A Quality-by-Design Approach to the Rapid Development of Robust HPLC Methods

Introduction

Chromatographic analytical method development is currently a time consuming process usually done by trial and error. The method development workflow typically involves three major activities done sequentially: column screening, formal method development, and robustness verification. Column screening, or scouting, is the activity of selecting the correct analytical column. Evaluating organic solvent type and pH is sometimes included in this phase. Formal method development identifies the settings of the remaining important instrument parameters that best separate all compounds of interest. Robustness verification, normally done as part of method validation, demonstrates the insensitivity of method performance to the cumulative small deviations of critical instrument parameter settings around their setpoints expected during normal use over time.

In a previous white paper the authors described the problems and information limitations inherent in both traditional sequential and classical Design of Experiments (DOE) approaches to column screening. The white paper described a new methodology for automated HPLC column and solvent system selection using Quality-by-Design (QbD) principles. The new methodology, adapted to multiple instruments and instrument data systems, overcomes the problems and limitations inherent in current screening approaches.

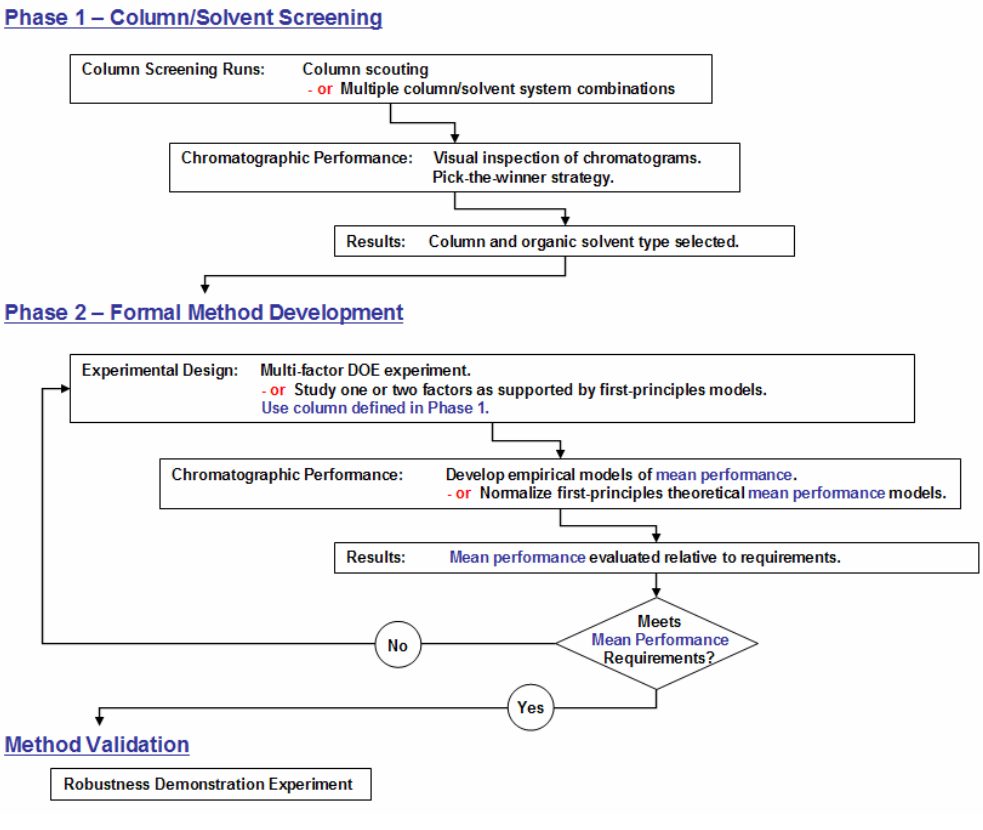
This white paper describes the extension of the new QbD-based methodology to the formal method development work phase. Regulatory guidances state that a best-practices approach should addresses robustness during formal method development. Therefore, a critical element of the new methodology is the integration of automatically computed robustness metrics into method development experiments. The new methodology thus automates a best-practices approach in which HPLC methods can be rapidly developed and simultaneously optimized for mean chromatographic performance and method robustness.

Current HPLC Method Development Practice

Reversed-phase HPLC is by far the most widely used HPLC separation methodology in pharmaceutical and biotechnology analytical applications. Reversed-phase HPLC is therefore the basis of the discussions and examples used in this paper. However, the reader will recognize that the instrumentation, software, and Quality-by-Design (QbD) based methodologies presented here are applicable to other HPLC approaches such as normal-phase and HILIC.

Figure 1 presents a diagram of the HPLC method development workflow as it is commonly practiced today. As the diagram indicates, Phase 1 in the workflow addresses analytical column selection. In some cases identification of the appropriate solvent system is also done in this phase. In a previous white paper the authors described a new methodology for automated HPLC column and solvent system selection using Quality-by-Design (QbD) principles which overcomes the problems and limitations inherent in current screening approaches.

Figure 1. Current Method Development Workflow



The second method development phase addresses the remaining important parameters. The goal of this phase is identification of the parameter settings that meet all critical method performance criteria in terms of both compound separation and total assay time. However, current approaches to this work only characterize how candidate methods will perform on average (mean performance), with the result that robustness can only be qualitatively inferred when considered at all. Addressing method robustness is normally relegated to Phase 3 where it is limited to a demonstration experiment involving the final method.

The lack of accurate robustness characterization in method development is the reason that many methods must be redeveloped each time they are to be transferred downstream in the drug development pipeline in order to meet the stricter performance requirements that will be imposed on them. The statements reproduced below express how important this integration is in the view of the FDA and the ICH.

FDA Reviewer Guidance [2]. COMMENTS AND CONCLUSIONS

HPL Chromatographic Methods for Drug Substance and Drug Product.

