Original Article

Risk Assessment of Clean Room Used in Pharmaceutical Industries in Design, Manufacturing, Equipping and Operating Phases by FMEA Based on Some Chemical Engineering Concepts

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Abstract

A clean room is an environment commonly used in sensitive production lines, such as pharmaceuticals, food and so on, where dust, aerobic microbes, particulates and chemical vapors are kept in a low and controlled environment. In this applied and new paper, for the first time, the assessment of the significant risks associated with the possible modes of risk in the design, construction, equipping and operation phases of a clean room, together with the risk factors and their consequences and effects, is investigated by the FMEA method. Preventive and control measures are suggested to mitigate the effects of the risks. In addition, risk numbers are calculated before and after preventive measures. It was founded that by taking appropriate and effective control measures (especially in the design and construction of a clean room), the risks could be significantly and effectively reduced. By taking precautionary measures, the risk numbers were reduced by 50% in each case, which halved the risk of occurrence.

Keywords: Risk Assessment, Clean Room, Pharmaceutical Industries, Chemical Engineering, FMEA

Introduction

A clean room is a closed room or environment that is controlled by various parameters such as particles, temperature and air pressure, etc. The most important feature of a clean room is pollution control, and is therefore essential in industries that require pollution-free space. The definition of a clean room according to ISO 14644-1 is as follows: A room where the concentration of airborne particles is controlled and used as a way to minimize the entry and production and storage of materials in the constructed room and other relevant parameters such as temperature, humidity and pressure are controlled to the required extent [1]. According to E Federal Standard 209, a clean room is referred to as a room where the concentration of particles in the air is controlled to a certain extent [2]. The clean room is used in various industries such as medical, pharmaceutical, chemical, agricultural, biology, etc. [3]. The main feature of a clean room is its pollution control. Different industries require air with varying degrees of cleanliness and clean air is defined by varying degrees of cleanliness. This classification varies according to different standards [4].

Air cleaning technologies have become more commonly utilized in industrial applications following a rapid advancement in science and technology. There is a high volume of airflow rate and high air distribution resistance by multistage filtration often in cleanrooms [5].

One of the most common and effective methods for identifying, classifying, analyzing and evaluating risks is the FMEA method. The FMEA method was first used to analyze various issues related to errors and their different states in industries such as automobiles, and after being proven to different capabilities and functions for researchers, was also applied in software industries [6]. The FMEA method is a systematic approach that, in addition to identifying hidden and obvious flaws and errors in the process, seeks to correct them by taking the correct measures. This method focuses on preventing flaws and enhancing immunity. On the other hand, FMEA reduces costs by optimizing processes. One of the

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most important features of FMEA is pre-accident preventive action rather than post-incident reactive action [7]. In this new and applicable paper, we first discuss the clean room risk assessment used in the pharmaceutical industry by the FMEA method in the design, manufacture, equipping and operation phases based on some concepts of chemical engineering.

Methods

FMEA:

The intensity of each of the risks is expressed based on Table 1 (defect intensity). The criterion for selection of the intensity index is determined based on the highest frequency. The obtained results in the intensity column (S) would be added to the risks analysis record sheet. Then, the occurrence of this incident would be determined based on Table 2, accordingly. These data also would be recorded in the risk analysis form.

Table 1: risk intensity (defect)

degree	Intensity (S)
1	trivial
2	low
3	serious
4	Critical
5	Disastrous

Table 2: risk occurrence probability

Row	Occurrence
1	Impossible
2	Unlikely
3	Sometimes
4	Probable
5	Repetitive

The risk index abbreviated as RIN is obtained from the multiplication of defect effect intensity (S) by the defect occurrence probability (O) which should be compared to the allowed rate of risk as shown in Table 3 (5).

