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Quality by Design in Action 1: Controlling Critical Quality Attributes of an Active Pharmaceutical Ingredient

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ABSTRACT: The importance of Quality by Design (QbD) is being realized gradually, as it is gaining popularity among the generic companies. However, the major hurdle faced by these industries is the lack of common guidelines or format for performing a risk-based assessment of the manufacturing process. This article tries to highlight a possible sequential pathway for performing QbD with the help of a case study. The main focus of this article is on the usage of failure mode and effect analysis (FMEA) as a tool for risk assessment, which helps in the identification of critical process parameters (CPPs) and critical material attributes (CMAs) and later on becomes the unbiased input for the design of experiments (DoE). In this case study, the DoE was helpful in establishing a risk-based relationship between critical quality attributes (CQAs) and CMAs/CPPs. Finally, a control strategy was established for all of the CPPs and CMAs, which in turn gave rise to a robust process during commercialization. It is noteworthy that FMEA was used twice during the QbD: initially to identify the CPPs and CMAs and subsequently after DoE completion to ascertain whether the risk due to CPPs and CMAs had decreased.

INTRODUCTION

Nowadays, Quality by Design (QbD) has become an essential part of any process development pertaining to drug substances,[1,2] drug products, and analytical method development.[3] QbD is based on Juran's concept of "planning quality into the product"[4] at the design stage itself, rather than "complying product to the quality or Quality by QC". Designing quality into the product can be achieved only by having a proper understanding of the relationship between the critical quality attributes (CQAs) and the critical process parameters (CPPs) and critical material attributes (CMAs), as shown in Figures 1 and 2. It is based on the concept of quality risk management,[5] where one needs to assess the risk of each of the process parameters (PPs) and material attributes (MAs) on the CQAs. Various QbD guidelines have been published by different regulatory agencies[6] to ensure risk mitigation for patients and also to fulfill their own key responsibility areas (KRAs) of acceptability, affordability, availability, and accessibility (known as the 4A's).[7] On the other hand, manufacturers are realizing that in addition to taking care of patient safety they also need to ensure that they adhere to the 4A's to retain their market share and to make some profits.

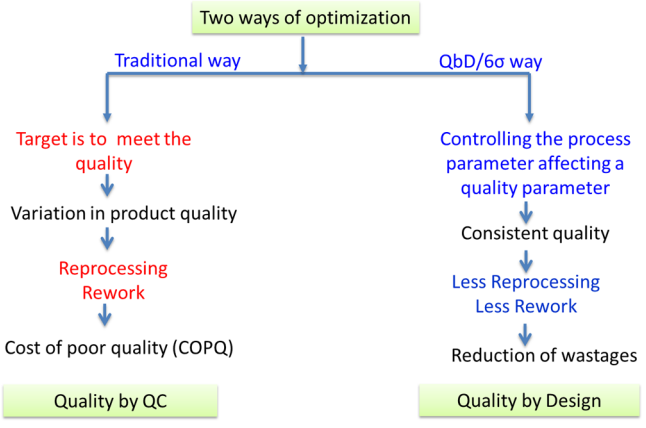

Figure 1. Two approaches for optimization.

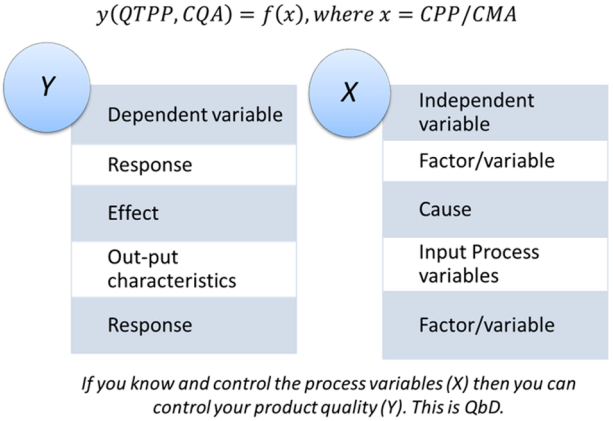

Figure 2. Relationship between CQAs and CPPs/CMAs.

One of the major hurdles to any robust process is inadequate understanding of the process, which results in inconsistent quality of the active pharmaceutical ingredient (API). Process robustness is achievable only through the implementation of proven risk-based statistical tools such as Six Sigma and QbD during the developmental and manufacturing phases of an API. Regulators have been flexible in accepting any quality risk tool

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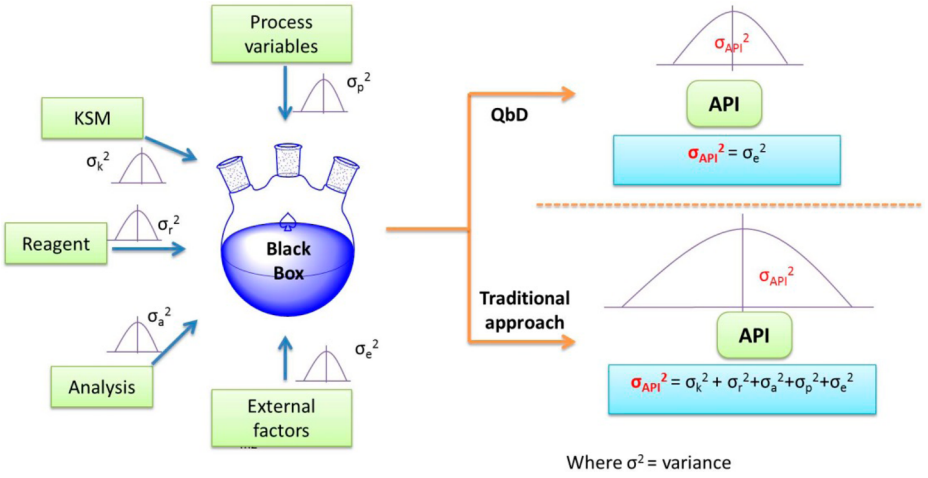

Figure 3. Various sources of variation in a process.

