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GMP Series

Implementing a World Class Deviation Management



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1 Deviations

Dr. Christian Gausepohl

Here you will find answers to the following questions:

- How are deviations defined?
- What must be observed in handling deviations?
- Who is responsible for managing deviations?
- What interfaces to other systems are there?

1.1 Introduction

In spite of qualified equipment, trained employees and validated processes, the daily routine in pharmaceuticals is rife with situations in which prescribed workflows are not observed or processes fail to deliver the expected results. For this reason it is important not only to define the workflows for production in “normal cases”, but also to specify how such deviations are to be handled. This will ensure that acceptable product quality can be obtained even in the event of unforeseen circumstances.

1.2 Definition

There are many different contexts for use of the term *deviation*. No clear, sharply outlined definition can be found in the various regulatory documents in the USA or the EU. The terms used are not always the same either (for example, *deviation*, *discrepancy*, *atypical situation*, *non-conformity*).

Therefore, it is imperative for a company to define internally what is understood by the term deviation, in order to avoid vagueness and possible misunderstandings concerning workflows and responsibilities.

In the narrower sense of the word deviations represent a failure to meet specifications (such as parameter settings) in the production process, in-process specifications or production requirements. In a broader sense, however, deviations from other procedures or instructions can also be assigned to the deviation system. Depending on how the deviation system is interpreted in any given company, confirmed out-of-specification laboratory results (OOS results), for example, can also be introduced into the deviation system. The advantage of such a comprehensive structure is that relevant data from different areas can be gathered jointly and subjected to a comparative evaluation.

When deviations are being handled, **interfaces** with the CAPA system and the Quality risk management system are created. In addition, deviations are taken into account in the *Management Review* as indicators of how stable processes and workflows are.

Ordinarily, deviations are unplanned by nature. However, there are systems in which *planned* deviations are prospectively handled. This is especially true in the case of short-term deviations and/or changes in workflows or processes that are intended to run once only in a controlled manner, for instance as part of an experiment. Other examples can include taking additional samples during the manufacturing process or taking a risk when using a starting material for which the release testing has not been fully completed (for example, microbiological results not yet returned). These planned deviations are basically subject to the same requirements concerning risk assessment and additional safeguarding actions to be taken, if applicable. The important thing is to set planned deviations apart from a change within the framework of Change Control, which involves planned, *permanent* changes in existing rules or features. A deviation is no substitute for the Change Control procedure.

Area	Example
Production process	<ul style="list-style-type: none"> • Manufacturing Formula • Process parameters (e.g. machine parameters) • Process specifications (e.g. target values in production process or yield limits) • Testing instructions for in-process controls (e.g. using obsolete versions) • In-process specifications • Anomalies in the process
Machines, plants, equipment, facilities, and media (including laboratory)	<ul style="list-style-type: none"> • Machine defects • System failures • Temperature, humidity, number of particles or pressure differences outside of limits • Deviations in microbiological monitoring • Calibration results outside of limits • Failure to keep calibration or maintenance intervals
Regulations	<ul style="list-style-type: none"> • SOPs
Quality control	<ul style="list-style-type: none"> • Results out of specification (OOS) • Results out of trend (OOT) • Results close to specification limit • Using expired reference standards
Storage	<ul style="list-style-type: none"> • Anomalies in pest-control sector • Exceeding temperature limits • Anomalies in goods received procedures

Figure 1 Examples for potential deviations in different areas

1.3 Requirements for deviation management

Certain things are always expected in dealing with deviations. For instance they should be thoroughly and completely recorded and investigated. The risk arising from the deviation must be assessed. It will also be necessary to look into whether or not other batches could be affected. Suitable actions for the affected batches must be specified, if applicable, and assessed with regard to their risk for other processes as well. The effectiveness of the actions must be examined. All this can basically be done in an integrated or a separate **CAPA-system**.

The information on the deviation as well as the assessment of the risk must be available to the **Qualified Person**, who must take this into consideration for a decision on the release.

The individual aspects are explained below using the description of a workflow as an example.

1.4 Workflow of deviation management

The systematic **processing** of deviations follows a scheme that can be subdivided into different phases for better clarity. Care must always be taken that the data collected and the correlations be documented in as well-structured and detailed a manner as possible, to enable clear understanding of the evaluations and the thoughts on which they are based, even after a longer period of time. The phases described here can be handled separately or all together. If an independent **CAPA system** is used, steps 4–6 are taken within this system.

The workflows can differ, depending on the company requirements as well as the degree to which computerized systems are used.

