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Quality by Design in Action 2: Controlling Critical Material Attributes during the Synthesis of an Active Pharmaceutical Ingredient

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ABSTRACT: Quality by Design (QbD) is of paramount importance not only for patient safety but also for the timely and uninterrupted supply of products at affordable prices into the market. Both of these objectives can be achieved only through a robust process, and one of the major obstacles for developing a robust process is the quality of input materials and reagents used for the manufacture of active pharmaceutical ingredients (APIs). This article demonstrates the use of QbD methodology to optimize the quality of input materials and make the process more consistent, thereby reducing the variation in the quality of API produced. This article highlights the use of failure mode and effect analysis (FMEA) for the unbiased identification of critical process parameters and critical material attributes associated with the manufacturing of key starting materials, which are later used as input for the design of experiments (DoE) study that is used for the optimization.

INTRODUCTION

The main aim of any Quality by Design (QbD) process is to address the variability in the critical quality attributes (CQAs) of an active pharmaceutical ingredient (API) to ensure that the risk to patients' health is mitigated. QbD also helps in controlling the cost of medicines and ensuring uninterrupted supply of medicines into the market. There are many sources of variability, and one of the major sources is the inconsistent quality of key starting materials (KSMs) and reagents used in the production process. Failure to study and properly control the quality of the KSMs can have far-reaching consequences for not only the process robustness but also the business, as shown in Table 1.

Table 1. Effect of process inconsistency from the supplier and/or manufacturer on API quality

		manufacturer's API process	
		robust	not robust
supplier's KSM process	robust	**case-1:** robust process	**case 2:** variability due to process
	not robust	**case 3:** variability due to KSM	**case 4:** disaster

From case 1 in Table 1, it is evident that consistency in the CQAs of an API is possible only if both the manufacturer and the supplier have robust processes for the API and KSM, respectively. Any kind of reprocessing/rework of an unsuitable KSM at the manufacturer's end is not a viable option, as it would increase the cost of production, which has to be borne either by the manufacturer or the patients. Hence, it is important for a manufacturer to engage the suppliers in its QbD journey in order to eliminate at least one source of variation (i.e., from KSM) from the manufacturing process. Another analogous scenario is the multistep synthesis, where the quality of the penultimate stage (KSM manufactured in-house) becomes detrimental to the CQA of the final API. In QbD terms, the desired quality of the KSM is described as critical material attribute (CMA). This article demonstrates the use of QbD to optimize the reaction parameters in order to achieve the desired quality of the KSM (the penultimate stage), which in turn results in minimizing the variability at the API stage.

In this regard, we have reported in a companion article[1] a possible sequence of steps involved in the implementation of QbD and illustrated it with a case study, where the effects of critical process parameters for stage 5 (CPP_5) and critical material attributes for stage 5 (CMA_5)[a] on the CQAs of the final API (compound **5**, Scheme 1) were studied. The present article is an extension of the companion article in which QbD is used in a similar way to control the CMA_5 in order to have a robust process at the API stage, as shown in Figure 1 and Scheme 1.

The various terminologies used in the present article are explained for the clarity of readers. As shown in Figure 1, the CQAs, CPPs, and CMAs associated with the final API (stage 5) are denoted as CQA_5, CPP_5, and CMA_5, respectively. CMA_5 itself is affected by two things: the critical process parameters related to stage 4, denoted as CPP_4, and the critical material

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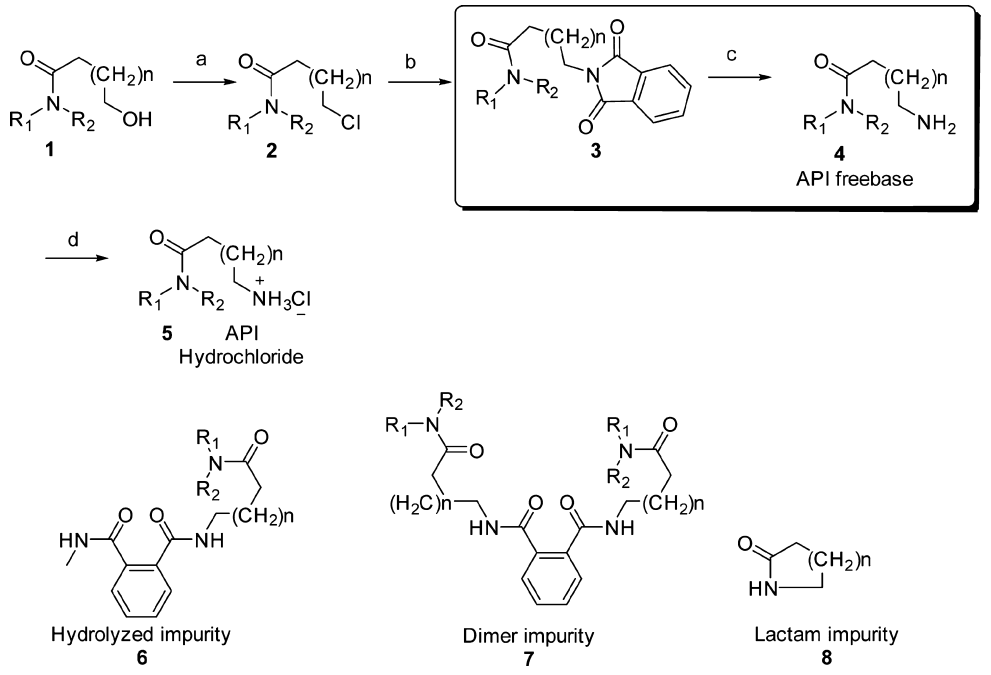
Scheme 1. Synthetic route to API hydrochloride and impurities observed at the final stage[a]



