Atul Pal *et al*, Int. Journal of Pharmaceutical Sciences and Medicine (IJPSM),
Vol.8 Issue. 6, June- 2023, pg. 57-72

ISSN: 2519-9889
Impact Factor: 5.9

Manufacturing Process Validation of API Drug Moxifloxacin to Evaluate the Critical Process Parameters and Quality Attribute

Atul Pal; P.K Dubey; Nimita Manocha; Archana Dubey
Swami Vivekanand College of Pharmacy, Indore
DOI: 10.47760/ijpsm.2023.v08i06.005

ABSTRACT: Product quality is the dependence of medicinal diligence and is deduced from careful attention to a number of factors including selection of quality corridor and accoutrements, acceptable product and manufacturing process design, control of the process variables, in- process and end- product testing. Process confirmation is an integral part of quality assurance program in diligence. By validating each step of product process we can assure that the final product is of stylish quality. This review provides information on objects and benefits of process confirmation, types of process confirmation, major phases in confirmation and nonsupervisory aspects. Guidelines and strategy for process confirmation of solid lozenge form are also bandied. The main thing of this work was to produce a precious Risk Management Approach that enables a Process confirmation over products lifecycle. Quality threat operation (QTO) has been described in nonsupervisory guidance for several aspects of process confirmation, similar as product lifecycle, extent of confirmation, determination of critical quality attributes (CQAs) and critical process parameters (CPPs), process design space(DS), and slice plans and statistical confidence situations. Verification of the process in Moxifloxacin Hcl produced batch, over the product life time is now an anticipation from non-supervisory authorities

Keywords: Quality, process variables, process confirmation, guidelines.

ISSN: 2519-9889
Impact Factor: 5.9

1.INTRODUCTION

Process validation is used to confirm that the resulting product from a specified process consistently conforms to product requirements. A risk-based approach helps to identify crucial parameters as sources of process variation that affect product quality. Controlling the sources of variation commensurate with the risk they represent to the process and final product attributes are the key concepts of assessing products` quality framework. In this thesis we are going to perform Manufacturing Process Validation of API Moxifloxacin Hydrochloride to Evaluate Critical Process Parameters and Quality Attribute**s.**

PROCESS VALIDATION AND GUIDELINES CHRONOLOGY

When a new process and product are developed or there's an attempt to understand an living process, knowing how accoutrements , processes and controls affect the final product is essential(Brindle, etal., 2012).The conception of Process confirmation has been changing over the last decades.In 1987 FDA(U.S. Food and Drug Administration) issued Guidance for Process confirmation(Guideline on General Principles of Process confirmation, May, 1987)(Figure 1) in order to drive diligence to reflect on process confirmation stylish practices. This Guidance defined the types of attestations as Prospective and Retrospective; also defined the Command(Installation qualification) including subjectively OQ(functional qualification) and PQ(Process qualification) 1; and enlightened worst case script studies, Process Revalidation and Process confirmation as a multiple batch demonstration(FDA, 2009). still, in the rearmost FDA guidelines this old Command/ OQ/ PQ approach doesn t demonstrate the process itself; outfit function is slightly half of the story. There are raw accoutrements and inputs, process controls, and product attributes associated with every unit operation in a manufacturing process

ISSN: 2519-9889
Impact Factor: 5.9

2. MATERIAL AND METHODS:

MATERIALS

Moxifloxacin Hydrochloride was obtained from Yarrow Chem Products Mumbai Acetic anhydride,Zinc chloride (anhydrous) Boric acid DM water obtained from loba chem. Products.

