Removing Subjectivity from the Assessment of Critical Process Parameters and Their Impact

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A new algorithm uses a statistical approach to critical process parameter assessment, allowing for faster, more consistent, and less subjective critical process parameter quantification, visualization, and documentation.

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Determining critical process parameters (CPPs) is vital to defining the control strategy for drug substance and drug product manufacturing processes (1). Deciding the criticality of a process parameter, however, can often become a subjective exercise, resulting in long discussions within product development teams as well as back-and-forth communication with government regulators during new drug application review.

A data-driven statistical approach was developed (2) to help reduce subjectivity and debate in determining the criticality of process parameters in the manufacturing of drug substance and drug product. The approach uses the distance of a critical quality attribute (CQA) from its quality limit, together with the estimated parameter effect size, to designate the criticality of a process parameter.

The method relies on straightforward calculations. However, performing these calculations manually can be time-consuming and error-prone when the statistical model involves multi-factor interactions and higher order parameter effects. To incorporate this systematic approach into daily practice, statisticians have developed a web-based computational tool that uses this method.

This article examines how the algorithm was developed, focusing on the calculation of process parameter effect size on a CQA. It also discusses how analytical and numerical solutions of parameter effect size resulted from conventional linear models.

Using grid search to develop a numerical approach makes the algorithm flexible and simple enough to cope with all types of linear models that could have main effects, as well as higher order interaction and parameter effects. In addition, the resulting tool supports the linear model with transformation and provides a bias correction for modeling responses in the transformed scale.

A statistical approach to identifying CPPs

The assessment of CQAs and the control of the CPPs that impact these attributes are crucial to the overall control strategy for biopharmaceutical product manufacturing (2).

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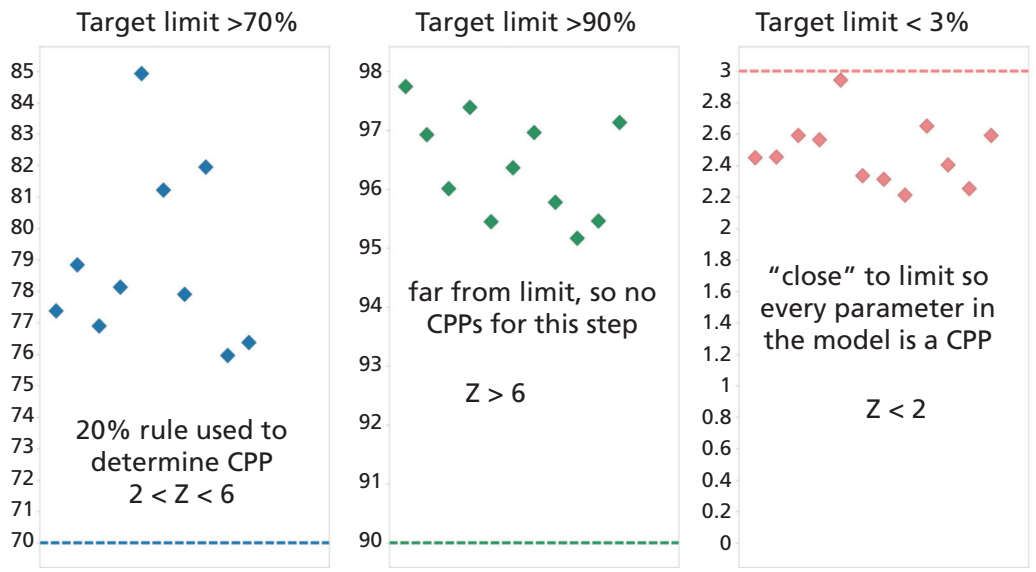
Figure 1: Use of the Z score in CPP assessment.



The International Council for Harmonization ICH Q8(R2) (3) describes a CPP as "a process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure that the process produces the desired [level of] quality."

There are many different approaches for assessing process parameter criticality. Statistics, typically using data from a designed experiment, plays an important role in these evaluations. However, assessing the impact based solely on statistical significance (e.g., *p*-value) is inadequate, because it does not take into account the strength of the relationship between variables and the process risk.

The new statistical approach (1) helps determine when a statistically significant relationship between a process parameter and a critical quality attribute imposes a practical concern, based on how close the data are to the target limit.

