Quality by Design (QbD) Solutions for Analytical Method Development

A systematic approach to reducing variability

Andreas Tei
Pharmaceutical Segment Manager
Agilent CrossLab Group
Content

- **Introduction**
  - Traditional approach of method development and transfer
  - QbD approach for method development

- **Agilent solutions for method development**
  - Agilent method development systems
  - Intelligent system emulation technology (ISET)
  - Method scouting wizard software
  - Third party QbD software

- **A practical approach of method development under QbD principles**
  - Screening
  - Optimization
  - Robustness study, Design of Experiments
  - Transfer & Verification
Quality by Design - A systematic approach to obtain a “consistent quality” output

ICH Q8-Q11

ICH = The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
QbD in analytical method development

- Analytical method development is an important part of the drug development process therefore the quality principles which have been described in the ICH guideline Q8 (R2) should be implemented to eliminate risks or failures.


(ICH = International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Founded in 1990 by an FDA initiative)
Traditional Development and Transfer of Methods
A chromatographic challenge!

Parameters determined by the trial-and error and OFAT approach.

- Slope 14.5% min MeOH
- pH 7 +/- 0.2
- 45°C +/- 2
- 1.0 mL/min +/- 0.1

± 50%  
± 0.2  
± 10%  
± 10%  
± 10°C
OFAT Approach: Method Transfer is a balancing act

- **Variability of critical method attributes (resolution, tailing, etc)**
- **Small changes in pH, temperature or flow rate shows a large effect**
- **Even buffer solutions from different operators deliver different results**

10% of analytical methods are discarded per year to avoid high revalidation costs after the method showed instabilities on the QC system.
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

• A list of critical method parameters (**CMPs**- flow rate, temperature etc.) and critical method attributes (**CMAs**- resolution, peak tailing etc.) has to be determined

• Key is the statistical “Design of Experiment” (**DoE**) where multiple **CMPs** will be varied in each experiment with the goal to create a Design Space

• The meaning of a Design Space has been defined in the ICH Q8 (R2) guideline
One-Factor-At-The-Time (OFAT) vs. DoE Approach

Impact of CMPs (e.g., %org phase, col temp, pH) on CMAs (e.g. peak resolution, symmetry, tailing factor) is measured
DoE: Modifying different variables while keeping other set points

- Col temp (°C): 30, 40
- Flow rate (ml/min): 0.8, 1.6
- % organic phase (methanol): 10, 20
- Inj. Volume (µl): 0.6, 3.0

Surface Plot to visualize the location of the optimum parameter set

CMAs:
- Resolution
- Max number of peaks
- ASP tailing factor
- Symmetry
Creating a Design Space

The Design Space as a result of a multivariate analysis

The contour plot indicates the robust region based on the results of the multivariate study (example data: Fusion QbD Software (S-Matrix))

List of CMPs and CMAs for robustness testing

<table>
<thead>
<tr>
<th>CMV</th>
<th>Coded name*</th>
<th>Method nominal</th>
<th>Robust range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pump flow rate (mL/min)</td>
<td>A</td>
<td>0.6</td>
<td>± 0.01</td>
</tr>
<tr>
<td>Oven temperature (°C)</td>
<td>B</td>
<td>33</td>
<td>± 1</td>
</tr>
<tr>
<td>pH</td>
<td>C</td>
<td>6.76</td>
<td>± 0.1</td>
</tr>
<tr>
<td>Buffer concentration (mM)</td>
<td>D</td>
<td>10</td>
<td>± 0.5</td>
</tr>
<tr>
<td>Injection volume</td>
<td>E</td>
<td>1</td>
<td>± 0.1</td>
</tr>
</tbody>
</table>

*Coded name used in models showing multiple interactions

<table>
<thead>
<tr>
<th>CMA</th>
<th>Mean</th>
<th>RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>API tangent resolution</td>
<td>2.7</td>
<td>3.3 %</td>
</tr>
<tr>
<td>API area</td>
<td>4,504.5</td>
<td>1.9 %</td>
</tr>
<tr>
<td>API RT</td>
<td>10.0</td>
<td>0.7 %</td>
</tr>
<tr>
<td>ADPK RT*</td>
<td>9.2</td>
<td>0.67 %</td>
</tr>
</tbody>
</table>

*Adjacent peak

* The coded names are used in robustness model displays
Advantages of the QbD approach

- **DoE** is leading to process and method understanding as the relationship between the different critical method parameters will be described and visualized in surface or contour plots.

