Macedonian pharmaceutical bulletin, 68 (Suppl 1) 125 - 126 (2022)
Online ISSN 1857 - 8969
*DOI:*10.33320/maced.pharm.bull.2022.68.03.058
Short communication

Risk-based contamination control strategy of manufacturing non-sterile pharmaceutical products

Martina Gjorgjevska, Angela Nastevska, Stojne Tanevska

Bionika Pharmaceuticals, Skupi 57, 1000, Macedonia

Introduction

Contamination is one of the biggest risks to patients' health and the quality of pharmaceutical products. One of the main principles of the good manufacturing practice (GMP) is to pay special attention to the factors that pose a risk of contamination (Eudalex GMP guidelines).

According to the new guidelines of *Annex 1: Manufacture for sterile medicine products*, manufacturers of pharmaceutical products need to develop a Contamination Control Strategy, by implementing the principles of risk analysis, the critical control points are defined and the effectiveness of undertaken controls and measures for management of risks associated with contamination are analyzed.

The aim of this paper is to present the advantages and need for implementation of risk assessment as a necessary tool for identifying potential hazards and risks of contamination and manufacturing a product that will meet the quality specification.

Risk tools

The conduction of the risk analysis is done in accordance to ICH Q9: Quality Risk Management and two tools are used: Ishikawa diagram and FMEA.

Ishikawa diagram – The cause-and-effect diagram is a tool we used to identify, examine and display the possible causes of contamination. With this method we illustrated the connection between the risk (contamination) and all the factors that contribute to its occurrence.

The identified hazards for the possible occurrence of contamination are then analyzed using the tool *FMEA (Failure Modes and Effect Analysis).* The method takes into account the parameters probability of occurrence, severity of the risk and the possibility of its detection. The risk class is determined by the value of RPN (Risk Priority Number) which is a numerical value. RPN is determined by the formula: *RPN = probability (P) x severity (S) x detection (D)*

Summary from the performed contamination risk analysis

With Ishikawa diagram eight possible causes of contamination are shown: production process, materials, facility/premises, cleaning, training, personnel, equipment and environment.

Eleven risks have been identified during analyzing the *manufacturing process* that could potentially lead to contamination. The identified risks are analyzed through FMEA, where potential root causes of the risks are identified. According to the obtained RPN values, 20 of the causes are classified as low risk, 28 as medium risks and 3 as high risks. Twelve risks arising from the *materials* were identified, which were then analyzed using the FMEA tool. They are classified in accordance to their RPN values as 16 low risk factors, 22 medium risk factors and 8 high risk factors. In accordance to Ishikawa diagram, we have identified eight risks from *facility/premises* that could lead to contamination. They are shown and analyzed later with FMEA tool and 24 potential root causes are identified. Nine of the identified root causes are classified as low risks, 13 as medium risks and 2 with high risk for potential contamination.

Additionally, through the *cleaning* process, eight risks were identified, and with the FMEA tool 31 roots causes were analyzed, ie 7 are classifies as low risk, 22 as medium risk and 2 as high risk for potential contamination. The possible cause of contamination - *training* is analyzed with Ishikawa diagram and 9 risks

*martina.gjorgjevska@bionikapharm.com

are identified that were later additionally analyzed with the FMEA and 30 possible root causes were identified of which 6 are classified as low risk in accordance to their RPN number, 16 as medium risk and 8 as high risk.

The risks that originate from the *personnel* are identified as well with the Ishikawa tool, and the causes that could lead to them are analyzed. According to their RPN number, 4 are classified as low risk, 19 as medium risk and 5 as high risk. Eight risks for possible contamination that originate from the *equipment* are identified. They are classified in accordance to their RPN number as following: 6 of the identified root causes are classified as low risk, 25 as medium risk and 5 as high risks. With analyzing the process *environment,* we have identified 9 risks with the Ishikawa tool that were later analyzed with FMEA and 51 potential root causes were identified. From them 23 are classified as low risk, 21 as medium risk and 7 as high risk.

Using the FMEA tool, the existing controls for decreasing the risk level are analyzed, through which the risks are reduced to an acceptable level that ensures that the company proactively prevent the possibility of contamination, i.e., that safe and efficient products are manufactured in accordance with the GMP principles.

Discussion

In accordance to the performed risk analysis for potential sources of contamination and their evaluation, the company's strategy for proper development of Contamination Control Strategy and the measures for proactive prevention of contamination has been determined.

The most important factors that can affect the occurrence of contamination have been identified as appropriate facility design and materials of construction, flow of materials, equipment choice, cleaning validation, and HVAC design, sampling/weighing of materials, material's labelling, personnel training and hygiene /gowning of the personnel.

The facility design and appropriately planning of the production processes, as well as the construction of the facility is very important for prevention of mix-up and contamination. The premises should be of suitable size and the materials of construction should be easy to clean and not to generate particulates and dust.

The flow of materials should be properly defined, the design of the premises should be performed in a way that will prevent the potential for mix-ups and contamination, the suitable transport equipment should be available and the personnel trained and tested for their knowledge.

The qualification of the personnel and determination who can train the personnel, the planning of trainings and the assurance that the personnel are trained for their activities is done in accordance to the training matrix.

The manufacturing equipment should be of adequate material that will be easy to clean and cleaning validation for each equipment has to be done. The personnel have to be trained for working on the equipment and accordingly monitored and tested for their knowledge.

Also, the design and maintenance of the HVAC system is important in order to avoid contamination. For good design we need to select a suitable grade of cleanroom together with a design intended to minimize contamination. The control of pressure regimes is shown in the site HVAC specification, where the pressure differentials and alarm parameters are justified and documented.

Conclusion

Risk analysis was performed in order to determine the potential sources of contamination in the production facility and premises using two tools – Ishikawa diagram and FMEA. Eight main potential causes of contamination have been identified: production process, materials, facility/premises, cleaning, training, personnel, equipment and environment.

Accordingly, they were analyzed with FMEA, where the risks were analyzed and 308 potential root causes were identified. Measures for proactive prevention of contamination have been established, i.e. it is necessary that the facility and premises are well designed and constructed for their indented activities, the company has well-trained stuff, good design and maintenance of the HVAC system, cleaning validation is performed, the process of flow of materials is well established, as well that there is adequate documentation for all activities that guarantee safe and efficient product.

References

Eudralex, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary use. Volume 4, Chapter 2: Personnel; Chapter 3: Premises and Equpment; Chapter 5: Production. Brussels, 2014. Available at: https://health.ec.europa.eu/medicinal-products/eudralex_en

Eudralex, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary use. Volume 4, Annex 1: Manufacture for Sterile Medicine Products. Brussels, 2008. Available at: https://health.ec.europa.eu/medicinal-products/eudralex_en

ICH Harmonized guideline Q9 on Quality Risk Management, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, January 2006, Available at: https://ich.org/page/quality-guidelines