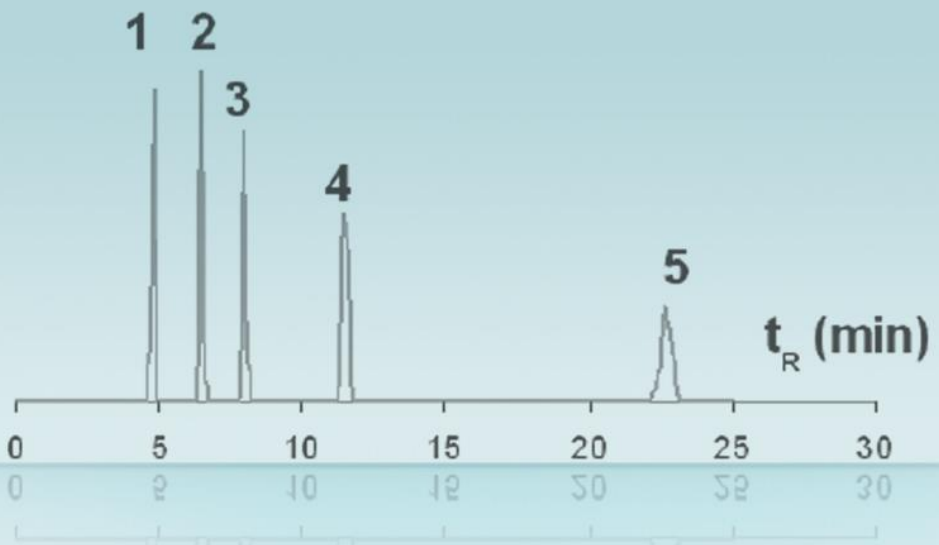



# Approche QbD pour le développement de méthodes robustes et flexibles : apport du logiciel Fusion QbD™

# INTRODUCTION – GENERALITES aQbD

**Space Design (=Method Operable Design Region = MODR)**

C'est le domaine multidimensionnel dans lequel il est démontré que les interactions des variables d'entrées et des paramètres de processus permettent d'avoir l'assurance de la qualité.

**Travailler dans cet espace n'est pas considéré comme un changement**.

Le déplacement hors de l'espace de conception est considéré comme un changement et devrait normalement initier un processus de changement d'approbation post-réglementaire.

[ICH Q8(R2) - Guidance for Industry, Pharmaceutical Development, August, 2009]

# INTRODUCTION – GENERALITES aQbD

## Le système LC peut être assimilé à un procédé

**Critical "Process" Parameters (CPPs)**
**Or Critical "Method" Parameters (CMPs)**

**Critical Quality Attribute (CQA)**
**Or Critical Method Attribute (CMA)**

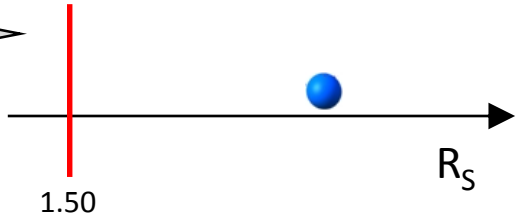
Temps Gradient
**(5.50 min)**

pH
**(2.7)**

Température colonne
**(34° C)**

● = un résultat

**Une injection = une mise en œuvre du procédé**




Seuil de rejet

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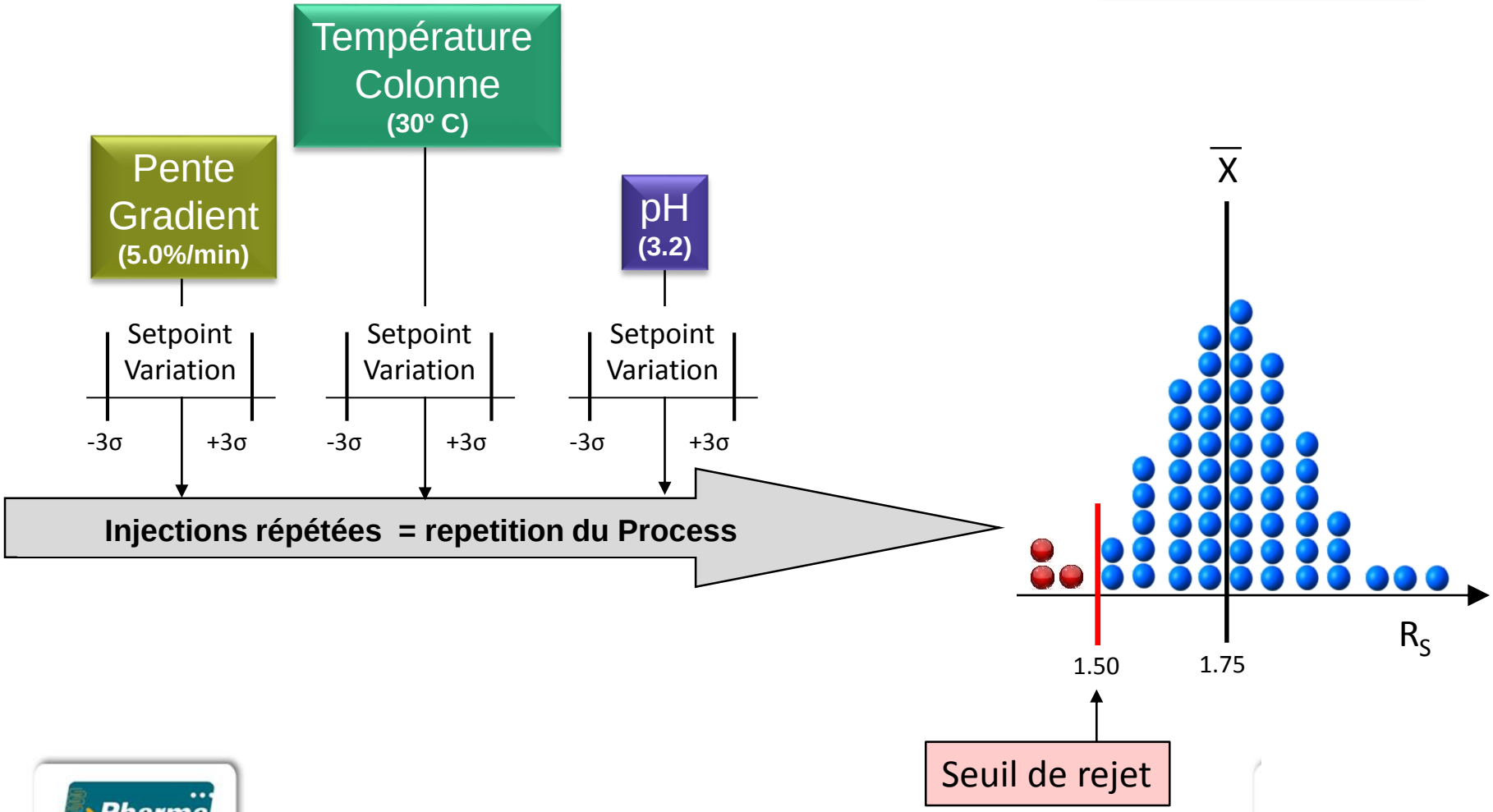
# INTRODUCTION – GENERALITES aQbD

**Critical "Method" Parameters (CMPs)**

**Critical Method Attribute (CMA)**

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# Liste des CMP potentiels

**Les facteurs possibles:**
(CMP)

la nature de la phase stationnaire
la nature des particules (poreuses/noyaux dur)
la longueur de la colonne
la taille des particules
l'âge de la colonne (historique)
le débit
le pH et la nature du tampon
la nature du solvant organique
la programmation du gradient
la longueur d'onde de détection
la température de la colonne
le volume d'injection
la chaine de mesure
….

# Analyse de risque

| | Réponses = CMA | | | | | SCORE |
|---|---|---|---|---|---|---|
| | Séléctivité | Résolution | k’ | Signal/bruit | Tailing | |
| *Pondération CMA* | *10* | *10* | *10* | *10* | *10* | |
| nature du tampon | 10 | 10 | 10 | 10 | 10 | **500** |
| nature du solvant organique | 10 | 10 | 10 | 10 | 10 | **500** |
| phase stationnaire | 10 | 10 | 10 | 1 | 10 | **410** |
| pH | 10 | 10 | 10 | 1 | 10 | **410** |
| programmation du gradient | 5 | 5 | 10 | 5 | 10 | **350** |
| température de la colonne | 5 | 5 | 5 | 5 | 5 | **250** |
| débit | 1 | 5 | 10 | 1 | 5 | **220** |
| âge de la colonne (historique) | 1 | 5 | 5 | 1 | 10 | **220** |
| volume d’injection | 1 | 5 | 1 | 10 | 5 | **220** |
| taille des particules | 1 | 5 | 5 | 5 | 5 | **210** |
| longueur de la colonne | 1 | 5 | 10 | 1 | 1 | **180** |
| particules (poreuses/noyaux dur) | 1 | 5 | 1 | 5 | 5 | **170** |
| longueur d’onde de détection | 1 | 1 | 1 | 10 | 1 | **140** |
| chaine de mesure | 1 | 1 | 5 | 5 | 1 | **130** |

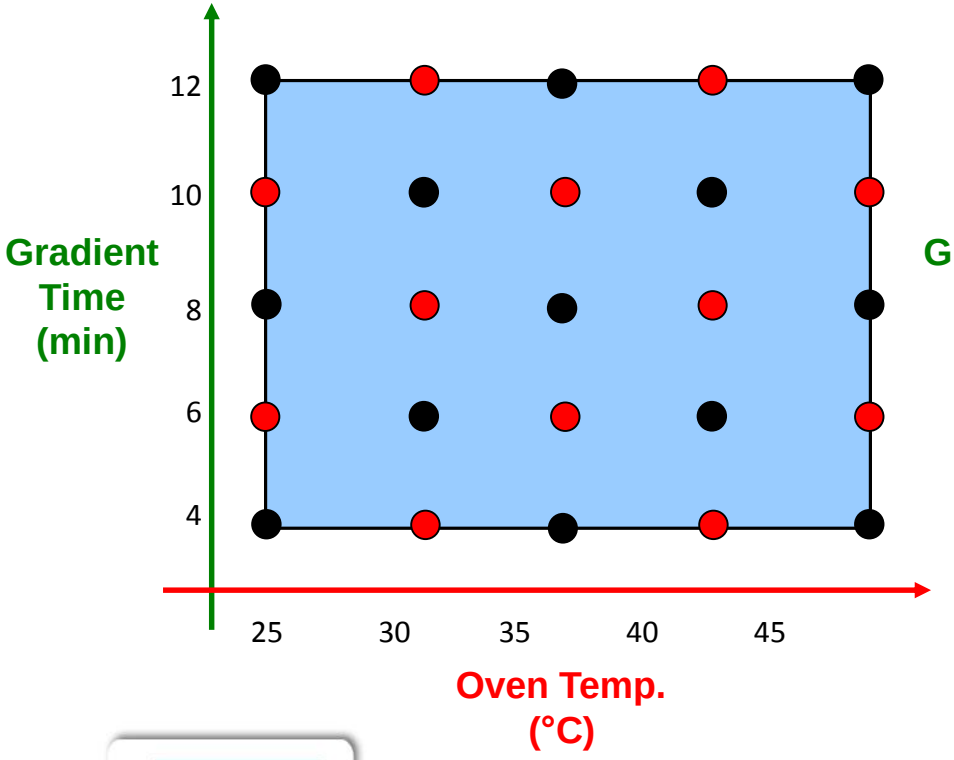
# Analyse de risque

| | Réponses = CMA | | | | | SCORE |
|---|---|---|---|---|---|---|
| | Séléctivité | Résolution | k' | Signal/bruit | Tailing | |
| *Pondération CMA* | *10* | *10* | *10* | *1* | *1* | |
| nature du tampon | 10 | 10 | 10 | 10 | 10 | **320** |
| nature du solvant organique | 10 | 10 | 10 | 10 | 10 | **320** |
| phase stationnaire | 10 | 10 | 10 | 1 | 10 | **311** |
| pH | 10 | 10 | 10 | 1 | 10 | **311** |
| programmation du gradient | 5 | 5 | 10 | 5 | 10 | **215** |
| débit | 1 | 5 | 10 | 1 | 5 | **166** |
| longueur de la colonne | 1 | 5 | 10 | 1 | 1 | **162** |
| température de la colonne | 5 | 5 | 5 | 5 | 5 | **160** |
| âge de la colonne (historique) | 1 | 5 | 5 | 1 | 10 | **121** |
| taille des particules | 1 | 5 | 5 | 5 | 5 | **120** |
| volume d'injection | 1 | 5 | 1 | 10 | 5 | **85** |
| particules (poreuses/noyaux dur) | 1 | 5 | 1 | 5 | 5 | **80** |
| chaine de mesure | 1 | 1 | 5 | 5 | 1 | **76** |
| longueur d'onde de détection | 1 | 1 | 1 | 10 | 1 | **41** |