Methods should not be validated as a one-time situation, but methods should be validated and designed by the developer or user to ensure ruggedness or robustness throughout the life of the method.

ICH Q2B [3]. X. ROBUSTNESS (8)

The evaluation of robustness should be considered during the development phase and depends on the type of procedure under study. It should show the reliability of an analysis with respect to deliberate variations in method parameters...

Although the goal is clearly stated, the guidances do not define how to accomplish such a task. The new methodology presented in this white paper has been developed in response to both the stated need for integrating robustness into the method development work and the lack of a defined "how to" approach. To meet the needs of a working analytical lab the new methodology was required to meet three important requirements:

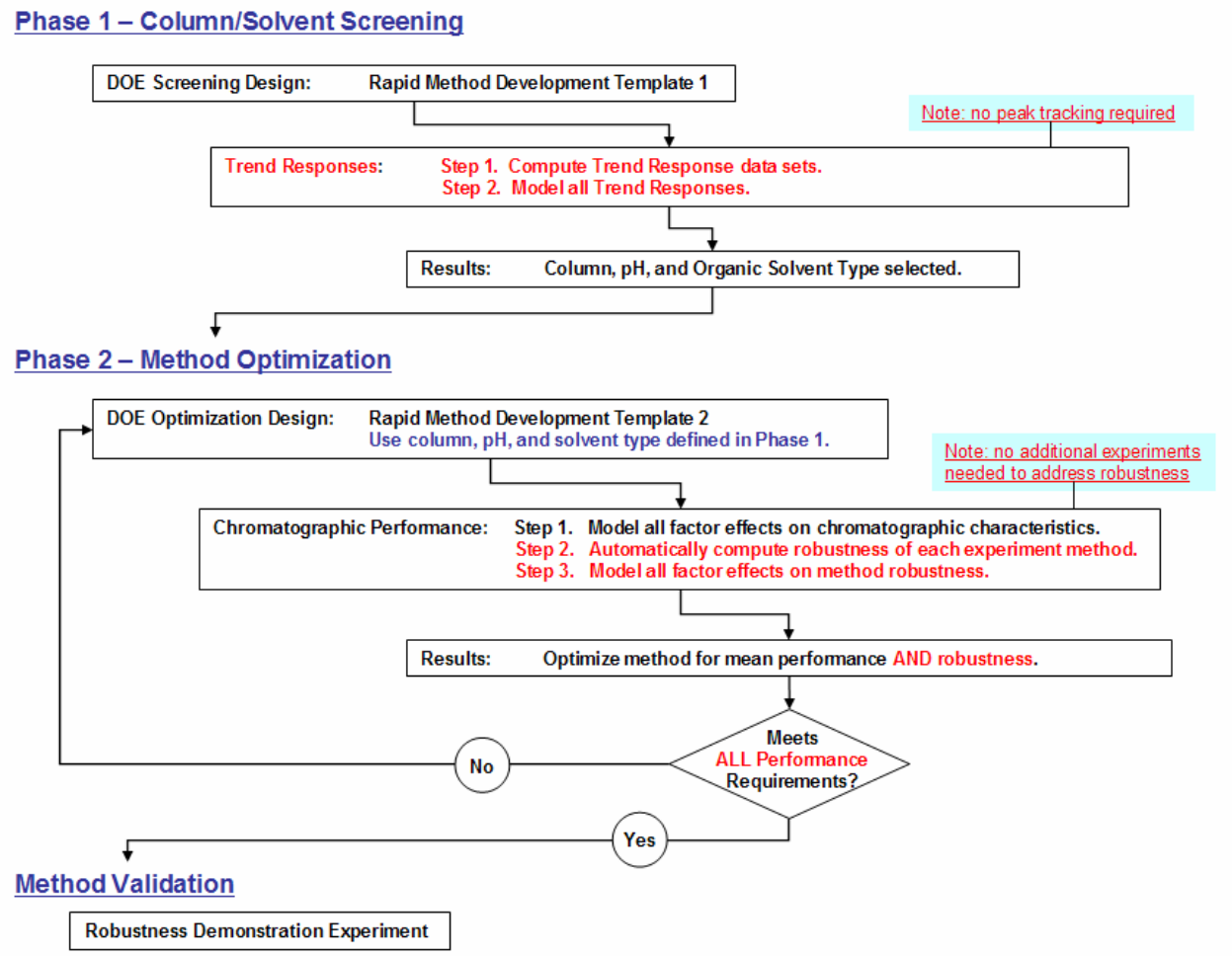
1. Be based on statistically rigorous QbD principles.
2. Integrate quantitative robustness metrics without requiring additional experiments.
3. Minimize the time and work burden by making maximal use of automation.

In meeting these three requirements, the new methodology represents the automation of a best-practices approach in which HPLC methods can be rapidly developed and simultaneously optimized for mean chromatographic performance and method robustness.

A New Quality-by-Design Based Methodology

Figure 2 is a flowchart of a new QbD-based method development workflow. This workflow harmonizes with current practice in many labs in that it is becoming common for method development to be carried out in phases. However, the new methodology couples statistical Design of Experiments (DOE) methods, consistent with a QbD-based methodology, with quantitative robustness metrics to transform the qualitative elements of current practice into a statistically rigorous quantitative methodology. Most importantly, the rigorous quantitation of candidate method robustness is accomplished in minimum time and effort without the need for any additional live experimental work.

Figure 2. New Method Development Practice Workflow



Although the flowchart presented in Figure 2 identifies the important changes to current practice that have been developed and implemented in both phases of the method development workflow, the details of the Phase 1 changes are beyond the scope of this white paper and have been presented in a previous white paper. The following sections of this white paper detail the novel computational techniques and execution strategy developed for Phase 2 of the method development workflow along with a proof-of-technology experiment carried out at a major international pharmaceutical company.

