Quality by Design (QbD) Approach to Rapid LC Method Development for Pharmaceuticals Using Automated Screening and Design of Experiments (DOE)

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Why is a QbD LC Method Development Important?

QbD approach to LC method development:

- Efficient
- Thorough

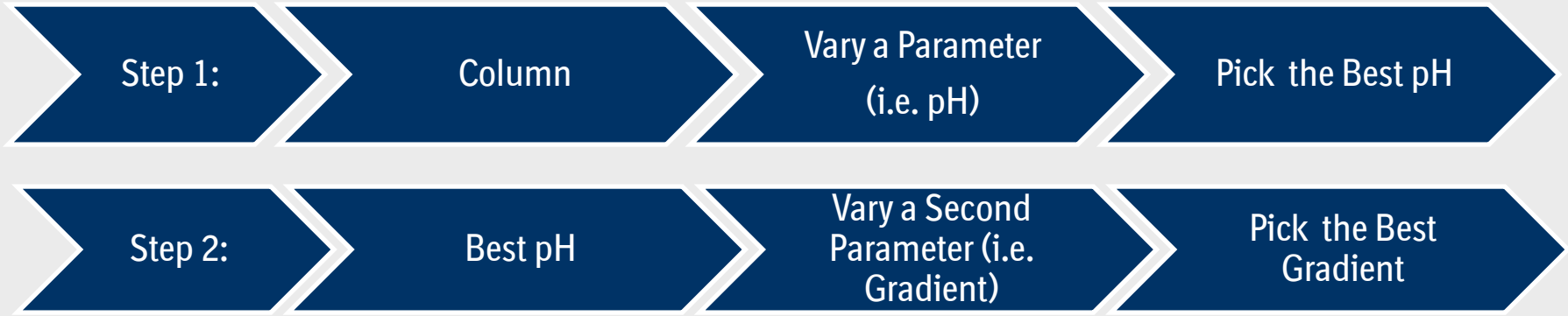
Result:

Development of a LC method that is robust and has meaningful SST criteria.

Traditional LC Method Development

One-Factor-at-a-Time (OFAT)

Sequential approach where one parameter is usually held constant and other parameters are varied one at a time



Problem - Does not allow for the expression of interaction effects needed to set meaningful method control strategies.

What is QbD?