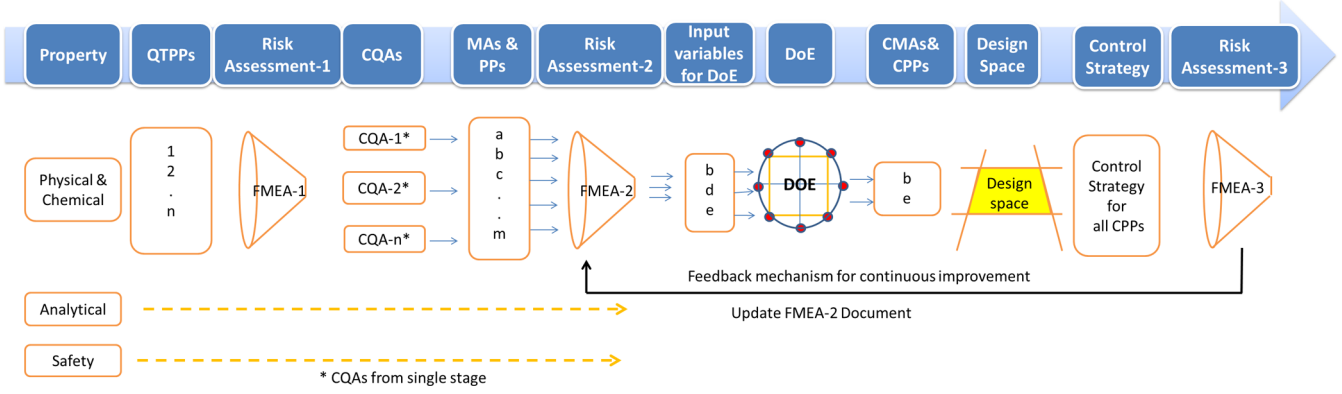

Figure 4. Sequence of steps for conducting QbD.

that can mitigate the risk to a CQA caused by various process variables (CPPs/CMAs).[8]

There are many sources of variation in a process. The total variance in any CQA of an API is the sum of the individual variances contributed by all of the sources, as shown in Figure 3 and by eq 1:

$$\sigma^2_{\text{API}} = \sigma^2_{\text{KSM}} + \sigma^2_{\text{reagent}} + \sigma^2_{\text{CPP}} + \sigma^2_{\text{analysis}} + \sigma^2_{\text{external factors}} \quad (1)$$

where σ^2_x denotes the variance of x. Additionally, the situation becomes much more complex if the process is a multistep synthesis, as represented by eq 2:

$$\sigma^2_{\text{API}} = \sigma^2_{\text{step 1}} + \sigma^2_{\text{step 2}} + \cdots + \sigma^2_{\text{step } n} \quad (2)$$

There are certain sources of variation that can be controlled during process optimization, such as variations of the key starting material (KSM) and reagents (collectively called the CMAs) and the CPPs. These controllable variables are also known as *assignable causes* of variation. However, there are certain sources of variation that cannot be controlled (variations due to external factors such as room temperature, production shift, age of the reactors, operators, etc.), and these are collectively called *common causes* of variation.[9] QbD helps in eliminating the assignable causes of variation by defining the range within which the CPPs/CMAs can be varied. Nevertheless, the common causes of variation cannot be eliminated, and we have to live with some degree of *inherent variability*. However, QbD helps in minimizing the effect of these common causes of variation by *randomization* and *blocking*[10] of experiments during the DoE study. Thus, QbD takes care of both types of variations and minimizes their effects on the CQAs of an API. Hence, QbD is a risk mitigation tool that ensures that the quality of an API produced in each batch remains the same, which in turn ensures that patient safety and the 4A's requirement of the regulators will be met.

PROCESS DEVELOPMENT OF AN API USING QBD

The basic outline of the application of QbD in the process development of a drug substance is shown in Figure 4, and a detailed process is represented by the flow diagram in Figure 5. The Regulators allow the manufacturers to use any established risk analysis tools or any risk assessment tool developed in-house, as long as it serves the purpose. A possible sequence of events for QbD is described as follows (Figure 4): (1) categorization of drug properties; (2) identification of CQAs from quality target product profiles (QTPPs) (risk assessment 1); (3) identification of CPPs and CMAs (risk assessment 2); (4) optimization of the effect of input variables; (5) control strategy; (6) re-evaluation of the risk to the CQAa (risk assessment 3); and (7) continuous improvement. These steps are discussed in more detail below.

Step 1. Categorization of Drug Properties. All of the properties of the drug substance are placed into physicochemical, analytical, and safety categories, as all of these are treated separately.

Step 2. Risk Assessment 1: Identification of CQAs from QTPPs. The risk assessment tool known as failure mode and

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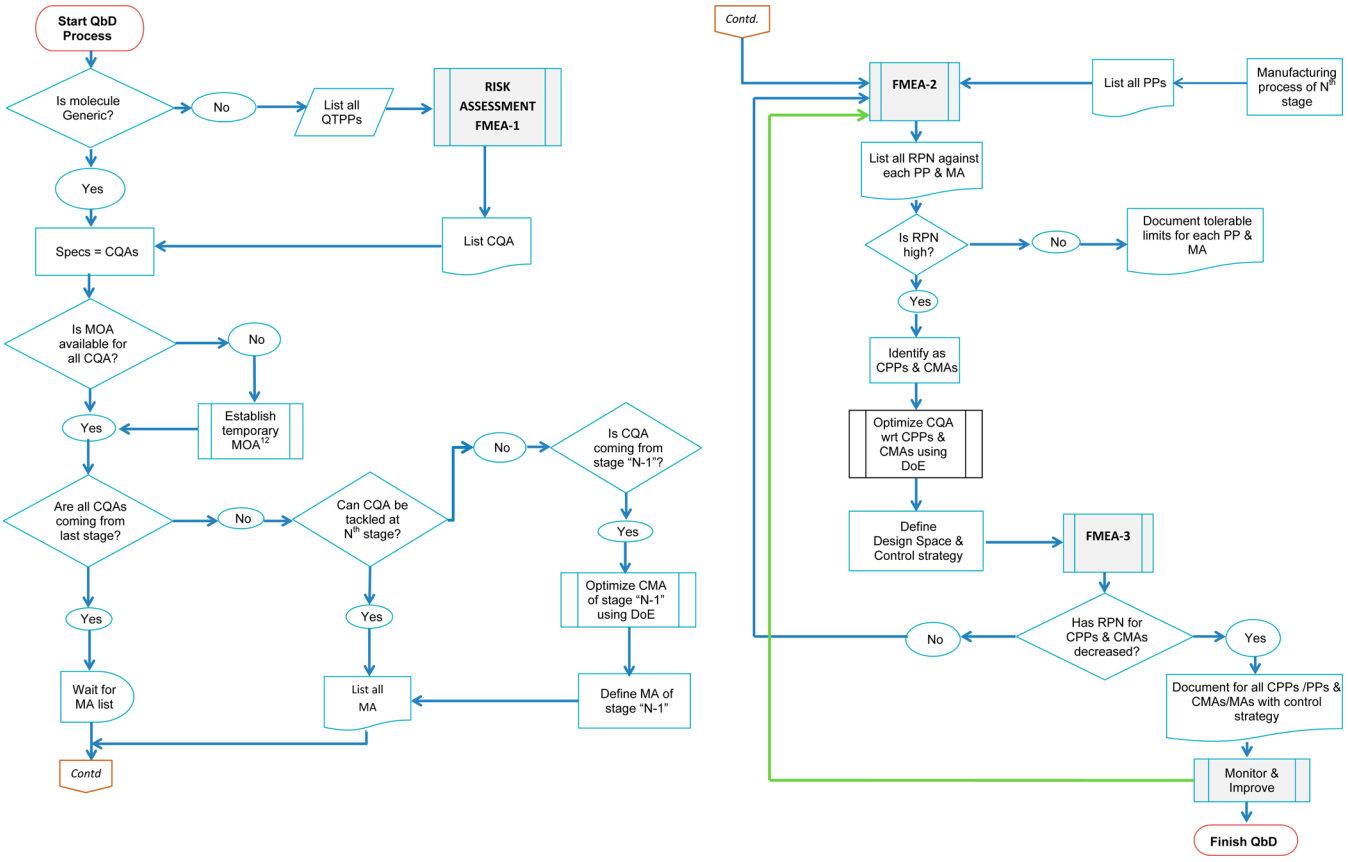

Figure 5. Process flow for QbD.

