Dr. Markus Limberger

GMP Series

Industry Guide to handle OOX Test Results

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Excerpt from the GMP Compliance Adviser

Contents

1 Test results outside defined criteria (OOX)

Dr. Markus Limberger

Here you will find answers to the following questions
- Where did the concept of OOX originate?
- What is the purpose of the OOX concept?
- What is the GMP-compliant approach when criteria are not met?
- What are the different types of cases?
- For which processes can the concept be used?
- What is the correct way to document the process?

1.1 Introduction

The main objective of the pharmaceutical industry when manufacturing and testing active ingredients, excipients and proprietary medicinal products is to guarantee the quality and safety of the product and thus the safety of the patient. The introduction of the Good Manufacturing Practice (GMP) guidelines for the production, testing, storage, transportation and distribution of medicinal products established an internationally recognised quality standard for meeting this objective. The GMP guidelines are now part of national and supra-national laws and guidelines (e.g. Medicinal Products Act, EU GMP Guidelines, Code of Federal Regulations). A GMP-compliant and proper handling of results that are outside defined criteria (OOX results) indicates the level of GMP understanding among the personnel/entities dealing with the situation. For this reason, regulatory inspections have a tendency to focus on this issue.

Despite the brisance that OOX results bring with them, a correct and confident handling of these types of result can be used during audits to demonstrate high quality standards. A structured approach to error analysis and data evaluation also provides very valuable information. This information can then be used to improve the standard of quality.

1.2 History and significance

At the end of the 1980s, the FDA carried out an investigation involving a number of generic drug manufacturers as a result of serious quality irregularities (including missing trial data and false approval documentation) in which FDA officials were also involved. Under new management, the FDA took drastic action against these types of violation and introduced *pre-approval Inspections* (PAI). A priority of these inspections was how results outside the norm (*out-of-specification results*) were being handled.

The legal case that the **FDA** won against Barr Laboratories in 1993 played a seminal role in the development of a concept for handling OOX results and the guidelines that followed. The measures specified in Judge Wolin's decision were meant to put an end to the practice of *testing into compliance* (i.e. testing until a specification-compliant result was achieved) despite the product being of inferior quality. Particular emphasis was placed on the approach taken when examining OOS results. These results should be examined using scientifically sound and valid methods (e.g. using a thorough and structured error analysis. In addition, concrete measures must be defined to ensure that a final decision can be made on whether to use the product or not (e.g. definition of repeat analyses).

Guidelines for dealing with OOS results

The court decision only applied to that particular court case, but was acting as state-of-the-art for science and technology from now on. The case led to the FDA drafting and presenting guidelines for handling OOX results in 1998, which were finalised in 2006 and are now recognised worldwide as the

gold standard (*Investigating Out-of-specification (OOS) Test Results for Pharmaceutical Production*). This is also due to the fact that although this topic is dealt with in the German Medicinal Products Act and the EU GMP Guidelines, it is dealt with in greater detail in the FDA guidelines. It is worth mentioning that bioanalytic tests (in-vivo tests, immunochemical analyses) and microbiological tests are not included in these guidelines.

In addition to this basic guideline, the *Guide to Inspections of Pharmaceutical Quality Control Laboratories* was issued in July 1993 and a revision of 21 CFR 211.192 (Federal Register Vol. 61, May 1996) initiated.

Another detailed resource is the MHRA's *Out of Specification Investigation,* published in the UK in 2013[1].

1.3 Terminology and definitions

To improve understanding of this chapter, important terms are explained below.

OOS result
Out-of-Specification result: these specifications are taken from the approval and registration documents of the medicinal product and the DMF (Drug Master File) as well as the resultant testing instructions. The requirements of the current pharmacopoeias (Ph. Eur., USP etc.) also apply.

OOE result
Out-of-Expectation result: Out-of-Expectation results can, for example, be exceeded internal warning limit values or relevant statistical parameters, or implausible results in the case of unilaterally determined criteria. It is also important that an OOE result is defined using a previously defined and documented criterion.

