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Short communication

Workflow for investigation of Out of Specification results in physico-chemical laboratory in Alkaloid

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Abstract

The efficient and accurate investigation of Out of Specification (OOS) results is crucial in maintaining the reliability and quality of products in a physico-chemical laboratory. This paper presents a comprehensive workflow designed to systematically and effectively manage OOS results in such laboratories. The workflow integrates established quality assurance principles, regulatory guidelines, and best practices to ensure robust and reliable investigations. The presented workflow comprises several key stages, each designed to address specific aspects of the investigation process. The workflow provides a structured and systematic approach to investigating OOS results in physico-chemical laboratories. By incorporating data-driven decision-making, root cause analysis, and corrective actions implementation, laboratories can uphold product quality, regulatory compliance, and customer satisfaction. This workflow serves as a valuable tool for laboratories seeking to enhance their OOS investigation processes and overall quality management systems.

Introduction

Out of specification result (OOS) is a result that does not correspond to the predetermined acceptance criteria (according to the drug master file, approved marketing authorization, official monographs, internally set criteria for raw materials/finished pharmaceutical products and etc.).

This workflow is applicable for physicochemical-based laboratory testing performed on active pharmaceutical ingredients (API), excipients, and finished pharmaceutical products (FPP) during release testing, ongoing stability studies, and analytical method transfer.

OOS investigation in Alkaloid

If the assessment of the obtained analytical results reveals a result that does not correspond to the predetermined acceptance criteria, such a result is declared as a result that falls under the definition of out of the specification result.

The workflow for the investigation of OOS results consists of predefined steps which are taken when handling these types of results. The root cause investigation has to be performed to ensure that the reason for the OOS result is evaluated, and the obtained results are representative and reliable (ECA, 2013).

The workflow of the OOS result investigation is divided into 3 phases.

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Phase I is initiated in the Quality Control (QC) laboratories, and thereinafter, if needed, the root cause investigation continues in Phase II and III, coordinated and organized by the Quality Assurance (QA) department with the support of other departments such as Production, Maintenance, Research and Development, as well as other concerned departments needed.

Where an investigation has revealed a root cause, the suspect result is invalidated, and the result should not be used to evaluate the quality of the batch (FDA, 2006; MHRA, 2010).

Phase I investigation

The laboratory investigation is being started in order to prove the correctness of the result obtained from testing. It is important to find out whether it is a true result or if the laboratory has made a mistake during analytical testing. All original entries and records from the instruments, the analytical dossier with all the necessary records and data, the analytical test procedure and the specification should be available and must be questioned for the laboratory investigation. The laboratory investigation is divided into two phases Phase Ia and Phase Ib (Fig. 1).

Some of the most common questions for evaluation of the obvious and found errors are listed in the appropriate checklist forms according to which the checkups are performed.

Phase Ia Investigation

The documented investigation begins with Phase Ia in which the analyst alone seeks for an obvious laboratory error by reviewing the entire workflow that led to the OOS result.

If Phase Ia does not reveal an obvious laboratory error the investigation continues with Phase Ib.

Phase Ib Investigation

In Phase Ib the analyst and the supervisor together seek for found laboratory error through a detailed review of the entire workflow that led to obtaining the OOS result.

If the analyst and the responsible person fail to find a laboratory error, the investigation continues, towards an investigation of the root cause (hypothesis testing with intentional error). The results obtained from the hypothesis testing are not evaluated in the final reported result and may only be used to confirm or discount a probable cause.

