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GMP Series

How to Manage Corrective and Preventive Actions (CAPA) in a GMP Environment



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Excerpt from the GMP Compliance Adviser

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1 Corrective and Preventive Actions (CAPA)

Dr. Bernd Renger

Here you will find answers to the following questions:

- What does CAPA mean?
- How can an effective CAPA system be established?
- Which interfaces are there to other systems?
- What content should a CAPA SOP have?

1.1 Introduction

In pharmaceutical operations, considered in the broadest sense of the term – in other words, in all GMP-regulated activities – a situation can always arise in which regulations and predefined procedures are not observed or in which procedures do not bring the best results or meet expectations. In such cases, rapid intervention is required in addition to the usual documentation, investigation, explanation and risk assessment in order to restore the balance of procedures and predefined processes (such as in the Quality Management System), to identify and eliminate potential weaknesses, or to optimise these processes to promote continuous improvement.

Examples of non-compliance with predefined procedures or inadequate processes can be:

- Deviations
- Out of specification results (OOS) or out of trend results (OOT)
- Complaints and recalls
- Processes out of statistical control
- Internal rejection of products
- Observations reported from inspections

Generally speaking, the points listed above could be summarised under the collective term *non-conformity*. However, for the sake of simplicity, this will be referred to hereafter as *deviation*.

For each deviation, the top priority is to take immediate action to eliminate the root cause of the deviation and/or to prevent additional damage, e.g. to re-establish the conformity of the batch, if this is possible (**Correction**).

Subsequently, in most cases there are relevant corrective actions to be taken to effectively prevent recurrence of the same deviation in the same process or other processes or procedures (**Corrective Action**).

An additional further possible step might be the proactive evaluation – based on a risk assessment – to determine how potential similar or different deviations can be prevented in this and other processes (**Preventive Action**).

A *corrective action* therefore always refers to the previous occurrence of a failure, an error or a deviation, whose recurrence should be prevented. In contrast, a *preventive action* attempts to prevent a potential error in advance, using suitable techniques. In order to identify potential errors and weak points, the usual tools of risk management may be applied, like e.g. FMEA or HACCP, but also statistical process control, Six Sigma Tools and standard follow-up measures for risk reduction.

In a modern pharmaceutical quality system that complies with **ICH Q10**, this procedure is referred to as **CAPA system** (*Corrective Actions and Preventive Actions*). In simple terms, the CAPA system must always be applied when deviations in the process or problems with the product or the supplied service occur or potential problems are anticipated. The identification of the possible failure cause(s) (*Failure Investigation or Root Cause Analysis*) is an essential prerequisite, in order to determine and implement the appropriate measures.

1.2 Regulatory Background

Initially, the system of corrective and preventive actions was not included and defined in the EU GMP Guidelines.

However, responsible pharmaceutical companies practicing a modern GMP culture have always applied elements of a CAPA system in their well established procedures for the handling of deviations or complex process problems, even if not designated as such.

The term CAPA originates from the medical device sector, and has been described as an essential quality system element e.g. in the DIN EN ISO 9001, ISO 13485 and the FDA 21 CFR 820 regulation.

An excellent summary of these broad descriptions of a CAPA system in the medical device sector was provided in the 2010 publication *Guidance on Corrective Action and Preventive Action and Related QMS Processes*. This document was drawn up within the context of the development of a standardised format for the release of a new medical device (*Summary Technical Document, STED*) by the *Global Harmonization Task Force* (GHTF) along with other harmonised guidelines to describe elements of the quality management system.

The principle of Corrective and Preventive Actions (CAPA) was first introduced into the pharmaceutical regulations by the "Quality Systems Guidance" published by the FDA in the year 2006. This formed the basis for the **ICH Guideline Q10** "Pharmaceutical Quality System", in which CAPA is presented as an essential element of the pharmaceutical Quality System. The initial plan was to incorporate ICH Guideline Q10 as Annex 21 into the EU GMP Guideline, but in 2011 it was decided to relocate this guideline into the newly created Part III of the EU GMP Guideline. This decision was based on the fact that the therein described model of a pharmaceutical quality system, which also includes the research and development activities of a company, is not obligatory, but one of several options.

