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A Flexible Regulatory Approach for Different Raw Materials Suppliers Using QbD Principles

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ABSTRACT

Quality by Design (QbD) studies areused in the pharmaceutical industry since 2004. The first step started with the Process Analytical Technologies guideline, which was followed by the International Conference on Harmonisation Q8, Q9, Q10 and Q11 guidelines. During the multi-parameter processes of pharmaceutical production, it is necessary to make different variations in either the formulation or the process. However, these variations cannot be performed without permission of Authorities. Design space is a production space provided by the control of critical parameters that are determined by the formulation and manufacturing process. In addition, working within this Design space is not considered a change. This study is based on the fact that Regulatory authorities do not have to be informed of changes as long as the Quality by Design studies remain within the Design space of the Quality by Design formulations. The objective of this study was to demonstrate the flexibility of post-approval changes on ramipril tablets, which contain components from three different active pharmaceutical ingredient manufacturers, within the scope of the Design space. This information was obtained using artificial neural network programs. The stability of the manufactured tablets was evaluated, the convenience of the Design space was also determined.

Keywords: Quality by Design (QbD), Design Space, Stability, Artificial Neural Network Programs

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INTRODUCTION

Quality by Design (QbD) is a systemic method of pharmaceutical advancement. It consists of the creation and improvement of different solutions and procedures to meet a set goal in the quality of a product [1]. By using QbD, the manufacturer can ensure quality through the understanding and regulation of elements in various solutions and procedures, which are subject to change. The aforementioned quality of a product can be approved through testing. Through the use of QbD, reviews of the chemistry, production and control of a new drug submitted for approval will become scientific evaluations of pharmaceutical quality. The QbD method requires that quality testing is included in the design space (DS) itself rather than in the manufacturing of products [2].

Therefore, according to the QbD method, the product formulation and the manufacturing procedures are specifically designed to meet the pharmaceutical quality requirements. The traditional method of maintaining product quality was to set production limits and perform quality tests to ensure that the product was uniform. Several sample batches of a product were used to set the quality requirements. Because even small changes to the production procedures and controls are immensely difficult and subject to strict conditions, it is not possible to perform improvements or ensure continuous strategies for quality assurance. In the QbD system, various elements of formulation and production are used to guarantee the pharmaceutical quality of a drug product.

ICH is a forum for registered institutions and experts from the pharmaceutical industries of the U.S., Japan and Europe. This forum accommodates the technical requirements for pharmaceutical registration in these three countries and issues up-to-date guidelines [3]. The pharmaceutical industry must apply the International Conference on Harmonization (ICH) guidelines, such as guideline Q1 regarding the stability and shelf life of a product. This guideline has established specifications and is estimated based on the different climate zones [4]. All changes that may affect the specification changes are called variations, and the authorities must be notified of these changes, including a change in the source of raw materials.

The new ICH guidelines Q8, Q9, Q10 and Q11 were published with regard to the QbD concept, and these improvements have added new dimensions to the pharmaceutical industry.

One of the most significant aspects of the ICH Q8 guideline is to define the principles of flexible regulatory approaches. Based on the knowledge gained from comprehensive pharmaceutical development studies, prior knowledge and increased understanding of product performance over a range of material attributes, manufacturing process options and process parameters, flexible regulatory approaches will be available to facilitate regulatory risk-based decisions, continual manufacturing process improvements, and real time manufacturing quality and reduce post-approval submissions [1].

The concept of the DS has gained popularity as a tool for pharmaceutical products. The ICH Q8 guideline defines the DS as “the multidimensional combination and interaction of input

variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality." Working within the DS is not considered a change. Movement out of the DS is considered a process change. The DS is proposed by the applicant and is subject to regulatory assessment and approval [1]. The DS has also been primarily used in pharmaceutical processes, although it can also be applied to quality aspects of a product that are obtained through stability studies.