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

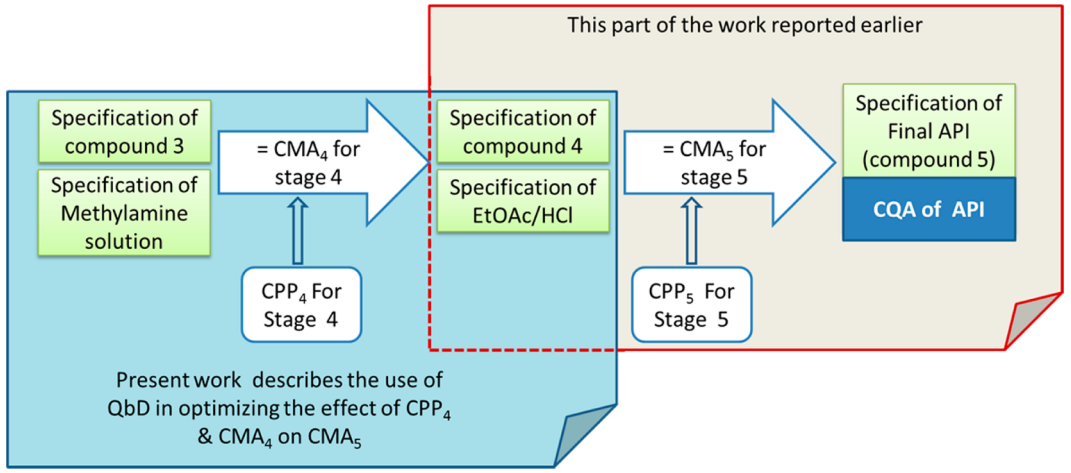


Figure 1. Various abbreviations used in the present article. Subscripts represent stage numbers.

Table 2. Screening of MA_5

		specifications	is it a CMA_5?	remarks
A	compound 4			
1	assay	as per analysis	no	compound 4 is added to the next stage based on the assay of compound 4 in the crude reaction mass.
2	residual Toluene		no	
B	impurities			
1	unreacted (3)	NMT 1%	yes	it was desired to keep these impurities at minimum level in order to have optimum yield.
2	hydrolyzed Imp. (7)	NMT 3%	yes	
3	dimer Imp. (8)	NMT 3%	yes	
4	yield	> 80%	yes	it was desired to have > 80% yield for optimum RMC.
C	EtOAc/HCl			
	HCl concentration	NLT 8% 8-12%	no	HCl concentration to be in range of 8-12%.

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Scheme 2. Synthetic scheme for stage 4

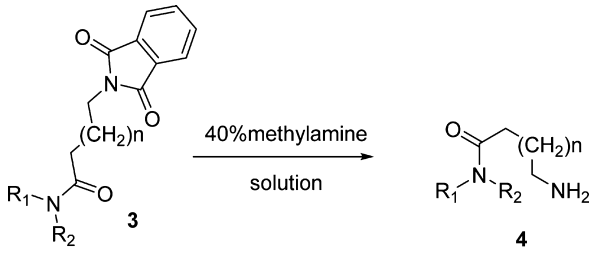

Table 3. CMA_4 for stage 4

S. no.	raw material	MAs: purity	MAs: assay range	is it a CMA_4?	remarks
1	compound **3**	NLT 98%	>98%	yes	starting material
2	methylamine solution	40% aqueous	35−40%	yes	reagent for reaction

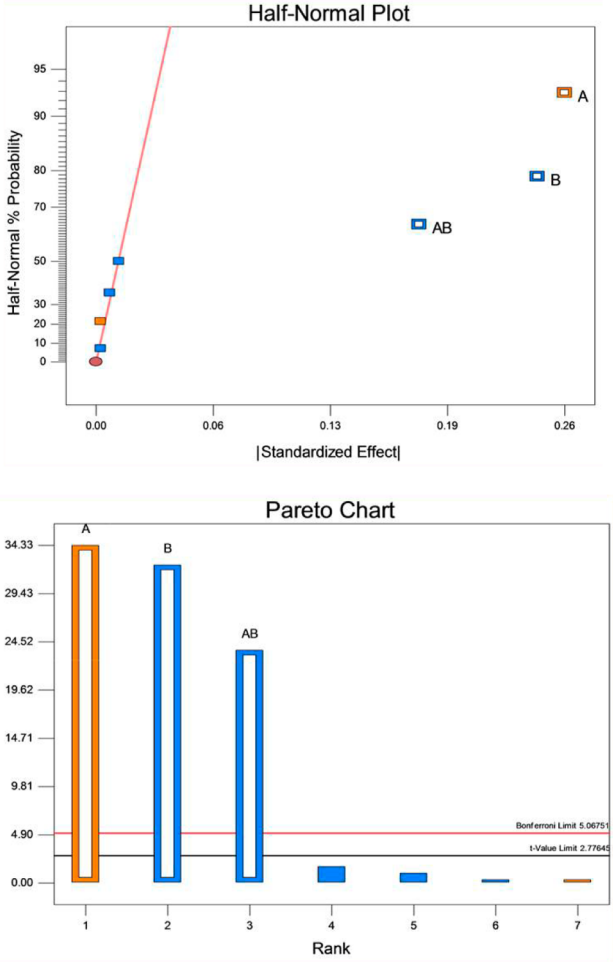

Figure 2. Half-normal plot and Pareto chart for unreacted **3**.

attributes of compound **3** and methylamine solution, which are together denoted as CMA_4.

In the companion article,[1] the focus of the QbD was to identify and optimize the important process parameters (CPP_5) along with important material attributes of the input materials

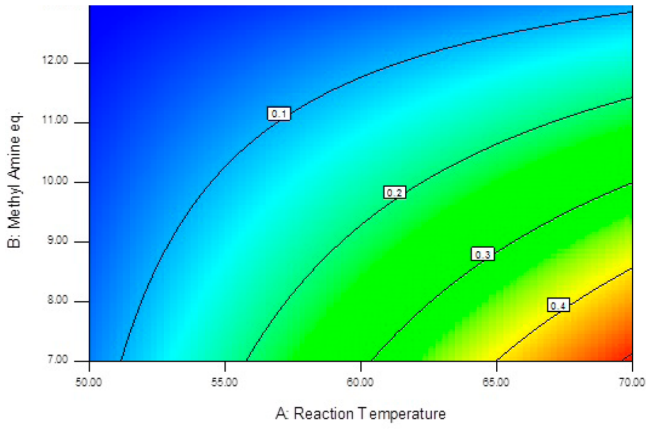

Figure 3. Effect of CPP_4 on unreacted **3** after 5 h.

