JMP049: Manufacturing Excellence in Pharma – Part 3

Design of Experiments (DOE), Definitive Screening and Custom Design, Optimization

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jmp STATISTICAL DISCOVERY FROM SAS

Manufacturing Excellence in Pharma – Part 3
Design of Experiments (DOE), Definitive Screening, Custom Design and Optimization

Key ideas

This case study requires the use of design of experiments (DOE) to advance the knowledge about the process. DOE is a scientific way to learn about the process more efficiently and effectively. JMP's unique approach to DOE helps to explore and exploit a multifactor opportunity space. Constructing a design to fit the problem is critical to the success. JMP's Custom Designer helps fit an optimal design to the problem, rather than fitting the problem to any existing design. It is important to compare the design to alternative designs before running the experiment. Analyzing the experimental results involves building a statistical model that includes process knowledge and customer requirements. Determining the most robust factor settings requires an application of prediction and simulation techniques. Smarter experimentation and simulation are the main pillars of any process innovation.

Background

FVM Pharmaceuticals is an international drug manufacturer, specialized in manufacturing finished formulations that cater to the most demanding global needs. FVM delivers contract manufacturing of tablets, capsules, and liquids.

A typical manufacturing process involves milling an active pharmaceutical ingredient (API) into a powder of uniform particle size. The milled material is then blended with other ingredients to bulk up and evenly distribute the API. This blended material is then compressed into tablets, which are finally coated to aid shelf life, taste, and other properties. At the end of the process, various quality parameters including critical to quality (CTQ) metrics are populated, which further drive batch acceptance.

The process starts with a raw material that is a concentrated emulsion containing two organic compounds. The raw material is supplied by two vendors, and the incoming quality is monitored by measuring the concentration of the compounds in milligram per liter (mg/l). Each day, a quality lab operator takes raw input material in two batches from each supplier into the process.

The process of chromatography is a laboratory technique for the separation of a mixture. The company is currently leveraging gas chromatography (GC), a common type of chromatography used in analytical chemistry for separating and analyzing compounds that can be vaporized without decomposition.

The task

Recently, the quality control team observed a significant variability in the quality of the drug delivered. To address this issue, a cross-functional team was formed to identify the root cause of the problem and solve it. Lawrence, head of the team and a quality engineer, is a firm believer of the data-enabled decision making. He also knows that building a strong quality culture into the process demands application of statistical techniques to discover the actionable insights. He is aware that bringing operational excellence into the manufacturing process is a sequential and multistage process starting from raw material to final inspection. At the same time, Quality by Design (QbD) involves ensuring quality throughout the production process (starting from raw material to finished product) while leaving enough flexibility in the manufacturing system.

Lawrence and his team conducted a detailed measurement system analysis to understand the different components or sources of variation in the process and concluded that there has been a significant difference between the batches. The team came to a consensus that the measurement variation results from either the non-optimized UHPLC method or the process settings. The deviations in the concentration

of the standard compounds (both Compound 1 and Compound 2) need to be within a standard specification limit.

From the brainstorming exercise and lab tests, the team learned that concentration levels of compounds are being influenced by temperature, eluent flow rate, %Acetonitrile/ml (all the four gradients), and wavelength. Lawrence and his team have a critical task ahead of them to identify optimal process settings to ensure that the concentration of the compounds remains within specification limits. The goal is to design a robust process that also accommodates the random variations.

With this background, Lawrence and his team decided to implement design of experiments (DOE), a scientific way to find the optimal factor settings with limited resources. The concentration levels of the standard samples of Compound 1 and Compound 2 are the two responses, with the goal of matching a target level. Temperature, eluent flow rate, %Acetonitrile/ml, and wavelength are the critical factors influencing the measured concentration of the compounds.

While these are the main effects, the team also wanted to understand the nonlinear effects (quadratic effects) of the critical factors on both responses. They also took experts' advice to focus on the quadratic effects of temperature, eluent flow rate, %ACN (all gradients) and wavelength on the responses. From an interaction perspective, the team was advised to restrict the study to only two-way interactions between temperature and eluent flow rate, and all two-way interactions between %ACN and eluent flow rate (except % ACN 6ml).

The description of the responses and factors along with the limits are presented below.

The data

The concentration of Compound 1 and Compound 2 are the two responses. The goal is to match the two standard sample targets. The description of the responses and factors along with the limits are presented in Exhibit 1.

Exhibit 1 Responses and Factors for a Designed Experiment

Responses	Goal	Target	Low (*)	High (*)
Compound 1 (mg/ml)	Match Target	300	280	320
Compound 2 (mg/ml)	Match Target	450	435	465

Factors	Nature	Lower Limit	Upper Limit
Temperature (°C)	Continuous	25	35
Eluent Flowrate (ml/min)	Continuous	5	15
%ACN (V = 0ml)	Continuous	5	20
%ACN (V = 1ml)	Continuous	5	20
%ACN (V = 5ml)	Continuous	35	70
%ACN (V = 6 ml)	Continuous	35	70
Wavelength (nm)	Continuous	192	270

(*) Range measurement error (High-Low) = 10% of compound concentration tolerance

Designing the experiment

DOE in JMP offers all of the classical textbook designs. However, JMP also offers computer-generated or optimal designs using custom design or augment design, and a modern option called definitive screening design (DSD).