"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 Q8

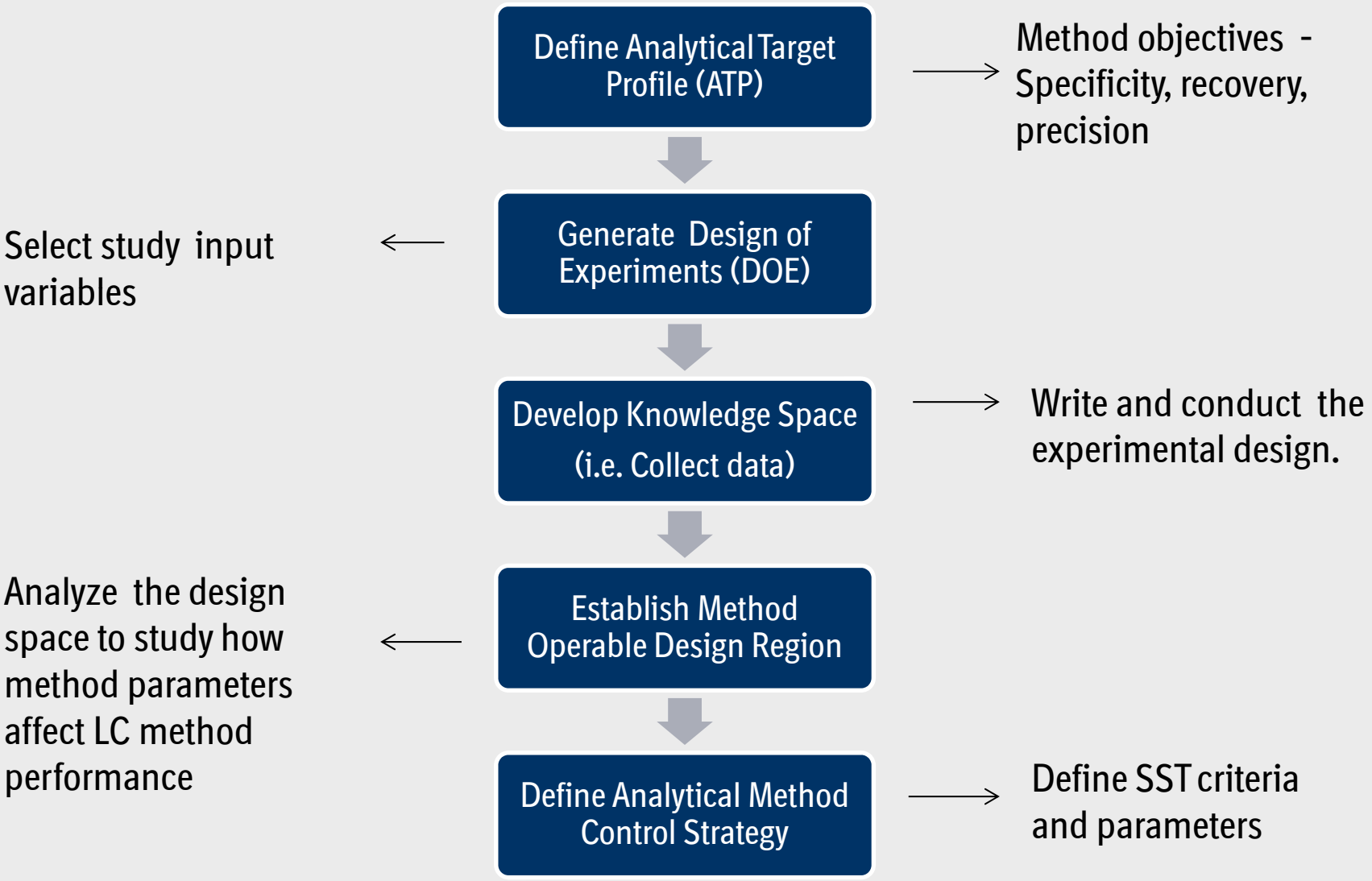
Goal:

Defendable process accepted by regulators without question

QbD can be applied to any process, most recently LC method development

Vogt, F and Kord, A. Development of Quality-By-Design Analytical Methods, Journal of Pharmaceutical Sciences, V100, No 3, March 2011

QbD LC Method Development Flow



Overcoming QbD Method Development Challenges

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Manual LC QbD

- Software 1 - Generate DOE
- Software 2 - Write the instrument methods and sequences
- Software 3 - Graph data to study how method parameters interact
- Manual - Select final method conditions