Technical Background

A successful Phase 1 effort that includes analytical column, pH, and organic solvent type means that these parameters can be set to a constant (fixed) in the second phase of method development. This significantly reduces compound co-elution and changes in compound elution order across experiment trials. As a result, compound peaks are more accurately tracked across the experiment trial chromatograms, minimizing inherent data loss. Peak tracking enables response prediction models (prediction equations) to be derived from the experiment data that accurately represent the effects of the study parameters on the chromatographic properties of the individual compounds being analyzed.

Again, consistent with QbD principles a statistical design of experiments (DOE) approach is used to define the required trials in the method optimization phase. The experimental work involves the four steps described previously with the following modifications:

1. **Define the design space.** This experiment is run using the column, pH, and organic solvent type identified as performing best in the Phase 1 experiment.

   The new practice uses a *Phase 2 – Method Optimization* experiment template that includes the factors identified below. As before, the template can be modified to, include other factors such as Column Oven Temperature and Additive based on the specific compounds that must be resolved.

Experiment Variable	Range or Level Settings
Phase 1 Constants	Column, pH, Organic Solvent Type
Pump Flow Rate (mL/min)	0.7 — 1.5
Gradient Slope (% Organic) — Vary Final Conditions	Initial %: 5.0 Final % Range: 60.0 — 95.0

   Note - it is critical to set wide ranges for the study factors. A robustness validation experiment normally sets the ranges to the ±3.0σ limits, as its purpose is to demonstrate the "null" hypothesis – i.e., that the factors have no statistically significant effects across their noise ranges. However, the inherently low signal-to-noise ratio in such an experiment makes it completely inappropriate when the goal is to obtain models that accurately represent all significant variable effects. Therefore, in a properly defined DOE study the variable ranges should be approximately 10 times the noise range defined by the ±3.0σ limits, and never less than 5 times the noise range.

2. **Generate a statistically designed experiment.**

3. **Run the various design conditions on the instrument.**

   Once the experiment is run, the critical compound peaks in each experiment chromatogram are identified using native CDS features (peak tracking). The Fusion AE software then automatically retrieves all experimental results for each experiment chromatogram from the CDS.

   Note - in method optimization chromatographic performance metrics such as resolution are used to assure that the method provides accurate Quantitation in normal use.

4. **Derive predictive models of the study parameter effects on the critical chromatographic characteristics under study.**

   The software automatically derives response prediction models that accurately represent all statistically significant factor effects on resolution for all identified peaks. If required other critical chromatographic performance characteristics such as peak asymmetry (tailing) can be addressed in similar fashion.

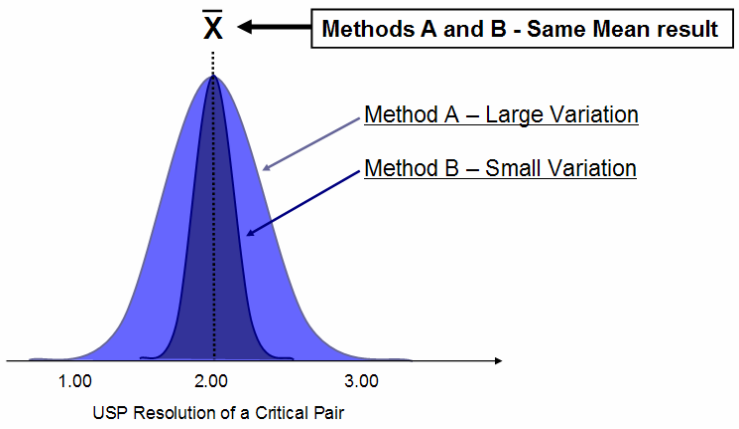
Obtaining the Robustness Models

Once the software derives the response prediction models (Step 4 above), a second novel approach automated within the Fusion AE software program fully integrates quantitative method robustness metrics and modeling into the method optimization workflow (S-Matrix patents pending). To integrate robustness into method development according to QbD principles requires that robustness be put on a quantitative footing. To do this the following two conditions must be met:

1. The robustness of any given candidate HPLC method must be able to be quantified.
2. Robustness differences between candidate HPLC methods must be quantitatively related to instrument parameter effects.

The reason that integrating quantitative robustness metrics into HPLC method development is so important is that different methods can provide the same mean performance but very different robustness. This is illustrated in Figure 4 for two methods designated A and B. Both methods have the same mean performance, but Method A performance varies excessively in response to inherent variation in critical HPLC instrument parameters while Method B performance does not. Since all current method development approaches only quantify a method's mean performance, Method B could easily be identified as an appropriate method. The robustness of the method can not be seen by inspecting the chromatogram obtained by running the method on the HPLC. Therefore, the poor robustness performance of the method may not be identified until a robustness experiment is conducted as part of validating the method prior to transfer. This is clearly too late in the process.