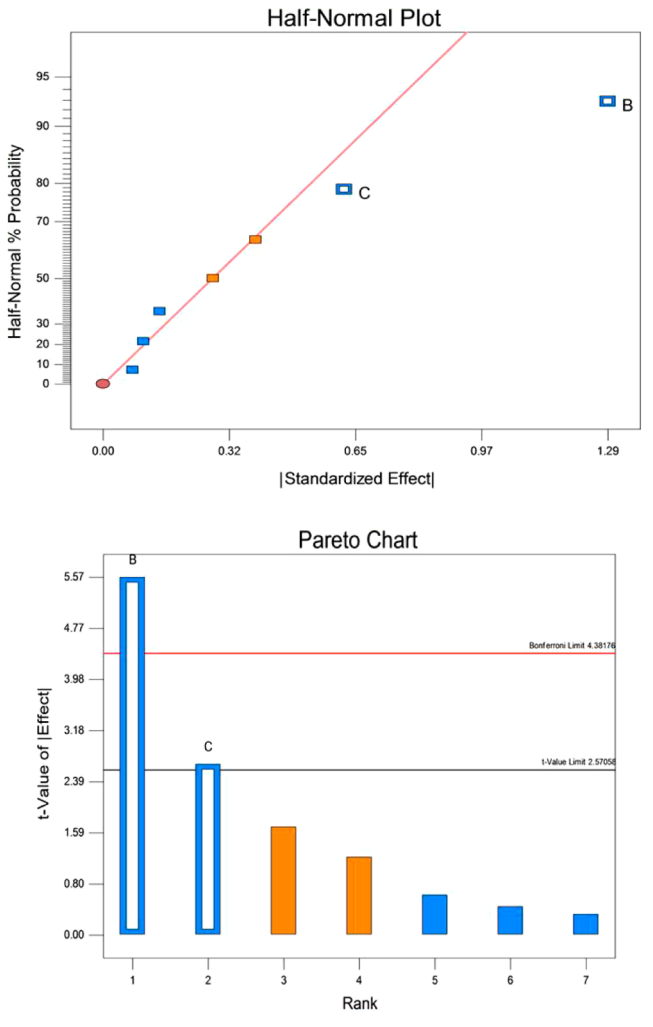

Figure 4. Half-normal plot and Pareto chart for impurity **6**.

(compound **4** and EtOAc/HCl solution), which together constitute CMA_5. The present article deals with the optimization of CMA_5 (i.e., the quality of compound **4**) by controlling the CPP_4 and CMA_4 involved in the deprotection of compound **3** to give compound **4**.

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Table 4. FMEA-2 for the identification of CPPs for stage 4

S. No	unit operations or process parameters (PPs)	potential failure mode	effect on CQAs of stage 5					potential effect(s) of failure on		failure mode	present control	occurrence	severity	(lack of) detection[2]	RPN	proposed control	remarks
			yield of 4	Purity	unreacted 3	hydrolyzed impurity 6	dimer impurity 7	stage (4)	API (5)								
1	charge toluene 11 volumes into the reactor at 30±5°C	more quantity of toluene	↕	↕	↕	↕	↕	no impact between 9-12 volumes	no effect	error in manual charging	charging by flow meter	5	2	2	20	not required	keep it constant between 9-12 volumes
		less quantity of toluene	↕	↕	↕	↕	↕					5	2	2	20	not required	
		charging of toluene at high temperature	↕	↕	↕	↕	↕	no Impact 25- 40 °C	no effect	failure of steam inlet valve	ensure steam valve is closed	5	7	2	70	replace steam line with hot water line	charging temperature to be held constant at 30±5°C
		charging of toluene at low temperature	↕	↕	↕	↕	↕			temperature fluctuation in RT water	no action	5	2	5	50	not required	
2	charge of compound **3** into the reactor at 30±5°C	more quantity of compound **3**	↓	↓	↑	↑	↑	incomplete reaction	unreacted compound **3** carried to API stage	weighing error error in methyl amine assay escape of methyl amine from container	calibration of weighing balance on daily basis in ware house qualifying methyl amine based on vendor COA	2	7	5	70	restricting the batch size in multiples of 50 kg suppliers to give compound **3** in 50 kg bags reanalysis of methylamine just before use	batch size to be held constant
		less quantity of compound **3**	↓	↕	↕	↕	↕	less yield	no impact	weighing error error in methyl amine assay		3	7	5	105	Suppliers to give compound 4 in 50 kg bags for	
		charging of compound **3** at high temperature	↕	↕	↕	↕	↕	no impact between 25- 40 °C	no impact	failure of steam inlet valve	ensure steam valve is closed	5	7	3	105	replace steam line with hot water line	charging temperature to be held constant at 30±5°C
		charging of compound **3** at low temperature	↕	↕	↕	↕	↕	no impact between 25- 40 °C	no impact	temperature fluctuation in RT water	no action	5	2	3	30	not required	
3	stir the reaction mass for 10-15 minutes at 30±5°C	stirring of reaction mass more than required time	↕	↕	↕	↕	↕	no Impact	no Impact	manual error	no action	3	1	3	9	not required	stirring time to be held constant between 15-20 minutes
4	heat the reaction mass to 55±5°C	heating of reaction mass more than required	↕	↕	↕	↕	↕	no impact as methyl amine is not added	no impact	manual error	ensuring RT water in condenser to stop toluene loss	5	3	3	45	replace steam line with hot water line	to be held constant between 55±5°C and heating time to be constant between 30-45 minutes
		heating of reaction mass less than required	↕	↕	↕	↕	↕					2	1	3	6		
		slow heating of reaction mass	↕	↕	↕	↕	↕					5	1	3	15		
		fast heating of reaction mass	↕	↕	↕	↕	↕					5	1	3	15		