OOT result
Out-of-Trend result: an Out-of-Trend result is the deviation of results compiled during a predefined chronological sequence (obvious deviations when compared with preceding results). OOT observations are mainly (but not exclusively) carried out during stability studies. The evaluation should be based on prospectively defined mathematical models or trend calculations.

OOC result
Out-of-Calibration result: Deviations from criteria when calibrating and qualifying devices. The result of a qualification/calibration is OOC when the result of at least one of the test items deviates from the acceptance criteria defined in the device SOP.

OOL result
Out-of-Limit result: deviations of process parameters, monitoring data and environmental monitoring. These events describe non-compliance with criteria which are not caused by the quality of the inspected product, but could significantly affect the quality of the product.

Laboratory error
Deviation of an analytical result from the true value as a result of an error made during testing, e.g. as a consequence of technical problems. A differentiation is made between obvious errors (obvious from the raw data) and non-obvious analysis errors. Non-obvious errors are caused by undetected latent errors which cannot be seen during visual inspection or identified/reconstructed from the initial raw data.

1. *MHRA (Medicines and Healthcare Products Regulatory Agency) Out of Specification Investigation, 2013*

Product error
Deviation of an analysis result from the true value, caused by insufficient product quality as a consequence of errors during manufacture.

There are two types of product error:
- errors that are not related to the manufacturing process (e.g. inaccurate weighing, incorrect labelling during packaging, incorrect environmental conditions)
- errors that are related to the manufacturing process (e.g. processes that are not sufficiently validated, technical failure during manufacture, equipment failure)

Sample error
Deviation of an analysis result from the true value as a result of incorrect sampling (e.g. sample mix-up, incorrect sampling method, incorrect labelling of the test sample etc.), changes to sample quality after they have been taken.

Confirmatory measurements
Confirmatory measurements are used to identify non-obvious laboratory errors. The results are never included in the final result. The types of confirmatory measurement that can be carried out include:
- Reinjection
- Redilution
- Re-extraction
- Rehomogenisation of the sample.

The measurements are carried out using the same samples (blended samples) as well as sample and standard solutions.

Full-scale investigation
Expansion of the error analysis to include sampling, storage, transport and production.

Retesting
Repeat of the entire analytical procedure using the same sample including sample preparation, preparation of new solutions and dilutions (complete analytical procedure).

Resampling
Repeat of sampling from original batch in accordance with a predetermined plan. It may only be carried out if a mistake was made during sampling, the sample was not properly stored or the sample is not large enough for a retest.

Sample preparation
Sample preparation includes all measures required to get the product for analysis into a state for feeding directly into the relevant analysis equipment.

Procedure
The analytical procedure includes all of the tasks involved in sample preparation, measurement and evaluation.

Measurement result
The values produced by analytical measurement (= raw data e.g. absorption values, peak areas, etc.).

1.4.2 Error analysis

After the OOS result is detected and the process initiated, the costliest but most important phase of the process begins: the error analysis. It is divided into several phases.

The process begins with an error analysis in the laboratory environment. A distinction is made between:

- obvious laboratory errors (error analysis 1, errors which can be identified using raw data) and
- non-obvious laboratory errors (error analysis 2, errors which cannot be identified using raw data).

Obvious laboratory errors

Obvious errors occur when the analysis is carried out incorrectly (undesired deviations from stipulated analysis parameters) or by documentation errors. The error analysis should at least check the typical sources of error shown in figure 2.

