

A Framework for Combining the Principles of QbD and Quality Risk Management for Metered Dose Inhaler Components

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Summary

Quality by Design (QbD) is a systematic approach to designing and manufacturing products and processes with quality in mind from the very beginning. It emphasizes understanding the product and process, identifying Critical Quality Attributes (CQAs), and controlling the design and manufacturing to ensure consistent quality. QbD is particularly relevant in the pharmaceutical industry where it is used to ensure the quality and safety of drug products.

Quality Risk Management (QRM) is a systematic process for identifying, assessing, controlling, communicating, and reviewing risks that could impact product or service quality. It is a proactive approach that helps organisations anticipate potential issues and take steps to mitigate them before they occur, ensuring consistent high quality and minimising risks to patients.

Adopting QbD methodologies provided by the FDA's process validation (PV) guidance^[1] and International Conference on Harmonization (ICH) Q8^[2], Q9^[3] and Q10^[4] can pose many challenges in determining the criticality of Key Process Variables (KPVs). KPVs are the controllable design and process parameters that can impact CQAs. In essence KPVs are all of the adjustable parameters in a product design or manufacturing process, while Critical Process Parameters (CPPs) are the subset of KPVs that have the most significant effect on CQAs and require tighter control. CPPs are identified through risk assessments that evaluate the potential impact of each KPV on the CQA.

Kindeva have recently developed a process for combining QbD and risk management principles to facilitate robust development and commercialisation of valves and canisters for metered dose inhalers using next generation propellants.

Key Message

A robust framework and methodology have been developed combining QbD and Quality Risk Management principles and will be used by Kindeva to develop the next generation of valves and canisters used in low GWP (global warming potential) metered dose inhalers.

Introduction

There are often two schools of thought; all KPVs are critical – the product cannot be made without controlling them, or no KPVs are critical, because as they are all controlled all CQAs will meet specification. The reality, of course, is somewhere between these two extremes. We need to understand for each parameter/variable how much impact it has on each CQA to help determine its criticality.

CQAs are the characteristics of the final product that must be within specified limits. Even when defined as critical, not all CQAs have equal impact on quality, safety and efficacy.

Risk is the combination of the probability of occurrence of harm and the severity of that harm. This can be assessed qualitatively or quantified, in a more structured way, using formal risk management tools.

Methodology

Kindeva have developed a template and process that follows the principles of ICH Q8, Q9 and Q10, by creating a structured framework that assesses the strength of the relationship between each KPV and each CQA (enabling the CPPs to be identified), converting this to an "impact score" and translating this into a level of harm in a risk matrix.

CQAs are weighted – not all of these are necessarily of the same importance.

The strength of relationship between each KPV and each CQA is assessed – this can be done through knowledge / experience or more formally via design of experiments. The stronger the relationship between the KPV and the CQA, the larger the score – a pragmatic approach to the scoring is to adopt

a 9-3-1 system often used in Lean Six Sigma methodology; 9 for a strong relationship, 3 for a moderate relationship and 1 for a weak or no relationship.

Multiplying the relationship score by the CQA weighting, and totalling across all the CQAs determines the “Impact Score”, which in turn drives the level of Risk Severity. This is done by finding the maximum Impact Score once all of the KPVs have been assessed and then converting this into five levels of risk severity.

Component / Process		KPV	What is the strength of the relationship between the Key Process Variable (KPV) and the Critical Quality Attribute (CQA) parameter for valves? 9 = strong relationship, 3 = moderate relationship, 1 = weak/no relationship												Impact Score

Figure 1 - Determining the Impact Score

Impact Score	Risk Severity (Impact)	
≥ 700	5	Very Significant
550 - 699	4	Major
400 - 549	3	Moderate
250 - 399	2	Minor
< 250	1	Insignificant

Figure 2 – Impact Score to Risk Severity Level

We then move onto risk probability determination via the “Metrology Score” and “Testing Score”. This works on the principle that the better and more frequently we measure our KPVs, the less likely there will be an issue associated with a key dimension or process parameter drifting out of control or out of specification.

The metrology score would ideally be determined following a formal Gauge R&R (repeatability and reproduceability) study, and the better the outcome of this, the lower the metrology score.

Of course, having great metrology is only half the story – the other element in determining risk probability reflects the amount of measurement done – the more frequent the measurement of the KPVs, the lower the testing score.

Multiplying the metrology and testing scores together, results in a score ranging from 1 – 100, which translates into five levels of risk probability.