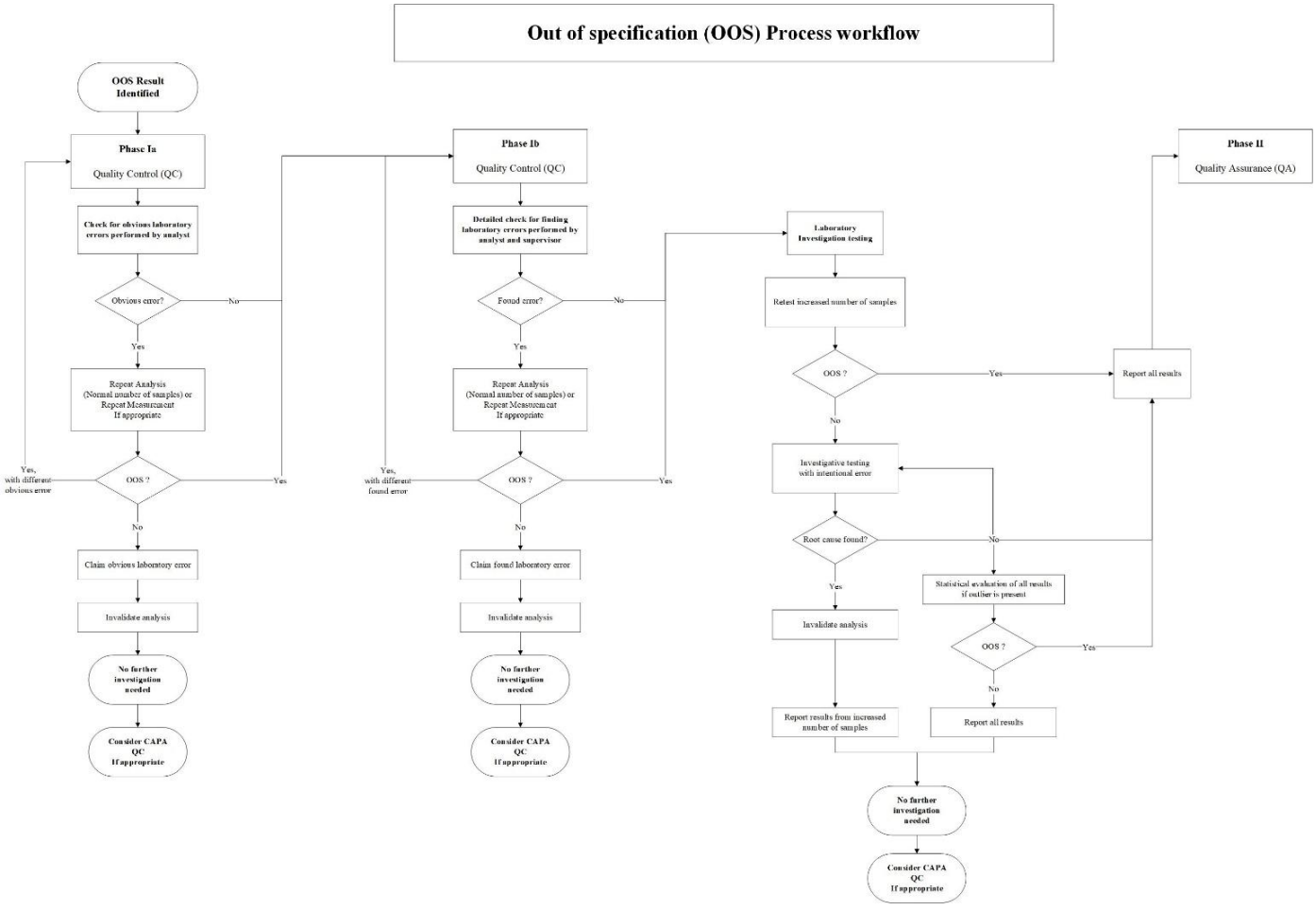

Fig. 1. Process decision tree for investigating out of specification (OOS) results in phase Ia and Ib.

