March 2018, BioPharm International Publication

Identifying and Controlling CPPs and CMAs

Thomas A. Little Ph.D.
2/22/2018

President/CEO Thomas A. Little Consulting, BioAssay Sciences
12401 N Wildflower Lane
Highland, UT 84003
1-925-285-1847
drlittle@dr-tom.com

Statistical methods to identify critical process parameters and critical material attributes—and approaches to control them—are needed to protect drug product and drug substances.

A key element of drug development and product/process characterization is the requirement to identify and control critical process parameters (CPPs) and critical material attributes (CMAs) that influence critical quality attributes (CQAs). CQAs have clinical relevance as they are defined to specifically measure drug attributes associated with safety and efficacy of the drug. In a previous article (1), a discussion of the selection of CPPs was presented. This article presents statistical methods to identify CPPs and CMAs and approaches on how to control them so they do not adversely affect the drug product or drug substance.

ICH Q8 Pharmaceutical Development (2) states in Part II, 2.5,*"… 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."

Line-of-sight for all CQAs and CPPs/CMAs

When working on drug development, there is a need to maintain line-of-sight (**Figure 1**) between CQAs and elements of drug development that may influence them. Elements of drug development that may impact CQAs are as follows:

- Excipient selection in formulation
- Formulation concentrations
- Formulation process for drug substance or drug product
- Process selection
- Processing method or sequence of operation
- Process equipment settings
- Materials and reagent selection
- Process parameter characterization
- Selection of normal operating ranges (NORs)
- Selection of proven acceptable ranges (PARs)
- Critical parameters in analytical methods.

By maintaining line-of-sight, the relationship of drug development parameters and CQAs is maintained and evaluated in a systematic manner, making knowledge gaps and oversights less likely. Quality risk management is a technique that evaluates and manages development risks associated with CQAs. ICH Q9 on quality risk management (3) states,*"Two primary principles of quality risk management are: the evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk."*