Figure 1 illustrates the approach, highlighting its three main components: a statistically significant relationship, a Z score, and use of the 20% rule. The Z score for a CQA (y) with a one-sided quality target limit (L), is calculated as shown in **Equation 1**.

$$Z = \frac{|\text{mean}(y) - L|}{s}, \qquad \text{[Eq. 1]}$$

where s is the estimated standard deviation of y.

The Z Scores can be applied to any CQA with either a one-sided or a two-sided target limit. For a two-sided limit, the Z score is determined by the limit closest to the mean.

The value of Z indicates how far, in standard deviation units, the data are from the quality limits. A large Z score is shown in the middle plot in **Figure 1**. Because the whole set of collected data is far from the lower quality target limit, the process is at low risk of producing out-of-limit (OOL) results.

The right-hand plot in **Figure 1**, however, shows data with a low Z score. This shows that this set of data is close to the targeted limit, and, thus, that the process is at higher risk of producing OOL results.

In established practice, Z scores of two and six are used as cutoff values in determining the criticality of process parameters. For example, if the data have a Z score greater than six, no CPP will be assigned to the CQA because the process is at low risk. Moving any parameter over its proven acceptable range will not compromise product quality.

If the data of a CQA are close to its target limit, however, and their Z score is less than two, it is generally appropriate to assume that all statistically significant parameters are CPPs. If the data of a CQA have a Z score between two and six, all statistically significant effects are potential CPPs and the data will be subject to the 20% rule (i.e., if the parameter's impact is greater than 20% of the quality target range [QTR], that process parameter will be considered a CPP). The QTR is the window where we expect or need the quality attribute to land at that step in the process. The CTR can be defined as |upper limit – min(y)| or |max(y)-lower limit| for one-sided target limit, and |upper limit – lower limit| for two-sided target limits.

If the parameter is determined not to have a statistically significant relationship to a CQA, or its effect size is less than 20% of QTR, subject matter experts should review the established science related to this process parameter in the context of the entire control strategy before designating this parameter as non-critical.

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Table I: Estimated effect size for parameter x_i under different scenarios assuming the regression model (1).

Scenario	Estimated effect size for parameter x_i
Only linear effect but no interaction with other parameters	$2\lvert\beta_i\rvert$
Linear effect and interaction with some parameters	$2(\lvert\beta_i\rvert + \sum_{j>i=1,\beta_{ij}\neq 0} \lvert\beta_{ij}\rvert)$
Quadratic effect and no interaction with other parameters	$2\lvert\beta_i\rvert I(\lvert\frac{\beta_i}{2\beta_{ii}}\rvert \geq 1) + \max\left(\left\lvert\beta_{ii} + \beta_i + \frac{\beta_i^2}{4\beta_{ii}}\right\rvert, \left\lvert\beta_{ii} - \beta_i + \frac{\beta_i^2}{4\beta_{ii}}\right\rvert\right) I(\left\lvert\frac{\beta_i}{2\beta_{ii}}\right\rvert < 1)$
Quadratic effect and an interaction with other parameters	Same as above but evaluated at all combinations of +/- 1 for all parameters involved in an interaction with x_i

Following a holistic review of control strategy, most parameters that are found to be insignificant will be defined as non-critical process parameters. Exceptions would only be made for parameters where significant scientific evidence suggests that they will have an impact on a CQA and where designating them as critical would improve the overall control strategy. However, such cases would be relatively rare.

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Parameter effect size

The effect size of a process parameter provides an estimate of the maximum change in a product quality attribute that is contributed by that process parameter. Parameter effect size calculation is carried out through the established functional relationships between process parameters and quality attributes. This paper focuses on the functional relationship (i.e., the statistical model). A conventional statistical linear model can provide an analytical solution of the parameter effect size. When the model has higher-order terms, however, the analytical solutions are in more complex forms, and a practical computational algorithm would be needed to be able to perform such evaluations routinely.