$$RIN = S \times O \qquad (1)$$

Table 3: risk matrix

			Intensity				
			Trivial	Low	Serious	Critical	**Disastrous**
			1	2	3	4	**5**
Occurrence probability	Impossible	1	1	2	3	4	**5**
	Unlikely	2	2	4	6	8	**10**
	Sometimes	3	3	6	9	12	**15**
	Probable	4	4	8	12	16	**20**
	Repetitive	5	5	10	15	20	**25**

The risks that are acceptable have a number below 5. If the calculated risk is lower than the accepted number, the risk is acceptable and if the risk is greater, the risk is unacceptable and corrective or preventive actions must be taken to eliminate or reduce the risk. The correction actions continue until the risk analysis team recognizes the risk as acceptable. The reason for choosing low number 5 for risk acceptance is the high sensitivity of the clean room to pollution and pollution control.

Results and Discussion

The results of the risk analysis are shown in Table 4.

Table 4: Risk Assessment Table with FMEA Method

FMEA											
Action Results			Preventive and control measures	Risk (RIN)	Probability (O)	Severity (S)	Causes	Effects	Hazards	Phase	Row
RIN	OCC	SEV									
5	1	5	Design of auxiliary / adjacent air flow and forced displacement of contaminated air and discharge	10	2	5	Contaminant sources in clean room	Mass transfer of pollutants to bulk materials and products	Clean room contamination	Design - Air flow direction	1
5	1	5	Turbulent air flow / turbulent with high Reynolds number (Re) and then diluting polluted air with clean air	10	2	5	Contaminant sources in clean room	Mass transfer of pollutants to bulk materials and products	Clean room contamination	Design - Air flow direction	2

4	1	4	*Application of multi-step Nano-filters with very high absorption power. *Differentiate pressure in clean room * Sealing gaps	8	2	4	External pollution enters through the bottom and margins of doors, joints and gaps	Increased likelihood of mass transfer of contamination to bulk materials and products	Contamination mass transfer from the outside into the clean room	-Design & Operations -To prevent the entry of contaminated outside air into the clean room	3
4	1	4	-System design to increase circulation and forced air circulation to prevent contamination. - Re-filtration of clean room air to make the air cleaner and more refined -Clean room clothes Made of non-laminated polyester fibers and carbon fiber / rubber type anti-slip and rubber shoes -Clean the materials before entering the clean room	8	2	4	-Levels of pollutant production -Vapors caused by interactions and chemical interactions between different substances. -Cleaning - Staff skin and clothing level	Increased likelihood of mass transfer of contamination to bulk materials and products	Pollution due to sources of contaminants inside the clean room	Design and Operations - Minimize internal pollution	4
3	1	3	Floors / walls and ceilings should be made of impermeable hard materials. Covered joints should be welded	6	2	3	To be - permeable surfaces such as floors / walls and ceilings - Openness junction	Clean room space pollution	-Material shedding - Leakage of liquids	Design - Manufacturing and Operations	5
3	1	3	Design and construction of pressure corridor or air valve	6	2	3	The absence of two interconnecte d doors	Increase the likelihood of mass transfer of contamination from outside into the clean room	A sudden influx of air when you open the door into a clean room	Design - Manufacturing and Operations	6
3	1	3	-Using stainless steel table and multilayer - Mount the tables on the wall	6	2	3	The use of single-layer table and the table is not connected to the wall	-Removing the connection clamps - Dust and pollution	Destruction of the surface and substrates of the joining table due to chemical interactions between some chemically active substances and the monolayer metal surface	Design - Manufacturing and Operations	7
3	1	3	The use of impermeable, comfortable and adjustable washable chair	6	2	3	Use of inappropriate and permeable armchair material	Increasing and spread of microbial and chemical contaminants	-Dust and contamination absorption inside the chair - Its destruction due to the penetration of certain chemicals into it	Equip- Operation	8
3	1	3	Trolley with stainless steel and cleanable	6	2	3	To use the trolley - Transportatio	Increasing and distribution of contamination in	-The interaction of chemicals between metal	Equip-Operations	9

