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Review Article

Viable Monitoring During the Filling of a Terminally Sterilized Pharmaceutical Product-Risk Based Approach

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Abstract

This article addresses a risk based approach to establish a routine monitoring program of viable (I.e. microorganisms) in a controlled environment used to produce pharmaceutical products that are intended to be terminally sterilized. Current applicable quality system regulation & GMP require appropriate environment to be established, maintained and monitored for the manufacturing of the terminally sterilized pharmaceutical meanwhile the appropriate environmental monitoring plan is not clearly specified & a risk based approach will be a valuable tool to design a suitable program

Introduction

Current regulatory environment emphasize on the use of enhanced knowledge over the manufacturing processes & product performance that can help in identifying the risks associated to the patient safety & the product quality. This article will describe briefly the Quality risk management & apply its elements on a model which is the Environmental monitoring during the filling of terminally sterilized products [1]. Such approach will insure the following

A. Product quality and patient safety

B. Meeting the regulatory expectations

C. Minimize the manufacturing cost through minimizing the monitoring frequencies.

The following procedure will be followed during the Risk assessment procedure

A. Identify The process

B. Identify Risk

C. Implement Risk Assessment

D. Determination of the RPN (Risk Priority Number)

E. Establish the monitoring frequency according to the determined RPN

Procedure

Identify the process

High flow chart for the manufacturing process of the terminally sterilized products:

Identify risk

Risk factors: The following factors represent the variables to be considered during the risk assessment process:

A. Risk factor (A): Amount of microbial contamination on, or in, a source.

B. Risk factor (B): Ease of dispersion, or transfer, of microorganisms

C. Risk factor (C): Proximity (location) of source from critical area.

D. Risk factor (D): Effectiveness of control method.

Table 1:

Variable	Very Low	Low	Normal	High	Very High
Risk factor (A) Amount of microbial contamination on, or in, a source	1-2 (Class A)	3-4 (Class B)	5-6 (Class C)	7-8 (Class D)	9-10 (Non -Classified)
Variable	Very Difficult	Difficult	Normal	Easy	Very Easy
Risk factor (B) Ease of dispersion, or transfer, of microorganisms	1-2	3-4	5-6	7-8	9-10

Variable	Too far	Away	Average	Near	Very Near
Risk factor (C) Proximity (location) of source from critical area	1-2 -3 rooms away from the filling rooms. Ex. Gowning Room.	3-4 -2 rooms away from the filling rooms. Ex. Air Lock #55	5-6 -Rooms Adjacent to filling rooms. Ex. Air lock #59'	7-8 -Filling Rooms. Ex. Vial filling Room	9-10 -Filling Machines. Ex. Vial Filling Machine.
Variable	Very Effective	Effective	Average	Low efficacy	Ineffective
Risk factor (D) Effectiveness of control method	1-2	3-4	5-6	7-8	9-10
Scores	8	256	1296	4096	10000
Sq. Root	4	16	36	64	100
Monitoring	Monthly	Weekly	Twice per week	Daily	Continuous

Risk numbering: The following table showing the risk numbering procedure (Table 1)

Risk priority number (RPN) determination: The RPN shall be determined by multiplying the risk number of the four variables [2]: (Figure 1)