Another new ICH guideline, the Q9 Quality Risk Management, explains what risk is, how it is evaluated and where Quality Risk Management could be applied. Quality Risk Management tools can be used in various stages of pharmaceutical operations, such as development, production, laboratory controls, stability testing, packaging and labeling, as well as inspection and assessment activities [5].

The Quality Risk Management guideline contains two main principles of the risk management model, which explain the risk management process and the terminology and tools used for risk evaluation. There is also a short reference list of detailed information regarding risk management methods (e.g., FMECA), which may be useful for prioritizing PAT applications [6].

The objective of the risk management guideline is to create a common understanding and provide an avenue of communication between the pharmaceutical industry and authorities to encourage transparency and communication to reach "the desired state" and realize risk management. The "desired state" is to manage potential risks related to a patient through the use of scientific knowledge. Risks that cover products, processes and facilities and risks that affect quality system robustness are evaluated, and controls related to risk mitigation are also performed. Additionally, the risk management process should be proportional to the potential risks to patients. This guideline defines a systematic approach, including the evaluation, control, communication and review steps of quality risks across the drug product lifecycle [5].

The newest guideline published by ICH in 2012 is Q11, the Development and Manufacture of Drug Substances. Q11 was created for drug substances, including biotechnological and biological entities, and is related to drug substance manufacturing and development. Various approaches to pharmaceutical development and drug substance understanding are described, and Q11 serves as a guideline regarding the type of information that should be provided in Module 3 CTD Sections 3.2.S.2.2 – 3.2.S.2.6 [7].

With respect to the principles mentioned in ICH Q8 and ICH Q9, ICH Q11 clarifies the principles and concepts regarding drug substance development and manufacturing.

The use of artificial intelligence in pharmaceutical technology can save time and money while providing a better understanding of the relationships between different formulation and process parameters. Guidelines and mathematical models are used to facilitate interpretation of the subject information and enable use in either a dependent or integrated manner. Many programs, such as artificial neural networks, genetic algorithms and neuro fuzzy logic help the

pharmaceutical industry with these issues. One program in which multi-layered receptive neural networks are used is the INForm product of the Intelligensys Ltd. Company/ UK [8].

According to EMA guidelines, changing the API manufacturer requires a variation application, which is usually a Type II application together with a 60-day-review. Stability study documents with the new API manufacturer should be submitted to demonstrate that there would be no effect on drug product quality [9]. For this study, ramipril tablets were manufactured using two different formulations and manufacturing processes according to the studies by Aksu B. et al. [10, 11]. For the flexibility of regulatory approaches, APIs from three different manufacturers were used in the manufacturing process. Drug product quality was ensured by controlling the critical quality attributes (CQAs) and critical process parameters (CPPs) within the DS. The following results of the stability study show that there is no significant change in the product quality even when a new API manufacturer is used.

MATERIALS AND METHODS

Equipment

The following equipment was used in this study: tablet compression machine (Manesty BB3B, BB3B), sieving machine (Erweka, AR 402), HPLC (Thermo Separation Products, AS 3000), ultrasonic bath (BanbelinSonorex, RK 1028H), dissolution apparatus (Distek, EVOLUTION 6100), powder mixer (Aymes, AISI304), granulator (Buchi B-290 (B-290)), Karl-Fischer titrator (Schott, D-551222), hardness apparatus (Sotax, HT4), particle size analyzer (Malvern Mastersizer 2000, SCIROCCO 2000 (ADA2000), friability apparatus (Sotax, F1), disintegration apparatus (Distek, DISINTEGRATION 3100), scanning electron microscope (SEM) (FEI, Quanda 250 FEG), FormRules software (INtelligent Formulation, V.3.32) and INForm computer program (INtelligent Formulation, V.4). The raw materials used for the formulations were ramipril (Neuland Labs Ltd./India, SMS Ltd./India and Unimark Ltd./India), hydroxypropyl methyl cellulose (HPMC) (viscosity: about 15 mPa.s) (BASF, Germany), lactose mono-hydrate (DMV, Holland), sodium hydrogen carbonate (Merck, Germany), croscarmellose sodium (CP Kelco, Holland), pregelatinized starch (Colorcon, England), yellow iron oxide (BASF, Germany) and red iron oxide (Merck, Germany), MgSt (FACI S.p.A-Italy) and SSF (JRS PHARMA- Germany).

