Essentials in Establishing and Using a Product or Process Design Space

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What is a Design Space?

The design space is generally considered to be the areas where the product or process parameters safely (without failure or high amounts of degradation) can be run and achieve all CQAs, product and process acceptance criteria and specifications. Knowledge of product or process acceptance criterion (specification limits) are critical in design space generation and use. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Movement within the characterized design space is not considered as a change and therefore allows for regulatory flexibility.

Specifically ICH Q8(R2) 3.0 Glossary defines design space as follows:

> *"Design Space: 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.*

Knowledge about the product and or process is fundamental to product or process development. Knowledge about how X factors influence Y responses relative to critical quality attributes (CQAs) is fundamental to defining and defending that knowledge. Ultimately knowledge must be in the form of an equation (either empirical or based on well-established scientific principles) to be useful. Process and material equations are typically multiple factor, including main effects, interactions and

quadratic terms and may be either linear (in their coefficients) or nonlinear. Once the equation has been defined, it can be subsequently converted into a design space.

Design space is established through proper characterization techniques and is often an extrapolation of the response surface. Two dimensional contour and three dimensional surface plots are typically used in the visualization of the design space. Visualization, documentation and communication of the design space helps to assure the product and or process set-points are well defined and within safe and robust operating regions. Design space should include both material and process parameters relationships to acceptance criteria (CQAs).

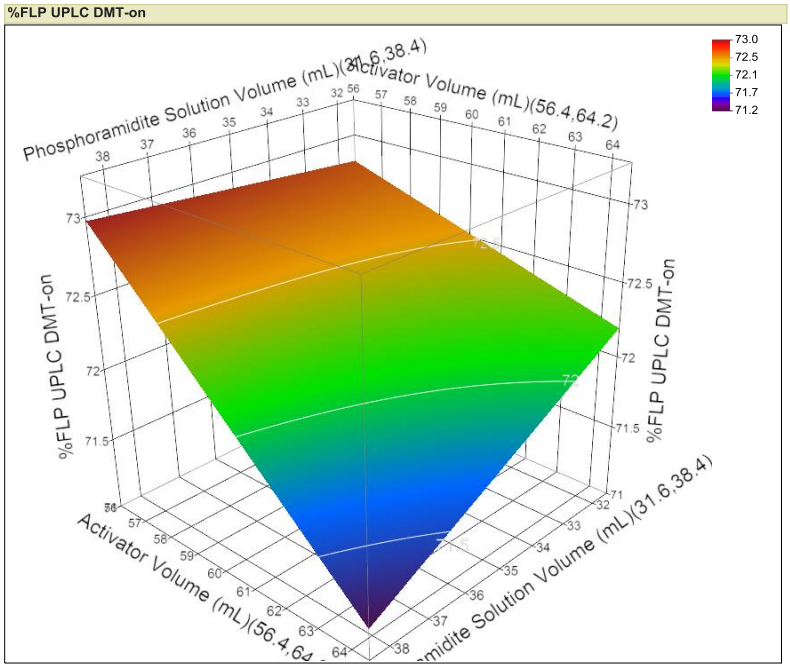

Figure 1.0 3D Design Space Visualization

Why Establish a Design Space?

There are three steps in the development of any product or process; 1) system design, 2) parameter design and 3) tolerance design. System design is the definition of the system (technology, API, excipients, cell line, methods, materials, equipment and/or sequence). Parameter design is the determination of all product and process set-points and targets. Tolerance design is the allowable range that each X factor and Y response can be allowed to vary. Tolerance design can be done either with statistical distributions (when low risk and no safety issues) and or with transfer functions (how X influences Y). Establishing a design space allows for the efficient determination and evaluation of all product and process set points and tolerance design windows. Design space is the result of system design, the selection of all reagents, excipients, API concentrations, materials, equipment, process set-points and tolerances.