← 2 to 4 weeks

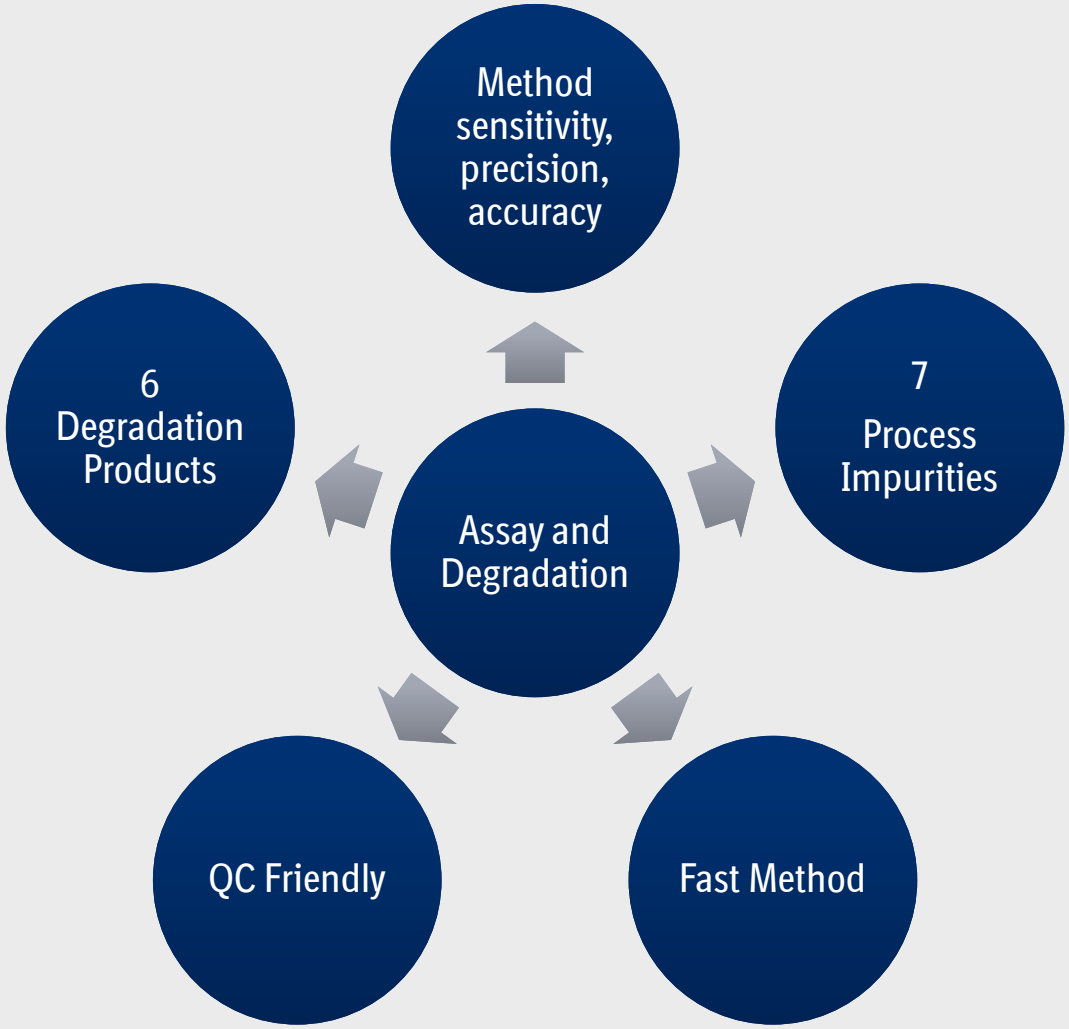
Automated LC QbD

- Software 1 – LC Specific - Fusion AE (S-Matrix Corp, Eureka, CA)
  - Generate DOE
  - Translate DOE to LC methods and sequences
  - Graph method parameters for visualization
  - Sort chromatographic data
  - Select and test final method

← 2 to 4 days

Define the Analytical Target Profile

Case Study



Preliminary Method Information

- Perform a forced degradation study
- Select suitable solvent for the samples
- Determine optimum wavelength for detection
- Prepare a spiked solution / selectivity mix

Select Study Variables

Acquity UPLC H-Class, Waters Corp. (Milford, MA), PDA detector

Columns (2.1 x 50 mm, 1.7-1.8 µM):	pH/Aqueous Mobile Phase:	Gradient Slope:
BEH C18	2.0 - 0.05% TFA	5% initial to 60-95% final organic content
BEH Shield RP18	2.8 - 0.1% Formic Acid	
BEH Phenyl	4.0 – 8 mM Ammonium Acetate / 0.1% Acetic Acid	
HSS T3	7.0 – 8 mM Ammonium Acetate	
BEH C8	10.8 – 0.05% Ammonium Hydroxide	
HSS C18		