Figure 4. Mean Performance versus Robustness

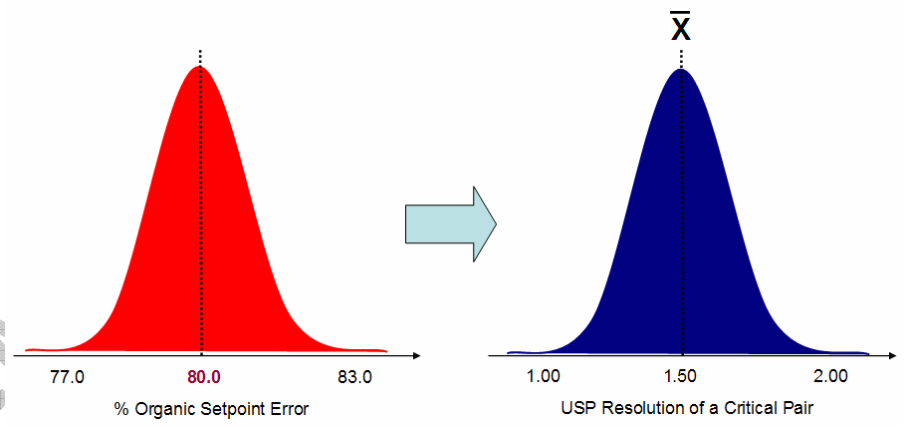


Quantifying Method Robustness

The robustness of an analytical method is its capacity to remain unaffected by small variations in method parameters. The phrase "*capacity to remain unaffected*" is understood to mean its inherent ability to provide quantitative data with the required accuracy and precision in normal use. As mentioned, chromatographic performance metrics such as resolution are used in method development to assure that the method provides accurate quantitation in normal use. The phrase "small variations" is understood to mean the expected random variations in the parameters about their setpoints that occur in normal use of the method over time. This is commonly referred to as setpoint error.

The robustness definition expresses the understanding that variation in method parameters will affect method chromatographic performance characteristics that in turn affect Quantitation. This is illustrated in Figure 5, which shows the effect of a ±3.0% Organic setpoint error on the resolution results for a critical peak pair obtained from 60 independent executions of a gradient method. In this case the setpoint error translates into a *response variation* of ±0.5 in the measured resolution of the peak pair. Note that the method setpoint of 80% Organic gives a resolution of 1.50 for the peak pair, while an individual assay may provide a resolution anywhere from 1.00 (not baseline resolved) to 2.00. In this case the mean performance of the method is acceptable, but the response variation due to setpoint error is unacceptable. This is evidenced by the fact that at a mean resolution of 1.50, the -3.0σ variation limit is located at 1.00. In other words the method is not sufficiently robust with respect to the expected variation in % Organic. Note that, given the effect of the % Organic setpoint error on resolution, achieving acceptable robustness in terms of this parameter requires a mean resolution of ≥ 2.0 for the critical-pair.

Figure 5. Impact of % Organic Setpoint Error on Resolution

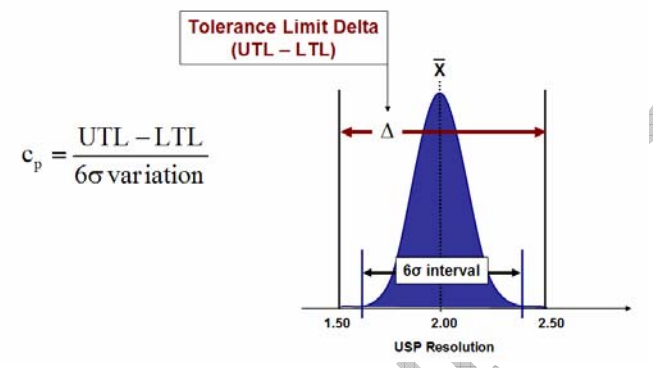


The new HPLC method development approach implemented in the Fusion AE software program uses the Process Capability index (C_p) to quantify method robustness. C_p is a Statistical Process Control (SPC) metric widely used to quantify and evaluate process output variation in critical product quality and performance characteristics. C_p is the ratio of the process tolerance to its inherent variation, and is computed as

$$C_p = \frac{UTL - LTL}{6\sigma \text{ variation}}$$

UTL and **LTL** are the upper and lower response tolerance limits, and **6σ variation** is the amount of observed response variation about the mean response value bounded by the ±3σ confidence interval limits. C_p is therefore a direct measure of inherent process variation relative to specified tolerances. Figure 6 illustrates the C_p calculation elements for the critical pair resolution response described above given a mean resolution ($\overline{X}$) of 2.0 and tolerance limits of ±0.5. In classical SPC a process is deemed *capable* when its measured C_p is ≥1.33. The value of 1.33 means that the inherent process variation, as defined by the 6σ variation limits, is equal to 75% of the tolerance limits (4/3 = 1.33). Conversely, a process is deemed *not capable* when its measured C_p is ≤1.00, as the value of 1.00 means that the 6σ variation limits are located at the tolerance limits.

Figure 6. Robustness C_p – Critical Pair Resolution Response



The C_p metric is applied directly to critical chromatographic performance characteristics (critical responses) to determine the relative robustness of a candidate method in terms of the characteristic. The remainder of this discussion describes how this is done using resolution as the critical response. To compute C_p requires resolution response tolerance limits and 6σ variation limits for each study factor - the two elements of the C_p calculation.

Tolerance Limits for C_p

Considering the tolerance limits first – they are readily defined using the following rules:

1. They must be in the units of the response.
2. They should be symmetrical.
3. They should be defined as a ± tolerance limit delta (TΔ) that delineates a relative tolerance range and ***not*** as absolute UTL and LTL values.

   TΔ must be able to be applied to different candidate methods to determine their relative robustness. Absolute UTL and LTL values can not be used, since the mean response will vary across the candidate methods being evaluated.
4. The magnitude of the tolerance limit delta should represent a reasonable robustness goal for the critical response being evaluated.

