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Responsibilities for Deviation Management

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1.E.4 Responsibilities

Deviation management is an important part of the Pharmaceutical Quality System, for whose existence and effectiveness the management is ultimately responsible. The responsible persons in the pharmaceutical company, e.g. the head of manufacturing and quality control and the qualified person, play an important role in this context. They are responsible for applying the existing system. They shall also participate in the root cause analysis and the implementation of the actions. Frequently, deviation management is managed via quality assurance as the system owner. In addition, quality assurance monitors compliance with framework requirements such as adherence to time limits, the status and effectiveness of CAPA actions.

1.E.4.1 Qualified Person

The deviation management system is of particular importance for the qualified person (QP). Ultimately, the QP must be able to rely on the functionality and effectiveness of the deviation management system

Since the QP has to evaluate the deviations for a batch within the scope of his/her release decision, it is advisable to involve the QP already in the approval of deviations. In this way, questions and perspectives of the QP can be taken into account at an early stage and not only at the time of release. It has proven useful to have minor deviations closed by central functions such as quality assurance in order to make the processes efficient and to relieve the QP. The deviations must be closed and the respective reports must be available to the QP at the time of the release decision. This can be done either electronically or in paper form. It makes sense to link electronic deviation systems with the system used for release. This ensures that all deviations (from the starting material through intermediate stages to the final product) are directly and completely available and included in the assessment.

Annex 16 describes which requirements are placed on the QP when dealing with deviations in the context of release (Figure 1).

Requirements for handling of unexpected deviations
Provided registered specifications for active substances, excipients, packaging materials and medicinal products are met, a QP may consider confirming compliance or certifying a batch where an unexpected deviation concerning the manufacturing process and/or the analytical control methods from details contained within the marketing authorisation (MA) and/or GMP has occurred. The deviation should be thoroughly investigated and the root cause corrected. This may require the submission of a variation to the MA for the continued manufacture of the product.

Requirements for the release of batches with deviations

Certification and release of batches with deviations is only possible if the following core

requirements are met:

The registered specifications are met.

This includes the registered specifications of active ingredients, excipients, packaging materials, and those of bulk and finished product. If these specifications are not complied with, the QP would not be able to certify/release the affected batch. For in-process controls, the individual risk must be assessed, e.g. depending on the quality attributes tested, the effect on subsequent production steps, and the possibility of testing the quality attribute on the finished product.

The deviation is unexpected.

Only unexpected deviations fall under the definition of Chapter 3 Annex 16. Conversely, this means that repeat deviations cannot be accepted because they are not unexpected. If a deviation is detected at a later stage in a manufacturing campaign, these deviations can still be considered as unexpected until the time of detection. Subsequent deviations are not acceptable and should be submitted as variations to the MA. Exceptions to this can only be accepted if this is approved by the authorities in order to avoid supply disruption and the implementation of actions (CAPA) is in progress.

The deviation relates to the processes and methods in manufacturing and testing from an approval or GMP perspective.

The deviations in production and quality control do not concern the registered specifications, but the production processes or analytical procedures described in the MA, or they are GMP deviations, such as non-compliance with instructions.

The deviation has been thoroughly investigated and its root cause has been eliminated.

The deviation has been investigated within the framework of the deviation management system, the root causes have been determined and the effects with regard to their risk have been examined within the framework of quality risk management. Actions have been initiated accordingly.

Impact on quality, safety or efficacy is negligible.

It must be shown that the possible impact on the quality, safety or efficacy of the batch or batches concerned is either non-existent or negligible. This is an elementary evaluation within the deviation management.

The need for a stability study has been assessed.

Consideration must be given to whether a stability study is neccessary for the affected batch(es) to detect possible effects of the deviations on the stability of the product.

For biological medicinal products, all deviations have been evaluated.

For biological medicinal products, special reference is made to the fact that any deviation may have unexpected effects on safety and efficacy, thus taking into account the higher

complexity.

If the above conditions are met, the QP may consider certification and release despite deviations. The rationale for the decision must be documented in a comprehensible manner. If multiple QPs are involved in the manufacture, control or certification of the batch, the final certifying QP must be aware of any deviations from regulatory or GMP compliance. This is usually described in the respective quality agreements. One possible way is to list the deviations in the respective certificate of compliance for the individual manufacturing step.

1.E.4.2 General responsibilities

Figure 2 shows how the responsibilities of the various functions can be distributed in deviation management. In this example, the deviation is initially reported by the technical department and the deviation is opened by the system. The actual analysis of the root cause and the preparation of the deviation report is carried out by an appropriately competent team (investigation team) (see also 1.E.3.4 Root cause analysis (phase 3a), section "Challenges in root cause analysis").

As the system owner, quality assurance is responsible for the deviation management system as such. In addition to the technical system, this also includes monitoring compliance with the requirements for the process as well as monitoring deadlines. In this example, quality assurance is also responsible for

- checking the content of the deviation, including the risk assessment and CAPA plans,
- the classification of the deviation (minor/major/critical), and
- the approval of the deviation on the quality assurance level (here: minor deviations).

In the further course, the tracking of CAPAs as well as the acceptance of CAPA extensions, the assessment and completion of the implemented actions as well as their effectiveness check also fall within the responsibility of quality assurance. Finally, quality assurance also performs a periodic system evaluation, data compilation and trend analysis for management review.

The heads of manufacturing and quality control evaluate deviations from risk and CAPA plans. In this example, they also approve the deviations at the department management level and the CAPA plans for their area. They also support the implementation of the CAPA plans in their department by providing the appropriate resources.

In this example, the QP approves the deviations including the CAPA plans at the QP level. In the case of complex or major deviations, the QP can also be called in for investigations as part of the root cause analysis and risk assessment in order to bring in the QP perspective at an early stage. Approval of the deviation also documents the corresponding risk acceptance. The QP must consider all deviations in the certification process according to the requirements of Annex 16. Based on the data compilations, assessments and trend analyses of the quality assurance, the QP can evaluate the deviation system with regard to its performance, reliability as well as strengths and weaknesses.

As part of its overall responsibility, management is responsible for providing the appropriate resources for deviation management. This concerns both the capacity and

the competence of the persons involved. The suitability and appropriateness of the deviation management system can be assessed on an ongoing basis via the management review.

Figure 2 Examples for functions and responsibilities in deviation management

Function	Responsibility
Techical department	• Notification of deviation • Compilation of initial data and information • Implementation of CAPA plans
Investigation team	• Root cause analysis • Final record • Risk assessment • Suggestions for CAPA plans
Quality assurance	• System owner • Supervision of compliance with general requirements, deadlines • Content check of deviation, risk assessment and CAPA plans • Classification • Approval of deviation on QA level • Tracking of CAPA actions • Approval of extensions for CAPA actions • Assessment and closure of CAPA actions, including effectiveness check • System evaluation as well as data compilation and trend analysis for the management review
Head of manufacturing/quality control	• Assessment of the deviation with regard to risk and CAPA plans • Approval of deviations at the department management level • Approval of CAPA plans • Implementation of CAPA plans • Support of CAPA implementation
Qualified person	• Involvement in investigations for complex or major deviations • Approval of deviations at QP level • Approval of CAPA plans • Risk assessment and risk acceptance • Consideration of the deviation in the certification process • Evaluation of the deviation system
Management	• Providing ressources for deviation management • Management review for the evaluation of deviation management in the pharmaceutical quality system

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