BRIEF MANUFACTURING PROCESS OF PRODUCTMOXIFLOXACIN HYDROCHLORIDE IP

Method for the preparation of Moxifloxacin hydrochloride from the ethyl 1-cyclopropyl- 6,7-difluoro-8-methoxy-4-oxo-l, 4-dihydro-3-quinolinecarboxylate. The reaction of with boric acid and acetic anhydride without using any catalyst gives (1- cyclopropyl-6, 7- difluoro-8-methoxy-4-oxo-l, 4-dihydro-3-quinoline carboxylicacid-O^3, 0^4) bis (acyloxy-O) borate which on condensation in presence of a base(s) with (S,S)-2, 8-Diazabicyclo [4.3.0] nonane in organic polar solvent results the novel intermediate (4aS-Cis)-l-Cyclopropyl-7- (2,8-diazabicyclo [4.3.0] non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid-0^3,0^4) bis (acyloxy-O) borate. This intermediate is reacted with hydrochloric acid in presence of solvent to give Moxifloxacin hydrochloride.

3. PROCESS VALIDATION OF MOXIFLOXACIN HYDROCHLORIDE MANUFACTURING OF MOXIFLOXACIN STAGE-I

RAW MATERIAL DETAILS:			
Sr. No.	**Raw Material**	**Standard Quantity**	**Actual Quantity**
1.	1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro- quinoline-3-carboxylic acid ethyl ester	100 gm	100 gm
2.	Acetic anhydride	175 gm	175 gm
3.	Zinc chloride (anhydrous)	2.5gm	2.5gm
4.	Boric acid	31 gm	31 gm
5.	DM water	1000 ml	1000 ml

EQUIPMENT DETAILS:	
Sr. No.	**Description**
1.	Glass assembly

ISSN: 2519-9889
Impact Factor: 5.9

2.	Buchner funnel
3.	Dryer

MANUFACTURING PROCESS

Sr. No.	Operation	Time (Hrs./Min.)		Temperature (°C)	
		Std	Actual	Std	
1	Ensure the Glass assembly is clean and dry	-	-		
2	Charge 175 ml Acetic anhydride.	-	-	RT	RT
3	Charge 2.5 gm zinc chloride.	-	-	RT	RT
4	Apply heating and raise temperature.	-	-	35-52°	**40°C**
5	Now start addition of slowly boric acid 31 gm.	-	-	35-52°	42 **°C**
6	Start heating raise temperature.	-	-	100-105°	102 **°C**
7	***It is exothermic reaction temperature raise slowly.***	-	-	100-105°	102 **°C**
8	Stir the reaction mass and record maintain in	)1 hr ± 15min	hr 05min	100-105°	102 **°C**
9	Apply cooling cool the reaction mass	-	-	65- 70°	67 **°C**
10.	Start addition of intermediate(1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester) 100 gm	-	-	65- 70°	67 **°C**
11.	After addition of intermediate raise the temperature	-	-	100-105°	101 **°C**
12.	Maintain the reaction mass apply cooling and cool thereaction mass	05 hr ± 30 min	hr 15min	100-105°	102 **°C**
13.	Send a sample for TLC				
14.	If TLC does not comply maintain the reaction mass	02 hr ± 30 min	hr 10min	100-105°	102 **°C**
15.	Send a sample for TLC	-	-		
16.	After complying TLC cool the reaction mass	-	-	30- 35°	33 **°C**
17.	Further chill the reaction mass	-	-	0-5°	4 **°C**
18.	Stir the reaction mass	35 ± 5 min	35 min	0-5°	3 **°C**
19.	Start addition chilled process water1000 ml maintaining temperature in the reaction mass			0-5°	3 **°C**
20.	Stir the reaction mass	01 hr ± 30 min	hr 10min	0-5°	4 **°C**
21.	Ensure the Filtration funnel ..... is clean and dry.	-	-	-	-
22.	Ensure that paper fixed properly	-	-	-	-
23.	Feed the reaction mass in funnel through Assembly.	-	-	-	-
24.	Apply vacuum	-	-	-	-
25.	Dry the material	-	-	-	-