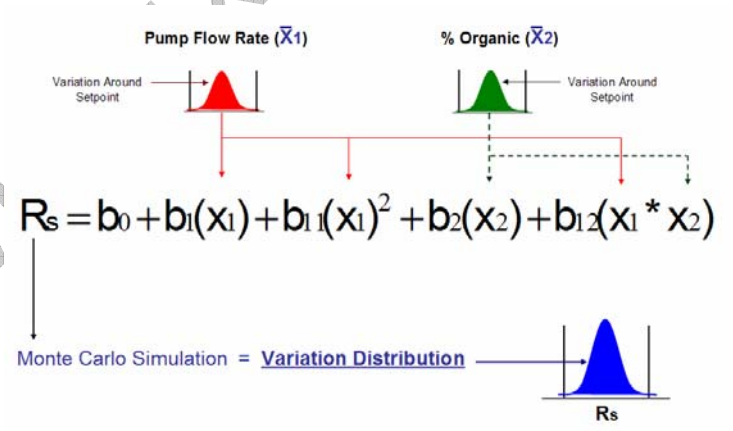
6σ Variation Interval for C_p

The Fusion AE software has built-in default values of the normally expected ±3.0σ limits (6σ variation limits) for several critical HPLC instrument parameters. The values in the table are guidelines that may be adjusted based on individual HPLC module specifications and equipment condition.

Translating an instrument parameter's 6σ variation limits into variation in a critical response requires an equation (model) that quantitatively defines the parameter's effect on the response. This *response prediction* model must accurately represent all significant parameter effects, including interaction effects, curvilinear effects, and non-linear effects. The new approach uses the response prediction models obtained from the DOE experiment together with Monte Carlo type simulation routines to predict how a candidate method will perform in terms of both the mean result and the response variation.

Figure 7 illustrates how a resolution response prediction model is used to obtain predictions of both mean response and response variation ***for a given candidate method***. First, 100,000 level settings are defined for each study factor using the normal distribution with mean value equal to the candidate method level setting and the ±3.0σ limits already defined for the factor. Next, the 100,000 combinations of factor error distribution level settings are input into the resolution prediction model, one combination at a time, which provides 100,000 response predictions. The distribution of these predictions correctly reflects the cumulative propagated error resulting from the study factor variations. Statistically characterizing this distribution then provides the 6σ variation value required in the C_p calculation. A resolution C_p value is then calculated for the candidate method. Repeating this process for each candidate method in a DOE experiment thus provides a C_p value for each candidate method coordinated with the mean response result. Note that this simulation approach requires no additional experiment data.

Figure 7. Response Variation Prediction



It is important to note that this approach correctly represents study factor variation as random, normally distributed setpoint error, and represents the entire error distribution of each factor in the robustness computation. Current practice robustness experiments normally only contain combinations of the ±3.0σ limit values around each factor's setpoint, and therefore do not provide data that correctly represents the robustness of the method being studied.

Once the C_p values are obtained for all candidate methods in the DOE experiment, the software automatically derives Robustness C_p models that quantify the effects of the study factors on method robustness for the resolution response. Resolution mean response and Robustness C_p models are then linked via numerical and graphical optimization routines to identify the study factor level settings that simultaneously meet goals for both mean resolution and resolution robustness.

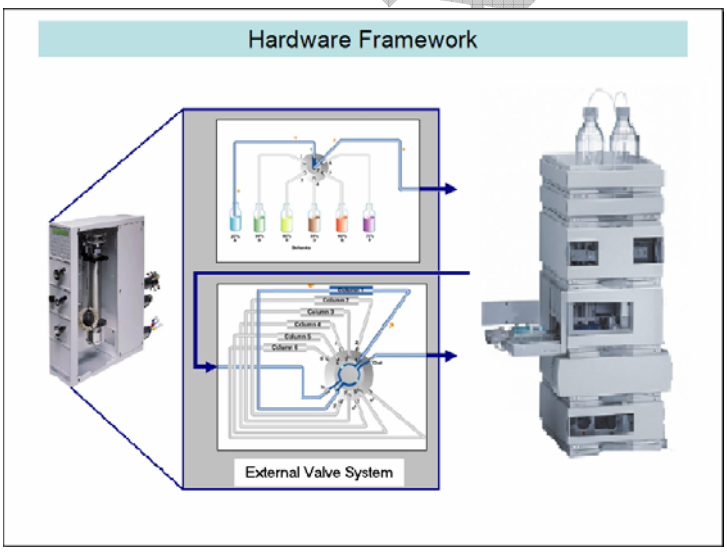
Following the successful column/solvent screening experiment (described in detail in a previous white paper) a *Phase 2 –Method Optimization* experiment was carried out at Pfizer's Ann Arbor laboratories using the same experiment sample. The experiment used the column, pH, and organic solvent type identified in the Phase 1 experiment. The experiment modified the template in terms of pump flow rate and gradient slope as shown below.

Experiment Variable	Range or Level Settings
Phase 1 Result Constants	Column 3, pH = 2.5, Acetonitrile
Pump Flow Rate (mL/min)	0.4 — 0.8
Gradient Slope (% Organic) — Vary Final Conditions	Initial %: 5.0 Final % Range: 70.0 — 95.0

The Experiment Platform - Hardware

Figure 3 illustrates the HPLC instrument system on which the screening and optimization experiments were run. The instrument system consisted of an Agilent Technologies 1100 HPLC configured with a G1311 quaternary pump, a G1313 autosampler, and a G1315 diode array detector. The HPLC instrument was augmented with a Varian, Inc. Column Valve Module (CVM) that contained a six-position solvent selector valve, a six-column switching valve, and column heating units. The solvent selector valve was connected to the Reservoir A line on the HPLC. This allowed automated multi-solvent screening of solvent linked study factors such as pH and additive. The column switching valve was connected to the main HPLC flow line. This allowed automated screening of up to six columns, or five columns and a bypass line.

Figure 3. HPLC Instrument with CVM



The Experiment Platform - Software

The experiments were generated and analyzed using the Fusion AE™ software program developed by S-Matrix Corporation. Fusion AE implements the phased QbD approach described in this paper using automated statistical experimental design, data analysis, and data modeling protocols. The software automatically converts the experiment designs into the native file and data formats required by the chromatography data system (CDS) software that directly controls the instrumentation. Additionally, the novel approaches to column/solvent screening and the integration of robustness into the method development process are fully automated in this software. The Varian® Galaxie™ CDS software program was used in these experiments. Galaxie provides full level-4 control of all Agilent Technologies HPLC instrument modules and also full control of all CVM components (column ovens and switching valves).

