Quality by Design (QbD) Solutions for Analytical Method Development

A systematic approach to reducing variability

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  - Traditional Development and Transfer of Methods
  - QbD Approach for Method Development
- Agilent Solutions for QbD Method Development
  - Agilent Method Development Systems
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- QbD Method Development Workflow
  - Screening
  - Optimization
  - Robustness study, Design of Experiments
  - Transfer & Verification

Introduction

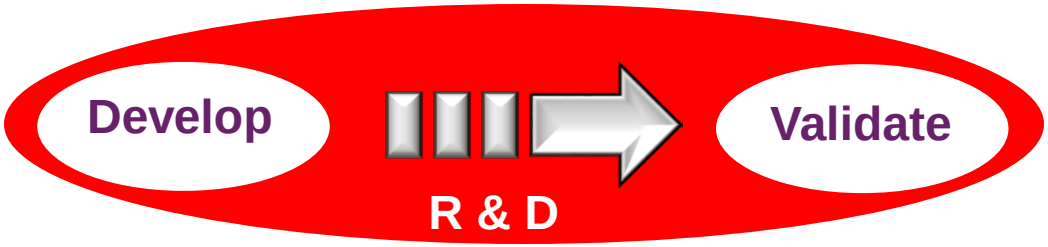
- QbD (*Quality by Design*) is defined in the ICH guideline Q8(R2)
  http://www.fda.gov/downloads/Drugs/Guidances/ucm073507.pdf
- The ICH guidelines suggest to apply ***Quality by Design*** principles in each step to eliminate risk or failures in drug development processes
- Analytical method development for a drug is also a process therefore quality principles from the ICH guideline should be implemented

(ICH = International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Founded in 1990 by an FDA initiative)

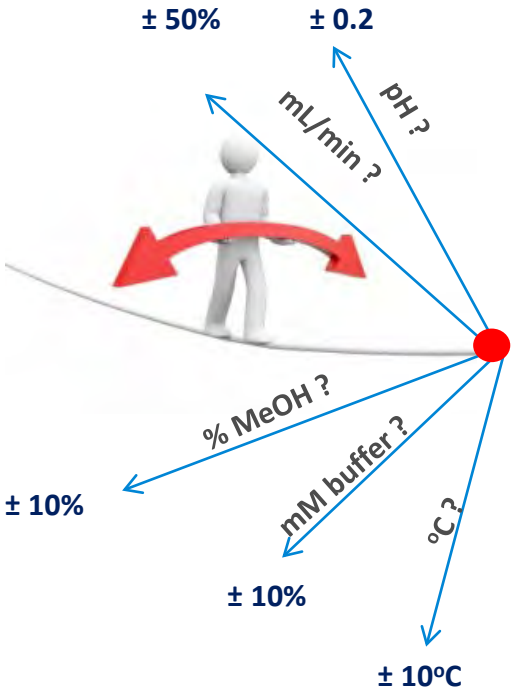
Appendix
Analytical QbD Terminology

QbD process terminology	Analytical QbD terminology	Examples
	Analytical Target Profile (ATP)	Accurate quantitation of API without interferences from degradants
Quality Target Product Profile (QTPP)	Quality Target Method Profile (QTMP)	pKa, Log P, Solubility
Critical Process Parameters (CPP)	Critical Method Parameters (CMP)	Flow rate, Temperature, pH
Critical Quality Attributes (CQA)	Critical Method Attributes (CMA)	Resolution, Peak Tailing, Peak Capacity
	Control Strategy	pH ± 0.1; Wavelength ± 2 nm

Traditional Development and Transfer of Methods
A chromatographic challenge ! This is the PAST !



Problems identified HERE



Fixed method specifications determined manually

Slope 14.5% min MeOH
pH 7
35°C
1.0 mL/min

Transfer

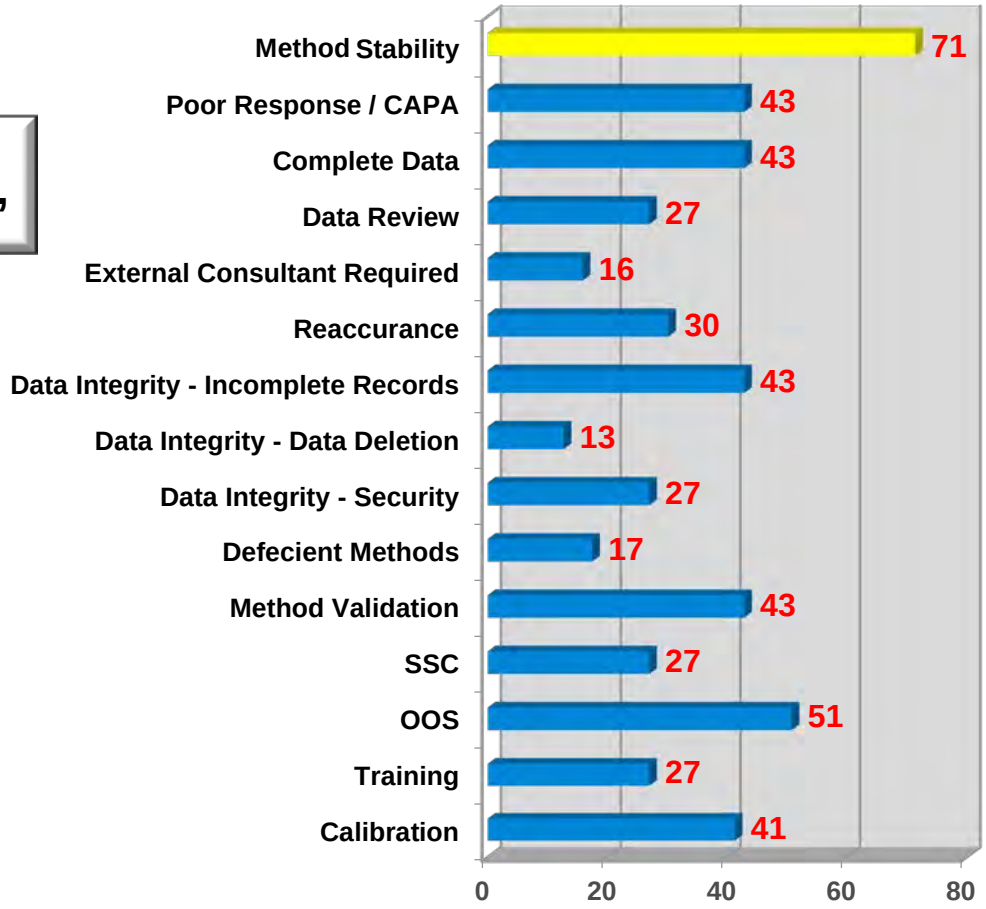
Transfer

Traditional Development and Transfer of Methods
Reported Issues After Method Transfer

- Variability in resolution of critical peaks from day to day
- Different results on different systems
- Buffer solutions prepared by different operators deliver different results
- Even small changes in pH show a large effect

FDA Warning Letter Search for “Stability”
Frequently stability issues reported

71 % of HPLC warning letters Include Reference to “stability”



QbD Approach for Method Development

- Analytical QbD begins by defining goals (Analytical Target Profile, ATP) and identifying potential method variables and responses that affect method quality

- Statistical „Design of Experiments“ (DOE) has been applied to the selected method variables leading to process and method understanding and to create a list of critical method parameters (CMPs- flow rate, temperature etc.) and critical method attributes (CMAs- resolution, peak tailing)

- The experimentally measured responses were modeled to determine the Design Space (defined in ICH Q8 (R2))

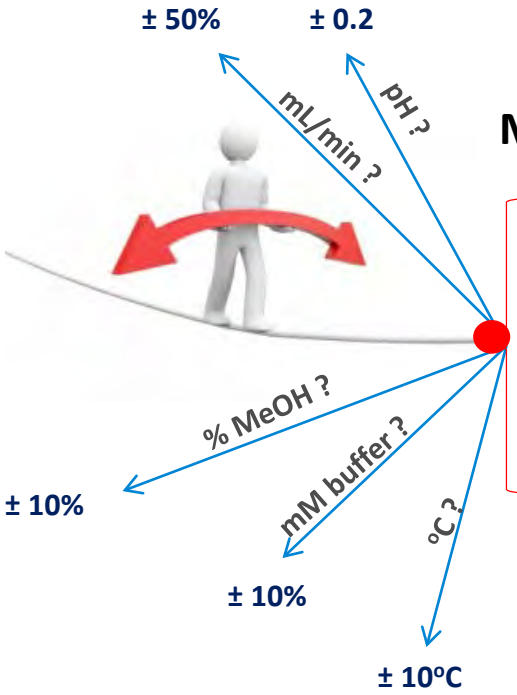
- A verified and validated method can be modified within the Design Space to compensate any unforseen variables yet delivering consistent results

Design Space: Definition

- Combination and interaction of variables that provides assurance of quality
- Working within the design space is not considered as a change. Again this is NOT a Change
- Movement out of the design space is considered a change and would require regulatory approval as expected.
- Design space is proposed by the applicant and is subject to regulatory assessment and approval (ICH Q8)

Traditional Approach vs. QbD Approach (New)

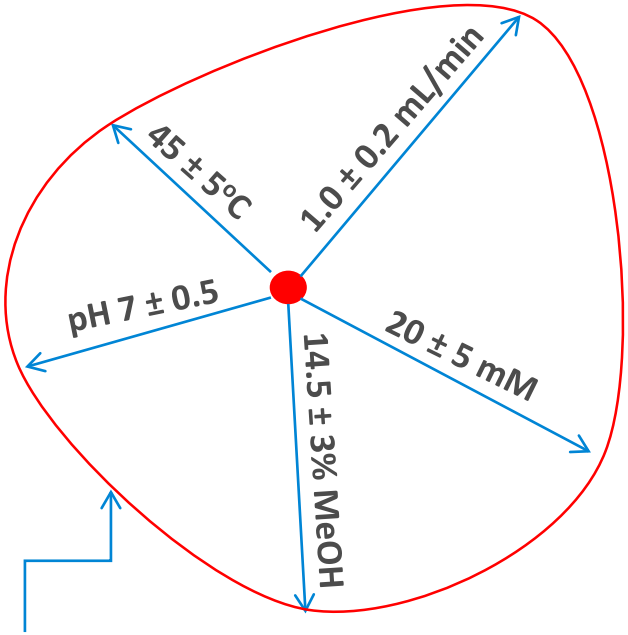
Traditional Approach
- Fixed Protocol



Method specifications:

Slope 14.5% MeOH
20mM buffer
pH 7
45°C
1.0 mL/min

QbD Approach
- Variable Protocol



Design space

Working within the design space will ensure the method's robustness

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  - -Agilent Method Development Systems
  - -Intelligent System Emulation Technology (ISET)
  - -High Dynamic Range Detection System (HDR)
- QbD Method Development Workflow
  - Screening
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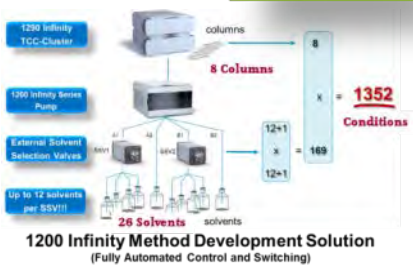
Agilent Solutions for QbD Method Development

Method Development System



1200 Infinity Method Development Solution
(Fully Automated Control and Switching)

ISET

Intelligent System Emulation Technology

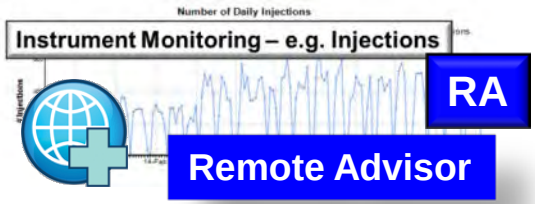
In How Instruments Are Qualified

In Usage

Harmonized Qualification

ACE

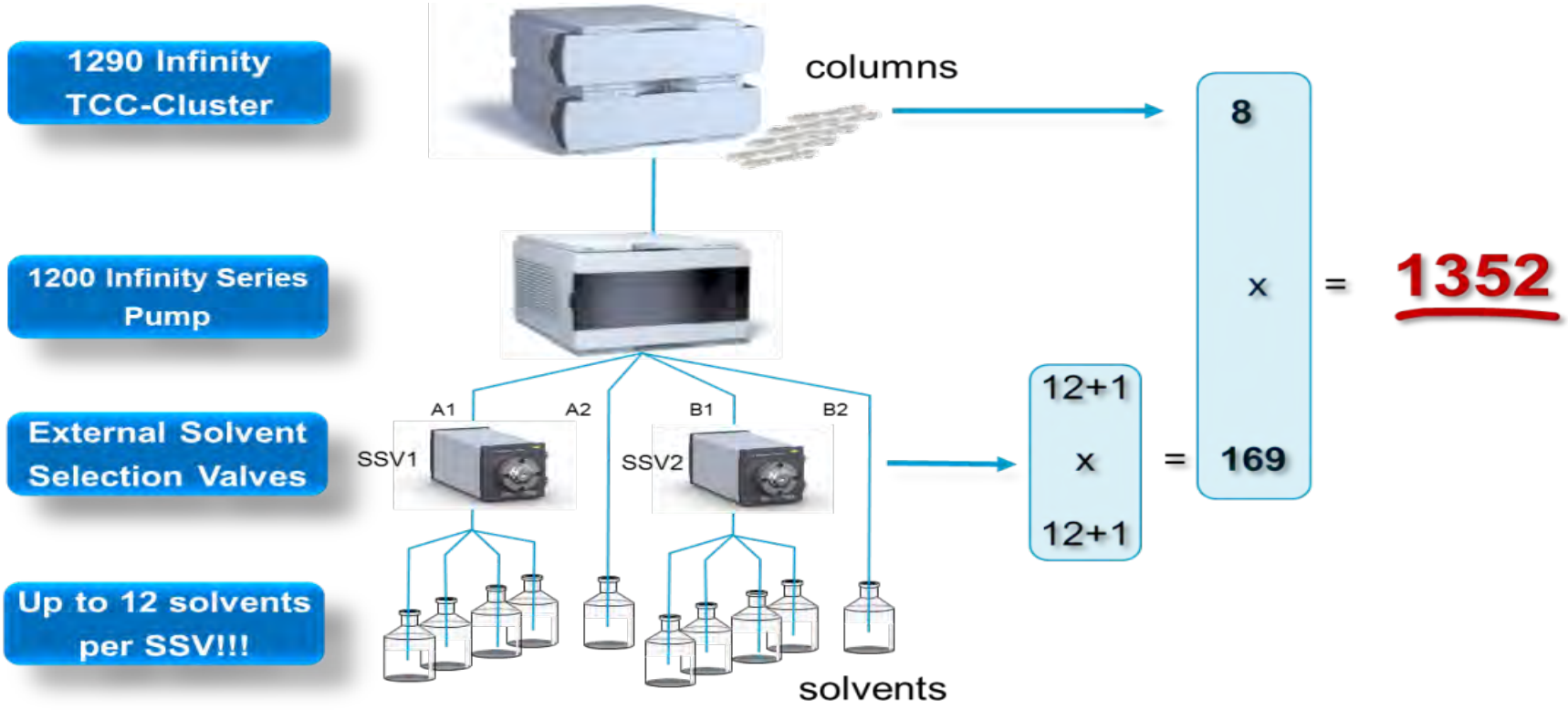
Equipment Qualification Report



RA

Remote Advisor

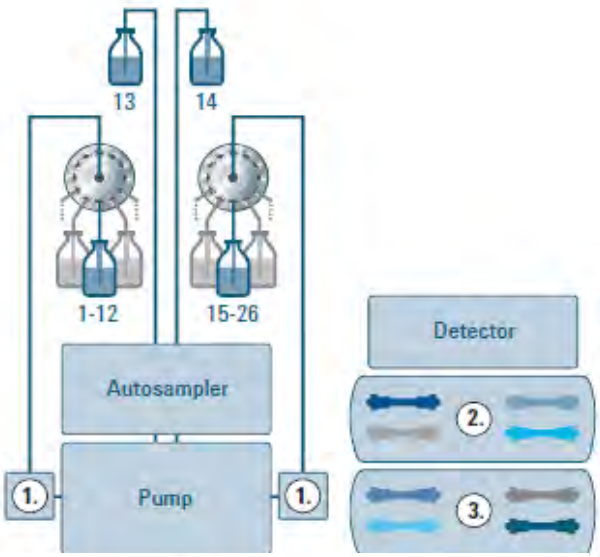
Agilent Method Development Systems



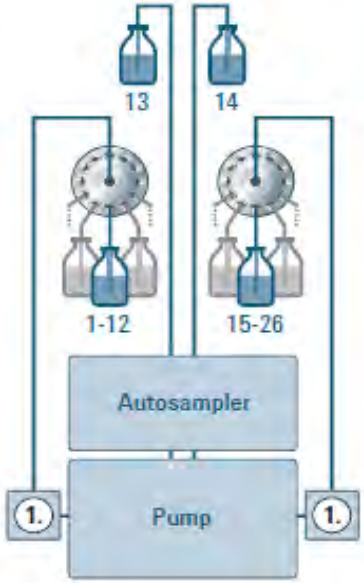
- 1352 different combinations of column chemistries and eluents
- A nearly infinite number of separation conditions is created by including different temperature and flow rates as variable parameters

1290 Infinity II Method Development Solution

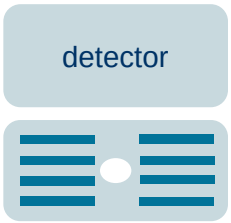
New: *Multi Column Thermostat*



1290 Infnity I System



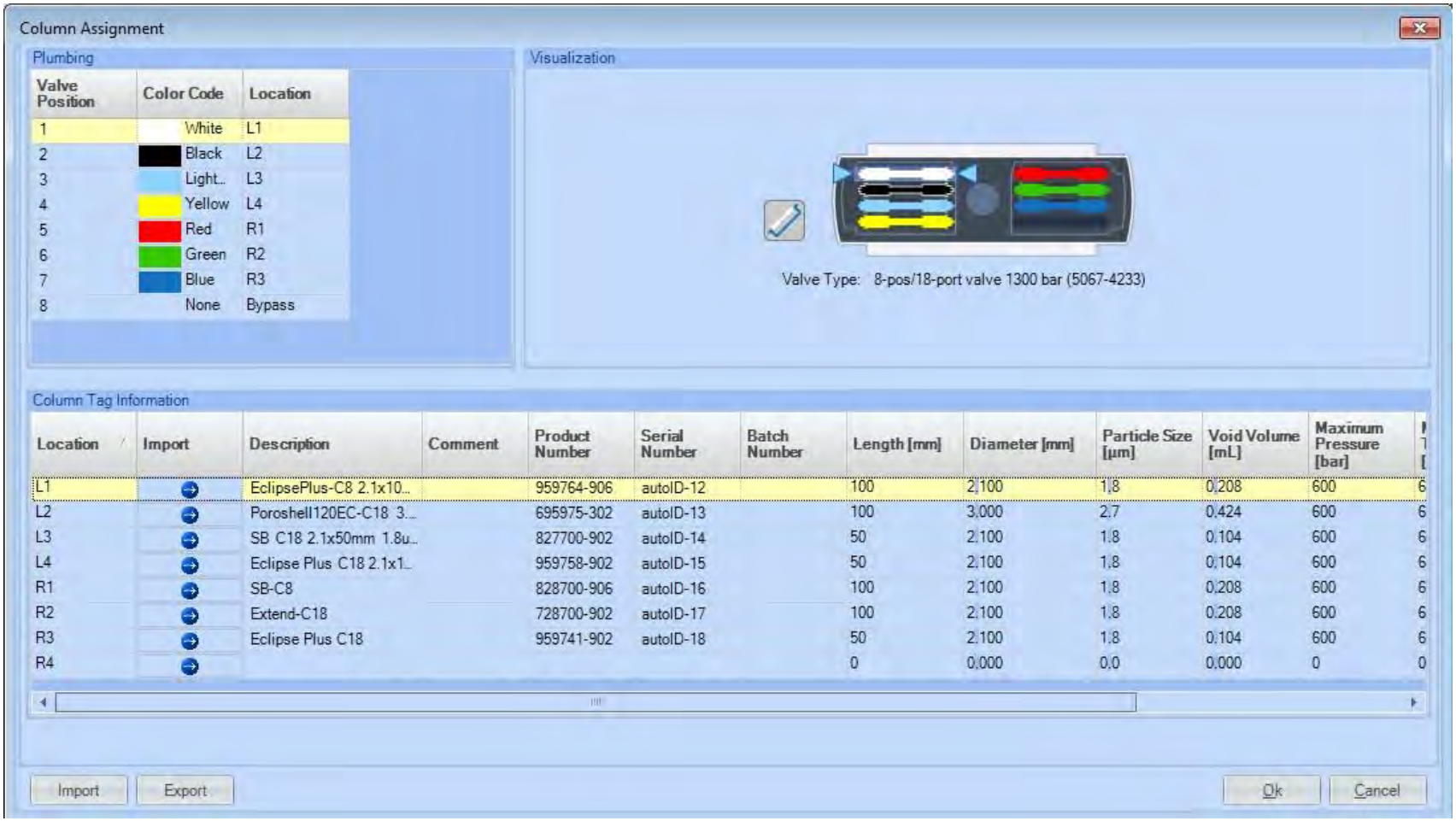
Multi Column Thermostat
MCT



1290 Infnity II System

1290 Infinity II Series Method Development Solution

New: *Column Centric View*



Assign the mounted columns to the available locations in the MCT

Column Selection: http://hplccolumns.org/database/index.php

Use to find similar columns

Step #1: Select a Column to Compare

Select a column to compare from the list below. A similarity factor, F_S, will be calculated for each of the other columns in the database (below).