ISSN: 2519-9889
Impact Factor: 5.9

26.	Wash the cake with 100 ml Chilled water.	-	-	-	-
27.	Suck dry the material	30 min	30 min		
28.	Unload the wet cake	-	-	-	-
29.	Ensure the tray dryer is cleaned and dry.Clean/Not Clean	-	-	RT	RT
30.	Ensure top most trays kept empty.	-	-	RT	RT
31.	Load the wet material	-	-	RT	RT
32.	Start fan of TD	-	-	RT	RT
33.	Start heating and raise temperature	-	-	RT to 55-60°	50 °C
34.	Dry the material and maintain temperature	10 ±1hr	) hr 20min	55-60°	58 °C
35.	Send composite sample to QC for M/C test	-	-	-	-
36.	Unload the material	-	-	-	-
37.	Send sample to QC for complete analysis as per specification.	-	-	-	-

INTERMEDIATE SPECIFICATION

Material Name : Moxifloxacin Hydrochloride Stage-1

(Test & Limits)

TESTS	SPECIFICATION
Description	Brown color liquid. Take a clean tube and observe the sample.
Gati-ester UnreactedBy TLC	NMT 1.0% **Mobile phase** 18 ml Chloroform, 2 Ml methanol **Test Solution Preparation :** Take 5 ml reaction mass dissolve in 5 ml MDC. **Ref solution preparation : -** 100 mg Gati ester and dissolve in 10 ml MDC. **Procedure :** Saturate the TLC plate in Mobile phase than Put the reference solution and test solution spot on silica gel F254 TLC plate 10 µl. Run the plate in mobile phase.

ISSN: 2519-9889
Impact Factor: 5.9

	Observation : Spot due to gati-ester in test solution is less intense then spotof gati-ester in reference solution.

INTERMEDIATE SPECIFICATION	
Material Name : Moxifloxacin Hydrochloride Stage-2	
(Test & Limits)	
TESTS	**SPECIFICATION**
Description	Light yellow coloured liquid. Take a clean tube and observe the sample.
Stage-1 Un-reacted By TLC	NMT 1.0% **Mobile phase** 18 ml Chloroform 2 Ml methanol **Test solution preparation : -** Take 5 ml reaction mass and dissolve in 5 ml MDC . The solution becomes bluein colour. . **Ref solution preparation : -** Dissolve 100 mg boron complex in 10 MDC . The solution is blue colour. **Procedure :** Saturate the TLC plate in TLC chamber Put the ref solution and test solution spot on silica gel 60 F254 TLC plate 10µl. Run the plate in mobile phase. **Observation :** Spot due to Stage-1 in test solution is less intense then spot ofstage-1 in reference solution.

INTERMEDIATE SPECIFICATION	
Material Name : Moxifloxacin Hydrochloride Stage-3	
(Test & Limits)	
TESTS	**SPECIFICATION**
Description	Light yellow coloured liquid. Take a clean tube and observe the sample.

ISSN: 2519-9889
Impact Factor: 5.9

Stage-2 Un-reactedBy TLC	NMT 1.0% **Mobile phase** 18 ml Chloroform, 2 Ml methanol

ISSN: 2519-9889
Impact Factor: 5.9

	Test solution preparation : - Take 10 ml reaction mass and filter it take 200 mg wet cakedissolve in 5 ml MDC, add triethylamine drop wise till the solution becomes clear. **Ref solution preparation : -** 5 mg Stage-2 and dissolve in 5 ml MDC. **Procedure :** Saturate the TLC plate in Mobile phase than Put the reference solution and test solution spot on silica gel F254TLC plate 10 µl. Run the plate in mobile phase. **Observation:** Spot due to Stage-2 in test solution is lessintense then spot of Stage-2 in reference solution.

EQUIPMENT DETAILS:	
Sr. No.	**Description**
4.	Glass assembly
5.	Buchner funnel
6.	Dryer
7.	Separating funnel

FINISHED PRODUCTS RESULTS		
Material Name : Moxifloxacin Hydrochloride IP		
(Test & Limits)		
TESTS	**SPECIFICATION**	**Results**
Description	A light yellow or yellow powder or crystals, slightlyhygroscopic.	Light yellow Crystallinepowder
Solubility	Sparingly soluble in water; slightly soluble in ethanol (95 per cent); practically insoluble in acetone.	Sparingly soluble in water; slightly soluble in ethanol (95 per cent); practically insoluble in acetone.

