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A Systematic Approach for Selecting Critical Process Parameters for Process Control

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Critical process parameters (CPPs) and their associated process controls are crucial to drug development, process validation and to the evaluation of every manufacturing unit operation. Although every manufacturer and regulator requires effective process control systems, few companies are satisfied with the performance of their internal and or CMO's controls. In many cases, process controls fail to perform adequately due to the fragmented nature of selection, application and implementation. Partially implemented process controls, for example, will not adequately cover the range of capabilities that are required for the drug-substance and or drug-product development and are likely to result in a lack of control of the process and product. Failure to control the process will result in difficulties with regulatory submissions, lot release as well as, extensive product loss or and a loss of regulatory and customer confidence.

The systematic approach for CPPs selection and use discussed in this paper was developed in line with the International Conference of Harmonization (ICH) Q8, Q9, Q10 and Q11 guidelines which recommend quality risk management and the identification of CPPs as part of a drug quality and process control development.

Specifically ICH Q8(R2) 2.5 on Control Strategy, states:

> *"…. These controls should be based on product, formulation and process understanding and should include, at a minimum, control of the critical process parameters and material attributes.*
>
> *A comprehensive pharmaceutical development approach will generate process and product understanding and identify sources of variability. Sources of variability that can impact product quality should be identified, appropriately understood, and subsequently controlled. Understanding sources of variability and their impact on downstream processes or processing, in-process materials, and drug product quality can provide an opportunity to shift controls upstream and minimize the need for end product testing. Product and process understanding, in combination with quality risk management (see ICH Q9), will support the control of the process such that the variability (e.g., of raw materials) can be compensated for in an adaptable manner to deliver consistent product quality."*

CPP selection has traditionally been difficult due to the lack of a systematic approach to the problem. CPPs may be found in media, upstream and downstream unit operations and drug-product processing. Due to the large number of unit operations and media complexity it is easy to overlook processing parameters and materials that may impact drug-substance and drug-product variation and CQAs. Failure to identify critical parameters will result in unexplainable variation during batch processing and lot acceptance.

The key steps to critical process parameter selection and their application to process control is a follows:

1. Identify critical quality attributes (CQAs) for drug-product and substance
2. Select API, excipients, materials and container closure
3. Define all unit operations and process flow
4. Define all product and process specification limits
5. Achieve acceptable results for method validation of all analytical methods
6. Complete quality risk management for factor/response selection for all critical unit operations and materials

7. Explore the design space all key factors identified during the risk assessment using DOE or other multivariate methods
8. Determine the factor effect size and select all CPPs
9. Evaluate CPPs for ease of control and practical application to process control

These steps are covered in detail below.

1. CQA identification

CQAs are those attributes that are important to the quality of the drug product and that remain consistent with those used in clinical studies. Generally industry associates them with ICH parameters such as identify, purity, potency, stability, safety and so forth. CQAs provide the justification and rational of what is critical to function and what ultimately needs to be controlled to assure compliance and fit for use. CQAs are the foundation upon which the CPPs must be associated. Line of site between CPPs and CQAs is considered a major component of the drug-development strategy.

2. Ingredient, materials and container closure

Key parameters and analytical methods that measure the attributes of the API, excipients, key materials and packaging/container closure must be examined using a quality risk management (QRM) approach to find those attributes that will be crucial to maintaining the quality and stability of the drug substance and drug product. Key findings of this review will add to the list of candidate process parameters that need to be controlled. Output of a QRM material assessment will generate some candidate CPPs.

3. Unit operation process definition

Similar to the selection and identification of the API and associated materials, identification of all unit operations and their associated equipment sets and equipment capabilities in upstream and downstream processes are crucial when selecting those parameters that need to be controlled to assure potency and drug lot consistency. Small changes in time, temperature, pH and other variables may result in changes to API characteristic, yield and impurity profiles. Output of a QRM unit operation assessment will generate some candidate CPPs. Because biologics are extremely sensitive to processing it is important that each unit operation be carefully evaluated for possible impacts to the large molecule and impurities.

4. Product and process specifications

Specification limits for product and process must be defined to protect the CQAs of the drug substance or drug product. These limits may be set based on a transfer function (e.g., how does X factor influence the Y response) from a characterization study or may be set statistically (based on some multiplier of sigma and or risk) for those parameters that show no harm (i.e., clinical) and where variation is known. Specification limits will form a key basis for CPP

determination. Specification limits are primarily defined for product control rather than for process control.