Data Set

In this study, 12 different batches of ramipril were manufactured using six different formulations and manufacturing processes and three different active pharmaceutical ingredient sources. As formulation variables, magnesium stearate and sodium stearyl fumarate were used as lubricants. The concentrations of lubricants used were 0.75%-1.0% for magnesium stearate and 0.6%-1.2% for sodium stearyl fumarate. The drying temperature (50ºC and 60ºC), moisture (0.5% and 1.0%) and sieve size (0.8 mm and 1.25 mm) were the procedure variables that served as a test for the wet granulation method. The formulation parameters were considered for both manufacturing methods. In addition to the formulation parameters, the process parameters were discussed for the wet granulated tablets because the process parameters were more

effective than the formulation parameters. Using the indicated formulation and process parameters, 128 variants were prepared from two laboratory batches using wet granulation, and 16 variants were prepared from two laboratory batches using direct compression. The data gathered during the experimental studies (85%) were used for software training, whereas the remaining 15% of the data were used as the test data.

Tablet Formulation and Manufacturing

In this study, the ramipril tablets were prepared according to the wet granulation and direct compression methods with three different active pharmaceutical sources as defined by Aksu B. et al. [10, 11].

EXPERIMENTAL

Software Tools

Three commercial artificial intelligence software tools were used to evaluate the production data generated in these studies. All software packages were provided by Intelligensys Ltd.,/ UK. The INForm ANN software package uses neural networks, and the FormRules V 3.32 data mining software package uses neurofuzzy logic [8]. Whereas the task of establishing a central model is undertaken by the neural network element, genetic algorithms embedded in the software are used for optimization [12].

GEP is a branch of genetic programming (GP), and both belong to a larger family called evolutionary computing. In evolutionary computing, members from various groups that most likely satisfy the data requirements are randomly selected. Each individual member is evaluated based on how it conforms to the training data. The best possible solutions help create a new generation. This new generation is formed either by using a method in which various elements of different solutions come together to create an individual that belongs to this next generation or through mutation. Several groups may be selected, and there may be specifications regarding the size of an eligible population.

Populations improved in this manner better fit the requirements of the experimental data. The evaluation of any given model is completed after several new generations. The quality of the training data and the parameters or the processes of modeling both play a role in the quality of the final model itself [13].

Training Software Tools Parameters

Because the training parameters have a direct effect on the organization of neural networks during the training process, INForm V.4 and FormRules V.3.32 parameters were changed to reach the maximum possible level of predictability in any given trained network. The parameters suggested in the INForm V.4 and FormRules V.3.32 were deemed appropriate after several other sets of parameters were considered. The FormRules settings, which are used for

training, are provided below. A nonlinear coefficient of determination R2 was used to estimate the validation data set to confirm the predictability of the trained models [10, 11].

Model = Structural Risk Minimization (SRM)
2nd order fuzzy set densities: 2⁄3
Fuzzy sets Max. sub model inputs: 4
Max. node per input: 15

The data obtained for the direct compression and wet granulation tablets were optimized using the INForm V.4 ANN. In the training of the INForm ANN model, the optimization was performed in accordance with the target values established to meet the requirements of the pharmaceutical industry and the individual facility. The optimized formulations and processes were obtained from the studies of B. Aksu et al. [10, 11]. The formulation and process parameters for the prepared tablets are given in Table 1 together with the optimized outputs.

Table 1: The formulation and process parameters for the direct compressed and wet granulated tablets.