Agilent Technologies Zorbax Eclipse PAH
Agilent Technologies Zorbax Eclipse Plus C18
Agilent Technologies Zorbax Eclipse Plus C8
Agilent Technologies Zorbax Eclipse XDB-C18
Agilent Technologies Zorbax Eclipse XDB-C8
Agilent Technologies Zorbax Eclipse XDB-CN
Agilent Technologies Zorbax Extend C18
Agilent Technologies Zorbax Rx-18
Agilent Technologies Zorbax Rx-C8
Agilent Technologies Zorbax SB-AQ

ID	F_S	Name	Manufacturer	Silica type
519	2.80	HSS C18	Waters	B
667	3.09	Cortecs C18	Waters	B
521	7.12	HSS T3	Waters	B
303	7.76	XTerra MS C18	Waters	B
327	8.07	Atlantis T3	Waters	B
291	8.09	Atlantis dC18	Waters	B
292	8.98	DeltaPak C18 100A	Waters	B
304	9.02	XTerra MS C8	Waters	B
404	10.92	XBridge C18	Waters	B
484	11.25	XBridge C8	Waters	B

10 ▼ Entries Per Page

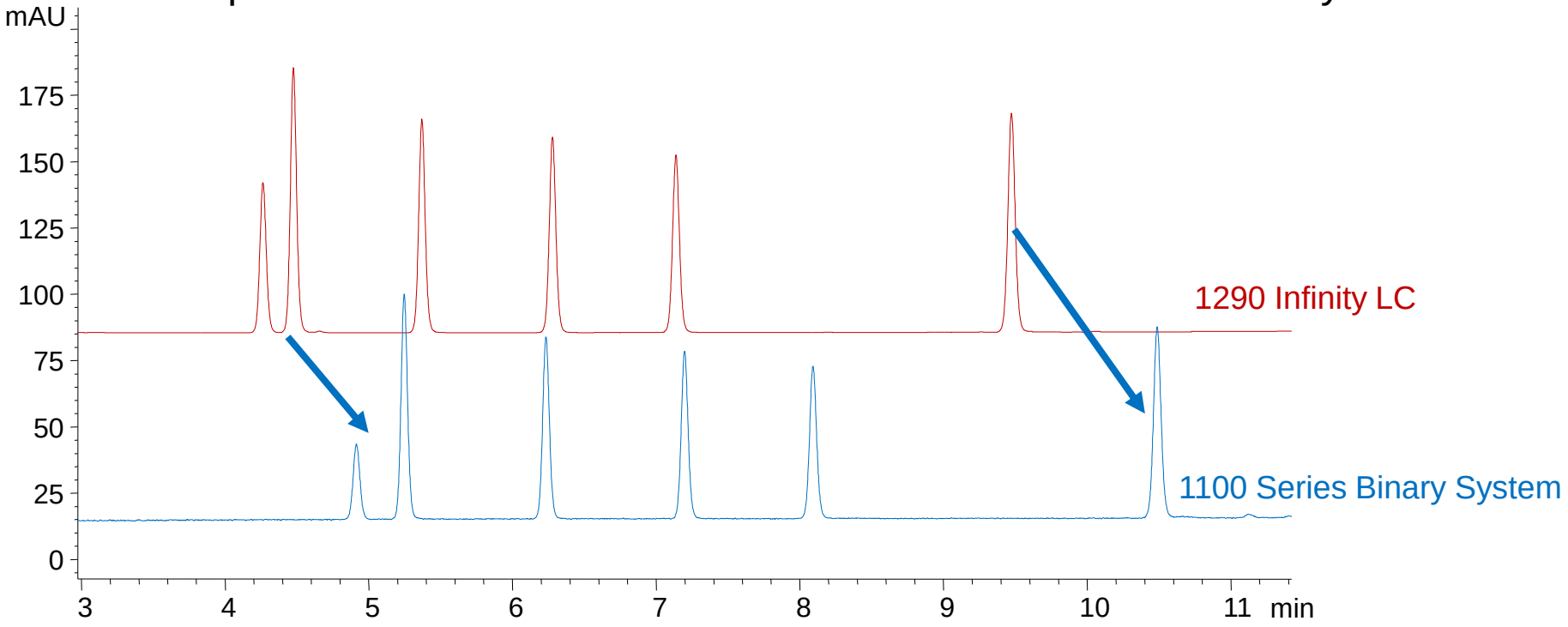
Intelligent System Emulation Technology (ISET)

- Seamless transfer of methods between LCs, regardless of the brand

Method Transfer Between Different LC Instruments

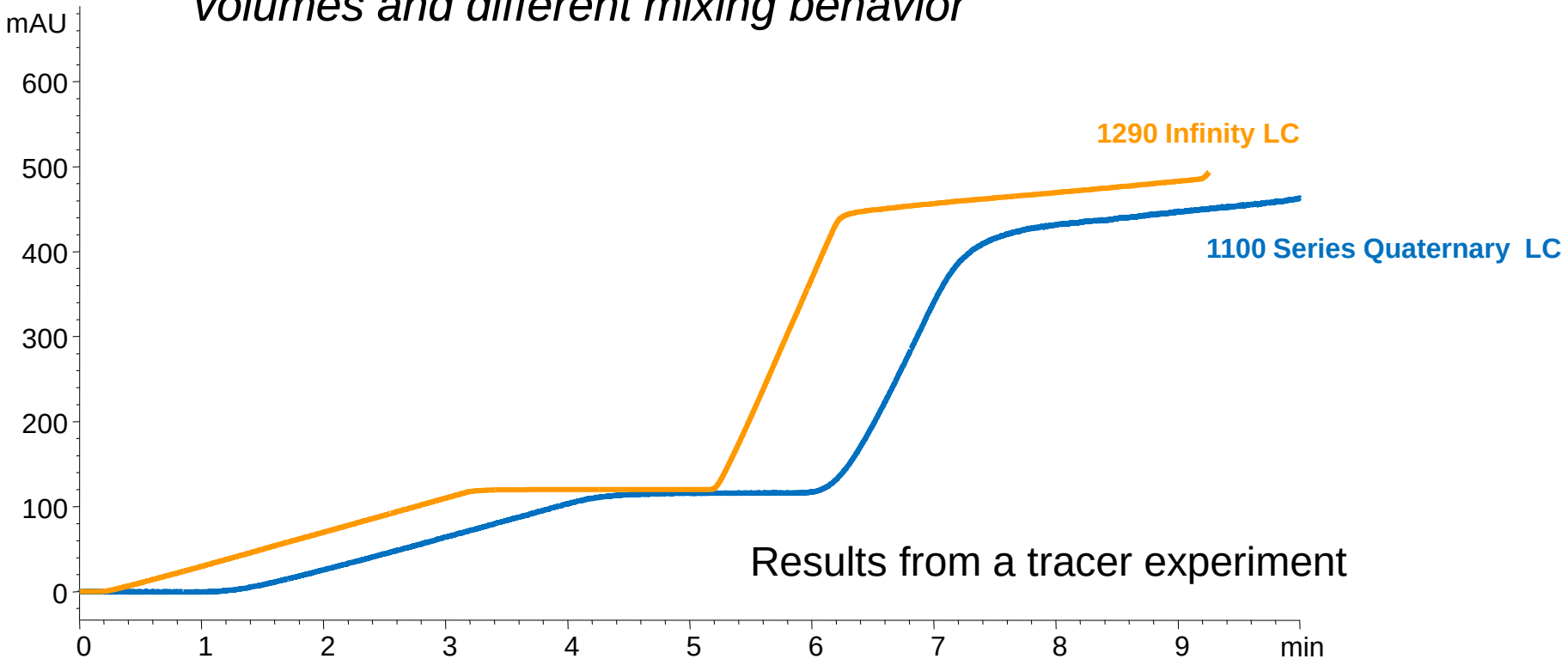
Method transfer from a UHPLC system with a minimized dwell volume and optimized mixing behavior to any other LC system is often challenging and affects rentention time and resolution (effects of DELAY and DISPERSION)

Example: Method Transfer from a 1290 UHPLC to a 1100 HPLC system



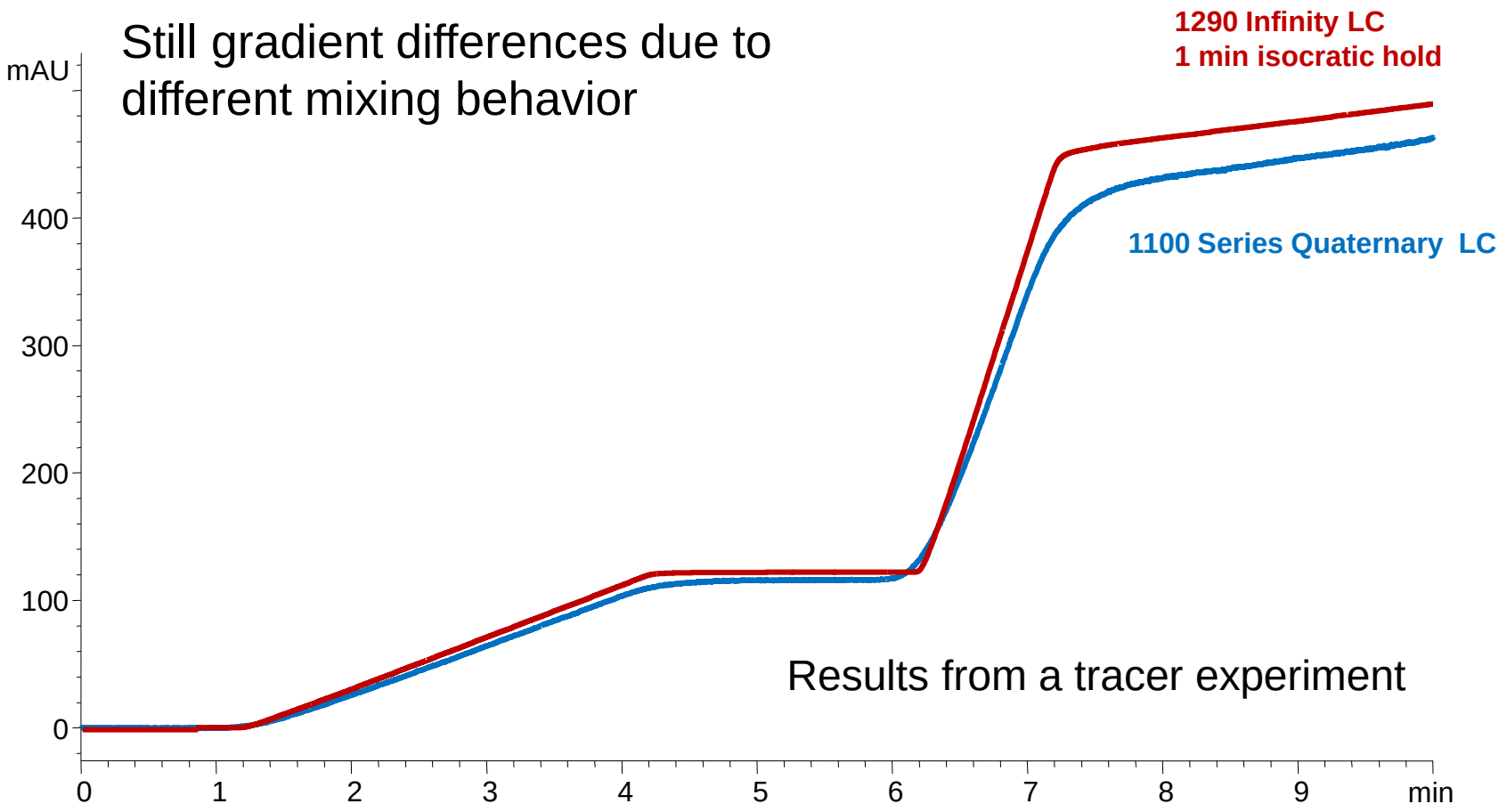
Method Transfer Between Different LC Instruments

Gradient differences due to different dwell volumes and different mixing behavior

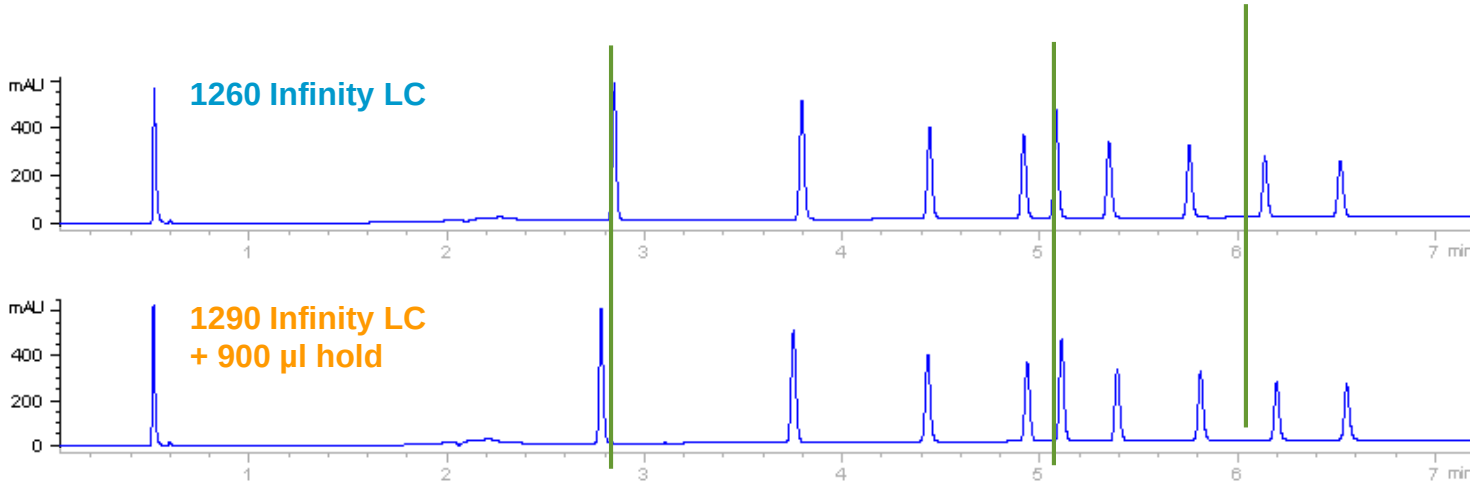


Method Transfer Between Different LC Instruments

Approach # 1: Isocratic holding step to synchronize



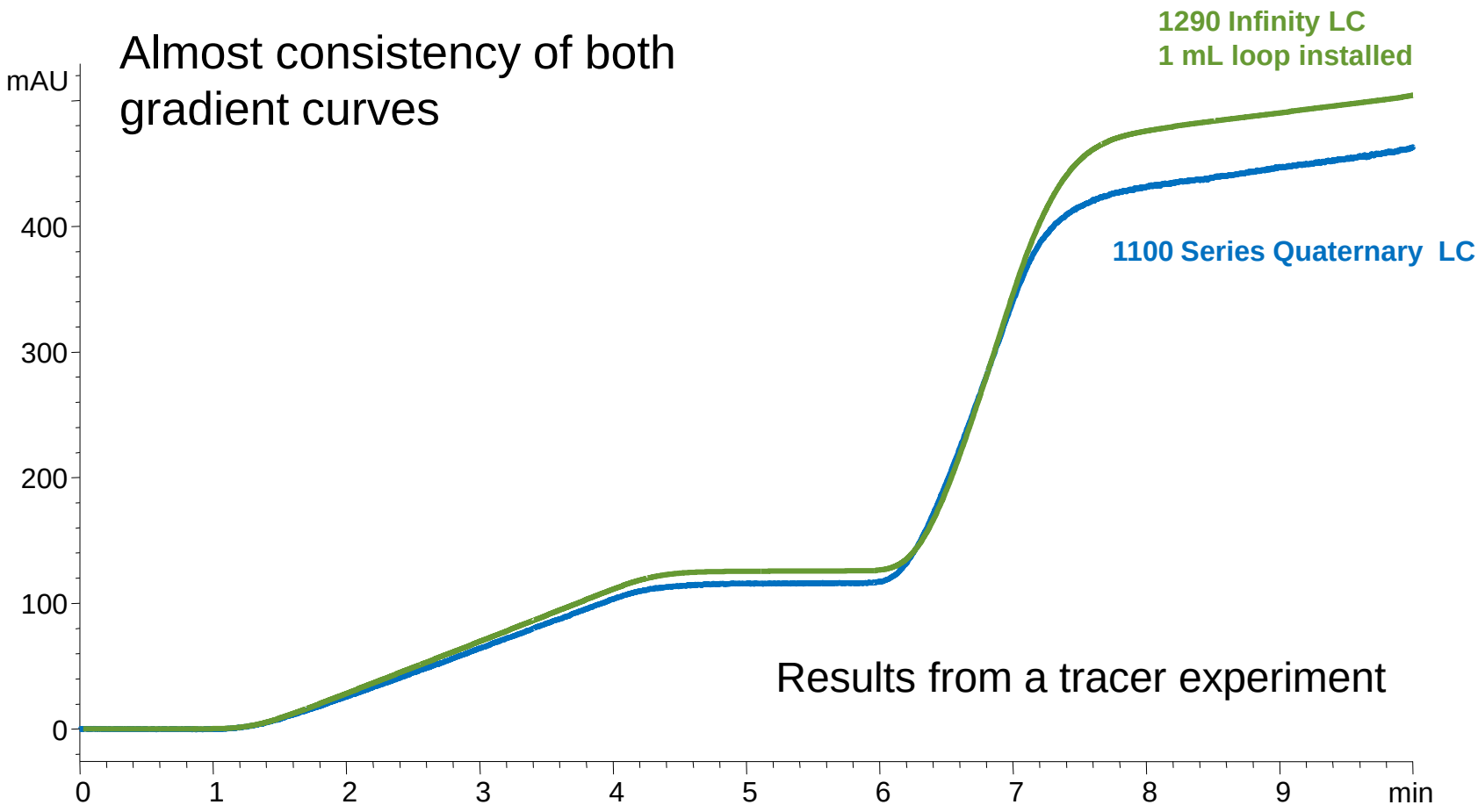
Approach # 1: Applying Isocratic Holding Steps Results



