Automating HPLC Analytical Method Development

Fusion AE™ Software Program White Paper
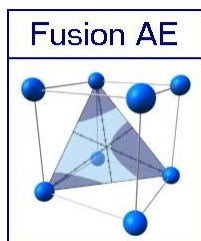
Introduction

Chromatographic analytical method development is currently a time consuming process usually done by trial and error. The standard approach is to vary one instrument factor at a time and assess the effect of the changes on key performance requirements such as critical pair resolution and total assay time. If no satisfactory result is obtained from changes to the selected factor, then a second factor is selected for study. This process is repeated until a method is obtained that meets the current performance requirements. Methods developed in this fashion are usually sub-optimal and not robust. This means 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.

Although some method development software tools are available, these tools are seriously limited in terms of (1) the number and types of instrument parameters they can simultaneously study, (2) the kinds of parameter effects they can visualize and quantify, and (3) the level of automation support that they provide. Until now, no overarching technology solution existed that overcame all these limitations. This white paper describes Fusion AE™, a software program developed by S-Matrix Corporation that provides an overarching automation technology for fully automated analytical method development adapted to multiple instruments and instrument data systems.

Acronym Definitions:

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
SDK – Software Development Kit (third-party software development interface)
SOP – Standard Operating Procedure

Table and Figures:

Bibliography:

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3. ICH-Q2B - Guideline for Industry. Q2B Validation of Analytical Procedures: Methodology. November, 1996.

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6. Turpin, Joseph (Eli Lilly and Company, Inc.) and Verseput, Richard (S-Matrix Corp.), (2003). "Analytical Method Development & Validation - Increasing Efficiency Through Automation". Presented at the PerkinElmer TotalChrom User's Conference, Atlanta, GA.

Analytical Method Development Approaches

The standard approach to chromatographic analytical method development is currently a time and resource intensive process of systematic trial and error. The basic approach is to define a starting point method using current knowledge of the compounds to be analyzed in terms of their structures and chemistries. The starting point method specifies initial settings for all key instrument parameters: column, pump flow rate, detector wavelength, mobile phase blend, gradient conditions, etc. The analyst then typically proceeds to refine the method according to one of the approaches presented below.

One Factor At a Time Approach

The most common systematic trial and error approach is the One-Factor-At-a-Time approach (OFAT). In this approach the analyst selects the instrument parameter believed to have the strongest affect on method performance, and varies that parameter across some experimental range while holding all other parameters constant at starting-point conditions. Table 1 is an example of such an OFAT study. In this study the analyst selected Pump Flow Rate, and varied it from 0.7 to 1.7 ml/min in a series of injections while holding all other instrument settings constant. As the Series 1 Resolution data in Table 1 show, given a critical-pair resolution goal of ≥1.5, no satisfactory result was obtained. The analyst therefore set the flow rate to a constant of 1.0 ml/min, selected Gradient Time as the next study factor, and ran a second series of injections in which the gradient time was varied. This process is typically repeated until a method is obtained that meets current performance requirements.

Table 1.   OFAT Approach to Method Development

Series 1 - Vary Pump Flow Rate (All Runs – Gradient Time = 8.5 min.)	Critical Pair Resolution
0.7	0.78
0.9	**1.22**
1.1	**1.25**
1.3	1.18
1.5	0.76
1.7	0.53
Series 2 - Vary Gradient Time (All Runs – Pump Flow Rate = 1.0 mL/min.)	
4.0	0.63
6.0	0.87
8.0	**1.31**
10.0	1.26
12.0	0.67

Analytical methods developed by the OFAT approach are usually sub-optimal and not robust. The root cause is that, in addition to linear additive effects, real world instrument parameters can have strong interaction effects on critical chromatographic properties. However, to visualize an interaction between parameters requires that both parameters vary in the same series of runs. Since only one parameter at a time is varied in an OFAT experiment, interaction effects are not even able to be expressed in the OFAT results. This is true even in cases where these effects can predominate within the experiment ranges.

Deviation from ideal behavior is the reason that none of the study conditions in the previously described OFAT experiment resulted in an acceptable critical-pair resolution. Figure 1 is a Response Contour Graph that visualizes the deviation from ideal behavior. The blue lines in this figure represent the OFAT experiment: the vertical line follows the path of the Series 1 runs (constant gradient time), while the horizontal line follows the path of the Series 2 runs (constant pump flow rate). The red "response contour" lines in the graph represent the actual critical-pair resolutions that would be obtained for all combinations of gradient time and pump flow rate within their experimental ranges. The strong curvature in the red lines is caused by a strong interaction between gradient time and flow rate that predominates within these ranges. Note that the OFAT experiment results in Table 1 imply that the study parameters are expressing individual non-idealized effects. However, they do not provide any incite into the interaction effect, nor do they indicate which parameter settings within the experiment ranges, if any, can achieve the critical-pair resolution goal.

Figure 1.   OFAT Response Contour Graph

Contour map of Resolution versus Gradient Time (X) and Pump Flow Rate (Y)
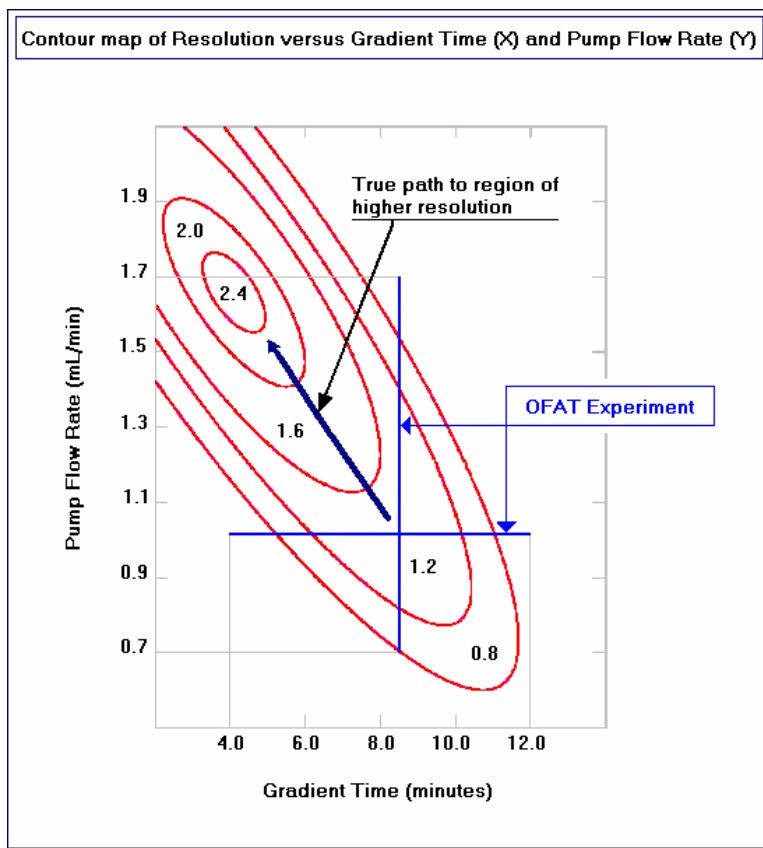
First Principles Equation Approach

This approach utilizes theoretical equations (models) that describe experimental parameter effects as the starting point for method development. For example, a chromatographic property such as capacity factor (k') is related to solvent composition by the theoretical linear model:

$$\text{Log } k' = \text{Log } k_w - S\phi$$

where k' is the solute capacity factor, k_w is a constant, S is the slope of the regression line, and ϕ is the fractional solvent composition.

The approach involves first running the instrument at two or three different values of solvent composition while holding all other instrument parameters constant at starting point method conditions. These first runs are often referred to as "tuning" runs. Regression analysis is then carried out on the resulting data using the theoretical linear model. This updates the model coefficients, which "normalizes" the theoretical model to the current system. Once the coefficients are updated, the model is used to predict the optimum solvent composition and the chromatogram that will result from setting the mobile phase to that composition. This approach can be used for any chromatographic property for which a starting-point theoretical model exists relating the property to an experimental parameter or a combination of parameters.