Wide ranges chosen to maximize the experimental design space

Generate DOE

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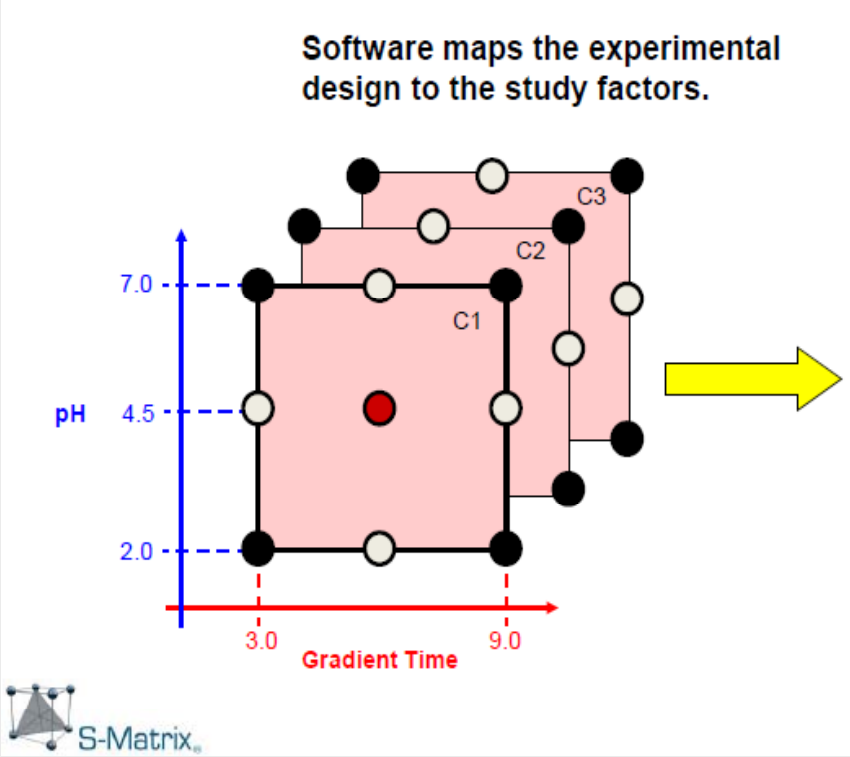
Software automatically generates DOE