							n of bulk materials and finished product - Inappropriate metals	clean room environment	surfaces with chemicals		
4	1	4	Design and construction of separate two way transmission valve system for entry and exit of objects	8	2	4	Absence of separate two way transmission valve system for entry and exit of objects	Increased likelihood of transmission of contamination to the production line	Clean room environment pollution	Design - Manufacturing and Operations	10
4	1	4	Lack of edge in design and construction	8	2	4	Edges in design and construction of clean room	Increased likelihood of mass transfer (both free and forced) contamination to the production line	Dust accumulation	Design - Manufacturing and Operations	11
3	1	3	Deployment of process equipment in appropriate locations without being in the air flow path	6	2	3	Deployment of process equipment in the air flow path \	Increased likelihood of mass transfer of contamination in clean room space	Disruption of airflow in clean room and proper air circulation	Design-deployment of equipment	12
2	1	2	Use compact insulators in the design and manufacture of clean room air conditioners	4	2	2	Lack of proper compact insulation in the design and manufacture of clean room air conditioner	Increased costs due to energy loss	Heat transfer and heat dissipation	Design and construction	13
3	1	3	covering the air conditioner inner seams with suitable materials	6	2	3	not covering the air conditioner inner seams with suitable materials	Increased chance of bacterial mass transfer and contamination to clean room space	Bacterial accumulation	Design and construction	14
2	1	2	Use of appropriate UV lamps in the air conditioner	4	2	2	No use of UV lamps in the air conditioner	Increasing the chance of bacterial mass transfer and contamination into the clean room	Bacterial growth and inadequate lighting	Design and construction	15
2	1	2	use of thermal profiles Has an arc in air conditioner	4	2	2	No use of thermal profiles Has an arc in air conditioner	Increased energy-related costs and increased likelihood of mass transfer and pollution displacement	Energy dissipation / heat transfer and pollution accumulation	Design and construction	16
2	1	2	installation of fans of air conditioner on the chassis	4	2	2	Failure to install of fans of air conditioner on the chassis	Noise Pollution	Creating sound and mechanical vibrations	Design and construction	17
3	1	3	Design of fan motor so that if HEPA and ALPA filters become clogged, the motor and driver will be changed.	6	2	3	Clogging of HEPA and ALPA air filters	Clean room space pollution	Lack of proper and complete air purification	Design and construction	18

2	1	2	Design and manufacture of stainless steel benches	4	2	2	Use of inappropriate materials in a clean room bench	Contamination mass transfer to clean room space	Corrosion and chemical destruction of bench surface over time	Equip	19
3	1	3	Use of proper and effective filters in Active Pass Box Design	6	2	3	-Using inappropriate filters in Active Pass Box Design -Clogging of Active Pass box Filters	contact of Inadequate purified air with transport materials and equipment and increased likelihood of contamination mass transfer into the clean room	Lack of proper air purification	Design, construction and operation	20
3	1	3	-Use of polymeric resin flooring -Types of Polymeric flooring consisted of epoxy resin and polyurethane create a highly integrated, impermeable 3D lattice with a very strong reaction between their constituents.	6	2	3	Use of improper flooring in the design and construction of clean room	Distribution and mass transfer of contamination(both free and forced) to all clean room space	Accumulation of dust and pollution	Design - Construction	21
4	1	4	Use of Clean Room T-Mops, Clean Room Napkins, Washing Bin, Clean Room Vacuum Cleaner and Cleaner Detergent and Disinfectant	8	2	4	Use of materials and improper equipment in cleaning the room clean	Increased likelihood of mass transfer of contamination to bulk materials and products	Destruction of surfaces as well as increased pollution production	Equipment and Operations	22
2	1	2	The use of PVC curtains for clean rooms	4	2	2	No use of PVC curtain in designing and making clean room	Increasing the costs of cleaning clean room and increasing energy costs	-Increased heating and cooling losses -Increase the entry of pests and environmental pollution - Increased transmission of noise pollution	Design - Construction	23
1	1	1	The use of plasterboard plates with a sealable PVC cover that is suitable for either positive or negative pressure in the clean room.	2	2	1	Not using proper coverage in clean room ceiling	Increased costs to find other ways to repair and maintenance	Difficult access routes for maintenance	Design - Construction	24
3	1	3	-Using seamless vinyl sheets with high quality and control in the design and construction of clean room floor - Vinyl sheet provides a continuous, impermeable surface that is smooth, easy to clean, and does not release particles into the air.	6	2	3	The use of inappropriate coatings in the design and construction of a clean room floor	Distribution and mass transfer of contamination to all clean room space	Pollution accumulation	Design - Construction	25
2	1	2	proper design for putting windows in clean room	4	2	2	Improper design for putting windows in clean room	Increasing likelihood of mechanical damage and electric shocks to windows	Increased probability of windows contacting with mechanical and	Design-build and equip	26