There are two important limitations to the first principles equation approach. First, starting-point theoretical models do not exist for all combinations of instrument parameters that can strongly impact critical chromatographic properties. This severely limits the possible scope of these studies, and therefore the opportunity to develop a method that is optimal in terms of both performance and robustness. Second, the available starting-point theoretical models are linear models. Like the OFAT approach, these models can not account for the interaction and nonlinear effects that real world instrument parameters can express. As a result, the stronger these effects, the more the actual results will deviate from the predicted optimum. However, the predictions from these models can be used to define a starting point for the statistical experiment design approach described below.

Expert System Augmentation

In an expert system, the first principles approach is augmented by (1) a searchable knowledgebase consisting of chromatographic properties and experiment parameter data such as column and solvent properties, (2) algorithms that retrieve the data and apply them to the theoretical linear models, and (3) a guidance logic software program that determines data selection and algorithm sequencing based on rules for solving the type of method development problem defined by the analyst. The augmentation tools supporting the expert system approach can further support the approach as a starting point for the statistical experiment design approach described below.

Statistical Experiment Design Approach

This approach uses a statistical experiment design to construct a data set from which empirical models can be derived that relate instrument parameter effects to chromatographic properties. These models are then used to predict instrument parameter settings that will meet requirements for method performance and robustness. The analyst carries out this approach in five steps:

1. **Analyst selects the instrument parameters (study factors)** that are known or presumed to be the most important effectors of the chromatographic properties for which required analytical method performance goals have been defined. Analyst also defines a range or selected levels to study for each of the study factors.

2. **Analyst selects a statistical experiment design.** The design defines a number of specific study factor combinations that must be run on the instrument. The specific combinations in the design assure that all the important effects of the study factors can be accurately determined by the subsequent data analysis.

3. **Analyst runs the various conditions defined in the design on the instrument.** The analyst then carries out a linear regression analysis on the combined design/results data set to obtain empirical models that quantitatively define the study factor effects on the chromatographic properties.

4. **Analyst uses the models to predict the optimum analytical method.** The analyst then experimentally verifies the prediction by running the predicted optimum level settings of the study factors and observing how closely the observed results match the prediction.

5. **If the predicted method meets the performance goals defined for the chromatographic properties, then the method is accepted.** If the best method obtained from the study does not perform adequately, the current study factors are set to a constant at their best performing levels, new study factors are selected, and the process is repeated until the analyst obtains a satisfactory method.

Unlike the First Principles Equation approach, there is no restriction on the combination of instrument parameters that can be selected for study. Unlike the OFAT approach, in a designed experiment multiple instrument parameters are varied simultaneously so that interaction effects can be revealed.

The empirical models resulting from the statistical experiment design approach can define the overall mean (average) performance of the method. The models can also define method robustness by predicting the effects of accumulated variations in the study factors, as shown in the subsequent section titled Rapid Method Optimization for Performance and Robustness. The statements reproduced below present how important integrating robustness into the method development process is to regulatory bodies.

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.

In the case of liquid chromatography, examples of typical variations are:

- Influence of variations of pH in a mobile phase
- Influence of variations in mobile phase composition
- Different columns (different lots and/or suppliers)
- Temperature
- Flow rate

Fusion AE™ – Automating the Statistical Experiment Design Approach

Traditionally, an analyst attempting to use DOE in analytical method development work encountered two severe impediments. First, detailed statistical knowledge was required to adapt generic DOE tools to the work. Second, many laborious manual operations were required to exchange experiment designs, data, and results between off-line DOE software, spreadsheets, word processors, and chromatography data systems. Fusion AE overcomes both of these impediments to seamlessly integrate the DOE approach into the analytical method development workflow. It does this by 1) adapting generic DOE software to analytical method development, and 2) automating data exchange with multiple instruments and data systems. These two powerful advancements to traditional off-line DOE software are described below.

Adapting Generic DOE Software to Analytical Method Development

A major difficulty associated with using generalized DOE software is that the user is required to adapt the desired study to the one-size-fits-all nature of the generic software interface. As shown in Figure 2, generalized DOE software provides no customization or "intelligence" regarding either the study factors or the instrument on which the design will be run. Although the user can edit the generic variable names to reflect actual study factors, the software does not allow the user to define settings specific to an HPLC platform such as number of desired repeat injections or the association of a variable such as Buffer to a mobile phase reservoir.

Figure 2.   Off-line DOE Software – Generic Interface

Figure 3 shows Fusion AE's alternative software interface. The analyst starts by selecting the desired method development *Experiment Type* (e.g. Screening or Optimization) and the *Target Instrument* (e.g. Varian ProStar or Agilent 1100) on which the experiment will be run. Fusion AE then automatically updates the standardized Experiment Setup template to the selected *Experiment Type* and *Target Instrument*. Dynamically updating the standardized template includes updating the list of study factors (Available Variables) that the analyst can choose from and configuring each factor based on the level of automation that the instrument allows. In addition, once a study factor is selected (Included Variables), the absolute allowable range of each factor is automatically updated to the factor's operating limits on the *Target Instrument*.

Figure 3.   Fusion AE Software – Application Specific Interface

Another major difficulty associated with using generalized DOE software arises from the fact that there are several types of statistical experiment design; each type contains a large number of different individual designs. Therefore, selecting the optimal design for a given study requires a thorough understanding of the different information properties of each variety and design, as well as any restrictions on use in terms of the nature of the study factors and the target system. In fact, one of the most common failures of DOE-based experiments is a Type 3 error failure (right answer, wrong question) which arises from inappropriate design selection.

Fusion AE overcomes this second major difficulty by providing two modes of experiment design selection: Automated and User Interactive. In the Automated mode the program's underlying logic automatically selects the most "efficient" design, meaning the design that meets the information requirements in the minimum number of experiment runs, given the selected experiment type (e.g. Screening versus Optimizing) and selected variables (e.g. pump flow rate and mobile phase blend). In the User-interactive mode, Fusion AE provides a menu of the statistical designs that are appropriate to the selected experiment type and variables with its recommended design pre-selected by default. However, in this mode the user can change the default to another of the available designs.

Automating Data Exchange with Multiple Instruments and Data Systems

Historically, the degree of instrument control offered by analytical method development software ranged from very limited to nonexistent. Most software programs offered no data exchange automation, while a few provided "real-time" control of one instrument from one manufacturer or were compatible with only one data system. Analytical Method development approaches and SOPs therefore had to be manually adapted to different instruments and different instrument data systems.