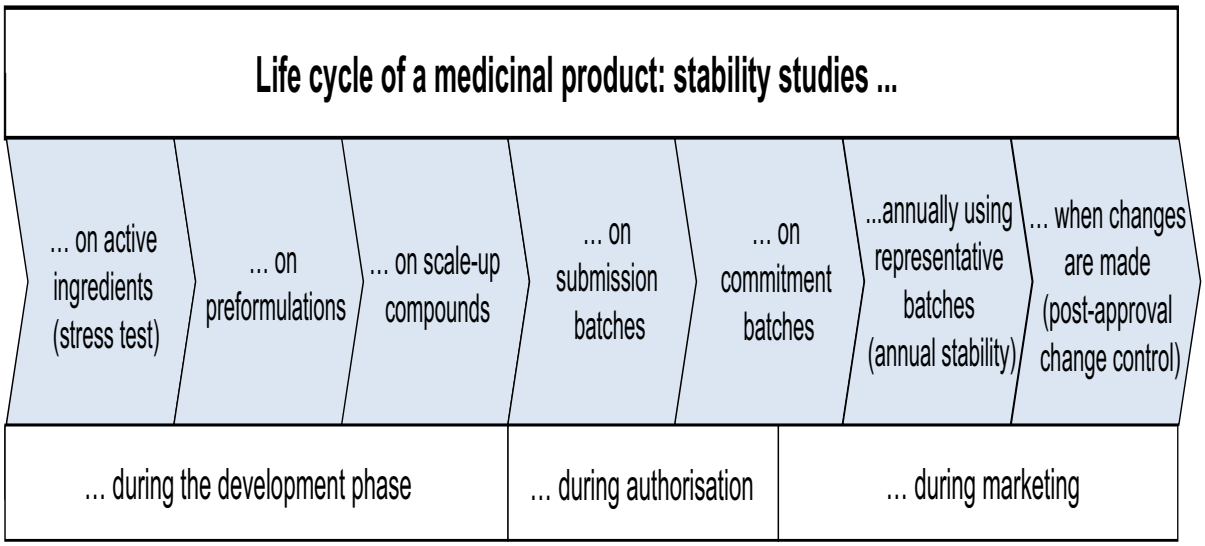

Figure 2 Sources of laboratory errors

The check is generally documented using a checklist. An example is shown in figure 3.

Error field	Checklist (yes/no/not applicable)
Test documents	Were the correct test documents used? Were the test documents used correctly? Were the test documents properly covered during training and understood? Was an error identified in the test documents? Has the test method been validated/transferred?
Sample	Were the correct samples used? Are the samples intact? Were proper storage conditions observed?

Figure 3 Checklist for evaluating obvious laboratory errors

To identify possible non-obvious laboratory errors, confirmatory measurements are carried out. It is extremely important to retain all affected test samples, blended samples and solutions under proper conditions and not discard them. The confirmatory measurements must be carried out using the same blended sample as well as the same sample and standard solutions.

Confirmatory measurements can include:

- Remeasurement using identical solution, e.g. reinjection: repeat injection of available test solutions using the same standard solutions (non-identifiable equipment failure)
- Redilution or re-extraction: repeat preparation of test solution using available stock solutions or repeat of the extraction phase of the corresponding test solution in accordance with the test specification (non-recognisable error during sample preparation)
- Rehomogenisation: repeat preparation of the test solution after additional homogenisation of the identical blended sample and measurement of the required aliquot (non-recognisable error during preparation of the blended sample or insufficient homogenisation).

This list could be extended indefinitely and depends on the approach taken to analytical testing. The selection of suitable confirmatory measurements must be planned individually with the responsible analytical entity.

Confirmatory measurements only serve to identify non-obvious laboratory errors and are generally not used in the evaluation of the test product. After a laboratory error has been identified, retesting must be carried out in accordance with the test specification. Any initial results must be invalidated and a reason given. Only the result of retesting is used when calculating the final result. The procedure is again concluded with the definition of CAPAs.

This part of the OOX process is graphically illustrated in figure 4.