ISSN: 2519-9889
Impact Factor: 5.9

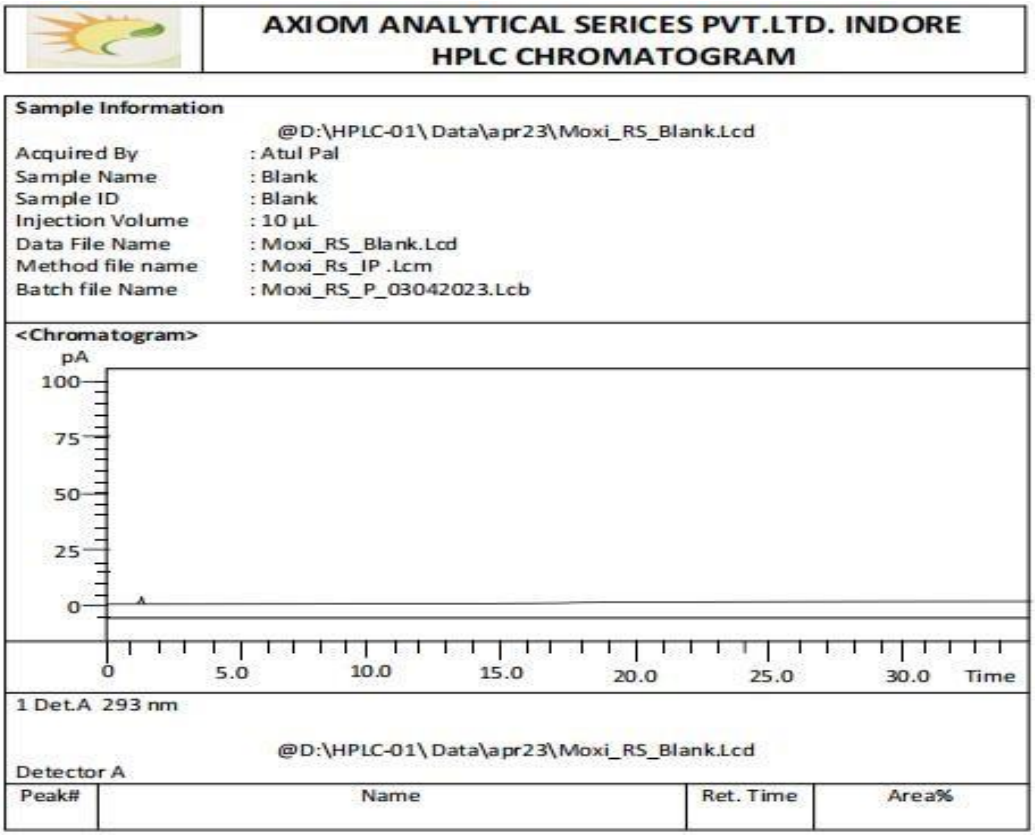
Identification A (By IR) Identification B (By Chemical)	(A) Determined by infrared absorption spectrophotometry Compare the spectrum with that obtained with moxifloxacin hydrochloride RS or with the reference spectrum of moxifloxacin hydrochloride. (B) Chloride test should be complies.	Complies Complies
Appearance of solution	The solution is not more opalescent than standard OS2 and not more intenselycoloured than reference solution GYS2.	Complies
pH (0.2%w/v)	3.9 to 4.6	4.35
Specific optical Rotation	-125° to -138°	-129°
Related substances Any Secondary Impurity All Secondary Impurities	 NMT 0.1% NMT 0.3%	 0.05% 0.05%
Sulphated ash	NMT 0.1%	0.05%
Water	NMT 4.5%	2.1 %
Assay on Anhydrous basis	NLT 98.0% and NMT 102.0%	99.58%

IJPSM

Atul Pal *et al*, Int. Journal of Pharmaceutical Sciences and Medicine (IJPSM),
Vol.8 Issue. 6, June- 2023, pg. 57-72

