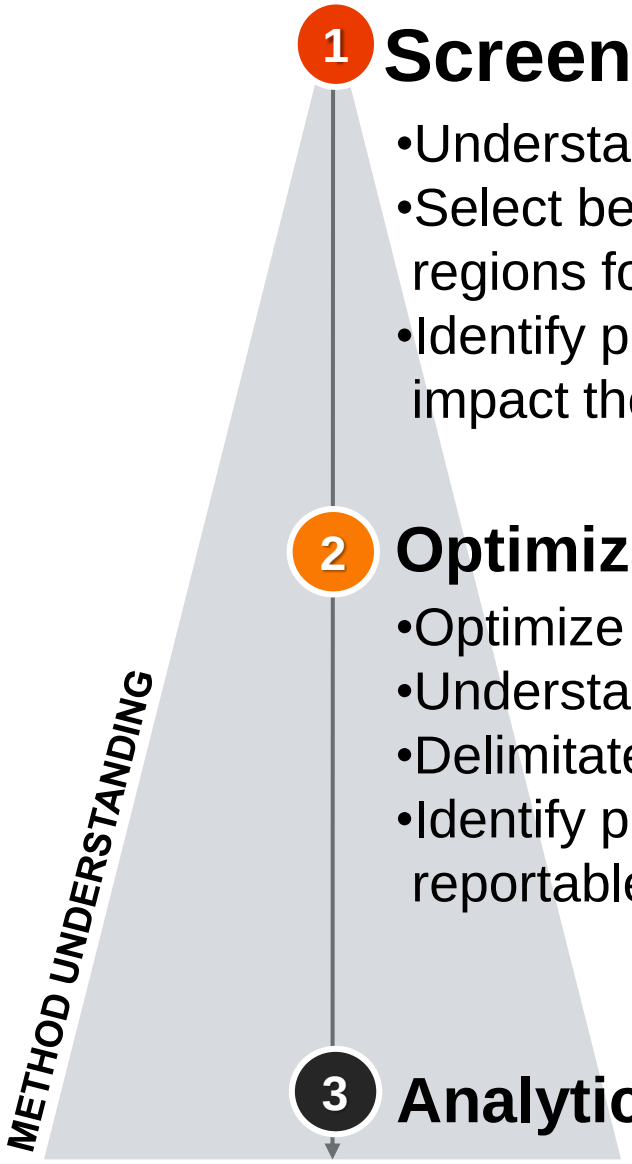
- DOE is a powerful **data collection and analysis tool** that can be used in a variety of experimental situations.



REGRESSION ANALYSIS
method used for the estimation of relationships (Regression model) between the analytical response (y) and one or more independent variables (x_1,x_2,x_3...)

$$\hat{y} = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{11} x_1^2 + \beta_{22} x_2^2 + \beta_{33} x_3^2 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 + \beta_{123} x_1 x_2 x_3 + \varepsilon$$

Design of Experiments (DOE)



1 Screening Design

- Understand the effect of CPPs on performance
- Select best performance conditions and workable regions for optimization
- Identify procedure variables that have the potential to impact the reportable value - **Selectivity!**

DOE types for screening

- Full factorial design, fractional factorial design, placket-burmann, mixtures design, optimal designs...

Best performance conditions from screening

2 Optimization Design

- Optimize performance
- Understand uncertainty associated with reportable results
- Delimitate an operating range (MODR)
- Identify procedure variables that have the potential to impact the reportable value - **Selectivity, Accuracy and Precision!**

DOE types for optimization

- Central composite design, Box Benken, Doehlert, mixtures design, optimal designs etc ... (Designs with resolution V are recommended)

3 Analytical Control Strategy

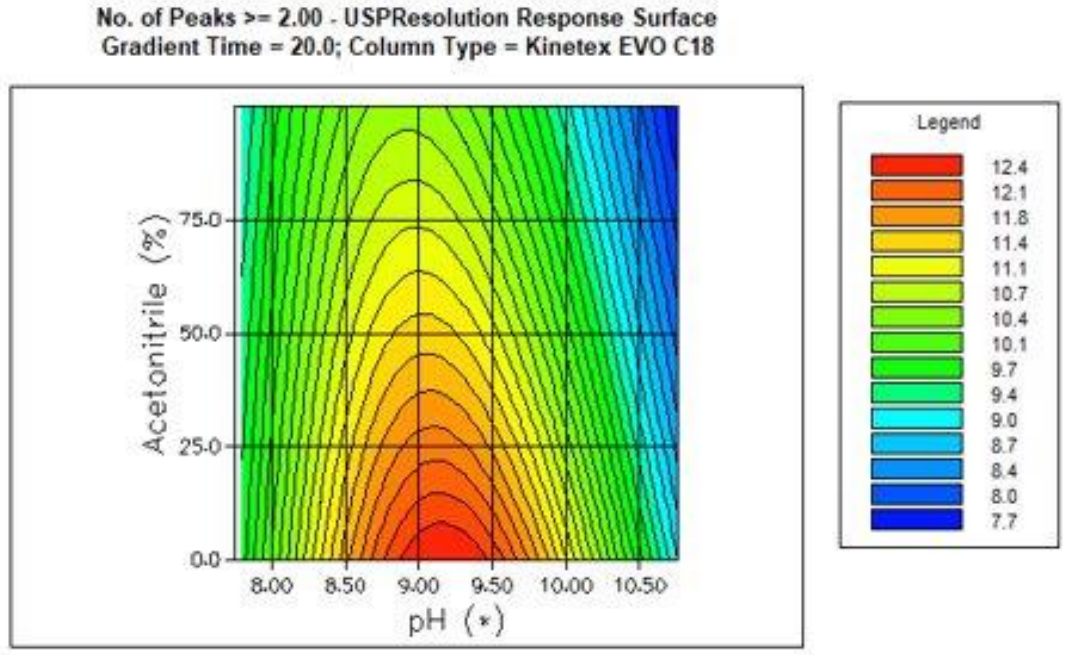
DOE and Predictive Modelling

What can we get from that?

- **Variables selection**
  - Understand the effect of input factors on analytical responses
  - Identify analytical conditions which have significant impact on the analytical responses
  - The interaction between factors can be estimated systematically.

- **Analytical response prediction**
  - Prediction of procedure performance within the experimental domain
  - Identify analytical conditions and workable regions for performance optimization

Importance of estimation of factors interaction effects:



The influence of the pH depends on the% of ACN in Solution B used

2-factor interaction

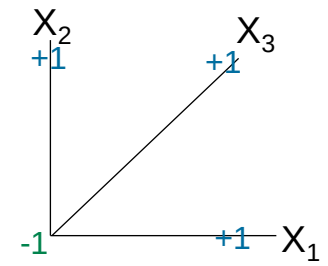
Design of Experiment (DOE)

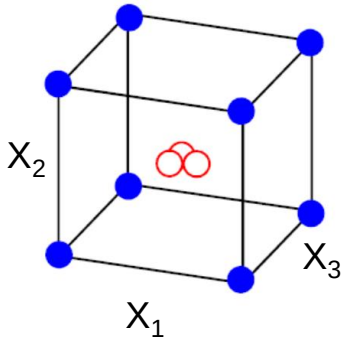
SCREENING

FULL FACTORIAL DESIGN

Factors (k) < 5

Ex.: 3 factors (k=3)
$2^k = 2^3 = 8$ experiments





All possible combination of factors are evaluated

Understand main effects and some factors interaction effects on the monitored analytical response

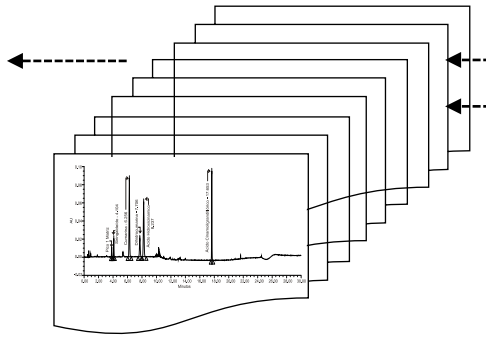
3 VARIABLES (k=3)
2^3 experiments = 8 experiments + Center Points

VARIABLES	Levels	
	Level (-1)	Level (+1)
X_1: Concentration Ion-Pairing Reagent	*5mM HFBA*	*10mM HFBA*
X_2: pH	Amm. Formate 5 mM pH 4.0	Amm. Acetate 5 mM pH 6.0
X_3: % MeOH in ACN	100%	0%

Injection volume, Flow rate, colum temperature, LC Column: Constant

RUN	Response Y
1	y_1
2	y_2
3	y_3
4	y_4
5	y_5
6	y_6
7	y_7
8	y_8
9	y_9
10	y_{10}
11	y_{11}

CHROMATOGRAM AQUISITION AND DATA PROCESSING



Center point: curvature checking;
Replicates at the center points: pure error estimate.