Definitive screening design (DSD): Definitive screening designs, invented by Bradley Jones and Chris Nachtsheim, provide sound information about main effects while allowing one to detect and identify factors causing strong nonlinear effects on the response. Depending on the number of active factors, one can potentially learn about dominant two-factor interactions. If few factors are active, the DSD can even support analysis of a complete response surface model. Because the required number of runs only slightly exceeds twice the number of factors, one can use these designs to screen many factors.

Custom design: If a predefined standard design doesn't fit the problem, one can construct cost-effective, optimal designs that are custom built for the specific experimental situation. The Custom Design platform in JMP creates a wide array of design types capable of addressing an extensive range of experimental goals and conditions. It has a unique ability to manipulate factors, constraints, factor types, and other experimental conditions and budget restrictions.

Construction of definitive screening and custom designs

Let us construct both a definitive screening design and a custom design. We will choose the design based on the lower prediction variance by using the Compare Design platform.

Exhibit 2 Definitive Screening Design

Choose DOE >Definitive Screening >Definitive Screening Design. Add two responses, Compound 1 and Compound 2. Select Match Target as a Goal. Specify the Lower Limit and Upper Limit as per the given data. Add the seven continuous factors and populate the lower and upper values. Ensure that Number of Blocks is set to 2 and Number of Extra Runs is set to 8. Click Make Design>Make Table.

We now have a definitive screening design with 25 runs, as shown in Exhibit 2, along with additional details on the design evaluation. By clicking on Make Table, we get a table that can be used to run the experiment and populate the results.

Let's construct a custom design based on the requirements using the Custom Design platform under DOE.

Exhibit 3 Custom Design

Choose DOE>Custom Design. Add two responses, Compound 1 and Compound 2. Select Match Target as a Goal. Specify the Lower Limit and Upper Limit as per the given data. Add seven continuous factors and populate the lower and upper values. Select all the seven factors from the Factors list and go to Model outline to select 2ⁿᵈ from the Powers drop-down. This will add all the quadratic terms to the model. To add the interaction effects of temperature and eluent flowrate, select Temperature from Factors and Eluent Flowrate from the model and click the Cross option. Repeat the step to add the interaction effects of eluent flowrate and all gradient factors of % ACN (except v= 6ml). The final list of model effects is shown above.

JMP gives you some guidance on the number of runs. The Minimum is the number (19) of terms in the model and gives a saturated design. The Default (24) is based on heuristics for creating a balanced design with at least four runs more than the number of terms, which allows for an estimate of model error that has at least four degrees of freedom.

Set the number of runs again to 25 and click Make Design. JMP will create an optimal design tailored to the given problem with 25 runs. It also provides metrics on design evaluation. Click Make Table to generate a table that gives the factor setting details of the 25 runs, as shown in Exhibit 4, and an option to populate the results.

Exhibit 4 Custom Design with 25 Runs

Run	Temperature	Elucent Flow Rate (ml/min)	% ACN (V= 0ml)	% ACN (V=1ml)	% ACN (V=5ml)	% ACN (V=6ml)	Wavelength (nm)	Compound 1	Compound 2
1	35	5	12.5	12.5	70	35	270	·	·
2	25	15	12.5	20	52.5	52.5	231	·	·
3	35	15	5	20	35	35	192	·	·
4	35	10	5	12.5	52.5	35	231	·	·
5	30	5	12.5	5	35	35	270	·	·
6	35	5	5	5	52.5	52.5	192	·	·
7	30	10	20	12.5	52.5	35	231	·	·
8	25	15	5	12.5	35	70	270	·	·
9	25	15	20	5	35	35	192	·	·
10	25	5	20	5	70	70	231	·	·
11	30	5	5	20	70	70	231	·	·
12	35	5	20	20	35	70	231	·	·
13	35	10	5	5	52.5	52.5	270	·	·
14	30	15	12.5	12.5	52.5	52.5	231	·	·
15	30	10	12.5	12.5	35	52.5	231	·	·
16	30	10	12.5	5	52.5	70	231	·	·
17	25	5	5	12.5	35	52.5	231	·	·
18	25	5	12.5	20	52.5	35	270	·	·
19	30	10	12.5	12.5	52.5	70	192	·	·
20	35	15	12.5	5	35	52.5	231	·	·
21	30	5	20	12.5	52.5	52.5	192	·	·
22	25	10	12.5	12.5	70	52.5	192	·	·
23	30	15	5	5	70	35	231	·	·
24	35	15	20	12.5	70	70	270	·	·
25	30	10	20	20	70	52.5	270	·	·

Now that we have two designs, namely definitive screening and custom, let us compare them.

Exhibit 5 Design Comparison


To create, open both designs and click DOE>Design Diagnostics>Compare Designs. Ensure that both Definitive Screening Design and Custom Design are populated on the left side. Choose to compare Custom Design with Definitive Screening Design. Select all the variables from the Custom Design list and Definitive Screening Design list. Click Match in the Match Columns section. Click OK.