ISSN: 2519-9889
Impact Factor: 5.9

Fig. 1 HPLC Chromatogram of Related Substances Test - Blank

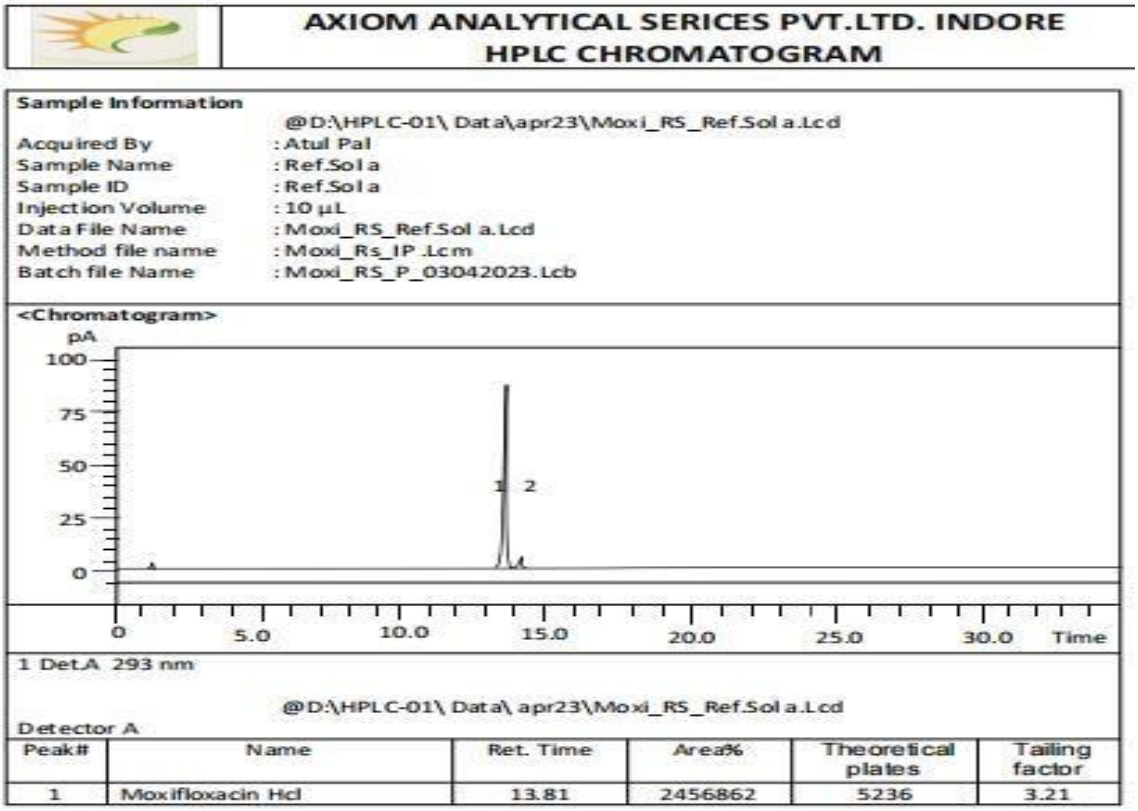


IJPSM

Atul Pal *et al*, Int. Journal of Pharmaceutical Sciences and Medicine (IJPSM),
Vol.8 Issue. 6, June- 2023, pg. 57-72