However, this shift did not in any way affect the regulatory requirements and expectations towards pharmaceutical manufacturers to establish a relevant CAPA system, as basic principles of the guideline were integrated into the newly revised Chapters 1, 2 and 7 of the EU GMP Guideline and are therefore binding.

1.3 Definitions

Certainly one main problem when establishing a pragmatic CAPA system is the fact that the terminology is not always correctly understood, because it is profoundly different from the colloquial use of the terms corrective and preventive.

This reveals the dilemma in many pharmaceutical companies, where corrections are confused with corrective actions and corrective actions are confused with preventive actions. As a consequence, real preventive actions in the sense of continuous improvement and Six Sigma are covered by totally different systems, in many cases isolated from Quality organisations.

The definitions according to ICH Q10/EU GMP Guideline Part III, which have been adopted from the ISO 9000:2005, are presented in figure 1. It is important to know and to take into account the correct definitions in the discussion and definition of a CAPA system and its implementation.

As is the case in the ISO system, preventive actions are seen more in the context of risk management and proactive improvement and do not focus on already detected failures and errors. Potential problems are generally sought after in the system.

Since this must not necessarily be the result of a corrective action, both components should be preferably seen individually and not – as is now very often the case – considered as automatically associated activities.

The *Global Harmonization Task Force* (GHTF) has become clearly aware of this weak point and therefore generally refused the use of the acronym CAPA in the "Guidance on Corrective Action and Preventive Action and related QMS Processes": "*The acronym "CAPA" will not be used in this document because the concept of corrective action and preventive action has been incorrectly interpreted to assume that a preventive action is required for every corrective action.*"

Correction

Action to eliminate a detected non-conformity

Note 1: There is a distinction between correction and corrective action. A correction can be made in conjunction with a corrective action

Note 2: A correction can be, for example, rework or reclassification.

Corrective Action

Action to eliminate the cause of a detected non-conformity or other undesirable potential situation.

Note 1: There can be more than one cause for a non-conformity.

Note 2: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence.

Note 3: There is a distinction between correction and corrective action. A correction can be made in conjunction with a corrective action

Preventive Action

Action to eliminate the cause of a potential non-conformity or other undesirable potential situation.

Note 1: There can be more than one cause for a non-conformity.

Note 2: Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence.

Figure 1 Definition of correction, corrective and preventive action according to DIN EN ISO 9000:2005-12

Unfortunately, this view has not yet established itself in the currently prevailing discussion and interpretation of CAPA in the pharmaceutical industry. Nor has the fact that – despite the adoption of the CAPA concept in the EU GMP Guideline – it is not absolutely necessary to open a corrective action or even a preventive action for every deviation.

Corrective Action

Action to eliminate the cause of a detected non-conformity or other undesirable situation.

Note: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence. (ISO 9000:2005)

Preventive Action

Action to eliminate the cause of a potential non-conformity or other undesirable potential situation.

Note: Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence. (ISO 9000:2005)

Figure 2 Definition of corrective and preventive action according to ICH Q10 (EU GMP Guideline Part III)

If the deviation can be corrected directly on-site and promptly by a brief instruction or reprimand of the employee, this should be considered a direct corrective action and documented accordingly in the corresponding quality system (deviation system, CAPA, or similar).

It is important to understand that corrective and preventive actions must not automatically result in an increase of requirements, controls or supervision. Making processes, workflows, requirements, or documentation simpler is often better suited to achieve sustainable improvements. This particularly applies to unclearly structured, and therefore misleading, SOPs and work instructions.

Similar to the review of deviations or complaints, the further **control and evaluation** of CAPA activities can also be done by a **panel of experts**, preferably appointed and controlled by the quality unit. The composition of this board can be the same or similar to the original catalyst (deviation review board, complaint review board, etc.)