A second-order linear model is commonly used in statistical design of experiments to reveal the functional relationship between process parameters and a quality attribute. The general form can be expressed as shown in **Equation 2**:

$$y = \beta_0 + \sum_{i=1}^{n} \beta_i x_i + \sum_{j>i=1}^{n} \beta_{ij} x_i x_j + \sum_{i=1}^{n} \beta_{ii} x_i^2 + \varepsilon, \quad \text{[Eq. 2]}$$

where x_i $(1\leq i\leq n)$ represents the i^{th} process parameters on [-1, 1] with center point 0, y represents the quality attribute, ε follows from the normal distribution $N(0,\sigma^2)$, β_i $(1\leq i\leq n)$ is the regression coefficient corresponding to the first order term x_i, and β_{ij} $(1\leq i\leq j\leq n)$ is the regression coefficient corresponding to the second order term $x_i x_j$.

Without loss of generality, let us consider how to estimate the effect sizes of x_i under four different scenarios. In the first three cases, the effect sizes have explicit analytical solutions, and the corresponding expressions are summarized in **Table I.** The effect sizes of other process parameters can be estimated similarly.

Figure 2(i) shows a contour plot of predicted values for the fitted model $\hat{y} = 8 + 5x_1 - 2x_2$. The maximum change of y due to x_1 is 10 (regardless of x_2) and the change due to x_2 is 4 (regardless of x_1).

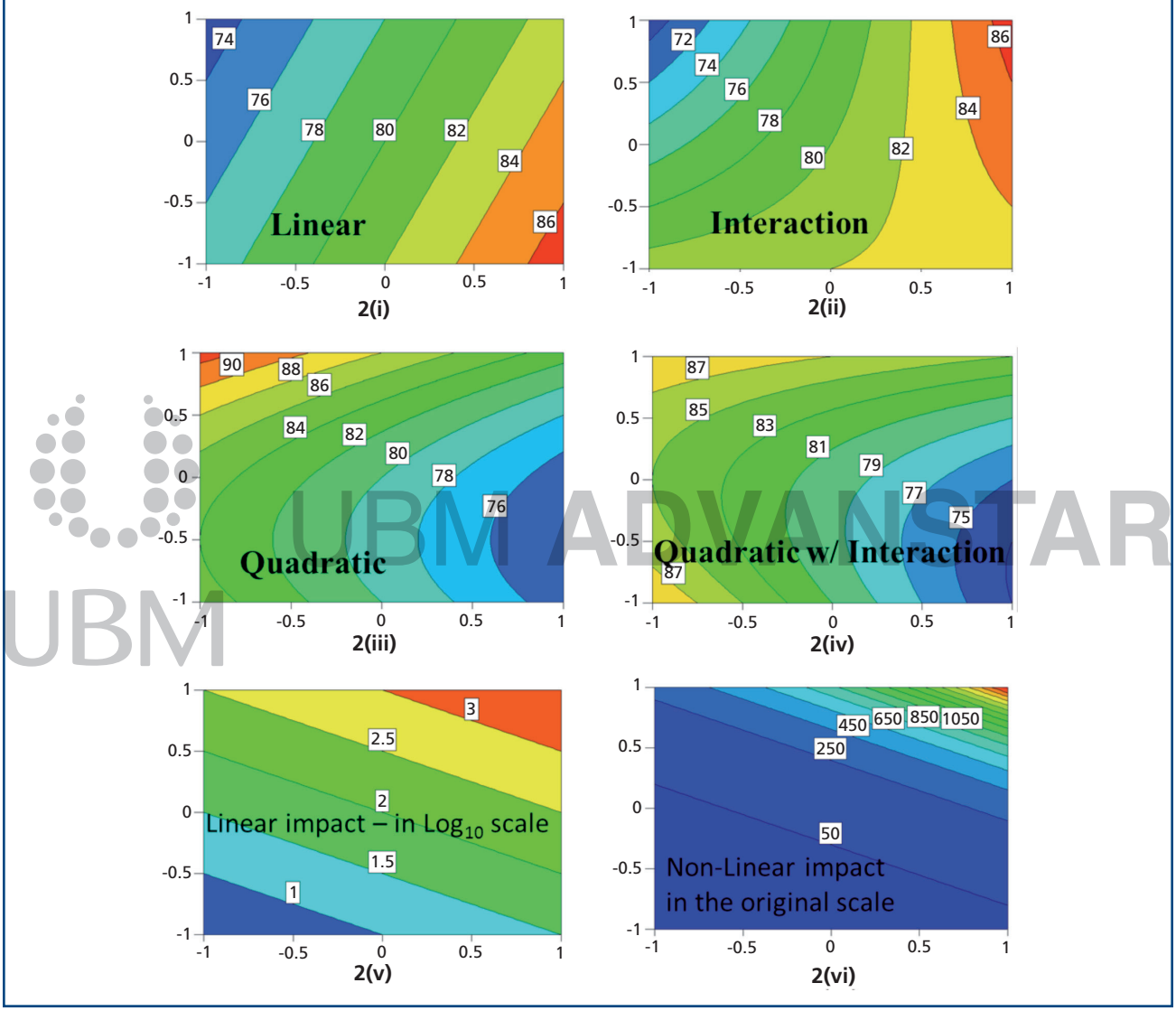
Figure 2(ii) shows a contour plot of predicted values for the fitted model $\hat{y} = 8 + 5x_1 - 2x_2 + 4x_1 x_2$. The maximum change of y due to x_1 is 2 given x_2 fixed at -1 (bottom edge); whereas the maximum change is 18 when x_2 is +1. Taking the larger value, the effect size of x_1 is estimated to be 18. Visually, these are simply the changes along the top and left edges, respectively. For the change due to x_2, the left edge shows a change of 11 while the right edge shows a change of 4. Therefore, the effect size for x_2 is 11.