- **DoE** is increasing the efficiency by avoiding unnecessary experiments during the method development process as often optimized and robust conditions are only found by chance using the classic trial-and-error and **OFAT** approaches.
POLLING
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  - Intelligent system emulation technology (ISET)
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  - Optimization
  - Robustness study, Design of Experiments
  - Transfer & Verification
Agilent Solutions for QbD Method Development

- **Harmonized Qualification**
  - ACE
  - Equipment Qualification Report
- **Intelligent System Emulation Technology**
  - ISET
- **Method Development System & Method Scouting SW**
  - Remote Advisor
• 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 Infinity I System

1290 Infinity II System

Multi Column Thermostat (MCT)
Intelligent System Emulation Technology (ISET)

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

PO-Nr. G2197AA
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 retention time and resolution.

Example: Method Transfer from a 1290 UHPLC to a 1100 HPLC system
Approach #1: Applying Isocratic Holding Steps

Results

- Results show still inconsistent results
- Requires a 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>)
Approach # 2: Adding a Physical Void Volume

Results

- Results show a good consistency
- Requires a manual determination of dwell volumes (issues of a variable dwell volumes when membrane dampeners are present)
- All mechanical changes are laboriously not flexible
Agilent Solution: Intelligent System Emulation Technology (ISET)

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

Injection

Graph showing mAU vs. min with programmed gradient, 1290 gradient, and 1200 gradient.
Agilent Solution: Method Transfer by ISET

Results: 1260 Infinity Binary LC to 1290 Infinity LC

• Consistency of results
Practical aspects how to measure dwell volumes, transfer & optimize methods
Automated Method Development Software
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

- **Check results at a glance**
  Integrated browser to view all results at a glance

PO-Nr. G2196AA
Method Transfer from UHPLC to HPLC

Agilent Method Translator

www.agilent.com/chem/1200calculator

HPLC Calculator v3.0
http://www.unige.ch/sciences/pharm/fanal/lcap/telechargement.htm

Crawford Scientific Calculator
Add-on Software Options for QbD Method Development

**ChromSword**
- Minimizes effect of human factors by studying method robustness.
- Tests effects of method variables on resolution and other parameters.
- Explores the design space of your method through changing simultaneously up to 7 method variables.
- Fully documents all method development and robustness study steps to meet regulatory compliance.

**AutoChrom (ACD Labs)**

**Fusion QbD (S-Matrix)**
- Statistical Experimental Design (OED)
- Ready to Run Methods & Sequences
- Automated, Audited Data Exchanges
- Automated analysis, graphing, and reporting.
- Report output formats: RTF, DOC, HTML, PDF.
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QbD Method Development & Method Transfer Workflow
From UHPLC to HPLC in a nutshell

1. Method development
   System
   Use of 1.8 µm particles
   and QbD software

2. Target System
   Emulation by ISET
   Robustness study
   by QbD software

3. Target Systems
   in QA/QC labs
QbD Based Method Development Workflow

Overall workflow which consists of four main steps namely

• Step # 1: Screening

<table>
<thead>
<tr>
<th>Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Column Chemistry</td>
</tr>
<tr>
<td>• pH conditions</td>
</tr>
<tr>
<td>• Organic Solvent</td>
</tr>
<tr>
<td>Selection</td>
</tr>
<tr>
<td>• Gradients,</td>
</tr>
<tr>
<td>temperatures</td>
</tr>
</tbody>
</table>
Step # 1: Screening Results

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
QbD Based Method Development Workflow

Overall workflow which consists of four main steps namely

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

**Screening**
- Column Chemistry
- pH conditions
- Organic Solvent Selection
- Gradients, temperatures

**Optimization**
- Optimize Gradient Profiles
- pH conditions
- Flow rates, temperatures
Step # 2: Optimization
Fusion AE QbD Software

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

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

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

- **Fusion AE QbD Software**
- **Optimization of flow rate, gradient slope, pH, column temperature**

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</table>
Step # 2: Optimization
Results: peak purity and separation after optimization 99.8%
Overall workflow which consists of four main steps namely