									electrical equipment		
3	1	3	-Applying Stainless Steel / Vinyl / Formica / Polica and Epoxy Coating as well as Sandwich Panel - In fact, the sandwich panel is said to be a place where the amount of environmental pollutants, including microbes and dust and airborne particles, is controlled and much lower than a typical indoor space.	6	2	3	Use of inadequate coating in wall design and construction	Accumulation of pollution and impossibility to wash the wall	Wall scaling and shattering over time due to damage caused by the interaction and reaction between chemicals, vapors and gases with the wall surface	Design - Construction	27
1	1	1	No window installation in temperature sensitive positions	2	2	1	Embedded window in place of the clean room that is heat sensitive	Increasing the probability of thermal degradation of that particular position due to rising temperature	Temperature increase in the position due to solar radiation heat transfer through windows	Design - Construction	28

According to Table 4, 28 rows of hazards were identified in the different phases listed in the table. According to Table (4), the lowest risk number is two for Row 28 and the highest Risk Number is 10 for Rows 1 and 2. Other risk numbers are between these two values. After the control and preventive measures, the risk numbers were reduced significantly. Preventive measures reduced the risk numbers by 50% in each case. This shows the effectiveness of control measures. Figures 1 and 2 show the risk numbers, respectively, before and after the control measures. The reason for this effective reduction in risk numbers is to halve the severity of the risks. The minimum and maximum risk numbers after the control measures are 1 and 5, respectively. Most value of the risk is related to the state of the mass transfer of contamination to the bulk material and especially to the final product (catastrophic). The lowest risk of thermal degradation is a particular position of the clean room due to the transfer of radiation heat to that particular position.

According to Table 5, the range of risk numbers and the percentage of number of hazards associated with them are shown. Prior to the control measures, 68% of the risks were higher than 5 and 32% were less than 5. Since in the clean room, the most important issue is pollution control, it should be reduced possibility of mass transfer of contamination to the bulk material and especially to the final product by appropriate control measures. Appropriate control measures can also reduce the likelihood of contamination mass transfer (free and forced forms) from different levels of the clean room to different parts of the clean room space. Another point that is clear from the risk analysis table is that with a more modern design as well as the use of new polymer materials in the design of a clean room, Useful and effective control and prevention measures could be taken to control pollution, also energy and cost savings.

