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Case Report

Implementation of Quality Risk Management for Manufacturing of a Non-Sterile Pharmaceutical Product- Case study

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Abstract

This article will address a model for implementation of quality risk management for the manufacturing of a non-sterile product through a real case. The risk addressed in the article is the microbiological contamination and the procedure followed was Failure Mode Effect Analysis (FMEA) mainly. It can be used by pharmaceutical scientist to evaluate the possible causes of microbiological contamination of their products and will show how to evaluate the risks and describe a monitoring plan based on the associated risks

Keywords: Pharmaceutical microbiology; Quality risk management; Pharmaceutical manufacturing; Microbial contamination

Introduction

The holder of a manufacturing authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorisation and do not place patients at risk due to inadequate safety, quality or efficacy [1]. As Per ICH Q9, Quality Risk Management, "Risk management is the systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk [2].

To protect patients in terms of quality, safety and efficacy of medicines, international medicines regulatory authorities (MRAs) are recommending pharmaceutical manufacturers to adopt a risk-based approach to the life-cycle of a pharmaceutical product [3]. The quality risk management system should ensure that [4]. The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient; the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

Procedure

The following procedure will be used to perform the risk assessment (the risk addressed is the microbial contamination of a non-sterile product).

A. First step is to develop a process flow chart to fully describe the manufacturing process

B. Second step is to form a project team

C. A Cause & Effect (Fishbone) diagram will be prepared by the team (using the process flow chart) to evaluate the possible causes of microbial contamination.

D. FMEA will be developed by the team (using the prepared Cause & Effect diagram) to evaluate the risk associated with different factors (Raw materials, Packaging materials, Utilities, etc.)

E. Pareto diagram will be used to highlight the most critical factors that may lead to microbial contamination of the product (using the developed FMEA)

F. Finally, a monitoring plan will be developed to insure that all the identified high risk factors are monitored frequently to insure the risk (microbial contamination risk) is controlled

Implementation of a risk management process

Identify process by plotting the process (Figure 1) [5].

Formation of the project team

The team should be composed of to reflect all function that could have a decision influence on quality or compliance

The team will include product-specific knowledge and expertise

The team will include:

A. The Quality Director

B. The Microbiology manager

C. The production manager

D. The engineering manager

E. The validation manager

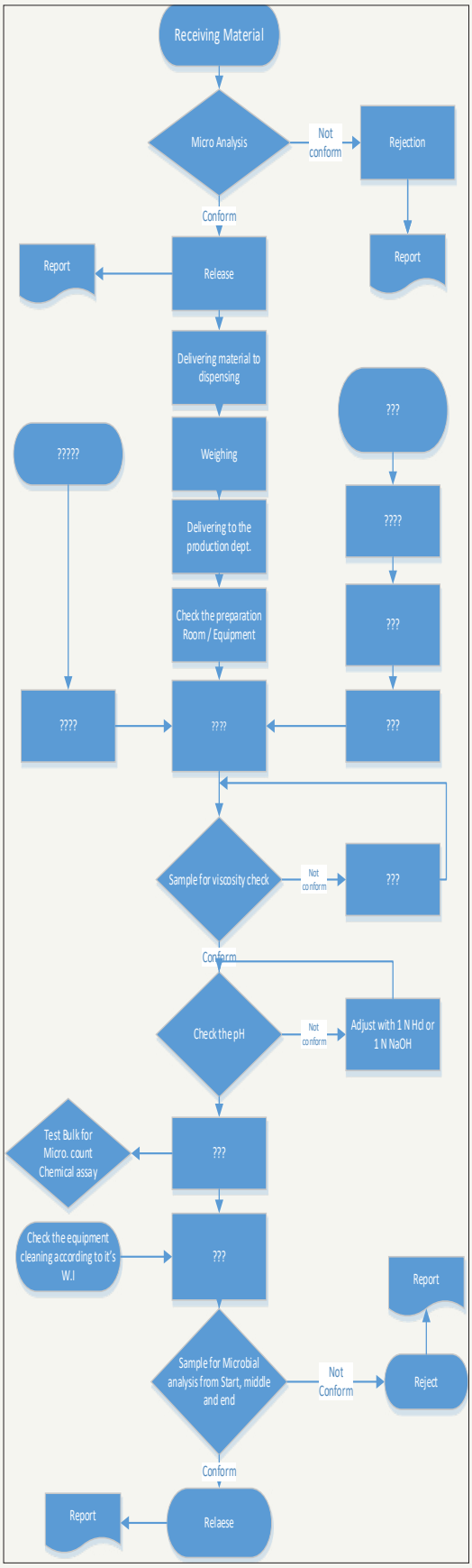

Figure 1

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The team will be responsible for:

A. Conduct a hazard analysis

B. Identify potential hazards

C. Identify hazards which should be controlled

D. Recommend controls and critical limit

E. Devise procedures for monitoring and verification

F. Recommend appropriate corrective action where deviations occur

Methods of risk assessment

One of the most common used methods is Fish –bone diagram which summaries all critical influencing variables on the product quality [6,7]; (Figure 2).