Automatically translated into LC methods and sequence

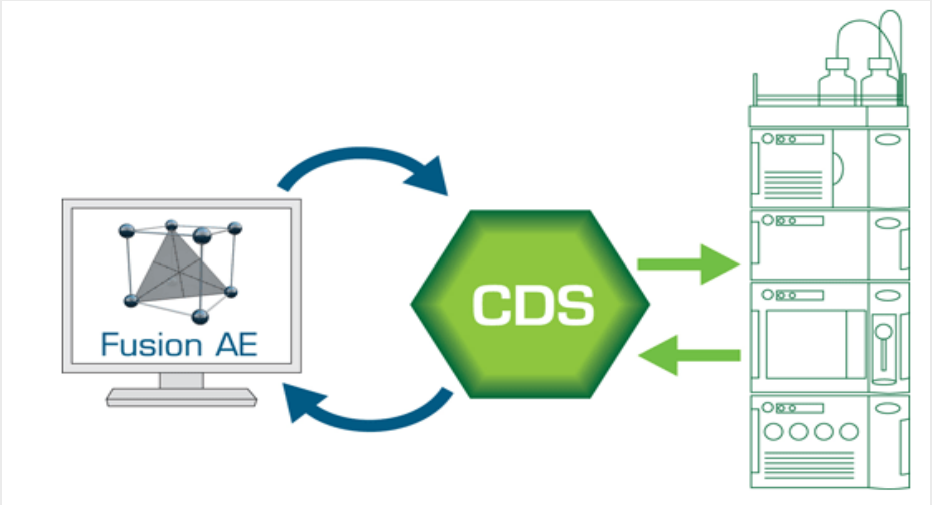


Experiment Design Matrix

Run No.	Sample Set No.	Final % Organic (%)	pH (*)	Column Type (*)
Wash - 1	1	80.0	2.0	HSS T3
Wash - 2	1	80.0	2.0	HSS C18
Wash - 3	1	80.0	2.0	BEH Shield
Wash - 4	1	80.0	2.0	BEH Phenyl
Wash - 5	1	80.0	2.0	BEH C8
Wash - 6	1	80.0	2.0	BEH C18
1.a.1.a	1	80.0	2.0	HSS T3
2.a.1.a	1	95.0	2.0	HSS C18
3.a.1.a	1	80.0	2.0	HSS C18
4.a.1.a	1	95.0	2.0	BEH Shield
5.a.1.a	1	80.0	2.0	BEH Shield
6.a.1.a	1	95.0	2.0	BEH Phenyl
7.a.1.a	1	80.0	2.0	BEH Phenyl
8.a.1.a	1	95.0	2.0	BEH C8
9.a.1.a	1	80.0	2.0	BEH C8
10.a.1.a	1	95.0	2.0	BEH C18
11.a.1.a	1	80.0	2.0	BEH C18
12.a.1.a	1	87.5	2.0	HSS T3
13.a.1.a	1	80.0	2.0	BEH Shield
14.a.1.a	1	95.0	2.0	BEH Phenyl
15.a.1.a	1	95.0	2.0	BEH C8
Wash - 7	1	87.5	2.8	HSS T3

Process Results in Chromatographic Data System

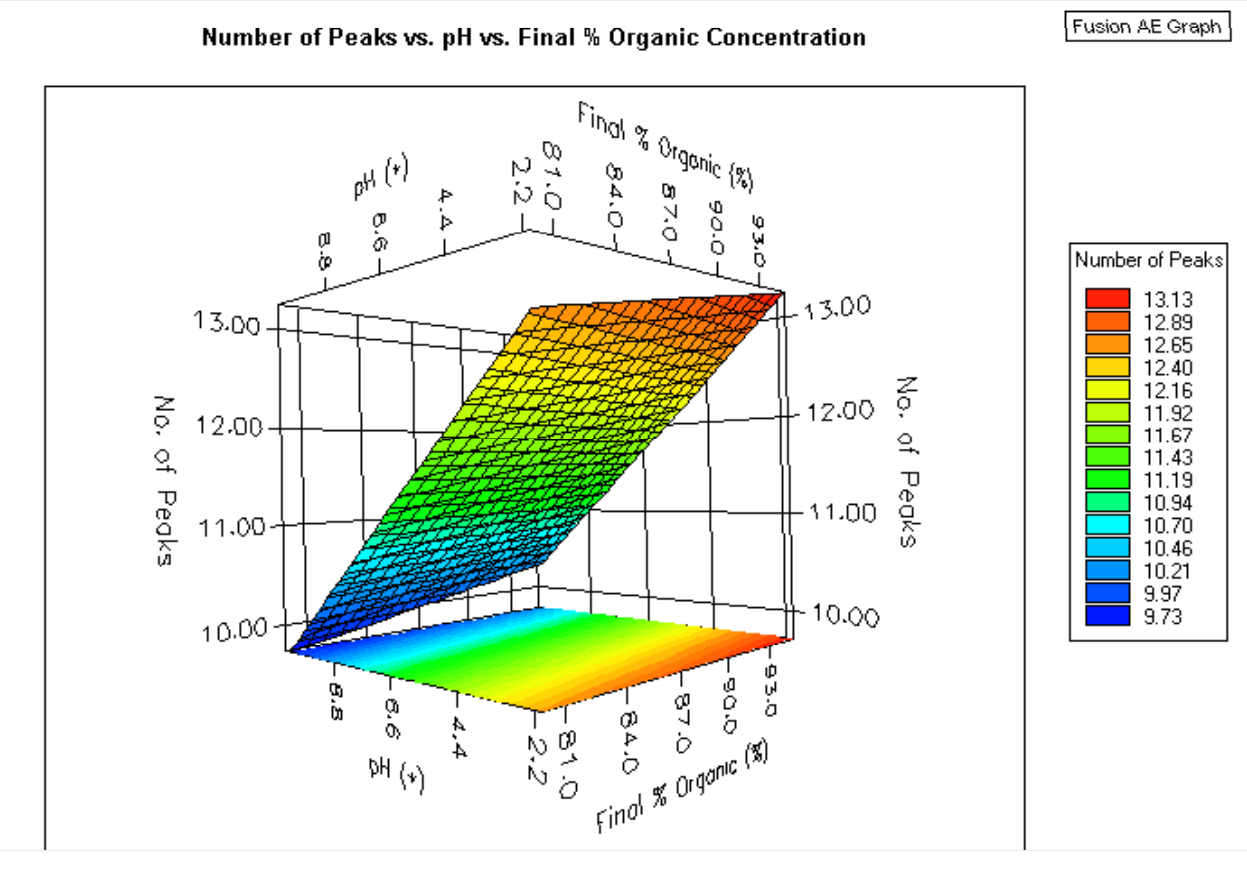
- Run DOE sequence
- Integrate chromatograms (partly automated)
- Visualize how method parameters interact with each other