Metrology Score (the quality of the measurement system for the KPV)			Testing Score (the amount of testing of the KPV)			Risk Probability (Likelihood)		
No MSA	Gauge is calibrated but no formal MSA has been undertaken	10	None	Is not measured at all	10	81 - 100	5	Almost Certain
Very Poor Test Method	% Contribution > 25% % Study variation and % Tolerance > 50% Number of distinct categories <= 2	9	Minimal	Measured by supplier and result provided by CofA	9			
Inadequate Test Method	% Contribution > 9% % Study variation and % Tolerance > 30% Number of distinct categories <= 4	8	Limited	Measured by supplier and result provided by CofA with skip-lot testing (e.g. 1 in 10) here	8	61 - 80	4	Likely
Barely Adequate Test Method	% Contribution 4 - 9% % Study variation and % Tolerance 20 - 30% Number of distinct categories 5 - 7	7	Some	Direct testing done at set-up of every batch	7			
Adequate Test Method	% Contribution 2.25 - 4% % Study variation and % Tolerance 15 - 20% Number of distinct categories 7 - 9	6	Moderate	Measured by supplier and result provided by CofA with every batch tested here	6	41 - 60	3	Possible
Reasonable Test Method	% Contribution 1 - 2.25% % Study variation and % Tolerance 10 - 15% Number of distinct categories 9 - 13	5	Moderately high	Direct testing done at set-up and in-process every batch	5			
Good Test Method	% Contribution < 1% % Study variation and % Tolerance < 10% Number of distinct categories >= 14	4	High	Direct testing done at set-up and in-process with a final stratified sample every batch	4	21 - 40	2	Unlikely
Very Good Test Method	% Contribution < 0.25% % Study variation and % Tolerance < 5% Number of distinct categories >= 28	3	Very high	Multiple levels of direct testing throughout every batch with real-time SPC	3			
Excellent Test Method	% Contribution < 0.04% % Study variation and % Tolerance < 2% Number of distinct categories >= 71	2	Every part - qualitative	Error detection in-station - some type of automatic gauging that will detect an OOS and/or prevent further processing	2	1 - 20	1	Rare
World Class Test Method	% Contribution < 0.01% % Study variation and % Tolerance < 1% Number of distinct categories >= 141	1	Every part - quantitative	There is validated direct 100% automated measurement. The process automatically removes OOS parts / components	1			

Figure 3 – Metrology and Testing Scores to Risk Probability Level

The risk severity and risk probability scores are inputted into a typical risk matrix to determine the risk level.

Impact Score	Risk Severity (Impact)											
≥ 700	5	Very Significant										
550 - 699	4	Major										
400 - 549	3	Moderate										
250 - 399	2	Minor										
< 250	1	Insignificant										
Risk Probability (Likelihood)												
81 - 100	5	Almost Certain										
61 - 80	4	Likely										
41 - 60	3	Possible										
21 - 40	2	Unlikely										
1 - 20	1	Rare										

RISK SEVERITY (Impact)		RISK LEVEL (RL)					
Very Significant	5	R2 (5)	R2 (10)	R3 (15)	R3 (20)	R3 (25)	
Major	4	R1 (4)	R2 (8)	R2 (12)	R3 (16)	R3 (20)	
Moderate	3	R1 (3)	R2 (6)	R2 (9)	R2 (12)	R3 (15)	
Minor	2	R1 (2)	R1 (4)	R2 (6)	R2 (8)	R2 (10)	
Insignificant	1	R1 (1)	R1 (2)	R1 (3)	R1 (4)	R2 (5)	

RISK PROBABILITY (LIKELIHOOD)				
Rare	Unlikely	Possible	Likely	Almost Certain
1	2	3	4	5

Risk Level R3	Action required
Risk Level R2	Action optional
Risk Level R1	No further action required

Figure 4 – Determination of Risk Level

Combining all the above (Figures 1 to 4) results in a large table, a typical example of which is shown below in Figure 5 (albeit would typically have around 100 rows for a typical metering valve).