EXPERIMENTAL DESIGN MATRIX

RUN	VARIABLES X_1	X_2	X_3
1	*5mM HFBA*	pH 4	100% MeOH
2	*10mM HFBA*	pH 4	100% MeOH
3	*5mM HFBA*	pH 6	100% MeOH
4	*10mM HFBA*	pH 6	100% MeOH
5	*5mM HFBA*	pH 4	100% ACN
6	*10mM HFBA*	pH 4	100% ACN
7	*5mM HFBA*	pH 6	100% ACN
8	*10mM HFBA*	pH 6	100% ACN
9	7.5mM HFBA	pH 5	MeOH:ACN (1:1)
10	7.5mM HFBA	pH 5	MeOH:ACN (1:1)
11	7.5mM HFBA	pH 5	MeOH:ACN (1:1)

RUN	VARIABLES X_1	X_2	X_3
1	-1	-1	-1
2	+1	-1	-1
3	-1	+1	-1
4	+1	+1	-1
5	-1	-1	+1
6	+1	-1	+1
7	-1	+1	+1
8	+1	+1	+1
9	0	0	0
10	0	0	0
11	0	0	0

Screening

- **FULL FACTORIAL DESIGN:** 2^K or 3^K designs (2 or 3 levels) 2-4 variables

- **FRACTIONAL FACTORIAL DESIGN:** 2^{k-p} designs 5-14 variables or >14 variables
  - Estimation of main effects and (some) interactions - depending on the resolution of the factorial design.
  - Resolution III: main effects aliased w/ 2-factor (2-F) interaction/ some 2-factor interaction may be aliased w/ each other
  - Resolution IV: main effects are NOT aliased w/ 2-F int.; some 2-factor interactions may be aliased w/ 2-F interaction
  - Resolution V: main effects are NOT aliased w/ 2-F interactions and 2-F int. Very similar results compared to the full factorial design

- **PLACKET-BURMANN** K=N-1 (with N experiments) >14 variables, N= 12,20,24,28,36

- **MIXTURE DESIGNS** 5-14 variables or >14 variables
  - When the responses depend on the proportions of the mixture components.
  - Factores with different number of levels e.g.: with 2 levels and with 3 levels

- **OPTIMAL DESIGNS** 5-14 variables or >14 variables
  - The experiments are selected based on pre-defined mathematical criteria and are model- oriented.
  - The position of the points is selected based on a mathematical criterium of possible subsets of experiments;
  - Irregular experimental regions,
  - Use of qualitative factors (w/ reduced number of runs)
  - Reducing the number of experiments
  - Fitting special regression models

1. *Montgomery. D.C. Designs and Analysis of Experiments. 8th edition. Wiley. 2013.*
2. *Lundstedt, T. et al.* Experimental design and optimization. *Chemometrics and Intelligent Laboratory Systems 42 (1998) 3–40.*

Optimization

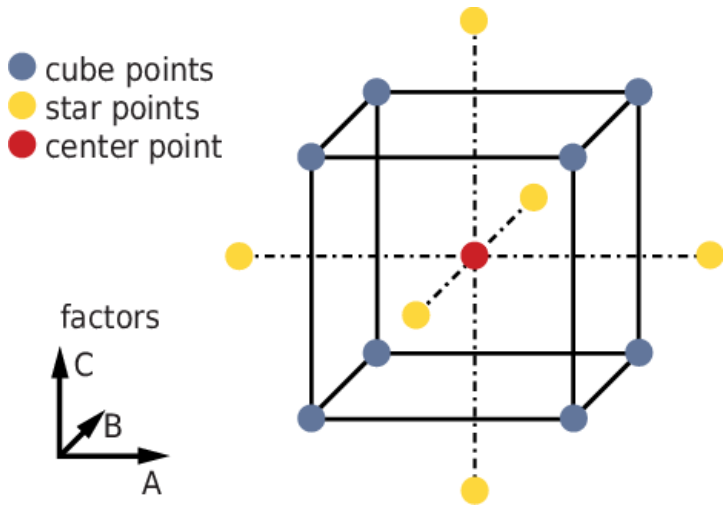
- Designs to build higher order models for prediction and optimization

$$\hat{y} = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + + b_{12}x_1x_2 + b_{13}x_1x_3 + b_{23}x_2x_3$$ **Linear terms**

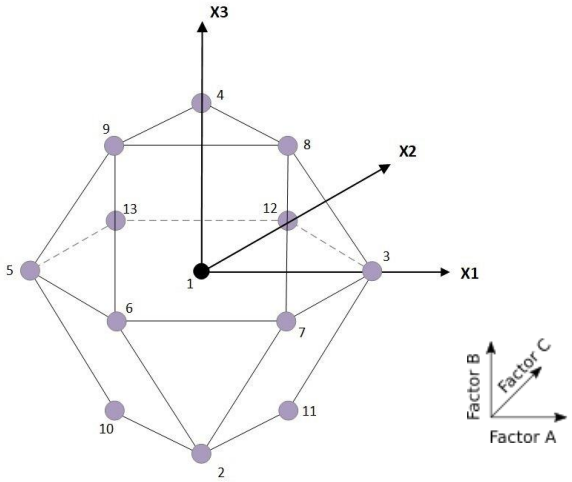
$$+ b_{11}x_1^2 + b_{22}x_2^2 + b_{33}x_3^2$$ **Quadractic terms**

$$+ b_{112}x_1^2x_2 + b_{113}x_1^2x_3 + b_{223}x_2^2x_3 + (\ldots)$$ **Higher order terms**

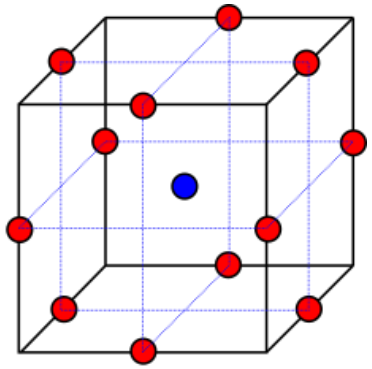
Composite Central Design (CCD)