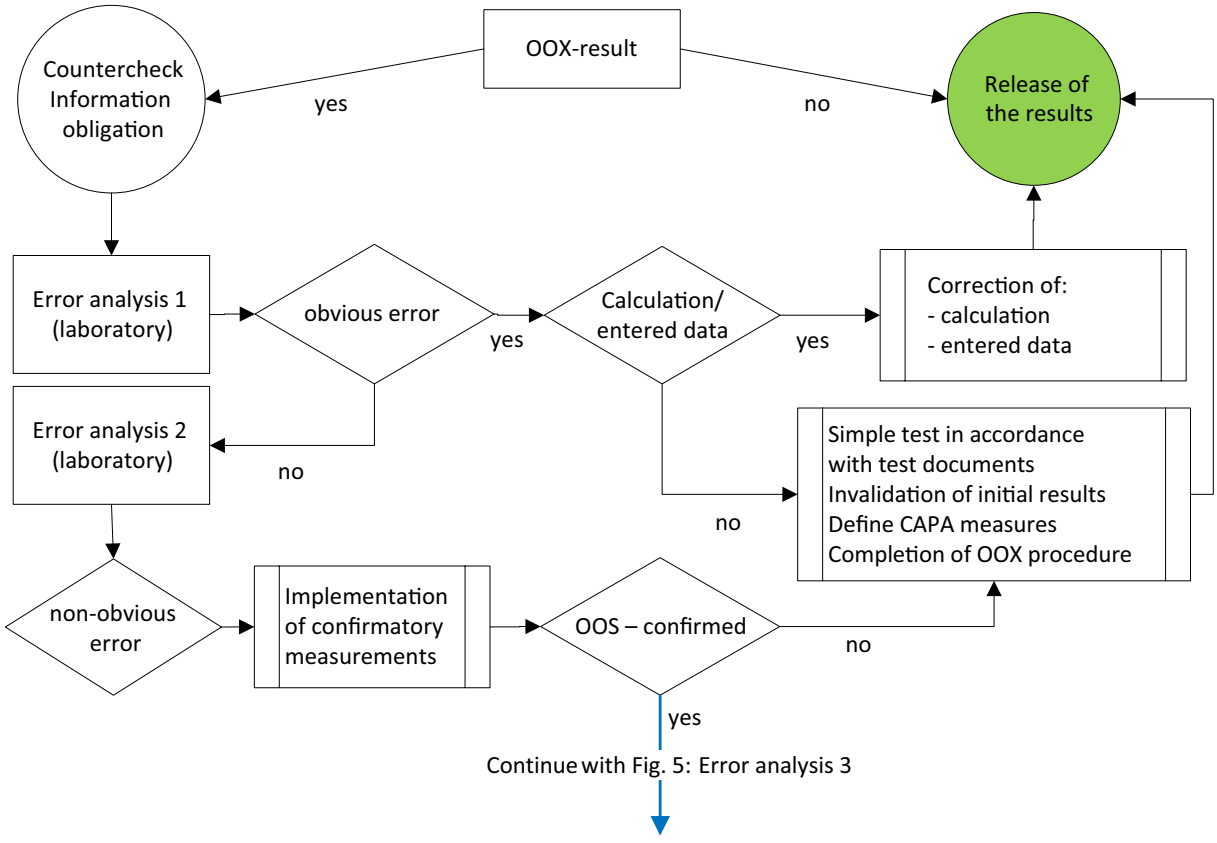

Figure 4 OOX process flow diagram (Part 1)