## Exemple pour 2 variables et 5 niveaux étudiés

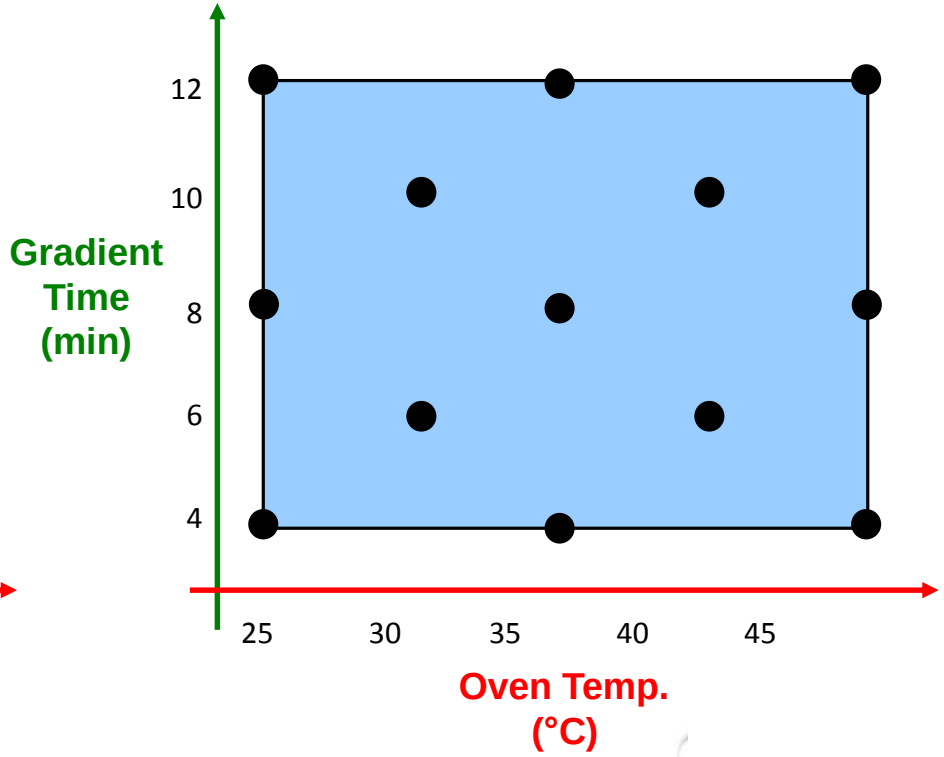
**OFAT = Toutes les combinaisons possibles**

**25 Methodes**




**DOE = Approche statistique**

**13 Methodes**

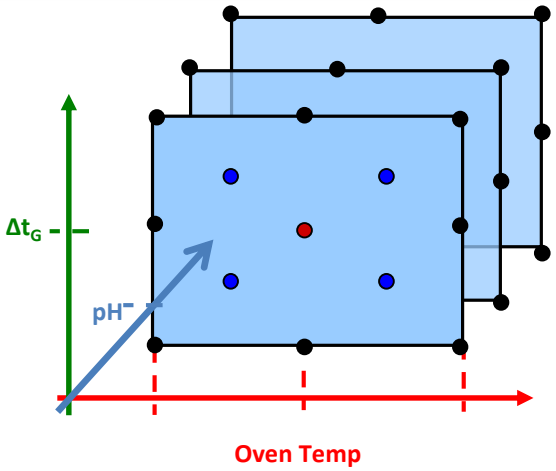



**OFAT** = **O**ne **F**actor **A**t a **T**ime

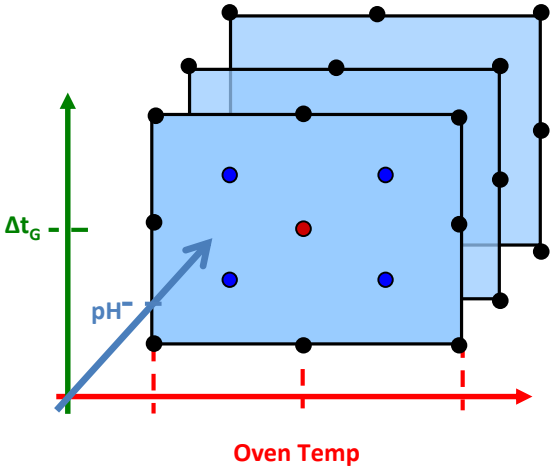
**DOE** = **D**esign **O**f **E**xperiments

# Mise en œuvre expérimentale

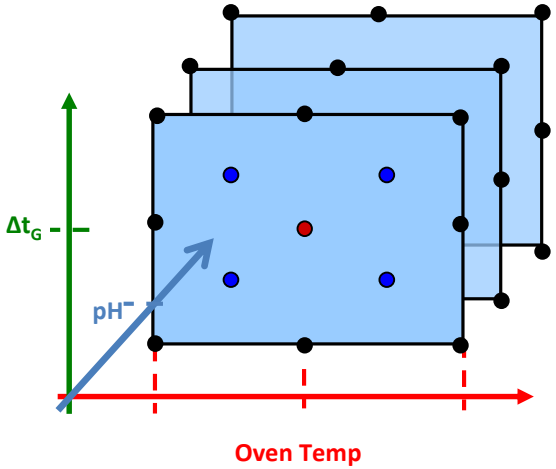
## 3eme Variable – pH



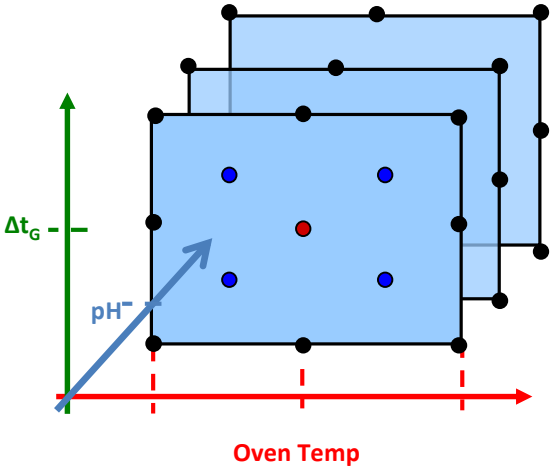

## 4eme Variable – Type de Colonne




C18




Phenyl




C8

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# Création d'un DOE – Utilisation de Fusion QbD

**Design of experiments (DOE)**

C'est une méthode systématique pour déterminer les relations entre les variables affectant un processus, Le DOE est utilisé pour trouver des relations de cause à effet à partir du traitement statistique des données.

## Fusion QbD

Intègre un **Assistant** qui sélectionne automatiquement le **DOE le plus efficace en fonction des paramètres choisi**

| | Run No. | Strong Solvent Type | Gradient Time | pH | Column Type |
|---|---|---|---|---|---|
| 1 | Condition Column - 1 | Acetonitrile | 4 | 2 | BEH C18 |
| 2 | Condition Column - 2 | Acetonitrile | 4 | 2 | BEH Shield RP18 |
| 3 | Condition Column - 3 | Acetonitrile | 4 | 2 | BEH Phenyl |
| 4 | Condition Column - 4 | Acetonitrile | 4 | 2 | BEH C8 |
| 5 | 1.a.1.a | Acetonitrile | 9 | 2 | BEH C18 |
| 6 | 2.a.1.a | Acetonitrile | 3 | 2 | BEH C18 |
| 7 | 3.a.1.a | Acetonitrile | 9 | 2 | BEH Shield RP18 |
| 8 | 4.a.1.a | Acetonitrile | 3 | 2 | BEH Shield RP18 |
| 9 | 5.a.1.a | Acetonitrile | 9 | 2 | BEH C8 |
| 10 | 6.a.1.a | Acetonitrile | 3 | 2 | BEH C18 |
| 11 | 7.a.1.a | Acetonitrile | 9 | 2 | BEH C8 |
| 12 | Condition Column - 5 | Acetonitrile | 4 | 2.89 | BEH C18 |
| 13 | Condition Column - 6 | Acetonitrile | 4 | 2.89 | BEH Shield RP18 |
| 14 | Condition Column - 7 | Acetonitrile | 4 | 2.89 | BEH Phenyl |
| 15 | Condition Column - 8 | Acetonitrile | 4 | 2.89 | BEH C8 |
| 16 | 8.a.1.a | Acetonitrile | 4.5 | 2.89 | BEH C8 |
| 17 | 9.a.1.a | Acetonitrile | 6 | 2.89 | BEH C18 |
| 18 | 10.a.1.a | Acetonitrile | 6 | 2.89 | BEH Shield RP18 |
| 19 | 11.a.1.a | Acetonitrile | 6 | 2.89 | BEH Phenyl |
| 20 | Condition Column - 9 | Acetonitrile | 4 | 4.16 | BEH C18 |
| 21 | Condition Column - 10 | Acetonitrile | 4 | 4.16 | BEH Shield RP18 |
| 22 | Condition Column - 11 | Acetonitrile | 4 | 4.16 | BEH Phenyl |
| 23 | Condition Column - 12 | Acetonitrile | 4 | 4.16 | BEH C8 |
| 24 | 12.a.1.a | Acetonitrile | 3 | 4.16 | BEH Phenyl |
| 25 | 13.a.1.a | Acetonitrile | 6 | 4.16 | BEH C18 |
| 26 | 14.a.1.a | Acetonitrile | 6 | 4.16 | BEH Shield RP18 |
| 27 | 15.a.1.a | Acetonitrile | 6 | 4.16 | BEH Phenyl |
| 28 | 16.a.1.a | Acetonitrile | 6 | 4.16 | BEH C8 |
| 29 | 17.a.1.a | Acetonitrile | 6 | 4.16 | BEH Phenyl |
| 30 | 18.a.1.a | Acetonitrile | 6 | 4.16 | BEH C8 |

# Création d'un DOE – Utilisation de Fusion QbD

**On retrouve ici les choix fait dans la définition du cadre général**

LC Method Development - Untitled1

File Edit Activity Tools Window Help

Select Instrument | Update Setup Data | Generate Design

Design of Experiments
- Create a Design
- Design Reports

Data Entry / Analysis
- Data Entry
- Data Analysis

Best Answer Searches
- Best Overall Answer
- Acceptable Performance Region
- Point Predictions

Visualization Graphics
- Single Response Series
- Multiple Response Series

Reporting Toolkit
- Fusion Reporter
- Audit Log Reporter

| Experiment Name | | Instrument Name | Experiment Phase | Experiment Type | Chromatography Type |
|---|---|---|---|---|---|
| Experiment 1 | Notes... | Fusion AE Tutorial UPLC | Method Development | Rapid Development 1 - Column/Solvent Screening | Reversed Phase (RPC) |

Experiment Setup | Sampling Plan

Method Type: Gradient

**Sélection du mode d' élution**

| Available Variables | Included Variables |
|---|---|
| Gradient Curve | Pump Flow Rate |
| Gradient Slope | Injection Volume |
| Sample Concentration | Oven Temperature |
| Buffer Concentration | Wavelength |
| Buffer Type | pH |

**Sélection des facteurs**

| Name | Units | Type | Amount |
|---|---|---|---|
| Pump Flow Rate | mL/min | Discrete Numeric | 0.500 |

State: Variable / Constant

| Name | Units | Type | Amount |
|---|---|---|---|
| Injection Volume | uL | Discrete Numeric | 10.0 |

State: Variable / Constant

Solvent Settings

No. of Strong Solvents: 1 | No. of Weak Solvents: 1

OK to Blend Strong Solvents | OK to Blend Weak Solvents | Mobile Phase Precision

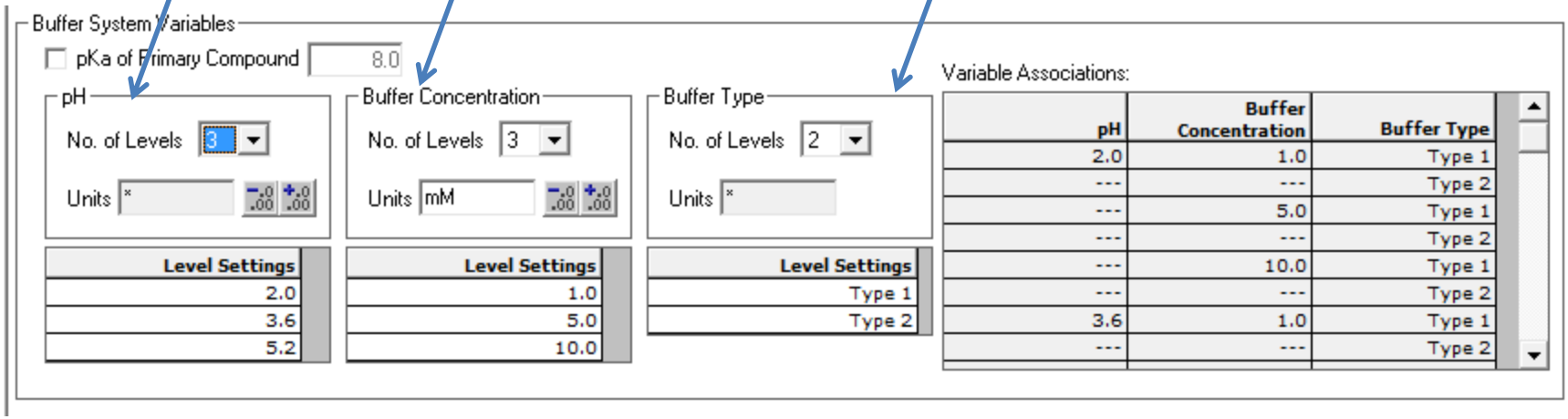
| Mobile Phase Name | Solvent Type | Reservoir |
|---|---|---|
| Acetonitrile | Strong (Organic) | B1 |
| Aqueous Solution | Weak (Aqueous) | A1 |

Available Reservoirs: A2, B1, B2, A1 (A1-1, A1-2, A1-3, A1-4, A1-5, A1-6)

**Définition (nature-domaine d'étude) de chaque facteur sélectionné**

# Création d'un DOE – Utilisation de Fusion QbD

**Les facteurs pH, concentration du tampon et nature du tampon apparaissent sur la même interface de réglage**



# Création d'un DOE – Utilisation de Fusion QbD

## Vue générale pour la définition des solvants et des paramètres de la pompe

**Solvent Settings**

No. of Strong Solvents: 1 — No. of Weak Solvents: 1

☐ OK to Blend Strong Solvents — ☐ OK to Blend Weak Solvents — Mobile Phase Precision

| Mobile Phase Name | Solvent Type | Reservoir |
|---|---|---|
| Acetonitrile | Strong (Organic) | A |
| Weak Solvent 1 | Weak (Aqueous) | --- |