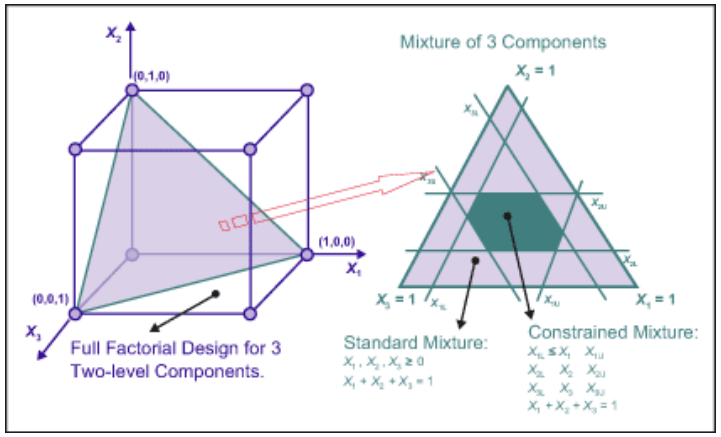
Doehlert



Box Benken



Mixture Designs

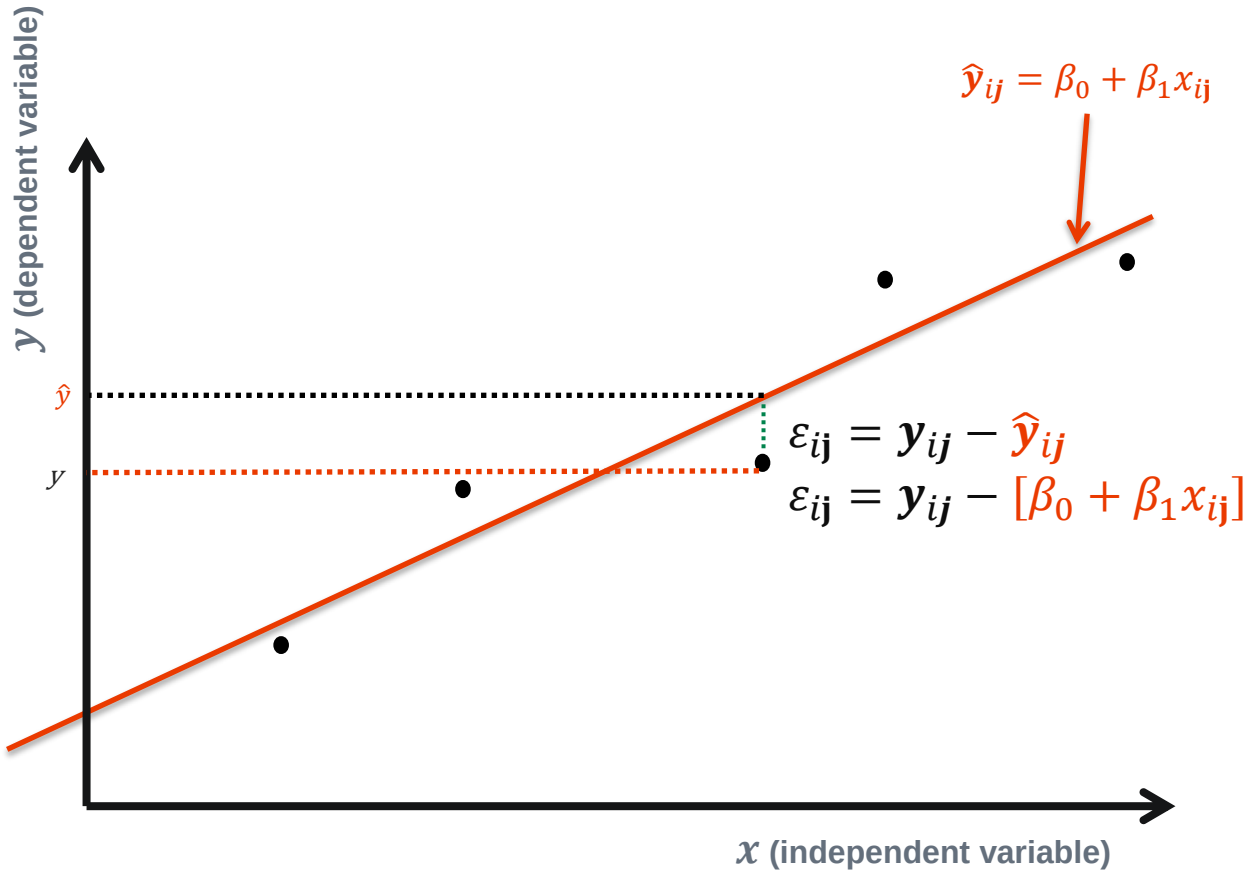


Optimal Designs

Lundstedt, T. et al. Experimental design and optimization. *Chemometrics and Intelligent Laboratory Systems 42 (1998) 3–40.*

Design of Experiment (DOE)

Prediction Models: How much can we trust it?



Least Squares Regression

Regression coefficients (β_0, β_1 ...) will be estimated by minimizing residual sum of squares(SSR)

$$\mathbf{SSR} = \sum_{i=1}^{k} \sum_{j=1}^{n_i} \varepsilon_{ij}^2$$

$$\mathbf{SSR} = \sum_{i=1}^{k} \sum_{j=1}^{n_i} [y_{ij} - \beta_0 - \beta_1 x_{ij}]^2$$

Least Square Regression Assumptions

The residue is normally distributed and has a population mean of zero $\varepsilon_{ij} \sim N(0, \sigma^2)$

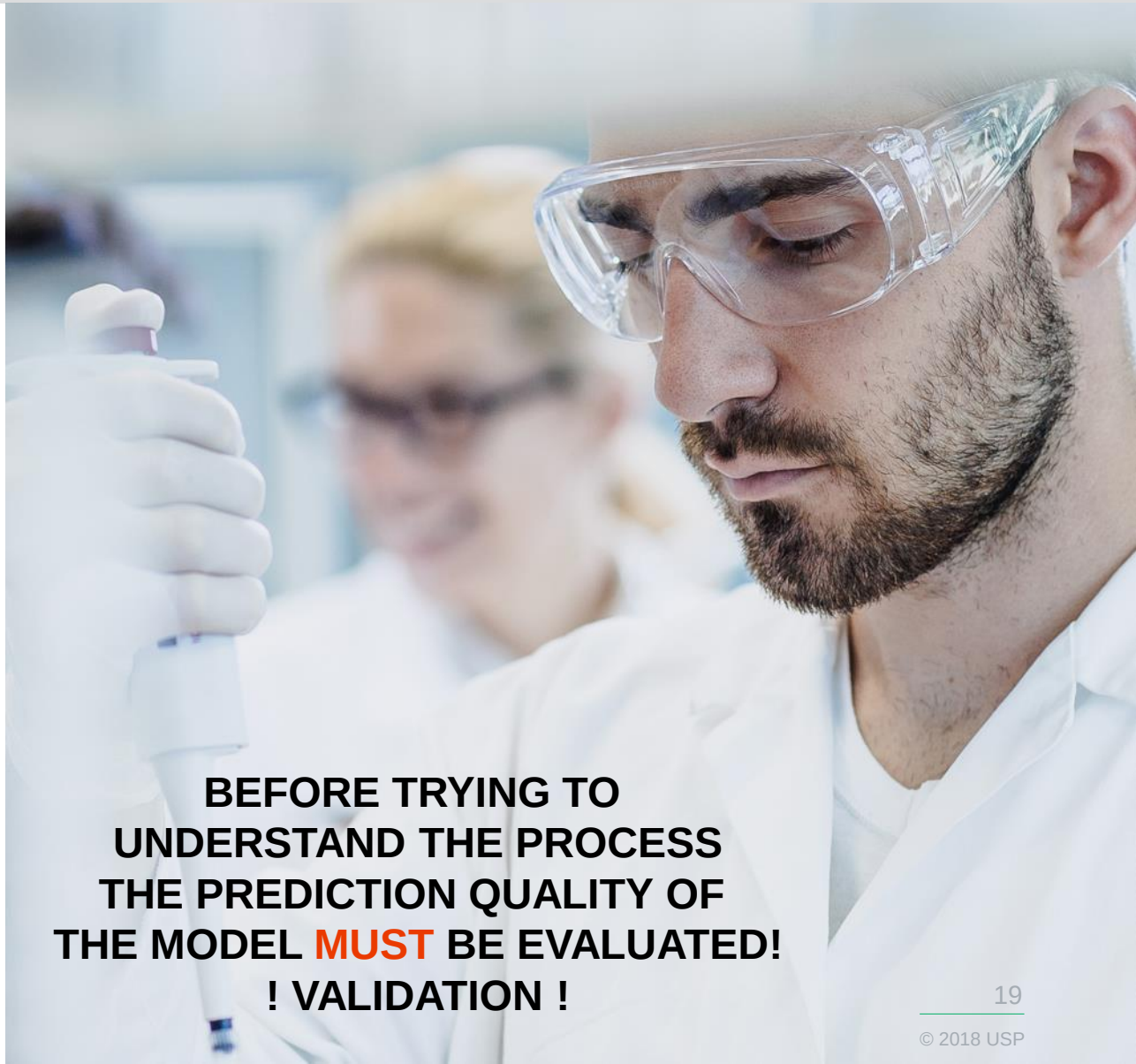
For every x, the variance of ε_{ij} is σ^2 - The residue has a constant variance (no heteroscedasticity)

Observations of the error term are uncorrelated with each other

Prediction Models Validation

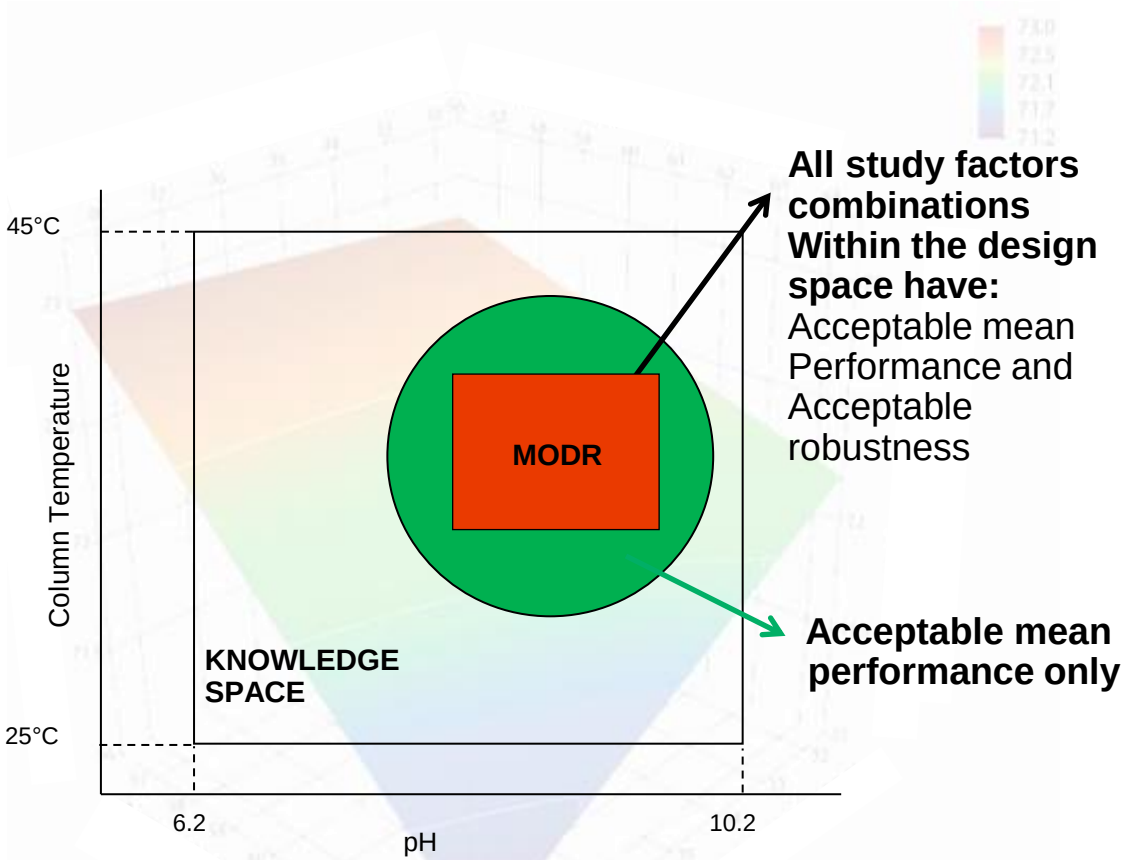
Statistical Analysis

- Check for heteroscedasticity: Transformation analysis if necessary
- Evaluation of model predictive ability: ANOVA
- Evaluation of model goodness of fit: ANOVA
- Residue analysis - evaluation of:
  - Outliers and homoscedasticity
  - Autocorrelation
  - Leverage points
  - Influent points
  - Outliers
- Regression coefficient significance analysis