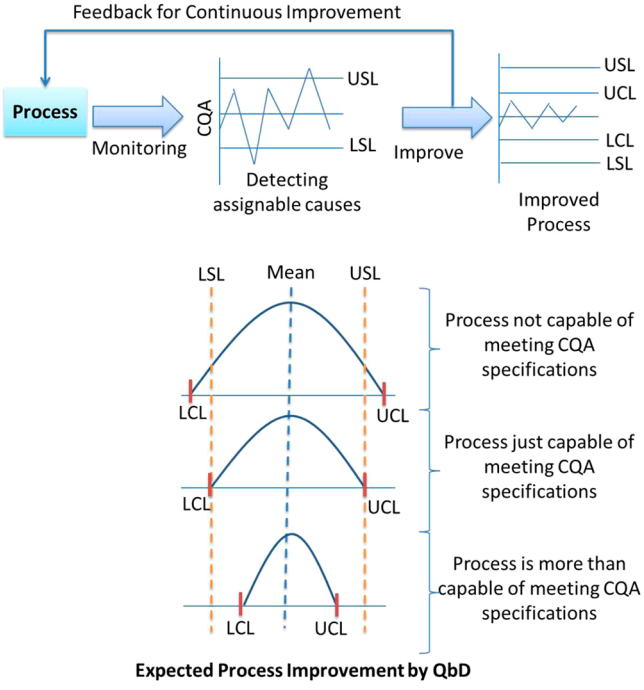

Figure 6. Ultimate goal of QbD. The CQA or the customer's requirement is represented by specification limits, whereas the process capability is represented by control limits.

effect analysis (FMEA) is applied to screen the QTPPs in each of the above categories. This stage is important as it shortlists the QTPPs that are critical for the patients and must be in the API. These shortlisted QTPPs become the CQAs. This process is denoted as FMEA-1 in Figures 4 and 5. This stage requires due diligence for a new chemical entity (NCE), but for a generic molecule, it is the same as the specifications set by the customer or as given in the pharmacopeia.

Step 3. Risk Assessment 2: Identification of CPPs and CMAs. Once the CQAs are identified, it becomes imperative to identify the PPs and MAs that can affect those CQAs. This is done by listing all of the PPs and MAs (or *input variables* for DoE, as shown in Figure 4) without any bias. Working backwards, i.e., listing the CQAs of the final API first, is recommended. This helps in identifying the origin of a particular CQA (e.g., an impurity), which in turn helps in controlling it at its point of origin (earlier stages).

Once all of the PPs and MAs are listed, a second risk assessment (denoted as FMEA-2 in Figures 4 and 5) is performed to identify the important input variables from the PPs and MAs, either by brainstorming with the subject experts or by coming to a decision based on past experimental data. If this process is performed without bias, it reveals the important input variables that will become the input variables for the DoE.

A tool such as FMEA, quality function deployment (QFD), or any tool developed in-house can be used for risk analysis, as the regulators are flexible about the choice of risk assessment tool. FMEA is the simplest of all the risk assessment tools. The input variables can be identified by using the following three criteria from FMEA analysis:

a. unit operation with highest risk priority number (RPN)
b. if there is no control strategy for any unit operation
c. if the effect of any unit operation on the CQA is not known

The FMEA template is shown in Table 2 with an example.

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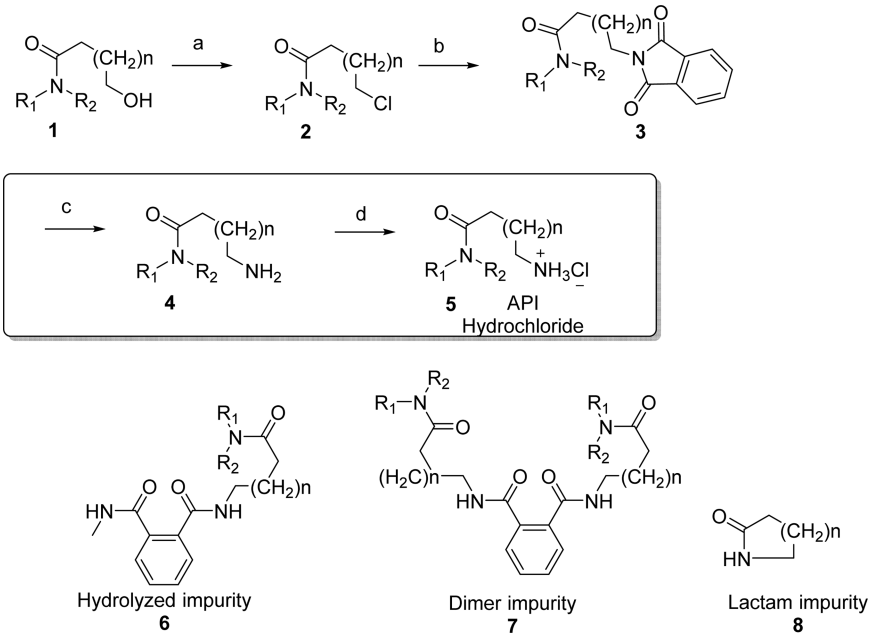
Scheme 1. Synthetic route to API hydrochloride 5[a]



[a]Reagents: (a) $SOCl_2$, toluene; (b) potassium phthalimide, DMF/H_2O; (c) 40% aqueous methylamine solution; (d) EtOAc/HCl gas.

Step 4. Optimization of the Effects of the Input Variables on the CQAs. On the basis of the screened input variables, a DoE is planned to gain an understanding of the relationship between the input variables and CQAs. The output of the DoE is the set of input variables that affect the CQA significantly and are termed as CPPs and CMAs. Additionally, the DoE also provides a design space within which CPPs and CMAs can be varied. It is possible that only a few of the input variables that were initially selected might actually affect the CQAs. *Many times it happens that the same CPPs affect two or more CQAs, in which case all of the CQAs should be studied together by DoE or by using multivariate analysis (MVA) tools.* The design space obtained from DoE provides an amicable region within which any CPP or CMA can be varied without affecting the CQAs. This becomes the basis for the control strategy.