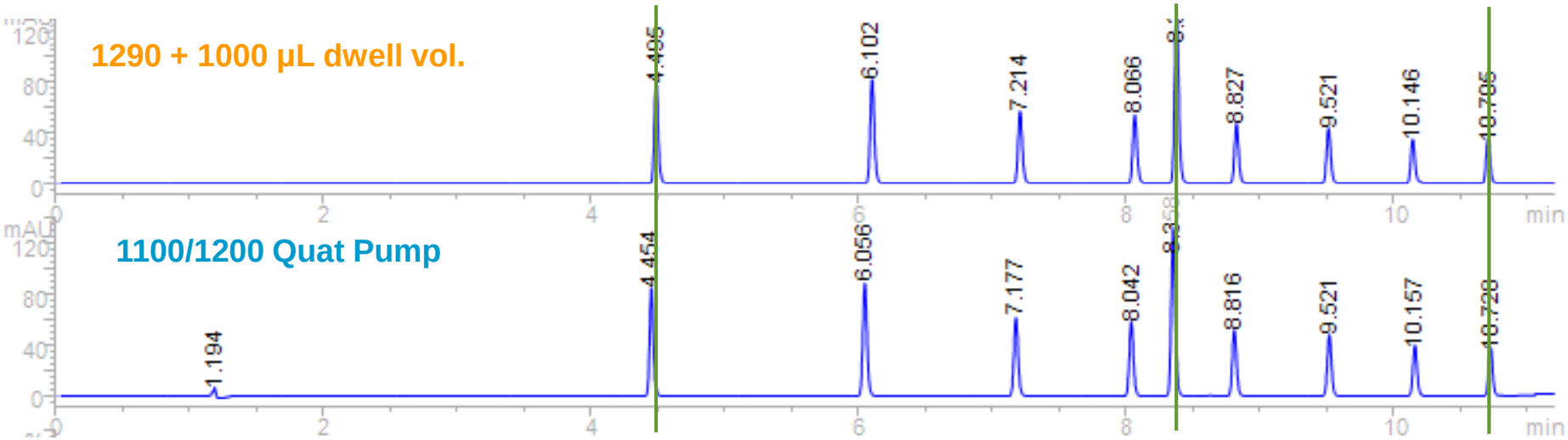
- Results shows a low consitency
- Requires manual determination of the dwell volume/ isocratic hold
  (in solvent delivery systems equipped with dampeners the dwell volume is pressure dependent and variable)
- Requires modification of the methods
  (should be avoided in validated environment,
  but doesn't require revalidation USP Chapter <621>)

Method Transfer Between Different LC Instruments

Approach # 2: Adding a physical void volume (Tubing)

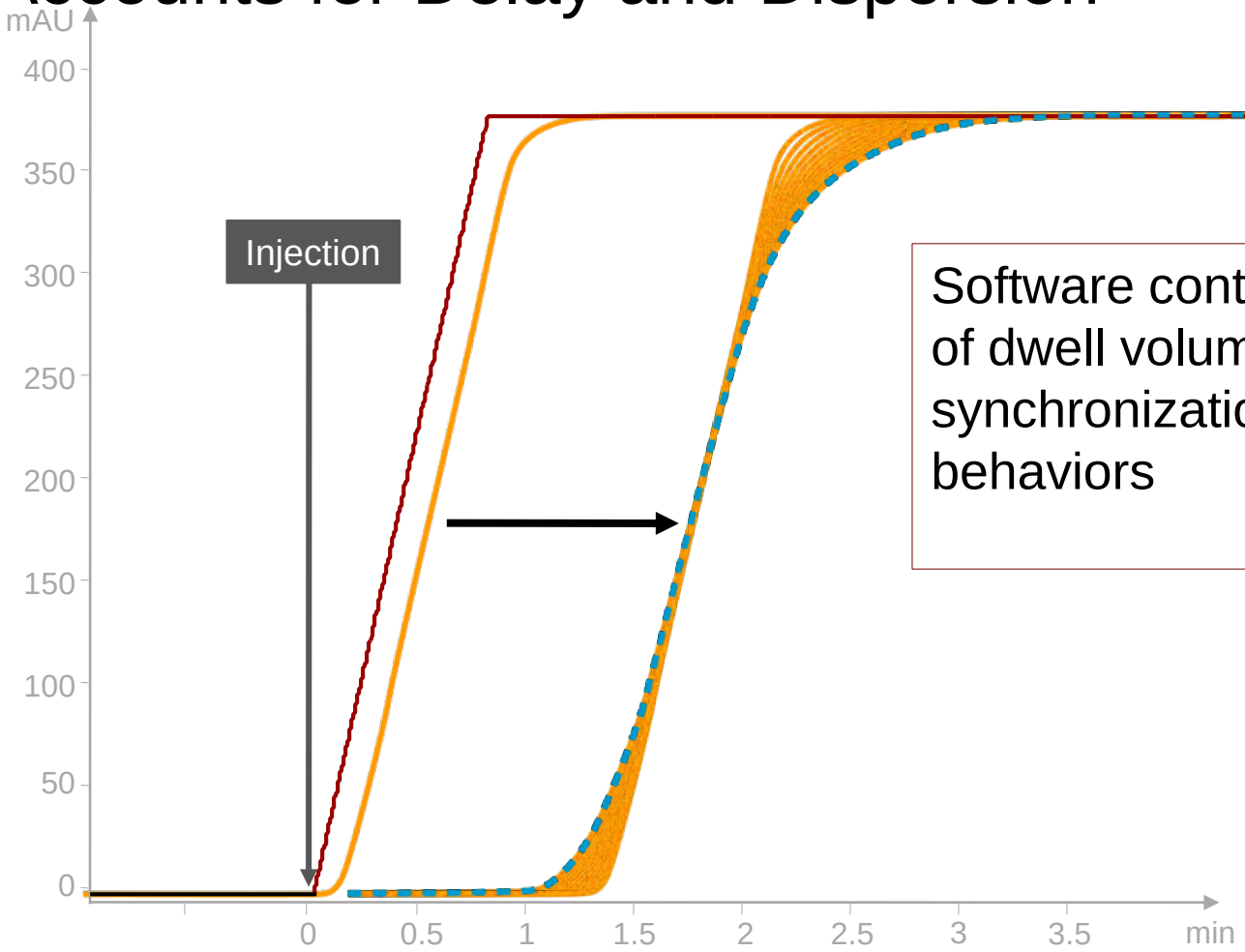


Approach # 2: Adding a Physical Void Volume Results



- Results shows a good consitency
- Manual determination of dwell volumes required (issues of a variable dwell volume with systems containing dampers)
- Mechanical changes are laborious and not flexible
- Maybe need a New IQ/OQ because change to physical system

Agilent Solution:
Intelligent System Emulation Technology (ISET)
Accounts for Delay and Dispersion

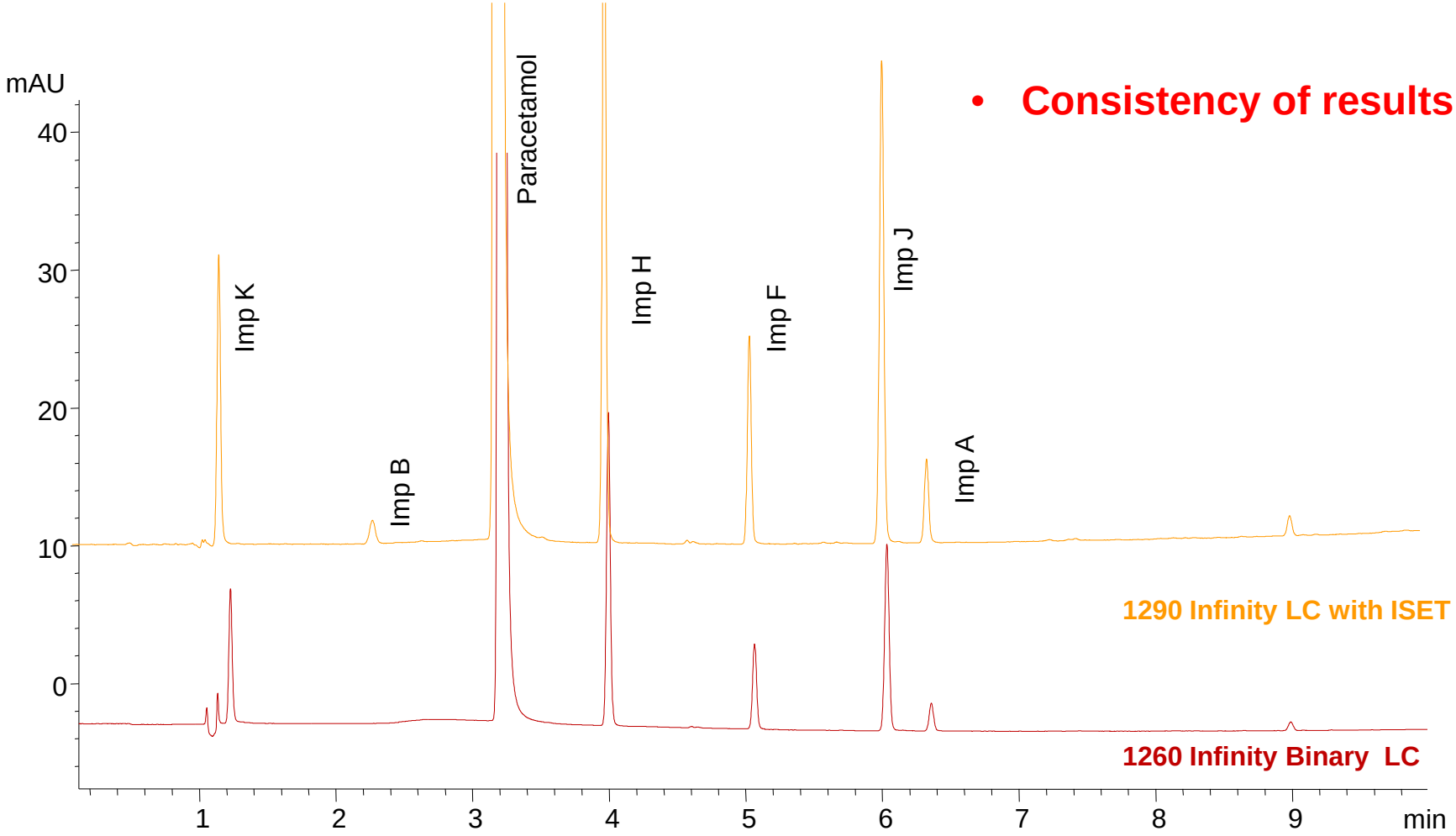


Software controlled compensation of dwell volume differences and synchronization of mixing behaviors

Programmed gradient
1290 gradient
1200 gradient

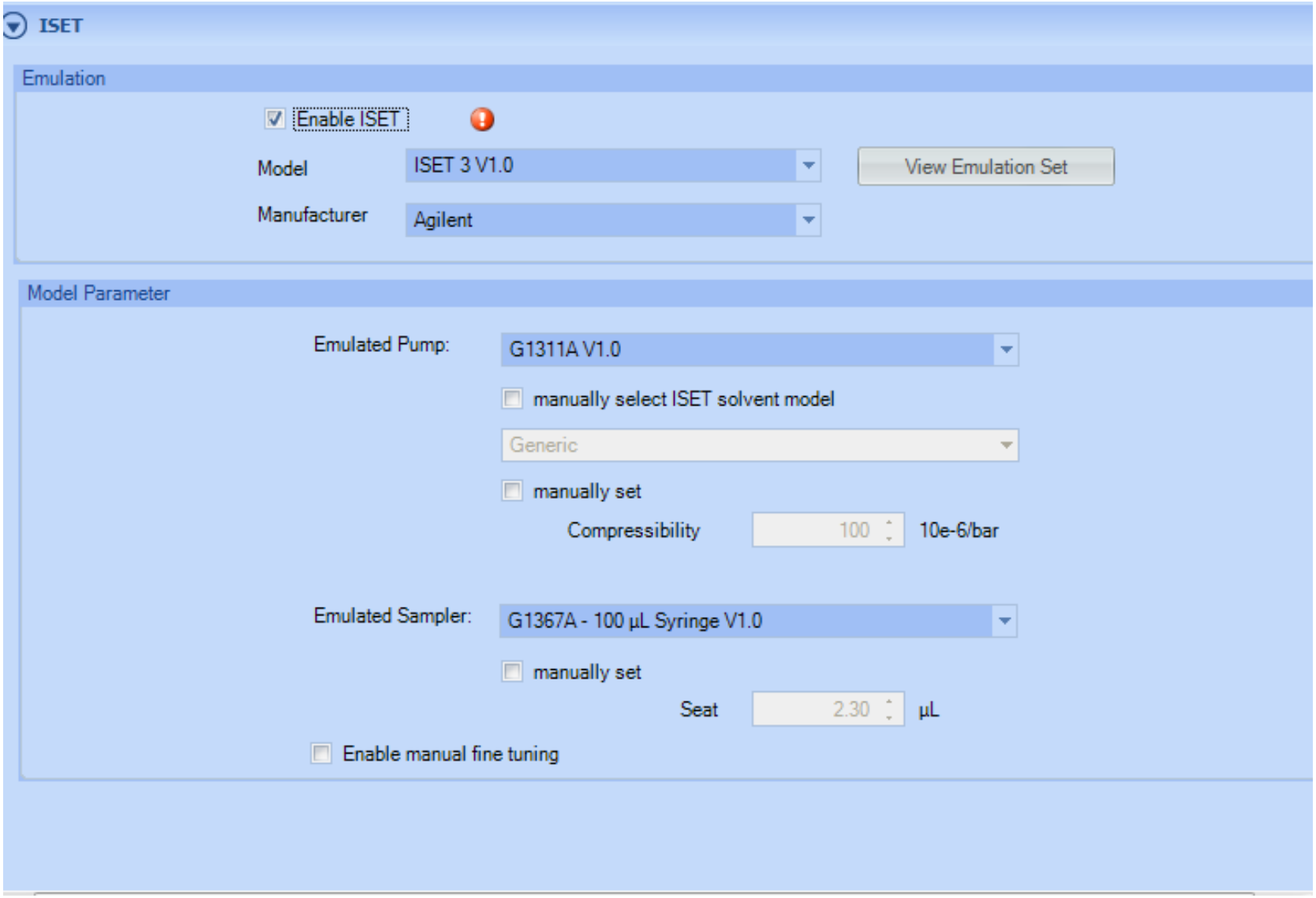
Agilent Solution: Method Transfer by ISET

Results: *1260 Infinity Binary LC to 1290 Infinity LC*

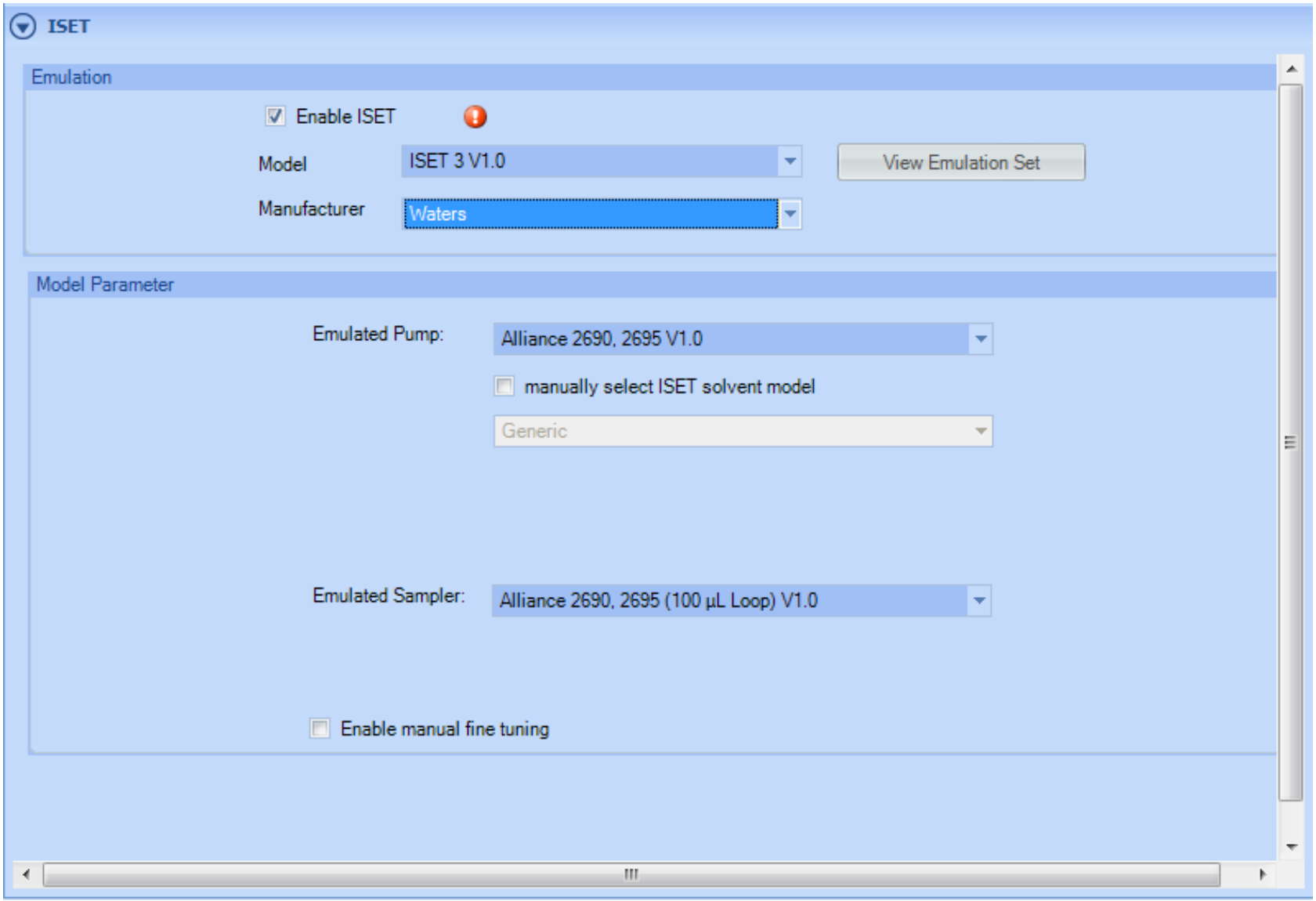


- **Consistency of results**

ISET Setup: Agilent Configuration



ISET Setup: Different Vendor- Adjust Design Space to Fit Other Instrument Vendors



