Robust Optimization, Simulation and Effective Design Space

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Developing product knowledge and process understanding is at the heart of modern drug development. Establishing a clear line of sight between critical quality attributes (CQAs) and process parameters and material attributes is a primary goal of drug development. Much has been said and there is often a poor understanding of the meaning and application of a design space.

ICH Q8 defines a design space as:

> *The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.*

This paper will explore technically rigorous approaches to the generation of process models, optimization techniques for selection of set points and application of a design space to defined CQAs and safe operational ranges.

Design of experiments (DOE) and other multivariate analysis techniques assist the developer in mapping out the design space and building process models. Once the DOE is complete the developer can use the DOE to build a process model, define the design space, run simulations for various optimums and to determine effective factor ranges where the OOS rates will be acceptable.

In reference to modern drug development Q11 states:

> *"Risk assessment can be used during development to identify those parts of the manufacturing process likely to have an impact on potential CQAs. Further risk assessments can be used to focus development work on areas for which better understanding of the link between process and quality is needed. Using an enhanced approach, the determination of appropriate material specifications and process parameter ranges could follow a sequence such as the one shown below:*
>
> - *Identify potential sources of process variability.*
> - *Identify the material attributes and process parameters likely to have the greatest impact on drug substance quality. This can be based on prior knowledge and risk assessment tools.*
> - *Design and conduct studies (e.g., mechanistic and/or kinetic evaluations, multivariate design of experiments, simulations, modelling) to identify and confirm the links and relationships of material attributes and process parameters to drug substance CQAs.*
> - *Analyze and assess the data to establish appropriate ranges, including establishment of a design space if desired."*

The following are generally accepted key steps for building a process model and using the model for development of product knowledge, process understanding and regulatory submission.

1. State all CQAs of interest and their limits (USL and LSL)
2. Define the scale (small and/or at scale)
3. Define all processes and materials that will be used
4. Complete a risk assessment (high level for all unit operations and low level for individual unit operations and materials)
5. Develop all single factor and multiple factor study designs and DOEs, include interactions and quadratics where indicated by the risk assessment
6. Build the process model from the analysis of experimental data and determine all critical process parameters and critical material attributes
7. Optimize the process and define the recipe and set points at their best value (robust optimization)
8. Evaluate the set points using the design space to evaluate margin
9. Evaluate the design space using simulation and evaluate PPM OOS
10. Set normal operating ranges and proven acceptable ranges with margin
11. Verify the small scale and at scale results, rescale the small scale model to match the at scale process
12. Define the effective design space used for process control and define the purpose of the design space.

Steps 7-12 will be discussed in detail in this paper.

7. Optimize the Process and Define the Set Points

When determining the recipe for a formulation or process (set points) there are two methods that can be used. The first is optimization and the second is robust optimization. Optimization works to find the best solution that meets all CQA requirements (figure 1.0), robust optimization works to assure the minimum transmitted variation occurs for all CQA goals. The difference in the two approaches is optimization works to achieve all goals and limits for all CQAs, robust optimization does the same but in addition it works to find the point in the design space where the first derivative (SAS/JMP) (figure 2.0) equals zero, also known as the sweet spot. Mathematically the sweet spot if found where the first derivative of each response with respect to each noise factor are zero. Software programs such as SAS/JMP have these features built in. Robust optimization reduces variation at the operational target and is generally preferred over other optimization strategies.

To achieve superior results and to find the robust optimum two factor interactions and quadratic terms must be included in the model. This has to be considered during the risk assessment and part of the DOE design. Main effects only and or screening type experiments will not result in a robust solution.