		Optimization data for direct compressed tablets		Optimization data for wet granulated tablets	
		MgSt	**SSF**	**MgSt**	**SSF**
Inputs	HPMC conc. (%)	0.250 – 0.308	0.542 – 0.667	0.443 - 0.644	0.359 - 0.625
	Magnesium stearate (%)	0.600 - 0.900	---	1.046 - 1.076	---
	Sodium stearyl fumarate (%)	---	0.600 – 1.054	---	1.053 - 1.200
	Moisture (%)	---	---	0.70 - 0.95	0.50 - 0.78
	Sieve size (mm)	---	---	1.250 - 1.250	1.039 - 1.243
	Drying temp. (°C)	---	---	51 - 60	50 - 60
Outputs	Crushing strength (N)	61.424 - 69.455	61.518 - 69.393	54.432 - 72.548	52.496 - 72.219
	Dissolution in 30 min. (%)	94.014 - 94.805	94.427 - 94.697	89.415 - 101.988	89.300 - 101.991
	Assay (mg/tb)	4.663 - 4.670	4.680 - 4.685	4.480 - 5.361	4.169 - 5.344
	Impurity C (%)	0.010 - 0.015	0.014 - 0.015	0.010 - 0.010	0.010 - 0.010
	Impurity D (%)	0.208 - 0.219	0.228 - 0.256	0.076 - 0.086	0.061 - 0.098

MgSt magnesium stearate, *SSF* sodium stearyl fumarate

Risk Assessment

In this study, a risk analysis was performed for the wet granulation method because it is more extensive than direct compression and uses the same formulation parameters. The determined CQAs for the wet granulation method according to the risk assessment involved direct compression. Additionally, the effects of different active pharmaceutical ingredients were incorporated into the risk assessment.

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The risk assessment was performed to identify the critical material attributes (CMAs) and CPPs, which may have an effect on future CQAs. To accurately estimate the risk involved in such materials and the design and procedure variables, the widely used risk assessment method FMEA was used. FMEA enables a simpler overview and evaluation of any possible mistakes or failures and how these mistakes or failures would affect the quality or performance of a product.

To understand the required level of attention necessary for each step of a process and to prioritize accordingly, a risk score matrix is used. The matrix is determined using a total risk priority number. After modes of failure and the necessary CQAs and CPPs are established, the next step is avoid, diminish or manage the risks. The results of FMEA identify methods to diminish risks to within acceptable limits and designate a strategy to manage these risks.

As a part of the assessment, a system of ranking named risk qualification was established. The three rankings were severity (S), probability (P) and detectability (D) and are shown in Table 2. Severity (S) assesses the implications of a failure and how this failure may affect the quality of a product. The possibility of a failure is called the probability of occurrence, whereas detectability is the capability to detect failure modes. The S, P and D scores are multiplied to calculate a risk priority number (RPN) to list each risk according to its rank. Each score is given an assessment point from one to five, and the multiplied RPN scores are classified as follows: low (1 – 45), moderate (46-90) and high (91 – 125). For a high RPN, the potential risks were deemed to have a critical adverse effect on the product quality. Table 3 shows the risk score matrix, which is a part of FMEA.

Table 2: Ranking of severity (S), probability (P) and detestability

SEVERITY		
Score	**Definition**	**Description**
1	Very low	Predicted to have no impact on product quality (quality within specifications).
2	Low	Predicted to have a minor impact on product quality (failure to meet specifications).
3	Moderate	Predicted to have a noticeable impact on product quality, but can be recovered.
4	High	Predicted to have a definite impact on product quality that may require rework.
5	Extreme	Predicted to have a severe impact on product quality and cause batch failure that is not recoverable.
OCCURRENCE		
Score	**Definition**	**Description**
1	Unlikely	Failure is unlikely to occur./Failure has never been seen but it is theoretically possible.
2	Rare	Failure is rare but has a remote probability./Failure has been seen once or twice.
3	Occasional	Failure infrequently occurs./Failure has been observed in several experiments.
4	Moderate/Probable	Failure potential is low./Failure has been observed in several experiments and may require in-process controls.
5	High/Frequent	Failure is expected to occur regularly. /Failure potential is high.
DETECTABILITY		
Score	**Definition**	**Description**
1	Always	Failure can be detected in all cases./Failure is clearly visible.
2	Regular	Failure can be detected almost every time.
3	Likely	Failure cannot be detected occasionally./Failure may be missed sometimes.