Method Operable Design Region (MODR)

Robustness and MODR



- MODR is a multidimensional combination and interaction of procedure parameters where all study factors combinations have been demonstrated to provide:
  - Acceptable Mean Performance
  - Acceptable Robustness

- Challenges for implementing the MODR:
  - Lack of guidelines with framework for
    - operating range creation
    - MODR proper validation
  - Knowledge gaps: demonstration that MODR works across important 'ruggedness factors' (such as the use of different systems, columns, environment, analysts etc)

- Key Aspects for MODR generation:
  - Use of suitable types of DOE or other modeling predictive methods which can precisely estimate effect of
    - 2-factors interactions or
    - higher-order interactions (if necessary depending on the complexity to model the analytical response).
  - robustness evaluation.

Case Study

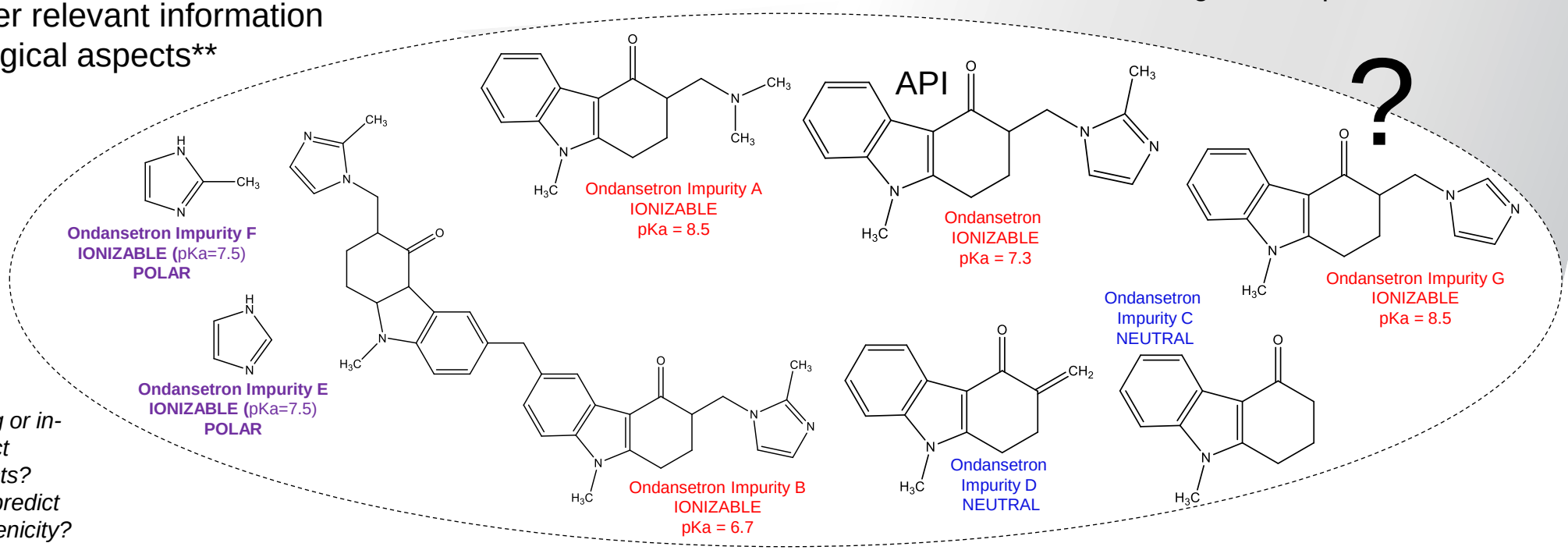
Analytical Target Profile (ATP) Establishment

The procedure must be able to accurately quantify Ondansetron related compounds (Impurity A, B, C, D, E, F and G) in a range from 0.05% to 0.15% (relative to nominal concentration of API) in the drug substance Ondansetron with an accuracy = 100% ± 2% and a precision RSD ≤ 5% for the reportable value.

GATHER PRIOR KNOWLEDGE:

- Chemical structures
- Physico-chemical properties
- Any other relevant information
- Toxicological aspects**

Initial Risk assessment:
Prior knowledge on potential presence of impurities, excipients, degradation products*



** Pilot stress testing or in-silico tools to predict degradation products?*
*** In-silico tools to predict impurities carcinogenicity?*

Selection of CMPs and CQAs - QRM

Initial Risk Assessement

LC Columns Stationary Phase

REVERSED PHASE

Hybrid %CL Silica

C18 — *Hydrophobic interaction* — *↓ Ionic interaction (-Si-O⁻)/Positively charged imp.*

Polar group embeeded in the alkyl chain — *Hyd. Bonding Dipole-dipole int.* — *↓ Ionic interaction (-Si-O⁻)/Positively charged imp.*

Polar endcap

Core-shell — *↑ efficiency?*

C8 — *Hydrophobic interaction etc..*

Phenyl hexyl — *Hydrophob. and π-π interaction*

HILIC

Partition/ionic interaction — Silica

Partition — Diol

Dipole-ion interaction — Ciano

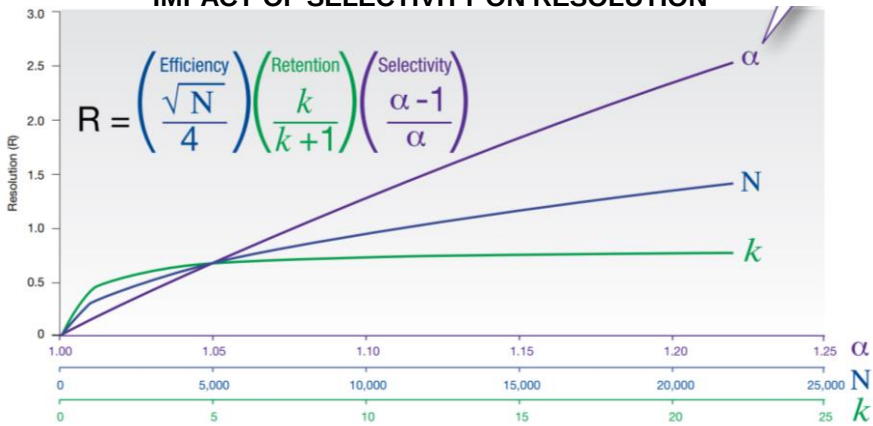
Dipole-Ion interaction — PFP

Column Temperature

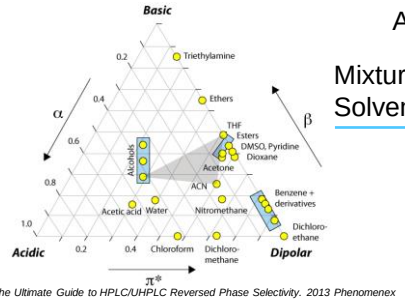
Especially for matrices containing ionizable compounds – evaluate this factor during optimization…

Gradient

IMPACT OF SELECTIVITY ON RESOLUTION



The Ultimate Guide to HPLC/UHPLC Reversed Phase Selectivity. 2013 Phenomenex



The Ultimate Guide to HPLC/UHPLC Reversed Phase Selectivity. 2013 Phenomenex

Organic Solvents

Type of Organic Solvents: ACN, MeOH, THF...