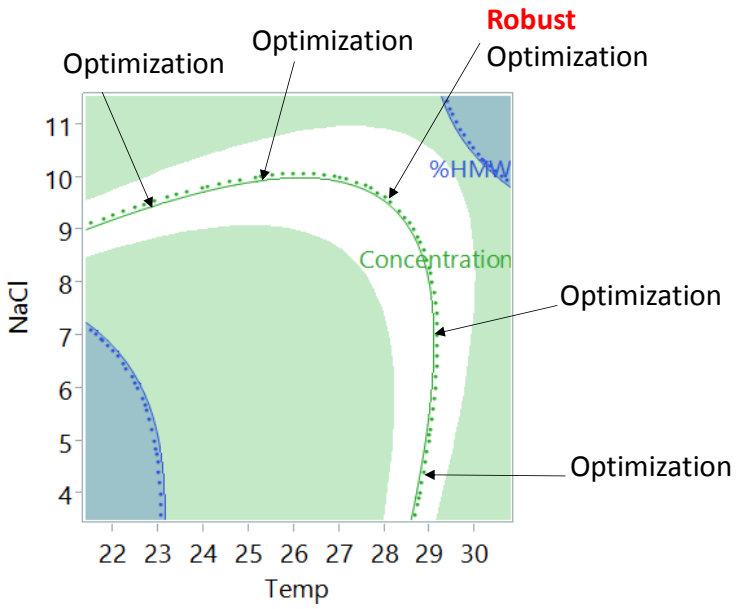

Figure 1.0 Robust Optimization for a Target Concentration

$$\sigma_y = \sqrt{\left[\left(\frac{\partial y}{\partial x_1}\right)\ \sigma_{x_1}\right]^2 + \left[\left(\frac{\partial y}{\partial x_2}\right)\ \sigma_{x_2}\right]^2 + \left[\left(\frac{\partial y}{\partial x_{\ldots n}}\right)\ \sigma_{x_{\ldots n}}\right]^2}$$

Figure 2.0 Partial Derivative for Robust Optimization

8. Evaluate the Set Points using the Design Space

Once the set points have been selected the visualization of the design space can be generated. Every DOE can create a design space. Care needs to be exercised in understanding and interpreting a design space. The visualization of the design space is of the mean (average) in the response surface (figure 3.0) relative to the limits of the CQAs. Many think that being anywhere in the white space will achieve a good result and in the colored or shaded area is bad, that is an incorrect interpretation of the graph. Just being in the white area is no assurance that each batch, vial or syringe will be in specification only that the average from the process model will be within the limits. Also any visualization of the design space is static, the actual design space is dynamic depending on the settings of the other factors. Only simulation can explore and evaluate settings within the design space, examine potential failure rates and evaluate the dynamic nature of the process.

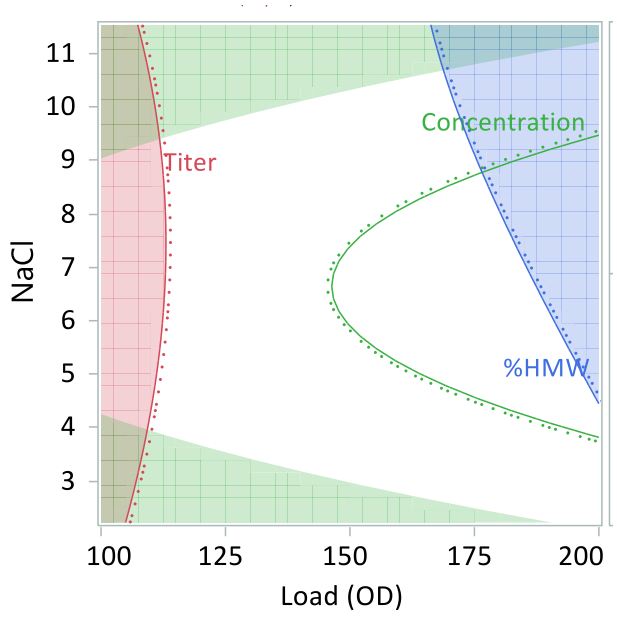

Figure 3.0 Visualization of the Design Space

9. Evaluate the Design Space using Simulation

To simulate batch to batch, unit to unit or vial to vial variation at the set point, Monte Carlo simulation is used. Out of specification (OOS) capability in parts per million (PPM) should be targeted to less than 100 for each CQA or lower. The

simulation includes three key sources of variation, 1) the mathematical expression or model from the characterized product or process, 2) variation of each factor at the targeted set point and 3) the residual variation not accounted for by the model (T. Little.) The residual variation is the root mean squared error (RMSE) from the model and includes the variation from the analytical method as well as any other uncontrolled factor when building the model.

A good understanding of the process or equipment capability will aid the developer in building the simulation (Figure 4.0). Normal, truncated and non-normal distributions are used to inject the simulated noise + RMSE and reflect it onto the model to predict the CQA response. The more accurately the variation at set point is understood the more accurately it will reflect OOS release rates of drug substance or drug product.