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Table 4. continued

S. No	unit operations or process parameters (PPs)	potential failure mode	effect on CQAs of stage 5					potential effect(s) of failure on		failure mode	present control	occurrence	severity	(lack of) detection[2]	RPN	proposed control	remarks
			yield of 4	Purity	unreacted 3	hydrolyzed impurity 6	dimer impurity 7	stage (4)	API (5)								
5	addition of 40% methyl amine solution (CPP-2)	low concentration of methyl amine	↓	↓	↑	↑	↑	incomplete reaction	may give rise to SMUI	error in methyl amine assay escape of methyl amine from container	qualifying methyl amine based on vendor COA cap sealed after sampling	5	7	3	105	reanalysis of methylamine just before use	specification of assay to be constant between 35-40%
		high concentration of methyl amine	↕	↕	↕	↕	↕	maximum available concentration is 40%	no impact	none, as assay cannot be more than 40%	QC analysis	2	3	3	18	not required	
		more eq. of methyl amine	?	?	?	?	?	to be investigated		manual error	issue only required no. of carboys	?	?	?	?	impact to be studied using DoE	
		less eq. of methyl amine	↓	↓	↑	↑	↑	give rise to impurities with less yield				5	9	5	225		
6	add methyl amine solution at 55±5°C (CPP-1)	addition at high temperature	↓	↓	↑	↑	↑	to be investigated, as it can escape before it reacts		manual error	use of steam and temperature indicator	9	9	3	243	replace steam line with hot water line	impact need to be studied by DoE along with reaction temperature
		addition at low temperature	↓	↓	↑	↑	↑					5	8	3	120		
7	maintain the reaction mass at 55±5°C for 5 Hrs (CPP-3)	more maintenance time than the required time	↓	↓	↑	↑	↑	to be investigated, as it can escape before it reacts		manual error	log book for recording time	5	8	5	200	impact need to be studied by DoE	
		less maintenance time than the required time	↓	↓	↑	↑	↑	to be investigated. May give rise to SMUI		manual error		5	9	5	225		
		maintenance at high temperature	↓	↓	↑	↑	↑	to be investigated, as it can escape before it reacts	may give rise to SMUI	manual error	hourly record of temperature and adjusting the temperature accordingly	7	8	5	280	impact need to be studied by DoE	
		maintenance at low temperature	↓	↓	↑	↑	↑	incomplete reaction				5	8	5	200		
8	separate the organic layer	less settling time	↓	↕	↕	↕	↕	yield loss	less yield	manual error	settling time of 15 minutes	3	5	3	45	settling time to be 30 minutes	
9	concentrate the organic layer to remove toluene	residual toluene	↕	↕	↕	↕	↕	improper assay	OVI	failure of hot water and vacuum pump	no control	5	5	3	75	IPC for residual toluene and correction factor to be included while reporting yield	yield reporting after OVI corrections
10	calculate the yield of **5**	residual toluene giving wrong weight	↕	↕	↕	↕	↕	residual toluene not included while reporting yield	OVI			5	5	3	75		

↑	increase in **desired** CQA	Good
↓	decrease in **undesired** CQA	Good
↑	increase in **undesired** CQA	Bad
↓	decrease in **desired** CQA	Bad
↕	no effect of CPPs on CQA	

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Table 5. Summary of FMEA output (CPP_4) from Table 4

S. no.	unit operations or process parameters (PPs)	RPN	is it critical?	control strategy
1	charge 10 volumes of toluene into the reactor at 30 ± 5 °C	≤45	no	9−12 volumes
2	charge compound **3** into the reactor at 30 ± 5 °C	≤45	no	30 ± 5 °C
3	stir the reaction mass for 10−15 min at 30 ± 5 °C	9	no	15 min
4	heat the reaction mass to 55 ± 5 °C	≤45	no	55 ± 5 °C
5	**add methylamine solution at 55 ± 5 °C (CPP_4-1)**	**120−243**	**yes**	**to be tested**
6	**amount of 40% methylamine solution (CPP_4-2)**	**225**	**yes**	**to be tested**
7	**maintain the reaction mass at 55 ± 5 °C for 5 h (CPP_4-3)**	**200−280**	**yes**	**to be tested**
8	separate the organic layer in 15 min	45	no	30 min
9	concentrate the organic layer to remove toluene	75	no	OVI correction to be given
10	calculate the yield of **5** in the crude reaction mass	75	no	

Table 6. Ranges for the three CPP_4 considered for DoE

symbol	CPP_4	variable	unit	low (−)	high (+)
A	CPP_4-1	reaction temperature	°C	50	70
B	CPP_4-2	amount of methylamine	equiv	7	13
C	CPP_4-3	reaction time	h	4	6

APPLICATION OF QBD TO CONTROL THE CMA_5

The stepwise QbD process described in the companion article[1] was adopted to identify the CPP_4 and CMA_4 required for controlling all CMA_5.

Step 1: Listing of All Material Attributes (MA_5) of Compound 4 Involved in the Synthesis of the Final API. The maximum number of CQAs pertaining to the final API (**5**) originated from compound **4**. Hence, all of the CQAs (unreacted **3**, residual toluene, impurities **6** and **7**) of the API stage become the MA_5 that need to be controlled by optimization of the conversion of compound **3** to compound **4**, as shown in Table 2. In addition, the quality of EtOAc/HCl used at stage 5 is also included in MA_5.

Step 2: Risk Assessment 1: Identifying the CMA_5. All of the MA_5 of in situ-manufactured compound **4** are captured in Table 2, and few of them are identified as CMA_5 on the basis of criticality.

Step 3: Identification of CMA_4 and CPP_4 Required for the Synthesis of Compound 4. After the CMA_5 associated with compound **4** were identified, it was important to identify the CMA_4 (i.e., the quality of compound **3** and of methylamine) and CPP_4 that are critical to obtain the desired CMA_5.

Step 3.1: Identification of CMA_4. The main inputs involved in the manufacturing of compound **4** are compound **3** and methylamine solution (Scheme 2). Hence, the material attributes of both of the inputs material that are critical to the quality of compound **4** are described as CMA_4 and are captured in Table 3.