Mixture of Organic Solvents

Ion-Pairing Reagents

Type of Ion-Pairing Reagents: TFA, PFPA, HFBA, NFPA

Alkylchain Length — *↑ length: ↑ retention of Imp. F and E + good selectivity?*

Concentration of Ion-Pairing Reagents — *↑ Conc.: ↑ retention of polar compounds in RPLC /ionizable compounds*

pH of Mobile Phase

pH > (pKa + 2): Ionizable compounds NON ionized — *Stable LC columns?*

(pKa - 2) < pH < (pKa + 2): Ionizable compounds PARTIALLY ionized — *Robustness + good selectivity ?*

pH < (pKa + 2): Ionizable compounds TOTALLY ionized — *RPLC – LC columns with technology to reduce ionic interaction*

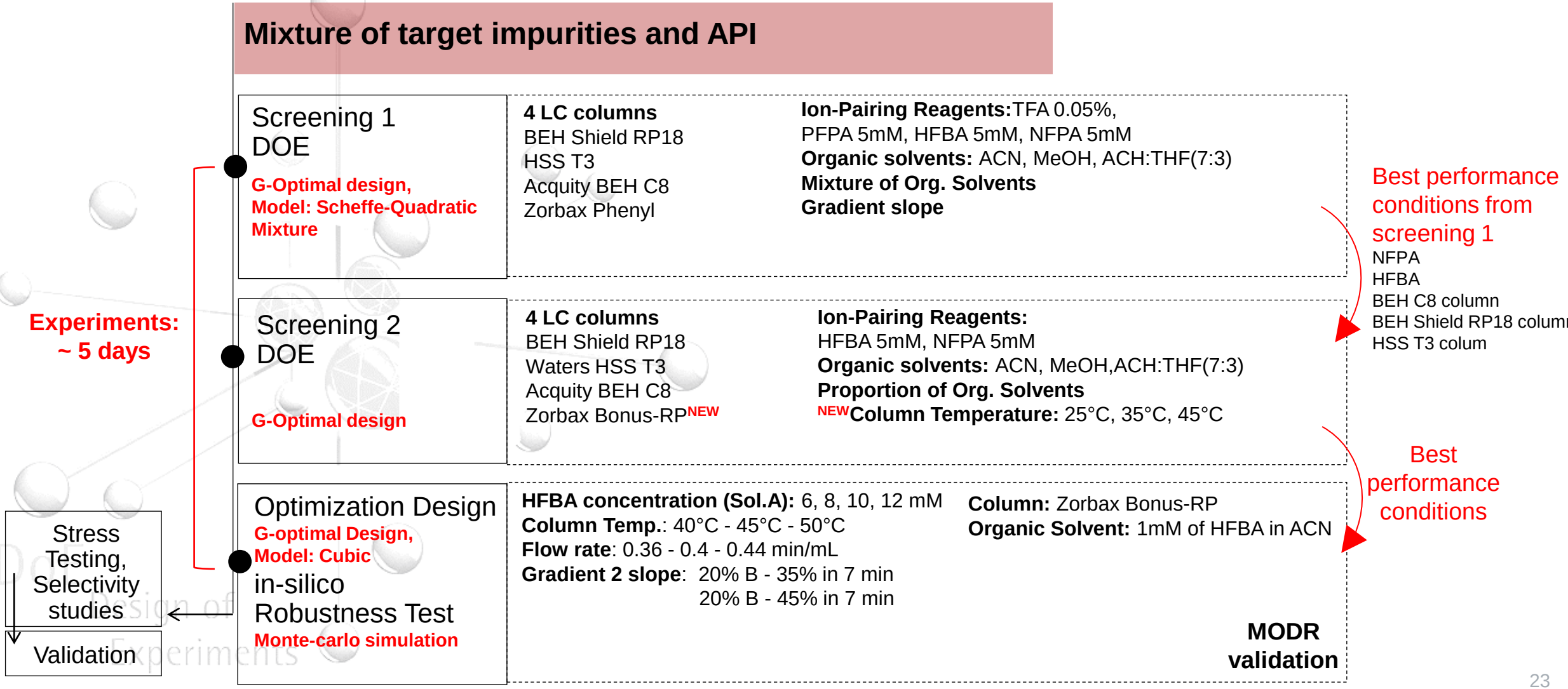
HILIC – Explore partition and ionic exchange?

Ion-Pairing Chromat. – ↑ retention of polar compounds

CRITICAL PROCEDURE ATTRIBUTES (CPA)

- Number of total peaks
- N° of peaks with Rs ≥ 1.5
- N° of peaks with Rs ≥ 2.0
- Tailing Factor
- Retention Factor (k)
- ...

