Pharma Quality Partners
Quality Excellence Through Partnership

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Guide to Out of Specification Analytical Results

Accepted Investigation Methodology

Introduction

Successful pharmaceutical drug product manufacture is dependant on accurate, precise reproducible and robust analytical testing. The lifecycle of any finished drug product dosage form includes a mass of analytical tests, from the testing of raw materials and packaging components, to in-process tests that assure critical processing steps have been successful, to finished drug product testing that assures compliance to registered quality specifications.

Analytical technology continues to advance and mind-blowing new analysis equipment, methods and applications are appearing in the pharmaceutical analytical toolkit year on year. In the not too distant past analysis methods such as Liquid Chromatography - Mass Spectroscopy required expensive complex room filling instruments, whereas today bench-top sized affordable systems are now almost common place in pharmaceutical analytical laboratories. Advances in computerised system hardware and data handling software bring a new set of challenges. This is evidenced by the recent focus on data integrity by pharmaceutical regulatory authorities worldwide. Despite the fast paced march of modern technology however, all analysis remains vulnerable to two key sources of error. Humans and Machines! And these two sources of error are also inherent in the manufacturing processes used to produce finished drug products. As long as these errors have influence there will always be the risk of Out of Specification (OOS) and Out of Trend (OOT) analytical results.

Understanding the correct methodology to investigating OOS/OOT analytical results is important to assuring the quality of analytical test results. A robust OOS/OOT investigation methodology is truly valuable in determining root cause and facilitating continuous improvement in any organisations Pharmaceutical Quality Management System (PQS).

Through this guide Pharma Quality Partners Ltd aims to provide the end-user with an understanding of the OOS/OOT methodology accepted by both the EU and US regulatory authorities. Are you confident that your PQS OOS/OOT processes meet expectations? Is the quality of your analytical data assured?

Finding Regulatory Guidance?

The US Food and Drug Administration (FDA) and the UK Medicines and Healthcare Regulatory Agency (MHRA) both publish guidance documents for the pharmaceutical industry on the topic of Out of Specification Investigation. The investigation processes defined in both regulatory authorities publications are essentially the same with only very slight differences being defined that do not overly impact the common approach being promoted. Following the processes defined in either is seen as being compliant with both, though it is useful to be aware of the slight differences (these are pointed out in this guidance document where applicable).

The FDA guide is entitled "Guidance for Industry Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production – October 2006" and is available at the following weblink.

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070287.pdf

The MHRA guide is entitled "Out of Specification Investigations" and is available at the following weblink.

http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/is-insp/documents/websiteresources/con100182.pdf

Accepted OOS/OOT Investigation Methodology

General Requirements & Definitions

The US FDA guidance states that OOS investigation must be conducted wherever an OOS result is generated. The purpose of such an investigation is to determine a root cause for the OOS result. The root cause must be due to the measurement process or the manufacturing process. The entire investigation process aims to determine which is the real underlying cause of the anomaly. US FDA expectation is that OOS investigation is required even if the intention is to reject the batch or material. A written record detailing, the investigation conducted, the conclusions determined and any follow-up actions taken must be documented.

By comparison the MHRA guidance states that OOS/ OOT investigation must be conducted for:

- Batch release testing and testing of starting materials
- IPC testing if data is used for batch calculations/decisions and if in dossier or on the Certificate of Analysis
- Stability studies for marketed finished products and/or APIs
- Previous released batch is used as a reference sample
- Batch for clinical trials

The MHRA guide also defines three types of investigation as follows:

OOS

Test result that does not comply with the pre-determined acceptance criteria (i.e. For example, filed applications, drug master files, approved marketing submissions, or official compendia or internal acceptance criteria)

Test results that fall outside of established acceptance criteria which have been established in official compendia and/or by company documentation (i.e., Raw Material Specifications, In-Process/Final Product Testing, etc.)

OOT

Is generally a stability result that does not follow the expected trend, either in comparison with other stability batches or with respect to previous results collected during a stability study. However the trends of starting materials and in-process samples may also yield out of trend data. The result is not necessarily OOS but does not look like a typical data point. Should be considered for environmental trend analysis such as for viable and non viable data (action limit or warning limit trends)

Atypical / Aberrant / Anomalous

Results that are still within specification but are unexpected, questionable, irregular, deviant or abnormal. Examples would be chromatograms that show unexpected peaks, unexpected results for stability test point, etc.

Is There Any Exceptions?

Yes the guide does provide some exceptions where OOS/OOT type investigations will not be required. This is mainly the case with Pharmacopoeial tests that have pre-defined additional levels of testing e.g.

- Dissolution Testing – S1, S2
- Uniformity of Dose – test additional 20 dosage units
- In-process testing while trying to achieve a manufacturing process end-point e.g. pH
- Studies conducted at variable parameters to check impact of drift e.g. process validation exercises

But the regulators also advise caution and give clear expectation that such tests may need to be explored as OOT if first level testing is normally passed.