Exhibit 6 Power Plot, Fraction of Design Space Plot and Prediction Variance Profile
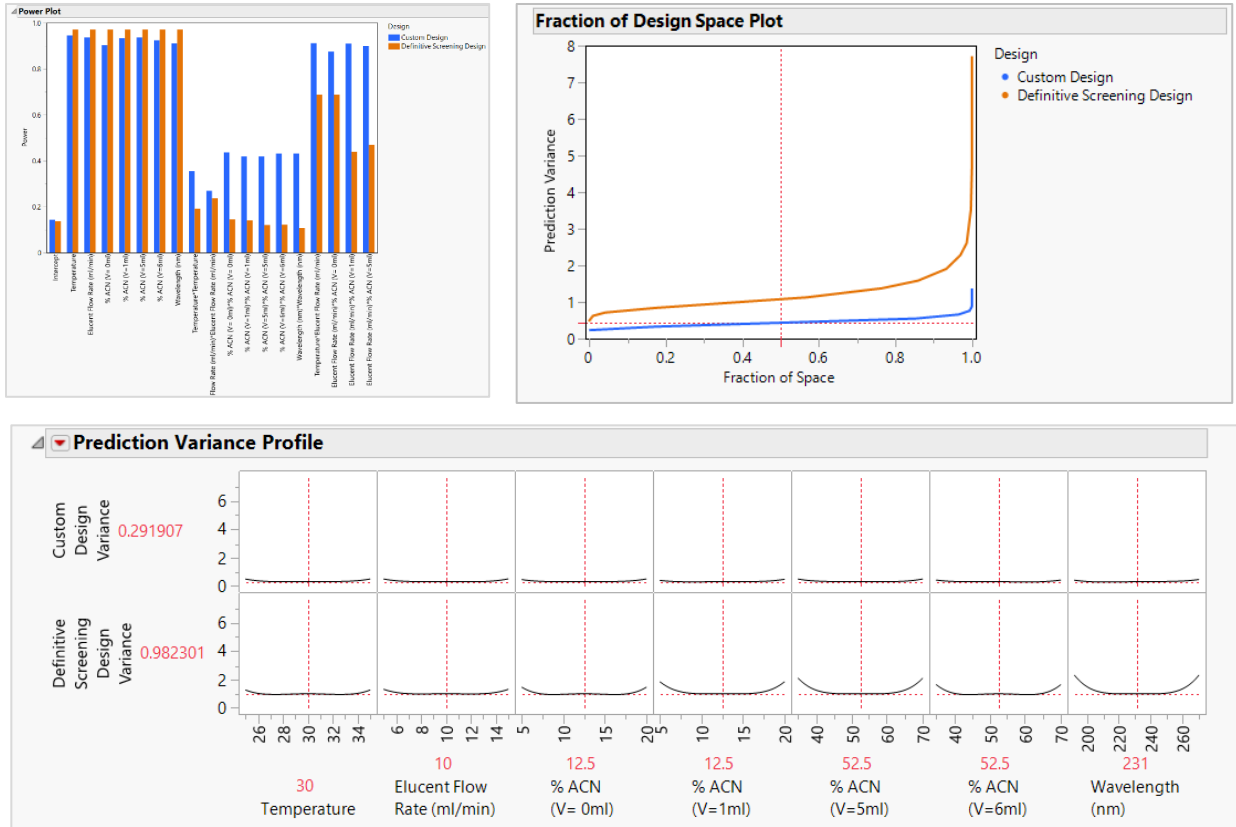
The power plot shows the power values from the power analysis in graphical form. The plot shows the power for each effect and for each design in a side-by-side bar chart. From the power plot, it can be inferred that there is a higher power for quadratic and interaction effects in the custom design as compared to DSD.

The fraction of design space plot shows the proportion of the design space over which the relative prediction variance lies below a given value. The fraction of design space plot shows that custom design has a lower prediction variance.

The prediction variance profile outline shows profilers of the relative variance of prediction for each design being compared. Each plot shows the relative variance of prediction as a function of each factor at fixed values of the other factors. To find the maximum value of the relative prediction variance over the design space for the reference design, select the Maximize Variance option from the red triangle next to Prediction Variance Profile.

After comparing the designs, the team decided to use the custom design since it has the lower prediction variance. They used the 25-run custom design and ran the experiments using the factor settings. The measured results, including the factor settings, are populated in the data set Custom_DoE_Results.jmp (note: all runs are randomized by default; therefore, the given design table does not exactly match with your own design).

Evaluation of custom design

The Design Evaluation outline provides different ways to evaluate a custom design. For this example, open Design Evaluation and examine the color map on correlations. If you only see black and white, please use the red triangle next to the Color Map on Correlations drop-down and select Use Blue to Red color theme for the color map.

