14.H.4 Example for handling of an OOS result

The implementation of the FDA Guideline is shown by means of an example. Many other options are undoubtedly possible (Häusler, 1999). The procedure is illustrated by a flow diagram (see figure 14.H-8). In practice, the use of forms to document the individual steps has proven extremely useful (see figure 14.H-9, figure 14.H-10 and figure 14.H-11).

Example:

Following the content HPLC analysis of product® batch 272 MFD 1299, it is discovered that one of the two values is outside the specification. According to the company SOP, an OOS investigation must be carried out to determine whether the "true" value is inside or outside. Note: all solutions must be retained until the investigations have been concluded.

As the first step, the supervisor must be informed (cf. flow diagram). It must be clarified together with the supervisor whether this is an apparent analytical error. To this end, a formal check is carried out using the Investigation of OOS results (Investigation stage 1) form (see figure 14.H-9). The sample is identified in the header (label) and the reason for the investigation is stated in the section entitled OOS result. The clarifications are documented with the help of the checklist (YES/NO). If a statement does not apply, a cross is inserted at N/A (not applicable). If no apparent analytical error can be found based on these data, this must be entered at diagnosis and a cross inserted for the initiation of OOS investigation stage 2. Corresponding entries may be made at measures. The form must be dated and signed by the analyst and supervisor.

Before further investigations are carried out during the next step, the subsequent procedure must be written down in the so-called **testing protocol** (see figure 14.H-10). This must show:

Tasks in testing protocol
• „What" is to be done (retesting, resampling, etc.)? • „Who" will be carrying out the investigations (1st analyst, 2nd analyst, etc.)? • „How" will the investigations be carried out, which equipment, which reagents, additional analysis of reference samples (state batch and number of analyses)? • „How often" will the analysis be repeated (final criterion to prevent "analysis into compliance")?

Figure 14.H-7 Data in testing schedule

A justification for the procedure must be given and the form must be signed (and therefore approved) by the analyst and supervisor prior to implementation. These specifications are then meticulously implemented and the results evaluated. The

results are summarized in a report in the form entitled Investigation of OOS results (Investigation stage 2) (see figure 14.H-11). It is recommended that all results be entered. Conclusions must then be drawn and it must be stated which individual values will be entered in the result (information on certificate). In our example, both original values will be declared invalid and not taken into account in the result. The error category of the original OOS result must also be recorded. The processing of the investigation is also extremely important. At measures, a statement must be made explaining how OOS results are to be avoided in future. The testing procedure, which is clearly not „state-of-the-art", must also be updated. .

