

Deviation management in the context of ICH Q9/Q10

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The Spanish Association of Industrial Pharmacists (AEFI) monograph *ICH Q9 Quality Risk Management* not only describes the general principles of risk management set out in that guideline, but also takes an approach that is highly practical for the pharmaceutical industry. It therefore contains examples of how to use various risk analysis tools, including definitions, usage, objectives, operation, and advantages and disadvantages in each case. This article forms part of one of the examples of the use of failure mode and effects analysis (FMEA) risk analysis tools.

En la monografía de AEFI *Gestión de los riesgos de calidad ICH Q9* además de recoger los principios generales de Gestión de Riesgos desarrollados en esta Guideline, se ha realizado una aproximación eminentemente práctica para la industria farmacéutica. Por ello se presentan ejemplos de aplicación de las diferentes herramientas de análisis de riesgos incluyendo su definición, aplicación, objetivos, operativa y ventajas e inconvenientes en cada uso. Este artículo forma parte de uno de los ejemplos de aplicación de las herramientas de análisis de riesgos FMEA (failure mode and effects analysis).

Key words: ICH Q9/Q10, risk management, critical and non-critical deviations, flowchart, failure mode and effects analysis

Introduction: deviation management issues

In general terms, a deviation is non-compliance with an established standard. The EU Guide to Good Manufacturing Practice (GMP) states that any deviation from the approved requirements and procedures must be documented and explained.

The concept of deviation is so broad that deviation management as applied to the pharmaceutical industry presents a few problems, such as:

- A tendency towards deviation overload, because “everything is reported”. This can result in poor investigation of the root cause, and poor analysis of the effectiveness of the corrective and preventive action (CAPA) implemented.
- Thorough handling of all deviations can exhaust the available resources and mean that a really important problem is not dealt with properly. From a business point of view, it is best to assign resources according to the importance of each incident/deviation.
- Evaluating the criticality of each individual deviation also uses up valuable resources. If critical points in the process and critical product quality attributes have not been defined in advance, each new deviation that arises means a new investigation.

- Difficulties in quantifying the effectiveness of corrective/preventive actions taken, and in communicating them to the rest of the organisation.

Using risk management to handle deviations

ICH Q9 (now incorporated in the EU GMP Guide as Annex 20) suggests applying the risk management process to both productive processes and procedures involved in the quality management system. Deviation management is one of the latter, and can be optimised by using risk management tools in two main ways: prioritisation and decision-making.

- *Prioritisation:* The tool is used to classify undesirable events according to pre-established criteria. The aim is to tailor the handling of the deviation, depending on the risk it presents to product quality. This is a preliminary “screening” phase that allows the subsequent treatment of irrelevant events to be simplified.
- *Decision-making:* The tool is used to examine the impact of the deviation on product quality, and to justify ensuing preventive and corrective actions. This is really a risk analysis of the process in which the deviation arose. In this way, events are not assessed in isolation, but their severity and probability are already defined in the history. New entries update the process risk matrix, facilitating risk review.

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Using risk management to deal with deviations provides a consistent framework for decision-making based on documentary and scientific records, while also enabling decisions to be confidently upheld before the regulatory bodies.

Two examples are given below for using risk management tools to classify and handle deviations:

- Flowchart for deciding the criticality of deviations;
- Failure mode and effects analysis (FMEA), introducing the probability of a problem not being detected.

Of the many tools described in ICH Q9, FMEA is one that is adapted and used in a related sector, *ie* the medical devices industry.

In the examples, it is assumed that the process in which the deviation arose has undergone appropriate risk analysis, so the following are known:

- Failure (deviation) history with associated severity assessment criteria;
- Probability data for the most commonly occurring failures (deviations);
- Critical points and/or stages in the process;
- A definition of the product's critical quality attributes.

The same methodology is employed in both examples:

- Analysis phase (differs according to the tool used in each case);
- Classification phase;
- Treatment phase.

Using a flowchart to manage deviations

In order to classify and define the handling of events (potential deviations), a system such as the following can be set up.

Analysis phase

The aim of this phase is to place the event that has occurred into one of the pre-established categories.

This is done using a decision tree based on a set of questions with yes/no answers, directly defining the category of the event:

- Q1: Are the corrective actions to be taken described in a procedure?
- Q2: Does the deviation affect critical quality attributes?
- Q3: Does the deviation affect critical process parameters or stages?
- Q4: Does the deviation affect the calibration of instruments that measure critical process parameters or quality attributes?

Classification phase

Having followed the strategy, the event is classified into one of the following categories:

- Incident;
- Non-critical deviation;
- Critical deviation.