Step 3.2: FMEA-2 for the Identification of CPPs. After defining CMA_4 that were affecting CMA_5, it was then time to identify the CPP_4 that were critical to CMA_5. As described before, a risk-based analysis of the process was used for the identification of CPP_4, and this risk assessment was done using failure mode and effect analysis (FMEA). However, before FMEA is started on any process, it is important to have a process description, as it is the main input for the FMEA. The process involved in the manufacture of compound **4** is briefly described below:

> Toluene and compound **3** are charged into an round-bottom flask, and the mixture is stirred for 10−15 min and then heated to 55 ± 5 °C. Then 40% aqueous methylamine solution is added at 55 ± 5 °C, and the resulting mixture is further maintained at 55 ± 5 °C for 4−6 h for completion of the reaction. The reaction mass is then cooled to 50 ± 2 °C, followed by separation of the toluene layer. The aqueous layer is once again extracted with toluene, and the combined toluene layers containing the free-base API **4** are concentrated under vacuum below 50 °C. After the entire toluene layer is distilled, the reaction mass is cooled to 30 ± 5 °C and sent for assay analysis. On the basis of the assay, this crude mass is then directly taken for the final stage, where it is converted to its hydrochloride form (**5**)."

Each unit operation described above was subjected to an extensive FMEA procedure by a cross-functional team (R&D, AR&D, PE, and Production), as captured in Table 4. This FMEA helped in filtering out the three CPP_4 (reaction time, reaction temperature, and amount of methylamine) on the basis of high risk priority numbers (RPNs), which were then taken as the main output of any FMEA procedure. As summarized in Table 5, there were three CPP_4 that were to be studied for their impact on the CMA_5 of compound **4**, and the remaining seven PPs were held constant. Apart from this,

Table 7. Results of the 2^3 full factorial design

factors			responses (CMA_5 from Table 2)			
CPP_4-1: reaction temperature (°C)	CPP_4-2: amount of methylamine (equiv)	CPP_4-3: reaction time (h)	unreacted **3** (%)	hydrolyzed impurity **6** (%)	dimer impurity **7** (%)	yield (%)
50	7	4	0.08	2.26	1.49	85.63
70	7	4	0.5	2.69	2.55	75.00
50	13	4	0.01	0.62	0.25	87.20
70	13	4	0.1	1.19	0.56	85.00
50	7	6	0.07	1.32	0.94	83.35
70	7	6	0.52	1.83	1.55	80.37
50	13	6	0.01	0.54	0.13	86.63
70	13	6	0.08	0.60	0.21	79.98

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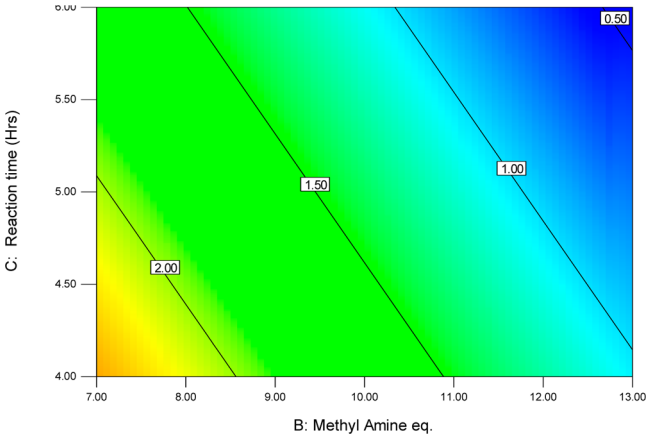

Figure 5. Effect of CPP_4 on hydrolyzed impurity **6** at 60 °C.

two CMA_4 (Table 3) were also well-defined prior to any further optimization.

Step 4. Optimization of the Effect of CMA_4 and CPP_4 on the CMA_5. *Step 4.1. Optimization of the CMAs.* It is important to control the CMA_4 (i.e., the quality of compound **3** and methylamine) in order to have control over CMA_5 (the desired specifications of compound **4**). The CMA_4 were already well-defined as shown in Table 3. It was then time to optimize the CPP_4 affecting the conversion of compound **3** to compound **4**.

Step 4.2. Optimization of the Effect of CPP_4 on CMA_5. A 2^3 full factorial experimental design was planned to study the effect of three CPP_4 (outcome of FMEA analysis; Tables 4 and 5) on CMA_5, keeping all of the other PPs constant at the desired levels (Table 5). The investigational ranges for the three CPP_4 considered for the DoE are given in Table 6, and the results of the full factorial design are given in Table 7. The analyses of the DoE results for the various CMA_5 are discussed in the following sections.

*4.2.1. Effect of the Three CPP_4 on Unreacted **3**.* The half-normal plot and the Pareto chart (Figure 2) and the analysis of variance (ANOVA) (Table 8) show that the unreacted starting material **3** in the reaction mass was influenced not only by the reaction temperature and amount of methylamine but also by their interaction effect. Lower reaction temperature and excess methylamine lead to less unreacted **3** and a greater yield of product **4**. A higher level of unreacted **3** may be due to the loss of methylamine at higher temperature. The same is depicted in the contour graph given in Figure 3.

*4.2.2. Effect of CPP_4 on Hydrolyzed Impurity **6**.* In this case, the half-normal plot and the Pareto chart (Figure 4) indicate that the amount of hydrolyzed impurity **6** was affected inversely by the amount of methylamine and the reaction time, whereas the reaction temperature did not have any impact on this impurity. The same conclusion can be drawn from ANOVA analysis (Table 9) and the contour graph (Figure 5). In other words, a higher amount of methylamine and higher reaction time favors a reduction of impurity **6**.