Figure 2(iii) shows a contour plot of predicted values for the fitted model $\hat{y}=80-5x_1+4x_2+4x_2^2$. The maximum change of y along x_2,given x_1= -1, is the difference between the largest predicted value of 93 at x_2= 1 and the smallest predicted value of 84 at the inflection point -0.5. The maximum change is 9.

When x_1=1, the corresponding values are 83 and 74, still resulting in a max change of 9. It is necessary to find a single inflection point. Switching to x_1, the maximum change is 10 (regardless of the value of x_2).

Figure 2(iv) is similar to **Figure 2(iii)**, but now includes an interaction along with a quadratic effect. This fitted model is $\hat{y}=80-5x_1+3x_2+3x_1 x_2+4x_2^2$. Due to the interaction, the inflection points must be found along the both left edge and the right edge.

Figure 2: Contour plots of predictions for four examples:
(i) with only linear effects of two parameters on the quality attribute
(ii) with interaction effect of two parameters on the quality attribute
(iii) with quadratic effect of parameter x_1 on the quality attribute
(iv) quadratic with two factor interaction
(v-vi) For model $\log_{10}(y)=2+0.5x_1+x_2$
(v): the prediction of $\log_{10}(y)$ across the design space



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Along the left edge, the maximum change is 4, with 89 being the prediction at both the lower left and lower right and 85 being the minimum, at the inflection point of 0.5.

Along the right edge, the inflection point occurs at x_2=-0.75 and the change of 12.25 occurring along the right edge, based on a minimum of 72.75 at the inflection point and a maximum of 85 when x_1=1.

Effect size with transformed quality attribute

Transformation of a quality attribute is often used to improve the model fit or to correct violations of model assumptions. In the transformed scale, the effect size of a process parameter for an attribute can be obtained formally by applying the formulas previously introduced. If the situation calls for examining the change of a quality attribute in its original scale, the effect size must be evaluated on a case-by-case basis, depending on the transformation.

Assume that the model is constructed based on a monotone-transformed response, denoted as g(y), where g(•) is the transformation function. The second-order linear model with transformation can be written as shown in the following expression, labeled **Equation 3**.

Table II: Estimated mean of response with and without bias correction.*
***Note that μ is the prediction of transformed response g(y), and σ is the standard deviation of error. φ(·) is the probability density function of the normal distribution with mean μ and standard deviation σ.**