Table 1 presents the experiment design generated from the modified template along with the Resolution response results imported directly from the CDS for the experiment chromatograms. Resolution results were imported for four critical peak pairs (1-2, 2-3, 5-6, and 9-10), as the compounds corresponding to the other sample peaks were well resolved in all experiment chromatograms.

Table 1. Method Optimization Experiment Data Set

Experiment Design			Resolution Response Results			
Trial No.	Pump Flow Rate	Final % - Acetonitrile	2 - Res. USP	3 - Res. USP	6 - Res. USP	10 - Res. USP
1	0.4	82	0.00	1.00	6.52	0.76
2	0.6	95	1.41	2.45	1.37	0.00
3	0.8	70	3.33	9.81	17.33	4.37
4	0.7	89	3.28	1.27	2.90	1.62
5	0.4	95	0.00	0.82	5.05	1.23
6	0.5	76	1.09	0.88	1.60	0.00
7	0.6	70	3.91	0.85	3.48	2.04
8	0.4	95	0.00	0.00	4.97	4.22
9	0.6	82	2.30	1.00	2.26	1.05
10	0.4	70	0.00	0.00	0.77	0.00
11	0.7	76	0.00	4.18	3.80	2.32
12	0.8	82	4.89	0.00	4.25	2.76
13	0.4	70	0.00	0.00	6.83	0.00
14	0.8	95	0.00	3.12	3.08	1.74

Prediction models of the resolution responses were derived from the imported data for the four peak pairs using linear regression analysis. These mean prediction models were then used to generate Robustness C_p data for each peak pair for each experiment run as described in the Technical Background topic within this phase two section. Models were then automatically derived from the Robustness C_p data as also previously described.

Optimizing for Mean Performance and Robustness

Since mean performance and robustness goals are specific to the particular method and its stage of development, the software's numerical and graphical optimizers are "educated" by entering method performance goals for each chromatographic property studied, including robustness, into an optimization search setup dialog. Figure 8 is an image of the setup dialog implemented in the Fusion AE software program. The dialog enables three types of goals to be defined for numerical and graphical solution searches:

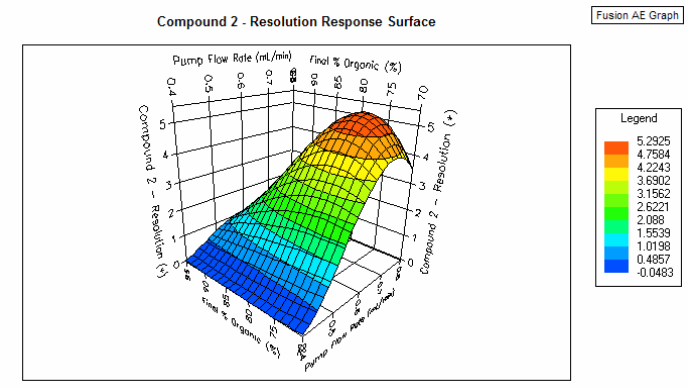
- **Maximize** – *Lower Bound* defines lower acceptability limit (e.g. Resolution, *LB* = 2.5, Robustness C_p, LB = 1.0).
- **Minimize** – *Upper Bound* defines the upper acceptability limit (e.g. Retention Time of last retained peak sets total assay time goal).
- **Target** – *Lower and Upper Bounds* define lower and upper acceptability limits around target (e.g. USP Tailing, *LB* = 0.8, *UB* = 1.2).

Figure 8. Optimization Search Setup Dialog

A numerical optimizer will thoroughly search the design space using the prediction models to identify the study factor level settings that will simultaneously meet or exceed all response goals. The numerical search routine investigates the design space at a level of granularity much finer than that represented by the experiment design runs. Numerical optimization is not described in detail here, since most scientists have at least some familiarity with numerical optimization routines and techniques through the use of the Solver routine provided within the Microsoft® Excel™ software program. However, a graphical optimization approach implemented in the Fusion AE software program is described in detail, as there is much less familiarity with this approach to optimization.

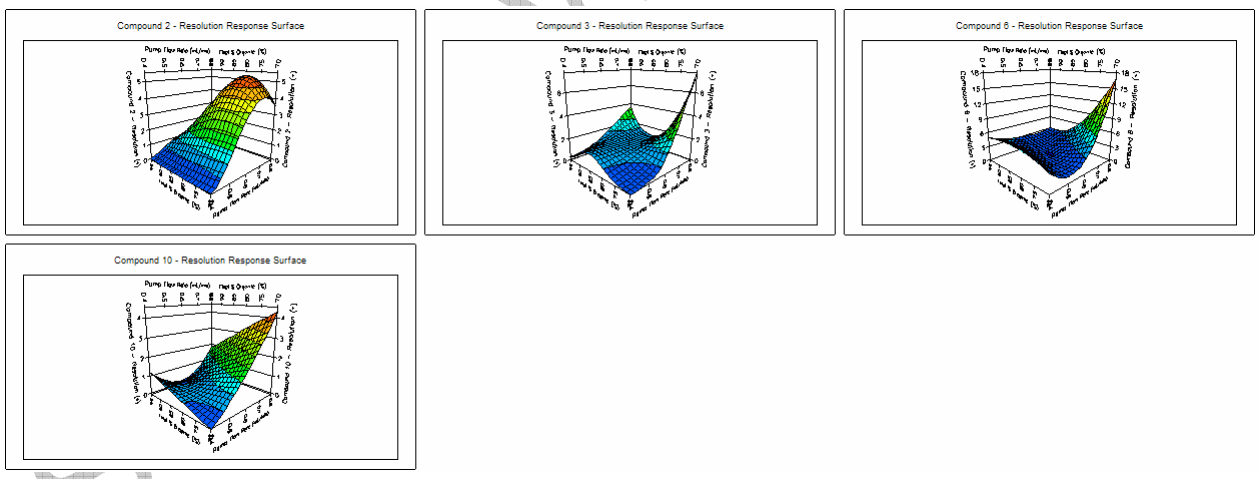
In current practice graphical optimization is restricted to generating a 3D resolution response surface graph and visually examining it to identify the factor level setting combination that meets the resolution goal. Figure 9 presents such a graph showing the change in resolution (Z axis) for one peak pair (1-2) as a function of changing the two experiment factors pump flow rate (X axis) and initial hold time (Y axis). A graph such as this is sometimes referred to as a resolution map. Response surfaces can be generated for any modeled response for any paired combination of study factors included in the experiment design. When the experiment design includes more than two factors the 3D response surface graph will correspond to a single level setting of each remaining (non-graphed) factor.