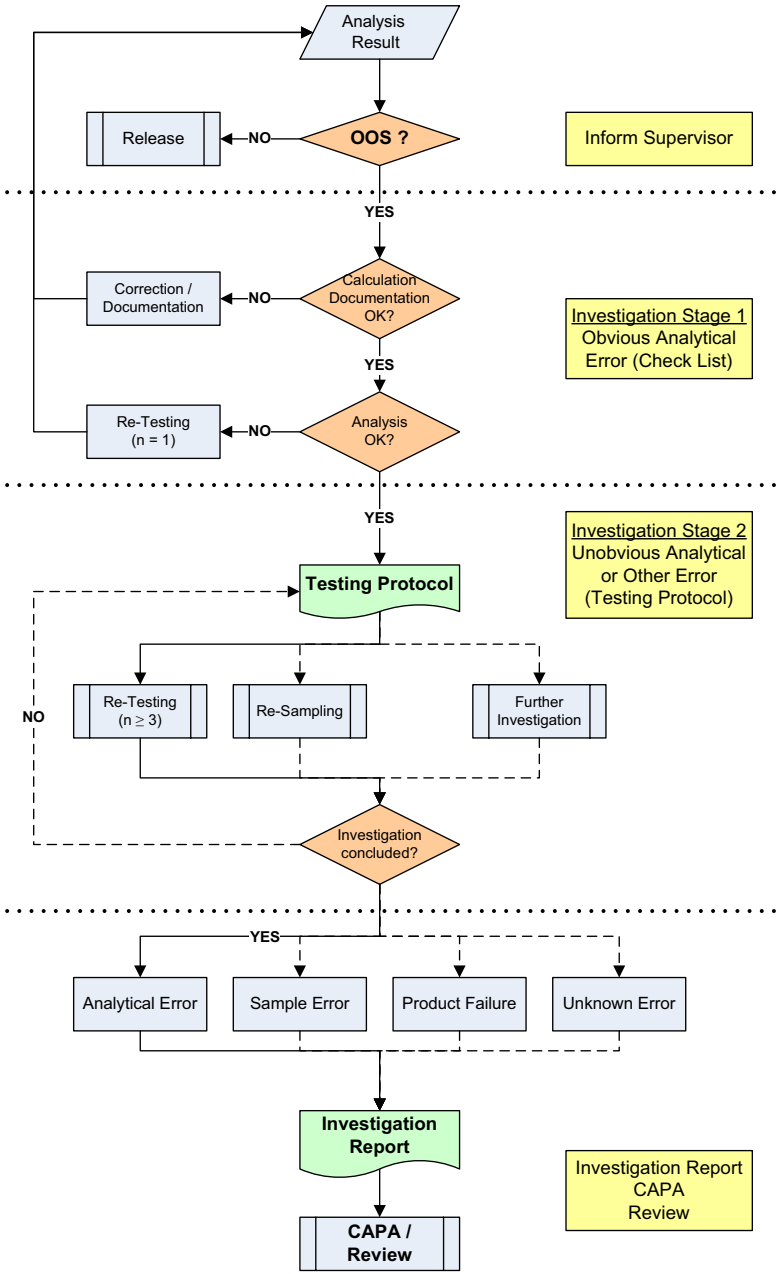
14.H.5 Trend tracking

According to the FDA, clear and complete records of OOS occurrences must be kept (in paper or electronic form). One of the follow-up activities of an OOS result is periodic review of the cases concerned. For the purposes of assessment, an OOS result may not be regarded in isolation, instead, the system should be considered as a whole. Trending makes it possible for potential risks to be revealed at an early stage therefore assisting in the prevention of future OOS results.

One of the required steps of an OOS investigation is to search previous investigation reports to determine whether a similar occurrence has previously taken place. The information gathered in this search is included in the investigation report and an assessment of the existence of a possible trend is made. If it is concluded that a trend is present, corrective and preventive actions are specified in the investigation report.

The product, the equipment, the methods and also the analysts are subject to trending. If the assay values for one product are frequently outside the specification, this may be a sign that a previously undetected laboratory or manufacturing equipment problem exists. Equipment that has a tendency to produce OOS results may have to be repaired, maintained or recalibrated. The possibility of increasing the frequency at which calibration and maintenance is carried out or replacement of equipment in extreme cases should be considered. An analogous procedure applies to the analytical methods. As the example shows, a method may need to be described in more detail to insure that it is being performed as intended and as validated. Finally, the staff must also be included in the trend investigation. If OSS errors are frequently caused by a particular member of staff, this person may have to receive additional in-depth training.

There have been instances where the retraining of laboratory analysts has been specified as a corrective action when the true root cause on an OOS has not been identified. In some cases this is a valid corrective measure. However, the tendency to attribute many OOS results of unknown cause to laboratory error with the subsequent corrective action to retrain the analysts should be minimized. Investigations containing frequent corrective actions specifying retraining of analysts can be viewed by an investigator as exposing a flaw in the overall lab training program.