Component / Process	KPV	CQAs										Impact Score	Risk Severity	Metrology Score	Testing Score	Risk Probability	Risk Level	
		What is the strength of the relationship between the Key Process Variable (KPV) and the Critical Quality Attribute (CQA) parameter for valves?																
		9 = strong relationship, 3 = moderate relationship, 1 = weak/no relationship																
		Weighting																
		Shot weight : Mean and Individual	Leak rate : Mean and Individual	Valve function : No fire / Continuous / MW	Pressure filling : Fill weight target and unit	Valve to withstand the pressure filling process	Extractables : Characterised and meet spec	Capacity of firing at least 200 actuations	Particulates : Acceptable level from valve	Materials of construction : Suitable for use	Actuator fit : Valve dimensions compatible	Connector fit : Valve dimensions compatible						
		10	10	10	8	7	10	10	5	10	10	10						
Stem siliconisation process	Level of silicone oil applied to stems	3	1	9	3	1	3	9	3	3	1	1	346	2	8	7	3	R2
Stem design	Stem overall length (CD1)	1	1	1	1	1	1	1	1	1	1	1	100	1	5	6	2	R1
Stem design	Stem top length (CD2)	1	1	1	3	1	1	1	1	1	1	1	116	1	6	6	2	R1
Stem design	Stem tip diameter (CD3)	1	1	1	1	1	1	1	1	1	1	9	1	7	5	2	R1	
Stem design	Stem top diameter (CD4)	3	1	1	1	1	1	1	1	1	1	1	120	1	7	5	2	R1
Stem design	Stem bottom diameter at groove (CD5)	3	1	1	1	1	1	1	1	1	1	1	120	1	6	6	2	R1
Stem design	Stem bottom diameter below flange (CD6)	3	1	1	1	1	1	1	1	1	1	1	120	1	4	7	2	R1
Stem design	Stem flange diameter (CD7)	1	1	1	1	1	1	1	1	1	1	1	100	1	5	5	2	R1
Stem design	Stem groove depth (CD8)	1	1	1	1	1	1	1	1	1	1	1	100	1	6	4	2	R1
Stem design	Stem top inside diameter (CD9)	1	1	1	1	1	1	1	1	1	1	1	100	1	7	4	2	R1
Stem design	Stem side pierce diameter (CD10)	1	1	1	9	1	1	1	1	1	1	1	164	1	5	5	2	R1
Stem design	Stem side pierce height (CD11)	3	1	3	1	1	1	1	1	1	1	1	140	1	5	5	2	R1
Stem design	Stem groove length (CD12)	3	1	3	1	1	1	1	1	1	1	1	140	1	5	6	2	R1
Stem design	Stem flange depth (CD13)	1	1	1	1	1	1	1	1	1	1	1	100	1	6	7	3	R1
Stem design	Stem top radius (CD14)	1	1	1	3	1	1	1	1	1	9	1	196	1	7	7	3	R1
Diaphragm design	Diaphragm material (EPDM EJ596-85)	1	3	1	3	1	9	3	3	3	1	1	266	2	5	6	2	R1
Diaphragm extraction process	Diaphragm extraction process	1	1	1	1	1	3	1	1	1	1	1	120	1	6	6	2	R1
Diaphragm design	Diaphragm outside diameter	3	3	9	9	1	1	3	3	1	1	1	314	2	5	7	2	R1
Diaphragm design	Diaphragm inside diameter	3	3	9	9	1	1	3	3	1	1	1	314	2	5	7	2	R1
Diaphragm design	Diaphragm thickness	3	1	3	3	9	1	3	1	1	1	1	232	1	8	6	3	R1
Tank seal design	Tank seal material (EPDM EJ596-85)	1	3	1	3	1	9	3	9	3	1	1	296	2	6	6	2	R1
Tank seal extraction process	Tank seal extraction process	1	1	1	1	1	3	1	1	1	1	1	120	1	5	5	2	R1
Tank seal design	Tank seal outside diameter	3	1	9	1	1	1	3	3	1	1	1	230	1	5	5	2	R1
Tank seal design	Tank seal inside diameter	3	1	9	1	1	1	9	9	1	1	1	320	2	6	7	3	R2
Tank seal design	Tank seal thickness	3	1	3	1	1	1	3	3	1	1	1	170	1	7	6	3	R1
Elastomer lubricant	Type of talc (Ph, Eur / USP)	1	1	1	1	1	3	1	1	3	1	1	140	1	6	6	2	R1
Elastomer tacking process	Amount of talc applied to elastomers	1	1	1	1	1	3	1	9	1	1	1	160	1	5	5	2	R1
Spring design	Spring wire material (Stainless steel #302)	1	1	1	1	1	1	1	1	1	1	1	100	1	4	6	2	R1
Spring design	Spring wire diameter	3	3	3	1	1	1	3	1	1	1	1	180	1	5	7	2	R1
Spring design	Spring number of total coils	3	1	1	1	1	1	1	1	1	1	1	120	1	6	7	3	R1
Spring design	Spring number of active coils	1	3	3	1	1	1	3	1	1	1	1	160	1	7	6	3	R1
Spring design	Spring outside diameter	3	1	1	1	1	1	1	1	1	1	1	120	1	6	6	2	R1
Spring design	Spring inside diameter	3	1	1	1	1	1	1	1	1	1	1	120	1	6	7	3	R1
Spring design	Spring free length	1	3	3	1	1	1	3	1	1	1	1	160	1	6	7	3	R1
Valve Crimping	Crimp tightness (F2C)	9	3	9	9	9	1	3	3	1	3	1	450	3	9	9	5	R3
Valve Crimping	Crimp diameter	3	1	3	3	3	1	1	1	1	1	1	170	1	4	5	1	R1

Figure 5 – The Complete Analysis

Conclusions

This new approach developed at Kindeva can be extended to include other elements of the metered dose inhaler, for example the actuator and the filling process, and by combining risk management principles into the approach gives greater clarity of risks that need to be addressed.

The scores in Figure 5 would help define the CPPs and guide additional experiments, design changes, improvements to metrology or additional testing required to reduce the risk to acceptable levels ensuring consistent high quality and minimising risks to patients.

References

- [1] FDA, Guidance for Industry, Process Validation: General Principles and Practices, Revision 1 (Rockville, MD, January 2011)
- [2] ICH, Q8(R2) Harmonized Tripartite Guideline, Pharmaceutical Development, Step 4 version (August 2009)
- [3] ICH, Q9 Harmonized Tripartite Guideline, Quality Risk Management (June 2006)
- [4] ICH, Q10, Harmonized Tripartite Guideline, Pharmaceutical Quality System (April 2009)