Fusion AE overcomes this limitation through an innovative instrument control-based framework that S-Matrix has developed and is patenting. This framework automatically responds to instrument configuration differences to maximize the opportunity for automated experimentation. For example, the software does not allow a study to include column oven temperature if the target instrument does not have a column oven. Also, given a study that includes multiple columns, the software structures the exported experiment design correctly in response to the presence or absence of a column switching valve.
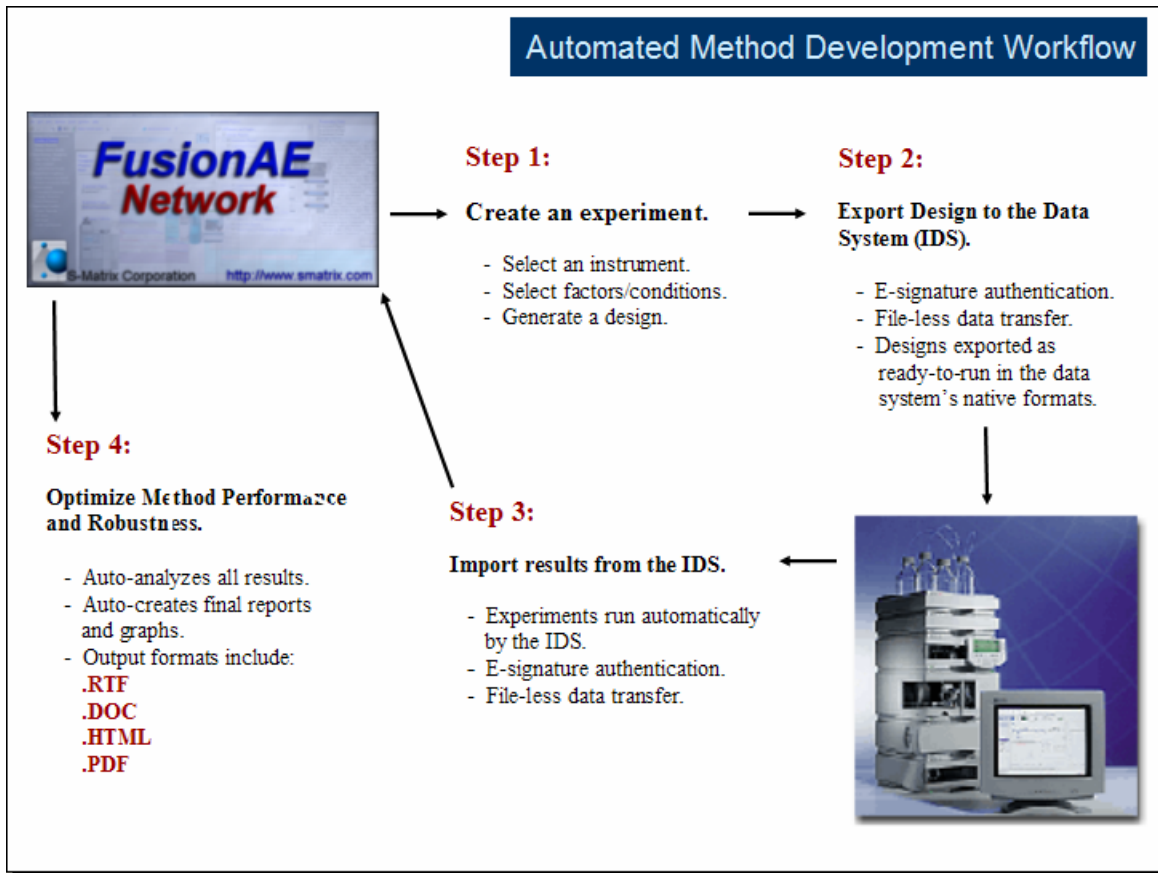
Additionally, the Fusion AE framework provides file-less data exchange (experiment designs, results, and instrument control) that is extensible to multiple instruments and data systems. This unique framework enables S-Matrix, Fusion AE customers, and instrument manufacturers to easily construct drivers for their instruments and data systems that Fusion AE can directly import. These drivers "educate" Fusion AE to the specific control elements and automation capacities of the instrument, as well as the mechanisms of automated data exchange.

Fusion AE™ – A Complete Method Development Software Solution

The Fusion AE automated software solution is illustrated in Figure 4. The figure depicts the automated method development workflow. Notable features of the software program include:

- **Rapid Method Development** – quickly optimize methods for performance and robustness.

- **Rigorous DOE methods and practice integration** – expert system automation, dynamically customized interface, and DOE wizard guidance.

- **Method connectivity** – early methods developed manually or using other software tools should be able to be further developed and optimized using the new software.

- **21 CFR 11 compliance toolset** – helps maintain compliance across integrated platforms.

- **Data exchange with multiple instrument data systems** – Fusion AE currently exchanges data with the following instrument data systems:

  - PerkinElmer® TotalChrom™.
  - Varian® Galaxie®.
 - Waters® Millennium®[32] and Empower™.

Figure 4. **Fusion AE Automated Method Development Solution**

Automated Method Development Workflow

FusionAE Network
S-Matrix Corporation   http://www.smatrix.com

Step 1:

Create an experiment.

- Select an instrument.
- Select factors/conditions.
- Generate a design.

Step 2:

Export Design to the Data System (IDS).

- E-signature authentication.
- File-less data transfer.
- Designs exported as ready-to-run in the data system's native formats.

Step 4:

Optimize Method Performance and Robustness.

- Auto-analyzes all results.
- Auto-creates final reports and graphs.
- Output formats include:
  .RTF
  .DOC
  .HTML
  .PDF

Step 3:

Import results from the IDS.

- Experiments run automatically by the IDS.
- E-signature authentication.
- File-less data transfer.

Fusion AE™ – Rapid Method Optimization for Performance and Robustness

The Fusion AE Method Development application module offers fully **Automated** and **User Interactive** wizard guided modes for experiment design and data analysis, as shown in Figure 5. In the Automated modes design generation and analysis of all results data sets are accomplished with a single button click. The Automated analysis mode has a One at a Time option that allows you to select one or more of the available results data sets (Responses) for fully automated or user interactive, wizard guided analysis.

Figure 5. **Automated and User Interactive Wizard Modes**
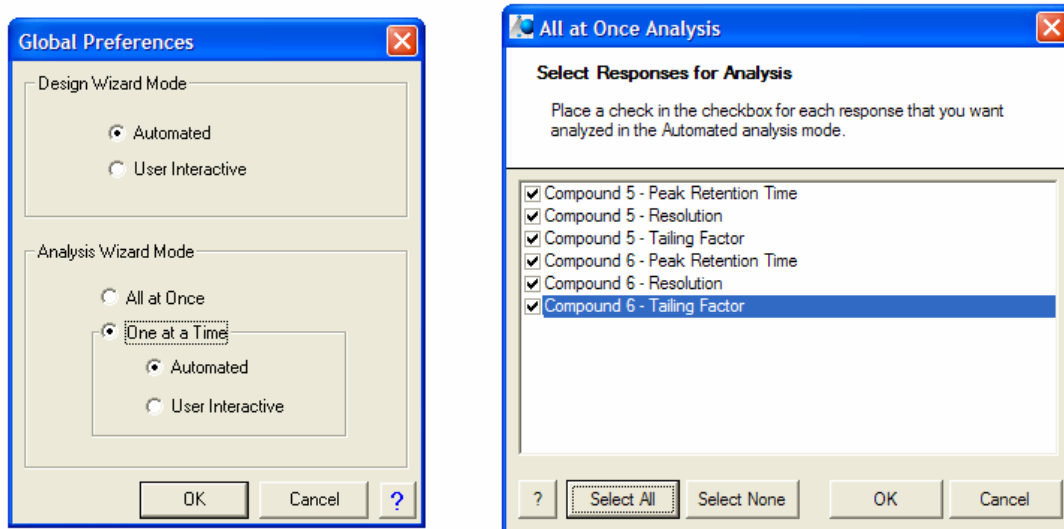

Once you select an analysis mode, Fusion AE instantly performs six different types of integrated numerical analyses on each results data set: error analysis, transformation analysis (nonlinear data estimation), regression analysis, residuals analysis, and outlier analysis. Once analysis is complete, Fusion AE automatically constructs and displays analysis reports for each selected compound and result that include descriptive graphics for user review.

Each analysis quantitatively defines and ranks the linear, interactive, and nonlinear effects of the parameters on the chromatographic properties under study. Each analysis also yields a model (equation) of the parameter effects. Fusion AE enables you to 1) **Numerically** identify the parameter settings that provide optimum method performance, and 2) **Graphically** visualize the optimum region (robustness ranges) around the optimum performance settings using these models. To do this you first "educate" the software by entering your method performance goals for each chromatographic property studied. As shown in Figure 6, you can assign one of three types of goals to each property:

- **Maximize** – *Lower Bound* defines lower acceptability limit (e.g. Resolution, *LB* = 2).
- **Minimize** – *Upper Bound* setting for last retained peak defines the upper acceptability limit on total assay time (e.g. Retention Time, *UB* = 10 minutes).
- **Target** – *Lower and Upper Bounds* define lower and upper acceptability limits around target (e.g. USP Tailing, *LB* = 0.8, *UB* = 1.2).