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4	Low	Failure is probably not detected./Failure may be missed often.
5	Very low/or no detection	Failure cannot be detected./Failure cannot be detected with the available equipment or method.

Table 3: The risk score matrix for ramipril tablets prepared by the wet granulation and direct compression methods

	Crushing strength (N)	Tablet weigh t (mg)	Friability (%)	Disintegration time (min)	Ramipril assay (mg\tb)	Dissolutio n in 30 min.	Imp. A (%)	Imp. B (%)	Imp. C (%)	Imp. D (%)
API source changes										
HPMC conc.										
Lubricant										
Blending rate										
Blending time										
Drying temp.										
Moisture										
Sieve size										

Risk Score (RPN)	**RPN rank**
<50	Low
50≤ RPN <125	Moderate
≥125	High

With respect to the FMEA result and prior knowledge and experiences, the HMPC concentration, lubricant type, crushing strength, disintegration time, dissolution in 30 min, impurity C and impurity D were classified as CQAs, and the moisture, sieve size and drying temperature were classified as CPPs.

Whereas certain risk scores state that the blending time and rate pose risks such as friability, the ramipril assay and Imp A and B in the matrix, these were not considered CQAs. Friability can be managed indirectly, however, by the crushing strength controls. Additionally, because homogeneity can be managed during tablet pressing, and because high-risk CQAs caused by the blending time and rate are controlled, it has not been necessary to monitor either the medium or low risk level quality parameters for risks. Moreover, all analyses indicated that impurities A and B are valued at zero; therefore, they are not considered risk sources.

Measurement of Critical Quality Parameters

A Sorax HT4 hardness tester was used to determine the crushing strength of the tablets.

The dissolution testing equipment used to perform the dissolution tests was used in accordance with the requirements of the USP method II (paddle) of pharmacopeia. Analysis of the ramipril was performed using the “Ramipril EP Reference Standard”.

To perform the test, 10 to 20 tablets were crushed into a powder and were placed in a suitable solvent at a predetermined concentration. HPLC was used to analyze the ramipril in the dissolution environment samples. The "Ramipril EP Reference Standards A, B, C, D" were used in the analyses instead of the ramipril.

HPLC Analysis

Isocratic chromatography was used to analyze the ramipril in the dissolution tests. The HPLC system consisted of a Thermo Separation Products (AS 3000, USA) instrument equipped with a series 105 pump, a series 105 auto-sampler, and a series 095 UV/VIS detector. The analytical column used was a Luna C18 column (50 mm x 2.0 mm, 3 μm, Phenomenex Company, USA). The signal was monitored at 240 nm. The mobile phase consisted of methanol:phosphate buffer at a ratio of 45:55 (v/v). The flow-rate was 0.4 ml/min, and the injection volume was 100 μl. The chromatography time was 8 min, and the retention time was 4.7 min. The HPLC method developed was validated according to ICH guidelines [14].

Gradient chromatography with the same HPLC system was used for the analysis of the ramipril. The analytical column used was a Luna C18 column (100 mm x 2.0 mm, 3 μm, Phenemonex Company, USA). The signal was monitored at 240 nm. The mobile phase consisted of Solution A (8% methanol:92% phosphate buffer) and Solution B (80% methanol:20% phosphate buffer). The flow-rate was 0.5 ml/min, and the injection volume was 100 μl. Chromatography was performed for 20 min. The HPLC method developed was validated according to ICH guidelines [14]. The gradient program is shown in Table 4.