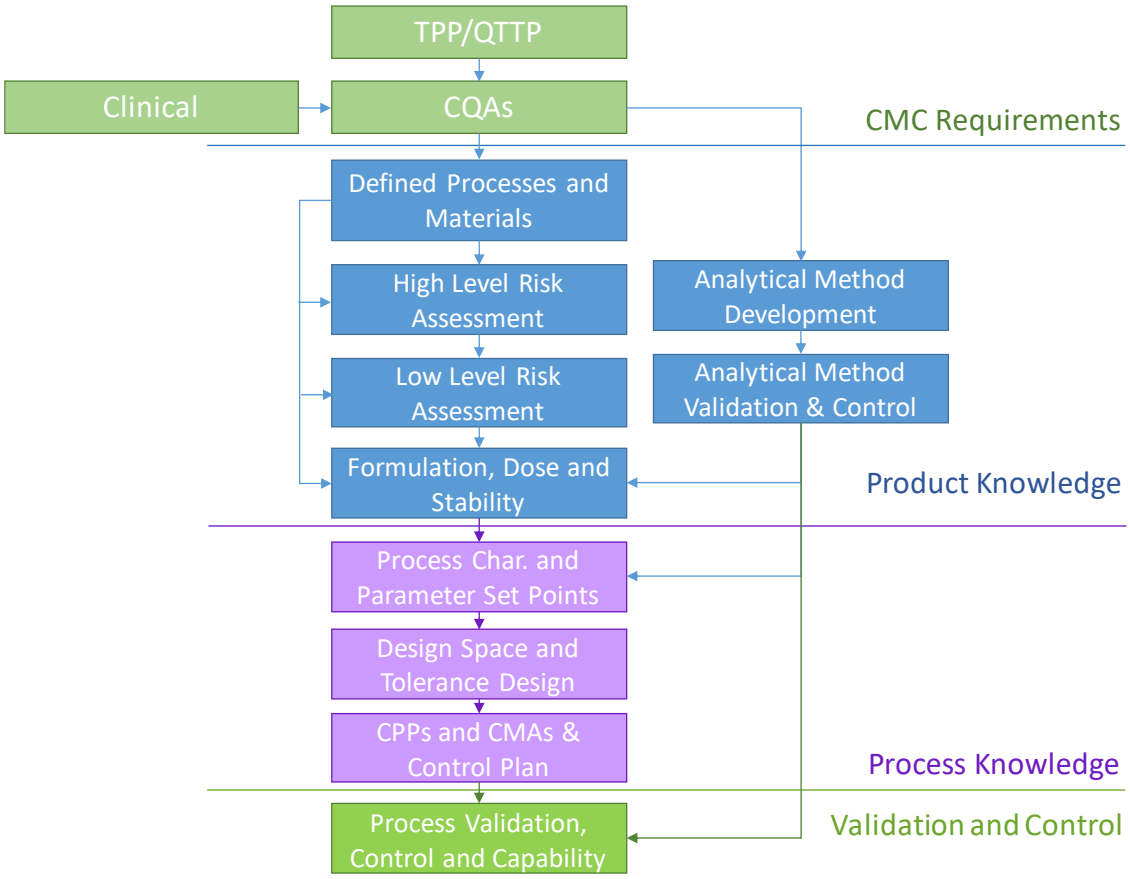


Figure 1: Line of sight and critical process parameters.

Quality risk management is normally used to identify development areas with risk to CQAs; however, it is not sufficient to identify the CPPs and CMAs. High-level risk assessments will indicate unit operations with risk, and low-level risk assessment will identify potential factors that may impact CQAs. Risk assessment alone is not sufficient to detect and control CPPs. It can only be based on measurement of how factors directly influence the response.

CPPs may be found in formulation, 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 influence drug-substance and drug-product variation and CQAs. Failure to identify critical parameters will result in unexplainable variation during batch processing and lot acceptance.

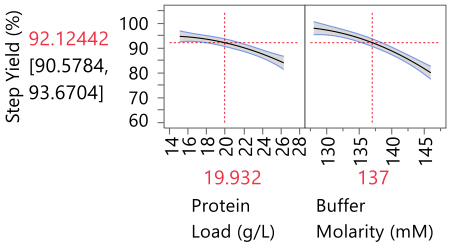
The key steps to CPP/CMA selection and their application to process control is as follows:

- Identify CQAs for drug product and substance. Include responses for productivity (%viability or titer).
- Select API, excipients, processes, materials, and container closure.
- Define all unit operations and process sequence of operation.
- Define all product and process specification limits and acceptance criteria (include in-process controls and release testing).
- Qualify/validate all analytical methods.
- Complete high-level quality risk management and identify unit operations with risk to CQAs.
- For unit operations with risk, complete a low-level factor/response selection for all factors, interactions, quadratics, and materials.
- Generate design of experiments (DoEs) for unit operations or materials with risk.
- Explore the design space all key factors identified during the risk assessment using DoE or other multivariate methods.
- Determine the factor effect size and scaled estimates.
- Determine the % of tolerance, % of margin, or % of mean, and identify all CPPs/CMAs.

Identification of CPPs based on the scale estimate from DoEs

DoE and multifactor experiments help to isolate the influence of every factor and interaction on the critical responses associated with the drug substance or product. Analysis of the DoE will generate the scaled estimates (one-half the change in Y relative to the change in X) also known as the half effect (**Figure 2**). Scaled estimates are the direct measure of how factors influence CQAs and key responses.

Prediction Profiler



Scaled Estimates

Continuous factors centered by mean,
scaled by range/2

Term	Scaled Estimate	Std Error	t Ratio	Prob>|t|
Intercept	92.124296	0.745461	123.58	<.0001 *
Protein Load (g/L)	-4.752041	0.600452	-7.91	<.0001 *
Buffer Molarity (mM)	-8.947703	0.575128	-15.56	<.0001 *
(Protein Load (g/L)-19.9321)*(Protein Load (g/L)-19.9321)	-2.107	1.145099	-1.84	0.0793
(Protein Load (g/L)-19.9321)*(Buffer Molarity (mM)-137)	-5.231745	0.62338	-8.39	<.0001 *
(Buffer Molarity (mM)-137)*(Buffer Molarity (mM)-137)	-3.151341	1.08283	-2.91	0.0081 *

Figure 2: Scaled estimates from a designed experiment.

Multiplying the scaled estimate by two for all main effects and two-factor interactions, and by one for all quadratics determines the full effect of each factor and or model term. Dividing the full effect by the tolerance, margin, or mean measures the factor or model term as a % of tolerance, % of design margin, or % of the mean. The reason ±20% of tolerance is considered critical, it will cause shifts in the CQA response and most likely result in out-of-specification (OOS) results (**Figure 3**), thus it makes the factor or material attribute critical:

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.

