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Short communication

Continuous process verification on blister packaging

Biljana Petrovska Jakimovska, Dance Dukoska, Irena Zdraveska, Maja Lazarova, Milkica Gligorova

AD Alkaloid, bul.Aleksandar Makedonski 12, 1000 Skopje, North Macedonia

Introduction

Continuous process verification (CPV) is the collection and analysis of end-to-end production components and processes data to ensure product outputs are within predetermined quality limits.

CPV approach support validation status of the Product Quality Review during the product lifecycle.

In the pharmaceutical industry CPV can be used as a tool for better understanding of the process and to analyze existing results.

Continuous process verification - definition and significance in the pharmaceutical production

According to EMA, the CPV is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated. According to FDA, the CPV represents the third phase of process validation, following "design and development" (the first phase) and "process qualification" (the second phase) and is described as "an ongoing program" to collect and analyze product and process data related to product quality. The activities encompass monitoring of process parameters, trending of data, change control, retraining, as well as corrective and preventive actions. This approach demonstrates that a process that operates within the predefined specified parameters always results in a product that meets all its Critical Quality Attributes (CQA) and control strategy requirements (EMA, 2016; FDA, 2011).

The scope of continuous process verification will be impact by a number of factors, including:

- Previous development and manufacturing knowledge from similar products and/or processes;
- The extent of process understanding gained from development studies and commercial manufacturing experience;
- The complexity of the product and manufacturing process of the product
- The level of process automation and analytical technologies is used for
- For legacy products, with reference to the product lifecycle, process robustness and manufacturing history since point of commercialization as appropriate (Gamal, 2009).

Methods

Statistical process control (SPC) is process improvement technique for continuous collection and analysis of data from quality attributes (QA) and critical quality attributes (CQA) of the product where variability in production process has to be minimal and key performance indicators (KPI) need to be very close to a specific target. Collected data will be analysed with appropriate statistical tools in order to evaluate the performance of process of blister packaging, as well as to ensure that during production QA and CQA are been properly monitored. Collected data can be plotted on an SPC chart in order to provide evaluation of stability of blister packaging process i.e. if the process is "in" or "out" of statistical control. The risk analysis evaluates the critical parameters and functions of the primary packaging process (using the FMEA method with the priority number of risks obtained as a numerical product of three coefficients: severity, frequency and detection, according to the risk analysis procedure).

*bjakimovska@alkaloid.com.mk, ddukoska@alkaloid.com.mk, izdraveska@alkaloid.com.mk

Control limits are elements of control charts, limits within the values are moving. They have distance of three sigma above and below the process average. Upper Control Limit (UCL) is the maximum value (+ 3 sigma) that indicates statistical control. Lower Control Limit (LCL) is the minimum value (-3 sigma) that indicates statistical control. In stable, well established processes, control limits are expected to be narrower than regulatory specification limits (Ostrove, 2016).

After identifying and establishing the QA and CQA, their increased monitoring is required in order to provide stability of blister packaging process through control charts and detection of trend according predefined acceptable criteria. If trends are being detected and/or results are out of control, the reason for their occurrence is being investigated. If trends and/or results out of control are not been detected and it is proven that the process is stable, and then process capability is measured by indexes Process Capability-Cp / Process Capability Index-Cpk.

Discussion

In order to confirm the process of primary packaging, statistical analysis of the process capability for the parameter yield of the finished product will be perform as the key parameter that shows that the process is under control that confirms:

- Specified number of tablets is in the blister;
- Presence and correctness of the serial number and expiration date on the blister;
- The blister is properly sealed / hermetically sealed;
- The appearance (physically and aesthetically) of the obtained blisters is satisfactory.

Critical Process Parameters (CPP) will be monitor during blister packaging process in order to provide continuous assurance:

- Minimum and maximum operating range of blister pocket formation temperature;
- Minimum and maximum operating range of sealing temperature of blister;
- Minimum and maximum operating speed range of blistering machine.

Cp index values greater than 1 show that the primary packaging process is always capable to give high yield within specified limits. In addition, if index Cpk is greater than 1, then the process is considered to be centered. The process will be consider stable if the CPPs move within the set limits, and capable if the Cp for the CPP is greater than one.

As part of the review process, Cp and Cpk, needs to be calculated in order to demonstrate that the manufacturing of the product is consistently produced according to the preapproved specifications.

It may be considered that moving ranges-control charts and process capability indexes are valuable tools for process understanding and for following the quality of the product continuously.

Conclusion

The purpose of CPV on blister packaging is to identify the occurrence and cause of process variability, to monitor degree of variability, to determine its impact on processes, as well as control it, which in turn reduces the process risks and improves its stability and capability.

References

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