Table 4: Chromatography conditions for the dissolution method.

Gradient Program:			
Time (min)	Solution A (%)	Solution B (%)	Flow rate (ml/min.)
0	67	33	0.5
10	12	88	0.5
12	0	100	0.5
15	0	100	0.5
16	67	33	0.5
20	67	33	0.5

The ramipril assay was used for the impurity analyses. This assay utilizes the aforementioned system, equipment and chromatographic conditions. Preparation of the solutions, both standard and sample, is described in the next section.

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Solutions Preparation

Stock Standard Solution: Ramipril standard (12.5 mg) was precisely measured and placed in a 100 ml volumetric flask. Solvent (25 ml) was also added to the flask. Phosphate buffer was added to bring the total volume to 100 ml. The resulting solution was then thoroughly mixed and filtered through a 0.45 µm membrane filter. The filtered impurities were then disposed of.

Working Standard Solution: Approximately 0.5 ml of ramipril stock standard solution was placed in a 100 ml volumetric flask, pipetted, brought to 100 ml with diluent and mixed. The solution was then mixed and filtered through a 0.45 µm membrane filter. The filtered impurities were then discarded (ramipril: 0.625 µg/ml).

Sample Solutions (2): Twenty tablets were powdered after being weighed. The resulting powder (162.5 mg), of which approximately 6.25 mg was ramipril, was placed in a 50 ml volumetric flask. After a solvent mixture (12.5 ml) was added, the solution was placed in an ultrasonic bath for 10 minutes. Then, 20 ml of phosphate buffer was added to the mixture, which was shaken for 20 minutes. Subsequently, the volume of the solution was brought to 100 ml with phosphate buffer and filtered through a 0.45 µm membrane filter. The filtered impurities were discarded, and the remaining solution was analyzed by HPLC (ramipril: 125 µg/ml).

Operation: After a standard solution was injected into the HPLC system, the average and RSD, the latter of which should not be in the solution at a concentration greater than 50%, were calculated. Sample solutions were made twice and were injected into the system three times. A standard solution was injected into the system 3 times, and the average and RSD were calculated (RSD = Max. 2.0%).

Calculation of Impurities

$$\frac{A_i}{A_{Std}} \times \frac{W_{Std} / 100 \times 0.5 / 100}{W_N / 50 \times L_a} \times P_s \times 100 \times W_T$$ = % Impurity (%Ramipril)

A_i : Each of the peak areas of Impurity A, Impurity B, Impurity C and Impurity D in the sample chromatogram

A_{Std} : Ramipril peak area in the standard chromatogram

W_{Std} : Ramipril standard mass, mg

P_s : Ramipril standard, %

W_N : Sample mass, mg

W_T : Average tablet mass, mg/tb

L_a : Amount of ramipril in tablet (5 mg)

The final product specifications for the ramipril tablets and control methods were specified and analyzed according to the European Pharmacopeia [15].

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RESULTS AND DISCUSSION

The stability of the manufactured tablets was evaluated under long-term storage conditions (25°C ±2°C/ 60%±5% RH) for twelve months and accelerated conditions (40°C ±2°C/ 75%±5% RH) for six months according to the ICH Q1A (R2) guideline.[4] The results are given in Tables 5-10.