**Available Reservoirs**

A, B, C, D — D-1, D-2, D-3, D-4, D-5, D-6

**Pump Program**

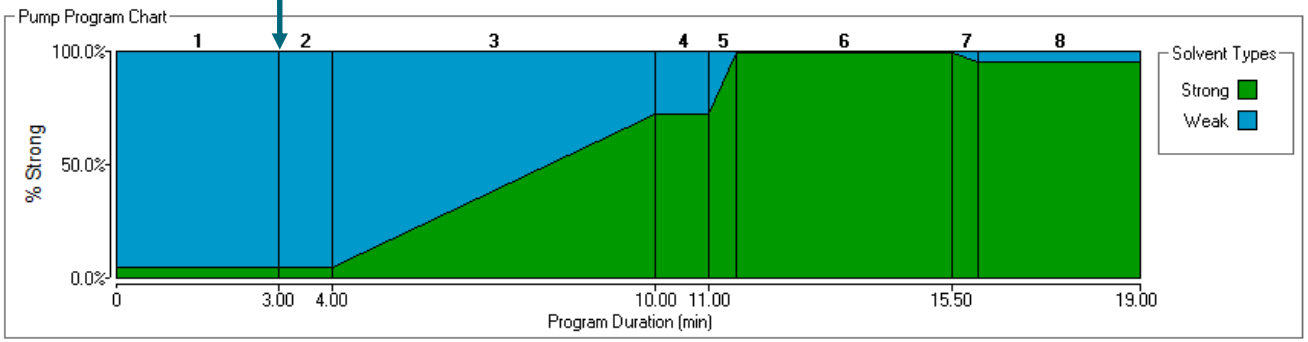
No. of Gradient Steps: 1 — Time Precision

| | No. | Step Name | Time State | Time - Lower Bound | Time - Upper Bound | % Strong Solvent |
|---|---|---|---|---|---|---|
| | 1 | Equilibration | Constant | 3.00 | --- | 5.0 |
| | 2 | Initial Hold | Constant | 1.00 | --- | 5.0 |
| | 3 | Gradient | Constant | 6.00 | --- | --- |
| | 4 | Final Hold | Constant | 1.00 | --- | 72.5 |
| | 5 | Ramp Up to Wash | Constant | 0.50 | --- | --- |
| ✓ | 6 | Column Wash | Constant | 4.00 | --- | 99.0 |
| | 7 | Ramp Down from Wash | Constant | 0.50 | --- | --- |
| ✓ | 8 | Re-equilibration | Constant | 3.00 | --- | 95.0 |

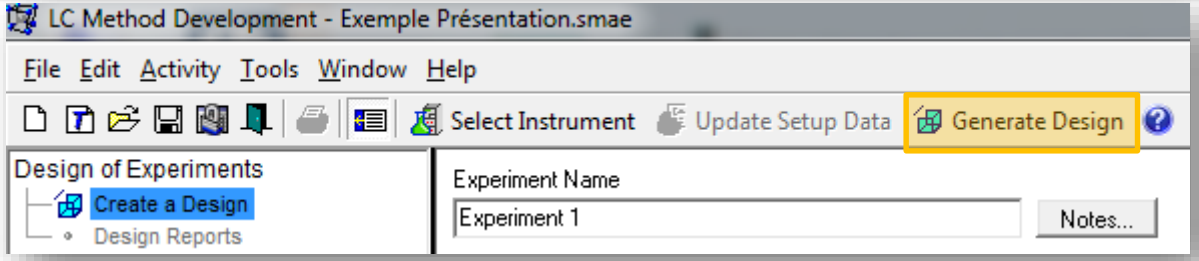
Program duration = 19.00 minutes

**injection**

**Pump Program Chart**



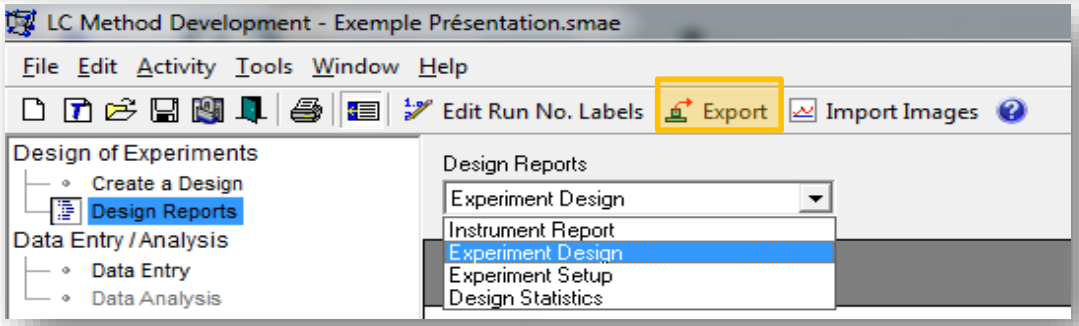
# Création d'un DOE – Utilisation de Fusion QbD

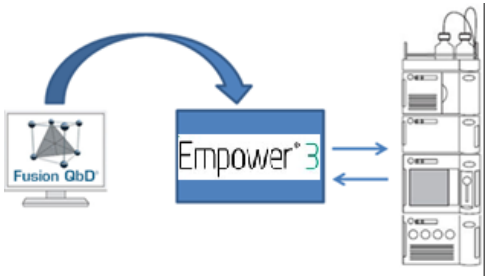


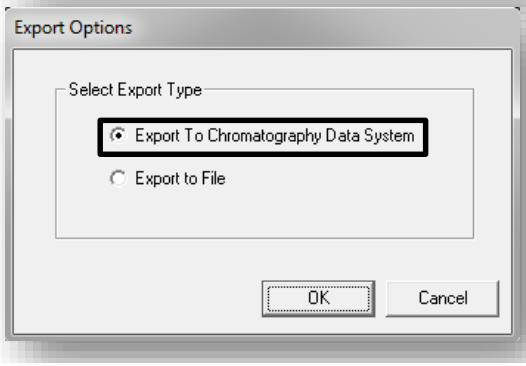

**Experiment Design Matrix**

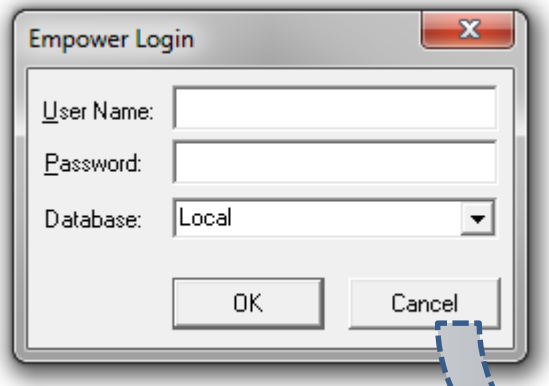
| Run No. | Sample Set No. | Gradient Time (min) | Oven Temperature (°C) | pH (*) | Column Type (*) |
|---|---|---|---|---|---|
| Condition Column - 1 | 1 | 2.0 | 30.0 | 2.0 | Column 1 |
| Condition Column - 2 | 1 | 2.0 | 30.0 | 2.0 | Column 2 |
| 1 | 1 | 8.0 | 30.0 | 2.0 | Column 1 |
| 2 | 1 | 4.0 | 30.0 | 2.0 | Column 2 |
| 3 | 1 | 2.0 | 30.0 | 2.0 | Column 1 |
| 4 | 1 | 10.0 | 30.0 | 2.0 | Column 2 |
| 5 | 1 | 2.0 | 30.0 | 2.0 | Column 1 |
| Condition Column - 3 | 1 | 2.0 | 30.0 | 3.6 | Column 1 |
| Condition Column - 4 | 1 | 2.0 | 30.0 | 3.6 | Column 2 |
| 6 | 1 | 8.0 | 30.0 | 3.6 | Column 2 |
| 7 | 1 | 10.0 | 30.0 | 3.6 | Column 1 |
| 8 | 1 | 2.0 | 30.0 | 3.6 | Column 2 |
| 9 | 1 | 4.0 | 30.0 | 3.6 | Column 1 |
| Condition Column - 5 | 1 | 2.0 | 40.0 | 2.0 | Column 1 |
| Condition Column - 6 | 1 | 2.0 | 40.0 | 2.0 | Column 2 |
| 10 | 1 | 6.0 | 40.0 | 2.0 | Column 1 |
| 11 | 1 | 6.0 | 40.0 | 2.0 | Column 2 |
| 12 | 1 | 6.0 | 40.0 | 2.0 | Column 1 |
| 13 | 1 | 6.0 | 40.0 | 2.0 | Column 2 |
| 14 | 1 | 10.0 | 40.0 | 2.0 | Column 1 |
| Condition Column - 7 | 1 | 2.0 | 40.0 | 3.6 | Column 1 |
| Condition Column - 8 | 1 | 2.0 | 40.0 | 3.6 | Column 2 |
| 15 | 1 | 10.0 | 40.0 | 3.6 | Column 2 |
| 16 | 1 | 2.0 | 40.0 | 3.6 | Column 1 |
| Condition Column - 9 | 1 | 2.0 | 60.0 | 2.0 | Column 1 |
| Condition Column - 10 | 1 | 2.0 | 60.0 | 2.0 | Column 2 |
| 17 | 1 | 6.0 | 60.0 | 2.0 | Column 1 |
| 18 | 1 | 2.0 | 60.0 | 2.0 | Column 1 |

# Exportation du plan vers la chaine de mesure



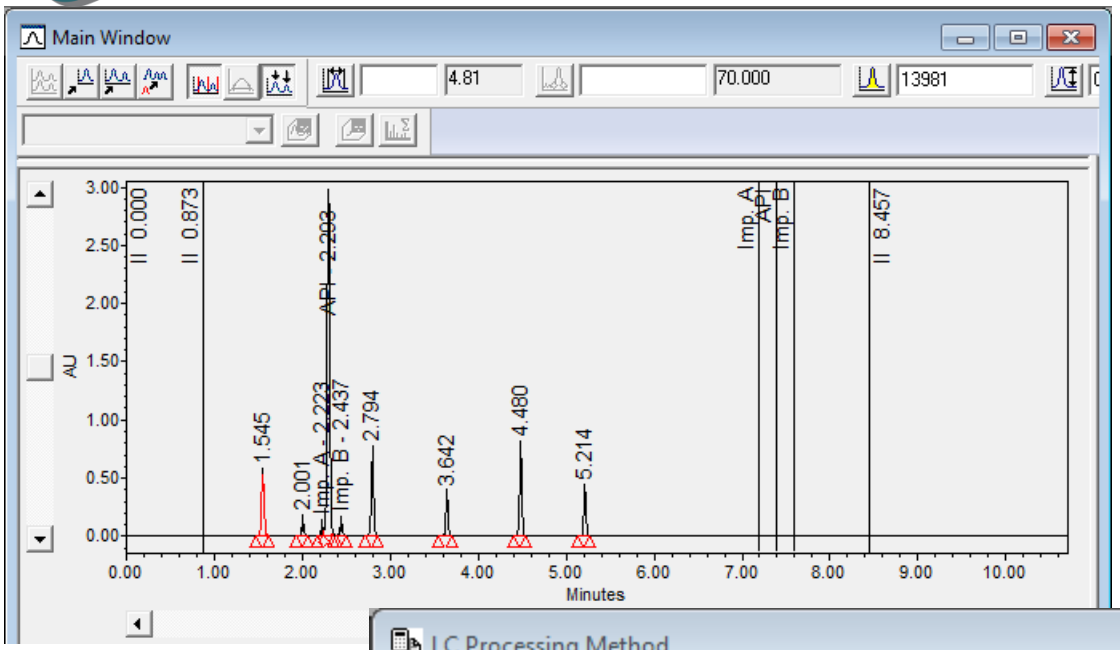




Sample Set Method: 231214_

| | Plate/Well | Inj Vol (uL) | # of Injs | Label | SampleName | Level | Function | Method Set / Report Method | Label Reference | Processing | Run Time (Minutes) | Data Start (Minutes) | Next Inj. Delay (Minutes) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | | | | | | Condition Column | 231214_ 001_014 | | | 5.10 | 0.00 | 0.00 |
| 2 | | | | | | | Equilibrate | 231214_ 001_001 | | | 15.00 | 0.00 | 0.00 |
| 3 | 1:A,1 | 1.0 | 1 | Unk-001-001 | 1 | | Inject Samples | 231214_ 001_001 | | Normal | 6.00 | 0.00 | 0.00 |
| 4 | | | | | | | Equilibrate | 231214_ 001_002 | | | 3.00 | 0.00 | 0.00 |
| 5 | 1:A,1 | 1.0 | 1 | Unk-001-002 | 2 | | Inject Samples | 231214_ 001_002 | | Normal | 6.00 | 0.00 | 0.00 |
| 6 | | | | | | | Equilibrate | 231214_ 001_003 | | | 3.00 | 0.00 | 0.00 |
| 7 | 1:A,1 | 1.0 | 1 | Unk-001-003 | 3 | | Inject Samples | 231214_ 001_003 | | Normal | 6.00 | 0.00 | 0.00 |
| 8 | | | | | | | Equilibrate | 231214_ 001_004 | | | 3.00 | 0.00 | 0.00 |
| 9 | 1:A,1 | 1.0 | 1 | Unk-001-004 | 4 | | Inject Samples | 231214_ 001_004 | | Normal | 6.00 | 0.00 | 0.00 |
| 10 | | | | | | | Equilibrate | 231214_ 001_005 | | | 3.00 | 0.00 | 0.00 |
| 11 | 1:A,1 | 1.0 | 1 | Unk-001-005 | 5 | | Inject Samples | 231214_ 001_005 | | Normal | 6.00 | 0.00 | 0.00 |
| 12 | | | | | | | Equilibrate | 231214_ 001_006 | | | 3.00 | 0.00 | 0.00 |
| 13 | 1:A,1 | 1.0 | 1 | Unk-001-006 | 6 | | Inject Samples | 231214_ 001_006 | | Normal | 6.00 | 0.00 | 0.00 |
| 14 | | | | | | | Equilibrate | 231214_ 001_007 | | | 3.00 | 0.00 | 0.00 |
| 15 | 1:A,1 | 1.0 | 1 | Unk-001-007 | 7 | | Inject Samples | 231214_ 001_007 | | Normal | 6.00 | 0.00 | 0.00 |
| 16 | | | | | | | Equilibrate | 231214_ 001_008 | | | 3.00 | 0.00 | 0.00 |
| 17 | 1:A,1 | 1.0 | 1 | Unk-001-008 | 8 | | Inject Samples | 231214_ 001_008 | | Normal | 6.00 | 0.00 | 0.00 |
| 18 | | | | | | | Equilibrate | 231214_ 001_009 | | | 3.00 | 0.00 | 0.00 |
| 19 | 1:A,1 | 1.0 | 1 | Unk-001-009 | 9 | | Inject Samples | 231214_ 001_009 | | Normal | 6.00 | 0.00 | 0.00 |
| 20 | | | | | | | Equilibrate | 231214_ 001_010 | | | 3.00 | 0.00 | 0.00 |
| 21 | 1:A,1 | 1.0 | 1 | Unk-001-010 | 10 | | Inject Samples | 231214_ 001_010 | | Normal | 6.00 | 0.00 | 0.00 |
| 22 | | | | | | | Equilibrate | 231214_ 001_011 | | | 3.00 | 0.00 | 0.00 |
| 23 | 1:A,1 | 1.0 | 1 | Unk-001-011 | 11 | | Inject Samples | 231214_ 001_011 | | Normal | 6.00 | 0.00 | 0.00 |
| 24 | | | | | | | Equilibrate | 231214_ 001_012 | | | 3.00 | 0.00 | 0.00 |
| 25 | 1:A,1 | 1.0 | 1 | Unk-001-012 | 12 | | Inject Samples | 231214_ 001_012 | | Normal | 6.00 | 0.00 | 0.00 |
| 26 | | | | | | | Equilibrate | 231214_ 001_013 | | | 3.00 | 0.00 | 0.00 |
| 27 | 1:A,1 | 1.0 | 1 | Unk-001-013 | 13 | | Inject Samples | 231214_ 001_013 | | Normal | 6.00 | 0.00 | 0.00 |
| 28 | | | | | | | Condition Column | 231214_ 001_015 | | | 5.10 | 0.00 | 0.00 |