An important addition to the design space is the edge of failure graph (Figure 5.0.) The edge of failure graph is recommended to visualize the design margin and failure rates that will occur from the process in volume. Red dots are OOS and green are in specification.

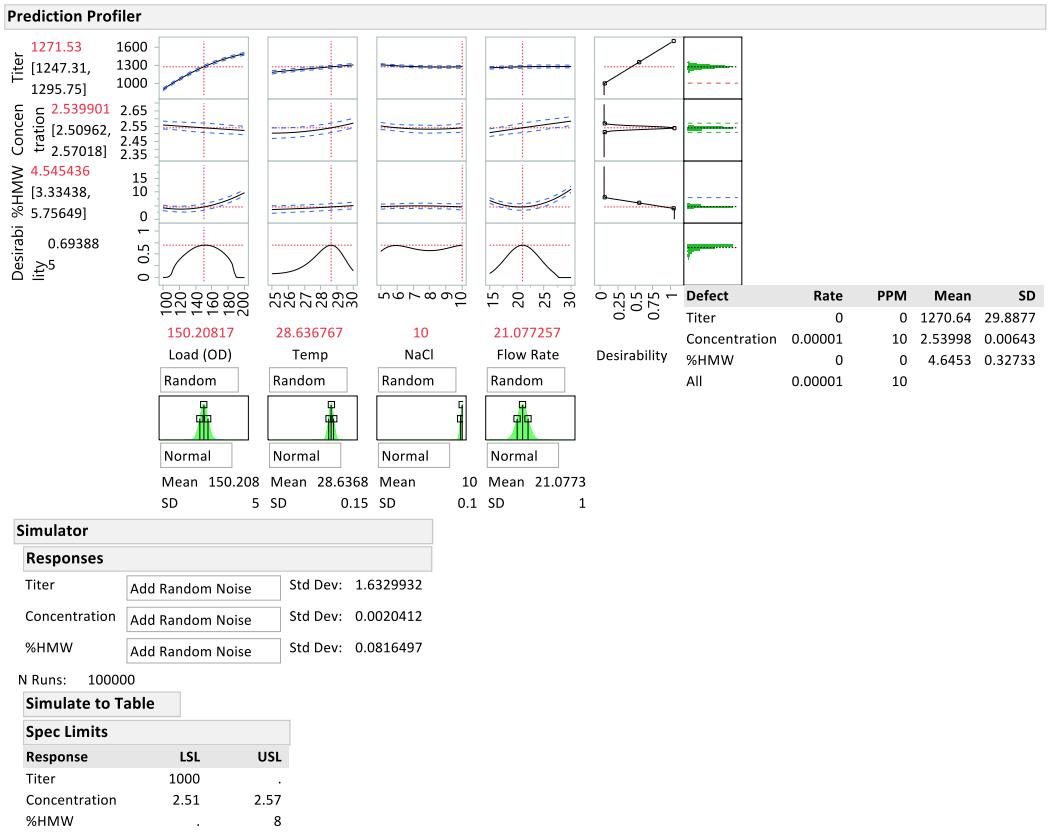

Figure 4.0 Simulation using the Process Model

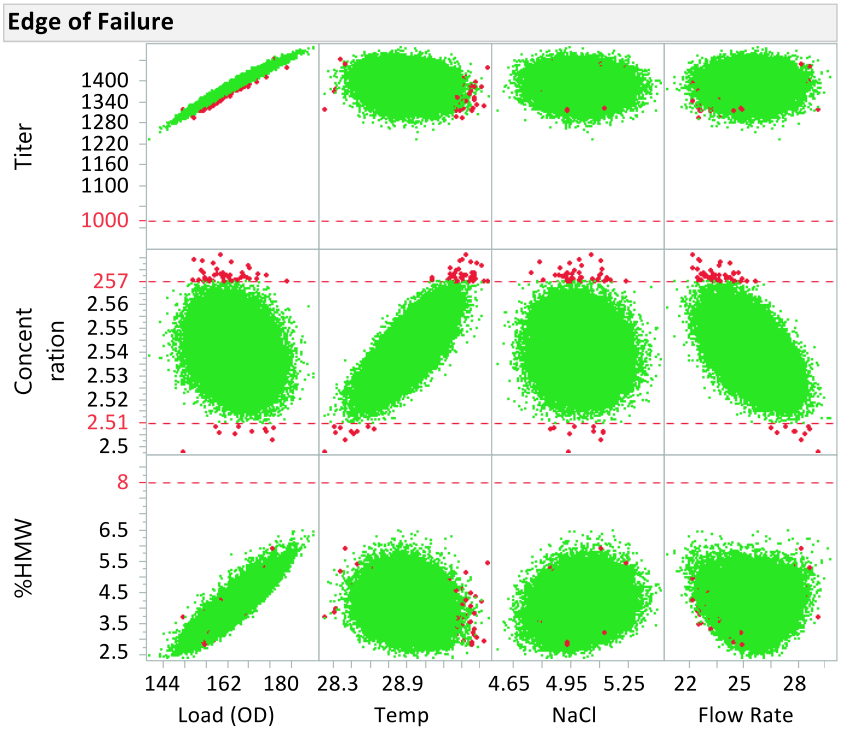

Figure 5.0 Edge of Failure and Simulated Design Margin

10. Set Normal Operating Ranges and Proven Acceptable Ranges

To evaluate normal operating ranges (NOR) and proven acceptable ranges (PAR) the simulation injects variation at set point, 3 sigma, 4.5 sigma and 6 sigma ranges (Figure 6.0) are typically evaluated for their associated PPM. Normal, non-normal, actual resampling from measurements and uniform distributions can be used to evaluate PPM rates. Typically the limits are set to assure the CQA PPM failure rates are below 100. Uniform distributions should be used if processing to range, normal distributions are typically used when processing to target; however, other distributions are possible based on the product and the problem.

					NOR Ranges			4.5 Sigma PAR Ranges			6 Sigma PAR Ranges		
Factors	Set Point	% of Mean	1 Std at Set Point	Parameters	-3	Nominal	3	-4.5	Nominal	4.5	-6	Nominal	6
Load OD	150.2	5%	5	Load OD	135.20	150.20	165.20	127.70	150.20	172.70	120.20	150.20	180.20
NaCl	10	1%	0.15	NaCl	9.55	10.00	10.45	9.33	10.00	10.68	9.10	10.00	10.90
Temperature	28.6	1%	0.1	Temperature	28.30	28.60	28.90	28.15	28.60	29.05	28.00	28.60	29.20
Flow Rate	21.07	5%	1	Flow Rate	18.07	21.07	24.07	16.57	21.07	25.57	15.07	21.07	27.07
				Nominal PPM*	0			2			10		
				Success Rate	100.0000%			99.9998%			99.9990%		

Based on 100,000 simulated purfication runs

*parts per million

Figure 6. NOR and PAR Range Evaluation

11. Verify the Small Scale and At Scale Results