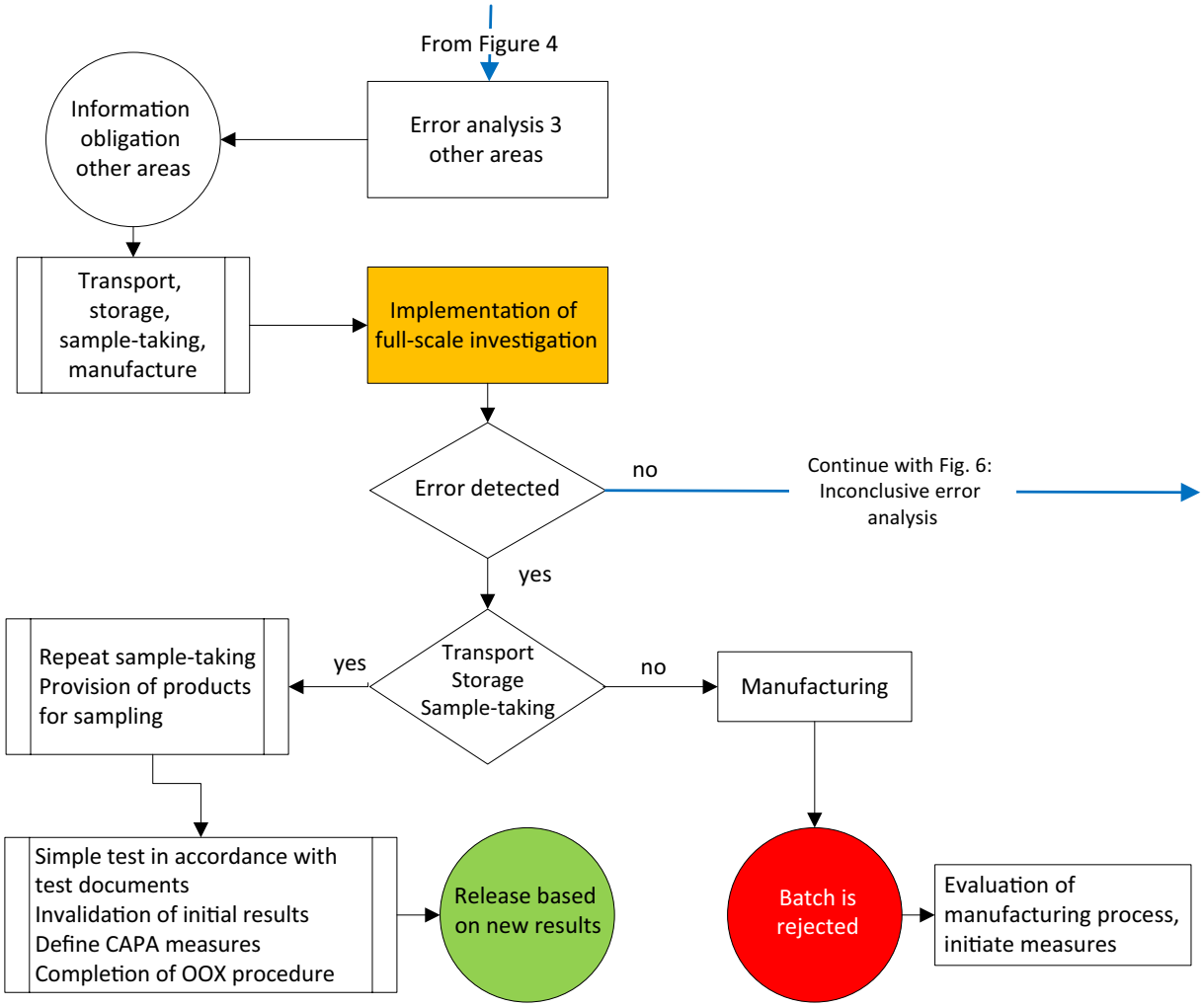

Figure 5 OOX process flow diagram (Part 2)

If the retesting results meet the specifications, an overall result is determined taking the initial result into account. This result as well as the individual results are included in the evaluation of the product. A comparison with other mean values, regardless of how they were calculated, must be strictly avoided. From an official point of view, this also applies to tests that describe batch variability, such as the content uniformity or dissolution testing.

The inclusion of the initial result can only be waived if justifiable reasons are given, because an error was not detected. The use of outlier tests is not recognised. The results of other test points can be presented as additional information and improve the evaluation of the retesting results. The OOS procedure is concluded when approved by the relevant functions.

Retesting results: OOS result is confirmed:

At least one retesting result is outside the specifications.

The OOS result is confirmed if at least one retesting result is outside the specifications. The overall result is reported with the initial result included. The batch is evaluated as OOS and rejected. A decision on how to proceed is made by the responsible QP.

It is important to note that the evaluation of the batch as an OOS batch does not remove the obligation to determine the reason for the reduced quality of the product. The process is not deemed complete until this question has been dealt with.