5. Validation of analytical methods

Limit of detection, limit of quantitation, precision and accuracy must be characterized for all analytical methods and method validation must be completed. Once these steps are done one can trust the numbers and know the error associated with any statistic of interest. Method validation should be done prior to product and process characterization studies and the design and implementation of process controls.

6. QRM for all materials and unit operations

A formal QRM process should be in place to systematically examine all materials and unit operations for their potential influence to drug CQAs. Risk ranking and other QRM tools are used to identify factors and unit operations that hold the greatest risk. Scientific understanding and historical data are typically the basis upon which potential risks are identified and prioritized. Candidate CPPs may be identified in this process that will later need to be ruled in or ruled out based on data and identified risk.

7. Design space characterization

Many of the prior steps provide inputs to effective design space characterization and optimization. Design of experiments (DOE) and multifactor studies are used to understand the sensitivity of key product and process parameters relative to drug-product and drug-substance specification limits. Factor selection prior to DOE design generation is the most important step in design-space characterization. The matrix shown in Figure 1 is used in the identification of the factors and responses that should be characterized and completed as part of risk assessment prior to DOE design.

DOE Factor/Response Matrix

Experiment Name:

Date:

Experimental Problem, Objectives and Goals: Experimenter(s):

What is the problem you are trying to solve? What is the purpose, study questions and goals?

			Responses (Y)							
		Goal (Max, Min, Target)	Match Target	Minimize	Maximize	None				
		Upper Limit								
		Target								
		Lower Limit								
		% GR&R - 1 stdev ME								
		Responses (Y)	Response 1	Response 2	Response 3	Reponse 4	Reponse 5	Reponse 6	Reponse 7	
Experimental Factors Xs			Relative Importance of the Ys (weight)							
Ease of Randomization	**Factor Types**	***Factors (X)***	1	3	1	1	1	1	1	Totals*
Easy	Continuous	Factor 1	0	0	0	0	0	0	0	0
		Factor 2	0	0	0	0	0	0	0	0
		Factor 3	0	0	0	0	0	0	0	0
		Factor 4	0	0	0	0	0	0	0	0
		Factor 5	0	0	0	0	0	0	0	0
		Factor 6	0	0	0	0	0	0	0	0
		Factor 7	0	0	0	0	0	0	0	0
		Factor 8	0	0	0	0	0	0	0	0

Figure 1. Factor Response Matrix and Risk Assessment

One should take care to open up the range of the X factors sufficiently to understand their influence on Y response and to be representative of the normal operational range of the process. Figure 2 shows a clear picture of the design space generated from a characterized process. The white area is within the specification limits the shaded area is outside the design specification limits.

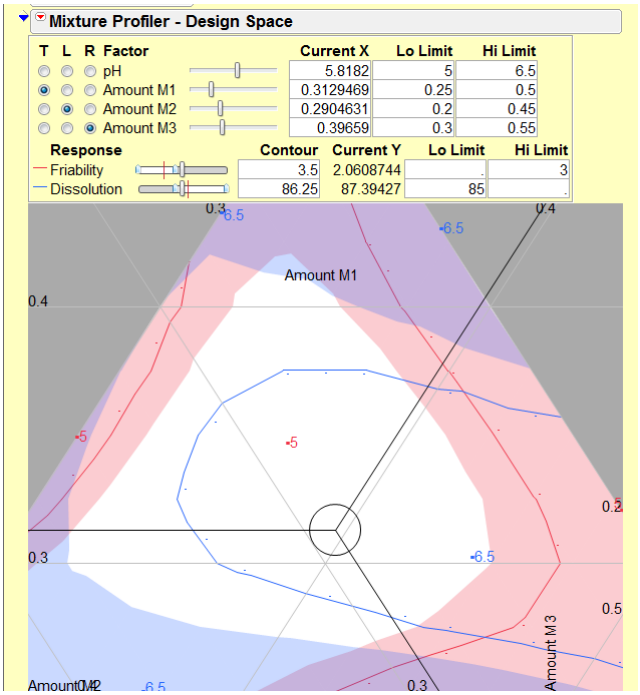

Figure 2. Design Space Characterization

8. Factor effect size and CPP selection

DOE and multifactor experiments help to isolate the influence of every factor and interaction on the critical responses associated with the substance or product. Analysis of the DOE will generate the scaled estimates (1/2 the change in Y relative to the change in X) also known as half effects as shown in Figure 3.