http://www.smatrix.com/fusion_lc_method_dev.html

Determine the Method Operable Design Region

Visualize critical method parameter performance



Determine the Method Operable Design Region

Sort the data based upon method goals

	Response Name	Goal	Lower Bound	Upper Bound	Relative Rank
☑	No. of Peaks	Maximize	2	14	1
☐	No. of Peaks >= 1.00 - USPResolution				
☑	No. of Peaks >= 1.50 - USPResolution	Maximize	2	13	0.9
☐	No. of Peaks >= 2.00 - USPResolution				
☑	Last Peak - RetentionTime	Minimize	5.200000000	6.300000000	0.8
☐	No. of Peaks <= 1.50 - USPTailing				
☑	API - USPResolution	Maximize	1.50	13.54	0.7

Select Final Method Conditions – Primary Method

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Determine what variable combinations allow all specified method goals to be met

Optimizer Answer #1: 7 of 48 Solution Searches

Study Variable Data

Study Variable Name	Optimizer Answer Level Setting
Final % Organic	95.00
pH	2.000
Column Type	BEH Shield

Predicted Response Data

Response Variable Name	Target	Optimizer Answer Predicted Response
No. of Peaks	Maximize	14.80
No. of Peaks >= 1.00 - USPResolution	Maximize	13.75
No. of Peaks >= 1.50 - USPResolution	Maximize	13.33
No. of Peaks >= 2.00 - USPResolution	Maximize	12.33
Last Peak - RetentionTime	Minimize	7.30175509141
No. of Peaks <= 1.50 - USPTailing	Maximize	13.86

Desirability Target = 1.0000
Desirability Result = 0.9030

→ Orthogonal method needed?