Agilent Application Notes

- Fast screening of mobile and stationary phases with the Agilent 1290 Infinity LC and seamless method transfer to an Agilent 1200 Series LC using ISET

  Agilent Application Note 5991-0989EN

- Developing faster methods for generic drugs within USP <621>allowed limits

  Agilent Application Note 5991-0278EN

- Effective use of pharmacopeia guidelines to reduce cost of chromatographic analysis

  Agilent Application Note 5991-1053EN

- Developing faster methods for generic drugs within EP 2.2.46E allowed limits

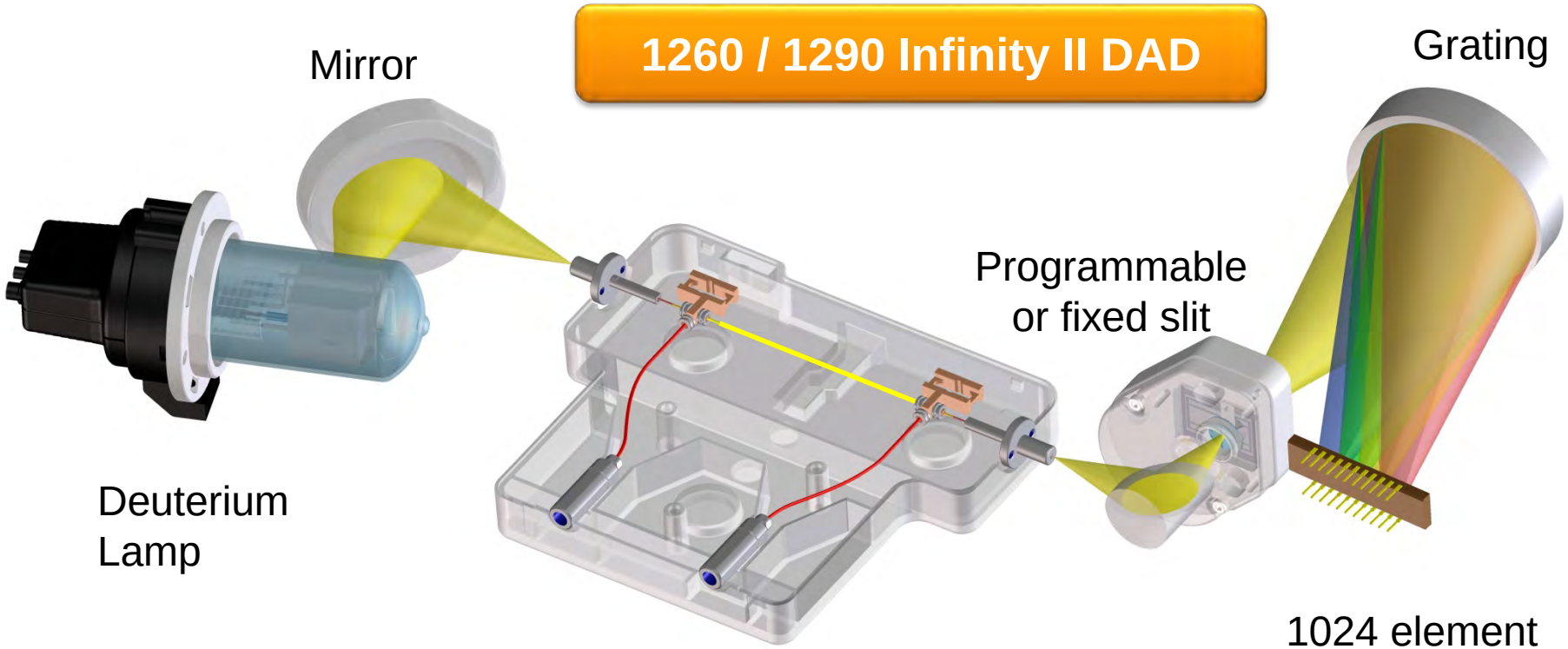
  Agilent Application Note 5991-0394EN

30x Wider Linear UV Range
Quantification of widely different concentration levels in one single run

Agilent High Dynamic Range Solution (HDR)

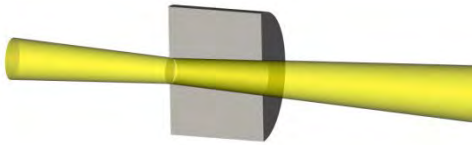
Optofluidic Waveguides: Max-Light Flow Cells

Total-internal reflection in a non-coated fused silica fiber

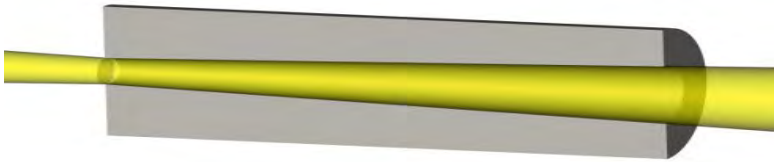


Effects of path length increase

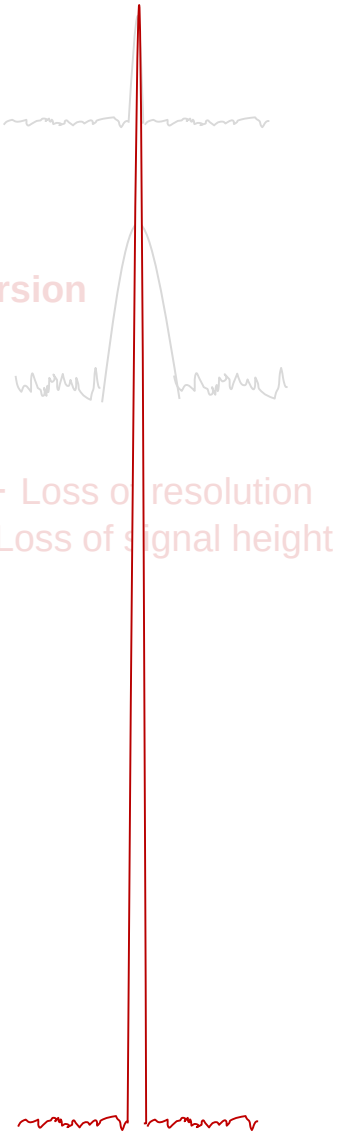
Conventional flow cells:



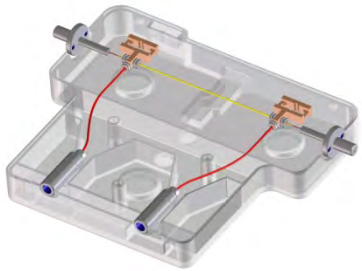
10 mm pathlength
small geom. cell volume (13 µL)
high light transmission



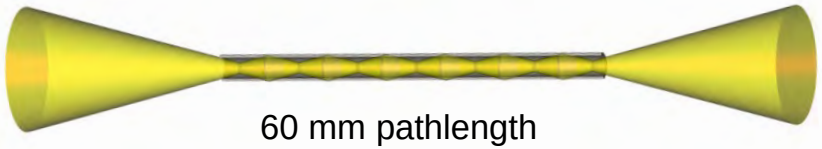
60 mm pathlength
large geom. cell volume (78 µL)
lower light transmission



Max-Light <u>High Sensitivity</u> cell:



Optofluidic waveguides
(total internal reflection)



60 mm pathlength
4 µL σ_V dispersion volume

Linearity, linear range and dynamic range

1200 Series Diode Array Detector, 10 mm flow cell

10 mm

Linearity and Sensitivity in ONE Run

Detector Signal [AU]

Upper limit 2.0

*Detector noise 7*10^{-6}*

HDR- DAD

Slope = Response Factor (Sensitivity)

HDR- DAD

Linear range

Dynamic range

LOD (3x S/N)

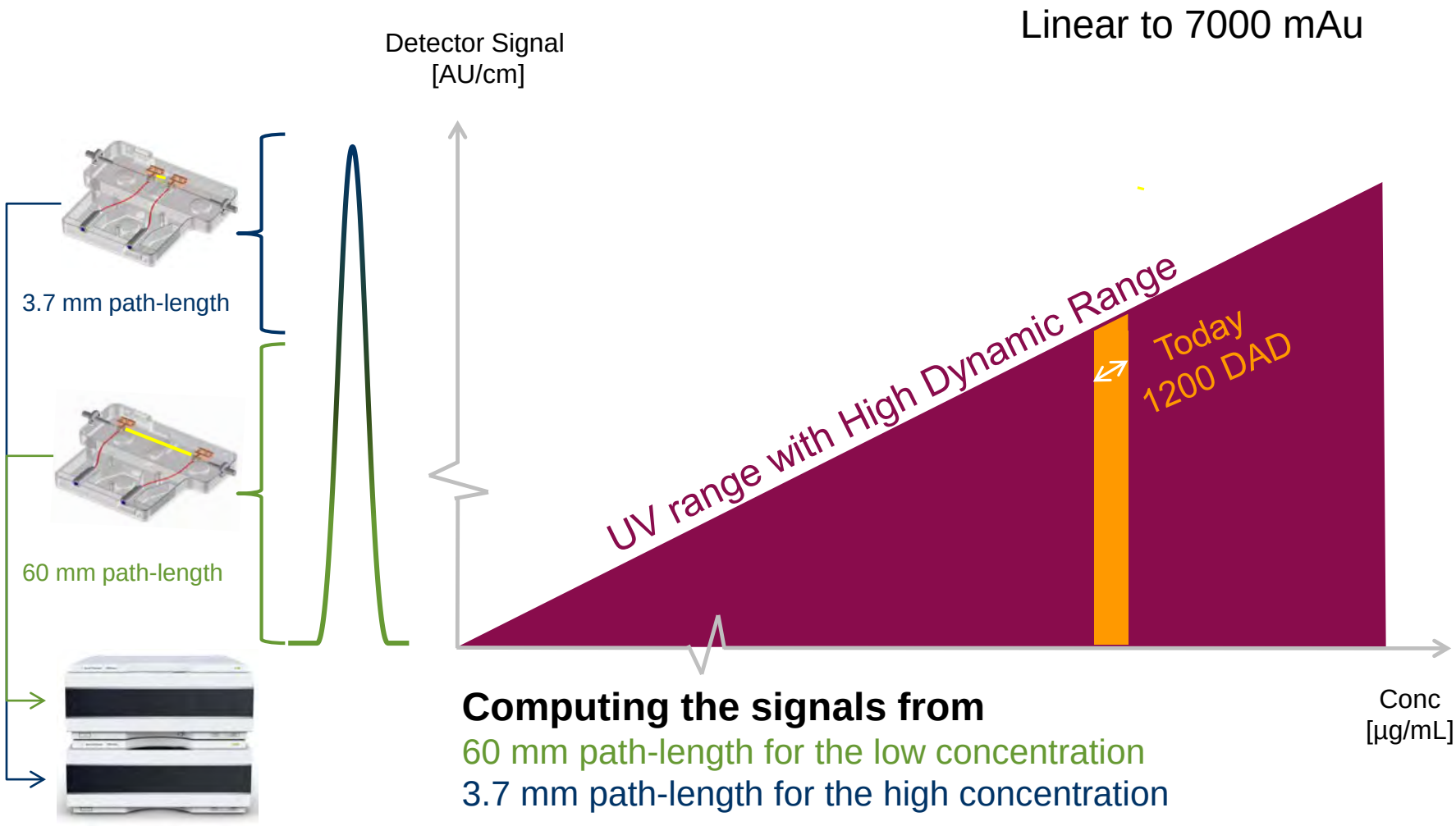
Conc (upper limit) linear range

Conc (upper limit) dynamic range

Conc [µg/mL]

30x Wider Linear Range with HDR-DAD

3.7 mm and 60 mm and Max-Light flow cell



Computing the signals from

60 mm path-length for the low concentration

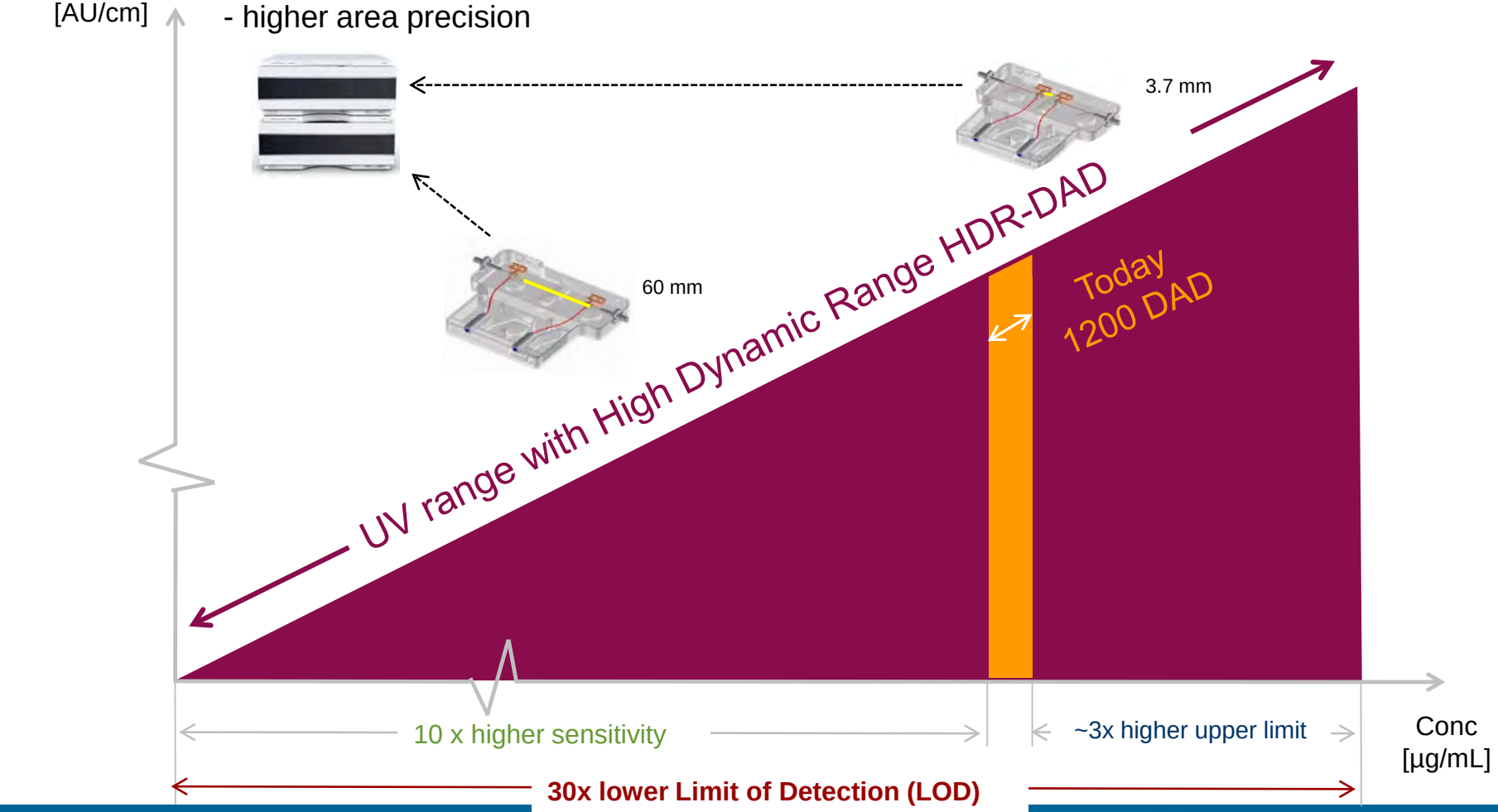
3.7 mm path-length for the high concentration

30x Wider Linear Range with HDR-DAD

3.7 mm and 60 mm and Max-Light flow cell

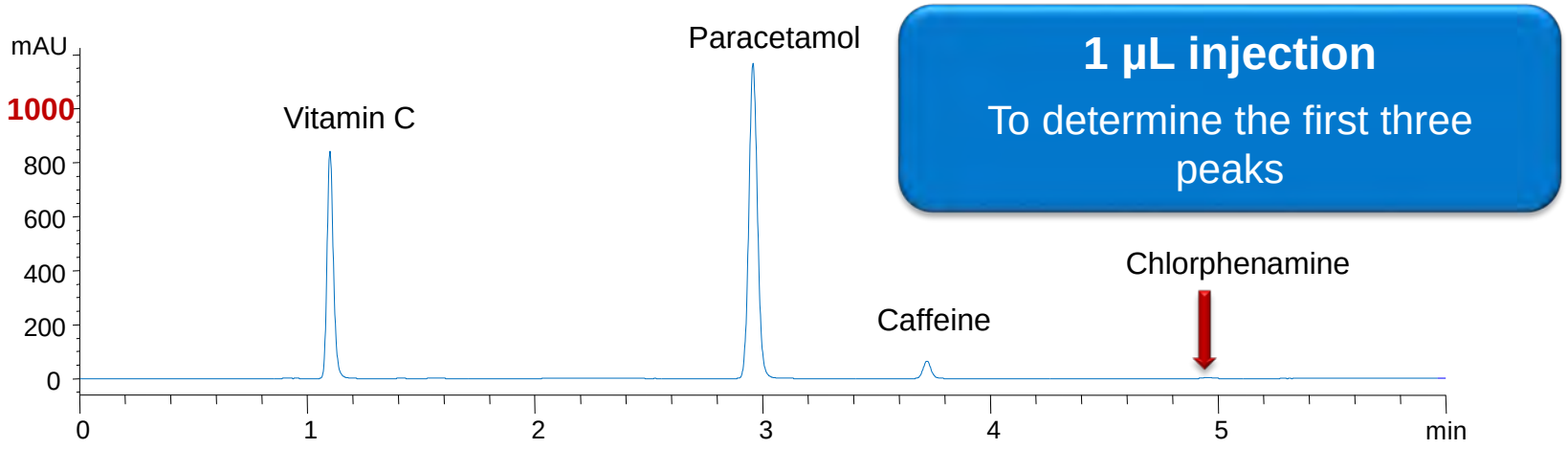
30x lower Limit of Detection (LOD) for impurity analysis