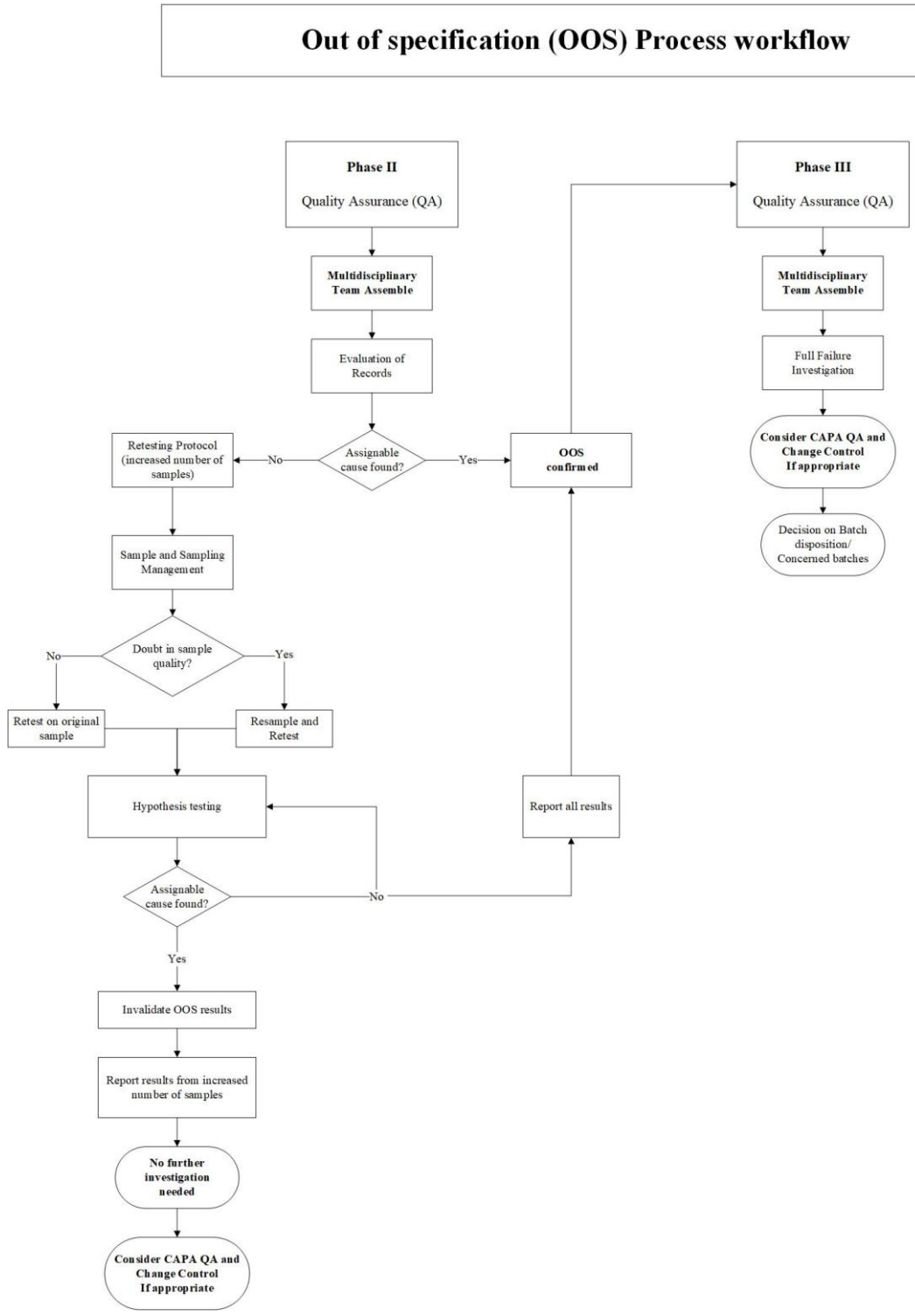

Fig. 2. Process decision tree for investigating out of specification (OOS) results in phase II and III.

Phase II and Phase III investigation

The OOS investigation is initiated in phase II by QA in continuation of the Phase Ib by defining a multidisciplinary investigation team that performs appropriate actions (exp. evaluation of the obtained results, review of the production and analytical documentation for the product, review on records of reported incidents / deviations / other relevant records and additional activities determined by the investigation team) towards identification of the root cause for the OOS results.

In Phase III, the multidisciplinary investigation team, in continuation of the Phase II, evaluates in which way the

OOS results could affect other product batches and assesses the quality, efficiency and safety of the material / finished pharmaceutical product batch.

In accordance with the investigation and the identified root causes in all investigation phases, appropriate Corrective Actions are issued (Fig. 2).

Evaluation of results

If an outlier is present the Huber's H15 method is used for statistical data evaluation, which calculates the robust mean value with a 99% robust confidence limit.

This robust statistical method includes the outlier(s) instead of rejecting it, using a robust procedure based on calculation with the median and deviation from the median.

The Huber's H15 method cannot be used in analyses where product variability is being assessed, such as tests for uniformity of dosage units and dissolution. (Ellison et al., 2009; ISO 5725-5, 1989; Miller and Miller, 2005; USP 35, 2012)

Conclusion

This OOS workflow investigation ensures high safety and efficacy of Alkaloid's finished pharmaceutical products while complying with regulatory requirements.

GMP regulations require that an investigation be conducted whenever an OOS test result is obtained. The purpose of the investigation is to determine the root cause of the OOS result. The source of the OOS result should be identified either as an aberration of the measurement process or an aberration of the manufacturing process.

To be meaningful, the investigation should be thorough, timely, unbiased, well-documented, and scientifically sound.

To conclude the investigation, appropriate evaluation of the batch quality, efficiency and safety is performed and appropriate batch decision is made.

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Резиме

Тек на истрага на резултати надвор од спецификација во физичко-хемиска лабораторија во Алкалоид

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Клучни зборови: надвор од спецификација (OOS), тек на истрага, клучни фази, евалуација на резултати

Ефикасната и прецизната истрага на резултатите надвор од спецификациите (OOS) е од клучно значење за одржување на доверливоста и квалитетот на производите во физичко-хемиска лабораторија. Овој труд претставува сеопфатен тек на истрага дизајниран за систематско и ефективно управување со резултатите од OOS во такви лаборатории. Текот ги интегрира воспоставените принципи за гаранција за квалитет, регулаторните упатства и најдобрите практики за да обезбеди цврсти и сигурни истраги. Презентираниот тек на истрага се состои од неколку клучни фази, од кои секоја е дизајнирана да одговори на специфичните аспекти на процесот на истрага. Текот на истрага обезбедува структуриран и систематски пристап за истражување на резултатите од OOS во физичко-хемиски лаборатории. Со донесување одлуки засновани на податоци, анализа на основната причина и имплементација на корективни дејства, лабораториите можат да го поддржат квалитетот на производот, усогласеноста со регулативата и задоволството на клиентите. Овој тек на истрага служи како вредна алатка за лабораториите кои сакаат да ги подобрат своите процеси за истражување на OOS и целокупните системи за управување со квалитетот.