Original Article

Robust And Flexible Analytical Method Development Through Quality By Design: A Review

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Abstract

Application of Quality by Design for analytical method development resulted into a method having robustness and ruggedness which is complying with ICH quality guidelines. Quality by Design begins with determination of goal. Critical quality attributes directly affect the quality are to be sorted out first. The best way for method development is Analytical target profile which describes method requirements. In method design use of various flowcharts, decision tree can be made for correct implementation. Assessment of risks is a connection between input method factors and critical quality attributes. The data obtained from the experimental design should be studied by the usage of various statistical methods. Many software packages are available for assisting and performing statistical analysis, reporting the results and generating a mathematical model. The next step after the development of method through quality by design is method validation.

Keywords: Quality by Design, goal, input variable, critical quality attribute, risk assessment.

1. BASIC PRINCIPLES

Product Quality occupies supreme importance in manufacturing of pharmaceuticals. FDA continually provides certain specifications to produce quality medicines to the patient [2]. It tries to suggest new ways for manufacturers encouragement which helps in improving manufacturing processes and to give assurance for reliable quality of product through the life cycle of product. The main consideration for any manufacturing unit is quality because of its direct influence on patient health. The company economic growth also depends on product quality.

Up to now the general procedure to develop an analytical method in chromatography was done by using trial and error method, by changing single variable at once and examining the separation extent until the emergence of components. This method takes ample time and requires more manual interpretation of data. The above method will not show robustness when experiment is performed in another lab. The OVAT method is useful only if the analyst wants to study the effect of one factor at a time and all other factors should be constant[1]. But all factors should be considered at a time to get accuracy in results with less time. The QbD elements have supreme importance in that case. Today in the pharmaceutical industry, we can see increasing importance of application of quality by design to analytical method known as analytical QbD.

Outcomes of applying QbD to analytical method

- The method is more robust giving higher confidence level if there is change in conditions.
- It gives good transfer success if developed method is moved from research lab to quality control lab.
- It gives flexibility for introducing new methods by continuous betterment throughout product life cycle.
- It gives good scientific understanding of the developed method.
- The Design space avoids the post-approval changes which increases the economic status of the industry.
- It gives high compliance with regulatory guidelines.

General Trail and Error method vs Quality by Design method

General Trail and Error method	***Quality by Design method***
Quality is acquired by different tests.	Quality is acquired through design and has good understanding of the method.
It involves only data submission which includes brief information without detailed notes.	It involves data submission with rich product knowledge and understanding of the process.
standards are from batch history	standards are from performance of product
Rigid method in which changes are not allowed.	Flexible method with more space in design to give continuous improvement.
It concentrates on reproducibility.	It concentrates on robustness.

2. IMPLEMENTATION OF ANALYTICAL QBD

Similar to process QbD, some elements are used into the analytical development by AQbD. The elements of process QbD are such as target profile of analytical method, critical quality attributes, design space, analysis risks, control strategy and life cycle approach.

2.1 Analytical target profile (ATP)

It includes method requirements to be measured. Generally the chromatographic method objectives are to separate, to quantify and to identify analyte, impurity or degradation product. Example for critical quality attribute is impurity.

2.2 Design of the Method

The design of the method is made by taking materials and reagents which are available and different experimental conditions into consideration. It is also made by regionally, geographically and instruments feasibility.

Design of the method uses flowcharts and decision trees for correct implementation [3]. Various conditions of experiment were carried with parameters like pH, temperature, different columns and mobile phase composition. Design of the method uses soft wares like design expert and sigma tech which forecast the results outcome without experiments. Design of the method aids the changes in future methods. It includes selection of analytical method for definite method development. Appropriate method is selected to meet the desired requirement. HPLC with PDA detector to estimate impurities is the example. The design may be altered whenever there is requirement in the life cycle of product. In this procedure the method can be transferred from research level to quality control level. Experimental design is necessary for the analytical method development. Risks can be assessed by knowledge of the present method and critical quality attributes cab be managed highly.