Transformation	Estimated mean E(Y) without bias correction	Estimated mean E(Y) with bias correction
log (Y)	$\exp(\mu)$	$\exp(\mu + \frac{\sigma^2}{2})$
$\sqrt{Y}$	μ^2	$\mu^2 + \sigma^2$
1/Y	$\frac{1}{\mu}$	$\frac{1}{\mu}(1 + \frac{\sigma^2}{\mu^2})$
$1/\sqrt{Y}$	$\frac{1}{\mu^2}$	$\frac{1}{\mu^2 + \sigma^2}\{1 + \frac{2\sigma^4 + 4\mu^2\sigma^2}{(\mu^2 + \sigma^2)^2}\}$
Y^2	$\sqrt{\mu}$	$\sqrt{\mu}(1 - \frac{\sigma^2}{8\mu^2} - \frac{15\sigma^4}{128\mu^4})$
$\log(\frac{Y-L}{U-Y})$	$\frac{Ue^{\mu} + L}{e^{\mu} + 1}$	$L + \int_{-\infty}^{\infty}(U-L)\frac{e^{\mu}}{1+e^{\mu}}\phi(t)dt$

$$g(y) = \beta_o + \sum_{i=1}^{n}\beta_i x_i + \sum_{j>i=1}^{n}\beta_{ij}x_i x_j + \sum_{i=1}^{n}\beta_{ii}x_i^2 + \varepsilon, \quad \text{[Eq. 3]}$$

where $\varepsilon \sim N(0,\sigma^2)$.

Without loss of generality, consider only the calculation of the x_i effect size. By definition, the effect size of parameter x_1 is the maximum change in predicted response due to parameter x_1 when the other (n-1) dimensional vector $(x_2,\ldots,x_n)$ is fixed at any point in the parameter space $[-1,1]^{n-1}$. Thus, the effect size due to parameter x_1 may be found by solving the following optimization problem, defined in the following expression (**Equation 4**):

$$\max_{-1\le x_2,\ldots,x_n\le 1}\{\max_{-1\le x_1\le 1} f(x_1,\ldots,x_n) - \min_{-1\le x_1\le 1} f(x_1,\ldots,x_n)\}, \quad \text{[Eq. 4]}$$

where $f(x_1,\ldots,x_n)$ denotes the prediction of response at a given design point $\{x_1,\ldots,x_n\}$. Manually solving this optimization problem is complicated. Due to transformation, the parameters $x_2,\ldots,x_n$ can have an influence on effect size regardless of the model form. To illustrate this point, consider a simple linear model with logarithm transformation of y as expressed in **Equation 5**.

$$\log(y) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \varepsilon, \quad \text{[Eq. 5]}$$

where x_1 and x_2 are the parameters, and $\varepsilon \sim N(0,\sigma^2)$. The prediction of y given x_1 and x_2 is expressed in **Equation 6.**

$$f(x_1,x_2) = e^{\beta_0 + \beta_1 x_1 + \beta_2 x_2 + 0.5\sigma^2}. \quad \text{[Eq. 6]}$$

Note that a bias correction for prediction is employed in **Equation 6.** Comparing this approach to inversely transforming the prediction of log (y), the bias correction provides unbiased, or, at least, less biased predictions for the response.

Discussion of this topic can be found in the literature (4, 5). **Table II** provides the bias-corrected prediction formulas for some commonly used transformation functions.

Also notice that, in **Equation 6**, the change of predictions contributed by x_1 relates to the value of x_2. The analytical formula of effect size is expressed in **Equation 7.**

$$\text{effect size}(x_1) = e^{\beta_0 + |\beta_2| + 0.5\sigma^2}\cdot\left|e^{\beta_1} - e^{-\beta_1}\right| \quad \text{[Eq. 7]}$$

In this case, unlike the situation found in the "main effects" model without transformation, x_2 has an impact on the effect size of x_1.

To illustrate this, **Figures 2(v) and 2(vi)** display contour plots from the model $\log_{10}(y)=2+0.5x_1+x_2$ in both transformed and original scales, respectively.

Note that, in the plot of transformed scale, the impact due to x_1 does not depend on x_2, and the same holds for the impact of x_2.

However, in the original scale, the maximum changes clearly occur along the top edge (i.e., the impact of x_1 when $x_2=1$) and the right edge (i.e., the impact of x_2 when $x_1=1$).

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This example shows that, even under the simplest case of linear model with transformation, the effect size of parameter must be evaluated across the entire design space.

When the model or transformation function is complicated, it would not be feasible to evaluate the effect size manually.

Using an algorithm to calculate parameter effect size

As described in the previous session, the effect size of a parameter can be calculated analytically and programmed with any computational language.