# Mise en œuvre des analyses




LC Processing Method

Integration | Smoothing/Offset | **Components** | Peak Ratios (MS Ion Ratios) | Default Amounts | Named Groups | Tir

Average By: None — Update RT: Never

RT Window (%): 5.00 — CCalRef1:

☑ Include Internal Std Amounts in % Amount Calculation

Sample Value Type: Amount — Auto Peak Label

| E | Name | Peak Label | Retention Time (min) | RT Window (min) | Peak Match | Channel | Y Value | X Value | Fit | Weighting | Interna |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Imp. A | Imp. A | 7.200 | 0.350 | Closest | | Area | Amount | Linear | None | |
| 2 | API | API | 7.400 | 0.370 | Closest | | Area | Amount | Linear | None | |
| 3 | Imp. B | Imp. B | 7.600 | 0.380 | Closest | | Area | Amount | Linear | None | |

# Récupération des résultats des expériences

LC Method Development - MD Training - RD 1 - Import Design Demo File.smae

File Edit Activity Tools Window Help

Edit Run No. Labels | Matrix Master | Create/Edit Response Data | Export | Import Responses

Design of Experiments
- Create a Design
- Design Reports

Data Entry / Analysis
- Data Entry
- Data Analysis

Best Answer Searches
- Best Overall Answer
- Acceptable Performa

| | Run No. | Strong Solvent Type | Gradient Time | pH | Column Type |
|---|---|---|---|---|---|
| 1 | Condition Column - 1 | Acetonitrile | 0.2 | 2 | BEH C18 |
| 2 | Condition Column - 2 | Acetonitrile | 0.2 | 2 | BEH Shield RP18 |
| 3 | Condition Column - 3 | Acetonitrile | 0.2 | 2 | BEH C8 |

Select a Project and Result Set

Select Project

Find | Filter | Reset

- Projects
  - Customers
  - Distributors
  - S-Matrix
    - ADL
    - FIT
    - FMV - A_L_R
    - RD1 - Demo Screening Expt
    - RD2 - Demo Optimization Experi
    - Test

User Types

Owner

Available Result Sets

| ResultSetName | ResultSetId | ResultSetDate | ResultSampleS... |
|---|---|---|---|
| FMD Screening ... | 1597 | 3/7/2011 6:31:... | FMD Screening... |
| FMD Screening ... | 1654 | 3/7/2011 6:31:... | FMD Screening... |

Result Set Information

Result Set ID: 1597
5.a.1.a (1604)
7.a.1.a (1606)
8.a.1.a (1607)
6.a.1.a (1605)
9.a.1.a (1608)
10.a.1.a (1609)
11.a.1.a (1610)
12.a.1.a (1611)
13.a.1.a (1612)
14.a.1.a (1613)
15.a.1.a (1614)

Showing Select Results

Fetch Selected Result Sets | Next >> | Cancel | ?

**Sélection des résultats**

Pharma Physic

# Récupération des résultats des expériences

Select Responses

Channel:

PDA Ch1 254nm@1.2nm

☑ Import Chromatogram Trace Data

☑ Import Prediction Chromatogram Data

Trend Responses

Add | Delete | Undo Changes | Restore Defaults

| | | Operator | Value | Response |
|---|---|---|---|---|
| 1 | ☑ | No. of Peaks | | |
| 2 | ☑ | No. of Peaks >= | 1.50 | USPResolution |
| 3 | ☑ | No. of Peaks >= | 2.00 | USPResolution |
| 4 | ☑ | No. of Peaks <= | 1.20 | USPTailing |
| 5 | ☑ | Max Peak | 1 | USPResolution |

USPResolution
USPResolutionAtHH
USPSignalToNoise
USPTailing
Width
WidthAt10Pct

Select All | Select None

I = Incomplete
D = Duplicate

Named Compounds in CDS

Available | Included

Response Data

☑ Show All CDS Responses

Available

2ndDerivativeApex
2Sigma
3Sigma
4Sigma
5Sigma
AboveIdentificationThreshold
AboveMaximumThreshold
AboveQualificationThreshold
AboveReportingThreshold
Amount
Area