Phase 1 Investigations

Both US FDA and MHRA guidances discuss the concept of Phase 1 investigation. MHRA split this phase of investigation into two distinct sub-parts namely Phase 1A and Phase 1B. However the US FDA wraps both parts into a single Phase 1 investigation concept. *(See Page 12 for a flow diagram of the OOS Investigation Methodology)*

Phase 1 investigations are about seeking out obvious laboratory error and the sub-parts are defined as follows:

Phase 1A - Documentation of an obvious error. This phase of investigation is usually conducted by the analyst themselves and does not necessarily require supervisory or managerial governance. Of course it is prudent that any investigative reporting of an obvious error by an analyst would be reviewed and approved by a supervisor in order to assure the data integrity and GMP compliance of the investigative process.

Phase 1B - Establishment of laboratory based assignable cause (root cause). This phase of investigation is expected to be supervisor or manager led, to involve the analyst and to be conducted in line with a pre-defined investigation checklist. The focus of course at this stage is review of work undertaken to determine if any laboratory error has occurred.

There are only five accepted obvious errors that can result in a OOS investigation being closed at the Phase 1A stage. These are:

- Calculation error – analyst and supervisor review and both initial and date correction
- Power outage – analyst and supervisor document event
- Equipment failure – analyst and supervisor document event
- Testing errors – e.g. spilling of sample, incomplete transfers of sample – analyst documents event immediately
- Incorrect instrument parameters – e.g. Incorrect detector wavelength – analyst and supervisor document event

Where the above obvious errors are not determined, a Phase 1B investigation must be undertaken. Phase1A investigations must be trended in the interests of continuous improvement in the pharmaceutical quality management system.

Phase 1B involves an assessment of possible root causes relating to data, equipment, analysis method and the analyst only. It is expected that this phase of investigation has the direct oversight and lead of a supervisory or managerial figure that holds higher office or responsibility in the laboratory organisational hierarchy than the analyst who has generated the OOS analytical result. It is also expected that the assessment process is structured and conducted in accordance with a comprehensive checklist (note both the FDA and MHRA guidances provide details as to what aspects the checklist should typically include).

Any evidence or ideas that may indicate a possible root cause can be explored or verified by hypothesis testing. At the Phase 1 stage of OOS investigation hypothesis testing should be restricted to original samples wherever possible. Its also advisable that hypothesis testing gives consideration to analysis by a second analyst. Where an assignable cause is not determined by the Phase 1B investigation a Phase 2 investigation must be undertaken.

If the Phase 1B investigation is proving inconclusive it is advisable for the QC team to begin consulting with Production, Quality Assurance and the Qualified Person. If the investigation is likely to enter a Phase 2 process these stakeholders will be fundamental to the success of the investigation. It can often be the case that consultation with Quality Assurance and the Qualified Person leads to other considerations being brought into the hypothesis testing and investigation approach at Phase 1B. This may result in assignable cause being determined and avoid the need for more in-depth and complex Phase 2 investigations.

If an obvious error or an assignable root cause has been determined the Phase 1 Investigation may invalidate the original OOS result. The obvious error/root cause can be eliminated and an appropriate level of retest performed to obtain valid analysis results.

Hypothesis Testing the Right Way!

Hypothesis testing is a very useful tool in an OOS investigation to explore theories as to what may have gone wrong. Though its use is permitted as early as Phase 1 investigation and may carryover into Phase 2 investigation, there are some risks with using hypothesis testing. It can easily to over used or indeed be used inappropriately and the outcome can easily be one of weakening the overall investigation. Important points to keep in mind with regard to hypothesis testing are as follows:

1) Hypothesis testing must always be defined in a pre-approved protocol. This helps assure that testing is well planned, is scientifically sound and justified and prevents inadvertent use of inappropriate ad-hoc testing. Such testing can easily be interpreted as an attempt to "test into specification" and is likely to result in unfavourable scrutiny from regulatory authorities. Hypothesis testing is essentially a process of elimination. A well designed hypothesis testing protocol explores the possibilities, eliminates those proven as not the case and works in a structured manner towards defining the root cause or potential root cause(s) based on scientific and conclusive evidence.

2) The hypothesis testing protocol must define:

    - A description of the hypothesis test
    - The potential root cause being investigated
    - The samples that will be tested
    - Exact details on how to execute the test
    - How the data will be evaluated

3) The results from hypotheses testing must only be used to confirm or discount a root cause. They cannot replace the original (OOS) result or be reported as final analytical results.