The selection of the suitable experimental design is prominent for the Quality by Design approach[18]. The design selection is based on problem nature in investigation and objectives of experiments. Things required are:

a) The experimental number(N): the time required for each experiment is taken in to account
b) The parameter number (k) in the experiment: Mostly the experimental number increases as the parameter number increases. The concept of parameters to be removed is a sensitive matter[17]. This is done by Plackett- Burman design as a primary study for detecting the major effects.
c) The number (L) of the level for the chosen parameter: Proper care should be taken for the selection of the level number. Level number must be low and it can be raised if there is uneven property of output variable.[4].
d) The objective of the design of experiment: The selection of the design depends on the objective of the experiment. Generally plackett-burman design is used to detect main effects. The study of main effects and interaction effects requires fractional and full factorial design. The study of primary factor requires latin square design or a randomized complete block design.
e) Some of the main techniques used in DOE are as follows.

i) Randomized block method

This method is used when one specific factor impact is more relevant on the response variable. This parameter is known as primary factor[5]. The remaining factors are known as nuisance factors. In this case we can use this design as we concentrated on primary factor and maintaining constant values of other factors.

k = 2 factors (1 Primary factor X_1 and 1 nuisance factor X_2)
L1 = 4 levels of factor X1
L2 = 3 levels of factor X2
n= 1 replication per cell
N= L1xL2 = 4 x 3 = 12 runs

X_1	1	1	1	2	2	2	3	3	3	4	4	4
X_2	1	2	3	1	2	3	1	2	3	1	2	3

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ii) Latin square design

Here primary factor significance is reduced and the objective is to reduce the sample number [16]. The main thing is to carry out one experiment instead of performing a randomized complete block design. Latin square design is a peculiar method with rows and columns containing two blocking factors. In this design one factor occurs only one time in a row and in a column.

e,g. 3 factors A,B, C

A	B	C
C	A	B
B	C	A

iii) Full factorial design

It is the general and natural method of design. The easy method in full factorial design is with the two- level full factorial design. Consider k=2 factors and L = 2 levels per factor[15]. Then the size of sample is N= 2k. The levels are named as high (h) and low (l) or "+1" and "-1".

e.g. 2×2 factorial experiment (4 runs)

Run	A	B
1	-	-
2	+	-
3	-	+
4	+	+

iv) Fractional factorial design

The fractional factorial design is a part of full factorial design. This imparts sound details on core effects and other effects.

e.g. 2^3 fractional factorial experiment (8runs)

Run	X	Y	Z
1	l	l	l
2	h	l	l
3	l	h	l
4	h	h	l
5	l	l	h
6	h	l	h
7	l	h	h
8	h	h	h

v) Box – Behnken design

This is not a complete design. It includes three-level factors. They are meant to reduce the size of the sample if the parameter number increases.

e.g. 3 factors with 3 levels (15 runs)

Runs	A	B	C
1	-1	-1	0
2	-1	1	0
3	1	-1	0
4	1	1	0
5	-1	0	-1
6	-1	0	1
7	1	0	-1
8	1	0	1
9	0	-1	-1
10	0	-1	-1
11	0	1	-1
12	0	1	1
13	0	0	0
14	1	1	1
15	-1	-1	-1

vi) Plackett- Burman design

Plackett- Burman designs are highly inexpensive with two – levels factors. These are meant to the design space to identify large main effects.

e.g. plakett-burman design 11 two level factors (12 runs)