Figure 6.   Optimization Goal Settings
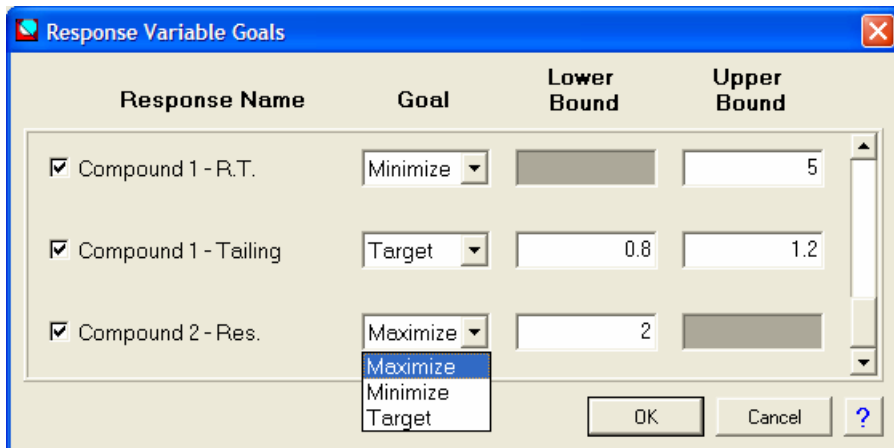
Once Fusion AE's Numerical Optimizer identifies the optimum method performance settings, the program's Graphical Optimizer lets you visualize the robustness region around the optimum settings. A Fusion AE Optimization Overlay Graph is presented in Figure 7. In this graph USP Tailing results for Compound 2 predicted by the analysis model are plotted against the experimental ranges of two study parameters: Pump Flow Rate (x axis) and % Buffer (y axis). The graph is interpreted as follows:

- Blue shaded region corresponds to parameter settings that *do not meet* the Tailing Factor lower and upper acceptability limits (bounds).
- Dark blue lines bordering the shaded and unshaded regions correspond to parameter settings that *exactly meet* the acceptability limits.
- Unshaded region corresponds to parameter settings that *exceed* the Tailing Factor lower and upper acceptability limits.

Figure 7.   Optimization Overlay Graph – USP Tailing, Compound 2
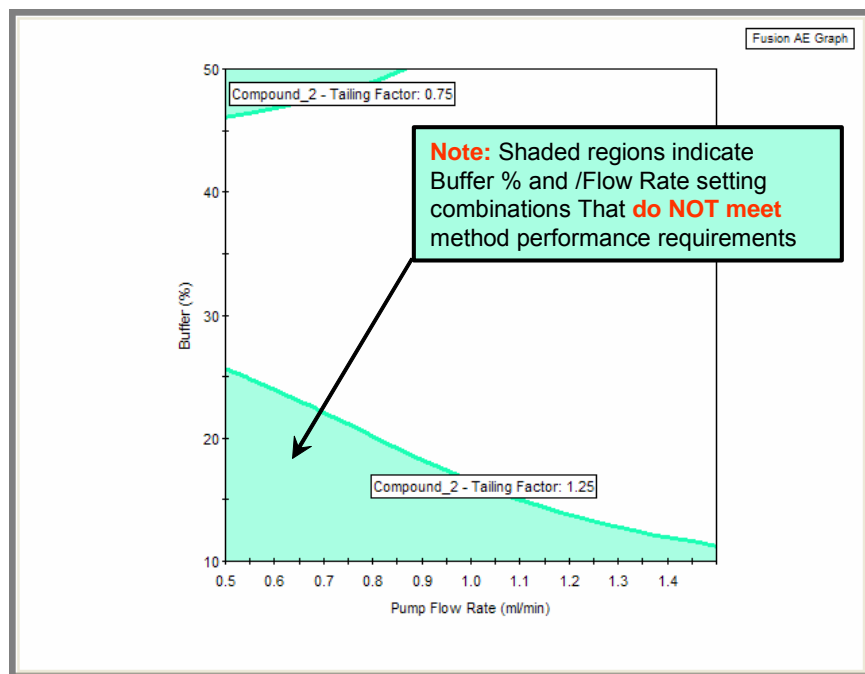
The graph in Figure 7 corresponds to one goal for one compound. However, three compounds were included in this method development study, and three results data sets were obtained for each compound: Tailing Factor (USP Asymmetry), USP Resolution, and Peak Retention Time. Figure 8 presents the Fusion AE Overlay Graph of predicted Tailing Factors for Compounds 2 and 3 as functions of the two study parameters represented in Figure 7. In this graph the Tailing Factor results for Compound 2 again appear in blue, but there is now a second set of shaded regions in yellow corresponding to parameter settings that do not meet the Tailing Factor acceptability limits defined for Compound 3. Note how the combined shaded regions demarcate a much reduced range of parameter settings that simultaneously exceed the acceptability limits for both compounds (the unshaded region).

Figure 8.   USP Tailing Goals – Compounds 2 and 3
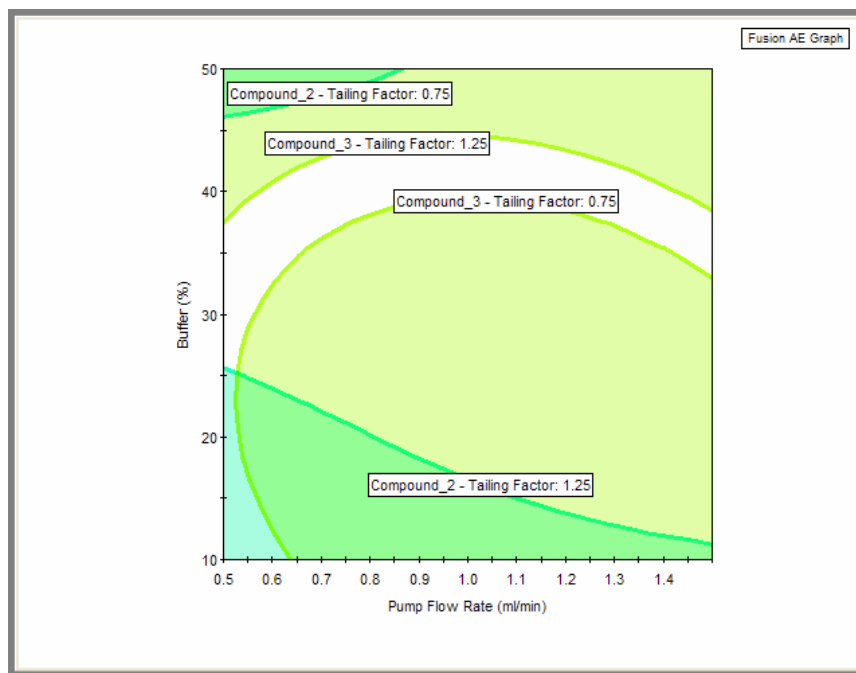
The graph in Figure 9 addresses the Tailing Factor, Resolution, and Retention Time goals for all three compounds, again as functions of the two study parameters represented in Figure 7. In this graph the shaded regions combine to demarcate a severely reduced range of parameter settings that simultaneously exceed the acceptability limits for both compounds.

Figure 9 also shows the location of the optimum point – also referred to as the "Sweet Spot." By definition the sweet spot corresponds to *achievable* settings of the graphed parameters within the unshaded region, since this region corresponds to coordinates that exceed all method performance goals. As the graph in Figure 9 shows, many coordinates meet this definition. However, to be truly optimal, the method must also be robust. This means that bracketing the set point with the total variation expected under normal operating conditions will not encompass any shaded region. For example, on this HPLC system the pump flow rate has a setting precision limit of 0.1 ml/min and an expected total operating variation of ±0.5 ml/min. As shown in Figure 10, the precision limit and operating variation locate the sweet spot at 1.3 ml/min, since ±0.5 ml/min brackets around pump flow rates of 1.2 ml/min and 1.4 ml/min encompass shaded regions on the graph.