Exhibit 7 Color Map on Correlations for Custom Design
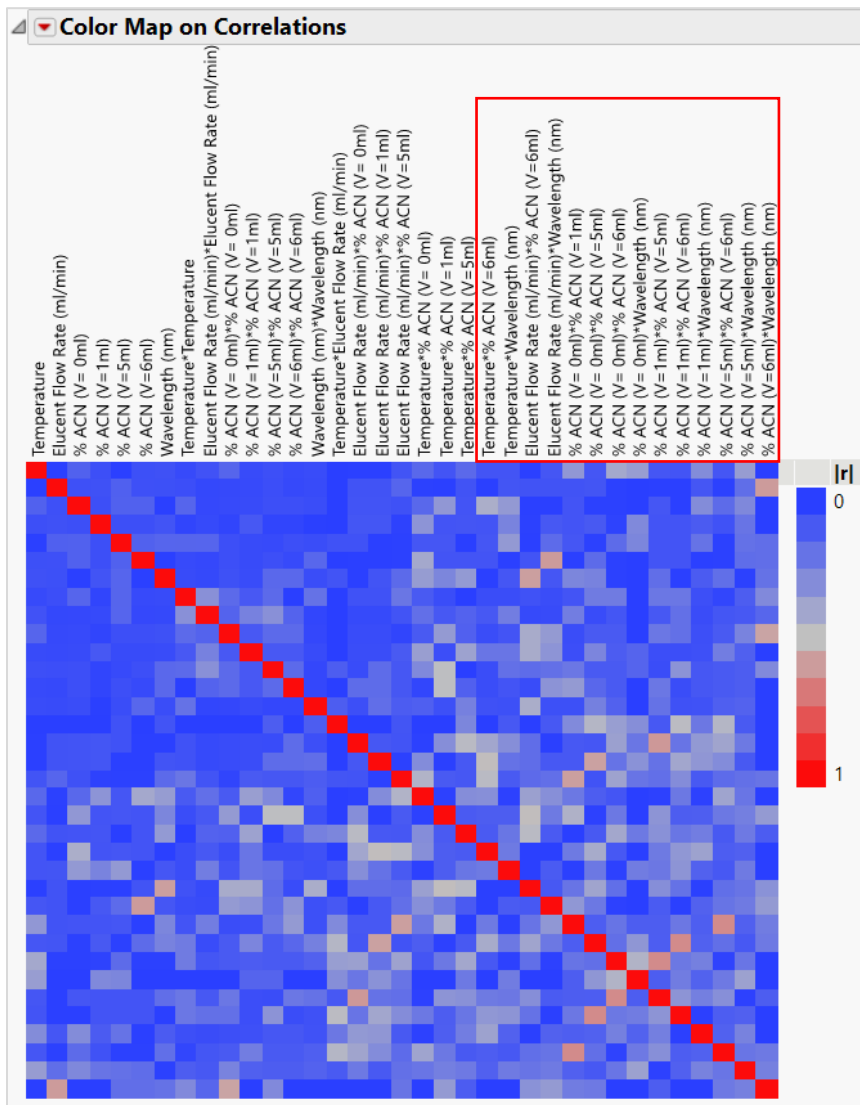
(Note: The two-way interactions in the red frame are not relevant, based on expert knowledge.)

The color map on correlations shows the absolute value of the correlation between any two effects that appear either in the model or in the alias terms outline. The main effects are represented by the seven terms in the upper left corner of the map. The blue, which corresponds to the correlation between two effects, indicate correlations of 0. The dark red represents a correlation of 1.

Red indicates absolute correlations of 1, reflecting that each term is perfectly correlated with itself. It follows that no main effect is confounded (totally correlated) with any two-way interaction. A closer look at this diagram reveals that collinearity is negligible, and all main effects are nearly orthogonal and can be estimated independently.

Analysis of experimental output

Let us consider Compound 1 as the response and fit a multiple regression model to find out the statistically significant model effects. Use the dataset Custom_DoE_Results.jmp.

Exhibit 8 Building Regression Model

To create, Analyze>Fit Model. Select Compound 1 as Y variable and all other variables from Temperature to Wavelength as Model Effects. To add the quadratic effects, select Temperature to Wavelength from the columns list and select Polynomial to Degree, ensuring the value of Degree is set to 2 so that the quadratic terms are added to the model effects. To add the two-way interaction effects, select the variables from the Columns list and Model effects list and click Cross. Alternatively, one can choose Response Surface option under Macro drop-down. Click Run. Note: One can also explore the stepwise regression by changing the Personality drop-down, including the option All possible models.

From the results, scroll down to Effect Summary and confirm that many effects are statistically not significant (p-value is less than 0.05). Remove the least significant effects one by one, which will rebuild the regression model each time. The resulting regression output is shown in Exhibit 9.

Exhibit 9 Summary of Fit, ANOVA and Parameter Estimates for Compound 1

Summary of Fit

RSquare	0.964036
RSquare Adj	0.938348
Root Mean Square Error	29.43681
Mean of Response	282.149
Observations (or Sum Wgts)	25

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	10	325190.42	32519.0	37.5281
Error	14	12131.36	866.5	Prob > F
C. Total	24	337321.77		<.0001*

Parameter Estimates

| Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	331.93018	19.0243	17.45	<.0001*
Temperature (°C)(25,35)	-88.60203	7.253126	-12.22	<.0001*
Eluent Flowrate (ml/min)(5,15)	-41.04818	6.72579	-6.10	<.0001*
%ACN (V = 0ml)(5,20)	31.538215	6.91661	4.56	0.0004*
%ACN (V = 1ml)(5,20)	-27.9162	7.368386	-3.79	0.0020*
%ACN (V = 5ml)(35,70)	-19.58999	7.257906	-2.70	0.0173*
Temperature (°C)*Temperature (°C)	49.041669	12.8711	3.81	0.0019*
Eluent Flowrate (ml/min)*Eluent Flowrate (ml/min)	-57.74613	15.11408	-3.82	0.0019*
%ACN (V = 0ml)*%ACN (V = 0ml)	-58.44641	13.94525	-4.19	0.0009*
Eluent Flowrate (ml/min)*Temperature (°C)	47.894533	8.026571	5.97	<.0001*
%ACN (V = 0ml)*Eluent Flowrate (ml/min)	20.435806	7.795239	2.62	0.0201*

The Summary of Fit report provides details on RSquare. An RSquare closer to 1 indicates a better fit to the data. The value of 0.964 indicates that the model explains most of the variation observed in the

response. The p-value in the ANOVA table tells us that the model is statistically significant overall. However, the ANOVA doesn't tell us which predictors are significant. For this, use the information reported in the Parameter Estimates table (showing similar information as in Effect Summary).