Requirements for handling deviations	
	<ul style="list-style-type: none"> • Complete record of the deviation • Complete investigation into root causes • Risk assessment of the deviation for the current batch • Expanding the search to other, possibly affected batches or products • Specifying actions for the affected batch • Specifying actions to prevent recurrence (corrective actions) • Assessing the risk from intended actions • Defining tests for effectiveness to assess suitability of the actions • Implementing the actions • Testing effectiveness of the actions • Periodic review of the system effectiveness

Figure 2 Elements of deviation management

In principle, the general workflows are comparable (figure 3).

Phase	Aspects	Elements
1	Event documentation	<ul style="list-style-type: none"> • initial documentation • first corrections, if applicable
2	Description of problem	<ul style="list-style-type: none"> • data collection • reconciliation with risk management system
3a	Failure investigation	<ul style="list-style-type: none"> • structured investigation into possible root causes
3b	Root cause analysis	<ul style="list-style-type: none"> • test models, if applicable • extension to other batches or products, if applicable • reconciliation with risk management system
4a	Risk assessment	<ul style="list-style-type: none"> • check on whether deviation affects other batches and products • decision on whether action is required and if so, what actions must be taken
4b	Specifying actions	<ul style="list-style-type: none"> • proposals for corrective and preventive actions, if applicable
4c	Action approval	<ul style="list-style-type: none"> • examining and approving actions • specifying test models and acceptance criteria for the test for effectiveness
5	Implementing the actions	<ul style="list-style-type: none"> • monitoring status
6	Test for effectiveness	<ul style="list-style-type: none"> • monitoring status • currentness of risk assessment
7	Periodic review	<ul style="list-style-type: none"> • Risk Review • Product Quality Review (PQR) • Management Review

Figure 3 Examples for assigning phases in the systematic handling of deviations

If **IT systems** are to be used, the system must be qualified accordingly, or the application validated since the data involved are GxP critical.

The demand that risk management be conducted became a reality for the first time in the 2008 revision of chapter 1 *Quality Management* of the EU GMP Guide. For a possible recommendation for use, attention is called to the ICH Q9 *Quality Risk Management*, which was originally included into the EU GMP Guide as Annex 20 and has been relocated to Part III of the Guide (*GMP related documents*) in 2011. In this connection it is also important to point out the ICH Q10, which formulates the demands

Questions	Actual situation	Planned state
What?	Contaminated drums of starting materials were discovered in the production area at weigh-in.	All drums should be properly cleaned from the outside.
	Cleaning (vacuum cleaning) is called for at this point.	Vacuum system is available.
Who?	no cleaning in storage area	clean-up by employees in storage area
	no effective control by production logistics Warehouse staff has repeatedly completed the production logistics part as well.	check upon receipt by Production Logistics Warehouse and production logistics are organized separately in the other shifts.
	discovered by employees in Production at weigh-in	Final check by employees in Production at weigh-in prior to processing
When?	at shift start 22:30 hours, 02 May 2012	–
How often?	observed for the fourth time (15 March 2012, 22 March 2012, 29 March 2012) late shift	–
How?	purely visual inspection with subsequent vacuuming	vacuuming in handling area of warehouse
Where?	weigh-in	handling area of warehouse
Why?	visual inspection yielded unsatisfactory results	counter-inspection reveals inadequate clean-up
	no counter-inspection possible since work in shifts dictates that employee performs both duties	discrete functions performed by different employees
	Employee reduced cleaning intensity to be able to perform both duties.	Rules for performance are on hand.

Figure 5 Examples of simply structured data collection

In the event of a manufacturing deviation a decision must be made beforehand on whether **further processing** is still possible and if so up to what point. If for reasons of stability, the intermediate product affected must be further processed before conclusion of the investigation, this should be approved beforehand by the persons responsible in Production and Quality Control or by the Qualified Person. A point to be considered here is whether the intermediate product affected poses a risk for the remaining production, for instance through increased microbiological contamination due to extended holding times.

1.4.3 Phase 3a: Failure investigation

The investigation of root causes represents one of the most important but at the same time most difficult aspects of deviation management. If the root cause remains unknown and the deviation management is based on an assessment of the risk, then the deviation will have to be handled against the background of an unknown probability of occurrence. This is not helpful in terms of risk control and risk acceptance and should not simply be tolerated in this way. If no clear root cause can be determined in spite of thorough investigation, the aspects that have been ruled out as well as all results and queries made during the search must be completely documented, so that in the event of an inspection the allegation of not having conducted a comprehensive search for causes can be avoided.