There are three important aspects:

- prompt follow-up of the implementation,
- sustainability, controlled via efficacy check,
- reporting of CAPA activities in the Management Review.

The **Qualified Person** plays a key role in this context, since CAPA procedures may in many cases have an effect on product quality and therefore impact batch certification and release to the market.

1.6 Efficacy and Sustainability

It is essential when defining CAPA activities to simultaneously decide how the efficacy of the corrective action or preventive action can be tested (efficacy check). This requires objective criteria to be specified to measure the result and outcome of the CAPA activities.

If the defined actions do not show the expected positive results, new corrective or preventive actions must be considered and decided upon. In the end this is a continuous, iterative process that should be repeated until it leads to a satisfactory result.

A schematic representation of this process is shown in figure 3. Once again, it is not mandatory to run through all steps.

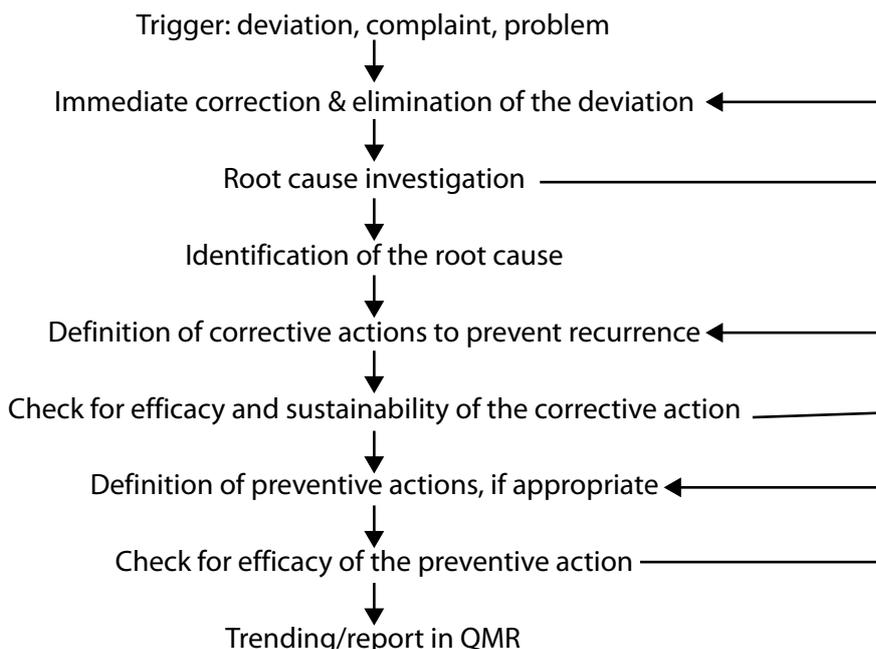


Figure 3 Process flow – failure detection and failure elimination/prevention in a CAPA system