Scaled Estimates-Purification

Term	Scaled Estimate	Std Error	t Ratio	Prob>|t|
Intercept	97.643351	0.144326	676.55	<.0001*
Bed Height(24,36)	0.2993734	0.057636	5.19	<.0001*
Flow rate during Gradient 1(150,250)	-0.002626	0.05774	-0.05	0.9639
Detrit Contact Time (min)(20,30)	-0.097283	0.057471	-1.69	0.0981
Volume Isocratic Wash, CV(1,3)	-0.121033	0.05965	-2.03	0.0490*
Sample Loading, mg/ml Resin*Detrit Contact Time (min)	-0.127408	0.061868	-2.06	0.0458*
Flow rate during Gradient 1*Volume Isocratic Wash, CV	-0.196646	0.06355	-3.09	0.0035*
Flow rate during Gradient 1*Flow rate during Gradient 1	-0.384831	0.155196	-2.48	0.0174*
Sample Loading, mg/ml Resin(12,18)	-0.462403	0.058317	-7.93	<.0001*

Figure 3. Scaled Estimates

One can onvert the scaled estimate into the full effect (total change in Y relative to change in X) and compare the full effect to the product specification tolerance. The formulas for conversion are as follows:

Full Effect=Scaled Estimates * 2
% of Tolerance = Abs(Scaled Estimates * 2)/(USL-LSL) for two sided limits
% of Design Margin= Abs(Scaled Estimates * 2)/(Average-LSL) for one sided LSL only
% of Design Margin= Abs(Scaled Estimates * 2)/(USL-Average) for one sided USL only

where:

USL is the Upper Spec Limit
LSL is the Lower Spec Limit
Average is the baseline process or product average from the DOE or other lots.

The following is one of many possible justifications for determining CPPs. To normalize and standardize the effect size, the percent of tolerance for two-sided specification limits and the percent of design margin for one sided limits was used to evaluate the effect size of a factor and or interaction. Values of less than 10% or were not considered practically significant. Values of 11% to 19% were considered Key Operating Parameters and values of 20% + are considered CPPs therefore critical to product, process and design performance as shown in Figure 4. Although thresholds for criticality are somewhat arbitrary, they have been set relative to the design space explored and as a percentage of the CQA attribute and therefore should have product performance relevance.

	Factor and Model Term	Scaled Estimate (Half Effect)	Full Effect	% of Tolerance	CPP Ranking
1	Bed Height(24,36)	0.2994	0.5987	19.96%	Key Operating Parameter
2	Flow rate during Gradient 1(150,250)	-0.0026	-0.0053	0.18%	Not Practically Significant
3	Detrit Contact Time (min)(20,30)	-0.0973	-0.1946	6.49%	Not Practically Significant
4	Volume Isocratic Wash, CV(1,3)	-0.1210	-0.2421	8.07%	Not Practically Significant
5	Sample Loading, mg/ml Resin*Detrit Contact Time (min)	-0.1274	-0.2548	8.49%	Not Practically Significant
6	Flow rate during Gradient 1*Volume Isocratic Wash, CV	-0.1966	-0.3933	13.11%	Key Operating Parameter
7	Flow rate during Gradient 1*Flow rate during Gradient 1	-0.3848	-0.7697	25.66%	Critical Process Parameter
8	Sample Loading, mg/ml Resin(12,18)	-0.4624	-0.9248	30.83%	Critical Process Parameter

Figure 4. CPP Identification

9. Application of CPPs for Control

CPP selection typically comes from several sources; risk assessments, scientific knowledge and from characterization and optimization studies. Once all CPPs have been identified the next step is to determine practical application of them for process control. Typical considerations include ease of use and or ease of adjustment, safety and other risk factors, on-line or in-line measurement, off-line or near-line measurement. Just knowing a factor is critical and knowing the relative effect size of the factor to the product specifications and CTQs is a great start but it is not sufficient. Care needs to be exercised to make sure the CPP factors can be used in a safe and effective way to consistently adjust process parameters to their intended targets. Linking SPC and PAT methods to the sensitivities identified during CPP selection is a big plus and ties the adjustment method together with process monitoring and control methods.

References:

ICH Q8(R2) Pharmaceutical Development, 2009

ICH Q9 Quality Risk Management, 2006

ICH Q10 Pharmaceutical Quality System, 2009

ICH Q11 Development and Manufacture of Drug Substances, Draft

PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, 2004