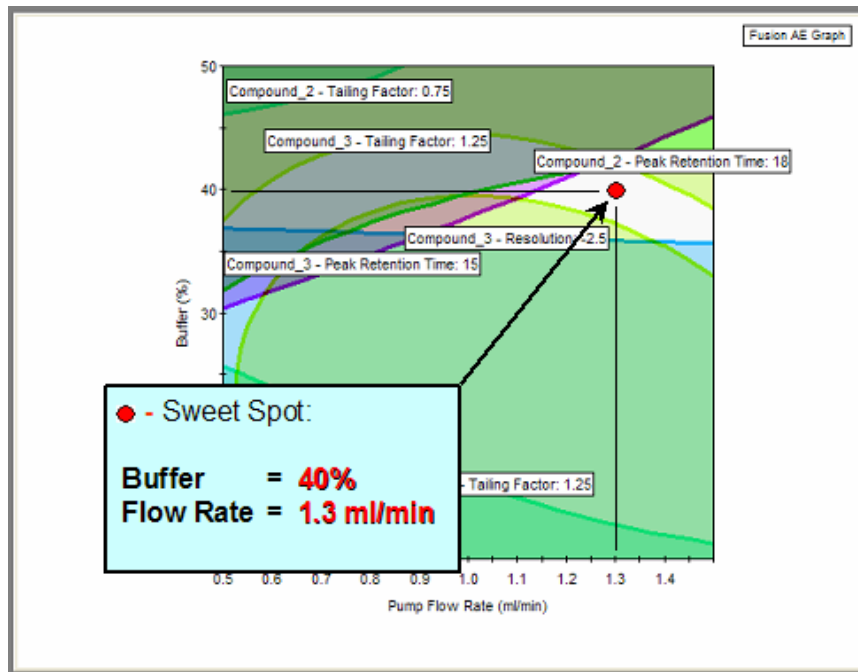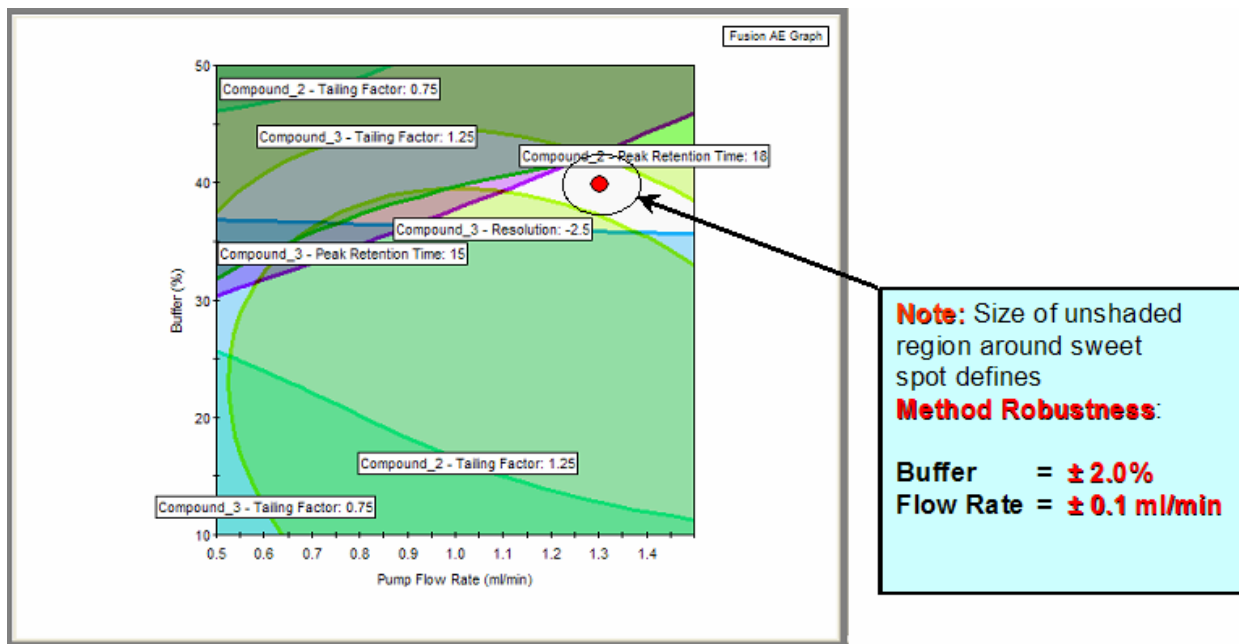## Figure 9.   All Performance Goals – All Compounds

Figure 10.   Region of Robustness

In Figure 11 the graphed range of pump flow rate has been reduced from the full experiment range to the expected total operating variation range of ±0.1 ml/min around the set point of 1.3 ml/min. The horizontal red lines in the graph indicate the Buffer % target setting of 40% (thick line) and the expected total operating variation of ±0.2% (thin bracket lines). Note that the Buffer % bracket lines do not encompass any shaded region across the full expected operating range of pump flow rate around its set point.

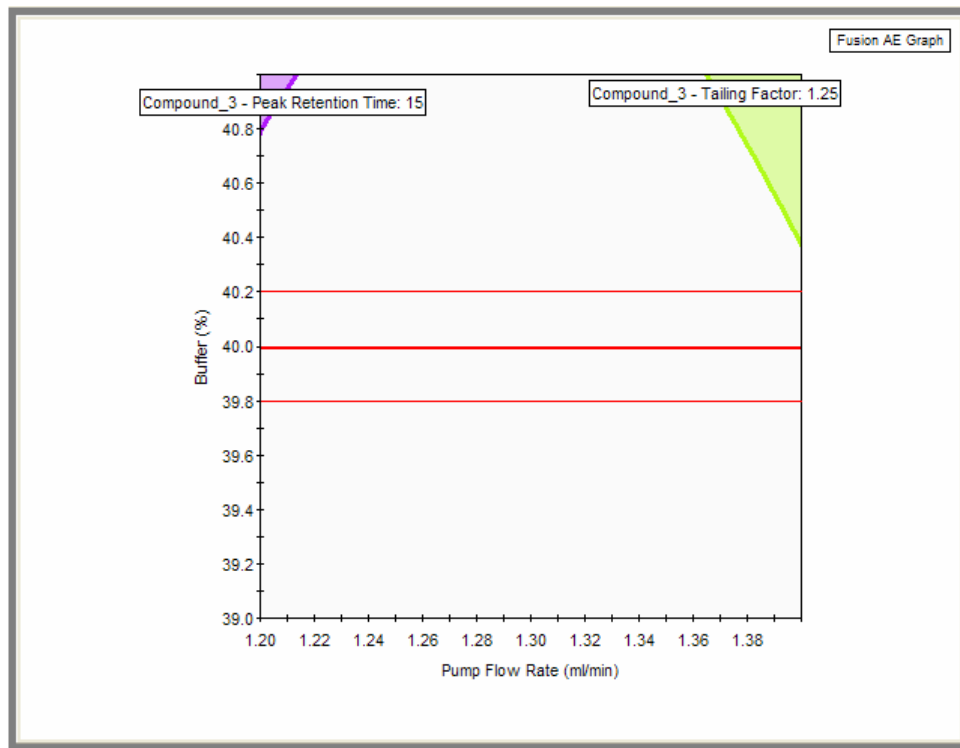**Figure 11.   Expanded Graph – Region of Robustness**

Figure 12 presents the chromatogram obtained by running the assay at optimum conditions: pump flow rate = 1.3 ml/min, ACN/Buffer ratio = 60/40. As the chromatogram shows, all compounds are well resolved under the optimum conditions with excellent peak shape and total assay time under 10 minutes.