Treatment phase

Based on the category into which the event has been placed, actions are taken as follows:

- *Incident*: If the event is classed as an "Incident" it is closed, as the actions required to resolve it are described.
- *Non-critical deviation*: The process deviation database is consulted to see how many times it has happened. If the specified maximum number of repeats allowed has not been exceeded, the event stays in the "Non-critical deviation" category. The appropriate corrective measures are then applied and the deviation is closed as an isolated occurrence. This event is then entered in the process deviation database, to feed into and update the general FMEA for the process.
- *Critical deviation*: The event is placed in this category:
 - when the answers given in the decision tree point to a "Critical deviation";
 - if it was first classified as "Non-critical", but has exceeded the maximum number of repeats allowed.

When a critical deviation occurs, a full assessment of its impact on product quality must be carried out, using the established tool for general process risk analysis.

It is worth noting that other tools, eg fault tree analysis, can be used to determine the root cause of any type of deviation. Once the cause is known, the appropriate corrective and preventive measures are put in place and the risk levels are recalculated. Lastly, the final report is written, and the event is closed.

This information will be used to update and feed back into general process risk analysis at the time of risk review.

Figure 1 illustrates the event-management scheme described above.

Example of using a flowchart to manage deviations

Description of event

Contamination of a work surface in the dispensing room for medicinal products for injection. Action limits are exceeded.

Key features

- Class B dispensing room (ISO 7);
- The product being dispensed undergoes terminal sterilisation employing an overkill cycle (with no incidents);
- The bioburden of the product is controlled on a batch-by-batch basis;
- The room is monitored weekly;
- Other work surfaces in the same room are within control limits;
- The micro-organism has been identified as *Staphylococcus aureus*;
- This is the first time it has been detected.

Once a full description of the event is available, it is analysed.