Term	Scaled Estimate	Multiplier	Full Effect	CPP	Lower DOE Limit	Upper DOE Limit
Protein Load (g/L)	-4.752040782	2	-9.504081565	-23.76020391	15.1	26.3
Buffer Molarity (mM)	-8.947703454	2	-17.89540691	-44.73851727	128	146
(Protein Load (g/L)-19.9321)*(Protein Load (g/L)-19.9321)	-2.106999834	1	-2.106999834	-5.267499584	.	.
(Protein Load (g/L)-19.9321)*(Buffer Molarity (mM)-137)	-5.23174488	2	-10.46348976	-26.1587244	.	.
(Buffer Molarity (mM)-137)*(Buffer Molarity (mM)-137)	-3.151340873	1	-3.151340873	-7.878352182	.	.

Figure 3: Critical process parameter identification and DoE limits.

CPPs are a function of the DoE range and their associated influence on CQAs. Increasing or decreasing the experimental range will influence CPP identification. During characterization we want wide limits and don't mind identification of many CPPs; however, when filing a drug with the health authorities we want to demonstrate our control of the parameters makes them not critical.

Control of CPPs/CMAs

ICH Q10 and Q11 (4,5) discuss the need for a control strategy. After the identification of CPPs/CMAs is complete, the next step is to control the influence of the factor so that it does not adversely cause uncontrolled variation in the process. The following are strategies that may be used to control CPPs/CMAs:

- Closed loop control on the factor (PAT/statistical process control with adjust within the defined design space). (6)
- Change the process or method to another method of processing that is better controlled.
- Modify equipment and associated control loops to a tighter range.
- Purchase equipment that is better controlled.
- Change materials.
- Institute raw material qualification on incoming materials.
- Improve vendor material control and certificate of analysis.
- Change a material usage factor based on concentration or potency to control the influence of raw material variation.
- Establish NOR and PAR associated with the product and restrict the operational range.

NOR and PAR Range Control

Normal operating ranges and proven acceptable ranges (NOR/PAR) are determined based on evaluating normal variation from the process (typically ±3 stdev for NOR and ±4.5 stdev for PAR) and its transmitted variation from a DoE simulation (Figure 4).

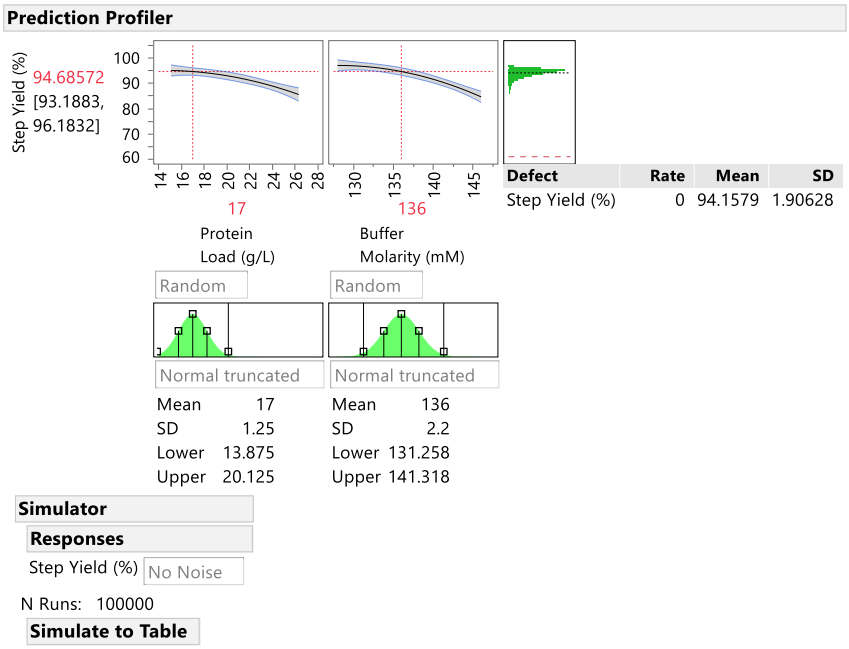
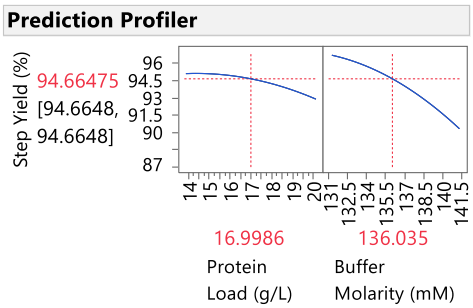


Figure 4: Simulation of NOR/PAR ranges.