However, when more process parameters are included in models, especially with higher order terms, it becomes more complex to derive the analytical solutions. A generalized, practical computational tool is needed.

A grid-search algorithm was developed to calculate the parameter effect sizes for any parameters in all types of linear models. Using this approach, the number of grid levels is set based on the complexity of the model that is being used.

If the process parameters involved interact in linear fashion with other terms, the number of grid levels can be simply set to two at the boundary of the parameter range.

However, if the parameters are involved in higher order curvature terms, the number of grid levels must be set to much larger than 2 in order to accurately locate the global optimum point.

The pseudo code used for the grid-search algorithm is shown below. Note that, when transformation of a CQA is involved, the effect sizes are calculated based on the predictions in original scale with bias corrections.

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A grid-search algorithm for effect sizes

Step 1: List all process parameters in the model: $x_1, x_2, \ldots, x_k$

Step 2: Set levels of grid for each of the parameters

For i in 1 to k

If x_i has only linear effects in the model, the number of grids is set to $n_i=2$;

Else if x_i has curvature effects, the number of grid levels can be set to $n_i=10^{4/k}$, where k is the number of parameter having higher order effect (e.g., if k=2, $n_i=100$). The grid points are selected over the ranges of parameters.

Step 3: Generate a matrix with combinations of grid levels of parameters (1, 2, …, k) as shown below:

$$[x_i] = [x_{i1}, x_{i2}, \ldots, x_{in_i}],\ i=1,2,\ldots,k$$

$$[x] = \text{expand grid } (x_1, x_2, \ldots, x_k)$$

Step 4: Predict CQA (i.e., y) from its model fit, $y=f(x)+\varepsilon$

$$\hat{y} = \text{predict } (f(x),[x])$$

Step 5: Determine the effect size (Δ) for each process parameter by finding the maximum change of the predicted CQA caused by the process parameter change when other factors are fixed at their possible levels:

For i in 1 to k

For j in 1 to n_i

For all p = 1, 2, …, k & p≠i

$$\Delta_{ij} = \text{range}(\hat{y} \mid [x_p] \& [x_i]=x_{ij})$$

$$\Delta_i = \max(\Delta_{ij})$$

Figure 3: Illustration of the grid-search algorithm for calculating factor effective sizes (5 x 5 grid)