Method development strategy



QbD - Available softwares

QbD SOFTWARE
FOCUSED ON METHOD DEVELOPMENT

ACD/Labs
ACD/AutoChrom

DryLab®
by MOLNÁR-INSTITUTE

Fusion QbD
S-Matrix

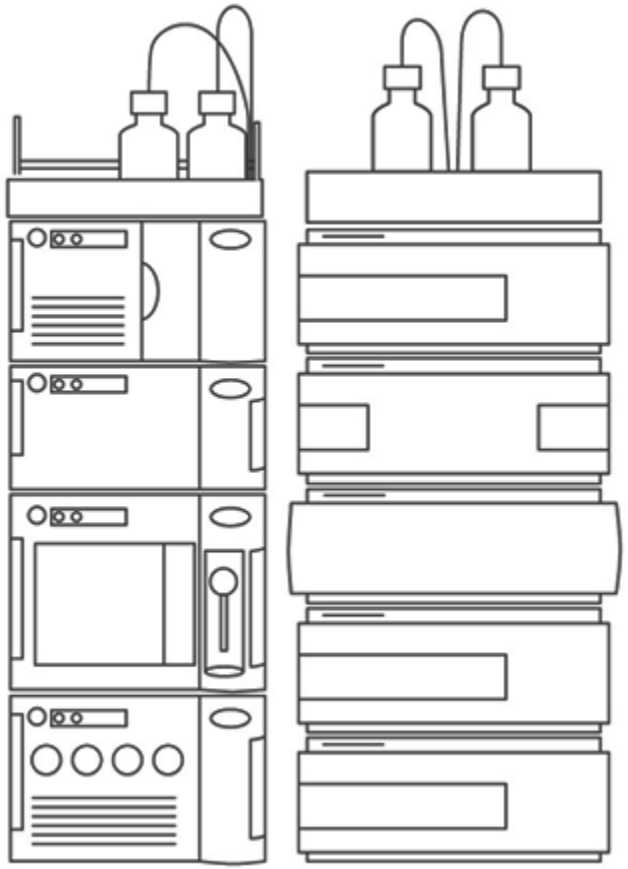
ChromSword

1. VARIABLE SELECTION

***Statistica, Matlab, Minitab, Design Expert, R program, Excel, etc...*

2. SELECTION OF EXPERIMENTAL DESIGN

3. EXPORT DATA MATRIX (EXPERIMENTS) TO CHROMATOGRAPHIC SYSTEM
INSTRUMENT METHODS AND SAMPLE SET



4. EXPERIMENTAL ANALYSIS AND CHROMATOGRAM AQUISITION

5. DATA PROCESSING

6. IMPORT ANALYTICAL RESPONSES CRITICAL QUALITY ATTRIBUTES

7. REGRESSION ANALYSIS

8. STATISTICAL ANALYSIS - Models validation

9. RESPONSE PREDICTION, ANALYTICAL CONDITIONS SELECTION

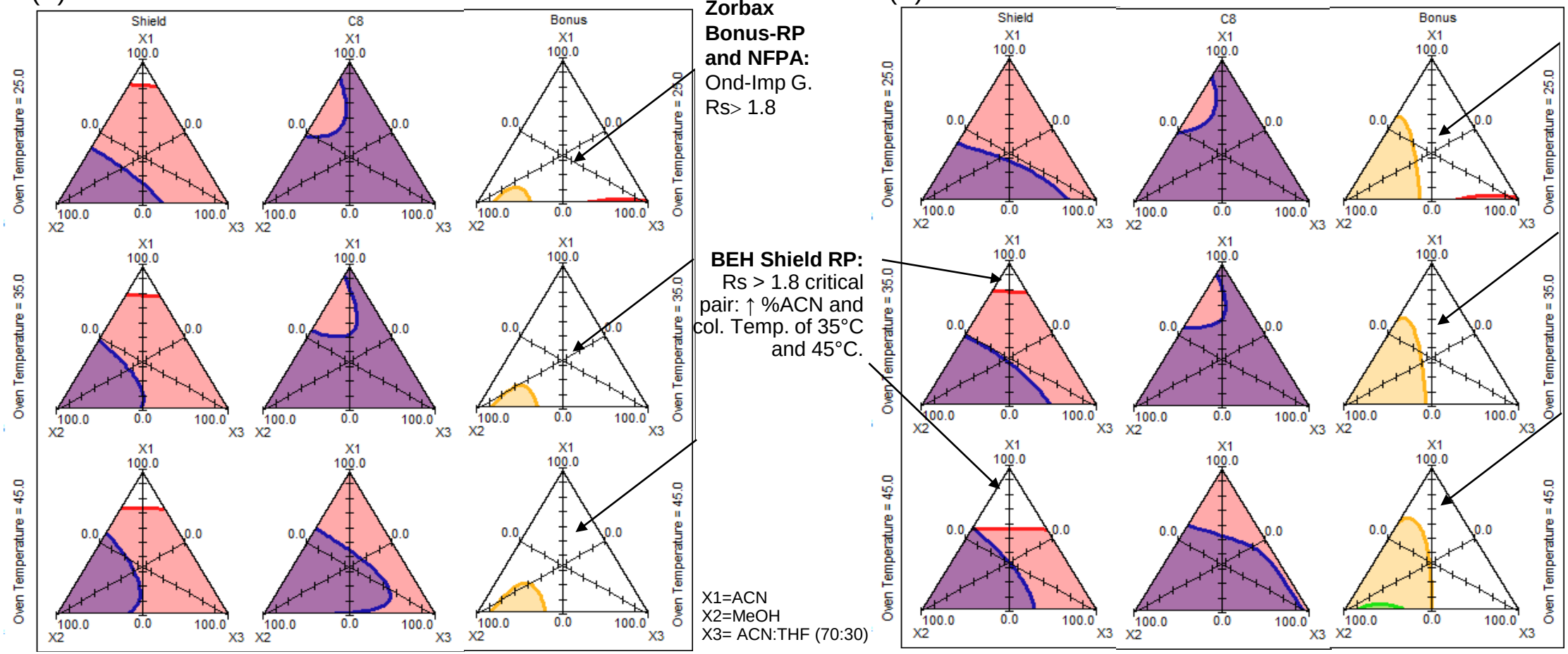
Case Study: Screening 2

	Name	Goal	Lower Bound	Upper Bound	Color
☐	No. of Peaks	---	---	---	---
☑	No. of Peaks >= 1.50 - USPResolution	Maximize	6.0		Blue
☑	First Peak - KPrime	Maximize	0.50		Green
☑	Tailing Factor	Target	0.700	1.100	Orange
☑	Resolution Critical Pair 1	Maximize	1.80		Red

Risk Assessment and Control

(A) NFPA

(B) HFBA



Zorbax Bonus-RP and NFPA: Ond-Imp G. Rs> 1.8

BEH Shield RP: Rs > 1.8 critical pair: ↑ %ACN and col. Temp. of 35°C and 45°C.

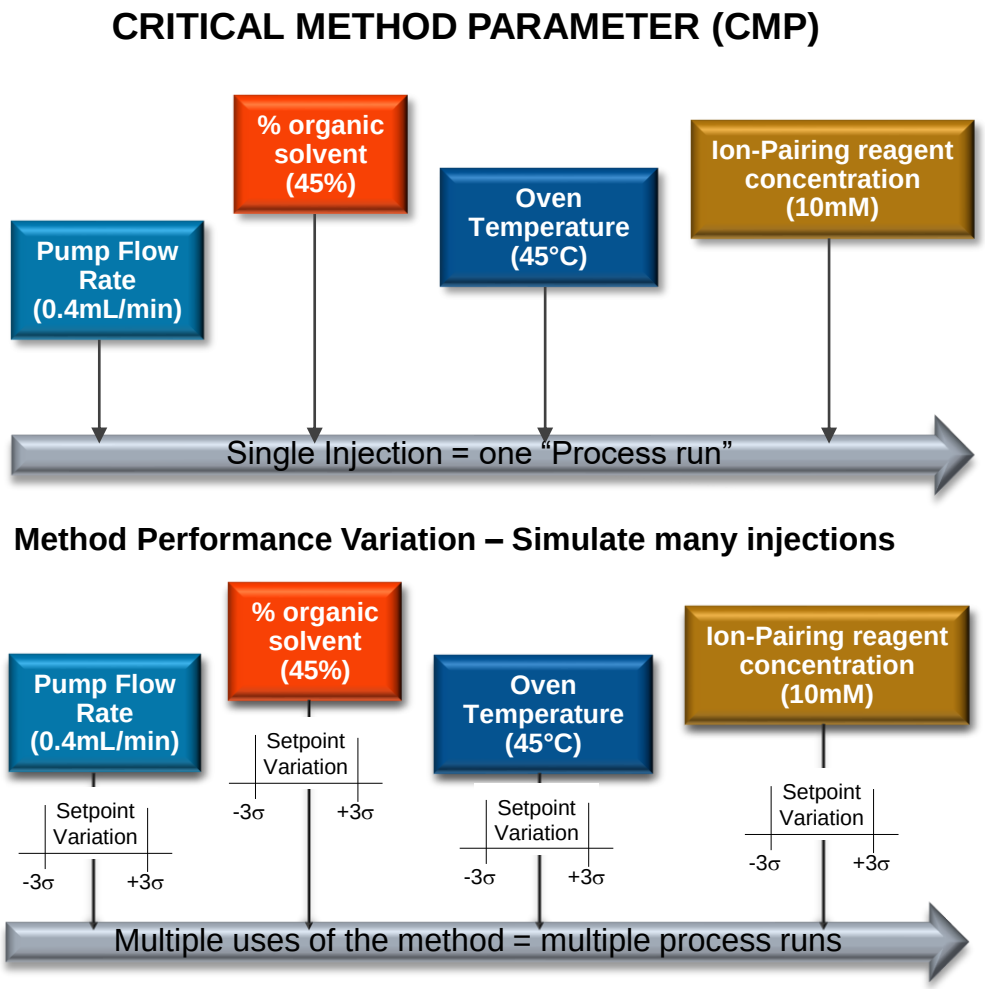
X1=ACN
X2=MeOH
X3= ACN:THF (70:30)

Zorbax Bonus-RP and HFBA: Ond-Imp G. Rs> 1.8

Figure 4. Acceptable performance region graphics obtained by the responses projection predicted by the regression models obtained in the screening 2 (A) HFBA and (B) NFPA.

Optimization Design

Uncertainty analysis & in-silico robustness study



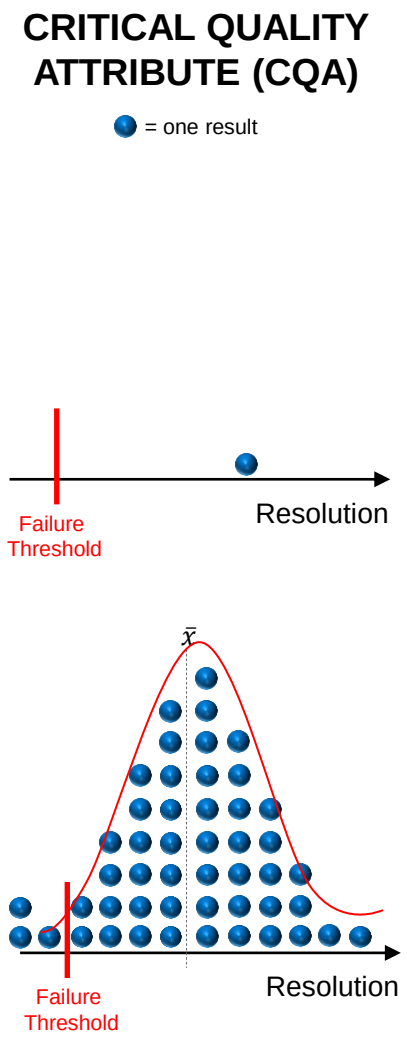


Figure adapted from published material on robustness by S-Matrix

Quality Risk Management

- Measurement Uncertainty Estimation: *Monte Carlo Simulation using DOE-derived models*
- In-silico Robustness study
- Establishment of specification for Performance Characteristics
- Process Capability Calculation
- Risk Control: Selection of conditions with Cpk>1.33
- Delimitation of MODR
- MODR Validation
  - Validation of prediction models: Statistical analysis
  - Performance Monitoring: Verification runs
- Optimization of Responses

Final Conditions + Validated MODR

Organic Impurities

Analytical Target Profile

The procedure must be able to accurately quantify Ondasetron related compounds (Impurity A, B, C, D, E, F and G) in a range from 0.05% to 0.15% (relative to nominal concentration of API) in Ondasetron with an accuracy = 100% ± 2% and a precision ≤ 2% for the reportable value.

