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Short communication

Management of deviations during life cycle of medicines and actions for elimination of the risks on the quality of the finished product

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Introduction

Deviations are unexpected events that occur during the production process, activity, documentation, analysis and storage of a medicine. These events should be documented at the time of occurrence and properly evaluated for possible future risk. Deviations occur almost every day in the pharmaceutical industry and their proper handling and minimizing recurrence is very important for the quality management system (Kumar et al., 2020).

Proper handling of the deviations plays an important role to assure product quality. Active involvement in the process is required by the quality assurance team and other affected departments, all together assembling a multidisciplinary team. This article will describe management of the deviations during the life cycle of medicines together with the activities that should be taken in order to eliminate the risks affecting finished product characteristics, focusing on the determination of the root cause and all the corrective/preventive actions needed to be taken in order to improve the overall process. The parameter hardness of film coated tablets, which deviates from the acceptance limit during production of three consecutive batches of product X, will be shown as an example.

Materials and methods

The production starts after finishing three validation batches from the product. After completion of the film coating process, the quality of the film coated tablets regarding the parameter hardness was evaluated in the laboratory for in-process control. Film coated tablets for which the parameter hardness deviated more than 1 kP than from the defined limits in the Master Production Protocol, were obtained. An investigation was conducted in order to determine the cause of the deviation and to define an appropriate corrective/preventive action, using an Ishikawa or “fishbone“ diagram.

The possible root cause was determined using the Ishikawa Diagram. Taking into account that the cause of the deviation can include the equipment, the process, the materials, the environment, or the personnel. In this case all of this steps were checked.

Results and discussion

The root cause analysis included detailed investigation on the interventions on the machine for film coating, Master Production Protocol and values for the parameter hardness in the previous stage (production of tablet cores) and all batches of raw materials that were used for these three batches.

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Investigation has shown that no deviations were observed outside the prescribed standard procedures during the entire production process.

The investigation on raw materials during the input analysis has shown that all the batches used had status "Conforms".

There were no deviations observed for the parameter hardness of film coated tablets, during the validation of the process.

The values of the results for the parameter dissolution test were within the specification limits for all the batches, without any variation observed.

After finishing the investigation, the focus was directed to the possibility that the deviation of the parameter Hardness of film coated tablets is due to the variation of one of the process parameters for the step film coating, set on the machine.

Temperature values were monitored during the process of film coating for each of the three batches, and compared with three previously produced validation batches of product *X*. Different values for inlet air temperature in the machine for film coating were detected. The values are within the set interval limits. This finding, known in literature as "a noise factor", emerges when a factor that varies naturally and uncontrollably in the process can be controlled for purposes of an experiment. This are factors that are variating in the prescribed limits.

Since the root cause of the deviation was identified, a risk assessment for the impact of the deviation of the parameter hardness on the properties of the finished product, was conducted, considering results from stability studies, statistical review of the results from tested parameters during the production process in correlation with the physico-chemical properties.

Conclusion

The risk analysis has shown that the deviation of the parameter hardness of film coated tablets, identified during the manufacturing process, has no impact on the properties and therefore on the quality of the finished product.

According to the obtained results for the dissolution test, which is directly correlated with the parameter hardness, it can be concluded that the risk of the non-compliant product is eliminated.

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