It must also be pointed out that raw data which is already documented must not be destroyed, and OOS procedures, especially repeat phases, should not be used as a standard process in the case of

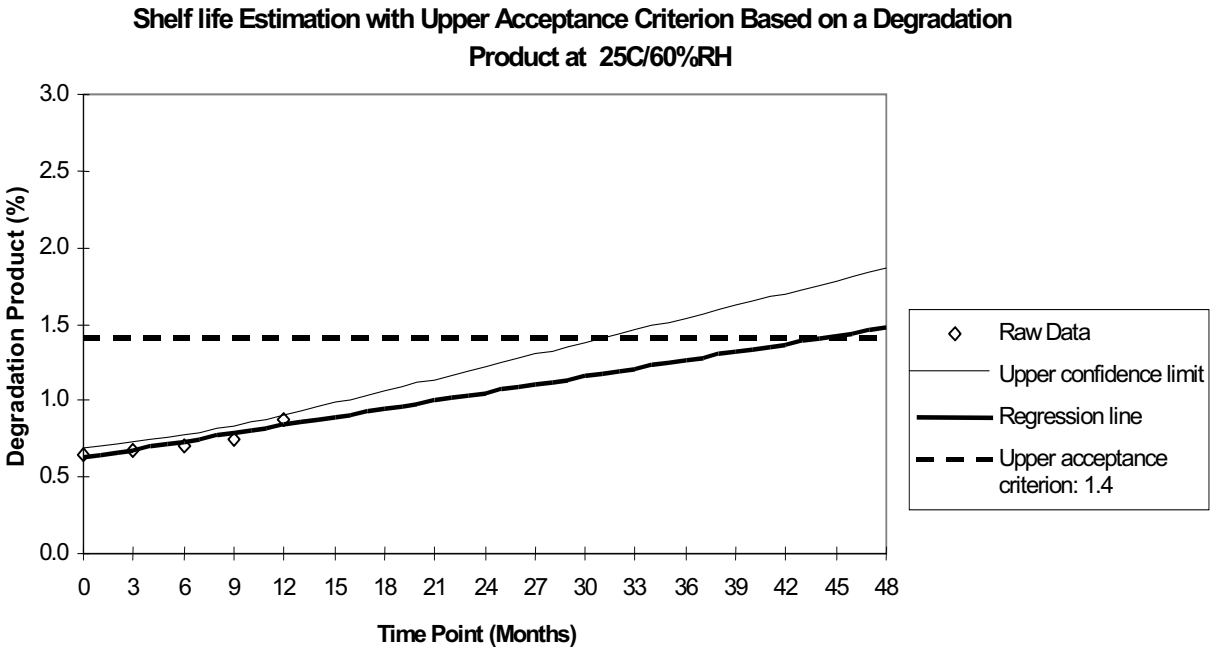

Figure 8 Example of the prediction of durability using a trend calculation for a by-product (taken from ICH Q1E)

case of IPC parameters or release data indicate an undesired insidious change which can result in the process "getting out of control". In this respect, the detection of OOT results can also facilitate early intervention. The operative approach to the OOT process corresponds to the OOS process.

1.7 OOX results during calibration and qualification

Out-of-Calibration and Out-of-Limit results can be summed up using the term OOX result. An OOC result is the non-fulfilment of criteria during the calibration and qualification of devices as well as the potential loss of the qualification and/or calibration status. The term OOC includes the areas of qualification and calibration. Non-compliance with defined process parameters (e.g. during manufacturing processes) is referred to as OOL.

1.7.1 Out-of-Calibration (OOC)

Even if non-compliance with set values during calibration or qualification is not caused by or directly related to the quality of the inspected product, it can still have a negative impact on quality and must be seen as critical.

Examples of OOC cases:

- Routine calibration of laboratory equipment (scales, pH meters, hardness tester, disintegration testers, Karl Fischer titrators, etc.): measures to be carried out immediately if the calibration limits are exceeded should be defined (e.g. in the device SOP). These measures must be carried out before the OOC procedure is initiated (e.g. checking and cleaning of equipment).
- Repeated non-compliance with SST criteria whereby normal user errors or method-immanent errors must be ruled out.
- Non-compliance with criteria during equipment qualification (IQ, OQ, PQ)
- Device errors

OOC process steps

After the OOC result is identified by the respective employee, the OOC procedure is initiated with the implementation of the mandatory countercheck (4-eyes principle) of raw data and fulfilment of the

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Special activities:
Seminar lectures on the following topics:

- Method validation and transfer,
- handling standard substances in a GMP environment,
- optimising and increasing the efficiency of laboratory processes,
- proper handling of OXX results,
- error analysis in pharmaceutical analysis