Methods for Design Space Generation

Design space generation always begins with CQAs, risk assessments, definition of materials, process sequence, scale and equipment. Experiments are designed that meet the development objectives and goals. Studies are converted from raw data into product, material and process models that explore the parameters/attributes that were identified in the risk assessment. Thoughtfully constructed designed experiments and or other representative data sets may be used in equation/model generation and subsequent design space generation.

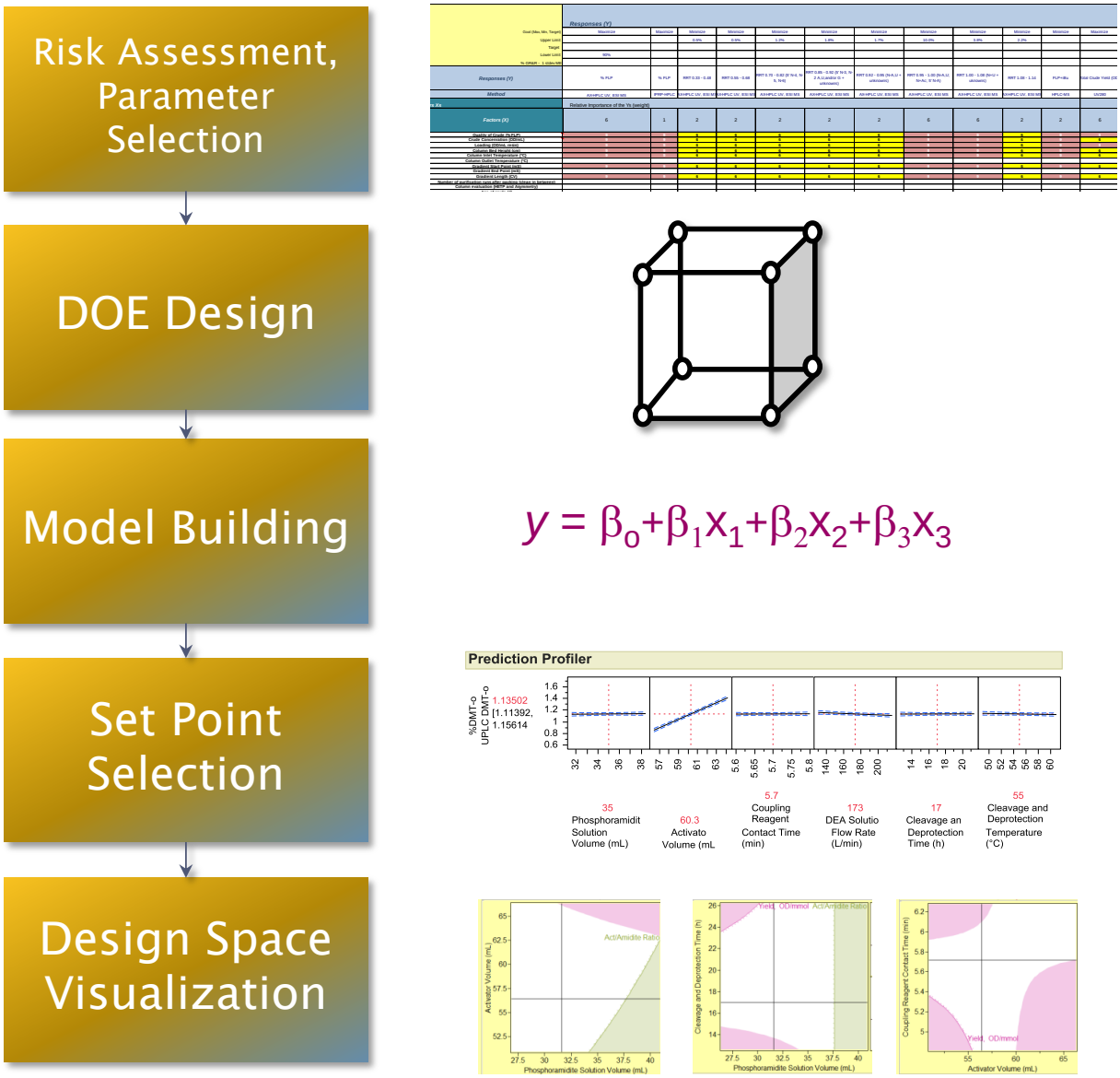

Figure 2.0 Design Space Generation Process

Phase Appropriate Design Space Generation

The design space should be defined by the end of Phase II development. Preliminary understanding of the design space may occur at any time; however, it must be defined prior to Stage I Validation (Process Validation, FDA 2011). Waiting to develop the design space until Phase II assures the specification limits and process definitions are stable and well defined prior to design space generation and evaluation.

Common Misconceptions in Defining a Design Space

There are several common misconceptions in generation of a design space. (Chatterjee, 2012)

1. Design of experiments (DOE) is the same as design space
    - DOE is not the only method for determining a design space other methods can be used including known scientific equations and regression techniques. DOE is generally the most common approach.
    - DOE helps to generate the equation prior to design space determination but it is only one step in the process.
2. Only critical parameters should be in a design space
    - Can include all parameters affecting product quality.
    - Can include parameters that were held constant.
3. Edge-of-failure is needed for a design space
    - Failure mode experiments provide useful information, but not required.
4. All of the area within the extrapolated design space is considered a safe operating region.
    - Extrapolations into uncharacterized regions within the design space add risk.
    - Design space is a mean (average) response surface model and does not assure all samples will meet all batch acceptance criteria. Simulation is typically used to determine C_{pks} and failure rates.

Steps in Design Space Generation

1. Determine the business case and CQAs. Make sure you know why the experiment is needed and what knowledge deficit it will fill. Why this experiment is needed and that experiment is not needed when rationalization of developmental areas.
2. Single unit operation and multiple unit operation approach. Design space can be generated for each unit operation and/or it can be generated across multiple unit operations. Generally across multiple unit operations experiments are more representative of the entire process the drug product or substance will experience.
3. Risk assessments are used to rationalize the selection of parameters, they can be organized as a Factor/Response type risk assessment relative to CQAs or they can be organized as a FMEA type approach relative to CQAs. Either way

a clear line of sight between CQAs and the process parameter and material potential impact aid in parameter selection. (Q9)