Table 8. ANOVA table for unreacted 3

source	sum of squares	degrees of freedom	mean square	*F* value	*p* value prob > *F*	
model	0.31	3	0.10	928.11	<0.0001	significant
A (reaction temperature)	0.13	1	0.13	1178.78	<0.0001	
B (amount of methylamine)	0.12	1	0.12	1045.44	<0.0001	
AB	0.06	1	0.06	560.11	<0.0001	
residual	0.00	4	0.00			
cor total	0.31	7				

Table 9. ANOVA table for hydrolyzed impurity 6

source	sum of squares	degrees of freedom	mean square	*F* value	*p* value prob > *F*	
model	4.10	2	2.05	19.04	0.0046	significant
B (amount of methylamine)	3.33	1	3.33	31.00	0.0026	
C (reaction time)	0.76	1	0.76	7.08	0.0449	
residual	0.54	5	0.11			
cor total	4.63	7				

Table 10. ANOVA table for impurity 7

source	sum of squares	degrees of freedom	mean square	*F* value	*p* value prob > *F*	
model	3.62	1	3.62	14.92	0.0083	significant
B (amount of methylamine)	3.62	1	3.62	14.92	0.0083	
residual	1.45	6	0.24			
cor total	5.07	7				

Table 11. ANOVA table for the percent yield

source	sum of squares	degrees of freedom	mean square	*F* value	*p* value prob > *F*	
model	68.86	1	68.86	19.08	0.0047	significant
A (reaction temperature)	68.86	1	68.86	19.08	0.0047	
residual	21.65	6	3.61			
cor total	90.51	7				

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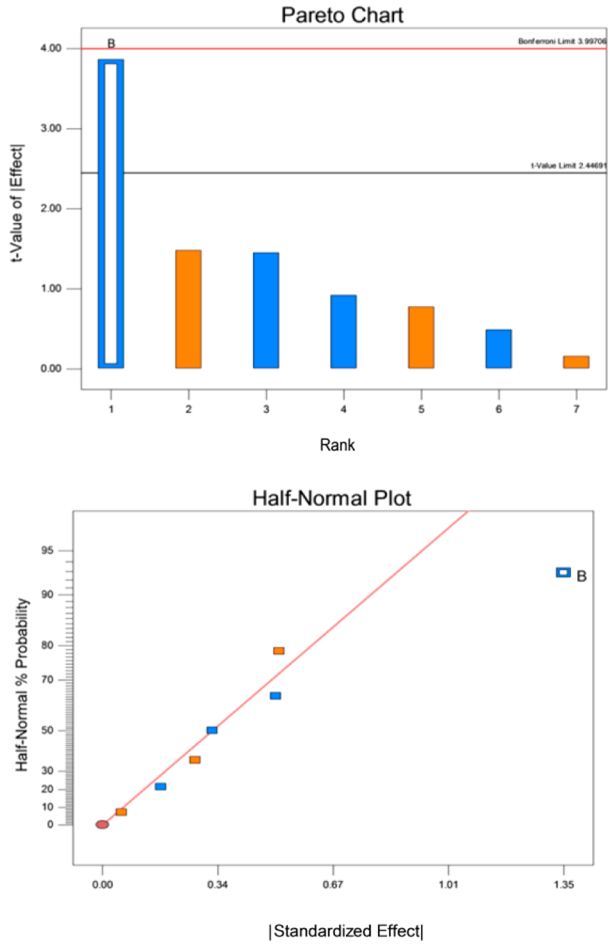

Figure 6. Pareto chart and half-normal plot for impurity **7**.

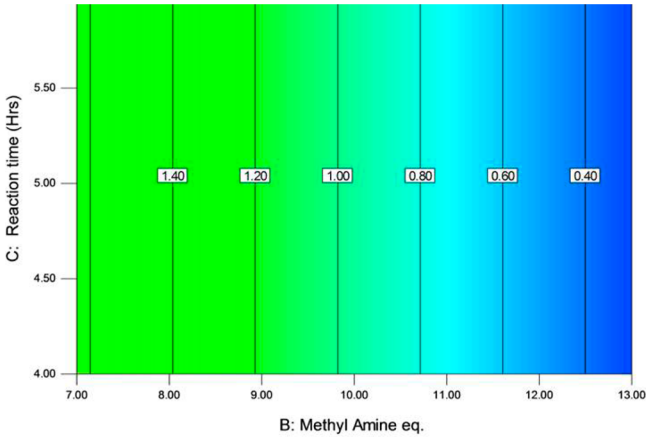

Figure 7. Effect of CPP_4 on dimer impurity **7** at 60 °C.

4.2.3. Effect of CPP_4 on Dimer Impurity **7**. It is evident from the Pareto chart and the half-normal plot (Figure 6) that the amount of impurity **7** was affected inversely by the amount of methylamine, while the other two CPPs had no effect on it. This fact was augmented by the ANOVA analysis (Table 10) and also by the contour plot (Figure 7)

4.2.4. Effect of CPP_4 on the Yield of Compound **4**. The half-normal plot and Pareto chart (Figure 8), ANOVA analysis (Table 11), and contour plot (Figure 9) show that the yield had an inverse relationship with the reaction temperature, while the other two CPP_4 had no effect. It might be possible that at higher

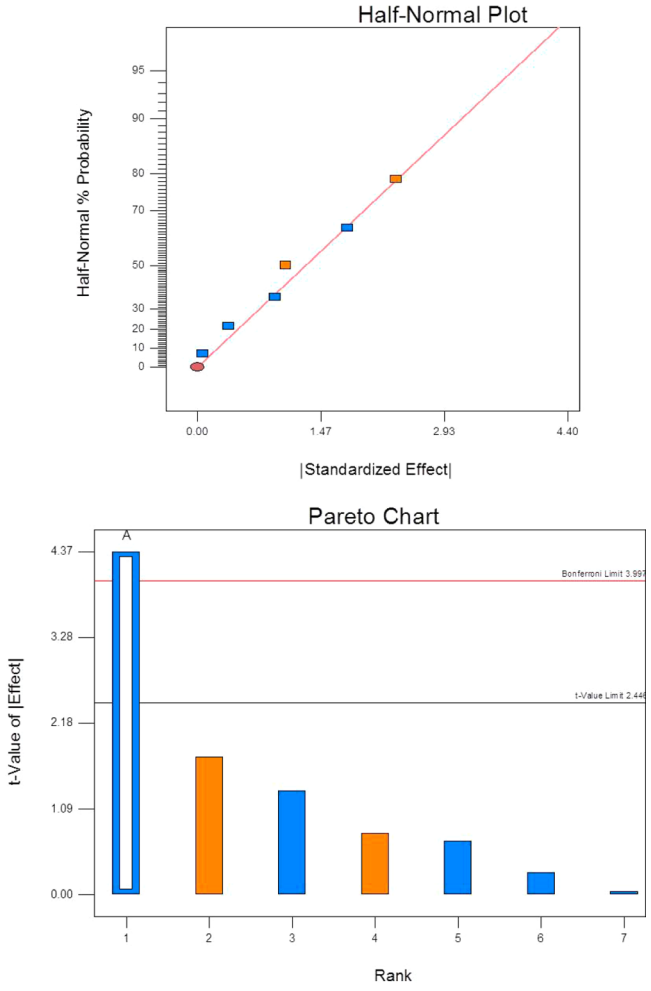

Figure 8. Half-normal plot and Pareto chart for the percent yield.