Step 5. Control Strategy.[11] Once the operating ranges of the CPPs are identified (from the design space), it is important to ensure that all of the CPPs remain within their ranges by providing proper control during the manufacturing phase (e.g., by the use of process analytical tools (PATs) such as ReactIR, pH control, etc.). It is crucial that the manufacturers include their suppliers during the QbD phase to ensure that the manufacturers have control of the CMAs for all of the KSMs, as shown in eq 1.

Another important substep of the control strategy is to monitor the CPPs along with the CQAs using individual-moving range (I-MR) control charts[9] during commercialization in order to capture any deviations in the process. All of the deviations need to be investigated, and the reasons for positive deviations must be incorporated in the process, whereas the reasons for negative deviations must be eliminated. This enables the manufacturer to plan for continuous improvement during the entire life cycle of the product (Figure 6).

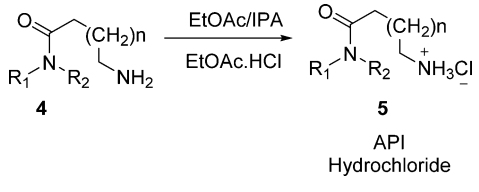
As a general practice, only the CQAs are monitored by the control charts. However, one needs to understand that as the CQAs are the outcome of the CPPs (Figure 2), it is imperative to monitor both.

Step 6. Risk Assessment 3: Risk Re-evaluation. After identification of the CPPs/CMAs and the design space and development of the control strategy, it is time for the third risk assessment (denoted as FMEA-3 in Figures 4 and 5), in which the risk to the CQAs is re-evaluated to determine whether it has been reduced after optimization with respect to the risk that existed during FMEA-2.

There are many tools for risk assessment, but the most widely applied tool is FMEA. If FMEA is applied in risk assessments 2 and 3, it becomes important to see whether the RPN of each CQA has decreased after risk assessment 3. If it has not, then one is working with the wrong CPPs/CMAs.

Step 7. Continuous Improvement: Monitoring and Improving the Process. Even after all of the above steps have been performed, it is seldom observed that commercialization happens without any hiccups, as the process takes its own time to mature. The main reason that any CQA goes beyond the specification limits is the narrow gap between the customer's expectations and the capability of the process, as shown by Figure 6. For a given CQA, its specification is recommended on the basis of patient safety data, whereas the final CQA of any product is the outcome of the process, or in other words, the final specification of any CQA is determined by its process capability[9] (Figure 6). If the process capability of any process is not under control, it would lead to out-of-specification (OOS) or out-of-trend (OOT) batches, which would trigger investigation. Some of the above deviations are good for the process (e.g., a yield increase) and some are bad (e.g., an increase in the impurity

Scheme 2. Synthetic scheme for the conversion of 4 to 5



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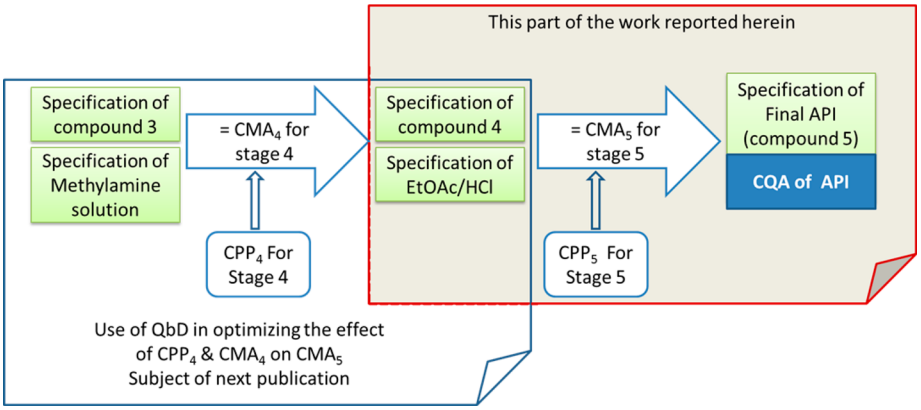

Figure 7. Various terms used in the current work and the companion article.

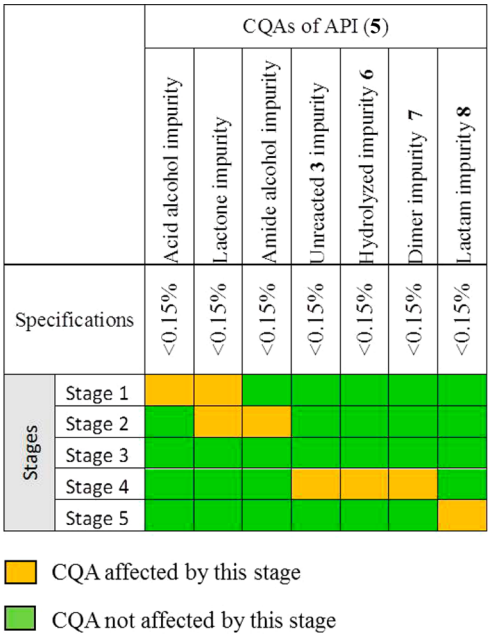

Figure 8. CQAs with their points of origin and specifications in the final API.

levels). The root causes for all OOS/OOT batches are then established, and a corrective and preventive action (CAPA) plan is proposed and implemented for process improvement. Causes of good deviations are then incorporated and those of bad deviations are eliminated from the process. This is followed by updating the FMEA-2 document. This is an iterative process during the entire life cycle of the product. Hence, QbD runs during the entire life cycle of the product and is a continuous journey of gaining more and more knowledge about the process. The main purpose of QbD is to reduce the variation in the process so that the CQAs remain well within the specification limits, as shown by Figure 6. The CQA or the customer's requirement is represented by upper and lower specification limits (USL and LSL, respectively), whereas the process capability is represented by upper and lower control limits (UCL and LCL, respectively).

CASE STUDY

Description of the Case Study. QbD was applied to a generic API whose synthetic route is shown in Scheme 1. QbD was applied on all stages, but only the last stage (**4** → **5**) is analyzed in this article to enable the readers to grasp the concept easily. The synthesis of the API hydrochloride (**5**) starts with the chlorination of amide alcohol **1** to give chloro compound **2**, which upon substitution with potassium phthalimide results in protected amine **3**. Deprotection of the phthalimide group with methylamine aqueous solution provides the API as a free base (**4**), which on treatment with EtOAc/HCl gives the final API as a hydrochloride salt (**5**). There were four major impurities (unreacted **3**, hydrolyzed impurity **6**, dimer impurity **7**, and lactam impurity **8**) that formed during the conversion of free base **4** to its hydrochloride salt **5**, as shown in Scheme 1.