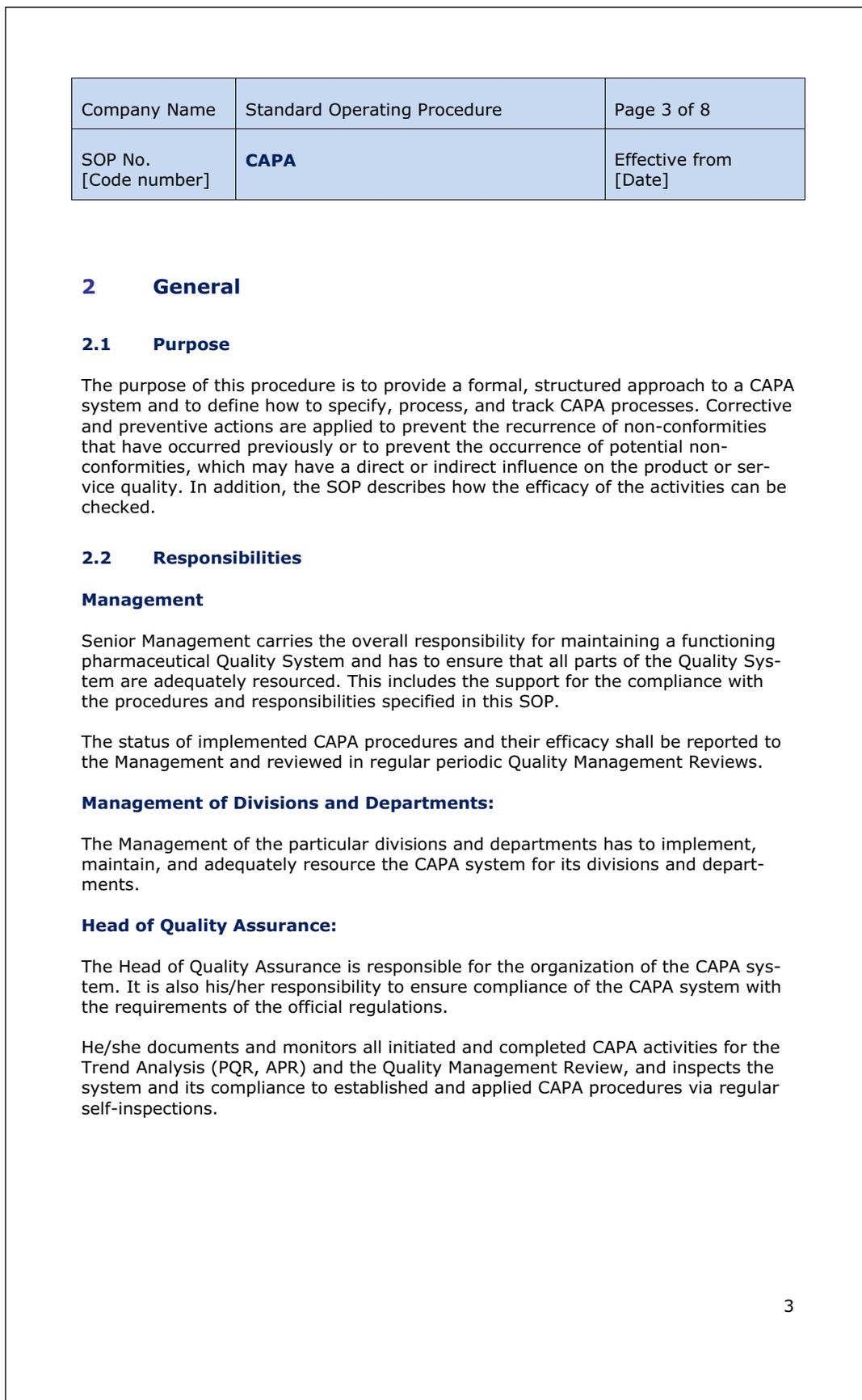


Figure 5 SOP Example (cont.)