ISSN: 2519-9889
Impact Factor: 5.9

Fig.2HPLC Chromatogram of Related Substances Test - Ref Sol a



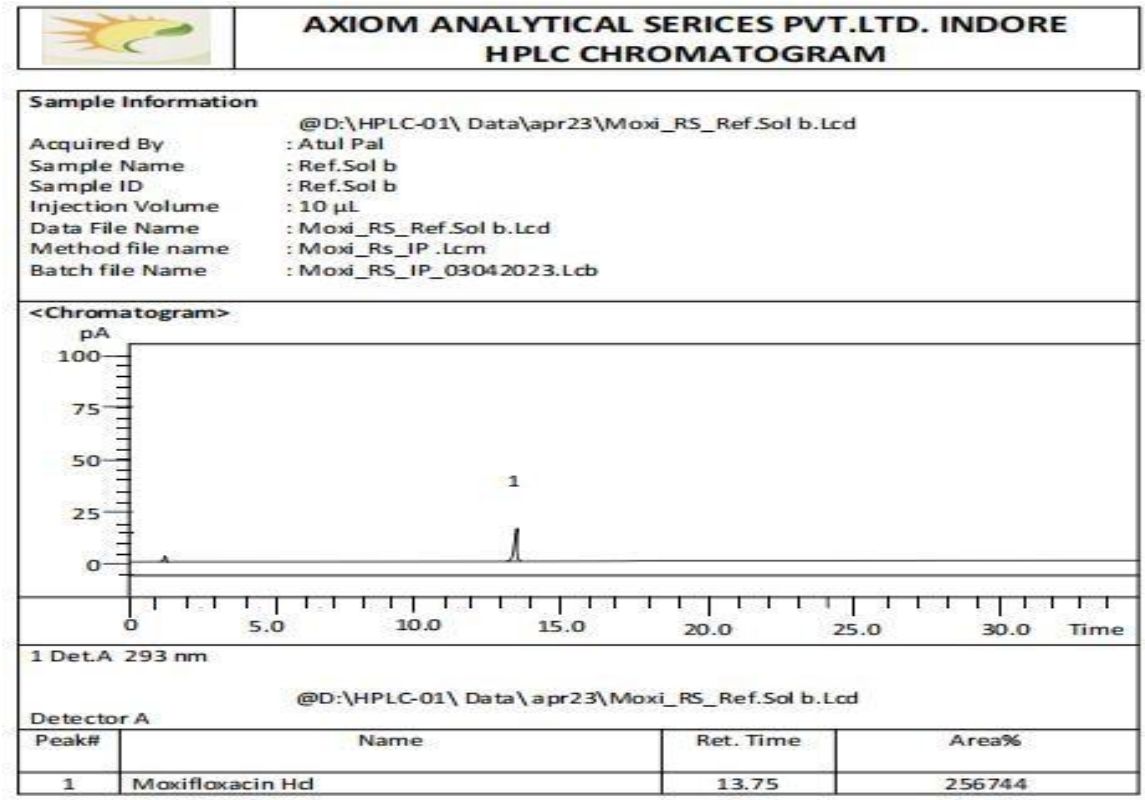
Peak#	Name	Ret. Time	Area%	Theoretical plates	Tailing factor
1	Moxifloxacin Hcl	13.81	2456862	5236	3.21

IJPSM

Atul Pal *et al*, Int. Journal of Pharmaceutical Sciences and Medicine (IJPSM),
Vol.8 Issue. 6, June- 2023, pg. 57-72

ISSN: 2519-9889
Impact Factor: 5.9

Fig.3 HPLC Chromatogram of Related Substances Test - Ref Sol b



IJPSM

Atul Pal *et al*, Int. Journal of Pharmaceutical Sciences and Medicine (IJPSM),
Vol.8 Issue. 6, June- 2023, pg. 57-72

ISSN: 2519-9889
Impact Factor: 5.9

Fig. 4 Assay Calculation Sheet Moxifloxacin Hcl

Axiom Analytical Services														
Moxifloxacin Hcl														
SHEET ID - AASRA/SHEET/009/00														
Parameter - : Assay														
W.Std .A.R.No.	1182													
W.Std. Potency %	99.50													
W.Std. weights	50.1		mg -->	50 mL	2mL-->	20	mL		Sample Wt	50.2	mg ---->	50	mL	
Product / B.No.	Pantoprazole-01									2.0	---->	20	mL	
Standard Injection_01	2512412			Area of Sample Solution Injection_1					2502456					
Standard Injection_02	2509856			Area of Sample Solution Injection_2					2501472					
Standard Injection_03	2508896					Avg Area			**2501964**					
Standard Injection_04	2512421													
Standard Injection_05	2499588													
Avg. Area of Standard	**2508635**													
SD	5292													
RSD %	0.21													
Sample Aera	x	Standard Weight	x	2	x	50	x	20	Poteny	x				
Avg. Standard Area		50		20		Sample Weight		2	100		100			
Assay on As Is Basis %		**99.04**												

- 4. IDENTIFICATION OF CRITICAL PARAMETERS : In the manufacturing process of Moxifloxacin Hydrochloride the following stage are identified as Critical Process Parameters.