Challenges faced in the failure investigation

- structured, detailed investigation of the failure
- adequate depth of the investigation
- no rash conclusion ("same as last time")
- no confusion of symptoms and causes
- no rash or opportunistic solutions
- no approaches oriented towards action or solution

Figure 7 Challenges of the failure investigation

sible risk. Generally, the follow-up costs of additional batches that are lost will be higher than those of a comprehensive root cause analysis and verification.

1.4.5 Phase 4a: Risk assessment

When the root causes have been assigned it will be necessary to check on whether additional batches of the same product or other products have possibly been affected. These checks can be referred to as *vertical or horizontal searches*. Figure 8 shows the particular investigations of each deviation observed, on a horizontal level (other products) as well as a vertical level (other batches). The investigative depth applied is not necessarily symmetrically distributed, but rather it depends on the data collected and/or the existing constellations, such as the batches of starting materials used.

The two deviations in figure 8, which were identified as isolated cases, appear at first glance to have nothing in common and no similarities. However, there could be a connection that can be traced back to a systemic error. An example of this would be fluctuating or varying results of the in-process controls (such as drying losses of granulates by infrared, or friability testing of tablets) caused by the universal use of an unsuitable calibration weight for scales.

For example, in the analogous case of deviations in calibration (such as non-observance of calibration tolerances on the set of scales), all possibly affected products or materials since the last valid calibration must be included in the investigation.

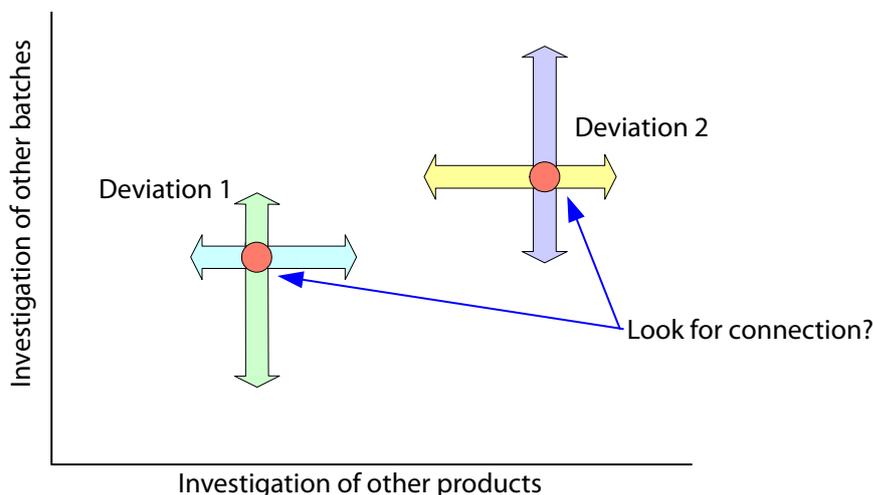


Figure 8 Horizontal and vertical search

Now, there can be a comparison with the established information in the **risk management system**. An assessment must be made as to whether the process or process environment can still be considered stable. The risk assessment and possible future costs must be taken into account here. There should be a definition of the degree of risk from which the escalation of information, i.e. forwarding the information directly to superior positions such as the company management, should take place. This *workflow* can be established with particular ease in computerised systems.

sidered for the decision on the release. Other controlled workflows that lead to the same result are also possible in electronic systems.

To ensure unequivocal identification it is helpful to number the failure investigation report, thus also numbering the deviations. For example, pre-numbered forms can be used or a unique numbering system can be created for this. These numbers should be referred to at a specific place in the investigation reports or batch-processing reports. Figure 11 shows an example.

GMP-Pharma GmbH
Failure investigation report (acc. to SOP 12345) No.:
pls. fill in immediately

Product / Machine
Batch no. / Inv. no.:
Material number

Description of the deviation (incl. immediate actions taken):
Date / Time of deviation:

Department Date / Signature:

Classification: minor / major / critical
 (by Head of Production) Date / Signature:

Failure investigation, incl. risk assessment Attached pages _____

Date / Signature:

Classification (by QA): minor / major / critical
Date / Signature:

Corrective actions:

Activity	done by	completion expected by

Date / Signature:

QA: Actions completed: YES / NO Date / Signature:

Preventive actions:

Activity	done by	completion expected by

Date / Signature:

QA: Actions completed: YES / NO Date / Signature:

QA: Conclusion Date / Signature:

Figure 11 Example of a simple, standardised failure investigation report

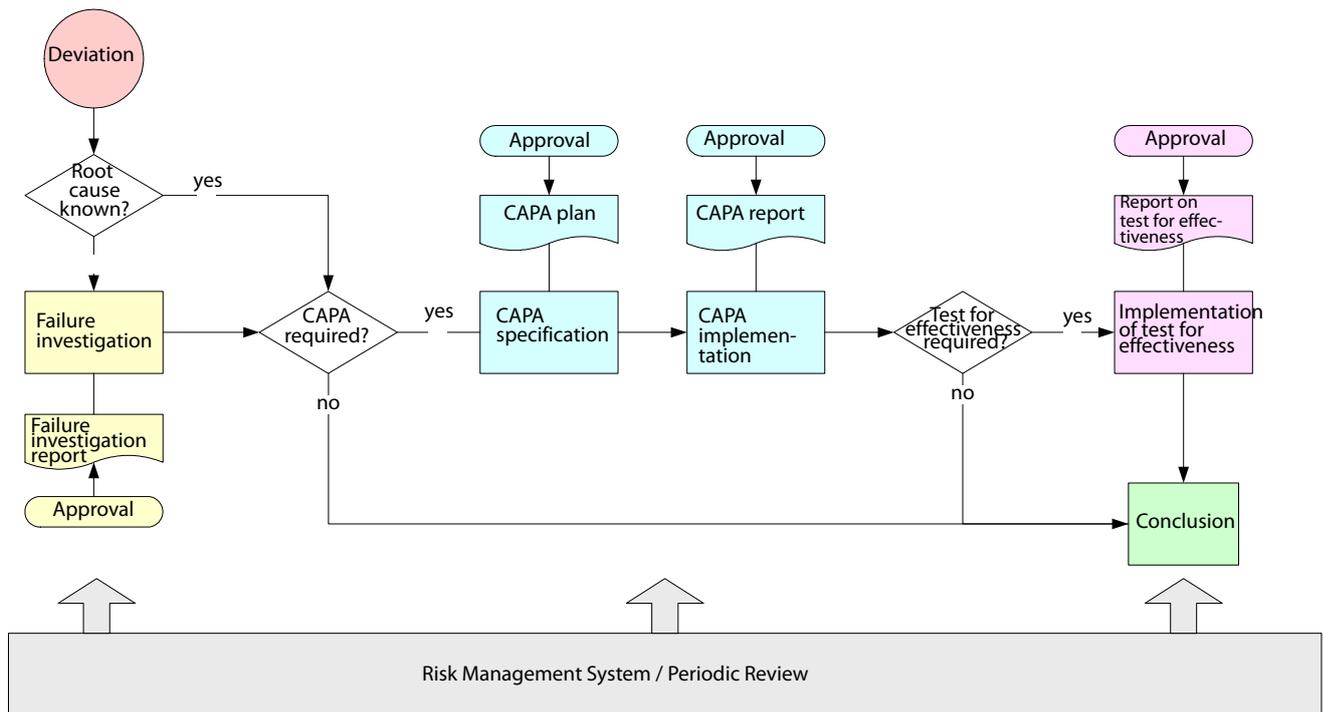


Figure 13 Example of a possible workflow of deviation management

Data collection and documentation

A notification of deviation is created by the Department Head and the known data are documented:

- date, time of notification of defect
- equipment affected
- product affected
- process status at the time of the defect
- description of immediate actions, including process parameters

Parallel actions

The temperature sensor is replaced and identified as being defective. The installation is followed by a new calibration. Both procedures are documented in the equipment logbook.

Risk assessment

In the first risk assessment the inlet air temperature of the process and the corresponding temperature curves of previous batches are examined. If the thermic sensibility of the product is taken into consideration, then a low risk for the quality and stability of the product is expected. This assessment is made by the Heads of Production and Quality Control as well as the Qualified Person.

Data collection und failure investigation

The review of the logbook and the calibration history reveals no anomalies or accumulation of defects at the coater in question. All maintenance and calibration intervals were observed. The possibility that the sensor was incorrectly or inexactly installed, thus causing the subsequent damage, is investigated and ruled out. The evaluation of the order lists reveals three additional defective temperature sensors (on fluidized bed dryers) within the past 12 months. It is found that the supplier of the sensor has changed to a new manufacturer. Up to now this information has been considered uncritical. A check reveals that possibly affected production equipment that also contains these temperature systems is equipped with alarm functions for monitoring the sensor activity. Therefore, a risk to other processes is ruled out.

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