Prediction Formula, Response Limits and Specification limits

Go to the red triangle next to response. Select Compound 1>Save Columns>Prediction Formula to save the prediction formula as a separate column into the data table.

Exhibit 10 Response and Specification Limits
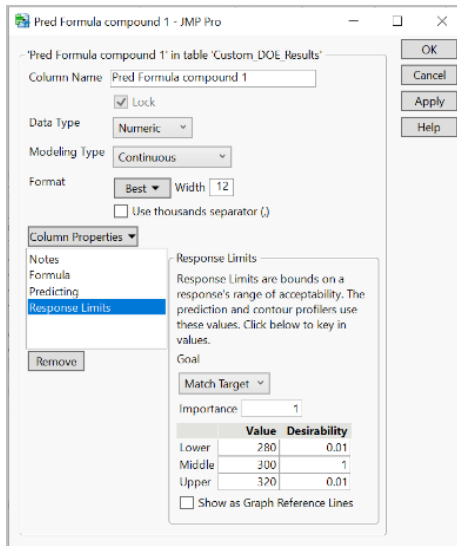
To create, select the newly created column Pred Formula Compound 1 in the data table and right-click to edit the column information. Under the column properties, select Response Limits and update the lower, middle, and upper limits as 280, 300 and 320 respectively. Set the goal as Match Target and populate the desirability values as 0.01, 1 and 0.01. Since our primary goal is to match a target, the middle value takes the desirability of 1>Apply. Select Spec Limits from the Column Properties drop-down and update the lower and upper limits as 280 and 320, respectively. This information will be used further in desirability profiling and optimization.

Repeat all the above-mentioned analysis steps for the Compound 2 to ascertain the statistically significant variables affecting this response, too. The Fit Model output for Compound 2 is presented below.

Exhibit 11 Summary of Fit, ANOVA and Parameter Estimates for Compound 2

Summary of Fit

RSquare	0.965345
RSquare Adj	0.944551
Root Mean Square Error	20.22141
Mean of Response	429.1664
Observations (or Sum Wgts)	25

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	9	170854.64	18983.8	46.4260
Error	15	6133.58	408.9	Prob > F
C. Total	24	176988.23		<.0001*

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	420.05129	10.58335	39.69	<.0001*
Temperature (°C)(25,35)	-60.12599	4.983292	-12.07	<.0001*
Eluent Flowrate (ml/min)(5,15)	-31.01553	4.595035	-6.75	<.0001*
%ACN (V = 0ml)(5,20)	20.982086	4.745405	4.42	0.0005*
%ACN (V = 1ml)(5,20)	20.746393	5.057633	4.10	0.0009*
Temperature (°C)*Temperature (°C)	62.591934	8.896357	7.04	<.0001*
Eluent Flowrate (ml/min)*Eluent Flowrate (ml/min)	-51.33267	10.3199	-4.97	0.0002*
Eluent Flowrate (ml/min)*Temperature (°C)	30.884169	5.518854	5.60	<.0001*
%ACN (V = 0ml)*Eluent Flowrate (ml/min)	-26.84522	5.37124	-5.00	0.0002*
%ACN (V = 1ml)*Eluent Flowrate (ml/min)	16.522124	5.531272	2.99	0.0092*

An RSquare value of 0.965 indicates that this model explains a significant variation in the response. The p-value of the ANOVA table tells us that the model is statistically significant overall. Detailed results are again shown in the Effect Summary and Parameter Estimates tables.

Please remember to populate the prediction formula for Compound 2 using the option under Save Columns.

Update the Response Limits by setting the goal again to Match Target. The values for response limits are 435, 450 and 465 for lower, middle, and upper limits, respectively. Set similar values for the desirability. Update Spec Limits from the Column Properties drop-down and update lower and upper limits as 435 and 465, respectively.

## Robust process setting using Profiler

After the Prediction Formula column has been populated and updated with both specification limits and response limits, the most robust factor settings or process parameters can be easily identified using the JMP Profiler. The Prediction Profiler displays the response surface traces for each factor and the response (or multiple responses). We can explore all dimensions of our opportunity space in one plot, since the number of factors is not limited. Each trace shows the predicted response as one factor is changed and the other factors are held constant at the given values. The Prediction Profiler recomputes the profiles and predicted responses (in real time) as the value of a factor is changed.