- for more reliable automated peak integration
- higher area precision



Analysis using conventional DAD

Two injections required to quantify main compounds and impurities

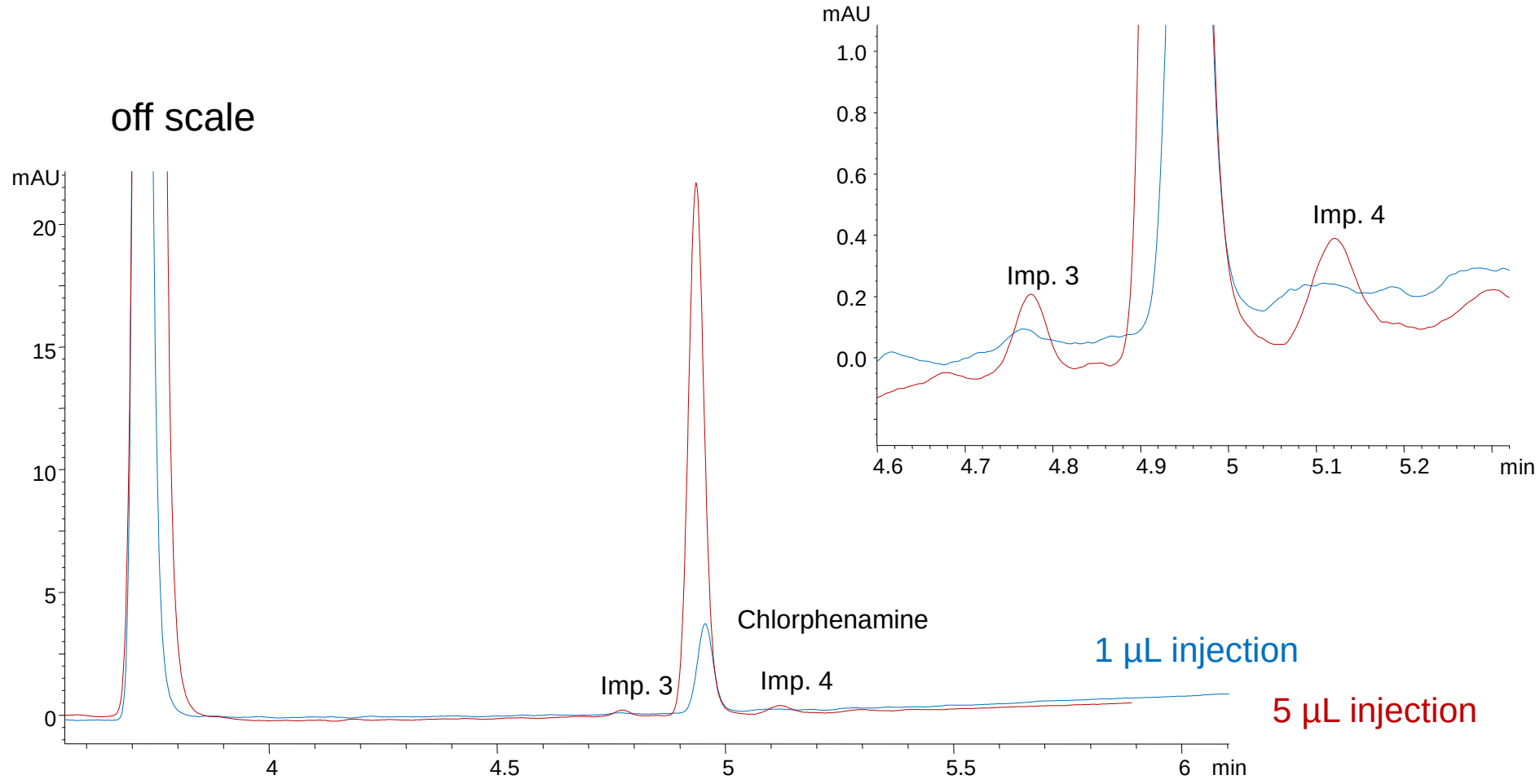


1 µL injection

To determine the first three peaks

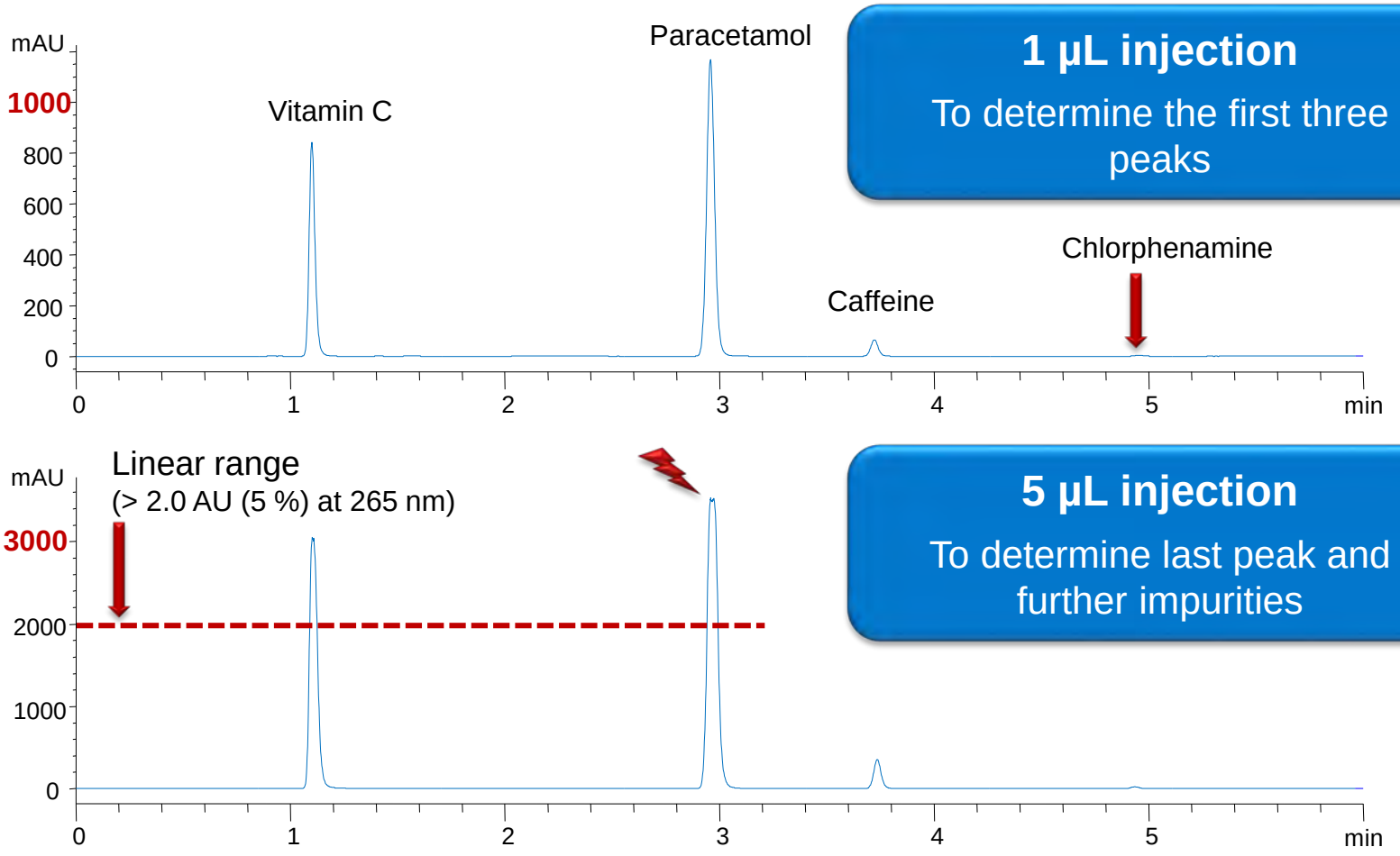
Analysis using conventional DAD

Two injections required to quantify main compounds and impurities



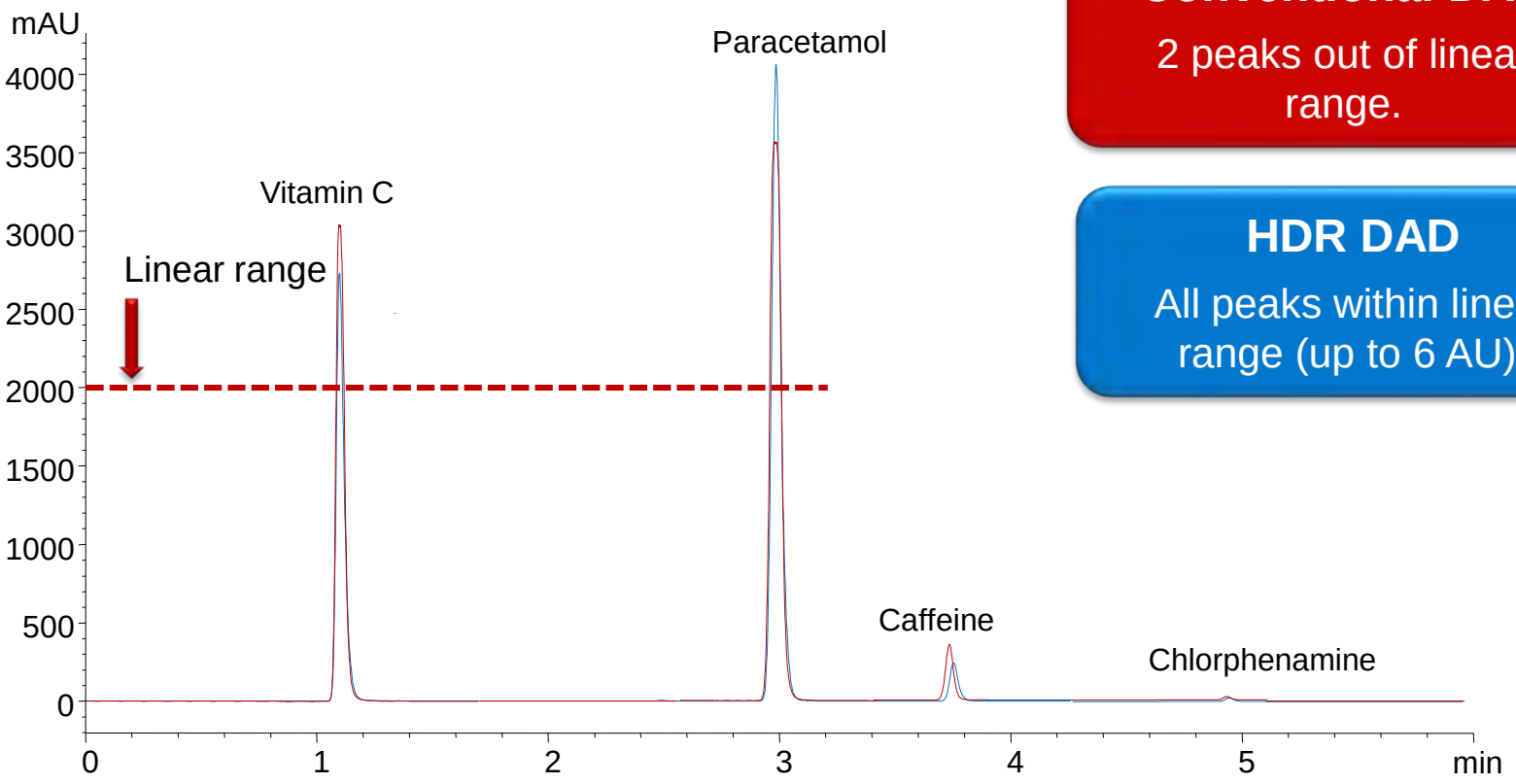
Analysis using conventional DAD

Two injections required to quantify main compounds and impurities



Analysis using HDR DAD

Comparison with conventional DAD



Conventional DAD

2 peaks out of linear range.

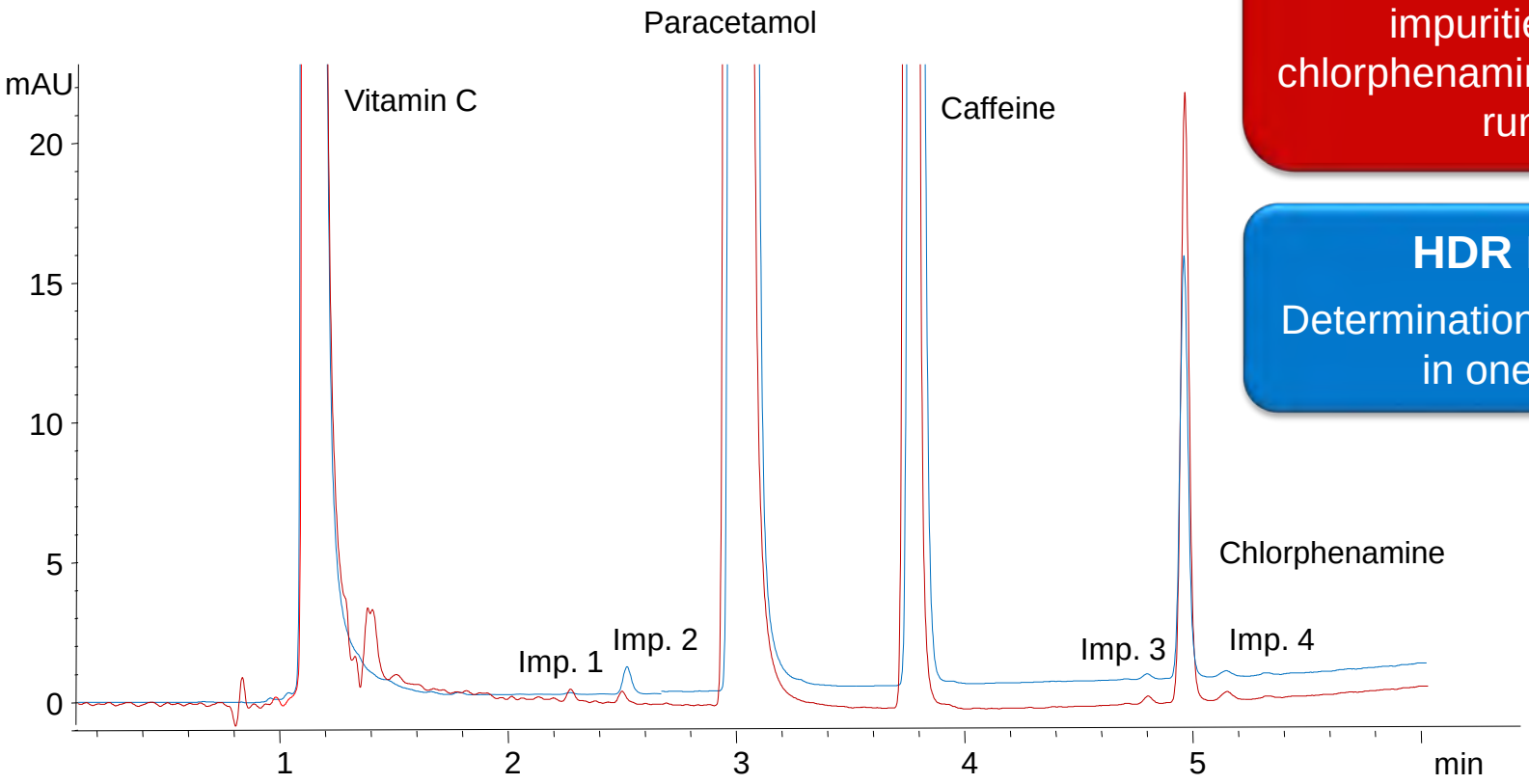
HDR DAD

All peaks within linear range (up to 6 AU).

Analysis using HDR DAD

Comparison with conventional DAD

Offset in time calibrated and software aligns the 2 signals



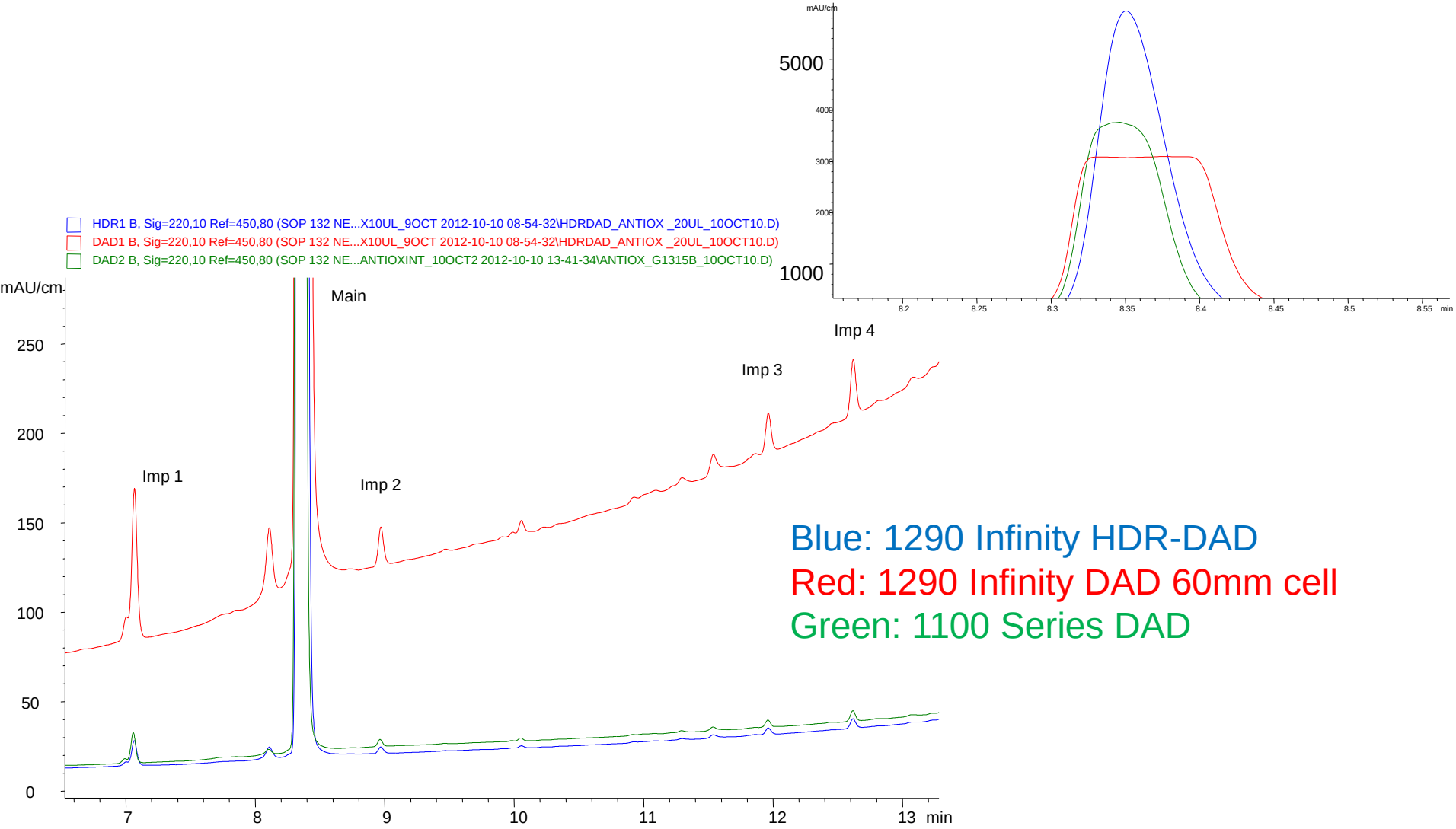
Conventional DAD

Determination of impurities and chlorphenamine in second run.

HDR DAD

Determination of all peaks in one run.