Included

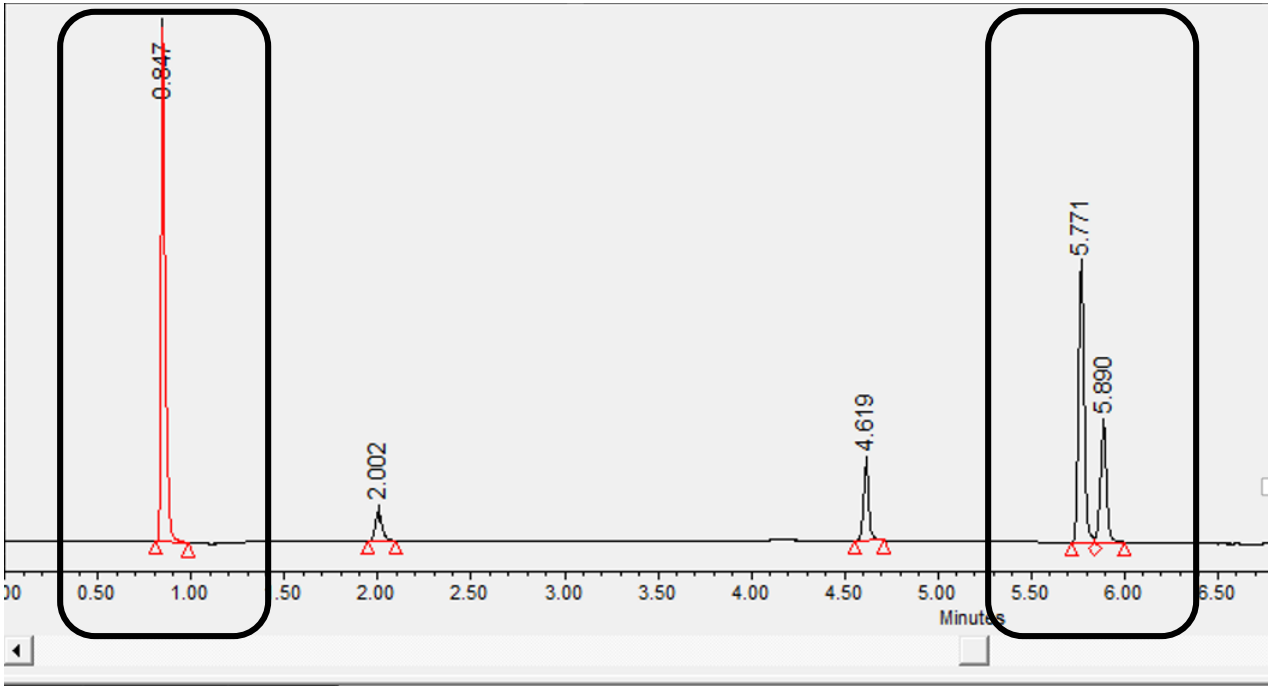
<< Back | Next >> | Cancel

# Récupération des résultats des expériences

**Fusion QbD repère automatiquement le 1er et le dernier pic de tous les chromatogrammes***

First Peak – Retention Time

Last Peak – Resolution

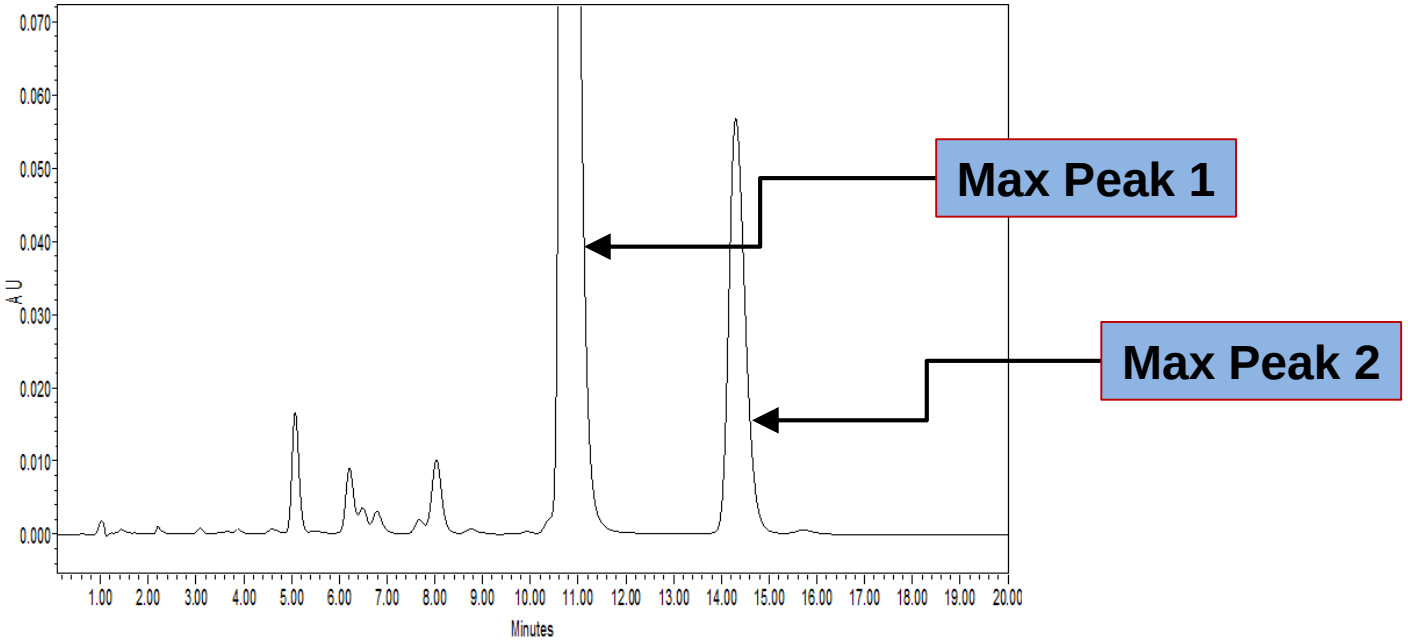



* - S-Matrix Patented

# Récupération des résultats des expériences

**Fusion QbD repère automatiquement l'API et les pics principaux***

**Max Peak 1 & 2**
**Rs**
**Tailing**

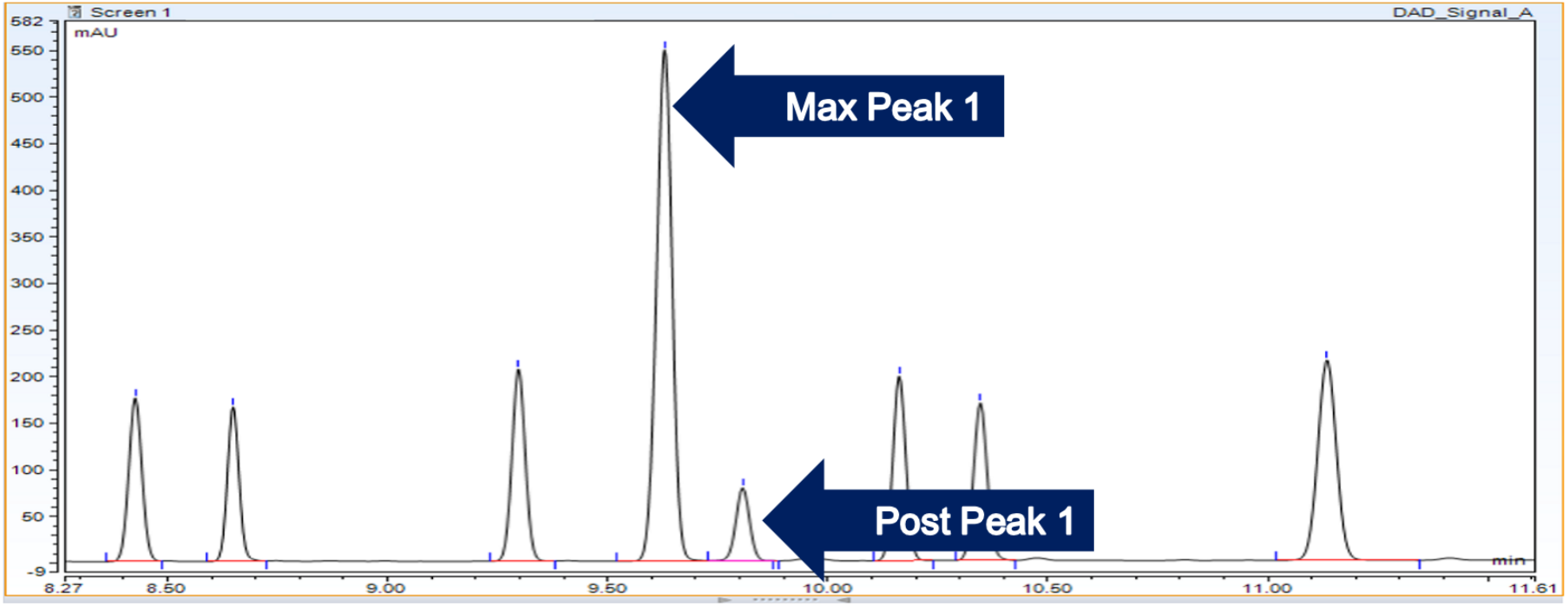



* - S-Matrix Patented

# Récupération des résultats des expériences

**Fusion QbD repère automatiquement les pics autour de l'API ou des pics principaux***

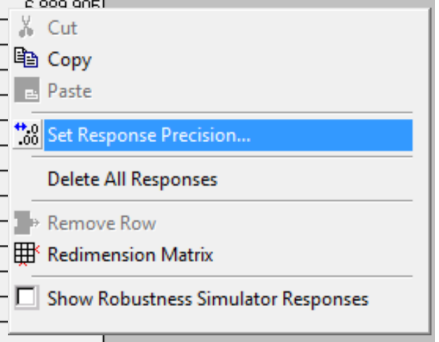
**Max Peak 1 – Rs**
**Post Peak 1 – Rs**




* - S-Matrix Patented

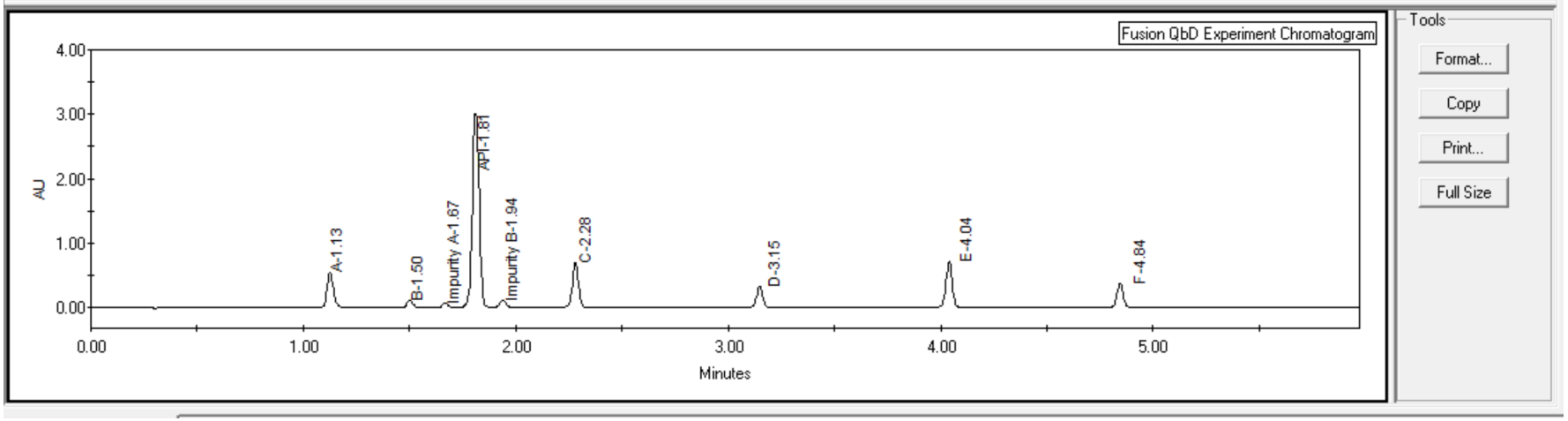
# Récupération des résultats des expériences

| | Run No. | Gradient Time | Oven Temperature | pH | Impurity A - USPResolution | API - USPResolution | API - USPTailing | Impurity B - USPResolution | API - Area |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Condition Column - 1 | 4 | 30 | 2.5 | | | | | |
| 2 | 1 | 8 | 30 | 2.5 | 3.91 | 1.16 | 0.99 | 2.62 | 6,679,438 |
| 3 | 2 | 5 | 30 | 2.5 | 3.32 | 2.39 | 1.08 | 2.41 | 6,637,205 |
| 4 | 3 | 8 | 30 | 2.5 | 3.90 | 1.16 | 0.99 | 2.61 | 6,730,730 |
| 5 | 4 | 5 | 30 | 2.5 | 3.32 | 2.39 | 1.08 | 2.41 | 6,655,009 |
| 6 | Condition Column - 2 | 4 | 30 | 3 | | | | | |
| 7 | 5 | 6.5 | 30 | 3 | 3.32 | 2.75 | 1.02 | 2.33 | 6,898,993 |
| 8 | Condition Column - 3 | 4 | 30 | 3.5 | | | | | |
| 9 | 6 | 5 | 30 | 3.5 | 0.80 | 5.11 | 1.11 | 1.32 | 6,784,668 |
| 10 | 7 | 8 | 30 | 3.5 | 1.23 | 5.53 | 0.99 | 1.14 | 6,877,353 |
| 11 | Condition Column - 4 | 4 | 35 | 2.5 | | | | | |
| 12 | 8 | 6.5 | 35 | 2.5 | 3.88 | 1.99 | 1.01 | 2.37 | 6,792,701 |
| 13 | Condition Column - 5 | 4 | 35 | 3 | | | | | |
| 14 | 9 | 6.5 | 35 | 3 | 3.22 | 2.83 | 1.01 | 2.02 | 6,889,905 |
| 15 | 10 | 6.5 | 35 | 3 | 3.22 | 2.83 | 1.02 | 2.02 | |
| 16 | 11 | 6.5 | 35 | 3 | 3.22 | 2.82 | 1.03 | 2.03 | |
| 17 | 12 | 5 | 35 | 3 | 2.68 | 3.16 | 1.07 | 1.93 | |
| 18 | 13 | 8 | 35 | 3 | 3.62 | 2.33 | 0.96 | 1.98 | |
| 19 | Condition Column - 6 | 4 | 35 | 3.5 | | | | | |
| 20 | 14 | 6.5 | 35 | 3.5 | 0.98 | 5.50 | 1.06 | 0.45 | |
| 21 | Condition Column - 7 | 4 | 40 | 2.5 | | | | | |
| 22 | 15 | 5 | 40 | 2.5 | 3.09 | 2.53 | 1.09 | 1.96 | |
| 23 | 16 | 8 | 40 | 2.5 | 4.15 | 1.51 | 0.98 | 1.98 | |
| 24 | 17 | 8 | 40 | 2.5 | 4.13 | 1.53 | 0.96 | 1.95 | |
| 25 | Condition Column - 8 | 4 | 40 | 3 | | | | | |
| 26 | 18 | 6.5 | 40 | 3 | 3.12 | 2.90 | 0.98 | 1.69 | |
| 27 | Condition Column - 9 | 4 | 40 | 3.5 | | | | | |
| 28 | 19 | 8 | 40 | 3.5 | 1.16 | 5.51 | 1.05 | 0.00 | 7,258,060 |
| 29 | 20 | 5 | 40 | 3.5 | 0.48 | 4.38 | 1.24 | 0.00 | 7,096,070 |
| 30 | Condition Column - 10 | 4 | 40 | 3.5 | | | | | |

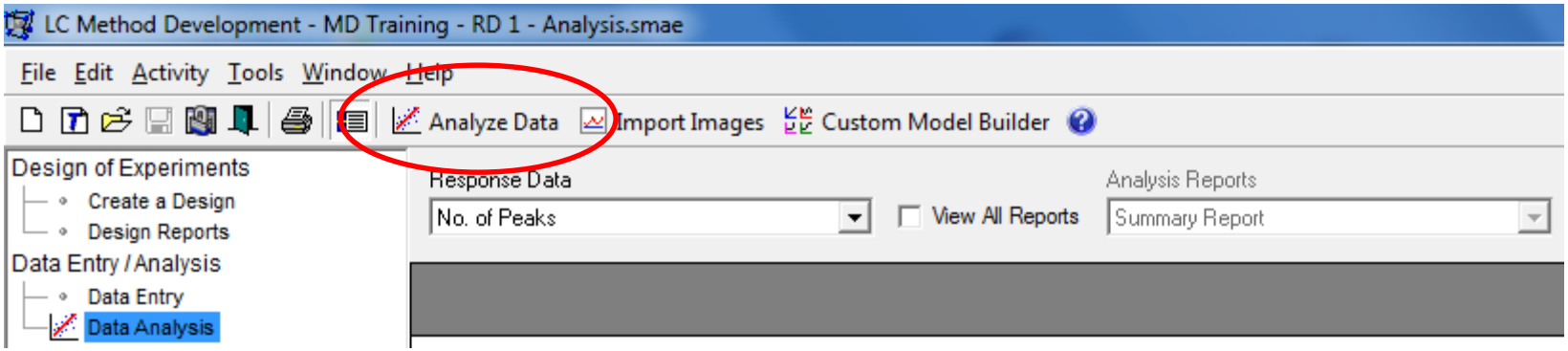


# Vérification des données et des chromatogrammes

| | Run No. | Gradient Time | Oven Temperature | pH | Impurity A - USPResolution | API - USPResolution | API - USPTailing | Impurity B - USPResolution | API - Area |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Condition Column - 1 | 4 | 30 | 2.5 | | | | | |
| 2 | 1 | 8 | 30 | 2.5 | 3.91 | 1.16 | 0.99 | 2.62 | 6,679,438 |
| 3 | 2 | 5 | 30 | 2.5 | 3.32 | 2.39 | 1.08 | 2.41 | 6,637,205 |
| 4 | 3 | 8 | 30 | 2.5 | 3.90 | 1.16 | 0.99 | 2.61 | 6,730,730 |
| 5 | 4 | 5 | 30 | 2.5 | 3.32 | 2.39 | 1.08 | 2.41 | 6,655,009 |
| 6 | Condition Column - 2 | 4 | 30 | 3 | | | | | |
| 7 | 5 | 6.5 | 30 | 3 | 3.32 | 2.75 | 1.02 | 2.33 | 6,898,993 |
| 8 | Condition Column - 3 | 4 | 30 | 3.5 | | | | | |
| 9 | 6 | 5 | 30 | 3.5 | 0.80 | 5.11 | 1.11 | 1.32 | 6,784,668 |
| 10 | 7 | 8 | 30 | 3.5 | 1.23 | 5.53 | 0.99 | 1.14 | 6,877,353 |
| 11 | Condition Column - 4 | 4 | 35 | 2.5 | | | | | |
| 12 | 8 | 6.5 | 35 | 2.5 | 3.88 | 1.99 | 1.01 | 2.37 | 6,792,701 |
| 13 | Condition Column - 5 | 4 | 35 | 3 | | | | | |
| 14 | 9 | 6.5 | 35 | 3 | 3.22 | 2.83 | 1.01 | 2.02 | 6,889,905 |



# Calcul des Modèles




**Un clic:** le logiciel génère automatiquement une équation (modèle) à partir des résultats d'Empower pour chaque Réponse (CQA)

**pH Level ($X_1$)** **Gradient Time Level ($X_2$)**

$$T.R. = \beta_0 + \beta_1(x1) + \beta_{11}(x1)^2 + \beta_{12}(x1 * x2) + \beta_2(x2) + \beta_2(x2)^2$$

(T.R. = Trend Response)

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# Recherche d'un Optimum

Best Answer Search - Response Goals Settings

Report Name: Numerical Search 1

Model Prediction Error C.I. for Report ± 2 Sigma

Response Settings

Maximize | Minimize | **Target**

**Target** means a specific answer is best.

**Target:** the most desirable answer **(Desirability = 1.0000)**.

**Lower Bound:** any answer <= this value is equally unacceptable. **(Desirability = 0.0000)** .

Recommended Setting: the value at or below the threshold of unacceptable performance.

**Upper Bound** : any answer >= this value is equally unceptable. **(Desirability = 0.0000)**.

Recommended Setting: the value at or above the threshold of unacceptable performance.

[ Desirability: Absolute Scale = Zero (0.0000) to One (+1.0000). ]

Best Overall Answer: Goal = **Target**

Example Response: Target = 75

Target – Valeur de l'objectif et limites

| | | | | Target | Upper Bound | Relative Rank |
|---|---|---|---|---|---|---|
| ☑ | No. of Peaks | Target | 8.0 | 9.0 | 10.0 | 1.0 |
| ☑ | No. of Peaks >= 1.50 -... | Target | 7.0 | 8.0 | 9.0 | 1.0 |
| ☑ | No. of Peaks >= 2.00 -... | Target | 7.0 | 8.0 | 9.0 | 1.0 |
| ☑ | No. of Peaks <= 1.20 -... | Target | 8.0 | 9.0 | 10.0 | 1.0 |
| ☑ | Max Peak 1 - USPResol... | Maximize | 2.00 | | 3.00 | |

Maximize – Seuil pour un minimum acceptable

The settings are valid.