Determine the Analytical Method Control Strategy

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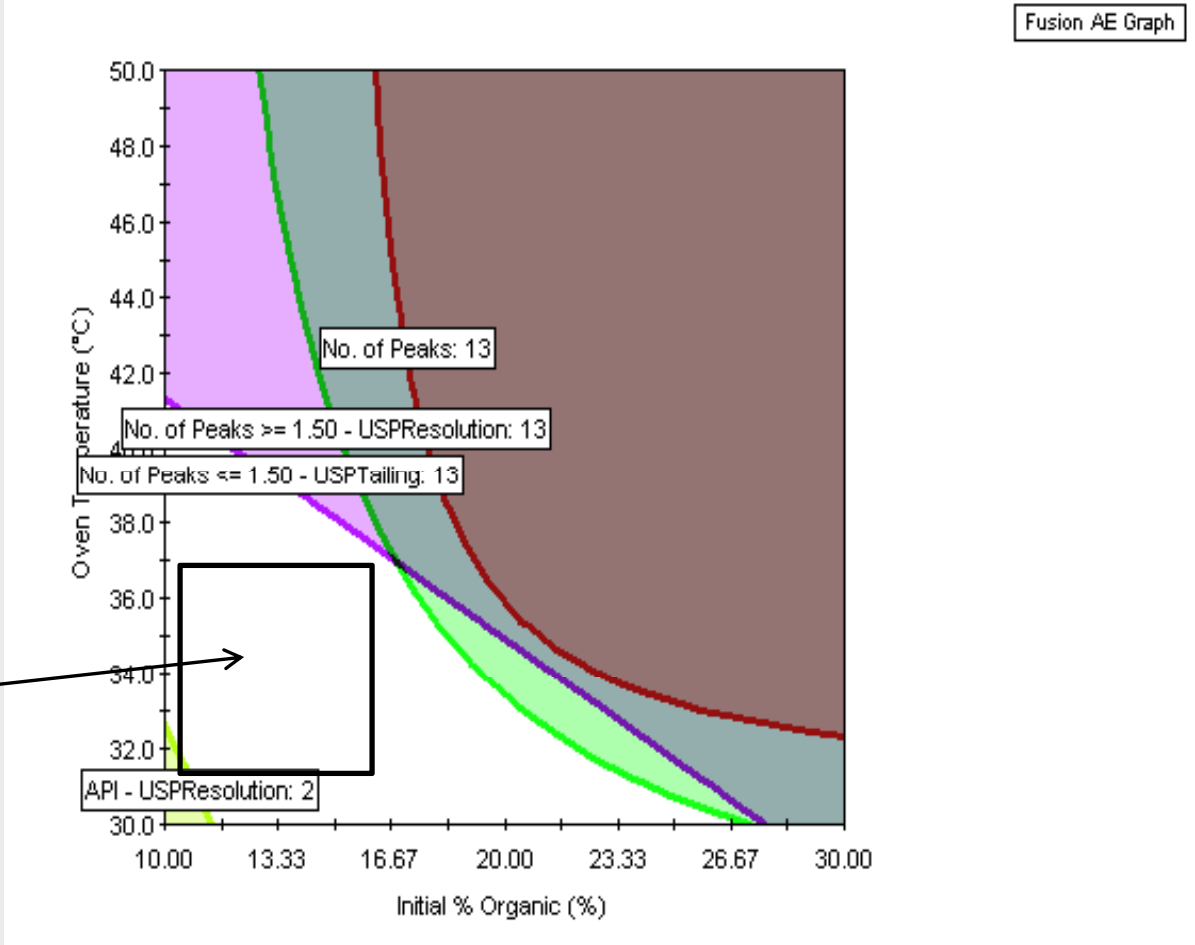
Visualize method robustness to determine method limits

Unshaded areas correspond to variable level settings that exceed all goals for mean method performance