Diluent: Acetonitrile:Water (25:75)
System Suitability Solution: 1 mg/mL of Ondasetron and 0.01 mg/mL of Imp. A, B, C, D, E, F and G in *Diluent.*
Solution A: 10mM if HFBA in water
Solution B: 1mM of HFBA in Acetonitrile
Mobile Phase: See *Table 1.*

Table 1

Time (min)	Solution A (%)	Solution B (%)	Slope
0	100%	0%	-
1.5	100%	0%	Slope 1
6	80%	20%	-
13.0	56%	44%	Slope 2
15.0	0%	100%	-
16	0%	100%	-
16.1	100%	0%	-
20	100%	0%	-

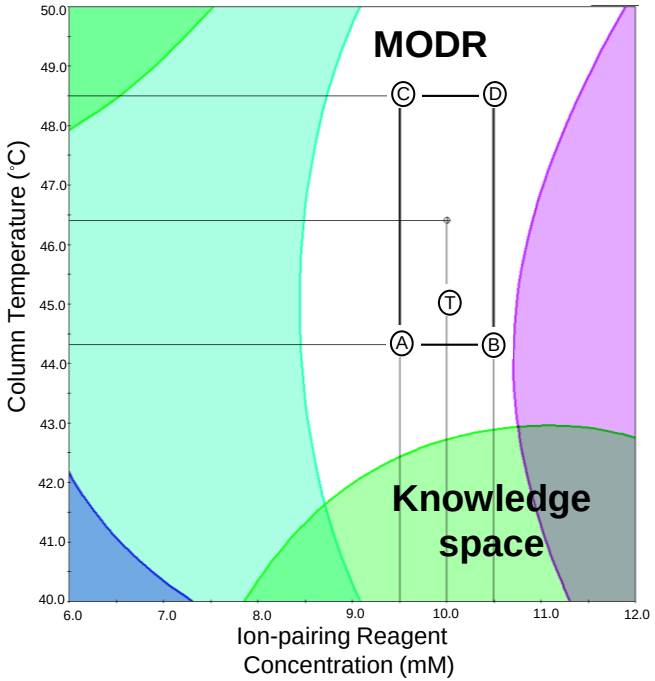
Chromatographic system
(See MODR and Chromatography <621>, System Suitability)
Mode: UHPLC
Detector: UV 220nm
Column: 1.7-um x 2.1-mm × 10-cm; packing L1 Zorbax RRHD Bonus RP18
Injection Volume: 2uL

Solution A, Column Temperature and flow rate: See Table 2 [Note - All conditions within the range described in this table should result in acceptable performance and robustness. MODR obtained based on a risk-based and multivariate approach]

Table 2. MODR

Chromatographic conditions	Target Value	Lower Value	Upper Value
Flow rate (mL/min)	0.40	0.39	0.41
Column Temperature (°C)	45	44.5	48.5
Solution A (HFBA concentration in water) mM	10	9.5	10.5
Final % Solution B (slope 2)	44	43	45

System Suitability
Sample:
Suitability requirements
Resolution: NLT 2.0 between Ondasetron and Imp. G and NLT 1.5 between impurities A, B, C, D, E, F and adjacent peaks
Tailing factor: 0.8 - 1.7 for all impurities (A, B, C, D, E, F and G)
%RSD: NMT 2.0% for replicate injections for all impurities
Retention factor (K): NLT 0.5 for Imp. E and F.



Control strategies established based on Quality risk Managment

Concluding Remarks

Benefits of applying QbD principles to method development

- Acquire high degree of understanding about method performance
  - Selection of optimized (selective) and robust conditions
  - Access an operating range (MODR)
  - Risk Management:
    - Risk assessment and control
    - understand and control sources of variability
    - Manage risks
- Understand the maximum variability or TMU that can be associated with a reportable result
  - establish suitable control strategies
  - establishment of more suitable control requirements for method transfer
  - Increase reliability of deciding if a product is OOS
- Facilitate knowledge and analytical procedure lifecycle management
- Promote continuous Improvement

Concluding Remarks

Fundamental to the concept of quality by design (QbD) is to start with the end in mind.

42(5) USP Stimuli Article: Analytical Control Strategy

START: METHOD DESIGN!
END: QUALITY

Chromatography

Trends in Analytical Chemistry, Vol. 42, 2013

Design Spaces for analytical methods

E. Rozet, P. Lebrun, B. Debrus, B. Boulanger, P. Hubert

Table 2. Details of the analytical Design Spaces published in the scientific literature

Analytical method	Analytes	Matrix	Modeling approach	Design Space type	Ref.
UHPLC-UV	Impurities and degradation product of ethinylestradiol	Tablets	Chromatographic theory	Mean response surface	[70]
UHPLC-UV	Dienogest, estradiol, ethinylestradiol, finasterid, gestodene, levonorgestrel, norethisterone acetate	Cleaning validation samples	Chromatographic theory	Mean response surface	[70]
UHPLC-UV	1-naphtol, duloxetine, related impurities and degradation products	Spiked and stressed capsule samples	Chromatographic theory	Mean response surface	[70]
UHPLC-UV	Bicalutamide and related impurities	Tablets	Chromatographic theory	Mean response surface	[70]
HPLC-UV	Paracetamol, 4-hydroxy-3-methoxy benzyl alcohol, DL-mandelic acid, phthalic acid, p-hydroxyphenylacetic acid, vanillic acid, m-hydrophenylacetic acid, isovanillic acid, benzyl alcohol and impurities	*na*	Empirical linear model and Chromatographic theory	Mean response surface	[71]
HPLC-UV	Phthalic acid, vanillic acid, isovanillic acid, aspirin, furosemide, doxepin, terbinafin, atorvastatin, clopidogrel and related impurities	Synthetic mixture	Empirical linear model and Chromatographic theory	Mean response surface	[72]
HPLC-UV	Phthalic acid, vanillic acid, isovanillic acid, anthranilic acid, vanillin, syringaldehyde, ferulic acid, ortho vanillin, benzoic acid	Synthetic mixture	Chromatographic theory	Mean response surface	[73]
UHPLC-UV	2 Active Pharmaceutical Ingredients and 9 impurities	Eye drop solution	Chromatographic theory	Mean response surface	[74]
HPLC-UV	19 antimalarial drugs	Synthetic mixture	Empirical linear model	Monte-Carlo Probability map	[59]
HPLC-UV	Diflunisal, Granisetron, Nifedipine, Phenytoine, Sulfinpyrazone	Synthetic mixture	Empirical linear model	Monte-Carlo Probability map	[75]
HPLC-UV	Δ9-tetrahydrocannabinol, Δ9-tetrahydrocannabinolic acid A, cannabidiolic acid, cannabigerolic acid, cannabidiol, cannabigerol, cannabinol, Δ8-tetrahydrocannabinol	DifferentCannabis products	Empirical linear model	Monte-Carlo Probability map	[67]
HPLC-UV	Tertiary alkaloids	Strychnos usambarensis leaves	Empirical linear model	Monte-Carlo Probability map	[68]
HPLC-UV	Aprophine alkaloids	Leaves of Spirospermum penduliflorum Thouars	Empirical linear model	Monte-Carlo Probability map	[69]
HPLC-UV	Sulfide, sulfone, sulindac, E-sulindac	Drug substance	Empirical linear model	Monte-Carlo Probability map	[76]
HPLC-UV	9 unknown compounds	Drug product	Empirical linear model	Monte-Carlo Probability map	[77]
HPLC	*na*	*na*	Empirical linear model	Bayesian Probability map	[64,78]

na: no data available

Mass Spectrometry

J. Am. Soc. Mass Spectrom. (2016)
DOI: 10.1007/s13361-016-1344-x

ACCOUNT & PERSPECTIVE

Optimizing Mass Spectrometry Analyses: A Tailored Review on the Utility of Design of Experiments

Elizabeth S. Hecht,[1] Ann L. Oberg,[2] David C. Muddiman[1]

[1]W. M. Keck FTMS Laboratory for Human Health Research, Department of Chemistry, North Carolina State University, Raleigh, NC 27695, USA
[2]Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, MN 55905, USA

Table 2. A 2005–2015 tabulated review of mass spectrometry publications that employed DOE to optimize off-line preparations and extractions, on-line parameters related to MS ionization and detection of species, and post-acquisition analysis parameters. Publications were queried in Web of Science (search date: 10/30/2015) using the following terms: **TOPIC:** ("design of experiment*" or "fractional design" or "factorial design" or "screening design" or "central composite design" or "Taguchi") *AND* **TOPIC:**("mass spectrom*" or "electrospray" or "MALDI" or "GC-MS" or "LC-MS" or "TOF") Refined by: **DOCUMENT TYPES:** (ARTICLE). For a review of LC optimizations, please see Hibbert et al. (2012) [7]