Maximize – Seuil pour equivalence des résultats for Equivalence

Modify Search Region | Finish | Cancel

# Recherche d'un Optimum

## Answer #1

### Variable Settings

| Variable | Level Setting |
|---|---|
| Strong Solvent Type | Acetonitrile |
| Gradient Time | 9.0 |
| pH | 4.11 |
| Column Type | BEH Phenyl |

### Predicted Results

| Response | Goal | Predicted Result | Desirability | -2 Sigma Conf. Limit | +2 Sigma Conf. Limit |
|---|---|---|---|---|---|
| No. of Peaks | Target | 8.9 | 0.9188 | 8.0 | 9.9 |
| No. of Peaks >= 1.50 - USPResolution | Target | 8.3 | 0.7172 | 6.6 | 8.4 |
| No. of Peaks >= 2.00 - USPResolution | Target | 7.7 | 0.7151 | 6.6 | 9.1 |
| No. of Peaks <= 1.20 - USPTailing | Target | 8.4 | 0.4269 | 6.7 | 10.2 |
| Max Peak 1 - USPResolution | Maximize | 3.00 | 1.0000 | 0.11 | 8.62 |

Cumulative Desirability Target = 1.0000
Cumulative Desirability Result = 0.7256

# Représentation Graphique

## Visualisation des plages de valeurs pour tous les CQA et des chromatogrammes correspondants dans tout l'espace expérimental

LC Method Development - RD2 - Analysis -981.smae

File Edit Activity Tools Window Help

Create Report | Update Report | Delete Report | Restore Report | Robustness Simulator | Hide Prediction Chromatograms

Design of Experiments
- Create a Design
- Design Reports

Data Entry / Analysis
- Data Entry
- Data Analysis

Best Answer Searches
- Best Overall Answer
- Acceptable Performance Region
- Point Predictions

Visualization Graphics
- Single Response Series
- Multiple Response Series

Reporting Toolkit
- Fusion Reporter
- Audit Log Reporter

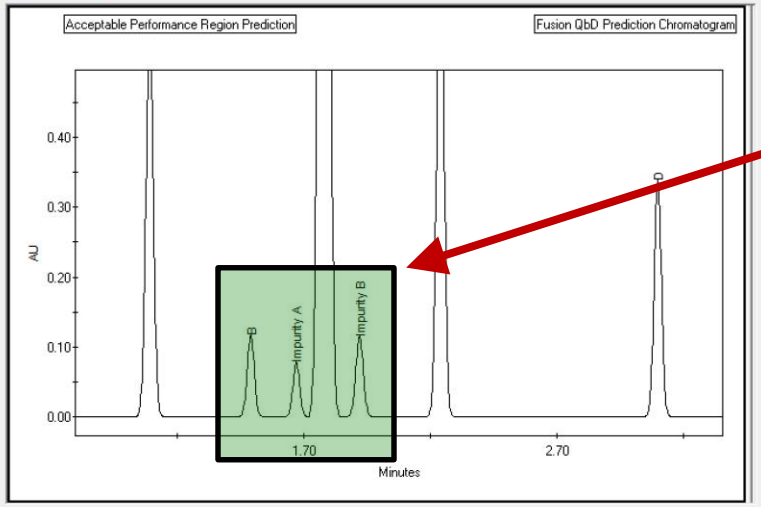
Reports: Final Design Space & PARs

Graph Settings

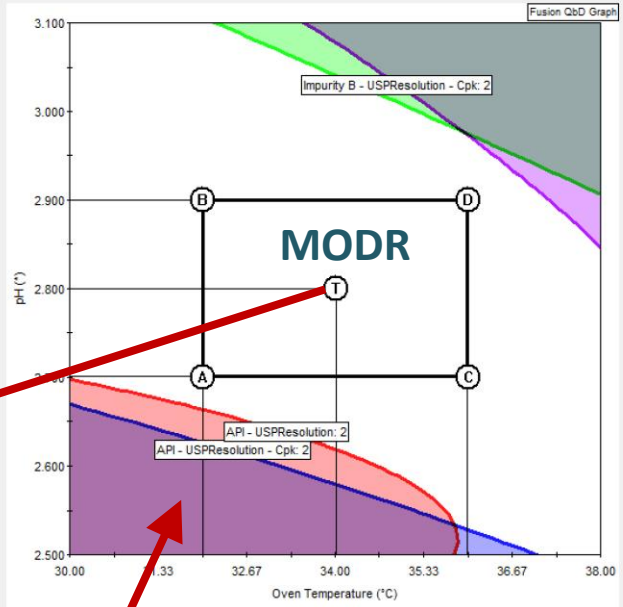
| | Name | Units | Lower Bound | Upper Bound | Pointer Coordinate |
|---|---|---|---|---|---|
| X | Oven Temperature | °C | 30.000 | 38.000 | 33.98 |
| Y | pH | * | 2.500 | 3.100 | 2.801 |

Gradient Time 7.0

Simulation Chromatogram




Graph




Response Settings

| Name | Goal | Lower Bound | Upper Bound | Target Predictions | Pointer Predictions | Contour Label | Color |
|---|---|---|---|---|---|---|---|
| Impurity B - USPResolution | Maximize | 2.00 | | 2.35 | 2.352 | | Green |
| API - USPResolution - Cpk | Maximize | 2.00 | | 2.96 | 2.823 | ✓ | Blue |
| Impurity A - USPResolution - Cpk | Maximize | 2.00 | | 6.93 | 7.06 | ✓ | Gray |
| Impurity B - USPResolution - Cpk | Maximize | 2.00 | | 3.52 | 3.53 | ✓ | Purple |
| API - USPTailing - Cpm | Maximize | 2.00 | | 4.18 | 4.21 | ✓ | Gray |

Validation Status: Your settings are valid.

Ready

**Région ombrée indique que les CQA ne sont pas dans les exigences de performance**

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# Représentation Graphique

## Un déplacement du pointeur permet de visualiser les modifications du chromatogramme

LC Method Development - RD2 - Analysis -981.smae

File Edit Activity Tools Window Help

Create Report | Update Report | Delete Report | Restore Report | Robustness Simulator | Hide Prediction Chromatograms

Design of Experiments
- Create a Design
- Design Reports

Data Entry / Analysis
- Data Entry
- Data Analysis

Best Answer Searches
- Best Overall Answer
- Acceptable Performance Region
- Point Predictions

Visualization Graphics
- Single Response Series
- Multiple Response Series

Reporting Toolkit
- Fusion Reporter
- Audit Log Reporter

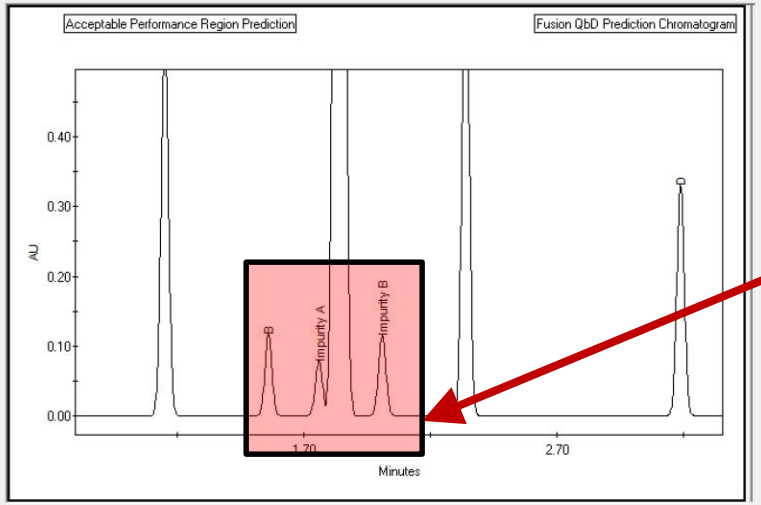
Reports: Final Design Space & PARs

Graph Settings

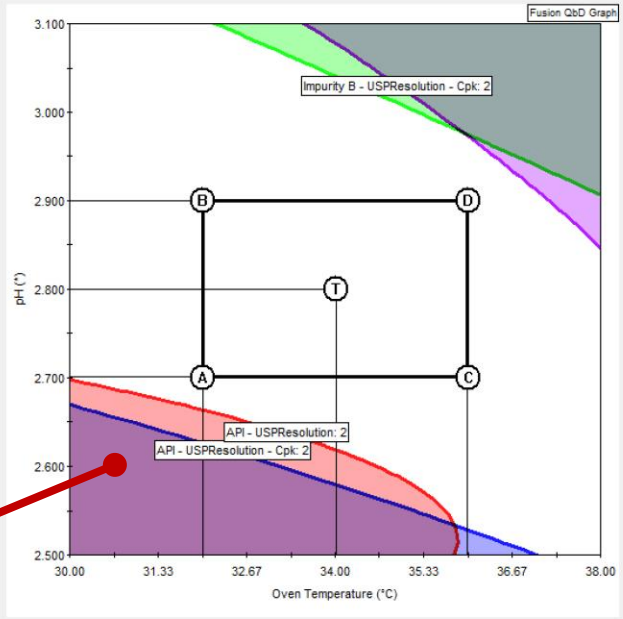
| | Name | Units | Lower Bound | Upper Bound | Pointer Coordinate |
|---|---|---|---|---|---|
| X | Oven Temperature | °C | 30.000 | 38.000 | 30.02 |
| Y | pH | * | 2.500 | 3.100 | 2.503 |

Gradient Time 7.0

Simulation Chromatogram




Graph




Response Settings

| Name | Goal | Lower Bound | Upper Bound | Target Predictions | Pointer Predictions | Contour Label | Color |
|---|---|---|---|---|---|---|---|
| API - USPResolution | Maximize | 2.00 | | 2.28 | 1.883 | ✓ | Red |
| Impurity A - USPResolution | Maximize | 2.00 | | 3.75 | 3.7662 | ✓ | Blue |
| Impurity B - USPResolution | Maximize | 2.00 | | 2.35 | 2.536 | | Green |
| API - USPResolution - Cpk | Maximize | 2.00 | | 2.96 | 1.315 | ✓ | Blue |
| Impurity A - USPResolution - Cpk | Maximize | 2.00 | | 6.93 | 12.14 | ✓ | Gray |

Validation Status: Your settings are valid.

Ready

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# Représentation Graphique

LC Method Development - RD2 - Analysis -981.smae

File Edit Activity Tools Window Help

Create Report | Update Report | Delete Report | Restore Report | Robustness Simulator | Hide Prediction Chromatograms

- Design of Experiments
  - Create a Design
  - Design Reports
- Data Entry / Analysis
  - Data Entry
  - Data Analysis
- Best Answer Searches
  - Best Overall Answer
  - Acceptable Performance Region
  - Point Predictions
- Visualization Graphics
  - Single Response Series
  - Multiple Response Series
- Reporting Toolkit
  - Fusion Reporter
  - Audit Log Reporter

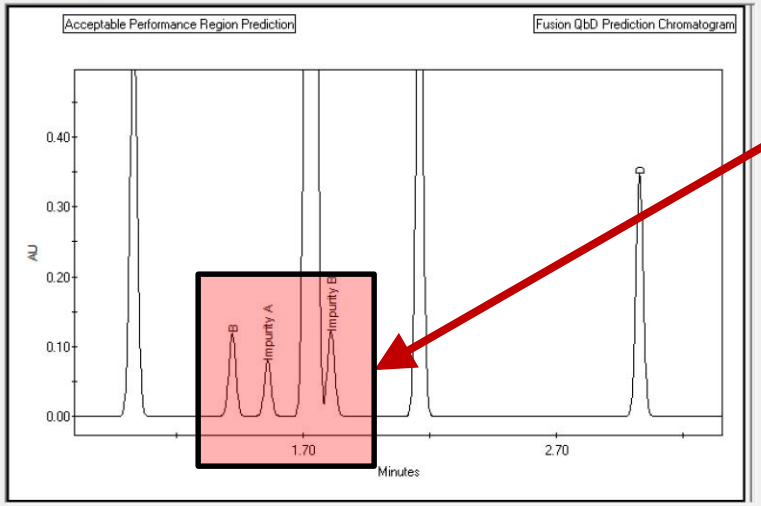
Reports: Final Design Space & PARs

Graph Settings

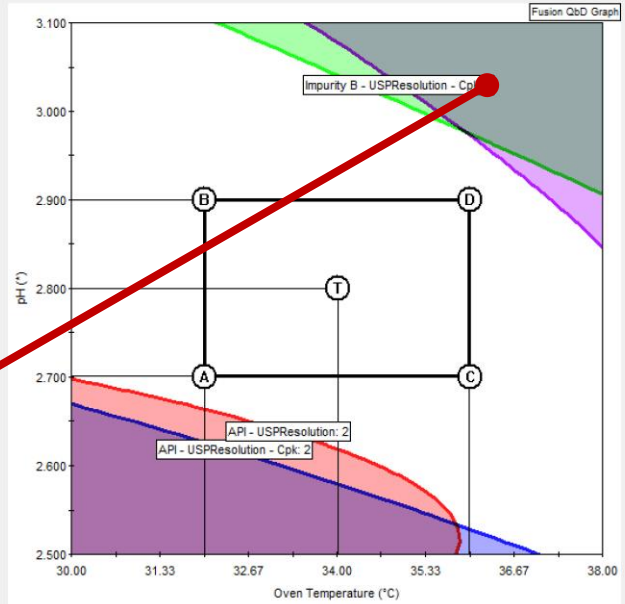
| | Name | Units | Lower Bound | Upper Bound | Pointer Coordinate |
|---|---|---|---|---|---|
| X | Oven Temperature | °C | 30.000 | 38.000 | 37.86 |
| Y | pH | * | 2.500 | 3.100 | 3.099 |

Gradient Time 7.0

Simulation Chromatogram




Graph




Response Settings

| Name | Goal | Lower Bound | Upper Bound | Target Predictions | Pointer Predictions | Contour Label | Color |
|---|---|---|---|---|---|---|---|
| API - USPResolution | Maximize | 2.00 | | 2.28 | 3.2670 | ✓ | Red |
| Impurity A - USPResolution | Maximize | 2.00 | | 3.75 | 2.789 | ✓ | Blue |
| Impurity B - USPResolution | Maximize | 2.00 | | 2.35 | 1.597 | | Green |
| API - USPResolution - Cpk | Maximize | 2.00 | | 2.96 | 4.121 | ✓ | Blue |
| Impurity A - USPResolution - Cpk | Maximize | 2.00 | | 6.93 | 3.12 | ✓ | Gray |

Validation Status: Your settings are valid.