The steps involved in the QbD as described above were applied to the salt formation stage of the API (**5**), as elaborated in the next section. Before the QbD is discussed, however, it is important to understand the terminologies used. The whole work was divided into two portions that are described in two

Table 1. Identifying important MA_5 for the manufacture of API 5

input for stage 5	specifications: maximum tolerable limits	specifications: process control limits[a]	are these MA_5 important?[b]	remarks
1. EtOAc/HCl	NLT 8%/8−12%	8−12%	yes	HCl concentration to be in the range 8−12%
2. compound **4**				
2.1. assay	as per analysis	as per analysis	no	taken to the next stage on the basis of the assay of **4**
2.2. residual toluene	as per analysis	as per analysis	no	
2.3. unreacted **3**	NMT 1%	0.5%	yes	even though **3**, **6**, and **7** would not participate in the next stage, it was desired to keep them at minimum level
2.4. hydrolyzed impurity **6**	NMT 3%	1.5%	yes	
2.5. dimer impurity **7**	NMT 3%	0.5%	yes	

[a]These control limits were proposed after optimization of compound **4** using DoE. [b]These important MA_5 would be taken as input variables for the DoE studies.

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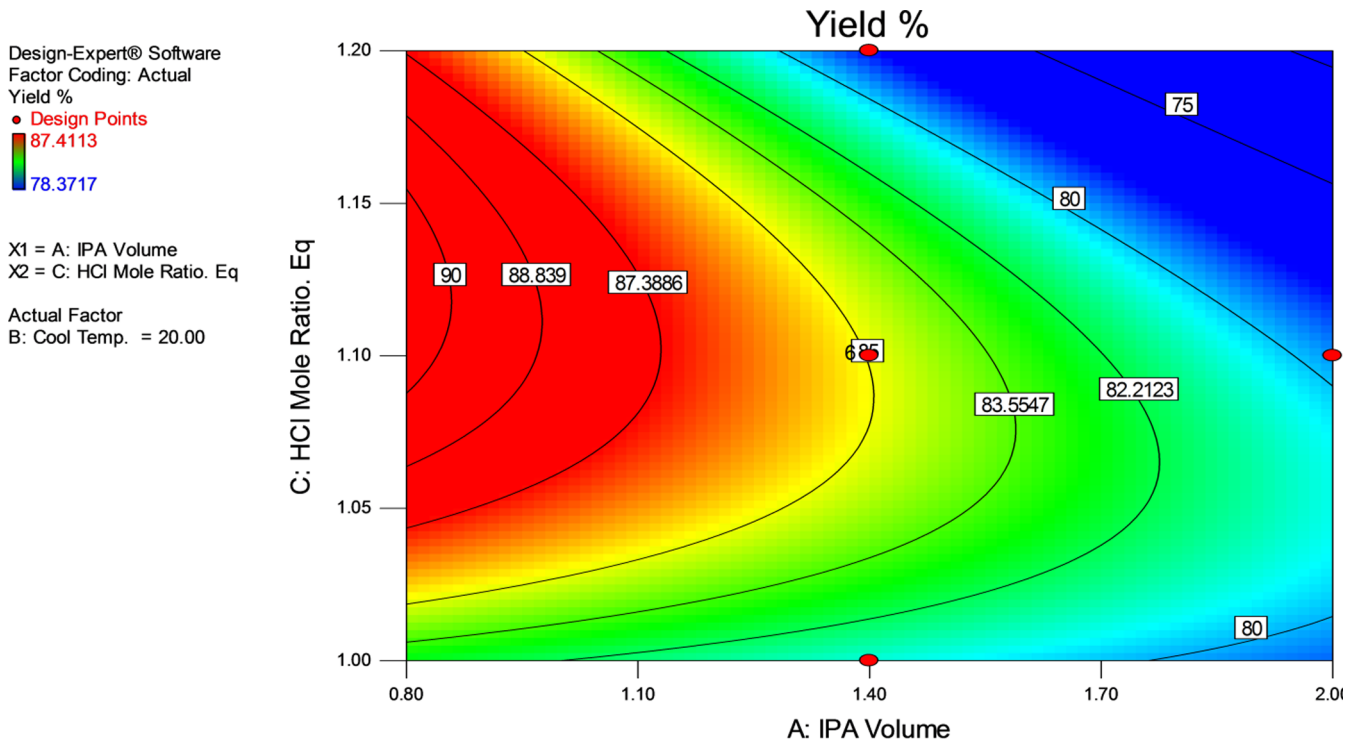

Figure 9. Contour plot of the percent yield variation with respect to the volume of IPA and amount of HCl at 20 °C.

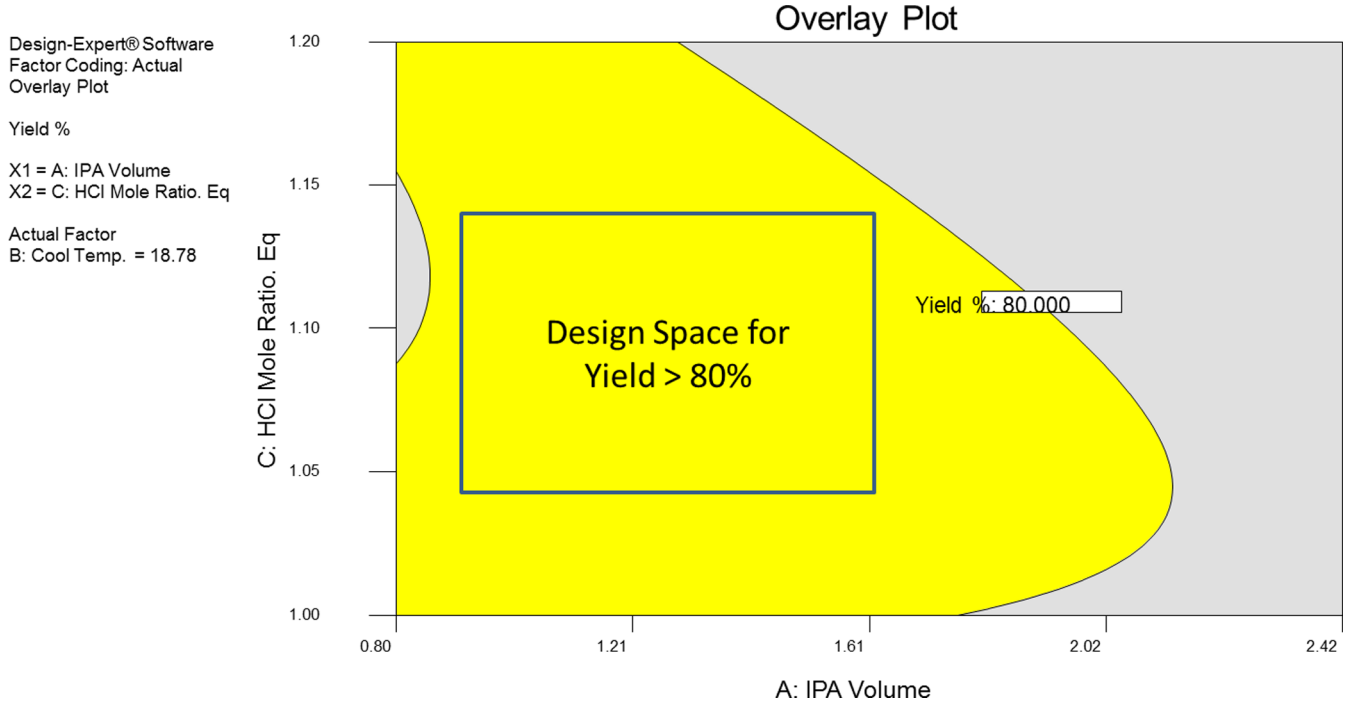

Figure 10. Design space.

separate articles, as summarized in Figure 7. Herein the term CQA is only applied to the final API hydrochloride **5**, or stage 5. These CQAs are affected by the critical material attributes and critical process parameters related to Stage 5, which are denoted as CMA_5 and CPP_5, respectively. The CMA_5 concluded from the current work serve as the input for the work to be described in the companion article (DOI: 10.1021/op500297g), where the effects of CMA_4 and CPP_4 on CMA_5 are studied.