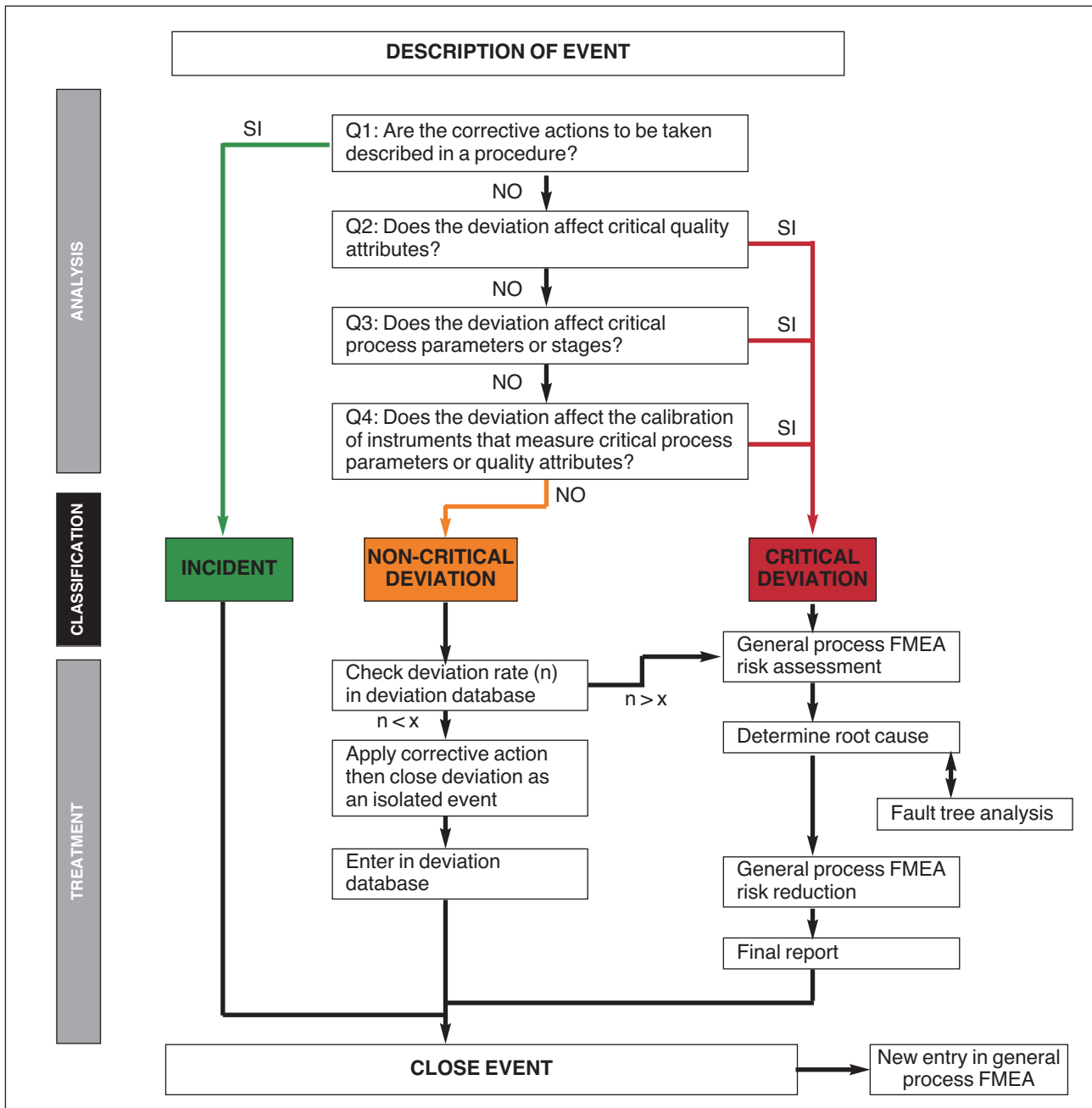


Figure 1. Flowchart for management of deviations.

Analysis and classification phase

- Q1: Are the corrective actions to be taken described in a procedure?
No, the actions are not described in a procedure.
- Q2: Does the deviation affect critical quality attributes?
Contamination of a surface is not regarded as a critical product attribute.
- Q3: Does the deviation affect critical process parameters or stages?
It is not considered to affect a critical stage, because terminal sterilisation is performed at the end of the process.
- Q4: Does the deviation affect the calibration of instruments that measure critical process parameters or quality attributes?
It does not affect calibration.

The answers given in the above decision tree, together with the fact that this is the first time such contamination has been detected, mean that the event is classified as a non-critical deviation.

Treatment phase

As this is a non-critical deviation and the maximum number of repeats allowed (n) has not been exceeded, it would merely require a corrective measure, such as subjecting the area to special cleaning. The deviation must also be entered in the deviation database to be counted.

Using FMEA to manage deviations

This example suggests using an FMEA-based risk analysis tool to classify and handle deviations.

Analysis and classification phase

The severity of the event's consequences and the probability of non-detection are assessed to determine the risk level. Depending on the risk level, events are classified as critical deviations, non-critical deviations or incidents, and the corresponding actions are taken.

The analysis is performed by reference to the assessment scales shown in **Table 1**. Using these criteria, the risk matrix shown in **Figure 2** is constructed. Events assessed using the matrix are given a risk level score, which falls into one of three categories:

- Risk level >9 (red zone): Critical deviation. Requires in-depth investigation, root cause and impact assessment;
- Risk level >3 (orange zone): Non-critical deviation. To be investigated in proportion to the risk;
- Risk level ≤3 (green zone): Incident. Record and close.

Treatment phase

Depending on the risk level score obtained, actions are taken as described above. This phase is exactly the same as in the previous example (**Figure 3**).

Example of using FMEA to manage deviations

Description of event

Tablet capping detected during in-process control.

Key features

- The event was detected by an operator during in-process control at the packaging stage (five blister packs emptied every 30 minutes);
- This event is very difficult to detect by either closed-circuit television or dynamic balancing.

Analysis and classification phase

Based on the above description of the event, the following score is obtained:

- Severity: 5 (as it may mean a lower dose of active substance);
- Probability of non-detection: 3 (as it is not detected by balance or on camera);
- Result: This gives a score of 15, so it is classed as a critical deviation.

Treatment phase

Having determined that this is a critical deviation, an analysis of the root cause is performed. In this example, after reviewing the batch record and process risk analysis, it is found to be due to excessive compression force, as reflected in some high individual hardness values, close to the upper limit of tolerance.

In order to reduce the risk, it is proposed to examine the influence of compression force and in-process hardness control results, in order to determine suitable control limits and thereby prevent tablet capping.

The deviation, its assessment, and the risk-mitigation

Table 1. Criteria for assessing severity and probability of non-detection of an event

Severity	5 = The deviation affects a critical quality attribute or parameter 3 = The deviation affects an attribute or parameter that is not critical to quality 1 = The deviation does not affect product quality but must be documented
Probability of non-detection	5 = No controls are carried out 3 = Final control on manufactured product only 1 = In-process control

		Probability of non-detection		
		5	3	1
Severity	5	25	15	5
	3	15	9	3
	1	5	3	1
Actions		Critical deviation (in-depth investigation)	Non-critical deviation (risk-proportional investigation)	Incident (record and close)

Figure 2. Matrix for assessing risk level of an event.

measures taken are entered in the process risk matrix for regular review of risks and effectiveness.

Conclusions

This article describes the use of two different risk analysis tools for managing deviations within the context of pharmaceutical production.

One of them involves using a decision diagram to classify deviations by their impact on product quality, based on definitions contained in ICH Q7A.