Ready

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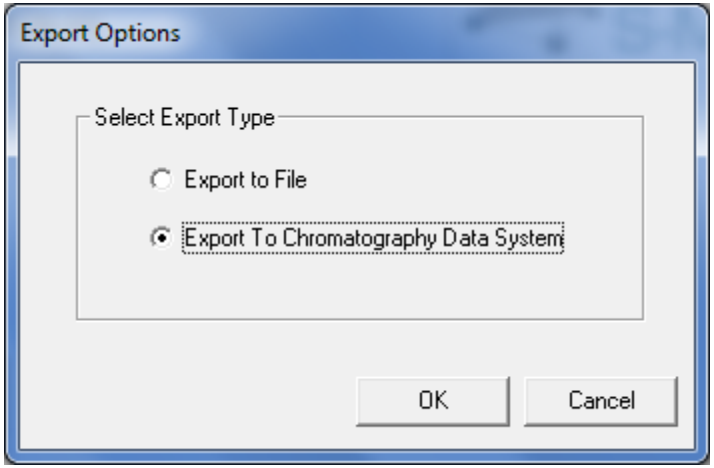
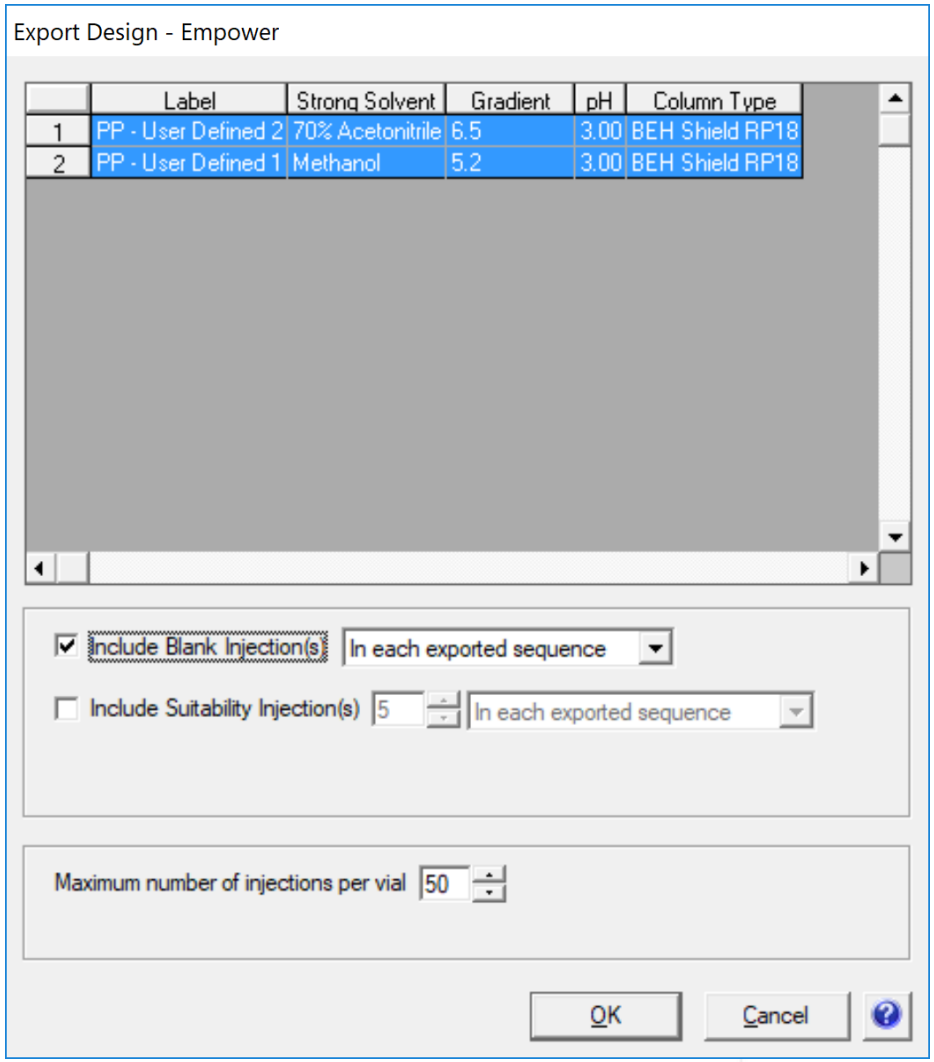
# Vérification du MODR



# Vérification du MODR

**Predicted Point - 5**

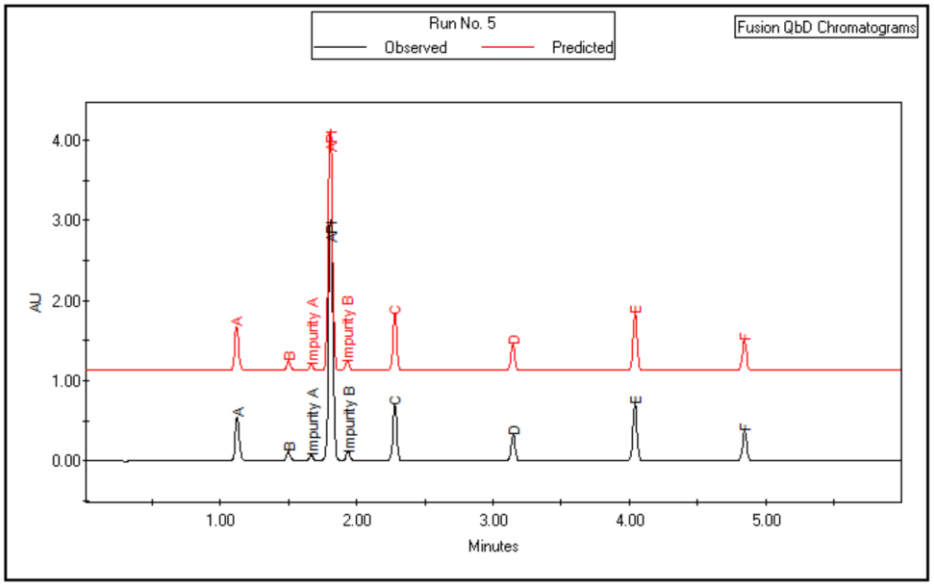
**Study Variable Data**

| Study Variable Name | Prediction Point Level Setting |
|---|---|
| Gradient Time | 6.5 |
| Oven Temperature | 30.0 |
| pH | 3.00 |

**Comparaison des résultats expérimentaux aux résultats du modèle**

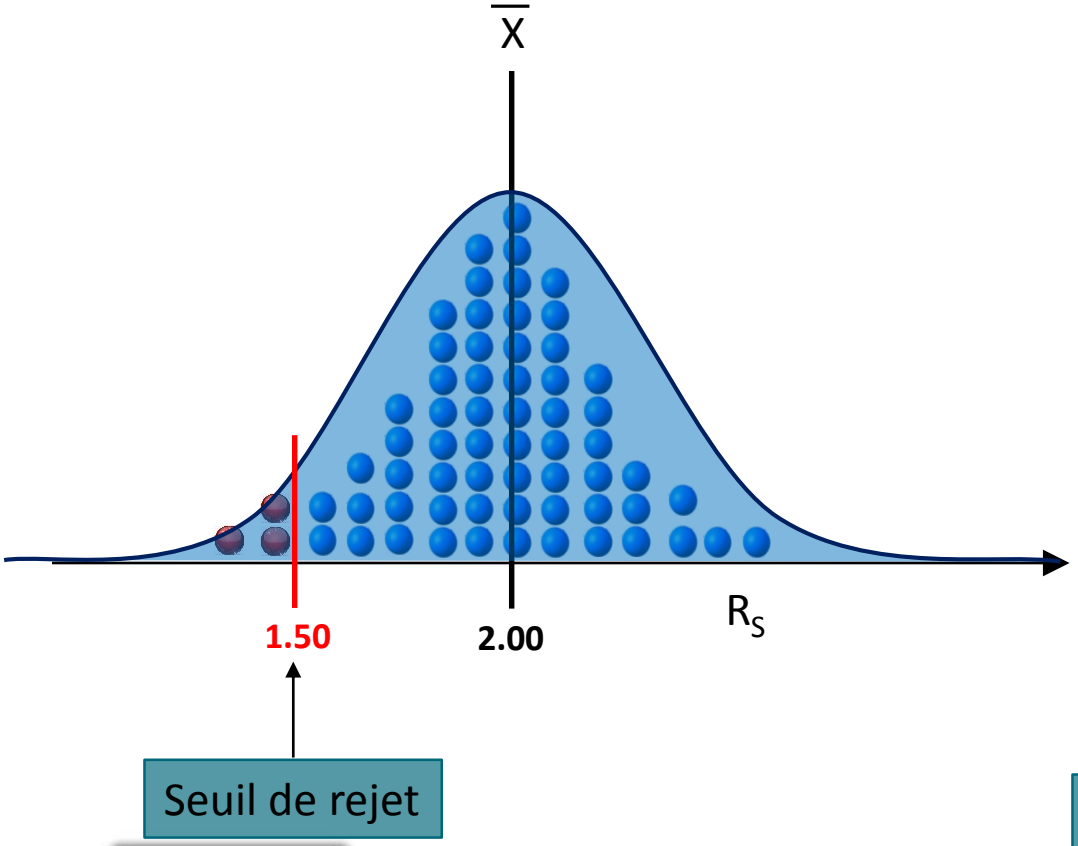
**Predicted Response Data**

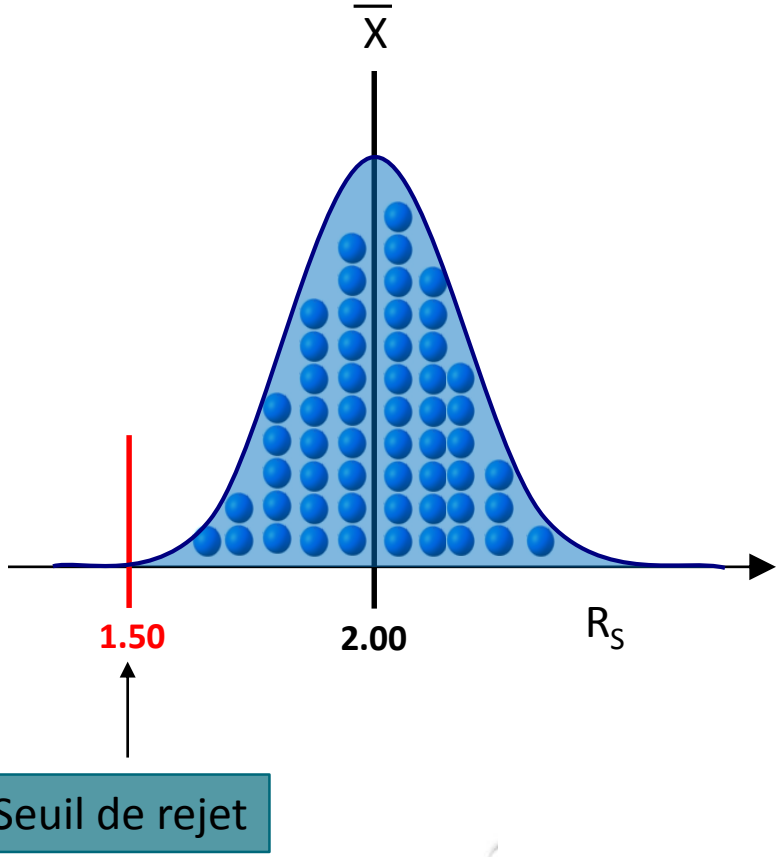
| Response Variable Name | Observed Result | Predicted Result | -2 Sigma Confidence Limit | +2 Sigma Confidence Limit |
|---|---|---|---|---|
| Impurity A - USPResolution | 3.3178 | 3.3039 | 3.2038 | 3.4056 |
| API - USPResolution | 2.7476 | 2.7264 | 2.6526 | 2.8003 |
| API - USPTailing | 1.0177 | 1.0106 | 0.9682 | 1.0590 |
| Impurity B - USPResolution | 2.3323 | 2.3337 | 2.2903 | 2.3771 |
| API - Area | 6,898,993.40 | 6,816,153.11 | 6,713,404.20 | 6,918,902.01 |



# Autre approche de la Robustesse (Simulateur)

Performance moyenne acceptable **vs** Performance individuelle toujours acceptable

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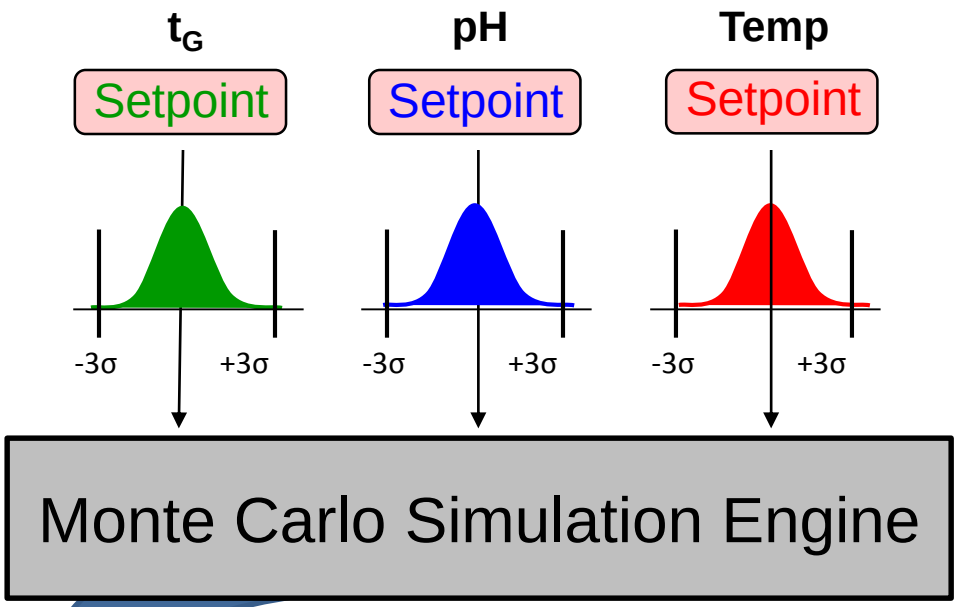
# Simulateur de Robustesse