Analysis Result
Release
NO
OOS ?
Inform Supervisor
YES
Correction / Documentation
NO
Calculation Documentation OK?
Investigation Stage 1
Obvious Analytical Error (Check List)
YES
Re-Testing (n = 1)
NO
Analysis OK?
YES
Investigation Stage 2
Unobvious Analytical or Other Error (Testing Protocol)
Testing Protocol
NO
Re-Testing (n ≥ 3)
Re-Sampling
Further Investigation
Investigation concluded?
YES
Analytical Error
Sample Error
Product Failure
Unknown Error
Investigation Report
Investigation Report CAPA Review
CAPA / Review

Procedure for results out of specifications (OOS results)	SOP no.	**QS-xx-nnn-vv**
	Valid from	**01. Jan 00**
	Enclosure	**2**
	Page	**1 of 2**

Investigation of OOS results (report level 1)

Sample identification (label)

OOS result

Testing point(s)	Result(s)	Specification(s)	Diagnosis
Content of active pharmaceutical ingredient	96.4 %		E
	94.8 %		NE
	x2 = 95.6 %	95.0 – 105.0 %	E

Checklist	**YES**	**NO**	**not applicable**
Documentation			
Write/transfer error	☐	☒	☐
Calculation error	☐	☒	☐
.....	☐	☐	☐
.....	☐	☐	☐
Carrying out			
Deviation from procedure	☐	☒	☐
Incorrect procedure	☐	☒	☐
.....	☐	☐	☐
Standard			
Correct standard	☒	☐	☐
Expiration date OK	☒	☐	☐
Storage OK	☒	☐	☐
Initial weight OK	☒	☐	☐
Dilution OK	☒	☐	☐
.....	☐	☐	☐
.....	☐	☐	☐

Figure 14.H-9 Form – checklist

Procedure for results out of specifications (OOS results)	SOP no.	**QS-xx-nnn-vv**
	Valid from	**01. Jan 00**
	Enclosure	**2**
	Page	**2 of 2**

Sample	**YES**	**NO**	**not applicable**
Correct sample	☒	☐	☐
Storage OK	☒	☐	☐
Initial weight OK	☒	☐	☐
Dilution OK	☒	☐	☐
.....	☐	☐	☐
.....	☐	☐	☐
Instrument			
Calibration OK	☒	☐	☐
Parameter set correctly	☒	☐	☐
Injector correct	☒	☐	☐
Detector correct	☒	☐	☐
.....	☐	☐	☐
.....	☐	☐	☐
.....	☐	☐	☐
System Suitability Test carried out	☒	☐	☐
.....	☐	☐	☐
.....	☐	☐	☐
.....	☐	☐	☐
.....	☐	☐	☐
.....	☐	☐	☐

Diagnosis	**YES**	**NO**
Apparent evaluation fault	☐	☒
OOS testing level 2	☒	☐

Measures **Repeating the evaluation in accordance with the authorised testing schedule**

	Analyst	**Supervisor**
Date	.....18.01.2000.....	.....18.01.2000.....
Signature	.....M. Schreiber.....	.....W. Schmitt.....

Figure 14.H-9 Form – checklist (cont.)

Procedure for out-of-specification results (OOS results)	SOP no. **QS-xx-nnn-vv** Valid from **01- Jan-2000** Appendix **3** Page **1 of 1**

Investigating OOS test results (testing schedule for stage 2)

Sample identification (label)

Investigations to be carried out (=test schedule)

☒ Repetition of analysis (retesting)

Analysts	Number of determinations
☒ Analyst 1	.....***6*** .....
☐ Analyst 2	.....
☐	.....

Instrument	Comments
☐ 1. Instrument	.....
☒ 2. Instrument	***inert, conditioned with active pharmaceutical ingredient***.....
☐	.....

Reagents	Comments
☐ same reagents	.....
☒ other reagents	***new mobile phase***.....
☐	.....

Other

☒ Analysis of reference sample: ***Batch 271 MFD 1099 (2 det.)*** .....

☐ .....

☐ Repetition of sampling (resampling)

☐ Sampling plan .....

☐ Additional investigations .....

Reasoning ***This class of active pharmaceutical ingredient may*** ..... ***adhere to surfaces, the analysis will therefore be repeated***. ***using an inert system that has been conditioned with the*** ... ***active pharmaceutical ingredient***.....

	Analyst	**Supervisor**
Date	..... 19-Jan-2000	..... 19-Jan-2000 .....
Signature	..... M. Schreiber	.....W. Schmitt .....