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

### Screening
- Column Chemistry
- pH conditions
- Organic Solvent Selection
- Gradients, temperatures

### Optimization
- Optimize Gradient Profiles
- pH conditions
- Flow rates, temperatures

### Design of Experiments
- Multivariate study
- Robust region
- Design Space
### Step #3: Design of Experiments

#### Results: Design Space

<table>
<thead>
<tr>
<th>Critical Method Parameters (CMPs)</th>
<th>Proven Acceptable Range (PARs)</th>
<th>Critical Method Attributes (CMAs)</th>
</tr>
</thead>
</table>
| 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) | **CMAs to create a Design Space**  
✓ The Design Space is a region in which changes to method parameters will not significantly affect the results. |
| 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 | | |
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

Method transfer

Target System Emulation by ISET
Robustness study by QbD software

1290 R&D
Emulation
1260 R&D

1260 QA/QC

2

Target Systems in QA/QC lab Verification
Robustness Study After Transfer
Modeling a HPLC design space on an emulated 1260 system

### HPLC design space parameters

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

![HPLC design space with new CMA](image)
Proof Of Robustness After Transfer

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

Critical Method Attributes remain within the limits

API Rs> 4 and API tailing = 1.2 for all runs

A
% B max: 86 %; pH: 7.6

B
% B max: 89 %; pH: 7.6

C
% B max: 86 %; pH: 7.8

D
% B max: 89 %; pH: 7.8

T
% B max: 87.5 %; pH: 7.7
Verification Of The Final Method with the Target System

Results: 1260 Infinity data compared to 1290 Infinity data in emulation mode

1260 target system

API Rs = 4.1
API tailing = 1.2

1290 emulated as 1260

API Rs = 4.2
API tailing = 1.2

Critical Method Attributes are within the defined limits
Title: QbD Based Method Development on an Agilent 1290 Infinity UHPLC system Combined with a Seamless Method Transfer to HPLC Using Intelligent System Emulation Technology

Type: Application Note

Publication Number: 5991-5701EN

Pages: 8

Target segments: Pharmaceutical QA/QC

Language: English

Author: Vinayak A.K.

LitStation Availability: May 5, 2015, CPOD
Conclusion

- Due to shorter runtimes when using sub-2-micron columns the efficiency of the method development process has been increased

<table>
<thead>
<tr>
<th>Experiments</th>
<th>Sub-2-µm columns (time in hours)</th>
<th>Conventional columns (time in hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>20</td>
<td>47</td>
</tr>
<tr>
<td>Optimization*</td>
<td>28*</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>67</td>
</tr>
</tbody>
</table>

- ISET can be used to emulate seamless different target systems

- QbD software has been applied to optimize the chromatographic conditions maximizing the resolution, purity and peak symmetry

- A multivariate study is used to create a design space compensating any unforeseen variables yet delivering consistent results

*An extra HPLC optimization time is added after the method transfer to conventional particle sizes to optimize CMAs.
POLLING
THANK YOU
## Appendix
### Analytical QbD Terminology

<table>
<thead>
<tr>
<th>QbD process terminology</th>
<th>Analytical QbD terminology</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Target Product Profile (QTPP)</td>
<td>Analytical Target Profile (ATP)</td>
<td>Accurate quantitation of API without interferences from degradants</td>
</tr>
<tr>
<td>Critical Process Parameters (CPP)</td>
<td>Quality Target Method Profile (QTMP)</td>
<td>pKa, Log P, Solubility</td>
</tr>
<tr>
<td>Critical Quality Attributes (CQA)</td>
<td>Critical Method Parameters (CMP)</td>
<td>Flow rate, Temperature, pH</td>
</tr>
<tr>
<td></td>
<td>Critical Method Attributes (CMA)</td>
<td>Resolution, Peak Tailing, Peak Capacity</td>
</tr>
<tr>
<td></td>
<td>Control Strategy</td>
<td>pH ± 0.1; Wavelength ± 2 nm</td>
</tr>
</tbody>
</table>
Appendix: Agilent Application Notes
Method Transfer by ISET

- 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*
Appendix: Agilent Application Notes
QbD based Method Development

- 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

- QbD Based Method Development on an Agilent 1290 Infinity UHPLC system Combined with a Seamless Method Transfer to HPLC Using Intelligent System Emulation Technology
  - Agilent Application Note 5991-5701EN