Application Example – Overlay



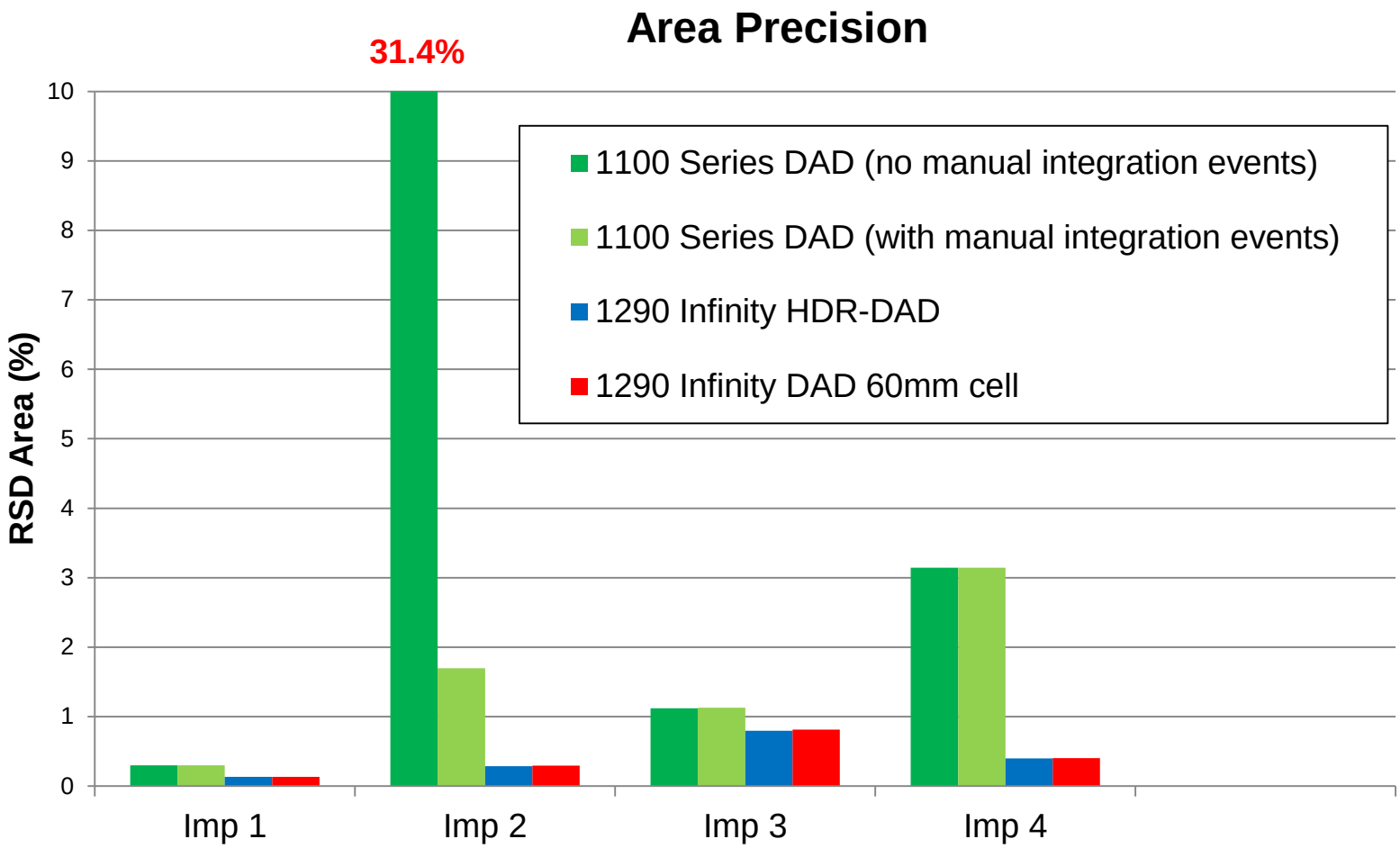
Blue: 1290 Infinity HDR-DAD

Red: 1290 Infinity DAD 60mm cell

Green: 1100 Series DAD

Reliable Automated Peak Integration

Saving Time – Increasing Confidence



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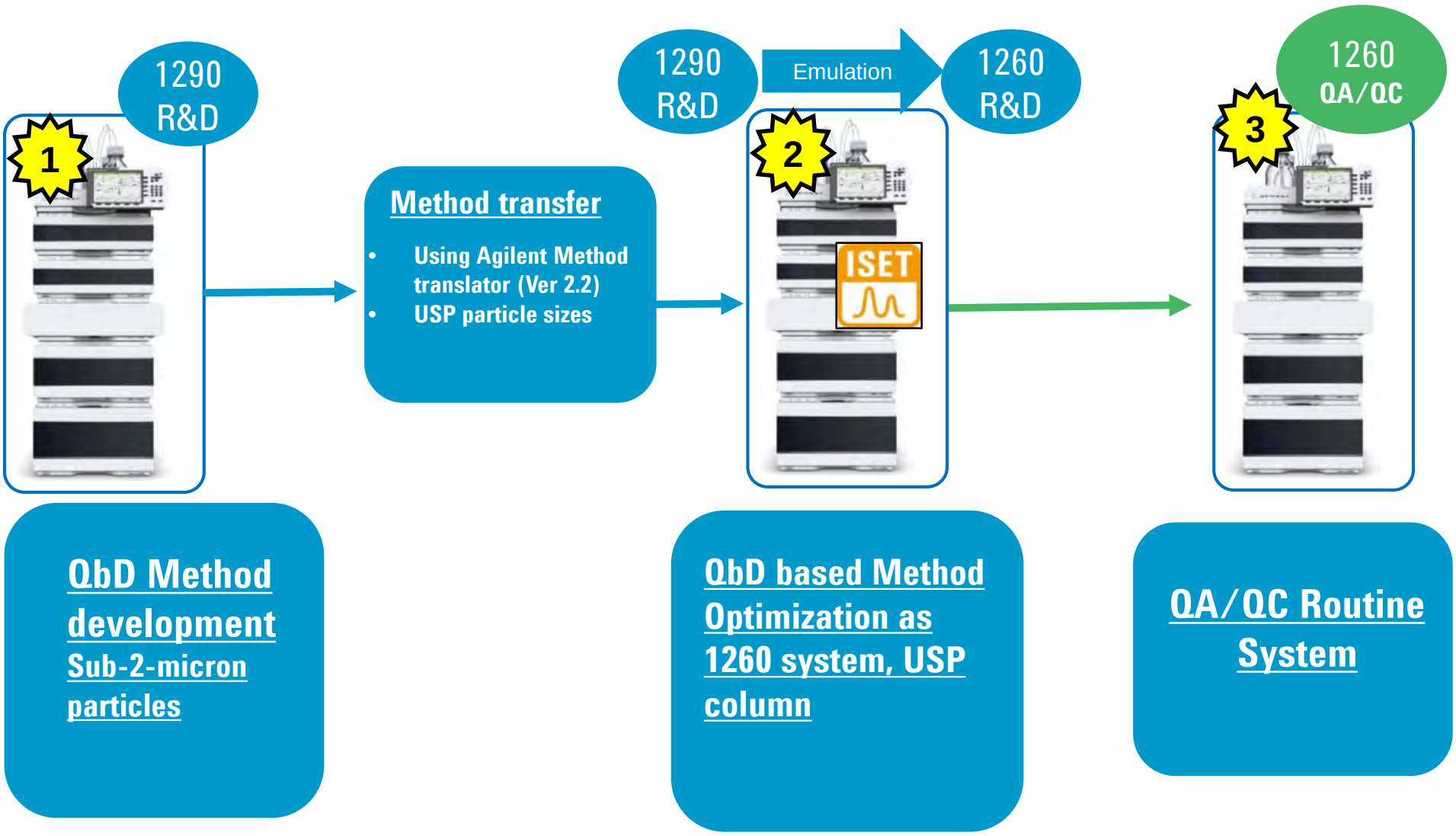
QbD Method Development & Method Transfer:

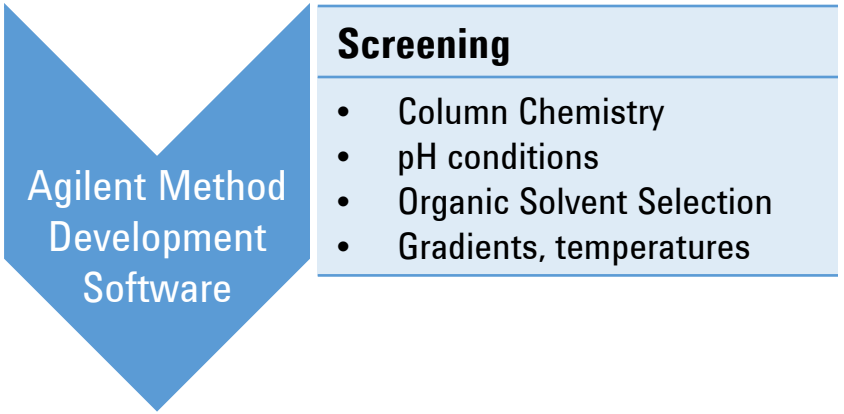
Workflow from UHPLC to HPLC in a nutshell



QbD Based Method Development Workflow

Overall workflow which consists of four main steps namely

- Step # 1: Screening
  - Many Analytical Runs



Step # 1: Screening

Agilent Chemstation Method Scouting Wizard Software

- **Define project**

Choose scouting combinations and base method.

- **Select columns**

All installed columns are shown automatically.

- **Select solvents**

Pump types and valves are automatically detected.

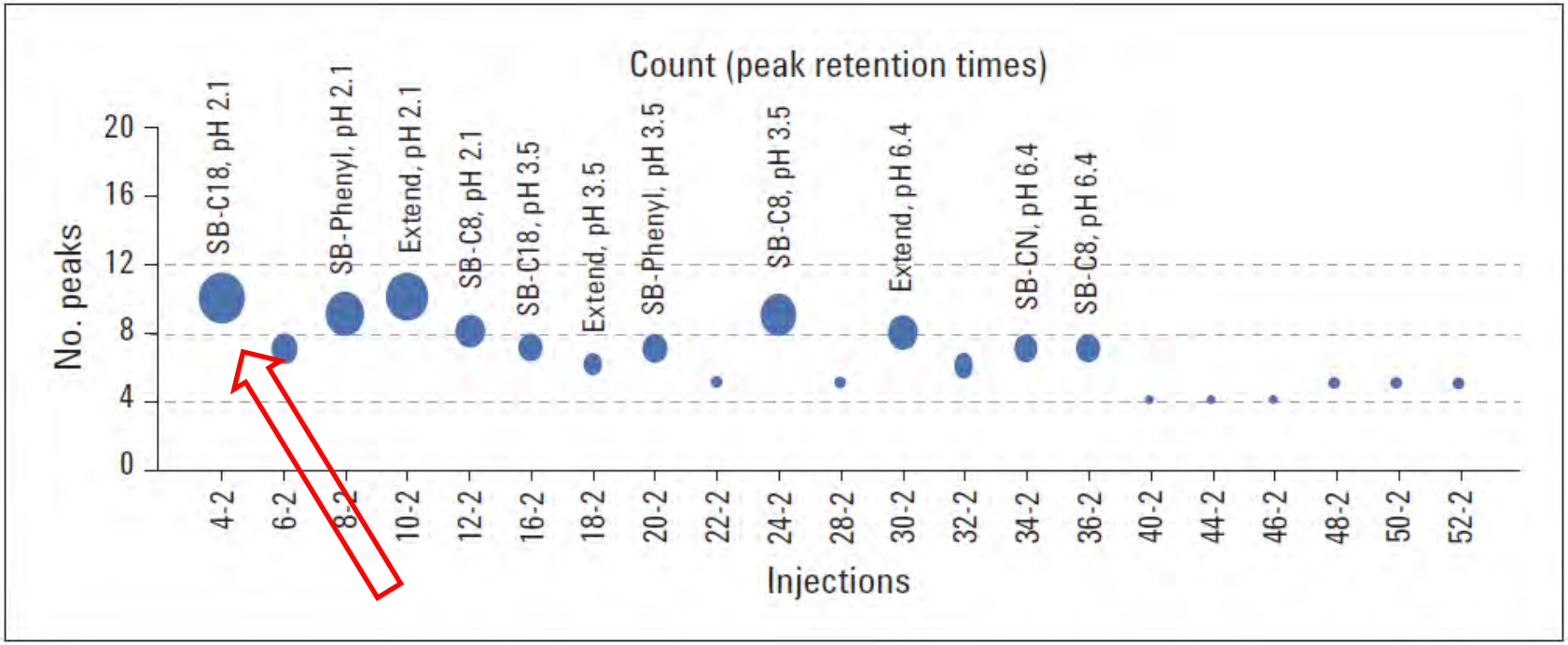
- **Define gradients**

Select between different gradients and temperatures.

- **Review and select screening methods**

Check for incompatible combinations.

Step # 1: Screening Results – Automated Report



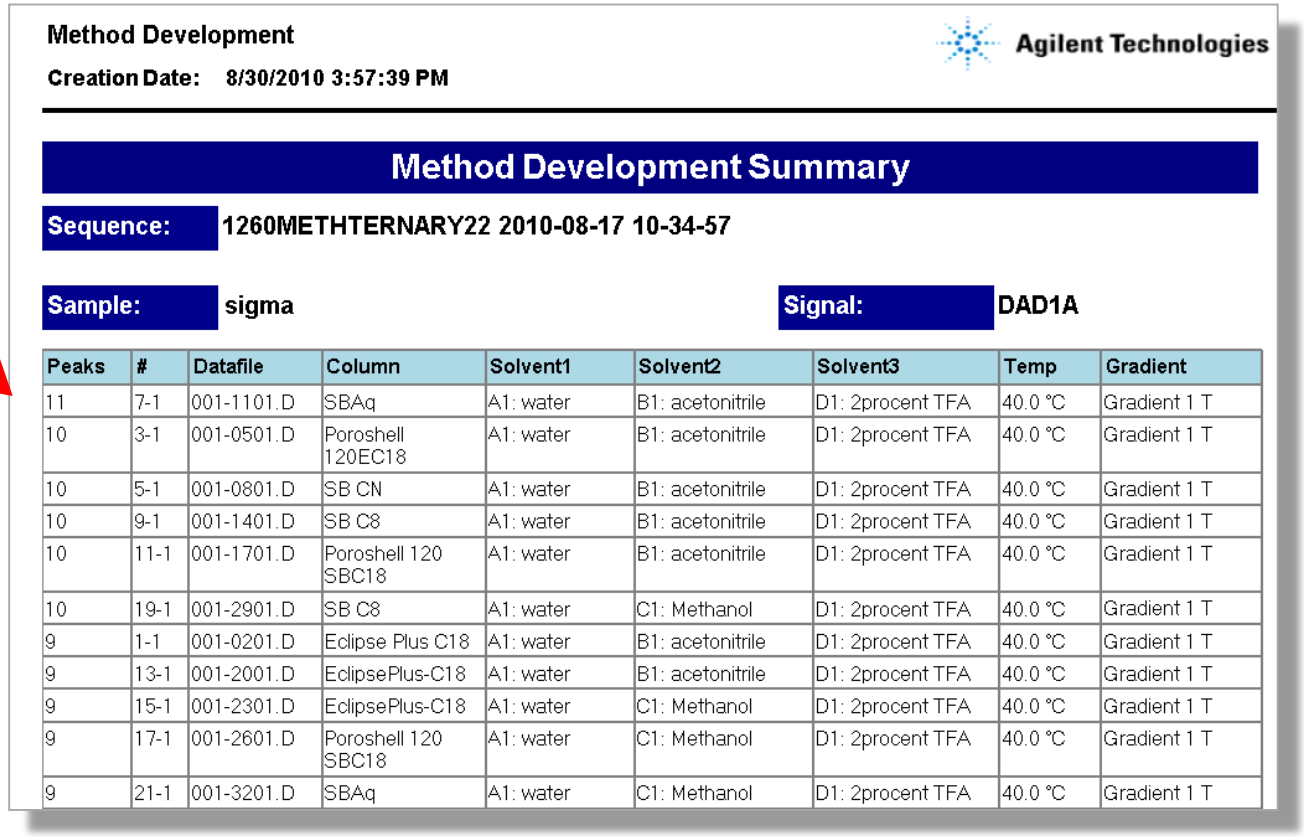
Bubble size represents the number of integrated peaks and, consequently, best mobile and stationary phase combination

For more details please see Agilent Application Note 5991-0989EN

Other Reporting options in Method Scouting Wizard

Many options for sorting and filtering....

Scouting conditions sorted for highest number of peaks



Method Development

Creation Date: 8/30/2010 3:57:39 PM

Agilent Technologies

Method Development Summary

Sequence: 1260METHTERNARY22 2010-08-17 10-34-57

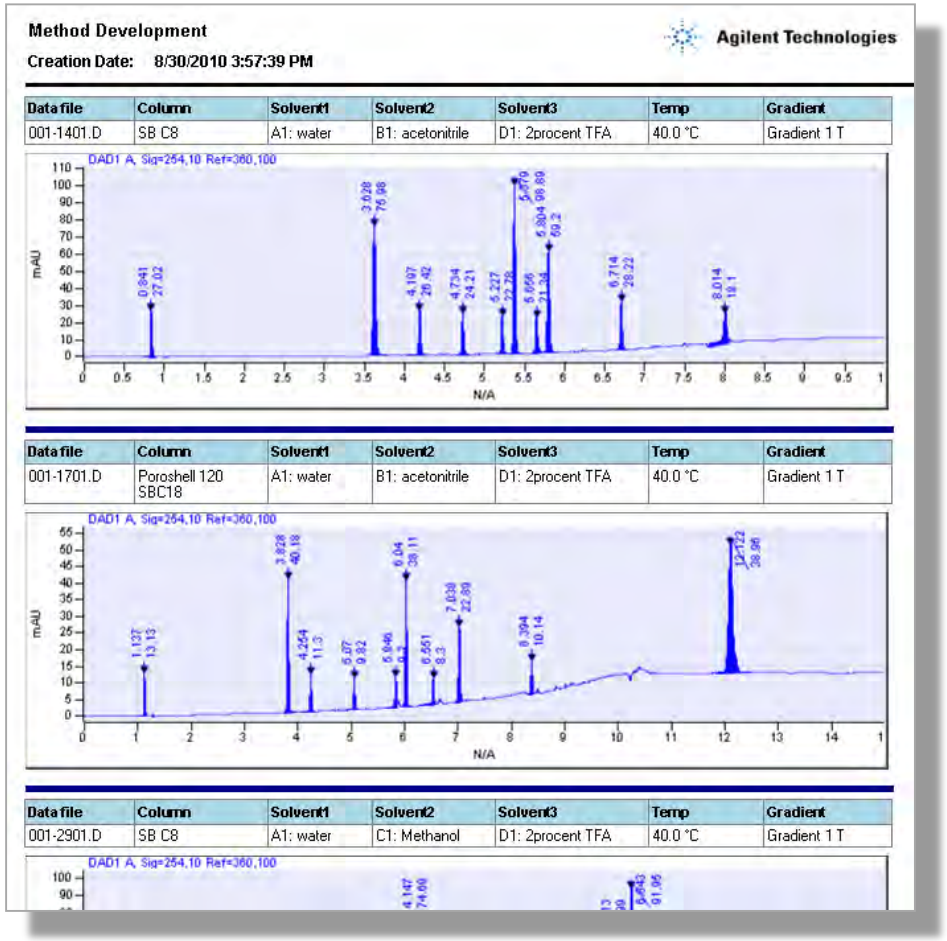
Sample: sigma **Signal:** DAD1A

Peaks	#	Datafile	Column	Solvent1	Solvent2	Solvent3	Temp	Gradient
11	7-1	001-1101.D	SBAq	A1: water	B1: acetonitrile	D1: 2procent TFA	40.0 °C	Gradient 1 T
10	3-1	001-0501.D	Poroshell 120EC18	A1: water	B1: acetonitrile	D1: 2procent TFA	40.0 °C	Gradient 1 T
10	5-1	001-0801.D	SB CN	A1: water	B1: acetonitrile	D1: 2procent TFA	40.0 °C	Gradient 1 T
10	9-1	001-1401.D	SB C8	A1: water	B1: acetonitrile	D1: 2procent TFA	40.0 °C	Gradient 1 T
10	11-1	001-1701.D	Poroshell 120 SBC18	A1: water	B1: acetonitrile	D1: 2procent TFA	40.0 °C	Gradient 1 T
10	19-1	001-2901.D	SB C8	A1: water	C1: Methanol	D1: 2procent TFA	40.0 °C	Gradient 1 T
9	1-1	001-0201.D	Eclipse Plus C18	A1: water	B1: acetonitrile	D1: 2procent TFA	40.0 °C	Gradient 1 T
9	13-1	001-2001.D	EclipsePlus-C18	A1: water	B1: acetonitrile	D1: 2procent TFA	40.0 °C	Gradient 1 T
9	15-1	001-2301.D	EclipsePlus-C18	A1: water	C1: Methanol	D1: 2procent TFA	40.0 °C	Gradient 1 T
9	17-1	001-2601.D	Poroshell 120 SBC18	A1: water	C1: Methanol	D1: 2procent TFA	40.0 °C	Gradient 1 T
9	21-1	001-3201.D	SBAq	A1: water	C1: Methanol	D1: 2procent TFA	40.0 °C	Gradient 1 T

Other Reporting options in Method Scouting Wizard

And of course chromatograms – with scouting conditions!