Figure 12.   Chromatogram of Experimentally Verified Sweet Spot
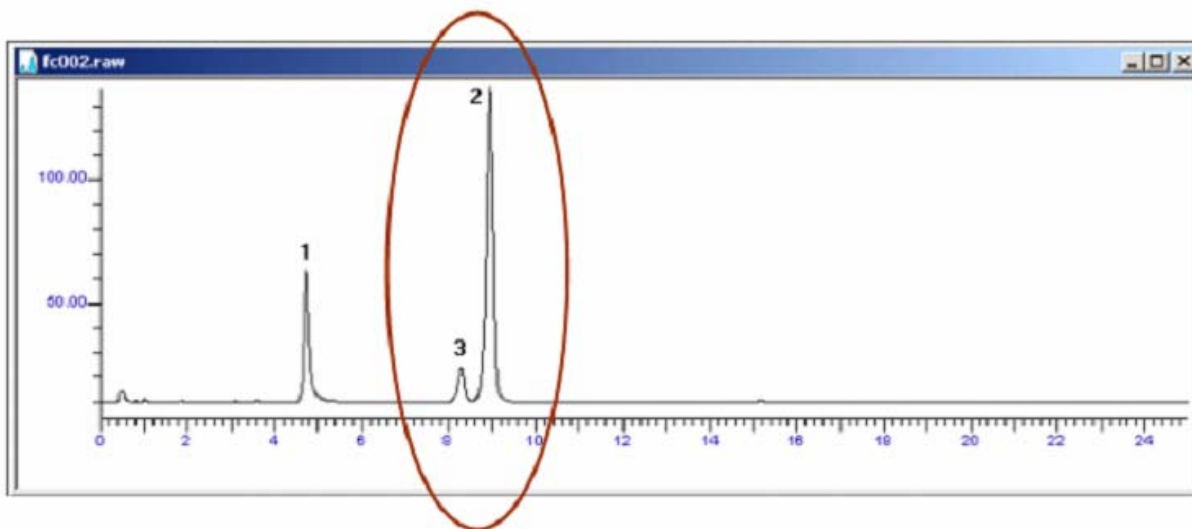
Fusion AE software benchmarking was carried out at the central research facility of a major international pharmaceutical company [6]. The benchmarking involved conducting "live" isocratic and gradient method development experiments in the walk-away mode with full instrument control and automated data exchange with the CDS.

Benchmarking Study #1 – Gradient Method

The Gradient Benchmarking study employed a product under current development that contained six compounds. A traditional method development approach was first tried using a popular first principles equation approach software tool. The best results obtained from this approach was not able to define a method that met all resolution and tailing factor requirements specified for the six compounds, as shown in Figure 13. Figure 14 shows the development results obtained using Fusion AE; two optimized and robust methods that both met all goals for all six peaks – one with a 30 minute total assay time and one with a very fast six minute total assay time. These results were obtained from a single experiment design run overnight in a fully automated mode. The Fusion AE results were experimentally verified by the lab.

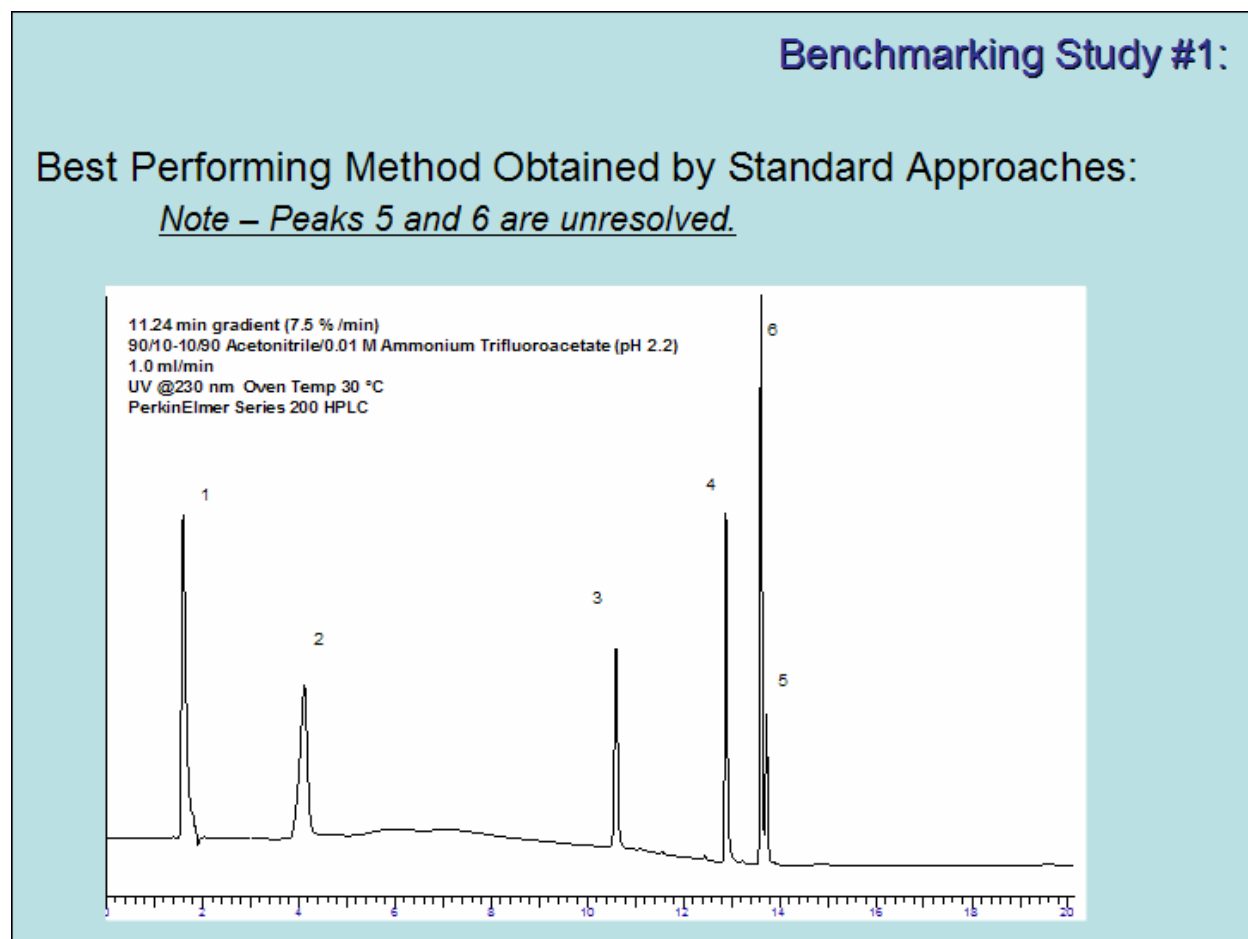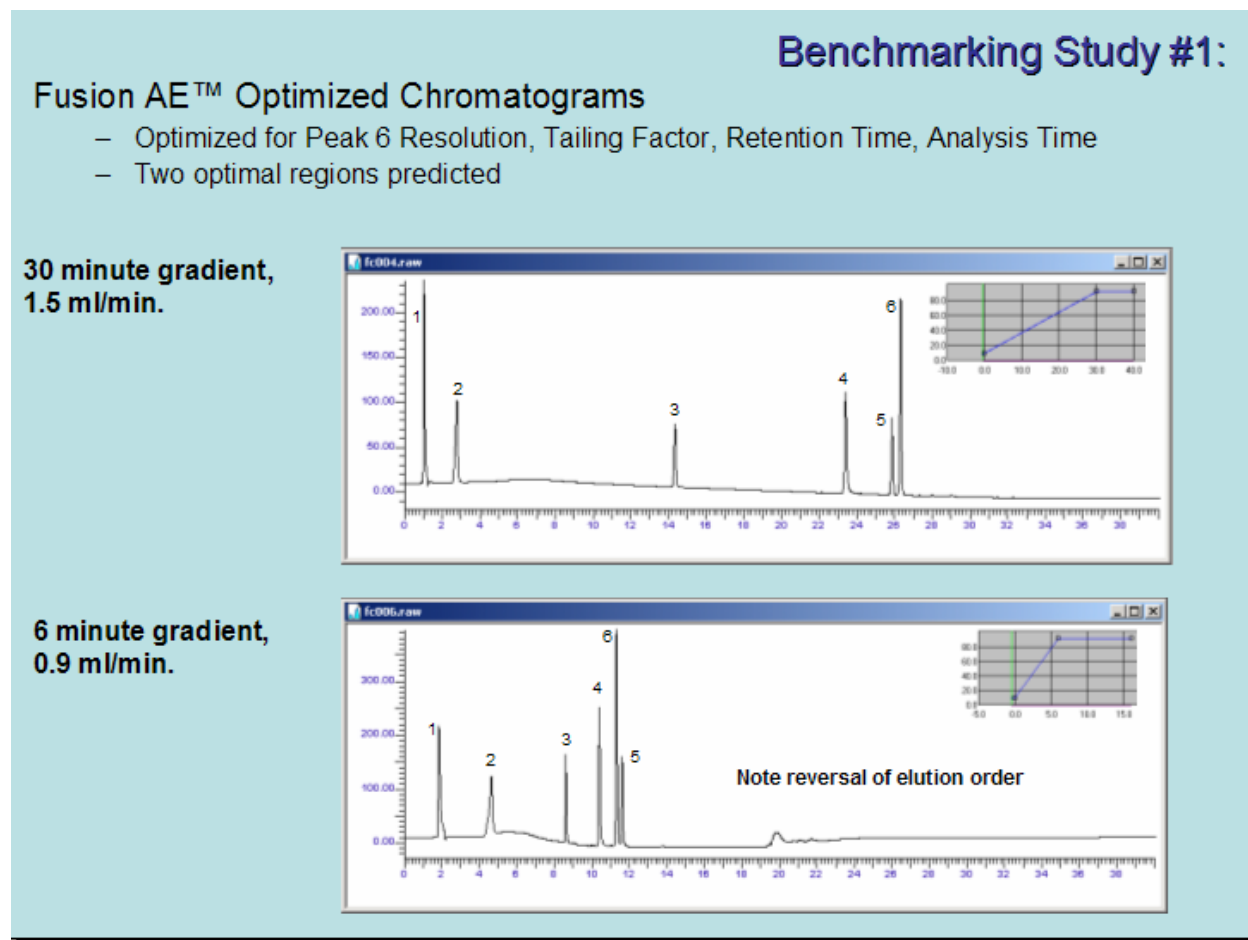**Figure 13.   Benchmarking Study #1 – Traditional Approach Result**