N Neuland Labs Ltd./India, *SMS* SMS Ltd./India, *U* Unimark Ltd./India

Table 5: Stability data of the tablets manufactured using the direct compression method with MgSt (25°C ±2°C/ 60%±5% RH)

Months	0			3			6			12		
	N	U	SMS	N	U	SMS	N	U	SMS	N	U	SMS
Crushing strength (N)	54	57	55	56	57	58	58	58	58	59	59	57
Assay (mg/tb)	4.91	4.87	4.84	4.91	4.97	4.99	4.90	4.85	4.79	4.92	4.77	4.87
Dissolution in 30 min. (%)	99	98	93	97	95	96	96	94	92	96	93.65	94.51
Impurity C (%)	0	0	0	0	0	0	0	0	0	0	0	0
Impurity D (%)	0.09	0.11	0.07	0.25	0.37	0.38	0.45	0.73	0.52	0.98	1.46	1.06

Table 6: Stability data of the tablets manufactured using the direct compression method with MgSt (40°C ±2°C/ 75%±5% RH)

Months	0			3			6		
	N	U	SMS	N	U	SMS	N	U	SMS
Crushing strength (N)	54	57	55	52	52	56	50	56	54
Assay (mg/tb)	4.91	4.87	4.84	4.88	4.87	4.88	4.86	4.68	4.66
Dissolution in 30 min. (%)	99	98	93	94	93	94	92	89	88
Impurity C (%)	0	0	0	0	0	0	0	0	0
Impurity D (%)	0.09	0.11	0.07	0.98	1.41	1.83	1.6	3.06	2.34

Table 7: Stability data of the tablets manufactured using the direct compression method with SSF (25°C ±2°C/ 60%±5% RH)

Months	0			3			6			12		
	N	U	SMS	N	U	SMS	N	U	SMS	N	U	SMS
Crushing strength (N)	56	58	52	57	60	58	60	59	58	62	63	67
Assay (mg/tb)	4.95	4.78	4.83	4.94	4.91	4.91	4.94	4.79	4.81	4.92	4.91	4.88
Dissolution in 30 min. (%)	98	98	94	97	96	95	96	89	92	93	94	92.6
Impurity C (%)	0	0	0	0	0	0	0	0	0	0	0	0
Impurity D (%)	0.08	0.10	0.07	0.25	0.42	0.40	0.48	0.86	0.59	0.98	1.53	1.22

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Table 8: Stability data of the tablets manufactured using the direct compression method with SSF (40°C ±2°C/ 75%±5% RH)

Months	0			3			6		
	N	U	SMS	N	U	SMS	N	U	SMS
Crushing strength (N)	56	58	52	52	60	55	50	55	53
Assay (mg/tb)	4.95	4.78	4.83	4.92	4.86	4.83	4.88	4.71	4.68
Dissolution in 30 min. (%)	98	98	94	93	95	94	90	86	88
Impurity C (%)	0	0	0	0	0	0	0	0	0
Impurity D (%)	0.08	0.10	0.07	0.98	1.39	1.86	1.20	3.26	2.41

Table 9: Stability data of the tablets manufactured using the wet granulation method with MgSt (25°C ±2°C/ 60%±5% RH)

Months	0			3			6			12		
	N	U	SMS	N	U	SMS	N	U	SMS	N	U	SMS
Crushing strength (N)	72	84	95	74	90	94	76	57	58	77	92	99
Assay (mg/tb)	5.02	5.14	4.85	5.00	5.00	5.06	4.98	4.98	4.98	4.98	5.05	4.97
Dissolution in 30 min. (%)	99	102	100	98	99	101	99	94	94	98	95.45	97.26
Impurity C (%)	0	0	0	0	0	0	0	0	0	0	0	0
Impurity D (%)	0.08	0.09	0.05	0.11	0.10	0.07	0.14	0.12	0.06	0.25	0.22	0.1

Table 10: Stability data of the tablets manufactured using the wet granulation method with MgSt (40°C ±2°C/ 75%±5% RH)

Months	0			3			6		
	N	U	SMS	N	U	SMS	N	U	SMS
Crushing strength (N)	72	84	95	70	68	85	68	53	54
Assay (mg/tb)	5.02	5.14	4.85	4.96	4.94	4.95	4.93	4.62	4.66
Dissolution in 30 min. (%)	99	102	100	96	98	99	90	84	88
Impurity C (%)	0	0	0	0	0	0	0	0	0
Impurity D (%)	0.08	0.09	0.05	0.30	0.20	0.10	0.95	0.60	2.34