Figure 9. Response Surface Graph: Resolution – One Peak Pair



However, it is very often the case in HPLC method development projects that multiple peaks must be resolved. This makes the current practice approach of visually inspecting multiple resolution maps very cumbersome. Figure 10 is a trellis of four resolution response surface graphs illustrating the changes in resolution of four critical peak pairs (1-2, 2-3, 5-6, and 9-10) as a function of changing the pump flow rate (X axis) and the final percent organic (Y axis). Attempting to identify the level setting combination of the graphed variables that will result in adequate resolution of all peak pairs by visually comparing the four graphs in Figure 11 is both tedious and difficult. The number of graphs that must be compared, and therefore the difficulty of the task, grows geometrically when one must also consider additional responses such as peak asymmetry and/or when more than two parameters are included in the experiment.

Figure 10. Response Surface Trellis: Resolution – Five Peaks



The graphical approach to optimization approach implemented in the Fusion AE software program builds on the fact that it is easier to identify the "best" level setting combination of the study factors using a 2D contour graph. Figure 11 presents a 2D contour graph corresponding to the 3D response surface graph in Figure 9. The relationship between the two graphs can be understood by thinking of the 2D contour graph as the 3D response surface graph as it would appear if viewed from directly above the surface.

Figure 11. Response Contour Graph: Resolution – One Peak Pair

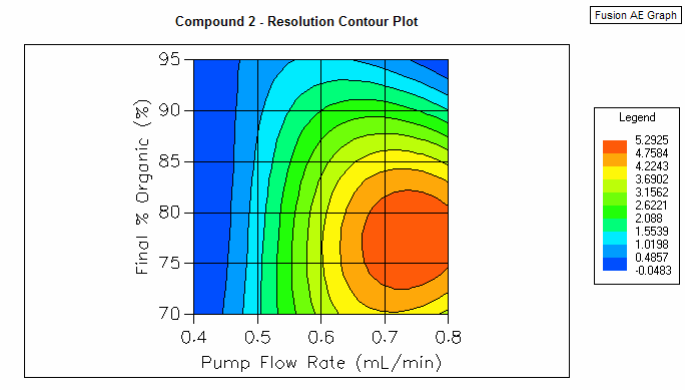


Figure 12 is a simplified version of the contour graph in Figure 11. In this graph a goal of Maximize is applied to the 1-2 Resolution response with a minimum acceptability value (Lower Bound). The graph is interpreted as follows:

- The Dark Red shaded region corresponds to parameter settings that *do not meet* the Resolution minimum acceptability goal (predicted responses are below the lower bound value).
- The Black line bordering the shaded and unshaded regions corresponds to parameter settings that *exactly meet* the Resolution goal (predicted responses equal the lower bound value).
- The unshaded region corresponds to parameter settings that *exceed* the Resolution goal (predicted responses are above the lower bound value).

Figure 12. Response Overlay Graph: Resolution – One Peak Pair

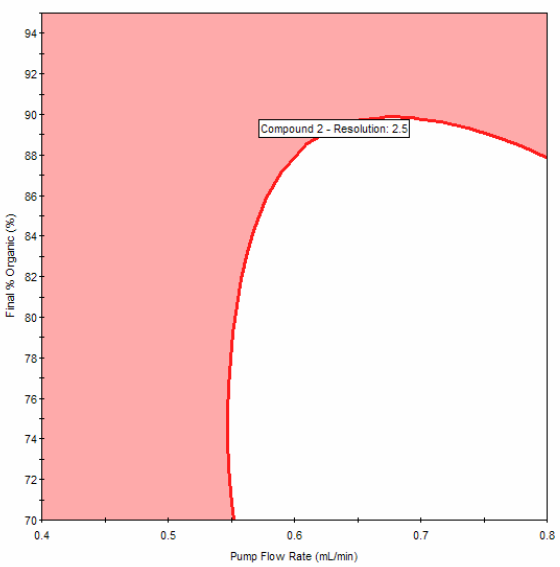


Figure 12 is called a Response Overlay graph, since multiple response goals can be displayed (overlaid) on the one graph. This is shown in Figure 13, which contains Resolution goals (*Maximize*, all Lower Bounds = 2.5) for all four critical peak pairs in the DOE-based method development experiment sample. Note that five individual graphs would have to be generated and visually inspected to determine the same information contained in this one response overlay graph in terms of level setting combinations that meet/do not meet all resolution goals.