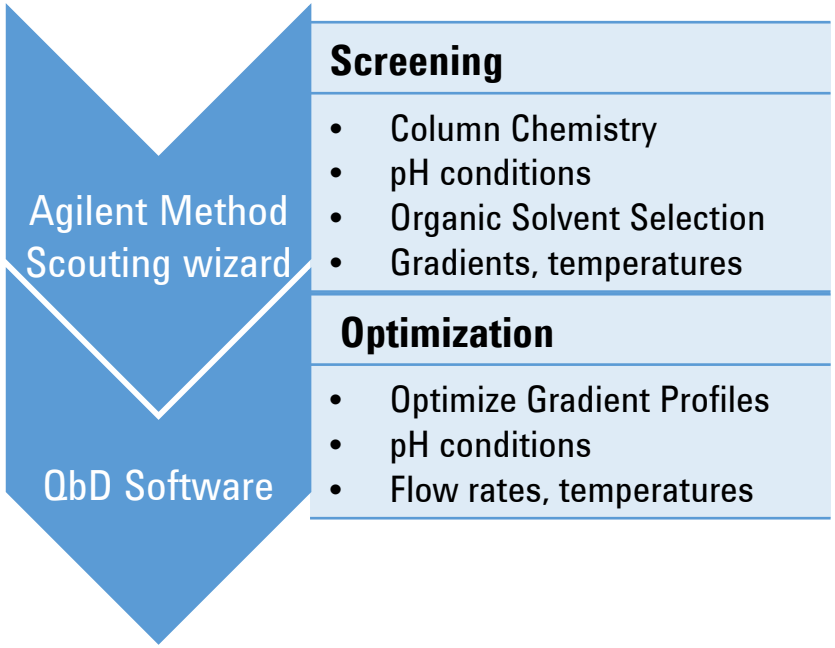
Data-file, column, solvents, temperature, gradient-name from Method Scouting Wizard



QbD Based Method Development Workflow

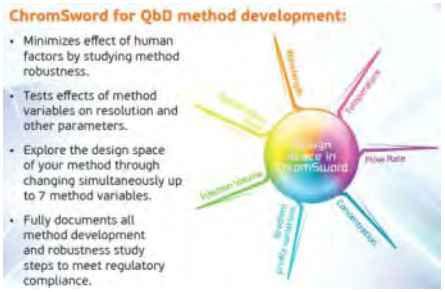
Overall workflow which consists of four main steps namely

- Step # 1: Screening
- Step # 2: Optimization



Add-on Software Options for QbD Method Development

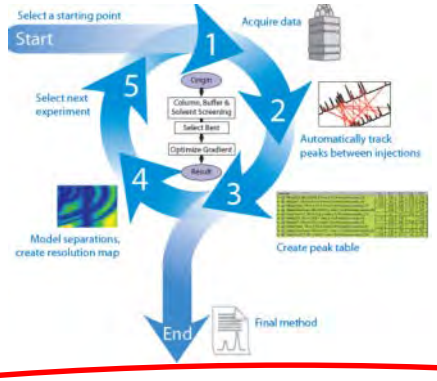
ChromSword

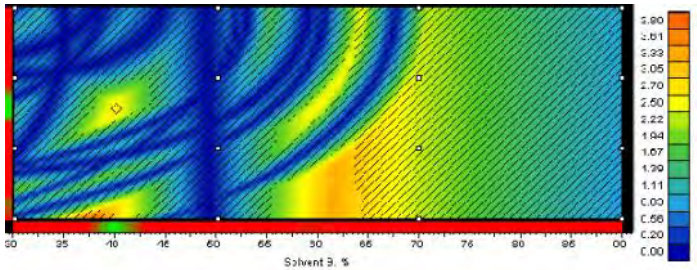


ChromSwordAuto

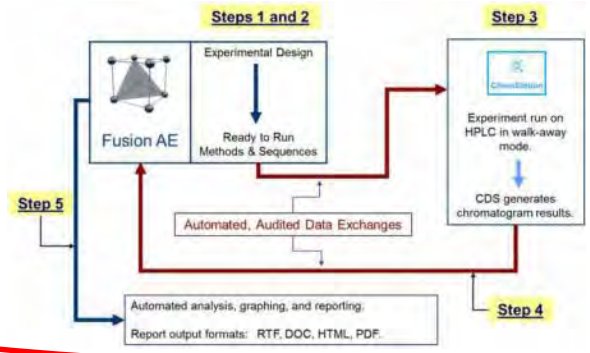
- Runs unattended method development with Agilent LC and LC-MS instruments.
- Rapidly finds methods for unknown samples to separate 100 or even more compounds.
- Starts method development without any preliminary information about a sample.
- Utilizes revolutionary peak tracking procedure to work with peaks less than 0.01% of total area.
- Provides total support for method development and robustness test workflow.

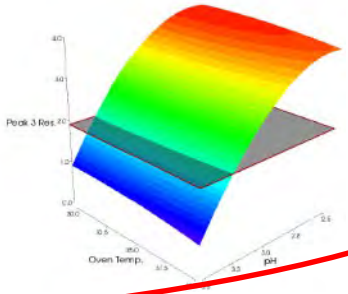
AutoChrom (ACD Labs)





Fusion AE (S-Matrix)





Step # 2: Optimization

Fusion AE QbD Software

Optimization of flow rate, gradient slope, pH, column temperature

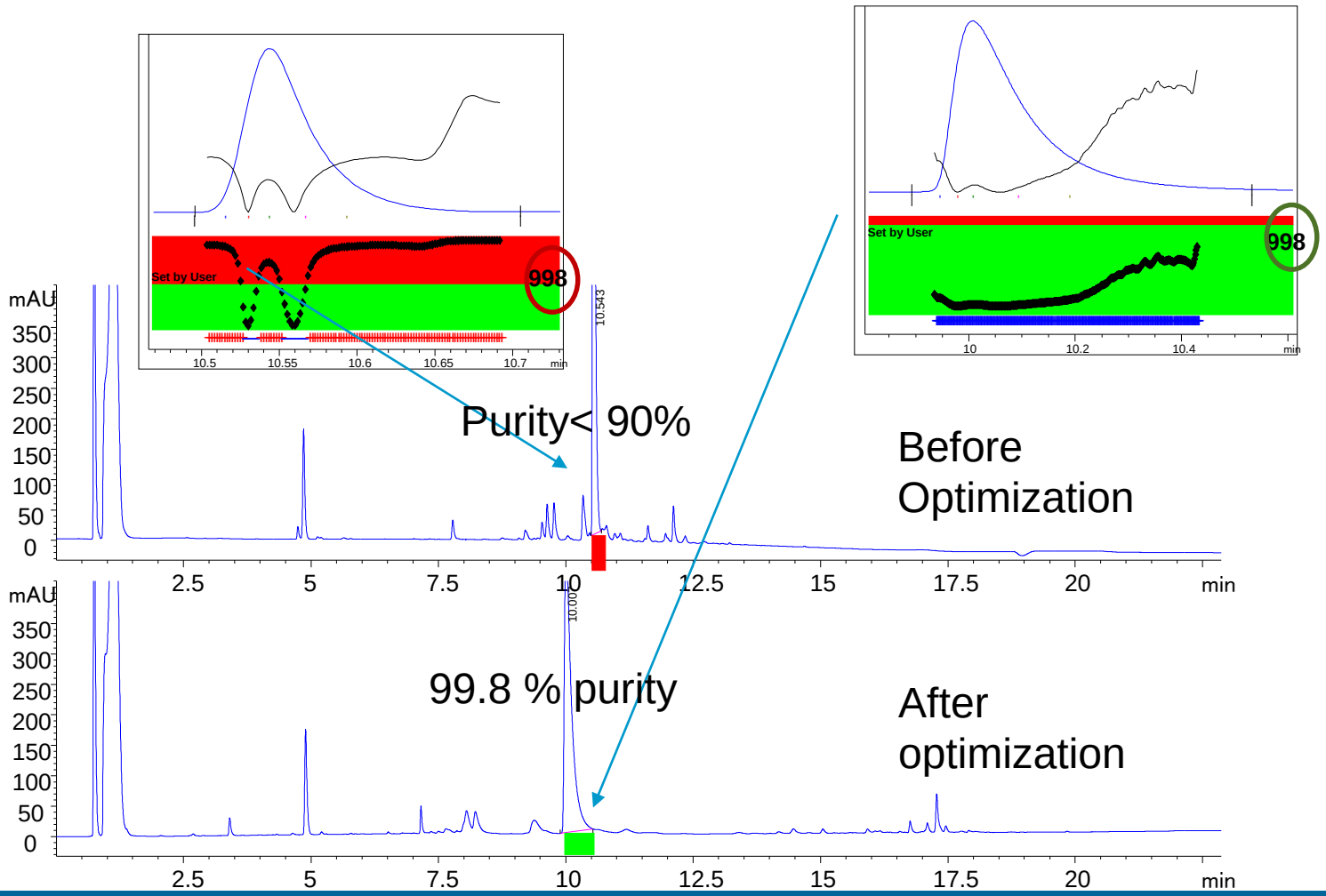
Variable Parameters	Study Range
Pump Flow rate (mL/min)	**0.550, 0.600,0.650**
Intermediate hold time (min)	**3.00 <= Intermediate Hold Time <= 7.00**
Final % Strong Solvent (Gradient 1)*	**30.0 <= Final % Strong Solvent <= 35.0**
Oven Temperature (°C)	**33.0, 36.0, 39.0**

Constant Parameters	Constant Value
Column Type	3.0X100 mm,1.8 µm ZORBAX RRHD Eclipse Plus Phenyl-Hexyl
Wavelength	245 nm ± 4 nm (ref off)
Strong Solvent type	Acetonitrile
pH	7.0
Injection Volume	1µl
Equilibration Time	2.50 min
Initial Hold Time	1.00 min
Gradient 1 Time*	5.17 min
Gradient 2 Time*	9.28 min
Final Hold Time	2.00 min
Final Hold % Organic	90.0 %B
Initial % Strong Solvent	5.0% B

Gradient 1: 5%B-(30-35)%B
Gradient 2: (30-35)%B-90%B

Step # 2: Optimization looking at DAD Spectral Analysis

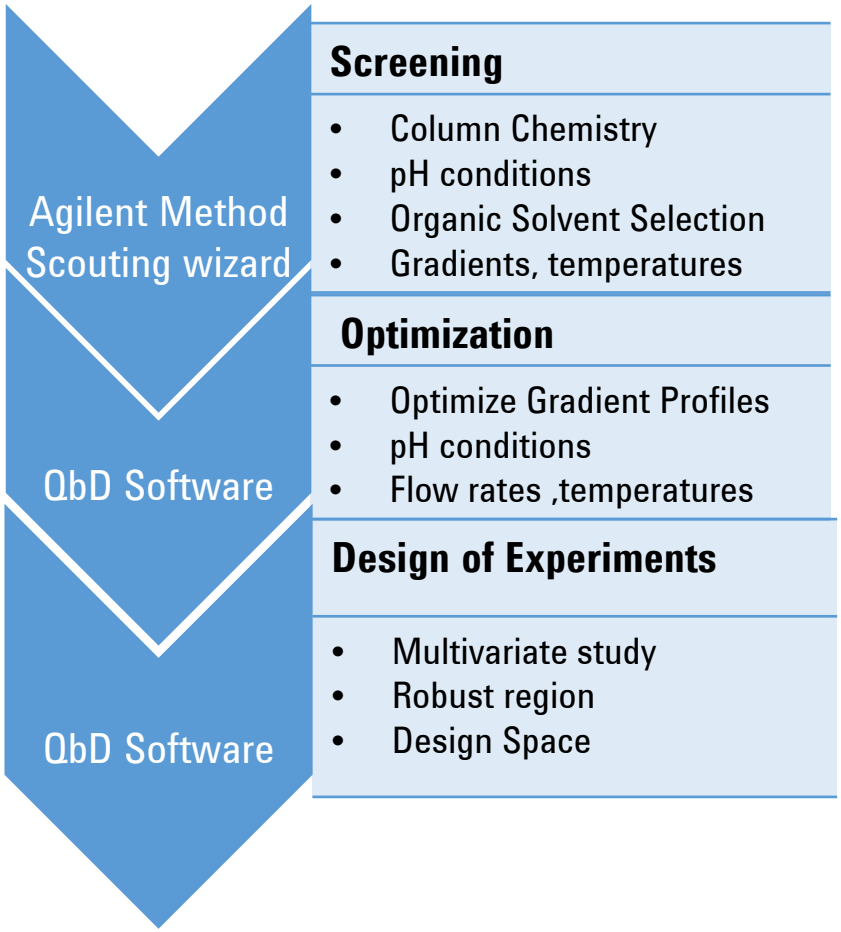
Results: peak purity and separation after optimization 99.8%



QbD Based Method Development Workflow

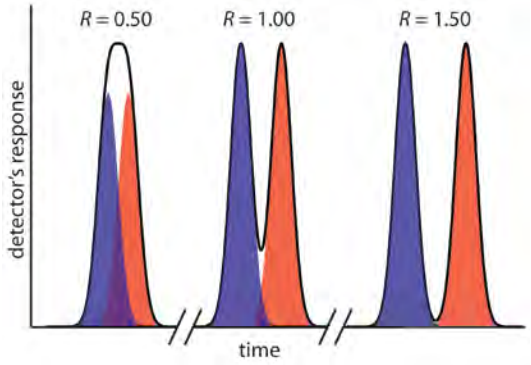
Overall workflow which consists of four main steps namely

- Step #1: Screening
- Step #2: Optimization
- Step #3: Robustness study

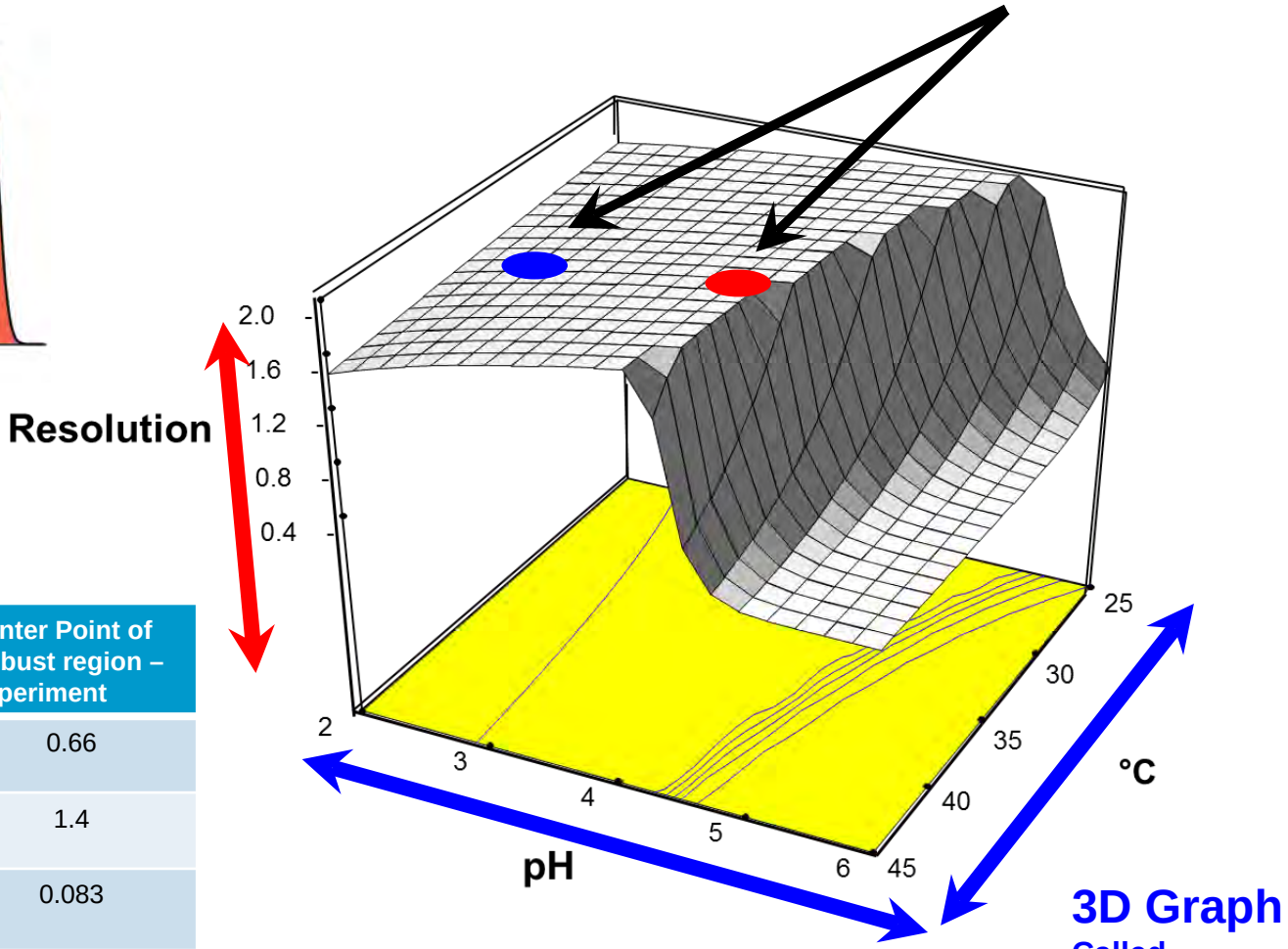


Step # 3: Design of Experiments

Investigate multivariate relationships



Moving critical pair in a more robust region



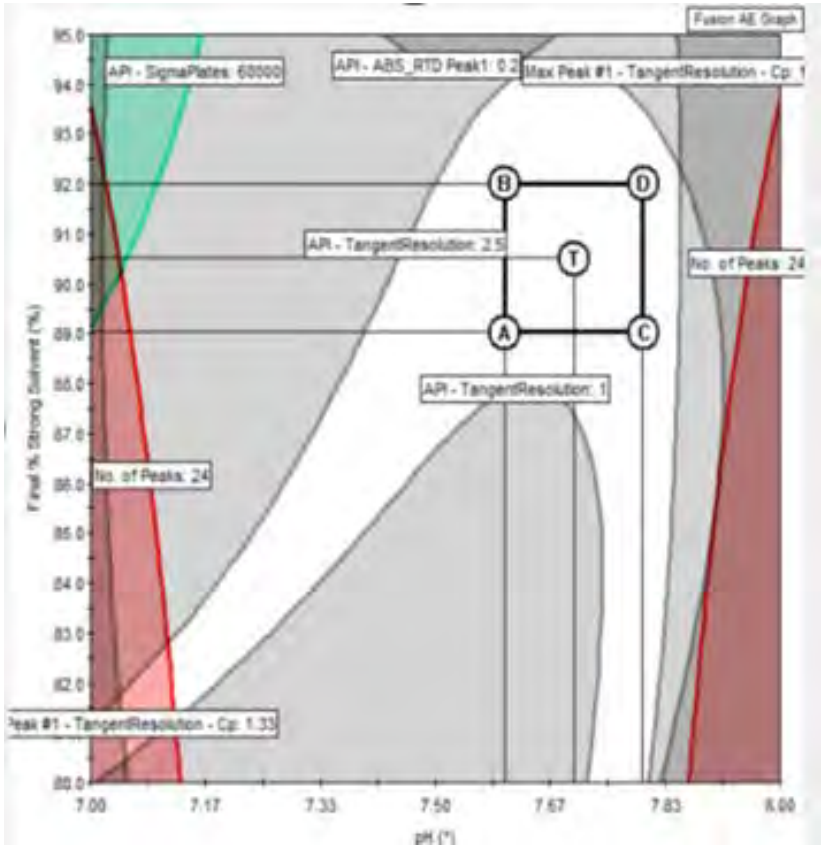
3D Graph
Called Response Surface

Optimized Parameters

	Center Point of Robust region – Prediction	Center Point of Robust region – Experiment
API-Symmetry	0.71±0.04	0.66
API-tailing USP	1.4±0.07	1.4
API-Tangent Width	0.081±0.004	0.083
API-Resolution	2.3±0.3	2.0