Table 11: Stability data of the tablets manufactured using the wet granulation method with SSF (25°C ±2°C/ 60%±5% RH)

Months	0			3			6			12		
	N	U	SMS	N	U	SMS	N	U	SMS	N	U	SMS
Crushing strength (N)	92	93	78	94	76	78	96	57	58	96	78	79
Assay (mg/tb)	5.05	5.18	5.01	5.01	5.07	4.98	5.00	5.00	4.96	5.00	5.09	5.14
Dissolution in 30 min. (%)	100	101	98	98	98	100	96	95	96	97	97.02	96.90
Impurity C (%)	0	0	0	0	0	0	0	0	0	0	0	0
Impurity D (%)	0.06	0.09	0.05	0.12	0.10	0.08	0.15	0.13	0.07	0.22	0.22	0.13

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Table 12: Stability data of the tablets manufactured using the wet granulation method with SSF (40°C ±2°C/ 75%±5% RH)

Months	0			3			6		
	N	U	SMS	N	U	SMS	N	U	SMS
Crushing strength (N)	92	93	78	85	78	81	65	52	51
Assay (mg/tb)	5.05	5.18	5.01	5.00	5.05	4.96	4.96	4.72	4.77
Dissolution in 30 min. (%)	100	101	98	93	98	99	90	90	92
Impurity C (%)	0	0	0	0	0	0	0	0	0
Impurity D (%)	0.06	0.09	0.05	0.25	0.22	0.13	0.70	0.72	0.23

N Neuland Labs Ltd./India, *SMS* SMS Ltd./India, *U* Unimark Ltd./India

After the stability studies and tests, all critical quality parameters (CQAs) for the ramipril tablets were within the range of limits defined in the pharmacopeia and the limits obtained by the optimization of the experimental results using the artificial neural network. Additionally, no changes were observed that affected the tablet quality. Therefore, a variation for the API source would not be necessary and, by using QbD principles and ANN, can be a useful tool for guaranteeing the manufacturing process and the quality of the finished pharmaceutical products.

CONCLUSIONS

The application of QbD principles to a product ensures a certain degree of flexibility in regulations. An improved understanding of the procedures corresponds to a shorter approval period and fewer inspections.[16] QbD is targeted toward a robust and repeatable process, which produces quality products without reworking or retesting and is financially important for the pharmaceutical industry and highly beneficial for the consumers. This is because it will ensure quality at all times, potentially alleviate shortages and decrease costs.

The recommended content for the 3.2.P.2 pharmaceutical development section of a regulatory submission in the ICH M4 Common Technical Document (CTD) format are defined by the ICH document Q8 (R2) [1, 17]. In this document, one of the fundamental principles of QbD suggests that testing the quality of products is not possible because the quality must be created by design. Only movement outside the DS is accepted as change, which typically initiates a regulatory post-approval change process. Activities within the DS are not considered changes. Although QbD is not necessary and is applied voluntarily, both industry and regulators have accepted the benefits of using a QbD approach in drug development and manufacturing. To guarantee the expected product quality, ICH Q8 describes CQAs as a property or a characteristic that could be physical, chemical, biological, or microbiological and that must be within the correct limit, range, or distribution [18].

The objective of this study was to show that one of the factors affecting the stability of the product, the raw materials source change in the formulation, does not affect the stability of

the product when performed within the DS.

With the raw material acquired from three different sources, the CQA lubricant type, crushing strength, disintegration time, dissolution in 30 min, impurity C and impurity D were established, and the critical parameters were monitored with FMEA. The results were optimized with INForm V.4 ANN, which confirmed that the results were in the formerly established the DS [10, 11].

According to these results, because the variations in the DS do not have to be reported to the authorities, the industry can continue its activities within the DS by obtaining raw materials from three sources.

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