The Prediction Profiler has additional built-in features:

- Maximize Desirability determines one combination of factor settings that results in a predicted response to optimize our desirability (as set in Response Limits). Please note that there can be different factor level combinations that maximize the desirability.
- The Simulator allows a Monte Carlo simulation to be created by adding a well-specified random variation to the chosen factor settings and to the response(s). A typical use is to fix the factors at their optimal settings and model noise to random values. By simulating many random factor-response combinations, JMP will determine a (random) defect rate, i.e., the portion of response values not meeting our response limits.
- Optional Sensitivity Indicators show a purple triangle whose height and direction correspond to the value of the partial derivative of the response function at its current value, making it quick and easy to spot the most sensitive cells in in large profiles.

All three features, Maximize Desirability, Simulation and Sensitivity Indicator, are explored here using Profiler to identify the robust factor settings for the process.

Exhibit 12 Profiler
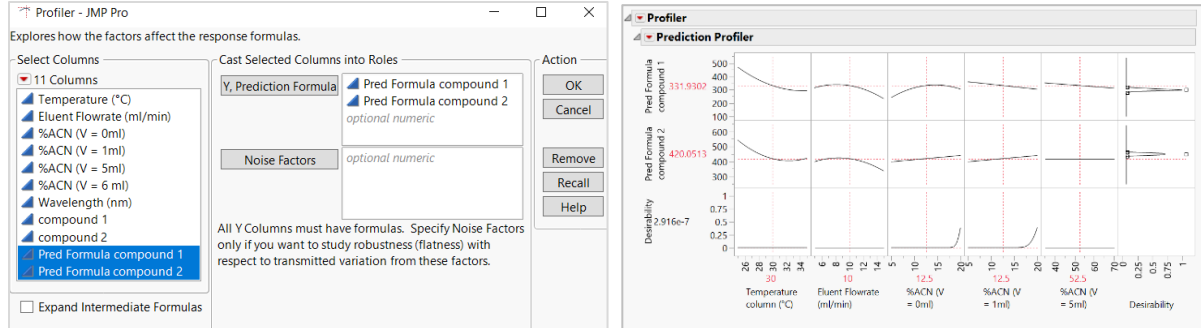
To create, Graph>Profiler>Y = Pred Formula Compound 1 and Prod Formula Compound 2 >Y. Select Prediction Profiler and then Sensitivity Indicator, which then reveals a purple triangle for each factor.

Simulation and optimization

Under the red triangle of Prediction Profiler, select Optimization and Desirability and then select Maximize and Remember. Check Desirability Functions if this option is greyed out. By do so, you will have populated the factor settings to the list of remembered settings under the setting name _Optimal_. Your values may be different, since there could be multiple optimal factor settings that can maximize the desirability. However, these are the factor settings for maximum desirability.

Statistics are always dealing with variation. It is the reason for confidence intervals, the subject of statistical tests and the rationale behind all modeling efforts. It may be unlikely that the subject matter experts will know the process settings in sufficient detail to know the distribution of values. By including this variation in the analysis, it makes the results much more representative of the actual population process produces. One way to explore the effects of variation is through Monte Carlo simulation.

Here the input parameters of the model derived earlier are not taken as fixed constants but can vary randomly. There are more than 20 options within the random function that can be used to simulate variability for each factor.

Let us set each parameter to its optimal value and add random normal distributions to model the noise with the mean at the respective values and standard deviations, as shown in Exhibit 13. The simulated response distribution (shown as a histogram) is the result of 10,000 simulation runs.

Exhibit 13 Profiler with Simulation
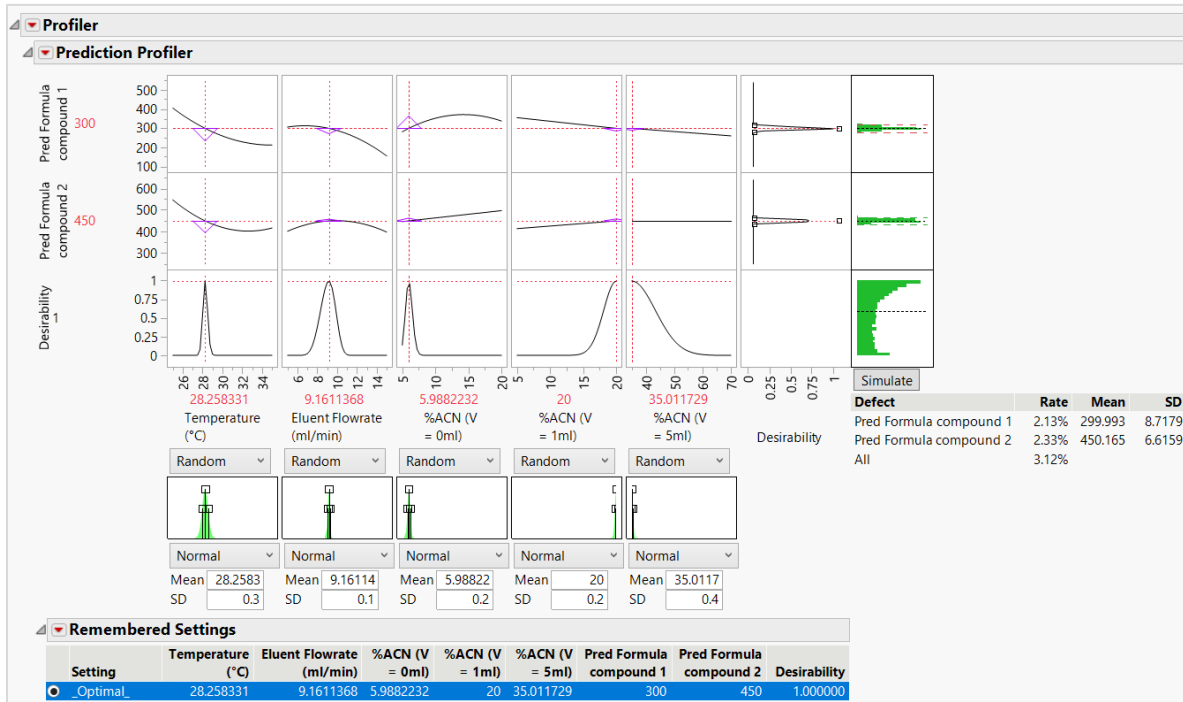
To create, Prediction Profiler>Simulator. Change the distribution of each of the factors to Random and select Normal and update the SD (standard deviation). Click Simulate to populate the defect rate, the mean and standard deviation for the simulated response for both Compound 1 and Compound 2.