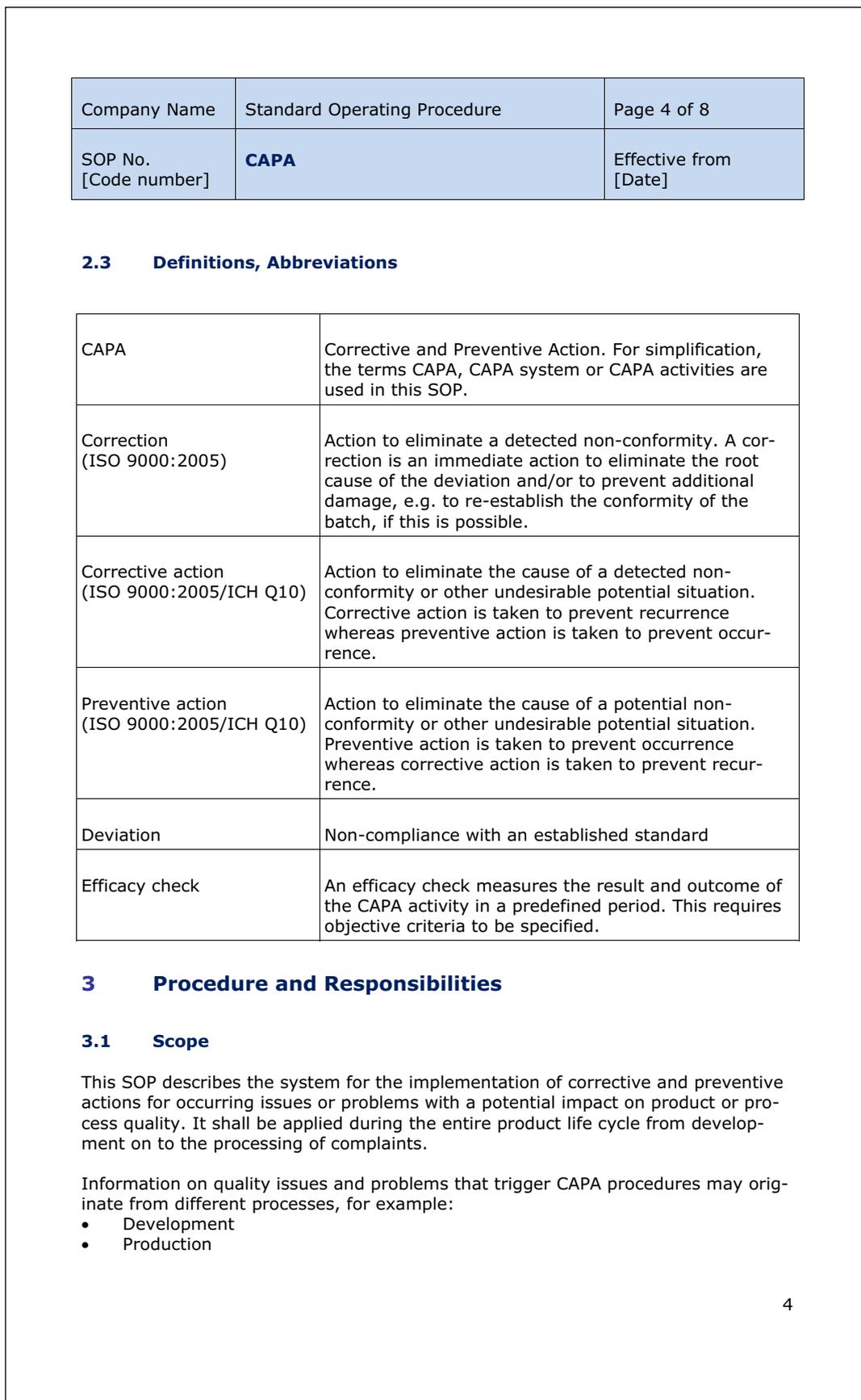


Figure 5 SOP Example (cont.)