Figure 14.   Benchmarking Study #1 – Fusion AE Optimized Methods

Benchmarking Study #2 – Isocratic Method

The Isocratic Benchmarking study focused on Compounds 4, 5, and 6 - the three hard to resolve compounds of the six-compound product. Again, a traditional approach was first tried using a software-based tool for studying mobile phase blends. The best results obtained from this approach were barely able to resolve Compounds 5 and 6, as shown in Figure 15. The methods did not have acceptable tailing and were definitely not robust. Figure 16 shows the Fusion AE result, which provided an optimized and robust method that met all goals for the three peaks with a very acceptable 10 minute total assay time. As before, these results were obtained from a single experiment design run overnight in a fully automated mode. The Fusion AE result was experimentally verified by the lab.

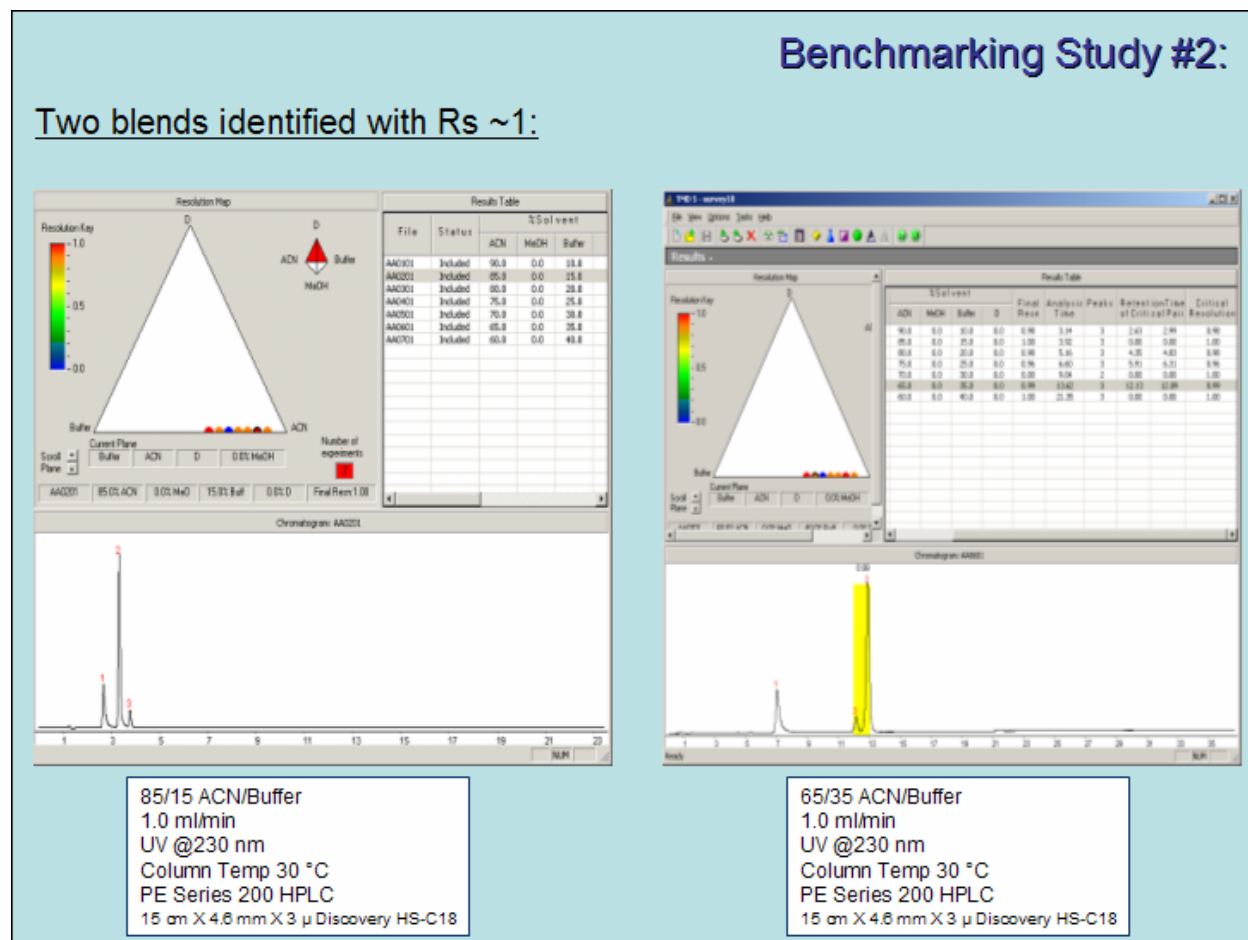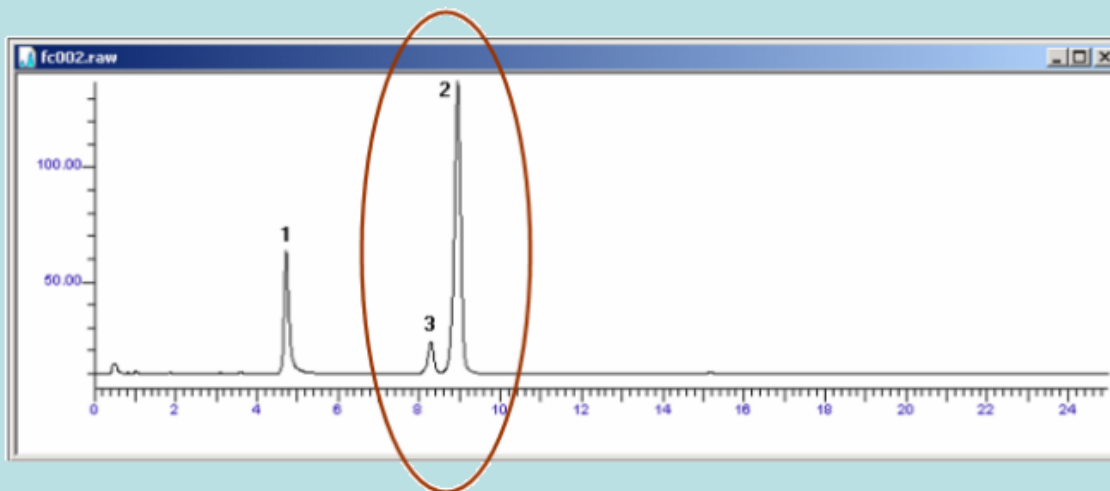**Figure 15.** **Benchmarking Study #2 – Traditional Approach Result**