For Compound 1, the simulation shows a sample defect rate of about 2.13%, a mean of 299.99 and a standard deviation of 8.71. For Compound 2, it shows a 2.33% defect rate with a mean of 450 and a standard deviation of 6.61, given the random variation in the factors. The overall defect rate is 3.1%. Again, your simulated values will differ slightly.

Sensitivity Indicator

A close observation of the Sensitivity Indicator (purple triangle) shows that the optimum factor settings are highly sensitive.

Change the factors to the values where the sensitivity is minimum. The direction and size of the purple triangle help you determine the robust factor settings where the response values would be less sensitive to the changes in factor settings. Being able to identify the factor settings that are least sensitive may be useful in creating robust processes.

Exhibit 14 Factor Settings at Low Sensitivity and Corresponding Defect Rate
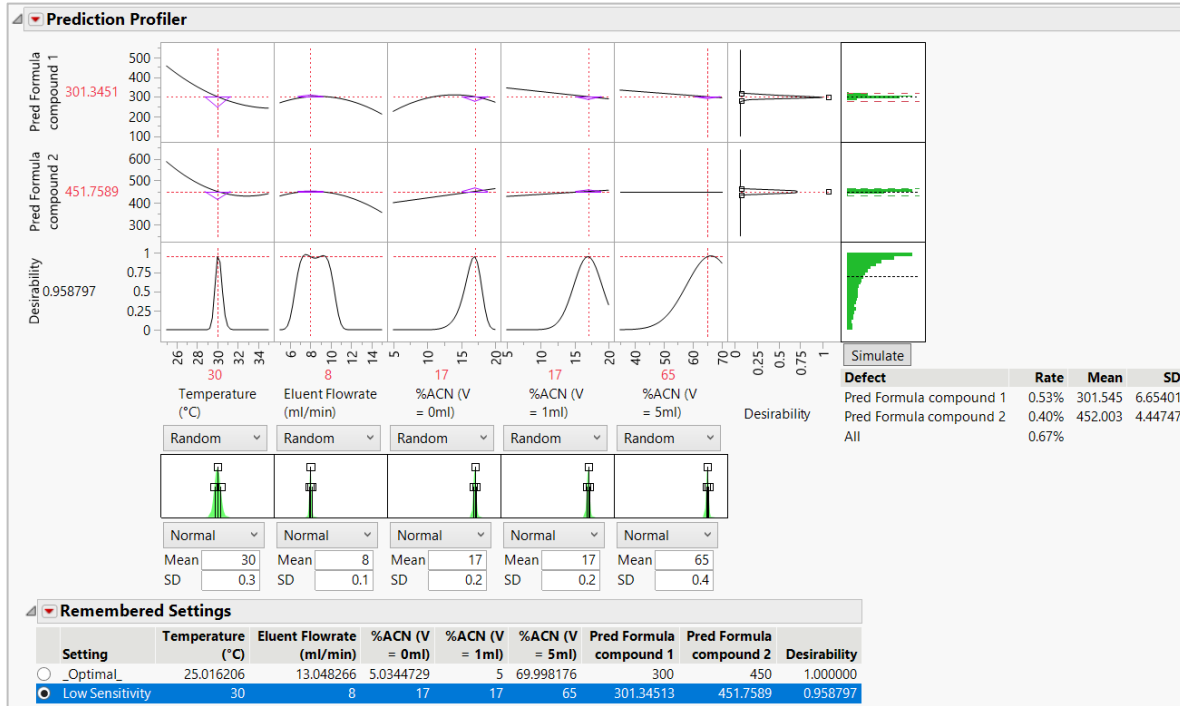

Exhibit 14 shows optimum factor settings where desirability is 0.95. The defect rate, mean and standard deviation values are much smaller than at the previously chosen optimum values.

After minimizing the sensitivity, this simulation estimates an average defect rate of about 0.53%, mean of 301 and a standard deviation of 6.6 for Compound 1. Compound 2 has a 0.40% defect rate with a mean of 452 and standard deviation of 4.4, given the same random variation in the factors. Again, your simulated values would differ slightly.

