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Short communication

Ongoing process verification in Alkaloid

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Introduction

Ongoing process verification (OPV) is documented evidence that the process remains in control during the production of commercial batches. OPV is a program for continuous collection and analysis of in process and finished product quality attributes (QA) and critical quality attributes (CQA) from validated processes for a given product. The data collected have to be analyzed with appropriate statistical tools in order to evaluate the performance of the process. The purpose of OPV is firstly to identify the occurrence of process variability and to monitor degree of variability. Secondly based on the monitoring of deviation management to determine its impact on processes, as well as to control it, which reduces the risks in the processes, improves their stability and capability.

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In order to perform Ongoing Process Verification, the process must be validated, and Quality Attributes and Critical Quality Attributes identified.

An ongoing program to collect and analyze product and process data that relate to product quality must be established.

The data should be statistically evaluated and reviewed by trained personnel. Statistical tools such as Descriptive statistics, Control Charts, and Capability Analysis should be used, where appropriate.

The control chart highlights poor quality by showing when a measurement lies outside the expected variation. More importantly, it shows when a process is trending toward failure.

The established control limits should be within the regulatory specification limits and are used to identify whether the process is in statistical control i.e. no special cause variation.

Multidisciplinary team is responsible for this process. Members of the team are from Quality Assurance Department, Production department, Research and Development Department and Quality Control Department.

The team is responsible for preparing the OPV plan and the OPV Report.

OPV Plan contains description of the process with the respective manufacturing flow charts. In OPV plan are presented parameters of the product which are going to be monitored and also quality attributes and critical quality attributes. Sampling plan as well as sampling frequency and sampling procedures, test methods and equipment used are specified in the OPV Plan.

OPV Report is prepared according previously made OPV Plan. The objective is to monitor the results, and to collect more knowledge for process performance, process variability and its trends. Statistical process analysis of QAs and CQAs is performed. The purpose is to assure that the manufacturing process remains in a state of control during the production of commercial batches and that the manufacturing process is capable of consistently yielding a product of reproducible quality. If there is need for improvement of the process, it should be noted in the conclusion of the Report.

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Regulatory Requirements

Regulatory requirements are specified in respective EU and FDA guidelines.

In Annex 15 Qualification and validation of EU GMP guideline is stated that *Ongoing Process Verification* should be used throughout the product lifecycle to support the validated status of the product as documented in the Product Quality Review.

There is very tight relation between Product Quality Reviews (PQRs) and OPV Reports. Although PQRs are made for all authorized medicinal products annually, the need for continuous monitoring of the process has huge meaning in detecting trends in a timely manner. In fact PQR should summarize conclusions obtained during OPV.

FDA Guidance for Industry Process Validation defines Stage 3 of Process validation **—** *Continued Process Verification*. The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture.

The collection and evaluation of information and data about the performance of the process, will allow detection of undesired process variability.

Evaluating the performance of the process identifies problems and determines whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control.

The production data should be collected to evaluate process stability and capability. The quality unit should review this information. If properly carried out, these efforts can identify variability in the process and/or signal potential process improvements. A process is likely to encounter sources of variation that were not previously detected or to which the process was not previously exposed. Data gathered during this stage might suggest ways to improve and/or optimize the process by altering some aspect of the process or product, such as the operating conditions (ranges and set points), process controls, component, or in-process material characteristics.

All guidelines follow a few principles:

- This process should be conducted under an approved protocol or equivalent documents and a report should be prepared to document the results obtained;
- Results of parameters identified as quality attribute or as critical quality attributes should be trended and checked to make sure they are consistent with each other;
- Out of trend results or significant atypical trends should be investigated;
- Statistical tools should be used, where appropriate;
- OPV can be established for new products and existing/legacy products.

Conclusion

Increased knowledge of the products and/or processes obtained by the collection and evaluation of OPV data provides regulatory and business value to pharma manufacturers. Implementing the OPV process gathers a large amount of data for the product, an organizational asset that leads to continuous improvement, a reliable supply chain, reduced regulatory and compliance risk, reduced cost of quality, and a better manufacturing plan.

It is very important to emphasize detecting any atypical trends through continuous monitoring in order to prevent failure in the future. The main purpose of OPV process is in detecting atypical trends in early stage.

The OPV process in fact gives our organization the opportunity to understand its production process in greater depth and to improve the quality of its products over time. Thus fulfilling the basic principle of the pharmaceutical profession, to serve patient safety.

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