Run	X1	X2	X3	X4	X5	X6	X7	X8	X9	X10	X11
1	+	+	+	+	+	+	+	+	+	+	+
2	_	+	_	+	+	+	_	_	_	+	_
3	_	_	+	_	+	+	+	_	_	_	+
4	+	_	_	+	_	+	_	+	_		_
5	_	+	_	_	+	_	+	+	+	_	_
6	_	_	+	_	_	+	_	+	+	+	_
7	_	_	_	+	_	_	+	_	+	+	+
8	+	_	_	_	+	_	_	+	_	+	+
9	+	+	_	_	_	+	_	_	_	_	+
10	+	+	+	_	_	_	+	_	_	+	_
11	_	+	+	+	_	_	_	+	_	_	+
12	+	_	+	+	+	_	_	_	+	_	_

vii) Taguchi design

Genichi Taguchi of Japan introduced this method to enhance the application of disconnected overall quality control. This method deals to sort out the best values of the dependent variables to convert the issue less delicate to the changes in independent variables[7]. This is known as Taguchi robust parameter design problem.
e.g. 8 runs with 7 parameters

Runs	X1	X2	X3	X4	X5	X6	X7
1	1	1	1	1	1	1	1
2	1	1	1	2	2	2	2
3	1	2	2	1	1	2	2
4	1	2	2	2	2	1	1
5	2	1	2	1	2	1	2
6	2	1	2	2	1	2	1
7	2	2	1	1	2	2	1
8	2	2	1	2	1	1	2

viii) Random Design

It is exactly the space filling method in which the design space is filled with the samples of uniform distribution and irregularly fashioned samples[13]. It is not particularly effective because the irregular method do not confirm as few samples are not grouped nearer to each other, so there is no uniformity in filling the design space.
e.g. factors (A, B, C and D) and 5 replicates

1 Z	2 Z	3 X	4 Y	5 Z	6 Y	7 W	8 W	9 X	10 Z
11 Y	12 X	13 W	14 X	15 Y	16 X	17 Y	18 Z	19 W	20 W

ix) Optimal Design

This is a response – surface-based method in which results are based on the Response Surface Methodology technique which is meant to be applied further.
e.g. optimal design for 3 factors (9 runs)

Runs	Initial design			optimised design		
	X1	X2	X3	X1	X2	X3
1	0.2	0.4	0.4	0.2	0.2	0.6
2	0.2	0.6	0.2	0.2	0.2	0.2
3	0.3	0.35	0.35	0.2	0.2	0.6
4	0.4	0.2	0.4	0.2	0.8	0.00
5	0.40	0.60	.00	0.20	0.80	0.00
6	0.45	0.45	0.10	0.20	0.80	0.00
7	0.50	0.25	0.25	0.80	0.20	0.00
8	0.60	0.20	0.20	0.80	0.20	0.00
9	0.60	0.40	0.00	0.80	0.20	0.00

2.3 DOE Statistical Analysis

After collecting the data as per the selected design, the statistical methods are used to analyse the results and to made the conclusion[8]. Various softwares are used to assist the users in selecting a design to those that carry out statistical analysis, report the results, and produces model using mathematics.

2.4 Design space development

The Design Space (DS) is defined as the overall mixture of input parameters in which forecasted CQAs accomplish the already mentioned criteria[11]. As a result, the DS is a zone of robustness and variations within the DS will not critically affect the method performance. Many outcomes are considred so graphically DS is represented through overlay responses.

2.5 Validation of the method

The developed method can be validated to assure the suitability of the developed method for its expected use. As per ICH Q2 (R1) guideline, the method after development can be validated for system suitability, linearity, detection limit and quantitation limit, accuracy, intra-day precision, inter day precision, specificity and finally robustness[6].

2.6 Monitoring performance and continual improvement

The aim of the method is to confirm continuously the developed method is in controlled state. An ongoing program should be included to procure and analyse the information which relates to significance of the method[9]. The main focus should be on deviations in the data from the acceptance criteria produced by the method when it is operated in its natural

conditions. By using the new Quality by Design, labs must report few OOS results and this is easy for the staff to find out their root cause[12].

Continual examining of developed analytical methods and factors through control charts or other tools may be appropriate. The methods are made in their different working environments so lean tools are applied to optimize work stations and give reductions in the life cycle of the method[10].

3. CONCLUSION

Now a days QbD based analytical method is mandatory for routine analysis of pharmaceuticals because analytical methods with QbD approach are robust, accurate, time saving, scientific knowledge gaining and economical.

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