Application of QbD to the Manufacture of API Hydrochloride 5. *Step 1: Listing of All of the Quality Attributes Associated with the API.* Since it is a generic molecule, all of the quality attributes are the same as the specification set by the customer with respect to the impurities, as shown in Figure 8. These quality attributes become the QTPPs.

Step 2: Risk Assessment: Identification of the CQAs from the QTPPs. As stated earlier, since the API was a generic molecule, all of the QTPPs eventually became CQAs because all of them were

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Table 2. FMEA analysis of the process used to manufacture final API hydrochloride 5

			CQAs API (5)													
S. No	**activity**	**potential failure mode**	yield	purity	hydrolyzed impurity **6**	unreacted **4** impurity	HCl content	dimer impurity **7**	lactam impurity **8**	**failure mode**	**present control**	**status of present control**	**occurrence**	**severity**	**detection (not)[13]**	**RPN**
1	charge 8.5-10 volumes of EtOAc into the reactor	more quantity of EtOAc	↕	↕	↕	↕	↕	↕	↕	measurement error	calibrated day tank	working	2	5	2	20
		low quantity of EtOAc	↓	↕	↕	↕	↕	↕	↕	measurement error	calibrated day tank	working	2	9	2	36
2	charge 1-1.5 Volumes of IPA into the reactor	more quantity of IPA	↓	↕	↕	↕	↕	↕	↕	measurement error	calibrated day tank	working but flow meter to be installed	5	9	7	315
		low quantity of IPA	↑	↓	↕	↕	↕	↕	↕	measurement error	calibrated day tank		5	9	7	315
3	charge crude stage **4** into the reactor	more quantity of 4	↓	↕	↕	↕	↕	↕	↕	analytical error	toluene correction to the assay	working	2	9	2	36
		less quantity of 4	↓	↕	↕	↕	↕	↕	↕	analytical error	toluene correction to the assay	working	2	9	2	36
4	stir the reaction mass till clear dissolution is observed	what if clear dissolution not observed	↓	↕	↕	↕	↕	↕	↕	manual error not critical	continue stirring till clear solution is obtained	working	2	9	2	36
5	add EtOAc.HCl into the reaction mass at 25±10 °C	charging at high temperature	↓	↓	↕	↕	↕	↕	↑	failure of chilled water line valve of RT water not closed	ensuring that RT water line is closed	working	5	9	5	225
		charging at low temperature	↓	↕	↕	↕	↕	↕	↕	RT water temperature fluctuation during winter	no effect	No control	5	7	7	245
		charging of more eq. of HCl	↓	↓	↕	↕	↕	↕	↑	manual error	releasing material on vendor's COA	working	5	7	9	315
		charging of less eq. of HCl	↓	↕	↕	↕	↕	↕	↕				5	5	9	225
		fast addition of EtOAc.HCl[14]	↓	↓	↕	↕	↕	↕	↑	manual error	addition at constant rate with flow meters in 45-60 minutes	working	5	5	5	125
		slow addtion of EtOAc.HCl	↕	↕	↕	↕	↕	↕	↕				5	5	5	125
6	maintain the reaction mass at 25±10 °C for 2 hour	more maintenance time	↕	↕	↕	↕	↕	↕	↕	no effect at 25±10 °C	not required	not required	5	2	3	30
		less maintenance time	↓	↓	↕	↕	↕	↕	↕	manual error	IPC for the absence of **4**	working	2	7	3	54
		maintenance at high temperature	↓	↓	↕	↕	↕	↕	↑	failure of chilled water plant	standby brine supply	working	2	7	3	54
		maintenance at low temperature	↕	↕	↕	↕	↕	↕	↕	No effect	Not required	Not required	2	5	3	30
7	filter the compound under nitrogen atmosphere.	filter under atmospheric conditions	↓	↕	↕	↕	↕	↕	↑	Failure of nitrogen plant	Standby nitrogen cylinders	working	3	9	3	81

↑ increase in **desired** CQA ↑ increase in **undesired** CQA ↕ no effect of CPPs on CQA

↓ decrease in **undesired** CQA ↓ decrease in **desired** CQA

critical to patient safety. Hence, in case of generic molecules, risk assessment to identify CQAs from QTPPs (FMEA-1 in Figures 4 and 5) is generally not required.

The important point to note here is that the stage considered for QbD involved only salt formation (Scheme 2) whereas all of the impurities listed as CQAs (Figure 8) came from the previous

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Table 3. Three important input PP_5 considered for DoE studies on the basis of FMEA[a]

		variable [RPN[b]] levels used for DoE	
symbol	input variable for DoE	low (−1)	high (+1)
A	volume of IPA	0.8 volumes [315]	2 volumes [315]
B	addition temperature	5 °C [245]	35 °C [225]
C	amount of HCl	1 equiv [225]	1.2 equiv [315]

[a]A 2^3 full factorial design with four center points was planned to study the effect of the three important input PP_5 on the CQAs with all of the other PPs kept at predefined levels. [b]Risk priority numbers (RPNs) were taken from Table 2.

Table 4. List of all PP_5 that were held constant for DoE studies

S. no.	PP	limit	justification
1	EtOAc volume	8−12 volumes	no effect on the responses at high volume
2	time the reaction mass is stirred until clear dissolution	not defined	not critical if stirred for a longer time, as it is just for dissolution
3	addition time of EtOAc/HCl	45−60 min	to control the exothermicity of reaction
4	cooling temperature before addition	10−15 °C	a low temperature was chosen to control the exothermicity
5	maintenance temperature	10−15 °C	same as the cooling temperature
6	maintenance time	2−2.5 h	no effect on the responses after 1 h
7	filtration	under nitrogen	dry atmosphere required

stages. On the basis of the laboratory data, all of those impurities at the final stage were washed away in mother liquors (MLs), as they could not form the HCl salt. Figure 8 provides a summary of all of the CQAs, their points of origin, and their limits in the final API.