Figure 13. Response Overlay Graph: Resolution – Five Peaks

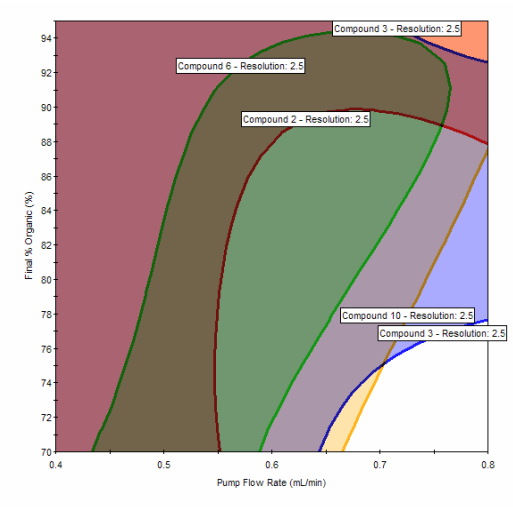
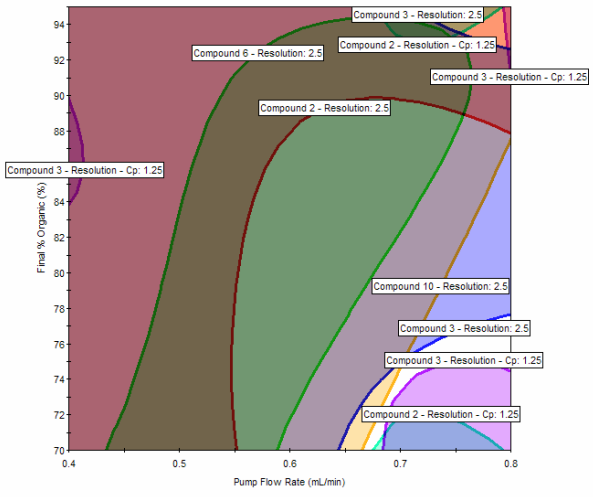


Figure 14 is the response overlay graph shown in Figure 13 with additional overlays of Robustness C_p goals (Maximize, all Lower Bounds = 1.25) defined for all peak pairs having predicted mean resolution values below 4.00. As indicated in the figure, modeling the computed Robustness C_p values defined for the DOE experiment methods enables these responses to be directly integrated into the optimization search along with all other critical responses. The unshaded region in this final overlay graph now represents the level setting combinations of the study factors that exceed the defined goals for both mean performance and robustness.

Figure 14. Response Overlay Graph: Resolution and C_p – Five Peaks



Finally, Figure 15 is the chromatogram obtained by injecting the sample on the HPLC set at the optimum parameter settings identified in the two experiments. These final method conditions are defined below. It is noteworthy that the total experimental work required to obtain this final method consisted of two multi-factor statistically designed experiments, both of which were carried out overnight in fully automated (walk-away) mode.

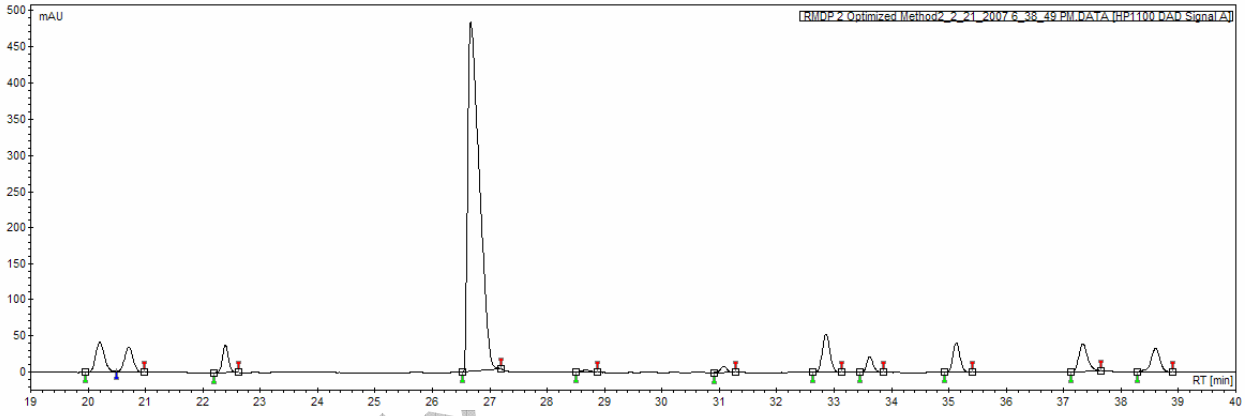
Phase 1 – Column/Solvent Screening

Column Type – Column 3
pH – 2.5
Gradient Time – 40 minutes

Phase 2 – Method Optimization

Pump Flow Rate – 0.67 mL/min
Final % Organic – 70 %

Figure 15. Chromatogram from Optimized Method



Conclusions

The *Phase 1 – Column/Solvent Screening* experiment identifies the correct analytical column, pH, and organic solvent type to use in the next phase of method development. Once these instrument parameters are identified, the second phase of method development involves experimentally manipulating the remaining important instrument parameters to obtain a method that meets all performance requirements. However, all current approaches to meeting this goal only address method mean performance. As a result, robustness is currently only evaluated separately as part of the method validation effort. The novel Quality-by-Design based methodology described here combines Design of Experiments methods with Monte Carlo simulation to successfully integrate quantitative robustness metrics into the method development process. This combination enables a best practices approach to method development and optimization as the regulatory guidances recommend without requiring any additional experimental work.

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Acronyms, Tables and Figures

Acronyms:

21 CFR 11 –	Title 21, Part 11, of the Congressional Federal Register
CDS –	chromatography data system
DOE –	design of experiments (also DOX)
FDA –	U.S. Food and Drug Administration
GC –	gas chromatography
HPLC –	high performance liquid chromatography
ICH –	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
PhRMA –	Pharmaceutical Research and Manufacturers of America
QbD –	quality by design
SDK –	Software Development Kit (third-party software development interface)
SOP –	Standard Operating Procedure

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