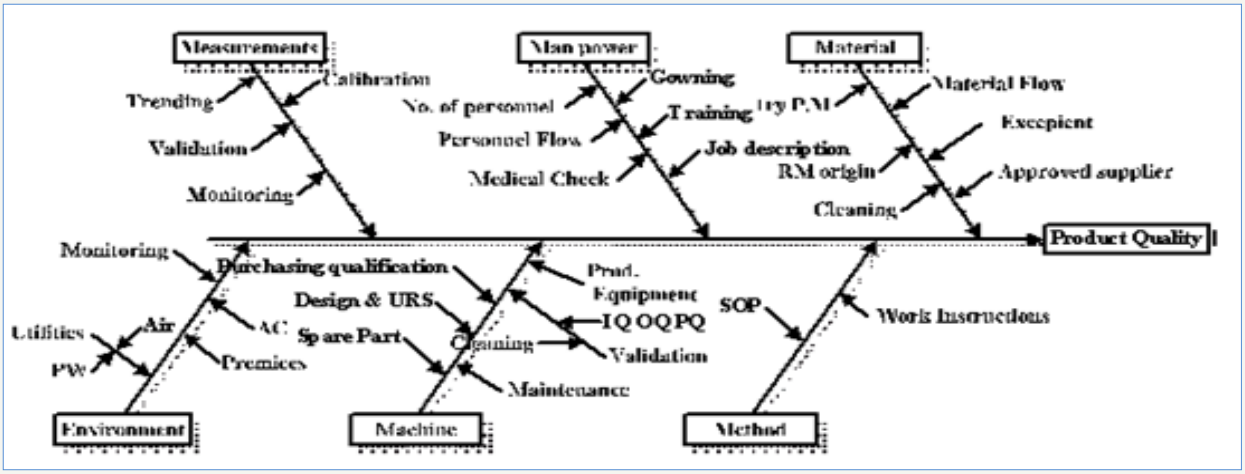

Figure 2: Cause & Effect Diagram.

Determining the risk ranking (using Pareto chart)

Vilfredo Pareto was an Italian economist who lived from 1848to 1923. His study of the wealth distribution in the Italian economy yielded a key finding that 80% of the land was owned by 20% of the population. Since then, his discovery what we call the Pareto principle has been found to hold true in many other situations. For problem solvers, the simple Pareto principle provides a powerful root cause analysis (RCA) tool to separate the vital few factors from the trivial many determining risk ranking for Raw materials & Primary Packaging materials using the Pareto Chart.

Risk assessment using FMEA [8,9]

Risk ranking policy

(Tables 1-7)

Table 1: The Product.

	Product Description	Raw Materials & Qty.	The Intended Use
	Code	Quantity	
The product name is XYZ	RM 1	73 kg	Treatment and prophylaxis of infectious diseases such as
1. Pityriasis versicolor,			
2. seborорhoeic dermatitis			
3. pityriasis capitis			
XYZ is a synthetic imidazole dioxolane derivative with fungicidal properties.	RM 2	32 kg	
A plastic bottle containing 60 ml.	RM 3	3.2 kg	
The product is intended for external use.	RM 4	3 kg	
The following table showing the batch components of XYZ shampoo.	RM 5	1.5 kg	
	RM: Raw material		

Table 2: The following table showing scoring policy.

S.No	Probability	Severity	Detection
1	Extremely Unlikely	None	Extremely Likely
2	Low Likelihood	Minor	High Likelihood
3	Medium Likelihood	Moderate	Medium Likelihood
4	High Likelihood	High Severity	Low Likelihood
5	Extremely Likely	Maximum Severity	Extremely Unlikely

Table 3: The following table showing Ranking policy.

Risk Priority Number(RPN)	Class
1-12	Low
13-27	Moderate
28-125	High

Table 4: Risk Assessment for Raw Materials & Packaging Material.

	Hazard	Reason	Probability	Severity	Detection	RPN	Class
Raw materials	RM1	Potential contamination hazard	4	4	3	48	H
	RM2	Potential contamination hazard	4	4	3	48	H
	RM3	Potential contamination hazard	2	4	3	24	M
	RM4	Potential contamination hazard	2	4	3	24	M
	RM5	Potential contamination hazard	1	4	3	12	L
Packaging Materials	Bottle	Potential contamination hazard	4	4	3	48	H
	Cap	Potential contamination hazard	2	4	3	24	M
	RPN: Risk Priority Number, H: High, M:medium, L: low						

Table 5: Risk Assessment of different processes.