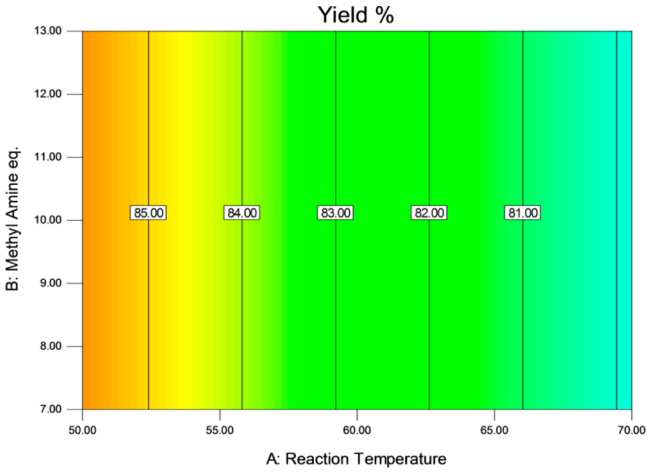

Figure 9. Effect of CPP_4 on the percent yield for a reaction time of 5 h.

temperature methylamine could escape from the reaction mass, thereby decreasing the yield and increasing the amount of intermediate hydrolyzed impurity **6**.

4.2.5. Summary of the Effects of CPP_4 on CMA_5. The contributions of all three CPP_4 and their interactions to the four CMA_5 of compound **4** are captured in Figure 10.

Step 4.3. Defining the Design Space for Compound **4**. Finally, a design space was generated by defining constraints for

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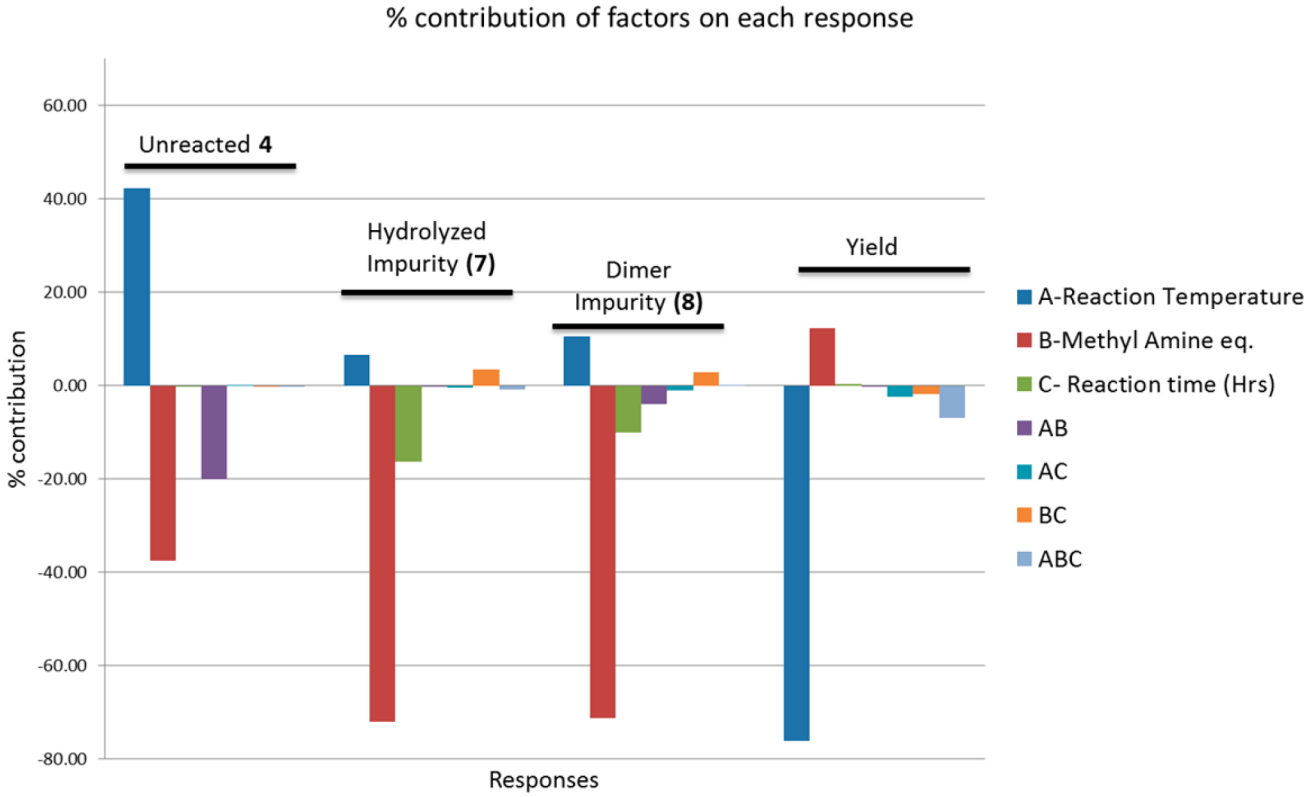

Figure 10. Contribution of CPP_4 on CMA_5 of compound **4**.