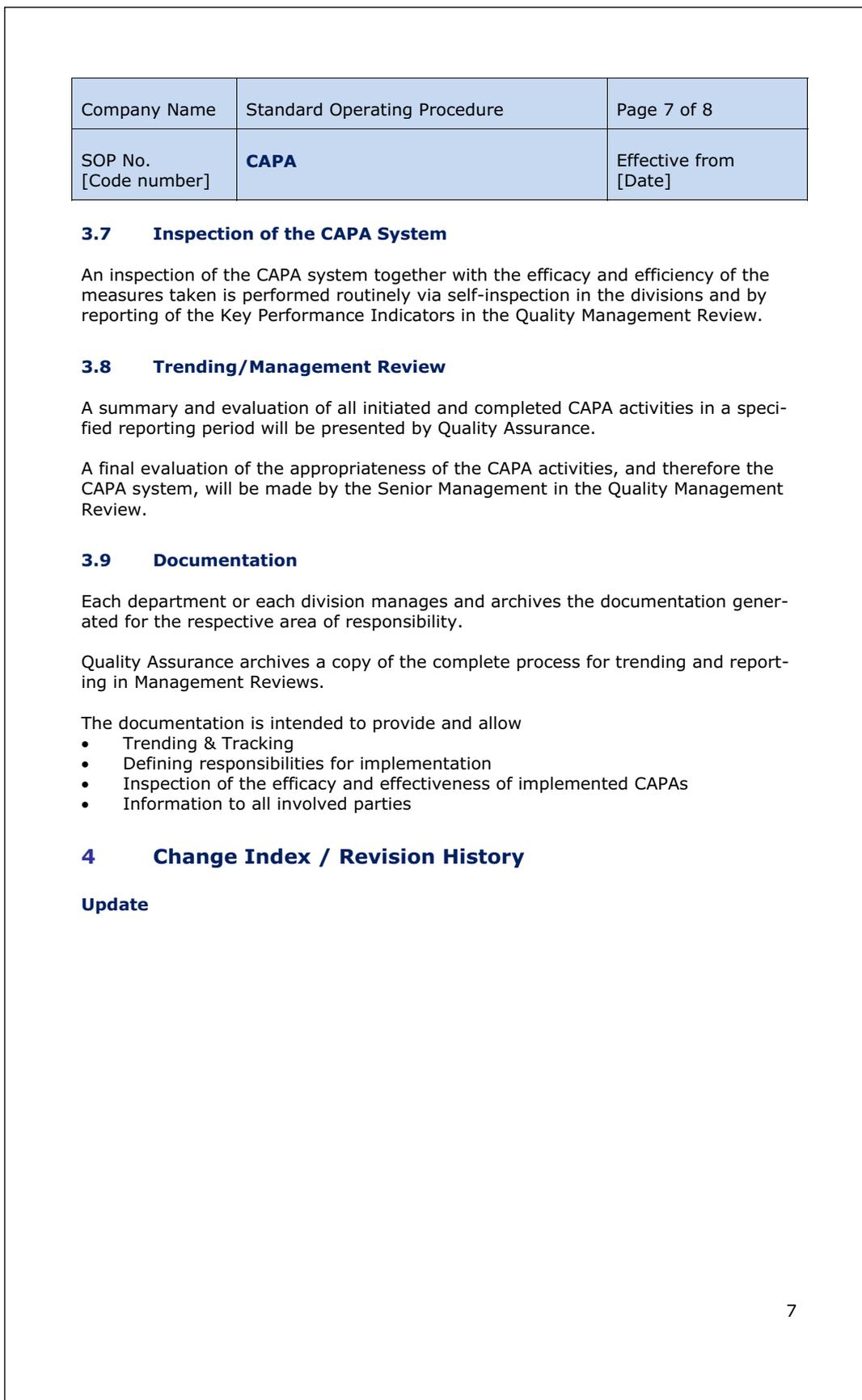


Figure 5 SOP Example (cont.)

Company Name	Standard Operating Procedure	Page 8 of 8
SOP No. [Code number]	CAPA	Effective from [Date]

5 Mailing List for SOP

- Management
- Head of Production
- Head of Logistics
- Head of R & D
- Head of Marketing and Sales
- Head of Purchasing
- Head of Quality Control
- Head of Quality Assurance
- Qualified Person (QP)
- QP for Pharmacovigilance

The relevant head of division decides about additional recipients within the division.

Confirmation of Receipt

I hereby confirm the receipt of the Work Instruction
„Title / Code Number“

Date, Signature

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Figure 5 SOP Example (cont.)

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Contributors

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1976 In 1976 he started his professional career with Hoechst AG as a R&D Chemist.

1984 After leaving Hoechst in 1984 he has held several management positions in Quality Control and/or Quality Assurance at Mundipharma (Limburg), Byk Gulden (later Altana Pharma, Singen) and Baxter BioScience (Vienna) before joining Vetter in 2004.

He is member of the Advisory Board of the European Compliance Academy and Chairman of the European Qualified Person Association, an organisation representing more than 1.300 Qualified Persons in Europe.

His main fields of interest are benchmarking and efficacy of quality operations, handling of deviations and OOS results, Quality Systems and role and responsibilities of the Qualified Person.