Table-2 Critical Process Parameters

Stage	**Operation Number**	**Critical Process Parameters**	**Standard Condition**	**Justification**
Stage I	4 to 5	Reaction Temperature during Addition	30 **°C** - 52 **°C**	During addition of boric acid the reaction is exothermic.The temperature below 30 °C the reaction does not complete and if temperature exceeds than 52 °C the degradation of reaction mass may be observed

ISSN: 2519-9889
Impact Factor: 5.9

CONCLUSION

Conclusion the way Raw-materials and a variety of parameters are related with Finished Product Moxifloxacin Hydrochloride must be capable of delivering a product of appropriate quality on a commercial scale. This study aimed to present a risk-based approach to evaluate the scope of process validation activities in RINI Life Science Through the use of the risk tools, an objective assessment of potential uncertainties and their effect on products` critical quality attributes were evaluated and organized to make the most optimal decisions. Furthermore, the described approach risk-based also provided a consistent methodology for decision making which was easily aligned with Rini Life science goals such as resources allocation and ensuring patient safety and quality products; by building quality into processes and consequently into products. Ultimately, through the consistent use of statistic tools to monitor the variation and maintain processes in state of control along product life cycle, the number of surprises and their impact will be minimized. The goal of this work was achieved. Assess to products risk framework will be provided to production teams during Process Performance qualification and over products life cycle based in scientific rational by using recognized language, structure and tools.

Certainly, the work described in this thesis has provided additional insights into what is already known about Active Pharmaceutical Ingredients Process Validation based on Risk Assessment in Rini Life science Pvt.Ltd. Optimization and improvementof Rini Life Science risk based tools, methods of analyses and procedures will lead the company to higher levels of quality and compliance.

REFERENCES

[1]. Guidance for Industry Process Validation: General Principles and Practices, Indian Pharmacopoeia, 2022

[2]. Guidance for Industry Process Validation: General Principles and Practices U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) Center for Veterinary Medicine (CVM) January 2021 Current Good Manufacturing Practices (CGMP) Revision 1.

[3]. Guideline on process validation for finished products - information and data to be provided in regulatory submissions, 21 November 2016 EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1

[4]. (ICH)International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use ICH harmonised tripartite guideline development and manufacture of

ISSN: 2519-9889
Impact Factor: 5.9

drug substances (chemical entities and biotechnological/biological entities) q11 current step 4 version dated 1 may 2012

[5]. Guidance for Industry: Process Validation: General Principles and Practices. U.S. Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER), Centre for Biologics Evaluation and Research (CBER), Centre for Veterinary Medicine (CVM), January 2011.

[6]. Oechslein C, Lazar M. S – Process Validation from view report of the FDA, Maas & Peither AG – GMPPublishing, LOGFILE No. 3/ February 2012.

[7]. Quality Management System – Process Validation Guidance GHTF/SG3/N99-10:2004 (Edition 2).

[8]. Nash R. A and Wachter A. H, Pharmaceutical Process Validation an International Third Edition. Revised and expanded, Marcel Dekkar, Inc., New York, 2003; 17 – 40. https://doi.org/10.1201/9780203912119

[9]. Patel R. C, Bhuva C. K, Singh R. P, Dadhich A, Sharma A., - Pharmaceutical Process Validation, Pharmatutor – ART – 1053.

[10]. Kathiresan K*, Moorthi C, Prathyusha Y, Gade B. R, Reddy B. K, Manavalan R, An overview of pharmaceutical validation; Research Journal of Pharmaceutical, Biological and Chemical Sciences; 2010;1(4):1026.