Step #3 : Design of Experiments
Results: Design Space

Critical Method Parameters (CMPs)	Proven Acceptable Range (PARs)	Critical Method Attributes (CMAs)
Column: Agilent ZORBAX RRHD Eclipse Plus C8 3.0X50 mm, 1.8 µm		**No. of peaks (>40)** **API resolution (>1.5)** **Peak purity (≥ 98%)** **Peak tailing (<1.5)**
Strong solvent: Methanol		
% Strong solvent: 90.5%	± 1.5%	
Aqueous solvent pH: 7.7	± 0.1	
Gradient range: 5% to 90.5%		
Oven Temperature: 45°C		
Gradient time: 15 min		
Flow rate: 0.6 mL/min		
Wavelength: 292 nm		



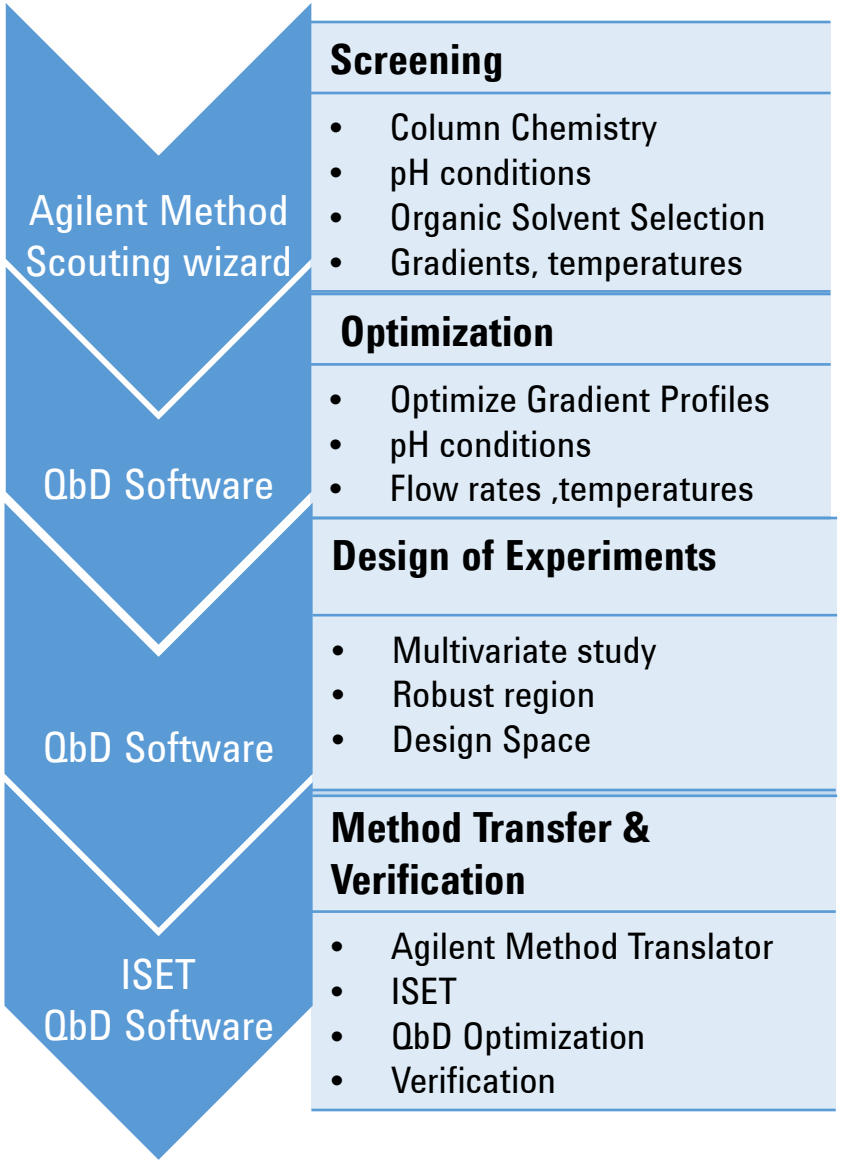
CMAs to create a Design Space

- ✓ The Design Space is a region in which changes to method parameters will not significantly affect the results.

QbD Based Method Development Workflow

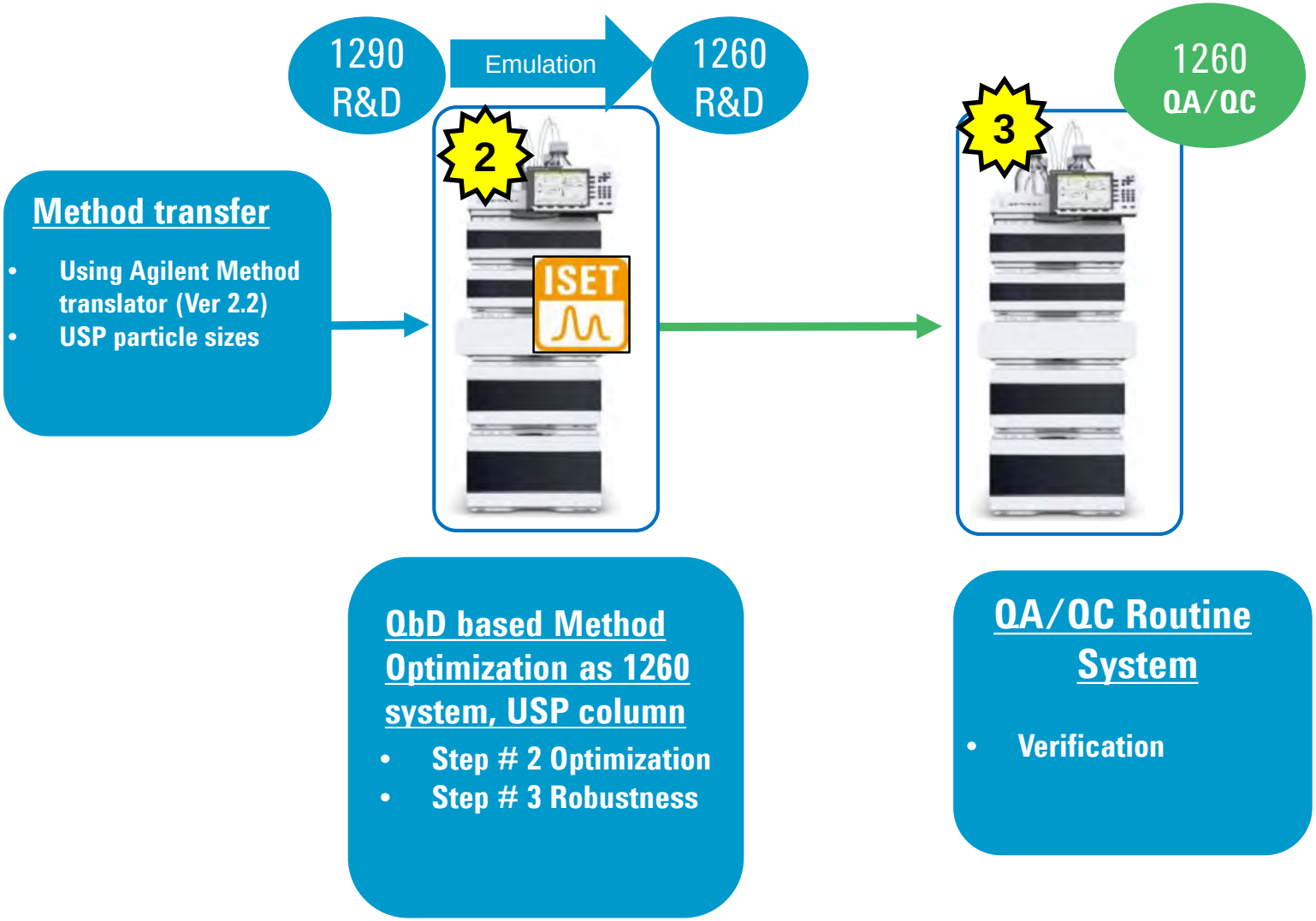
Overall workflow which consists of four main steps namely

- Step #1: Screening
- Step #2: Optimization
- Step #3: Robustness study
- Step #4: Method Transfer & Verification



Step # 4: Method Transfer & Verification

From UHPLC to HPLC



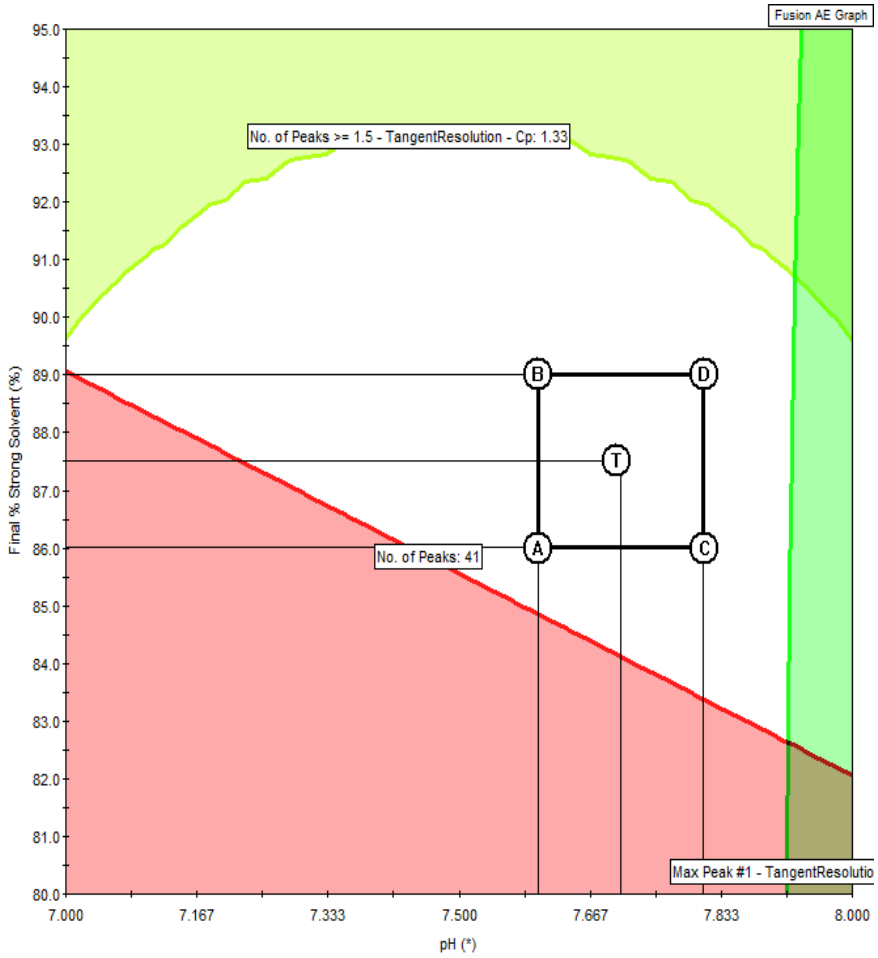
Robustness Study After Transfer

Modeling a HPLC design space on an emulated 1260 system

HPLC design space parameters

Critical Method Parameters (CMPs)	Proven Acceptable Range (PARs)	Critical Method Attributes (CMAs)
Column: Agilent ZORBAX Eclipse Plus C8 4.6X150 mm, 3.5 µm		**No. of peaks (>40)** **API resolution (>4)** **Peak purity (≥ 98%)** **Peak tailing (<1.3)**
Strong solvent: Methanol		
% Strong solvent: 87.5.%	± 1.5%	
Aqueous solvent pH: 7.7	± 0.1	
Gradient range: 5% to 87.5%		
Oven Temperature: 37°C		
Gradient time: 45 min		
Flow rate: 1.4 mL/min		
Wavelength: 292 nm		

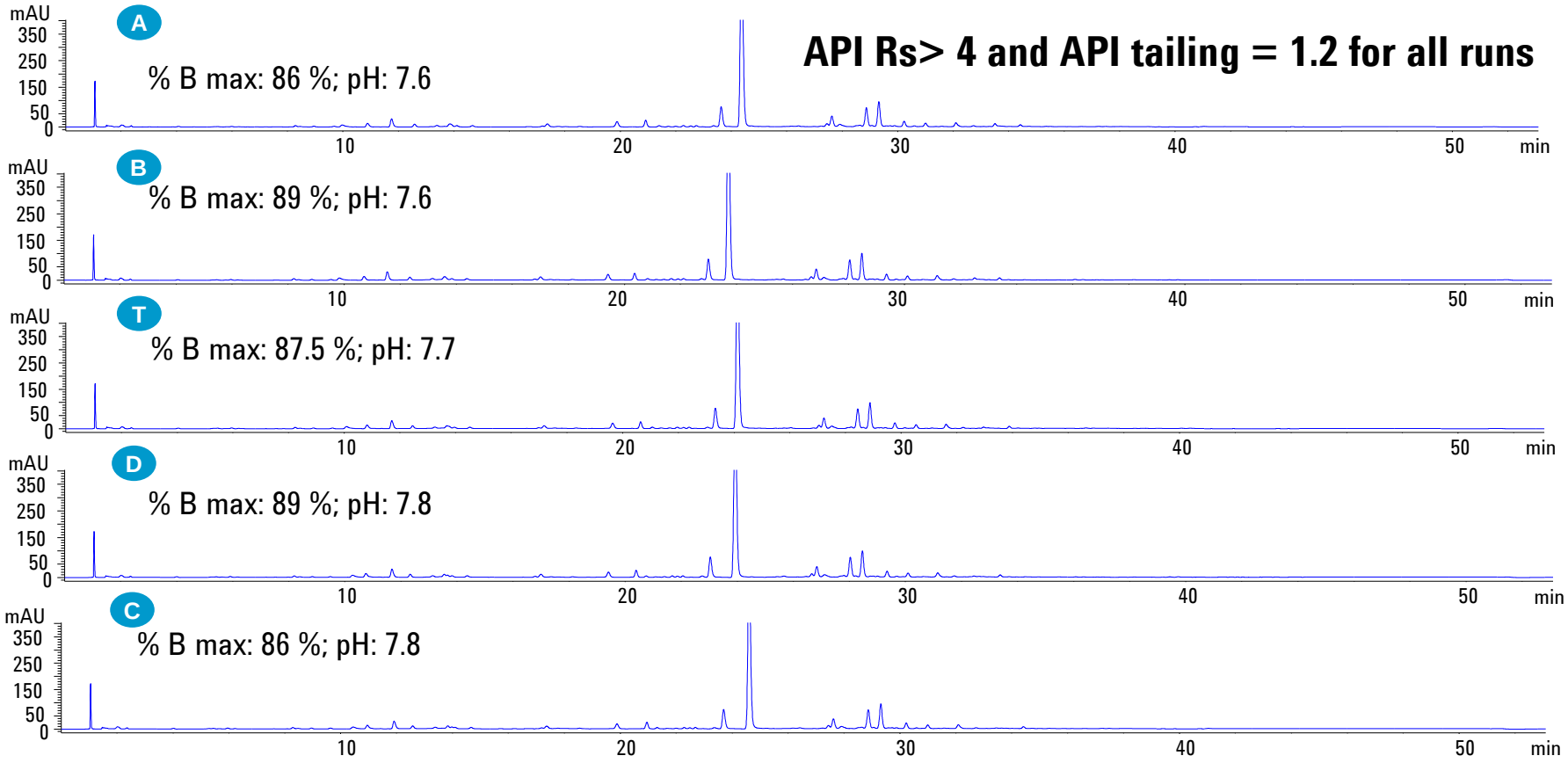
HPLC design space with new CMA values



Proof Of Robustness After Transfer

Conditions applied from center point and the four corner points of the Design Space

Critical Method Attributes are within the design space



Overall Summary

- QbD is a state of the art approach to remove variability of analytical methods
- ISET enables cross platform method development workflows
- Method Scouting Wizard Software enables even non expert chromatographers to develop robust methods
- The combination of ISET, Method Scouting Wizard Software and QbD software provides a unique and efficient way to develop and transfer robust methods

QbD based Method Development: Agilent Application Notes

- Quality-by-Design Approach to Stability Indicating Method Development for Linagliptin Drug Product
  - Agilent Application Note 5991-3834EN
- Automated QbD Based Method Development and Validation of Oxidative Degraded Atorvastatin
  - Agilent Application Note 5991-4944EN
- Development of an UHPLC Method for Azithromycin Tablets Using ChromSword Auto Software
  - Agilent Application Note 5991-5428EN

Key Points

Quality by Design (QbD) Solutions for Analytical Method Development

- Agilent 1290 Infinity Series Method Development Solutions support automated method development workflows

- Method transfers from Agilent 1290 Infinity Series UHPLC systems to other (U)HPLC systems are seamless by ISET (Intelligent System Emulation Technology)

- 1290 Infinity Series Method Development Solutions in combination with ISET and additional QbD software are supporting fast method development processes and method transfers to other (U)HPLC systems under QbD aspects

- Agilent Remote Advisor and ACE are excellent solutions to support method development workflows under QbD aspects for regulated environments

THANK YOU

Questions ?