Step 3: Identification of the Important Input Variables for the DoE Studies from All of the Material Attributes (MA_5) and Process Parameters (PP_5) Pertaining to Stage 5. Step 3.1: Identification of Important MA_5. As compound **4** was the starting material for the final API **5**, all of the attributes of compound **4** that could affect the CQAs were considered as MA_5 for the final API. This information was then used to identify important MA_5 along with their tolerable limits (based on initial lab experiments) for the final API **5**, as captured in Table 1. Furthermore, CMA_5 were made robust by DoE through optimization of the conversion of compound **3** to compound **4** (as described in the companion article).

Step 3.2: FMEA-2 for the Identification of Important PP_5. The synthesis of API hydrochloride **5** starts with compound **4** as an input and a KSM (Scheme 2); hence, it is important to consider the entire process for conducting an effective FMEA. A brief description of the manufacturing process for API hydrochloride **5** is given below:

> Ethyl acetate and isopropyl alcohol are added to a round-bottom flask. Crude compound **4** is added, and the mixture is stirred for 15 min to achieve complete dissolution. The solution is then cooled to 25 ± 10 °C, and ethyl acetate/HCl is added at the same temperature. The reaction mass is maintained for another 2 h at 25 ± 10 °C. The precipitated API hydrochloride salt is filtered under a nitrogen atmosphere, and the cake is washed with ethyl acetate. The material is then vacuum-dried, unloaded into a vacuum tray drier, and further dried at 47.5 ± 2.5°C until a constant weight is obtained.

In order to identify the important input PP_5 for the DoE studies from the list of all PP_5, it was prudent to consider separately each unit operation involved in the manufacturing process for its effect on each CQA using FMEA. Each unit operation became the input for the FMEA, as shown in Table 2. The output of the FMEA was the identification of important input PP_5 from the list of all the PP_5 on the basis of the RPN. All of these PP_5 with the highest RPNs became the input variables for the DoE studies, as shown in Table 3.

Step 4. Optimization of the Effects of the Important Input Variables (PP_5 and MA_5) on CQAs. Step 4.1. Optimization of the Important Input MA_5. Since compound **4** and EtOAc/HCl were the KSMs for the reaction, the quality of both KSMs was critical for the reaction. Therefore, acceptance criteria were defined for both KSMs. The acceptance criteria for HCl and compound **4** were decided on the basis of laboratory "what-if" studies as described in Table 2, where maximum tolerable limits were established for every individual impurity. Hence, the important qualities of both as described in Table 2 were taken as CMA_5.

Step 4.2. Optimization of the Effects of the Important Input PP_5 on CQAs. The FMEA analysis of the process (FMEA-2; Table 2) revealed three important input PP_5 on the basis of highest RPN (Table 3); hence, these were taken as input variables for the DoE studies for further optimization. The other PP_5 were kept at predefined levels as captured in Table 4. The output of the DoE is CPP_5. It is important to note that each of the three PP_5 may or may not be included in CPP_5.

The 2^3 full factorial design and the results of same are captured in Table 5. It is clear from the results that except for the yield, all

Table 5. The 2^3 full factorial design for optimization of the API reaction conditions

S. no.	IPA volume	cooling temp. (°C)	amount of HCl (equiv)	yield (%)	purity (%)	unreacted **4** (%)	impurity **6** (%)	impurity **7** (%)	impurity **8** (%)
1	2	5	1	78.37	99.96	0.01	0.02	0	0
2	2	5	1.2	80.54	99.89	0.01	0.01	0.03	0
3	2	35	1.2	74.01	99.98	0	0	0.04	0
4	0.8	5	1	82.72	99.85	0.01	0.05	0	0
5	0.8	35	1	82.72	99.94	0.01	0.01	0.03	0
6	2	35	1	80.54	99.92	0.01	0.01	0.01	0
7	0.8	5	1.2	87.07	99.96	0.01	0.03	0	0
8	0.8	35	1.2	87.07	99.99	0.01	0	0.02	0
9	1.4	20	1.1	87.07	99.97	0.01	0.02	0.01	0
10	1.4	20	1.1	84.90	99.97	0.01	0.02	0.02	0
11	1.4	20	1.1	87.07	99.93	0.01	0.01	0.03	0
12	1.4	20	1.1	84.90	99.95	0.01	0.01	0.02	0

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Table 6. ANOVA of the 2^3 full factorial design for yield optimization

source	sum of squares	degrees of freedom	mean square	*F* value	*p* value prob > *F*	
model	80.27	3	26.76	18.09	0.0011	significant
A (IPA volume)	61.28	1	61.28	41.42	0.0004	
C (equiv of HCl)	8.69	1	8.69	5.87	0.0459	
AC	10.30	1	10.30	6.96	0.0335	
curvature	39.65	1	39.65	26.80	0.0013	significant
residual	10.36	7	1.48			
lack of fit	5.62	4	1.40	0.89	0.5614	not significant
pure error	4.74	3	1.58			
cor total	130.28	11				

Table 7. Additional experiments to augment the 2^3 full factorial design to RSM

point type	volumes of IPA	addition temp. (°C)	equiv of HCl	yield (%)
axial	1.4	20	1.2	78.67
axial	2	20	1.1	78.67
axial	0.8	20	1.1	83.04
centre	1.4	20	1.1	84.90
axial	1.4	35	1.1	80.85
axial	1.4	5	1.1	83.04
axial	1.4	20	1	80.85
centre	1.4	20	1.1	85.22

of the CQAs were almost constant (no apparent variation was observed) and well within the specification limits as described in Figure 8. *This observation was quite obvious, as these impurities were not formed during the reaction but came from the KSM (compound* ***4****).*[14] Another process-related lactam impurity, **8**, was not observed with the current process. Because of the above observations, only the yield variation (which is also an important CQA[a]) was analyzed as explained below.

The analysis of variance (ANOVA) showed that the yield was a function of the IPA volume and the amount of HCl (Table 6). It was also evident that the interaction effect of both of the above input PP_5 was significant. Another important observation was that the curvature was significant. Variation of the addition temperature between 5 and 30 °C did not have any impact on the yield. *This indicates that the IPA volume and the amount of HCl were* CPP_5 *whereas the temperature was not.*

Since the curvature was significant (Table 6), the model was augmented to response surface methodology (RSM) with six axial points and two more centre points (Table 7). The ANOVA analysis of the RSM design (Table 8) showed that only the IPA volume plays a significant role in dictating the yield, whereas the amount of HCl between 0.8−1.4 equiv does not have any significant effect as such, although its interaction with IPA volume is significant. This is also evident by the regression results

Table 9. Validation of the model

				yield (%)	
run	volumes of IPA	addition temp. (°C)	equiv of HCl	actual	predicted (95% CI)
1	1.5	10	1.1	83.9	82−85
2	1.5	15	1.1	84.3	82−85
3	1.5	20	1.1	84.7	82−85
4	1.5	15	1.1	83.9	82−85

(eq 3), and the same has been depicted as a contour plot in Figure 9.

$$\%\ \text{yield} = -623.97 + 58A + 1240.5C - 61AC - 531C^2 \quad (3)$$

Finally, a design space was generated from the contour plot with predefined constraints (0.8−1.4 volumes of IPA and 1−1.14 equiv of HCl), as shown in Figure 10, and the model was validated as captured in Table 9. The results of the validation were as expected, and the results were within the 95% confidence interval (CI). Hence, the volume of IPA and the amount of HCl became CPP_5, which needed to be monitored during commercialization.