Edge of failure analysis is then used to evaluate and/or set the NOR/PAR limit. Setting a NOR or PAR limit will cause restriction in the factor range, and its characterized transmitted influence will be reduced.

Limiting the factors to the NOR and PAR range will reduce the influence of the factors, so they are now more controlled; however, does it also follow that they are now no longer critical and their variation will not result in OOS? To determine if the factor range restriction controls the factor (Figure 5) and is no longer critical, the following procedure is recommended:

- Run a new simulation at the NOR/PAR range at the optimized set point (target) for the process. Use either uniform distribution (worst case) or random truncated (best case).
- Make sure no random variation is injected into the model except from the factors of interest to correctly evaluate their influence.
- From the simulated table with the new range, refit the original DoE model into a multiple regression analysis (Fit Model in SAS/JMP).
- Calculate new scaled estimates from the simulation.
- Determine the new % tolerance, % margin, or % mean
- Determine how many of the factors, model terms are now CPP or CMA.



Term	Scaled Estimate	Multiplier	Full Effect	CPP	Lower DOE Limit	Upper DOE Limit	Operational Range
Protein Load (g/L)	-4.752040782	2	-9.504081565	-23.76020391	15.1	26.3	11.2
Buffer Molarity (mM)	-8.947703454	2	-17.89540691	-44.73851727	128	146	18
(Protein Load (g/L)-19.9321)*(Protein Load (g/L)-19.9321)	-2.106999834	1	-2.106999834	-5.267499584	.	.	.
(Protein Load (g/L)-19.9321)*(Buffer Molarity (mM)-137)	-5.23174488	2	-10.46348976	-26.1587244	.	.	.
(Buffer Molarity (mM)-137)*(Buffer Molarity (mM)-137)	-3.151340873	1	-3.151340873	-7.878352182	.	.	.

Term	Scaled Estimate	Multiplier	Full Effect	CPP	PAR Lower Limit	PAR Upper Limit	Operational Range
Protein Load (g/L)	-1.106640839	2	-2.213281678	-5.533204195	13.9	20.1	6.2
Buffer Molarity (mM)	-3.090917193	2	-6.181834387	-15.45458597	131.3	141.3	10
(Protein Load (g/L)-19.9321)*(Protein Load (g/L)-19.9321)	-0.655953162	1	-0.655953162	-1.639882906	.	.	.
(Protein Load (g/L)-19.9321)*(Buffer Molarity (mM)-137)	-1.631299465	2	-3.262598929	-8.156497323	.	.	.
(Buffer Molarity (mM)-137)*(Buffer Molarity (mM)-137)	-0.984150064	1	-0.984150064	-2.460375159	.	.	.

Figure 5: Before and after NOR/PAR limits and CPPs.

When reporting CPPs and CMAs to health authorities, it is important to report those factors from any characterization DoE that are having a strong influence (>20%) on any CQA or productivity measures. It is, however, equally important to show how those CPPs/CMAs will be systematically controlled. Establishing normal operation ranges (NOR) and proven acceptable ranges (PAR) that influence the factors and demonstrating how those limits reduce their influence so they are no longer critical is one good way to control CPPs/CMAs.

CPP/CMA control summary

CPP and CMA determination typically comes from several sources: risk assessments, scientific knowledge, prior knowledge, and from characterization and optimization studies. Risk assessments alone are not sufficient to determine factor effects on CQAs and productivity. A best practice is to base CPPs and CMAs on measurements and their calculated influence. Once all CPPs/CMAs have been identified, they need to be evaluated for control. There are a variety of control strategies that need to be vetted for control effectiveness for each CPP or CMA. Simulations and DoE are core tools that aid in evaluation and management of CPPs/CMAs.

Demonstration of control effectiveness so that the variation they may cause to the drug substance or drug product will be minimized and predictable is essential to drug development. A discussion of the identification and control of CPPs and CMAs should be included in regulatory filings and is a key demonstration of product knowledge and process understanding.

References

1. T.A. Little, *BioPharm International* 25 (7) (July 1, 2012).
2. ICH, *Q8(R2) Pharmaceutical Development* (ICH, 2009).
3. ICH, *Q9 Quality Risk Management* (ICH, 2006).
4. ICH, *Q10 Pharmaceutical Quality System* (ICH, 2009).
5. ICH, *Q11 Development and Manufacture of Drug Substances* (ICH, May 2012).
6. FDA, *PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*, *Guidance for Industry* (CDER, September 2004).