Test results outside defined criteria (OOX)

An excerpt of the GMP Series Download Industry Guide to handle OOX Test Results

by Dr. Markus Limberger

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.

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).

What are the different types of cases?

Although the procedure was initially used for out-of-specification (OOS) results only, it was subsequently expanded as part of a growing awareness of quality to include results that deviate from expectations (OOE), trends (OOT), calibration values (OOC) and process parameters (OOL). All of these considerations are used to identify specification non-compliance as early as possible and prevent an OOS case.

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. 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.

What is the GMP-compliant approach when criteria are not met?

It is generally accepted that the cause of the error must be determined using a structured predefined procedure so that appropriate corrective and preventive actions can be defined.
When non-compliance is identified, the process is initiated. It starts immediately with the implementation of the mandatory raw data countercheck (4-eyes principle) and the mandatory communication of information (line manager, Head of QC and QA, QP, pharmaceutical company).
The process flow comprises the following steps (see GMP MANUAL, Chapter 14.H for more details and flow diagrams):

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. The check is generally documented using a checklist. To identify possible non-obvious laboratory errors, confirmatory measurements are carried out.

Full-scale investigation

If the OOS result is confirmed by the confirmatory measurements, a laboratory error can be excluded. In that case, a full-scale investigation must be launched. This means that the error analysis is extended to include sampling, storage, transport and production. It is important that the responsibilities for the coordination and implementation of the error analysis are decided upon in advance.
If no error is detected during the full-scale investigation, the process proceeds to the next phase, i.e. retesting.

Retesting

If the error analysis is without a result at this point, the result of the initial test must be evaluated as inconclusive, i.e. a conclusion could not be drawn. To clarify the situation, retesting must be carried out on the same sample of the batch being tested. Retesting is carried out on at least n=6 independently prepared test solutions (comprising all sample preparation steps).
If necessary, an identical second device can be used for retesting and/or testing can be carried out by a second analyst.

Concluding the OOS procedure and subsequent measures

The procedure is formally concluded when signed and approved by the responsible management functions (e.g. QC, QA, QP). The responsible QP makes the final decision on whether to reject or release the affected batch.
All the results of the concluded OOS procedure are then archived, e.g. by the QA department. A central register is kept there and trend analyses or other evaluations of the cause of OOS cases are carried out. The evaluations are used to generate Key Performance Indicators (KPIs) and for addressing the subject at the General Management Review.
If CAPAs (Corrective Action and Preventive Actions) are specified as a result of the error analysis, they must be coordinated and carried out after the OOS procedure. The conclusion and effectiveness of the CAPAs must be monitored. This is normally carried out by QA within the framework of the CAPA system.

For which processes can the concept be used?

The OOX process also plays an important role during method transfers, validations and outsourcing. If the predefined responsibilities and documentation requirements are observed, the OOX process can also be carried out properly in an unproblematic way when third parties are involved. All persons involved should undergo thorough training.

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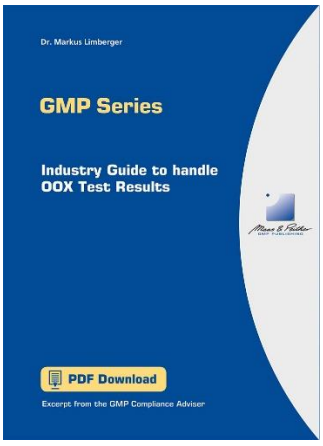

It deals in detail with the following issues:

- History and significance
- Terminology and definitions
- Out-of-Specification (OOS)

- Out-of-Expectation (OOE)
- Out-of-Trend (OOT)
- OOX results during calibration and qualification
- OOX process during transfer and validations
- OOX process and outsourcing
- OOX process and document management system

Our author Dr. Markus Limberger gives answers to the following crucial questions:

- 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?
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