4. DOE design and scale considerations in the DOE. DOE generation needs to be linked to the risk assessments and business objectives. Full factorial or D-Optimal custom designs are most common depending on the problem complexity. Make sure to include factors that may affect the process at scale if the experiments are run at small scale.
5. Data analysis and transfer function generation. A multivariate analysis software application needs to be used to analyze the data, eliminate any outliers, determine statistically significant factors, quantitate the effect size of each factor and generate the model (equation). Critical process parameters (CPPs) and critical material attributes (CMAs) can be defined based on effect size.
6. Set point selection and robust optimization within the design space. Once the model has been generated, optimization of all set points to find the most robust (stable) area within the design space is defined.
7. Visualization of the design space at set point. Profilers, interaction profilers, contour plots and 3D surface plots are used to visualize the design space. Specification limits and all acceptance criteria must be defined in order to determine the edges of the design space.
8. Determine the variation of each X parameter at the set point (one standard deviation) and make sure the method variation is known (one standard deviation intermediate precision.) The goal of simulation is to model 100% of the variation in the process. This includes the variation from the model (RSquare) plus the variation due to other factors and the variation from the analytical method. Variation due to stability may also be included as a noise factor.
9. Simulation, determination and visualization of design margin. Using all sources of variation, simulation is used to determine the failure rates at set point. K-sigma limits are used to open up the variation at set point and then determine failure rates, C_{pks} of 1.33 or higher are generally considered good design margin (PPM of 63 batch failures per million batches or less.) Random error is added to the model to make sure all sources of error are included.
10. Finalize the design space by determining the normal operating ranges (NOR) and proven acceptable ranges (PAR.) NORs are typically 3 sigma design windows and PARs are typically 6 sigma design windows around the set point.
11. Small scale and at scale design space verification. Verification runs at both small scale and at scale are used to verify the model. Comparing values from the verification runs to the model help to assure the model has reasonable predictive power. Verification runs for small and at scale processing conditions are essential for model verification. Rescaling the model for the full scale run conditions may need to be done.
12. Product and process control applications. Based on the equations selection of the control strategy can take place. Process controls can be one of the following, feed-forward, feedback, in-situ, XY control or XX control, in process testing and/or release specification testing and limits. Design space helps to determine control parameters based on parameter influence and sensitivity.