Finally verification runs at the robust optimum are performed to verify the model prediction and the actual measurements are in agreement. Typical acceptance criteria confirm the small or at scale measurements are within the 99% quantile interval from the simulated results. If there is a detected shift between the small scale and at scale data the model can be rescales/calibrated to match the at scale results. Some mechanistic understanding of the scale difference is generally recommended when scale effects are detected.

12. Define the Effective Design Space That Will Be Used for Process Control

Finally there is a difference between the visualization of the design space and the effective design space an applicant may want to file with the health authorities. The effective design space is the region where; 1) no OOS events occur, 2) the applicant will adjust to correct for processing conditions, raw material potency and or Dose or formulation requirements. In most cases the effective design space is much smaller in range than the visualized design space.

Summary

Knowing how to complete a risk assessment and design an appropriate experiment are only two key steps in a series of development activities. Knowing how to complete the development, select the robust optimum, simulate potential OOS rates for all CQAs, determine and evaluate design margin, find the NOR and PAR limits and define and defend the effective design space are essential skills that all those that work in drug development. These skills should be gained by instruction and by practical experience working on drug substance and drug product and with the health authorities on filing the design space and associated control plans.

References

ICH Q8, Pharmaceutical Development, Nov, 2005

ICH Q11, Development and Manufacture of Drug Substances, Nov 2012

Process Validation, General Principles and Practices, FDA, January 2011

T. Little, Robust Optimization, Design Space and Tolerance Design, 2015

SAS/JMP Software, Profilers, Version 12, May 2015