Final considerations

Exhibit 15 shows some examples of Contour Profiler plots, which were also used to explore the factor space and find the most robust settings. These robust factor settings would ensure that the specified targets (or desirability) are met, while response values would be the least sensitive to random variation in the factor settings (or robustness).

Exhibit 15 Optimal and Robust UHPLC Settings Shown by Contour Profilers
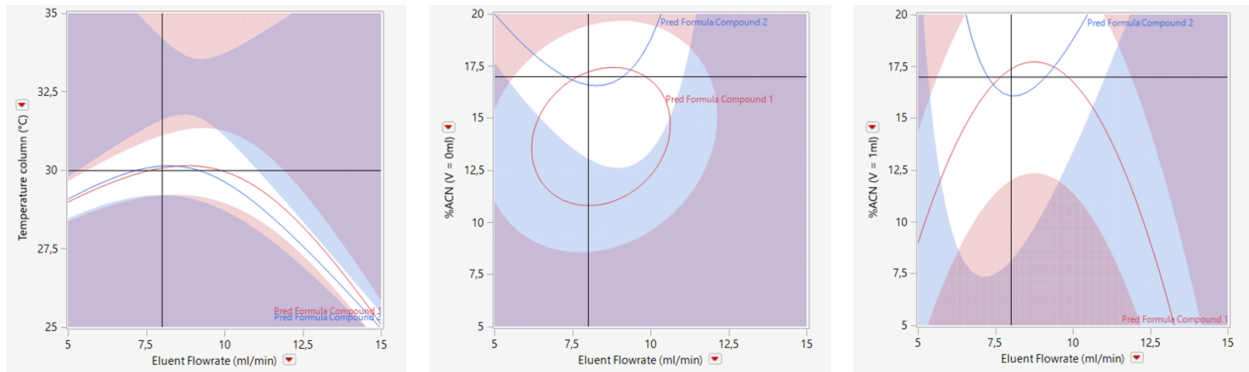
Thus, Lawrence's team achieved their goal of finding the most robust factor settings. The quality team implemented these learnings and validated the results. It was successfully proven (see Exhibit 16) that the new UHPLC measurements were accurate and consistent compared to the standard but slow GC measurements.

Exhibit 16 Comparison of GC and UHPLC Measurements for Both Compounds
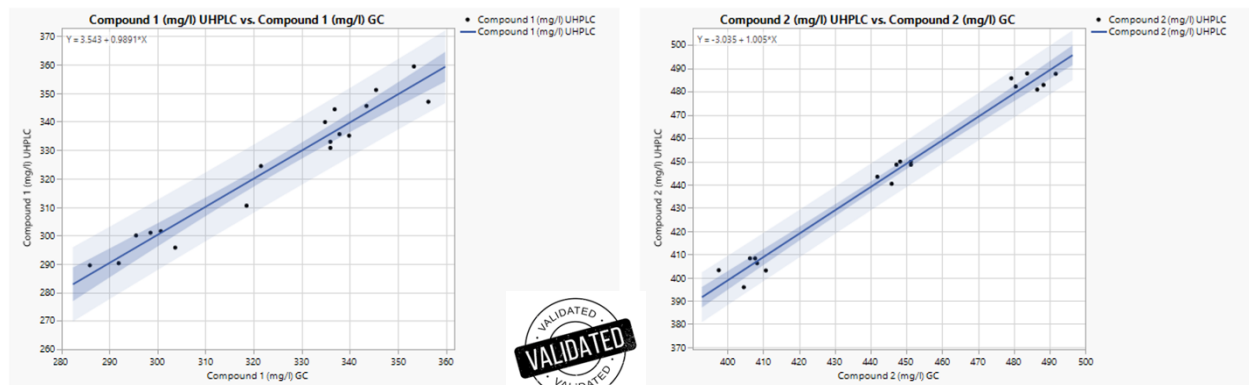
Summary

Statistical insights

A statistically designed experiment is the only way to determine which inputs are causing any effect or output in a process. This case introduced several options to build, evaluate and choose a design for a given problem. Many statistics are provided to guide the selection of the "best" design. By choosing a design type and options, you not only ascertain the required effort, but also what can be learned (estimated) from the experimental data. While the output from the modeling step shows many statistics for assessing the model fit, it is important to note that both the design and the model are a good match.

Managerial implications

To gain a better process understanding, a statistically designed experiment provides the most efficient and most effective method. Instead of choosing an existing design from a catalogue of choices, a more flexible optimal design was created to meet all requirements. After running the experiment to collect the best data for solving the problem at hand, we fit the data to a statistical model. Based on this model, the process can be better understood and data-driven decisions can be made. The Profiler is key for visualizing the process, which is not only eye-opening for non-technical staff but also the perfect tool for investigating what-if scenarios and for "storytelling" about our findings. Through built-in optimization and simulation, process settings can be found, leading to the best process output to meet our targets or to a more robust solution in the light of random factor variation.

JMP features and hints

This case used DOE platforms to create designs and then compare the designs. Custom Design was used to create tailor-made designs to suit complex experimental requirements. Fit Model was leveraged to identify the significant predictors and generate the predictive values of the response variables. The Profiler adds visual insight into the response-factor relationships, including interactions. Finally, the optimization and Monte Carlo simulation capabilities of the Prediction Profiler helped to arrive at the most robust process settings.

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