Also the transfer functions used in design space generation are used to calculate adjustment amounts when adjusting back to target.

13. Validation implications. Stage I Validation requires a discussion of process knowledge and suggests the demonstration of a design space. (Process Validation, 2011)
14. Submission implications. Depending on how the design space will be used will modify how the submission will be generated and communicated. If it is used to show process knowledge that is one kind of submission, if it is a basis for control with adjustments that will follow another type of submission and is more complicated.

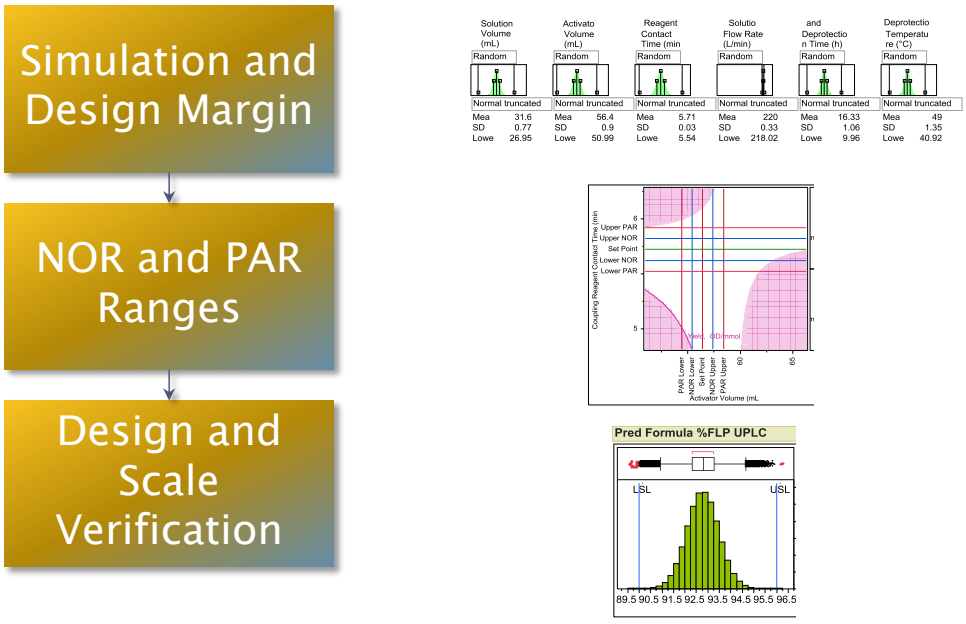

Figure 3.0 Design Space Use

Conclusion

Modern drug development ICH standards encourage design space generation in new product development. It is a best practice and increases product and process knowledge and reduces risk. Using a risk-based and multivariate approach is a best practice in generating the design space. Using the design space to establish set-points, tolerances and PAR ranges is what it is best at. Determination of failure rates and design margin during development is a best practice. Using the transfer functions from the design space for process control is a best practice. Clearly communicate the intended design space to regulators and how the design space is to be used. FDA generally welcomes discussion on design space with applicants so make sure and discuss the design space and submission logic with FDA working groups as needed.

References:

Sharmista Chatterjee, Design Space Considerations, FDA, AAPS Annual Meeting, October 14, 2012, Chicago, ONDQA/CDER/FDA

ICH Q8(R2) Pharmaceutical Development, 2009

ICH Q9 Quality Risk Management, 2006

Process Validation: General Principles and Practices, 2011