	Off-line preparation		Mass Spectrometry System						Post-acquisition software analysis	
			ESI-MS		MALDI-TOF		Other			
Proteomics	Tryptic digestion	CCD[8] Fractional factorial [9–11]	ESI parameter effects on peptides	Fractional factorial [12, 13] Full factorial [14]	SELDI-TOF protein chip array optimization	Fractional factorial [15]	Air amplifier settings	Fractional factorial [16]		
	Extraction/ precipitation	Box Behnken [17] CCD[18]	Ion pairing effects on peptides	Full factorial [19]			IR-MALDESI parameters	D-optimal [20] Fractional factorial [20]		
Metabolomics	Targeted extraction of classes of molecules (e.g., flavonoids, pesticides)	CCD [21–75] Box-Behnken [76–78] Full factorial [79–104] Fractional factorial [105–133] Plackett-Burman [31, 134–148] Taguchi array [149–156] D-Optimal [157–161] Doehlert [162, 163]	ESI, APCI, APPI/APC, and APPI parameter optimization on abundances of targeted classes	Screening/CCD [164–171] CCD [169, 172–181] Box Behnken [182] Full factorial [14, 183–187] Fractional factorial [188–190] Placket Burman [191, 192] Doehlert [193]	MALDI automated data acquisition parameter effects on metabolite detection	Fractional factorial [194]	GC-MS parameter effects on small metabolites	CCD [115, 195–203] Box Behnken [204, 205] Full factorial [206, 207] Plackett-Burman [200, 208] Taguchi Array [209] Doehlert [210]	IPO/ XCMS settings on # of accurate ID's	Box Behnken [211] Plackett-Burman/ CCD [212, 213]
	Solid phase micro-extraction (SPME)	CCD [214–253] Fractional Factorial [254–263] Plackett Burman [234, 235, 264–267] Full factorial [231, 268–280] Taguchi [281–285] D-optimal [286] Doehlert [287]	ESI parameter effects on drug identification mass accuracy	CCD [288] Full factorial [289] Fractional factorial [189]	TOF-SIMS ablation parameter optimization	Parameter optimization using ensemble methods (POEM) [290]	GC-MS headspace trap optimization	CCD [291] Full factorial [292–296]	LC-MS software analysis	Full factorial [297]
	GC-MS derivatization methods	CCD [162, 298–301] Box Behnken [302–304] Full factorial [221, 305–313] Fractional Factorial [314] D optimal [315, 316] Plackett-Burman [317, 318] Doehlert [319]	Internal standard concentration optimization	Full factorial [320]			Buffer composition effects on the analysis of drugs by ion mobility MS	Screening [321]	Software for GC-MS XIC analysis	Full factorial [297]

References

Title	Year	DOI	Techniques
Analytical Quality by Design : A Tool for Regulatory Flexibility and Robust Analytics	2015	10.1155/2015/868727	
Risk-based approach for method development in pharmaceutical quality control context: A critical review	2018	10.1016/j.jpba.2018.07.050	
Applications of mixture experiments for response surface methodology implementation in analytical methods development - Chemometrics	2020	10.1002/cem.3246	
Experimental design and multiple response optimization. Using the desirability function in analytical methods development	2014	10.1016/j.talanta.2014.01.034	
An Expository Paper on Optimal Design	2011	10.1080/08982112.2011.576203	
Optimizing Mass Spectrometry Analysis: A tailored Review on the Utility of Design od Experiments.	2016	10.1007/s13361-016-1344-x	MS
Experimental design in chromatography: Tutorial review. Journal of Chromatography B, 910 (2012) 2-13.	2012	10.1016/j.jchromb.2012.01.020	
Statistical designs and response surface techniques for the optimization of chromatographic systems	2007	10.1016/j.chroma.2007.03.051	
Design Spaces for analytical methods	2013	10.1016/j.trac.2012.09.007	LC

Title	Year	DOI	Techniques
Experimental design methodologies for the optimization of chiral separations: An overview	2019	10.1007/978-1-4939-9438-0_27	SFC, LC, CE, CEC
Development of a capillary zone electrophoresis method to quantify E. coli L-asparaginase and its acidic variants	2018	10.1016/j.talanta.2018.01.048	
Optimization of capillary zone electrophoresis for charge heterogeneity testing of biopharmaceuticals using enhanced method development principles	2017	10.1002/elps.201700145	CE
Optimization of the enantioseparation of a diaryl-pyrazole sulfonamide derivative by capillary electrophoresis in a dual CD mode using experimental design	2014	10.1002/elps.201300639	
Fast analysis of glibenclamide and its impurities: Quality by design framework in capillary electrophoresis method development	2015	10.1007/s00216-015-8921-x	CE
Optimization of capillary zone electrophoresis for charge heterogeneity testing of biopharmaceuticals using enhanced method development principles. ElectrophoresisOpen AccessVolume 38, Issue 24, Pages 3136 - 3146December 2017	2017	10.1002/elps.201700145	CE

References

Title	Year	DOI	Techniques
Aspects of the “Design Space” in high pressure liquid chromatography method development. J. of Chromatography A	2010	10.1016/j.chroma.2010.02.001	LC
Analytical quality by design methodology for botanical raw material analysis: a case study of flavonoids in Genkwa Flos	2021	10.1038/s41598-021-91341-w	UHPLC-MS
Quality by design optimization of a liquid chromatographic-tandem mass spectrometric method for the simultaneous analysis of structurally heterogeneous pharmaceutical compounds and its application to the rapid screening in wastewater and surface water samples by large volume direct injection	2021	10.1016/j.chroma.2021.462225	LC-MS
Development of an analytical method for the determination of pimavanserin and its impurities applying analytical quality by design principles as a risk-based strategy	2021	10.1016/j.jpba.2021.114091	LC-MS
Optimization of Ultra-High-Performance Liquid Chromatography-Electrospray Ionization-Mass Spectrometry Detection of Glutamine-FMOC Ad-Hoc Derivative by Central Composite Design	2020	10.1038/s41598-020-64099-w	LC-MS
Development of a generic reversed-phase liquid chromatography method for protein quantification using analytical quality-by-design principles	2020	10.1016/j.jpba.2020.113412	LC-MS
A systematic AQbD approach for optimization of the most influential experimental parameters on analysis of fish spoilage-related volatile amines	2020	10.3390/foods9091321	GC-HS-MS
Development of a Stability-Indicating Analytical Method for Determination of Venetoclax Using AQbD Principles	2020	10.1021/acsomega.0c02338	LC-MS
Analytical Quality by Design-based development and validation of ultra pressure liquid chromatography/MS/MS method for glycopeptide antibiotics determination in human plasma	2018	10.4155/bio-2018-0181	LC-MS
AQbD oriented new LC-ESI/MS method for quantification of sirolimus in drug and spiked plasma sample	2018	10.2174/1573411013666171113143806	LC-MS
Stability indicating liquid chromatographic assessment of dolutegravir by AQbD approach - Central composite design	2017		LC-MS
A platform analytical quality by design (AQbD) approach for multiple UHPLC-UV and UHPLC-MS methods development for protein analysis	2016	10.1016/j.jpba.2016.03.031	LC-MS
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	2020	10.1016/j.chroma.2019.460615	LC-MS
Analytical quality by design: Development and control strategy for a LC method to evaluate the cannabinoids content in cannabis olive oil extracts	2019	10.1016/j.jpba.2019.01.032	LC-MS
Application of quality by design to the development of analytical separation methods	2013	10.1007/s00216-012-6302-2	LC
Development of a fast and robust uhplc method for apixaban in-process control analysis	2021	10.3390/molecules26123505	LC

References

Title	Year	DOI	Techniques
Simultaneous optimization of mobile phase composition and pH using retention modeling and experimental design	2018	10.1016/j.jpba.2018.07.054	LC
Renewal of an old European Pharmacopoeia method for Terazosin using modeling with mass spectrometric peak tracking	2017	10.1016/j.jpba.2016.11.050	LC
Reliability of simulated robustness testing in fast liquid chromatography, using state-of-the-art column technology, instrumentation and modelling software	2014	10.1016/j.jpba.2013.10.029	LC
Automated UHPLC separation of 10 pharmaceutical compounds using software-modeling	2018	10.1016/j.jpba.2018.03.039	LC
Implementation of a design space approach for enantiomeric separations in polar organic solvent chromatography	2013	10.1016/j.jpba.2012.10.015	LC
Developing an improved UHPLC method for efficient determination of european pharmacopeia process-related impurities in ropinirole hydrochloride using analytical quality by design principles	2020	10.3390/molecules25112691	LC
Development of a unified reversed-phase HPLC method for efficient determination of EP and USP process-related impurities in celecoxib using analytical quality by design principles	2020	10.3390/molecules25040809	LC
Chemometric-assisted method development in hydrophilic interaction liquid chromatography: A review	2018	10.1016/j.aca.2017.09.041	HILIC
Rapid Method Development in Hydrophilic Interaction Liquid Chromatography for Pharmaceutical Analysis Using a Combination of Quantitative Structure-Retention Relationships and Design of Experiments	2017	10.1021/acs.analchem.6b04282	HILIC
QbD-Driven Development and Validation of a Bioanalytical LC–MS Method for Quantification of Fluoxetine in Human Plasma.Journal of Chromatographic Science, Volume 54, Issue 5, May 2016, Pages 736–743	2016	10.1093/chromsci/bmv248	LC-MS
Improved quality-by-design compliant methodology for method development in reversed-phase liquid chromatography	2013	10.1016/j.jpba.2013.06.013	RPLC
New methodology for the development of chromatographic methods with bioanalytical application	2012	10.4155/bio.12.47	LC
Application of new methodologies based on design of experiments, independent component analysis and design space for robust optimization in liquid chromatography	2011	10.1016/j.aca.2011.02.035	LC
Design of experiments approach to discriminatory dissolution method development of poorly soluble drug in immediate release dosage form	2019	10.5530/ijper.53.3.76	Dissolution

Thank You

Amanda Guiraldelli, Ph.D.
Scientific Affairs Manager
awg@usp.org

The standard of trust