Benchmarking Study #2:

Two blends identified with Rs ~1:

85/15 ACN/Buffer
1.0 ml/min
UV @230 nm
Column Temp 30 °C
PE Series 200 HPLC
15 cm X 4.6 mm X 3 µ Discovery HS-C18

65/35 ACN/Buffer
1.0 ml/min
UV @230 nm
Column Temp 30 °C
PE Series 200 HPLC
15 cm X 4.6 mm X 3 µ Discovery HS-C18

Figure 16.   Benchmarking Study #2 – Fusion AE Optimized Method

Fusion AE™ contains the same experiment design, data analysis, graphing, and optimization software routines as found in S-Matrix's D.o.E. Fusion™ generic DOE software package. This software package has been validated by recognized experts in design of experiments and by an international pharmaceutical company.

Software Validation by International Pharmaceutical Company

Page 1 of the Pfizer Validation Summary Report for D.o.E. Fusion is pictured below. The full report is available as a downloadable PDF file from S-Matrix's web site.
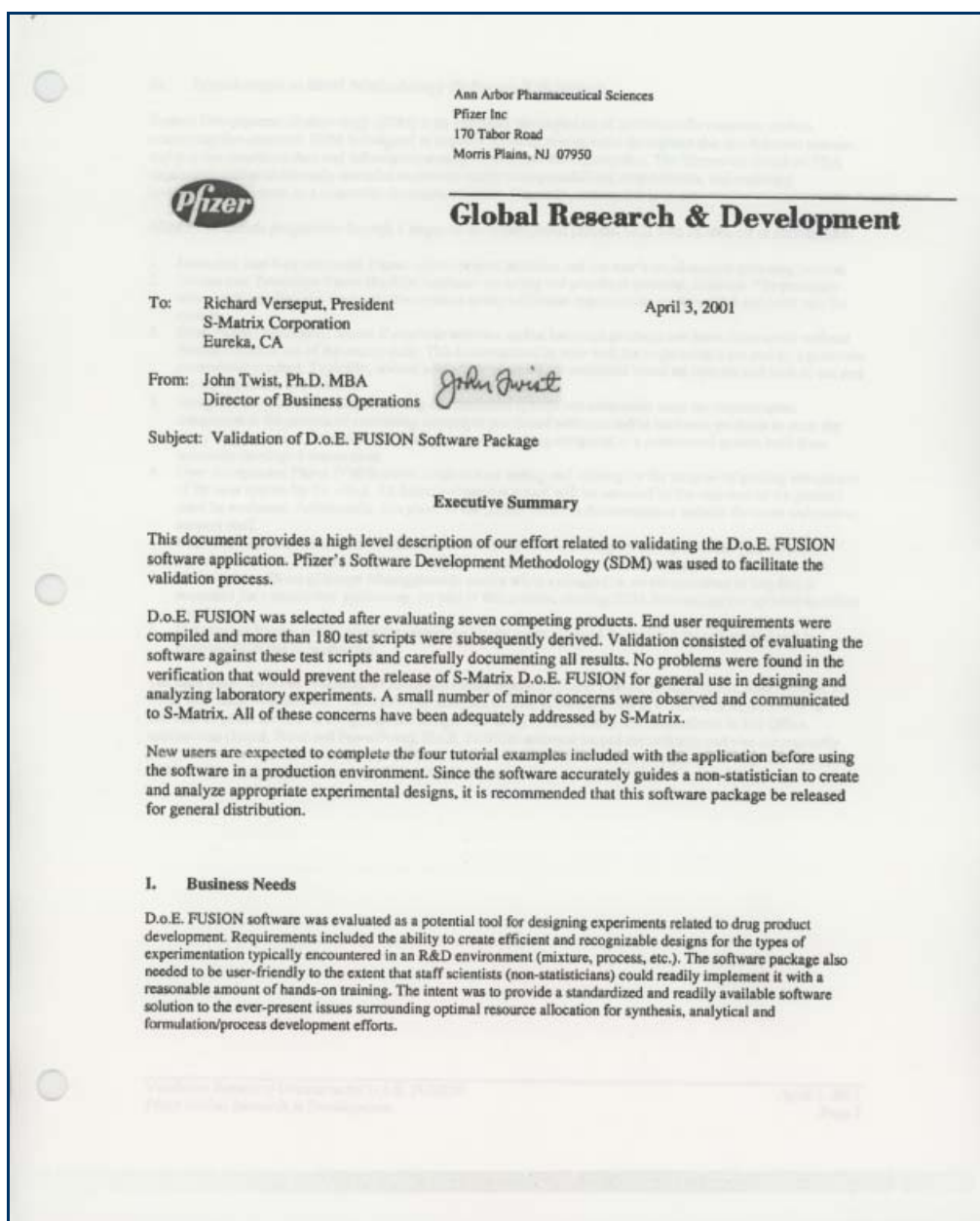
Software Validation by Dr. John A. Cornell, University of Florida

Dr. Cornell is considered the foremost authority on mixture experiment design. He is the author of the best selling book *Experiments With Mixtures* [1].

Dr. Cornell worked closely with S-Matrix on development of the following mixture design and analysis capabilities. The specific capabilities that he has guided are listed below.

1. Unconstrained and Constrained Mixture Designs
2. Unconstrained and Constrained Combined Mixture-Process Designs
3. Custom Model Combined Mixture-Process Designs
4. Mixture-Process Designs With Multicomponent Constraints
5. Analysis of Mixture-Process Designs

Software Validation by Dr. Douglas C. Montgomery, Arizona State University

Dr. Montgomery is a well known authority in the field of Industrial Statistics with a special emphasis on Design of Experiments. He is the author of the best selling book *Design and Analysis of Experiments* [4]. Dr. Montgomery worked closely with S-Matrix on all facets of our DOE software development program. He had substantial input into the product specification and guided development of both the expert-system overlay and the statistical routines underlying the software.

Software Validation Statement by Douglas C. Montgomery

"I believe that D.o.E. Fusion represents state-of-the-art in Design of Experiments software. In addition, the Technical Data Mining capabilities are excellently integrated with D.o.E., and represent sound statistical thinking in both the feature content and tailoring of the underlying statistical engines. Some of the major elements of the Software Validation Program I have undertaken with S-Matrix on behalf of D.o.E. Fusion include":

1. Model-Robust Designs
2. Experiment Planner Wizard
3. Custom Model Designs
4. Historical Data Mining and Matrix Master
5. Repair Design Generation
6. Design Blocking
7. Response Data Transformations
8. Trellis Graphics Using Conditioning Variables
9. Multiple Response Optimization