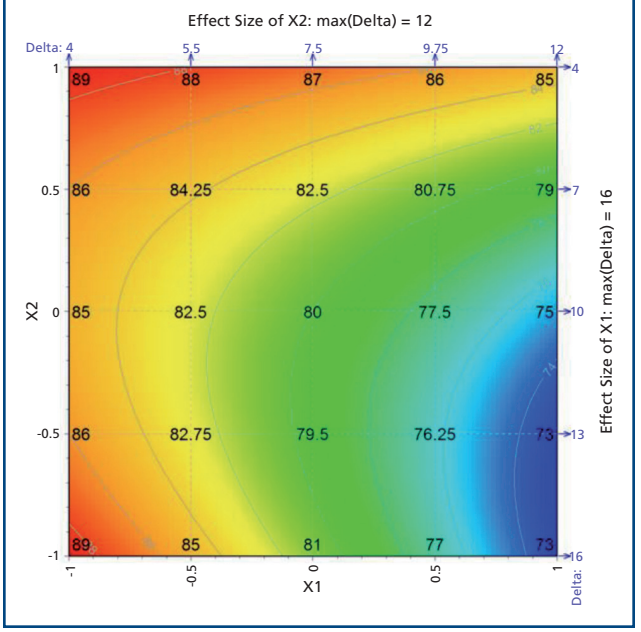


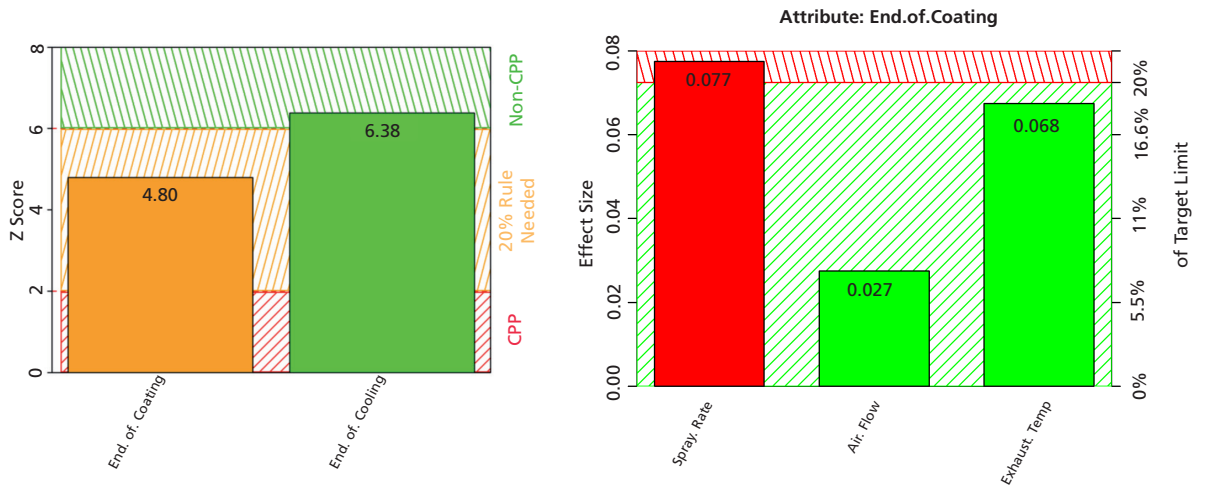
Figure 3 graphically shows how the grid-search algorithm finds the maximum changes in a CQA over the ranges of two process parameters. This CQA has an interaction/quadratic model $y=b_0+b_1 x_1 + b_2 x_2 + b_{12} x_1 x_2 + b_{22} x_2^2$. Notice that, for illustration purposes, the grid levels were set to 5 for each of the two process parameters.

An example with algorithm output

For a moisture-sensitive product, aluminum foil and/or foil packaging plus tablet water-activity controls are needed to ensure that the drug product quality is maintained throughout the desired shelf life.

A two-level full factorial design of experiment (DoE) was performed to evaluate the impacts of three film coating process parameters—spray rate, air-flow and exhaust temperature—on tablet water activity through the coating process. Tablet water activity at the end of coating and water activity at the end of cooling are identified as the critical quality attributes, with a target limit of not more than 0.6.

Figure 4: Using Z score and effect-size plots to evaluate the parameter criticality. CPP is critical process parameter. The plot on the left shows the Z scores, with reference lines at 2 and 6. On the right, the absolute effect size is shown on the left axis while the percentage of the quality target range (QTR) is shown on the right axis, with a reference line at 20% of QTR.



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The statistical models of the attributes are given below:

End of Coating = 0.324 + 0.0388 * Spray Rate - 0.0138 * Air Flow - 0.0338 * Exhaust Temp, $R^2 = 0.9763$

End of Cooling = 0.28 + 0.0225 * Spray Rate - 0.0150 * Air Flow - 0.0375 * Exhaust Temp, $R^2 = 0.9716$

Process parameter criticality was assessed based on Z scores of water activities and parameter effect sizes. Given the calculated average (0.32), the standard deviation (0.058) and the target limit of NMT 0.6, the Z score for water activity at the end of cooling process is 6.38. Because the Z score is greater than 6, all three parameters are considered to be non-critical.

Given the calculated average (0.28), the standard deviation (0.05), and the target limit of NMT 0.6, the Z score for water activity at the end of coating process is 4.80. Because this Z score is in between 2 and 6, additional assessment is required via the 20% rule to quantify individual parameter effect sizes. **Figure 4** displays the calculated z-score and the effect sizes by grid search. Because the effect size of spray rate is greater than 20% of QTR, spray rate is designated as a CPP.

Summary

The determination of CPPs is a critical part of process and product understanding. A recent statistical approach (1) provides an objective and consistent way to determine the CPPs based on the statistical analyses of experimental data. However, the calculations can be cumbersome, especially when the predictive models are complicated and multiple CQAs need to be considered.

The algorithm of effect size calculation presented in this paper offers a straightforward and universal solution, regardless of model complexity and the numbers of process parameters and CQAs. It is generic enough to be implemented in any commercial coding software package (e.g., R and SAS). In addition, prediction biases caused by certain transformations can be found and corrected, as shown.

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