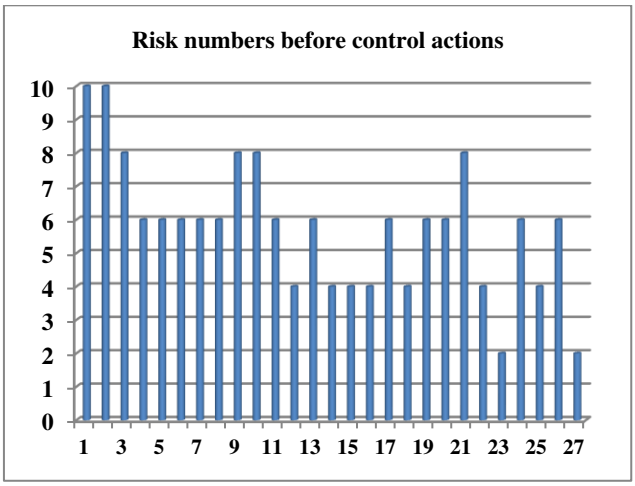

Figure 1: Risk numbers before control measures

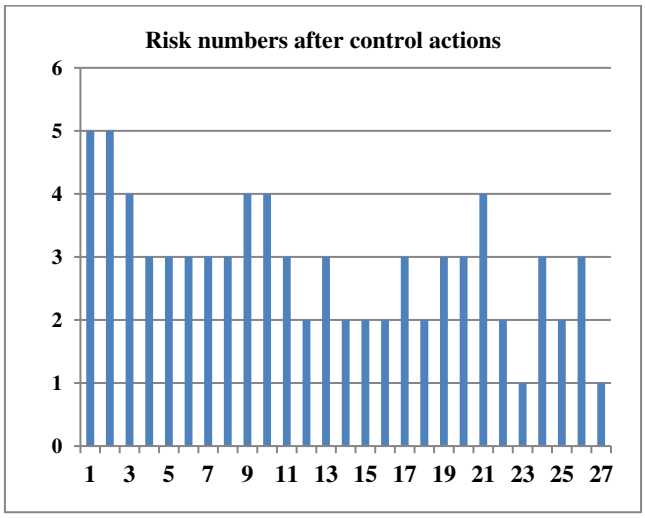

Figure 2: Risk numbers after control measures

Table 5: Risk Range and Percentage Related to Different Risks

(%) Percent	Risk numbers range	Row
67.86	**Less than 5**	**1**
32.14	**More than 5**	**2**

Conclusion

In this practical paper, the assessment risks of clean room used in pharmaceutical industries were first investigated using the concepts and principles of chemical engineering. Concepts such as mass transfer, heat transfer and heat dissipation, filtration, chemical interactions between materials in the clean room, and the various polymer coatings used in the design and construction of the clean room were included. It turned out that these fundamental approaches could be the best control and preventive measures - in detail - to control and reduce important risks in the clean room for a successful risk assessment.

Research Highlights

- For the first time, Risk Assessment of Clean Room Used in Pharmaceutical Industries was studied.
- For the first time, this Risk Assessment was studied in Design, Manufacturing, Equipping and Operating Phases by FMEA.
- For the first time, in this Risk assessment, Help was provided from some of the concepts of chemical engineering.

References

1. Whyte W., Cleanroom Technology: Fundamentals of Design, Testing and Operation, 2nd Edition, ISBN: 978-0-470-74806-0, 384 Pages, 2010
2. A. Bhatia, B.E., A Basic Design Guide for Clean Room Applications, PDH online Course M4 143PDH, 2012
3. Mirsaeedi, Leila; Principles of Designing Clean Room Architecture in the Pharmaceutical Industry, Quarterly Journal of Engineering and Construction Management, No. 1, 2017.
4. Clean Room Design Standards & Energy Optimization CREO, 2012
5. Lele Zhou, Wei Sun, Chen Huang, Hao Li, Zhijun Zou ,Chongwei Wu, Studies on Comparison of Particle Cocentration Models for Clearooms ,Procedia Engineering (205)3308–3315, 2017.
6. Nggada, S. H., Software failure analysis at architecture level using FMEA, International Journal of Software Engineering and Its Applications, 6(1): 61-74, 2012.
7. Chin, K. S., Wang, Y. M., Poon, G. K. K., and Yang, J B., Failure mode and effects analysis by data envelopment analysis, Decision Support Systems, 48(1): 246-256, 2009.