Variations attendues

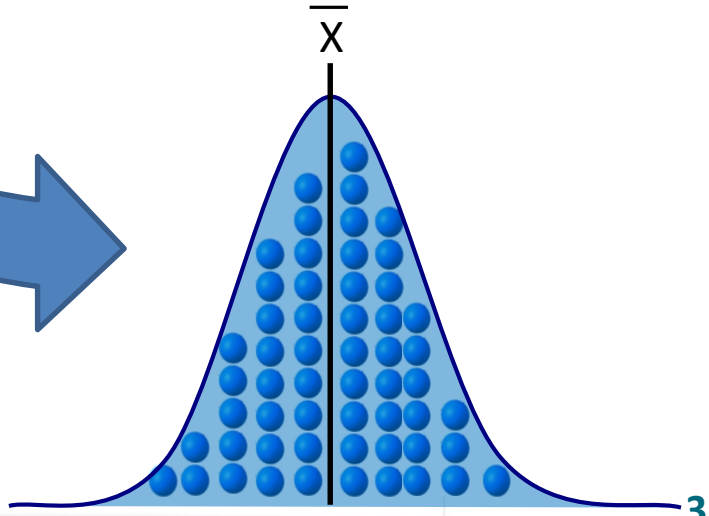
$\Delta t_G$: ± 2.0%

pH: ± 0.15

Temp: ± 2.0 °C




Simule les variations de performance de la méthode pour tous les CQA

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# Représentation Graphique

LC Method Development - FMD Training - Optimization - Completed.smae

File Edit Activity Tools Window Help

Create Report | Update Report | Delete Report | Restore Report | Robustness Simulator | Show Prediction Chromatograms

- Design of Experiments
  - Create a Design
  - Design Reports
- Data Entry / Analysis
  - Data Entry
  - Data Analysis
- Best Answer Searches
  - Best Overall Answer
  - Acceptable Performance Region
  - Point Predictions
- Visualization Graphics
  - Single Response Series
  - Multiple Response Series
- Reporting Toolkit
  - Fusion Reporter
  - Audit Log Reporter

Reports

Robust Design Space - 5.5 min

Graph Settings

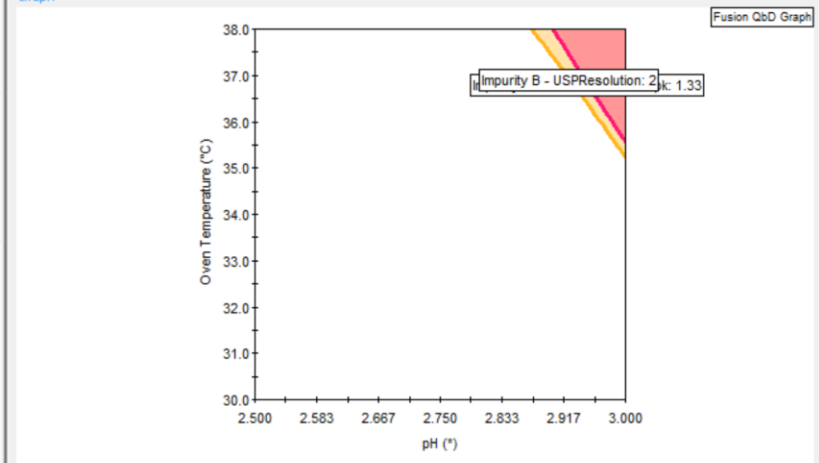
| | Name | Units | Lower Bound | Upper Bound | Pointer Coordinate |
|---|---|---|---|---|---|
| X | pH | * | 2.50 | 3.00 | --- |
| Y | Oven Temperature | °C | 30.0 | 38.0 | --- |

Gradient Time 5.5

Verification Run Settings

- Include Proven Acceptable Ranges (PARs)
- Include Verification Runs

Graph




Response Settings

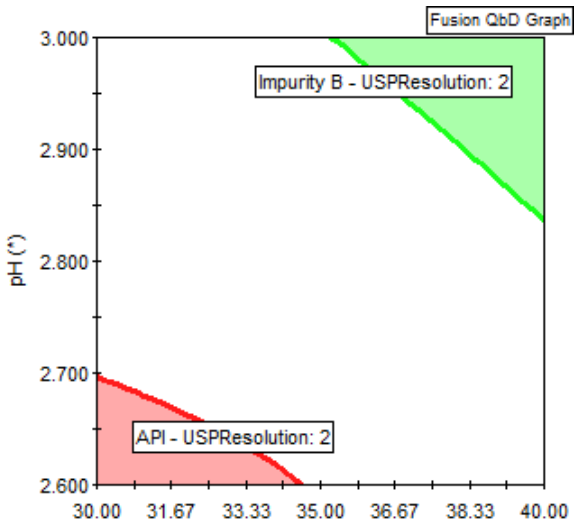
| Name | Goal | Lower Bound | Upper Bound | Pointer Predictions | Contour Label | Color |
|---|---|---|---|---|---|---|
| Impurity A - USPResolution | Maximize | 2.00 | | | ✓ | Red |
| API - USPResolution | Maximize | 2.00 | | | ✓ | Blue |
| API - USPTailing | Target | 0.90 | 1.10 | | ✓ | Green |
| Impurity B - USPResolution | Maximize | 2.00 | | | ✓ | Orange |
| API - Area | Maximize | 6,637,205 | | | ✓ | Teal |
| Impurity A - USPResolution - Cpk | Maximize | 1.33 | | | ✓ | Purple |
| API - USPResolution - Cpk | Maximize | 1.33 | | | ✓ | Lime |
| API - USPTailing - Cpm | Maximize | 1.33 | | | ✓ | Sky |
| Impurity B - USPResolution - Cpk | Maximize | 1.33 | | | ✓ | Fuschia |
| API - Area - %RSD | Minimize | | 2.00 | | ✓ | Gray |

Validation Status: Your settings are valid.

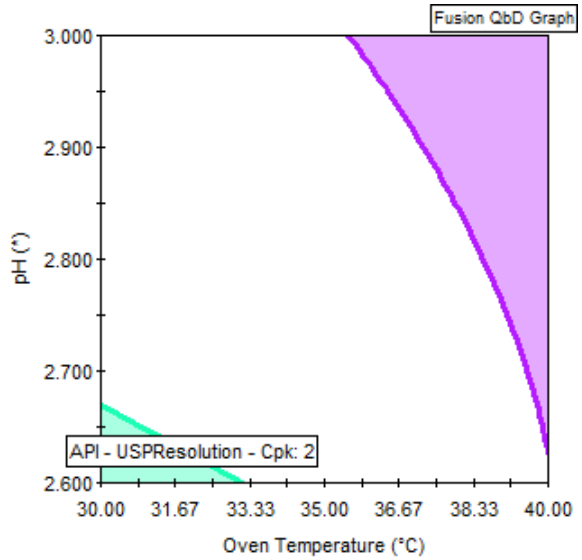
Ready | modified

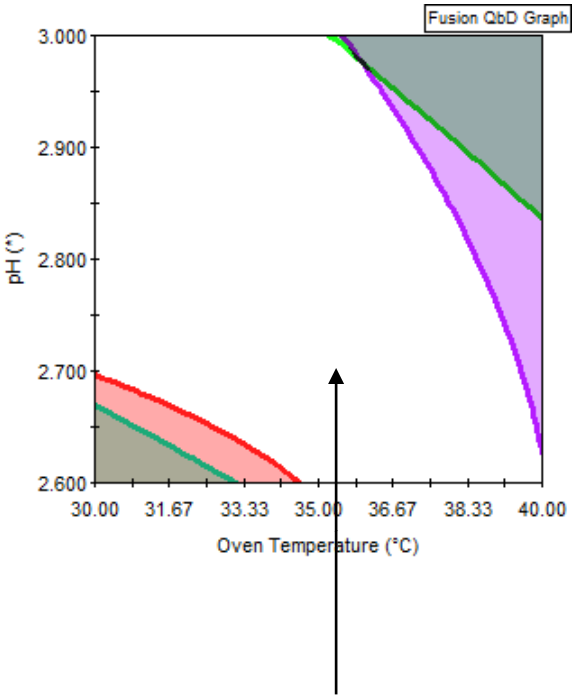
# Représentation Graphique

**Mean Response – Tous les CQA**




**Robustness – Tous les CQA**




**Robust Design Space –**

Joint region of acceptable method mean performance and **robustness**.

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# Représentation Graphique

## ICH Q8(R2) – Page 22

### C. Presentations of Design Space

**Example 1:** Response graphs for dissolution are depicted as a surface plot (Figure 1a) and a contour plot (Figure 1b). Parameters 1 and 2 are factors of a granulation operation that affect the dissolution rate of a tablet (e.g., excipient attribute, water amount, granule size.)

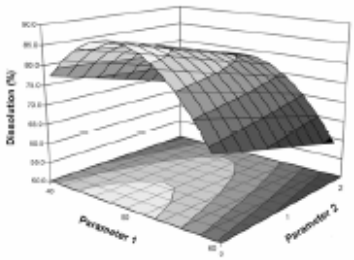



Figure 1a: Response surface plot of dissolution as a function of two parameters of a granulation operation. Dissolution above 80% is desired.

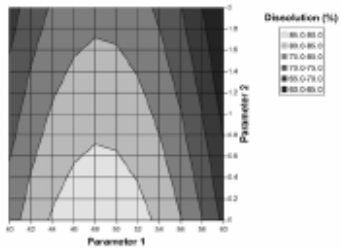



Figure 1b: Contour plot of dissolution from example 1a.

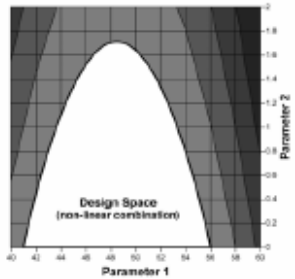



Figure 1c: Design space for granulation parameters, defined by a nonlinear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

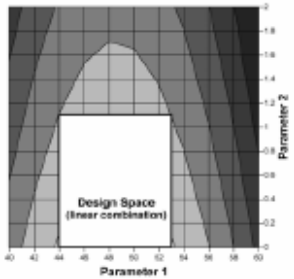


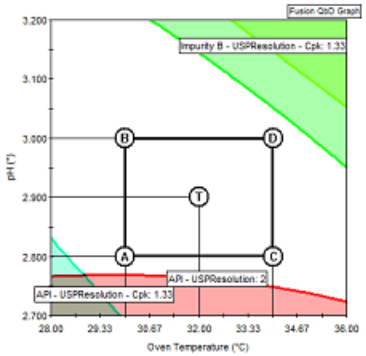

Figure 1d: Design space for granulation parameters, defined by a linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

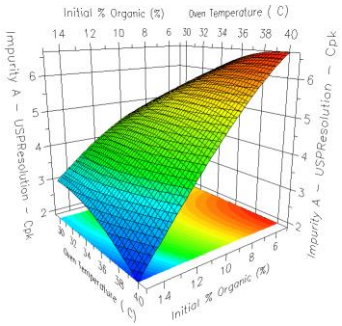
## Fusion QbD

Name: Administrator
Company: S-Matrix
Project: Project 1
Date: October 29, 2015 6:31:03 PM PDT [GMT-07:00]

S-Matrix

**D.S. + PARs - 10% Organic**




**Proven Acceptable Range Settings**

| Axis | Name | Units | Lower Bound | Upper Bound | Centerpoint |
|---|---|---|---|---|---|
| X | Oven Temperature | °C | 30.00 | 34.00 | 32.00 |
| Y | pH | * | 2.800 | 3.000 | 2.900 |

**Response Variable Goals**

| Name | Units | Goal | Lower Bound | Upper Bound | Color | Predicted Centerpoint |
|---|---|---|---|---|---|---|
| API - USPResolution | (*) | Maximize | 2.00 | --- | Red | 2.45 |
| Impurity A - USPResolution | (*) | Maximize | 2.00 | --- | Blue | 3.55 |
| Impurity B - USPResolution | (*) | Maximize | 2.00 | --- | Green | 2.35 |
| API - USPTailing | (*) | Target | 0.90 | 1.10 | Orange | 1.01 |
| API - USPResolution - Cpk | (*) | Maximize | 1.33 | --- | Teal | 3.05 |
| Impurity A - USPResolution - Cpk | (*) | Maximize | 1.33 | --- | Purple | 6.41 |
| Impurity B - USPResolution - Cpk | (*) | Maximize | 1.33 | --- | Lime | 4.05 |
| API - USPTailing - Cpm | (*) | Maximize | 1.33 | --- | Sky | 5.40 |

**Graph Variable Settings**

| Name | Units | Graph Setting | Range/Level(s) |
|---|---|---|---|
| Oven Temperature | (°C) | X Axis Variable | 28.00 <= Oven Temperature <= 36.00 |
| pH | (*) | Y Axis Variable | 2.700 <= pH <= 3.200 |
| Initial % Organic | (%) | Constant | 8.7 |

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Merci pour votre attention