[11]. Pharmaceutical Process Validation: Guide to Inspections of Oral Solid Dosage Forms pre/post Approval Issue for Development and Validation; issue (1/94); January, 2010.M8.

[12]. Green JM. A Practical Guide to Analytical Method Validation, Anal. Chem. News and Features 1996; 60:305A-9A. https://doi.org/10.1021/ac961912f

[13]. Akers, J. Simplifying and improving process validation. J. Parent. Sci. Technol. 1993, 47, 281–284. 10. Avallone, H.L.; D"Eramo, P. Scale-up and validation of ANDA/NDA products. Pharm. Eng.1992, 12 (6):36–39.

[14]. Chowhan, Z.T. Development of a new drug substance into a compact tablet. Pharm. Technol.1992, 16 (9):58–67.

[15]. Nash RA. Process Validation of a 17-Year retrospective study of solid dosage forms Drug DevInd Pharm1966; 22 (1):25-34. https://doi.org/10.3109/03639049609043869

[16]. Therapeutics Products Programme. Process Validation: Aseptic Processes for Pharmaceuticals. http://www.hcsc.gc.ca/hpbdgps/therapeutic; downloaded March 30, 2001.

[17]. Lambert J. Validation Guidelines for Pharmaceutical Dosage Forms. Health Canada / Health Products and Food Branch Inspectorate; 2004. pp. 7-15.

[18]. Gupta GD, Garg R, Aggarwal S. Guidelines on General Principles of Validation: Solid, Liquid and Steriledosage forms. Pharm Sci Tech, 2008; 6:28-33

[19]. Dashora K, Singh D, Saraf S. Validation – the Essential Quality Assurance Tool for Pharma Industries. Pharminfo, 2005; 3:45-47.

[20]. FDA Guidance Update: process Validation: General Principles and Practices; version 01; 2009.

[21]. Validation Master Plan Installation and Operational Qualification – Pharmaceutical Inspection Convention; Pharmaceutical Inspection Co-Operation Scheme; PI 006 – 2; July, 2004.

[22]. Kiffer,R.G, J. Pharma. sic. tec., 1995, 44, 5, p.249.

[23]. Kumar NL, MoorthyDG, Kumar RS, Sekaran CS. An overview of pharmaceutical validation: qualityassurance view point, 2011; 1(4):1003-1014.

[24]. Agalloco J. The validation life cycle. J ParenterSci Technol. 1993; 47(3):142-147.

[25]. Sharp JR. The Problems of Process Validation. Pharm J 1986; 1:43- 5.

[26]. *Applying Process Systems Engineering for Continuos Improvement in Pharmaceutical Production.* **Sugiyama, Hirokazu, et al. 2013.** Kuala Lumpur : 6th International Conference on Process Systems Engineering(PSE ASIA), 2013.

[27]. Berardinelli, Carl. 2013. A guide to Control Charts. *i Six Sigma.* [Online] 18 deFebruary de 2013 [2013 October 27] http://www.isixsigma.com/tools- templates/control-charts/a-guide-to-control-charts/.

[28]. **B**rindle, Alex, et al. 2012. Risk Analysis and Mitigation Matrix (RAMM) - Risk Tool for Quality Management. Official Magazine of ISPE; Reprinted from Pharmaceutical Engineering. January/

ISSN: 2519-9889
Impact Factor: 5.9

February de 2012, Vol.32 No.1.

[29]. Comprehensive review on aseptic fill/finish manufacturing as per regulatory guidelines. Chaurasia, Sandhya, et al. 2011. Bhopal, India : Medipoeia, 2011, Journal of Current Pharmaceutical Research, Vols. 5 (1):19-27.

[30]. Deeks, Trevor. 2006. PDA Training Course - "Risk-Based Approach and Risk Management in Pharmaceutical Manufacturing". London : Skanska Pharmaceutical Group, 2006.

[31]. Grunemberg A, Bosché P. Crystal modification of CDCH a process for its preparation and pharmaceutical formulations comprising this modification. US Patent 1998;5:849,752 A.