Phase 2 Investigations

Both US FDA and MHRA guidances discuss the concept of Phase 2 investigation. Unlike Phase 1 both guidances address this concept in exactly the same manner. *(See Page 12 for a flow diagram of the OOS Investigation Methodology)*

Phase 2 investigations are about conducting in-depth OOS investigations in the absence of obvious laboratory based error. This phase of investigation explores in-depth manufacturing based roots causes and can also further explore laboratory based root causes.

All Phase 2 Investigations should commence with a manufacturing investigation. If no obvious laboratory error has been determined by Phase 1 investigation, there is a likely case building that the OOS result may be genuine. If the original result proves to be genuine then the source of the quality defect can only be associated with the manufacture of the product. This does not of course mean that it is simply a production process error. A comprehensive investigation must take into account all possible contributory factors. The root cause can be present anywhere in the product lifecycle. For more established products with a solid quality history, root cause is most likely to be found in the parts of the product lifecycle post initial product development and realisation. In such cases the source of error is likely to be in stages of product manufacture associated with commercialisation ranging from source of raw materials and components through to production and final QC release testing. For newer products with limited product knowledge and relatively unknown quality histories root cause may be further back in the product lifecycle and investigation of development of the product may be in scope.

Where a Phase 2 manufacturing investigation determines no assignable root cause it is expected that laboratory based error is further explored. This is likely to involve in-depth hypothesis testing strategies that explore potential root causes to seek evidence of true root cause. Phase 2 investigations require the input of various stakeholders outside of the immediate QC testing group. Production personnel, Quality Assurance Personnel, Qualified Persons as well as Manufacturing Authorisation Holders and senior company management are likely to have vested interest in the investigation process. Structuring of pre-approved testing plans will be more successful with the combined input of a cross functional team of subject matter experts, who fully

understand the product, its lifecycle and its manufacturing and QC testing pedigree. Where exploring laboratory error the use of second analysts and comparative testing between analysts or even laboratories should always be considered in strengthening any hypothesis testing plans.

If an assignable root cause has been determined, the Phase 2 Investigation may invalidate the original OOS result. The obvious error/root cause can be eliminated and an appropriate level of retest performed to obtain valid analysis results. If the Phase 2 investigation is inconclusive retesting is permitted*. It must be performed a statistically significant number of times. The regulatory guidances quote numbers of 5, 7 and 9 replicates being statistically significant.

Wherever a Phase 2 investigation fails to conclude the root cause a Phase 3 Investigation must be undertaken.

**Note: Qualified Persons basing release decisions on inconclusive OOS investigations where statistically significant numbers of retests have been undertaken may need to consider Batch Specific Variations (UK) or consultation with national regulatory authorities before making final batch disposition decisions.*

Phase 3 Investigations

Both US FDA and MHRA guidances discuss the concept of Phase 3 investigation.

Phase 3 investigations are about evaluation of the outcomes of Phase 1 and Phase 2 investigation processes. Not only are they about taking into account the evidence from both the laboratory and manufacturing based investigations but they are also about looking at all other relevant information on which to base a quality decision about the implicated batch of product.

Information such as validation data, development data, stability data, other batches, other products and the impact of the event are appropriate considerations. But overall Phase 3 investigation is about making a decision on batch disposition. This is often a role that falls to Qualified Persons or Senior Quality Management.

It will be the case where Phase 3 investigation is required that root cause has not been determined for the OOS result. In such instances Corrective and Preventative Actions (CAPA) should be defined with the aim of preventing further quality defects of this nature. Defining CAPA in the absence of true root cause can be a difficult undertaking, but often in such cases at least a short list of potential root causes are likely to have been concluded by the investigation process. Further validation or development work my be necessary to gain deeper product or analytical method knowledge and such undertakings in themselves may be worthy CAPAs to focus on.

Summary

Where an OOS/OOT result is generated it can only be:

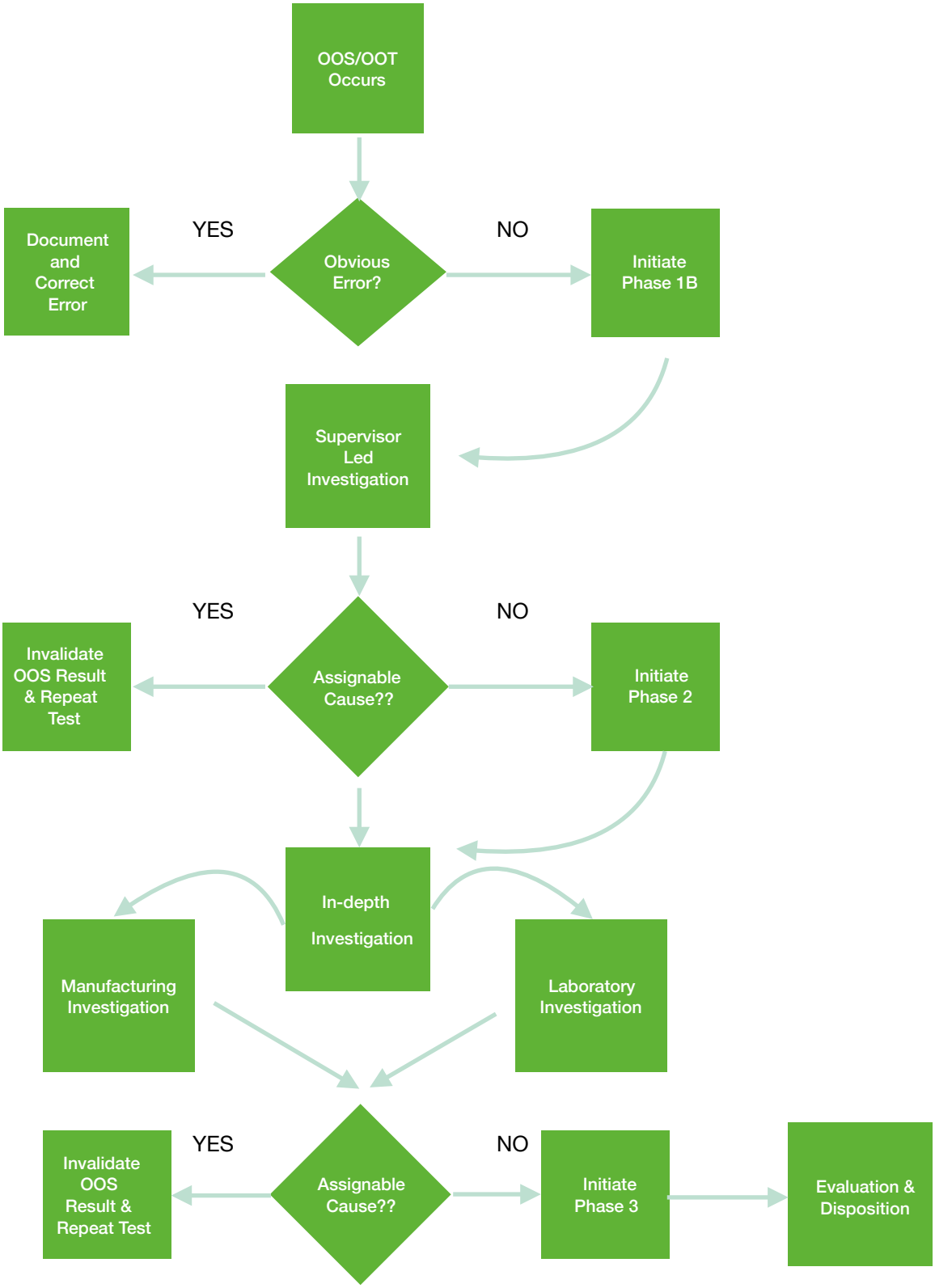
- Real and the product/material is truly OOS/OOT
- Real and is due to a manufacturing error
- False and is due to analysis error (materials, method, analyst, samples, equipment, data)

To invalidate an OOS/OOT result you must confirm an obvious error, assignable cause (root cause) or a manufacturing error. Without this there is no justification to invalidate an OOS result.

Be mindful of the potential to be seen as "testing into specification". This is easily implied or concluded from poor handling of OOS/OOT investigations and is usually promoted by poorly designed hypothesis testing strategies.

There is only one approach to OOS investigation accepted by EU and US regulators. It is the three phase process discussed in this guide.

Flow Diagram of OOS Methodology



Contact Us:

Hi I'm Justin Ahern, Managing Director of Pharma Quality Partners Ltd. We are a pharmaceutical quality consultancy and training service provider with a guiding business objective of "**Quality Excellence Through Partnership"**. We aim to achieve quality excellence for our clients by partnering our expertise in Qualified Person, GMP, Quality Assurance and Clinical Drug Development (Pharmaceutical Medicine) services with their business needs.

Our Essential QA Services and Clinical Drug Development Services are:

- Qualified Person (QP) Services & Training
- Pharmaceutical Quality Training Services
- GMP/GDP/GCP Compliance, Advice and Consultancy Services
- Pharmaceutical Quality Auditing Services
- ADME (Absorption, Distribution, Metabolism and Excretion) Services & Training
- Pharmacokinetics Services & Training
- Pharmacogenomics and Personalised Medicine Services & Training
- Clinical Pharmacology Training

We hope this guidance document will be useful to you and that you find it beneficial in gaining knowledge with respect to investigating OOS analytical results. This guide is of course free for you to use within the terms of the copyright. If you would like any further information on the topic in this guide, require any of our services or indeed would like to see further guides developed on topics of interest to you, we'd love to hear from you. We can be contacted as follows:

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