Table 12. Criteria for defining the design space

name of CPP/CMA	unit	goal	lower limit	upper limit
	CPP_4			
A (reaction temperature)	°C	in range	50	70
B (amount of methylamine)	equiv	in range	10	12
C (reaction time)	h	target	5.5	
	CMA_5 or Response			
unreacted **3**	% HPLC	minimize	0.01	1
hydrolyzed impurity **6**	% HPLC	minimize	0.53	3
dimer impurity **7**	% HPLC	minimize	0.13	3
yield	%	maximize	NLT 82	

all three CPP_4 and CMA_4 involved in the process, as shown in Table 12. It is worth mentioning that the rest of the process parameters that were not critical were held within their ranges as defined in the FMEA (see Tables 4 and 5). On the basis of the constraints defined for CMA_5 as shown in Table 12, an overlay plot of all the CPP_4 was generated (Figure 11), thereby defining a boundary within which CPP_4 could be varied with no effect on CMA_5. This amicable region, within which the process meets all of the specifications for CMA_5, is shown as the yellow region in Figure 11 and is called as proven acceptable range. This amicable range is defined in Table 12. However, the red rectangle inside the yellow region, which is our normal operating range, becomes the desired design space.

Step 5. Defining Control Strategies[3] for All of the CMAs and CPPs. The control strategies for all of the CMA_4 are presented in Table 3, and the control strategies for all critical/noncritical process parameters were determined after FMEA analysis (Tables 4 and 5). Finally, the control strategies for the three CPP_4 were defined after the DoE study and are captured in

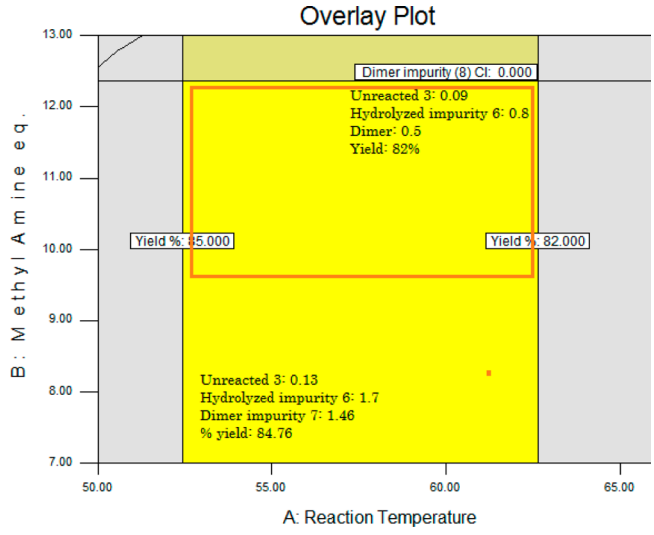

Figure 11. Design space (red rectangle) defined for the reaction time of 5.5 h.

Table 13. These CPP_4 and CMA_4 would be controlled and monitored closely in the future, during commercialization, using various process analytical tools (PATs) and statistical process control tools.[4]

Finally, the specification of compound **4** (CMA_5) was optimized on the basis of the design space, as captured in Table 14. It is worth mentioning that even though high levels of impurities at stage 4 could be tolerated in the next stage, the QbD helped in optimizing the reaction conditions, resulting in much lower levels of these impurities (compare Tables 2 and 14).

Step 6. FMEA-3: Assessing the Risk Mitigation. The last step of the QbD process was to assess the effect of DoE on the

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Table 13. Control strategies for the three CPP_4 with their revised RPNs after FMEA-3

S. no.	factor	acceptable range	control strategy	FMEA-3[a] O	S	D	RPN
1	reaction temperature 55 ± 5 °C (CPP_4-1)	~52−60 °C	replace steam line with hot water line	3	7	3	63
2	amount of methylamine solution (CPP_4-2)	9.5−11 equiv	reanalysis of methylamine solution just before use; specification of assay to be fixed between 35 and 40%	3	7	3	63
3	maintain the reaction mass at 55 ± 5 °C for 5 h (CPP_4-3)	5.5−6 h	replace steam line with hot water line	3	7	3	63

[a]O = occurrence, S = severity, D = (lack of) detection.

Table 14. Final specifications for compound 4

		specifications (CMA_5) maximum tolerable limit	process control limit[a]	is it a CMA_5?	remarks
1.1	assay	as per analysis	as per analysis	no	it is taken to the next stage on the basis of the assay of **4**
1.2	residual toluene	as per analysis	as per analysis	no	
1.3	unreacted **3**	NMT 1%	0.5%	yes	even though these would not participate in the next stage, it was desired to keep these at minimum levels
1.4	hydrolyzed impurity **6**	NMT 3%	1.5%	yes	
1.5	dimer impurity **7**	NMT 3%	0.5%	yes	

[a]These limits were the outcome of the DoE.

RPN of each CPP_4 by comparing the RPN with the value before DoE (i.e., as determined by FMEA-2). For the three CPP_4, these RPNs decreased significantly, as shown by a comparison of the values in Table 13 with those in Table 4.

CONCLUSION

This article has demonstrated the stepwise methodology of implementing QbD to determine the CMAs for any KSM. The emphasis was on optimizing the CMAs of the KSM to ensure that the quality of the final API stage would become consistent in the future. In addition, this exercise would eliminate at least one source of variation from the process. It is also evident that if a manufacturer is obtaining a KSM from outside/third party, then it is beneficial for the manufacturer to include the supplier in the QbD journey. Furthermore, the case study illustrates how FMEA can be used for the unbiased selection of CPPs and CMAs, which can then be used as an input for DoE studies. Finally, the operating ranges for all of the CPPs were finalized on the basis of the design space obtained after DoE, thereby providing a robust process.

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Notes

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

ANOVA	analysis of variance
API	active pharmaceutical ingredient
CMA	critical material attribute
CPP	critical process parameter
CQA	critical quality attribute
DoE	design of experiments
equiv	equivalents
FMEA	failure mode and effect analysis
h	hours
KSM	key starting material
MA	material attribute
NLT	not less than
NMT	not more than
PP	process parameter
QbD	Quality by Design
RPN	risk priority number
SMUI	single major unknown impurity
wrt	with respect to
σ^2	variance

ADDITIONAL NOTE

[a]The desired specifications of compound **4** and EtOAc/HCl are used as inputs for the manufacture of the final API (see Scheme 1).

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