Hazard	Reason	Probability	Severity	Detection	RPN	Class
Receiving material	Contamination through damaged containers	1	4	2	8	L
Sampling for micro analysis	Contamination during sampling procedure	2	4	2	16	M
Delivering RM to dispensing	Contamination during delivering	2	4	2	16	M
Dispensing	Contamination during the dispensing	3	4	3	36	H
Delivering RM to production	Contamination during transfer	2	4	2	16	M

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Compounding process	Contamination during compounding	3	4	4	48	H
Filling process	Contamination during the filling	4	4	5	80	H
RPN: Risk Priority Number, H: High, M:medium, L: low						

Table 6: Risk Assessment of different Utilities, Equipments and machines.

Hazard	Reason	Probability	Severity
Purified Water	Contamination through low micro. quality	3	4
Compressed Air	Contamination through low micro. quality	2	4
Different production machines.	Contamination by unclean machine	3	4
The filling machine	Contamination during the filling	2	4
Connection of tank & machine	Contamination through connection	2	4

Table 7: Risk Assessment of different premises.

Hazard	Reason	Probability	Severity	Detection	RPN	Class
Dispensing Area						
Air	Poor air quality	3	4	5	36	H
Personnel	Lack of training,	2	4	3	24	L
	Uncontrolled Gowning.	1	4	2	20	L
Cleaning	Inefficient cleaning program	1	4	3	12	M
Production Rooms (Compounding & Filling)						
Air	Poor air quality	3	4	3	36	H
Personnel	Lack of training,	2	4	3	24	M
	Uncontrolled Gowning.	1	4	5	20	L
Cleaning	Inefficient cleaning program	1	4	3	12	M
RPN: Risk Priority Number, H: High, M:medium, L: low						

Determining the risk ranking (using Pareto chart)

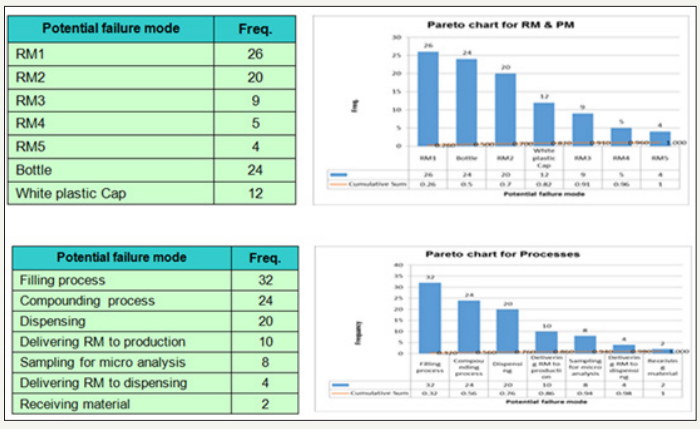

Figure 3:Determining Risk Ranking for different Processes using the Pareto Chart.

Vilfredo Pareto was an Italian economist who lived from 1848 to 1923. His study of the wealth distribution in the Italian economy yielded a key finding that 80% of the land was owned by 20% of the population. Since then, his discovery what we call the Pareto principle has been found to hold true in many other situations. For problem solvers, the simple Pareto principle provides a powerful root cause analysis (RCA) tool to separate the vital few factors from the trivial many [10]. Determining Risk Ranking for Raw materials & Primary Packaging materials using the Pareto Chart [11,12]; (Figure 3).

Conclusion

Using the QRM the following monitoring plan was developed which can be considered an effective monitoring plan. The developed plan is highly effective as it will monitor the most critical factors that may cause microbial contamination in a non-sterile product and it found to be a cost effective plan as it will eliminate monitoring the factors that will not affect the product quality (Table 8).

Table 8:

Risk Factor	Monitoring Plan
RM 1	Microbial testing for each lot received
RM 2	Microbial testing for each lot received
Bottles	Microbial testing for each lot received
Dispensing	Environmental monitoring of the dispensing area on weekly basis
Compounding	Environmental monitoring of the compounding area on weekly basis
Filling process	Environmental monitoring of the filling area on weekly basis
Purified water	Microbiological testing of purified water used in the preparation of the product or the cleaning of surface come in direct contact with the product on weekly basis
Different production machines	All machines/ equipments that come in direct contact with the product to be included in the cleaning validation program
Air	Air quality in compounding area, filling area & dispensing area should be tested for microbiological quality on weekly basis

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