Step 5. Control Strategy. Finally, a control strategy was planned for all of the CMA_5 and CPP_5. The control strategy for CMA_5 (compound **4**) is already described in Table 1,[b] whereas the control strategies for the other PP_5, which were not important, are captured in Table 4. The control strategies for the current two important CPP_5 are given in Table 10 along with the control strategy for the addition temperature, which was found to be unimportant in a given range.

Step 6. FMEA-3: Assessing the Outcome of the Risk Mitigation. The penultimate step of the QbD process is to assess the effect of DoE on the RPN and compare it with the RPN obtained from FMEA-2. For the three CPP_5, the RPN decreased significantly (compare the values shown in Table 10 with those in Table 2).

Table 8. ANOVA of the percent yield after RSM design

source	sum of squares	degrees of freedom	mean square	*F* value	p-value prob > *F*	
model	131.09	4	32.77	10.05	0.0008	significant
A	92.74	1	92.74	28.44	0.0002	
C	7.61	1	7.61	2.33	0.1524	
AC	35.77	1	35.77	10.97	0.0062	
C^2	68.05	1	68.05	20.87	0.0006	
residual	39.14	12	3.26			
lack of fit	31.87	7	4.55	3.13	0.1136	not significant
pure error	7.27	5	1.45			

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Table 10. Final CPPs and their control strategies

S. no.	factor	acceptable range	control strategy	risk assessment 3[a] O	S	D	RPN
1	IPA volume	0.8−1.6 volumes	only the calculated quantity of IPA is to be dispensed using a flow meter with additional calibration on the day storage tank	2	9	2	36
2	addition temperature[b]	10−30 °C	found to be noncritical from DoE, but the target was set at 20 °C	2	2	2	8
3	amount of HCl	1.04−1.14 equiv	assay of EtOAc/HCl solution to be done just before the batch is started to account for any HCl loss upon storage	2	5	2	20

[a]O = occurrence, S = severity, D = detectability (not). [b]After DoE, temperature was found not to be a CPP.

Step 7. Continuous Improvement: Monitoring both CQAs and CPP$_5$. Since this product is yet to be scaled-up, there are no data to present here. However, there is proper planning at hand in which it has been decided to monitor the CMA$_5$ for the API stage for each batch and also to monitor both the CPP$_5$ and CQA of the final API using an I-MR control chart. This I-MR control chart is most suitable for the API,[8] as any abnormality observed would be recorded and rectified.

CONCLUSION

This article emphasizes the application of QbD in controlling the CQAs of an API. It is evident from the article that a CQA is dictated by the CPP and CMA, and hence, its identification is critical for any robust process development. This article provides a possible sequence of steps for QbD implementation and illustrates how FMEA could be used for the unbiased selection of important PPs and MAs purely on the basis of the risk assessment of each PP and MA on the CQA. These important PPs can then be used as inputs for the DoE studies for further optimization and help in mitigating the risk associated with them. Additionally, performing FMEA-3 to verify the risk mitigation due to CMAs and CPPs ensures minimum risk to CQAs. Another important consideration for the QbD is the quality of input material from the vendor, and this aspect is considered in the companion article.

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Notes

The present article represents the authors' personal views on the subject.

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ABBREVIATIONS

4A's	acceptability, affordability, availability, and accessibility
95% CI	confidence interval with an in-built error (α) of 5%
ANOVA	analysis of variance
API	active pharmaceutical ingredient
CAPA	corrective and preventive action
CMA	critical material attribute
CMA$_5$	critical material attributes for stage 5
COA	certificate of analysis
CPP	critical process parameter
CPP$_5$	critical process parameters for stage 5
CQA	critical quality attribute
DoE	design of experiments
equiv	equivalents
FMEA	failure mode and effect analysis
Hrs	hours
I-MR	individual-moving range
KRA	key responsibility area
KSM	key starting material
LCL	lower control limit
LSL	lower specification limit
MA$_5$	material attributes for stage 5
ML	mother liquor
MVA	multivariate analysis
NCE	new chemical entity
NLT	not less than
NMT	not more than
OOS	out of specification
OOT	out of trend
PAT	process analytical tool
PP	process parameter
PP$_5$	process parameters for stage 5
QbD	quality by design
QFD	quality function deployment
QTPP	quality target product profile
RPN	risk priority number
RSM	response surface methodology
UCL	upper control limit
USL	upper specification limit
σ^2	variance

ADDITIONAL NOTES

[a]Yield is a quality parameter as it affects the timely availability of the medicine in the market at a desired price, which is crucial for all stakeholders (i.e., patients, regulators, and the manufacturer). The most important stakeholders are the regulators for the following reasons: The sole responsibility of regulators towards their citizens is to ensure not only acceptable (i.e., good quality) and affordable medicines but also availability of the medicines (no shortages) in their country at all points of time. The responsibility goes even beyond that. The medicines must be easily accessible to patients at their local pharmacies. These four requirements—acceptability, affordability, availability, accessibility (the 4A's)—are a KRA of any regulatory body. If they miss any one of the above 4A's, they will be held accountable by their government for endangering the lives of patients. Also, in general, the yield and impurity profile are inversely related.

[b]Control of the CMA$_5$ of compound **4** is described in the companion article.

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(7) Regulators negotiate with the drug product/substance manufacturers on the behalf of their fellow citizens. Hence, they not only have to ensure the acceptability (or quality) and affordability but also the availability of the drug product/substance in their country at all times. Finally, it is desired that the drug product should be accessible to all patients at their local pharmacies.
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(13) As stated earlier, the yield is a quality parameter, and another point to be noted here is the quantity of IPA to be charged, which has a very narrow range (1−1.5 volumes). A high volume of IPA results in yield loss, where as a low volume of IPA results in unreacted free base (compound **4** or impurity **4**) because of the thick slurry nature of the reaction mass. Low volumes also created problems during the transfer of the reaction mass from the reactor to the filter. A variation was observed when IPA was dispensed from the day tank. Hence, a flow meter was proposed to measure the volume accurately. This explains the high severity and high detectability.
(14) Many times it happens that DoE fails to provide a solution to control an impurity during a reaction (i.e., there is no effect of PPs on the impurity). In such situations there could be two reasons for DoE failure. The first is that one is working with the wrong variables, and the second is that the impurities come from earlier stages.

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