Area of method robustness



Verify Predicted Final Method

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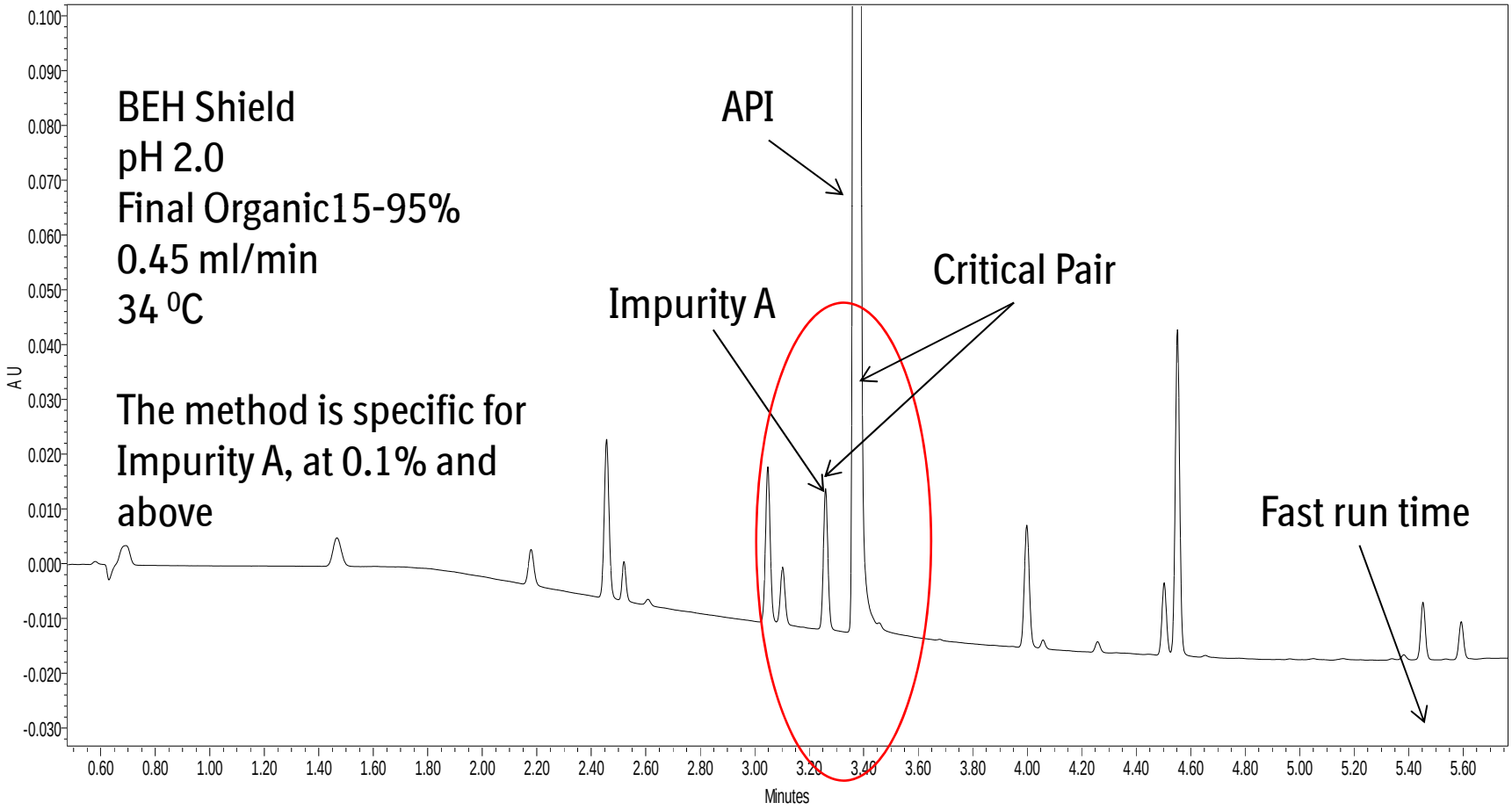
Ensure target performance profile and performance criteria are met



Total QbD LC Method Development Time with Automation

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QbD Method Development Task	Time (Hours)
Generate DOE screening design: Multiple columns, pHs and gradient conditions	0.5
Export design to Empower (CDS) and execute screening exp	15 (unattended)
Integrate peaks and automatically transfer results to Fusion	0.5
View automatically generated 2D and 3D surface plots to study critical factors	0.5
Sort results and find general conditions that meet method objectives	0.5
Perform fine optimization	0.5
Export design to Empower (CDS) and execute optimization exp	9.0 (unattended)
Integrate peaks and automatically transfer results to Fusion	0.5
Assess chromatographic performance characteristics: Automatically compute and visualize factors affecting method robustness, select final method	2.0
Total QbD method development (not counting sample/buffer prep)	~30 hrs

QbD Summary

- OFAT approach to LC method development:
  - Does not provide a true understanding of the method
  - May not provide true optimum method
  - Lengthy process

- QbD approach
  - Determines how parameters interact
  - Leads to a defendable, robust LC method

- QbD LC automation is key!
  - LC specific QbD software (i.e. Fusion AE)

Does Automated QbD Replace the Lab Analyst?

A trained lab analyst must:

- Select appropriate columns, mobile phases, wavelengths, sample solutions etc.
- Prepare and set up LC the system
- Use the Chromatographic Data System (CDS) to perform integration of the results
- Understand how to use the QbD software appropriately to screen, filter and interpret results

Conclusions

Automated QbD Results in:

- High quality robust methods
- Fast development
- Meaningful SST criteria
- QbD LC method development can be performed by analysts with minimal statistical knowledge

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Further questions:

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