The second option is to apply an FMEA tool that uses the probability of not detecting the fault to determine the degree of risk associated with the deviation.

In both cases, deviations can be prioritised and the way they are dealt with can be tailored to the risk they pose to quality.

By finally incorporating the information generated into the general risk analysis for the process, knowledge of the process can be constantly updated in terms of:

- Critical points: redefining the control limits;
- Critical product quality attributes and how they relate to process parameters;
- Process capacity data;
- The effectiveness of actions within the CAPA system.

This approach enables deviations to be handled effectively, reduces the resources needed by eliminating irrelevant incidents, and exploits the information obtained

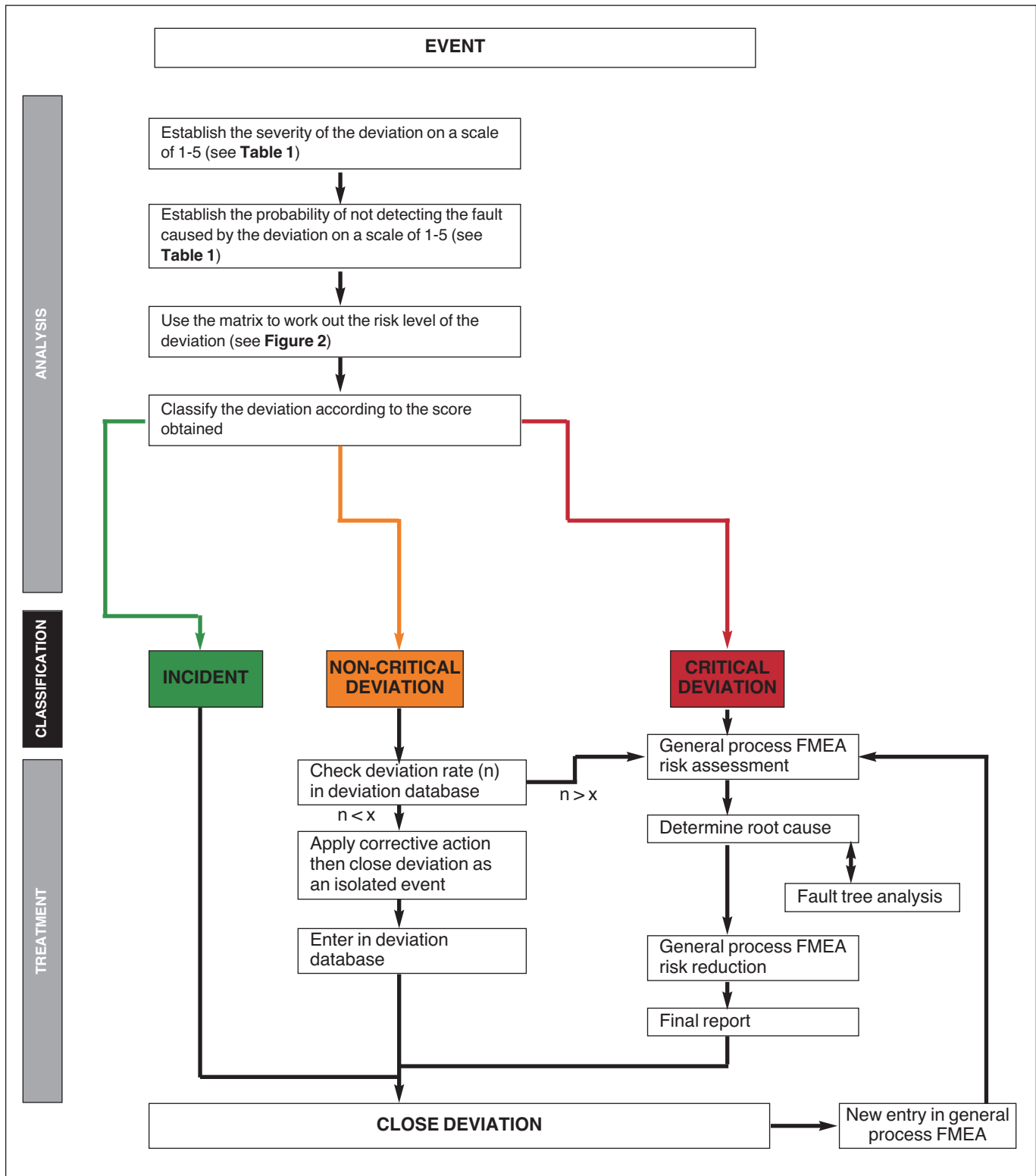


Figure 3. Management of deviations using failure mode and effects analysis.

from critical deviations to allow a better understanding of the process.

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