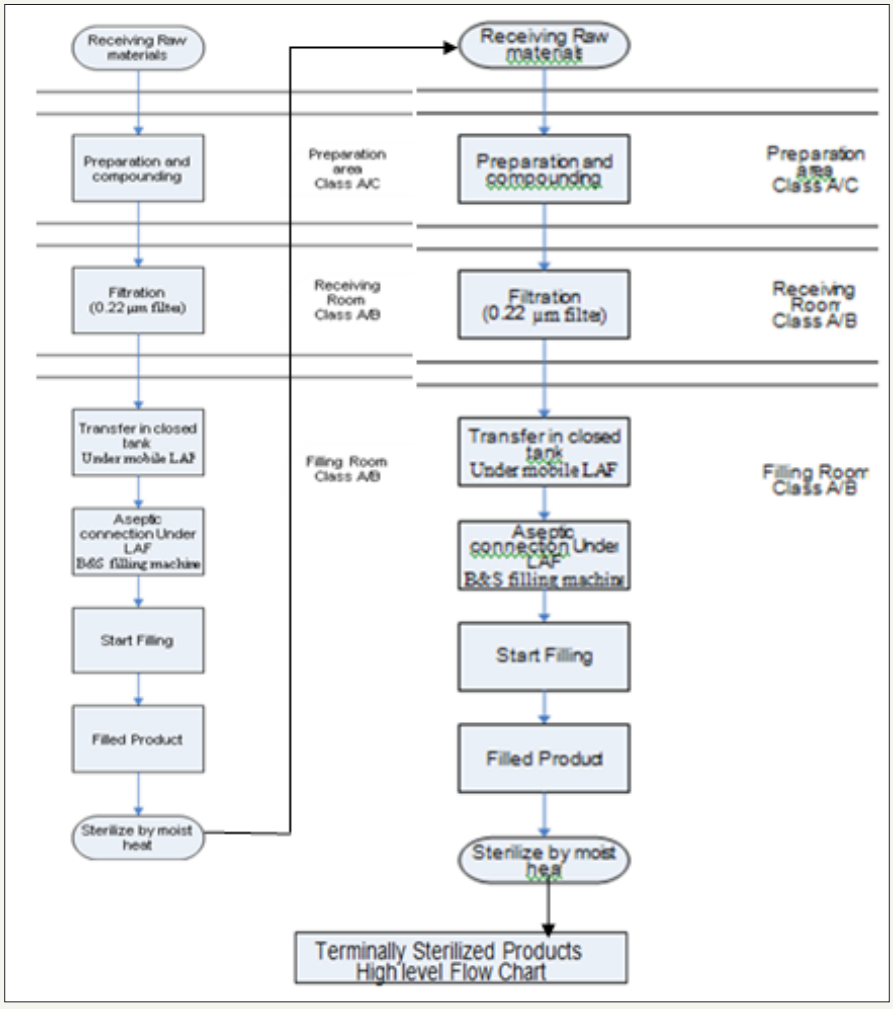

Figure 1:

RPN= Risk factor (A) * Risk factor (B) * Risk factor (C) * Risk factor (D)

Monitoring frequency according to the determined RPN: As a safety factor the frequencies shall be determined [3] according to the square root of the determined RPN: The following table showing the environmental monitoring frequencies according to the determined RPN [4]: (Table 2)

Table 2:

RPN	Square Root	Frequency
1-16	≥4	Monthly (cover a part of the process)
17-256	≥16	Weekly (cover a part of the process)
257-1296	≥36	Twice per week (cover a part of the process)
1297- 4096	≥64	Daily (cover a part of the process)
4097-10000	≥ 100	Contentious (cover the whole process)

Table 3:

Variable	Evaluation	Score
Risk factor (A) **Amount of microbial contamination on, or in, a source**	**Very Low** **As the product is filtered through 0.22 μm filter**	**1**
Risk factor (B) **Ease of dispersion, or transfer, of microorganisms**	**Very Difficult** **As the prod received to sterile closed container and transferred Under Mobile LAF**	**1**
Risk factor (C) **Proximity (location) of source from critical area**	**Far** **2rooms away from the filling rooms.**	**2**
Risk factor (D) **Effectiveness of control method**	**Very Effective** **A. Manufacturing Area Qualified** **B. Sterilization cycles validated** **C. HEPA filter Integrity Tested** **D. Differential pressure drop Alarm installed** **E. Effective cleaning and disinfection procedure (Historical Environmental Mentoring Data)**	**1**
Score (RPN) = 1 *1*2*1		**4**
Monitoring		**Monthly**

Table 4:

Variable	Evaluation	Score
Risk factor (A) Amount of microbial contamination on, or in, a source	Very Low As the product is filtered through 0.22 μm filter Filling under LAF Machine parts sterilized, sterilization cycles validated Empty dehydrogenated. Depyrogenation cycles validated Very Low	1
Risk factor (B) Ease of dispersion, or transfer, of microorganisms	Very Difficult Filling under LAF Filling Machine located in class B area	1
Risk factor (C) Proximity (location) of source from critical area	Very Near Filling Machines	9

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Risk factor (D) Effectiveness of control method	Very Effective	1
	Manufacturing Area Qualified	
	Sterilization cycles validated	
	HEPA filter Integrity Tested	
	Differential pressure drop Alarm installed	
	Effective cleaning and disinfection procedure (Historical Environmental Mentoring Data)	
	Regular media fill challenges	
	Qualified Personnel	
	Successful media fill challenge through the past years.	
	The products sterilized in its final container	
Score (RPN) = 1*1*9*1		9
Monitoring		Weekly

Risk assessment of the receiving process: Evaluation of impact of the environment on the product quality (Microbiological safety) during [5] the Receiving process: (Table 3) and Evaluation of impact of the environment on the product quality (Microbiological safety) during the Filling process [6]: (Table 4)

References

1. (2008) ICH Q9, Pharmaceutical Quality System, ICH Harmonised Tripartite Guideline.
2. (2008) Technical Report 44. Quality Risk Management for Aseptic Processing. PDA J Pharm Sci Technol 62: (S1).
3. (2012) Technical Report No. 30 (Revised 2012): Parametric Release of Pharmaceutical and Medical Device Products Terminally Sterilized by Moist Heat, Parenteral Drug Association.
4. (2012) General Chapter <1116> Microbiological Control and Monitoring of Aseptic Processing Environments. USP 36/NF 31; US Pharmacopeia, USA.
5. Eudra (2008) The Rules Governing Medicinal Products in the European Union: EU Guidelines to Good Manufacturing Practices for Medicinal Products for Human and Veterinary Use-Annex 1, Manufacture of Sterile Medicinal Products; European Commission, Belgium 4:
6. Moldenhauer J. Environmental Monitoring, A Comprehensive Handbook. Parenteral Drug Association 1(2):