Figure 14.H-10 Form – testing schedule

Procedure for results outside the specifications (OOS results)	SOP no.	**QS-xx-nnn-vv**
	Valid from	**01. Jan 00**
	Enclosure	**4**
	Page	**1 of 1**

Testing of OOS results (report level 2)

Sample identification (label)

OOS result

Testing point(s)	Result(s)	Specification(s)	Diagnosis
Content of active pharmaceutical i	96.4 %/94.8 %		E/NE
	x2 = 95.6 %	95.0 – 105.0 %	E
Repeated examinations	98.2 %/99.1 %/		
	98.0 %/98.3 %/		
	98.5 %/98.4 %/		
	x6 = 98.4 %	95.0 – 105.0 %	E
Batch 271 MFD 1099	98.8 %/98.4 %		
	x2 = 98.6 %		
Release analysis	98.4 %/98.0 %		
(18th Nov. 1999)	x2 = 98.2 %		

Conclusions

Cause of fault: ☒ Unapparent evaluation fault

☐ Sample ☐ Product ☐ unknown

☐ other:

The results from the first examinations are invalid and will be deleted. The values of the repetition of the evaluation are used for the result. The batch may be approved.

Measures **The testing procedure is being revised and it has been noted that for the evaluation, an inert system, conditioned with an active pharmaceutical ingredient, is to be used.**

	Analyst	**Supervisor**
Date	.....19.01.2000.....	.....19.01.2000.....
Signature	.....M. Schreiber.....	.....W. Schmitt.....

Figure 14.H-11 Form – investigation stage 2

In September 2006, the FDA issued their finalized Guidance for Industry, Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations, a section of which addresses trending. This guidance describes the development of modern quality systems which is part of FDA's announced efforts to "enhance and modernize the regulation of pharmaceutical manufacturing and product quality – to bring a 21st century focus to this critical FDA responsibility".

On the topic of trending, section IV.D.1 of the guidance, states that "*Quality systems call for continually monitoring trends and improving systems. This can be achieved by monitoring data and information, identifying and resolving problems, and anticipating and preventing problems.*

Quality systems procedures involve collecting data from monitoring, measurement, complaint handling, or other activities, and tracking this data over time, as appropriate. Analysis of data can provide indications that controls are losing effectiveness. The information generated will be essential to achieving problem resolution or problem prevention …

Although the CGMP regulations (§ 211.180(e)) require product review on at least an annual basis, a quality systems approach calls for trending on a more frequent basis as determined by risk. Trending enables the detection of potential problems as early as possible to plan corrective and preventive actions. Another important concept of modern quality systems is the use of trending to examine processes as a whole; this is consistent with the annual review approach. These trending analyses can help focus internal audits …"

Necessary measures are derived from OOS results. A priority must be to put in place corrective and preventive actions by applying suitable measures. Spurious influencing factors must be eliminated to prevent unnecessary additional OOS results in the future. This will also have a direct impact on cost savings. The most urgent measures have been referred to during the trend analysis.

Summary
The handling of OOS results is the central issue of every inspection by the authorities. Companies understand the need to comply with and implement the GMP Guidelines in this area.
The release analyses of active pharmaceutical ingredients and drug products are included in the scope where specifications have been defined in the submission file for marketing authorization, in pharmacopoeias or by manufacturers.
As a basic principle, the investigation of OOS results must be carried out according to a protocol. A flow diagram and forms make it easier for all parties concerned to comply with their own OOS SOP.
The investigations must be processed carefully, efficiently, impartially and must also be fully documented and be based on scientific facts.
Preventative measures must be taken based on the conclusions drawn from the investigation to avoid further OOS results.
The trending of data (product, equipment, methods and analysts) uncovers potential problems. This leads to the development and implementation of corrective and preventive actions, which significantly decrease the occurrence of OOS incidents.
Severe measures will be taken as a consequence of non-compliance with the requirements of the authorities (FDA). Offences will be regarded as possible fraud. Apart from a refusal to grant approval for the USA market, this may also lead to further legal action and shutdown of business operations (in USA).