1 Purpose

The purpose of this guideline is to outline the requirements for the reporting, investigation and handling of individual deviations, and to outline a systematic approach for the trending of deviations, to enable ongoing improvement in deviation performance.

2 Scope and Applicability

This document applies to all cGMP activities performed by the manufacturing sites. It applies to all facilities, processes, systems, and procedures used during manufacturing and quality control, that may directly or indirectly affect product quality. The objective is to facilitate investigations into individual deviations and the reduction of deviations across Operations, through a systematic and collective approach.

Prospective (or planned) deviations are out of scope. Out-of-Specification (OOS) analytical results are not covered by this document.

3 Definitions

3.1 Investigation

A formal and documented review of an issue, deviation, incident or problem, to identify its root cause and determine the actions required to address it.

3.2 Deviation

Departure from a process/procedure OR an unexpected result.

3.3 Root Cause

The basic cause of a deviation, from which effective actions can be defined to prevent recurrence.

3.4 Corrective Action

An action taken to correct or eliminate the causes of an existing deviation, issue, incident or problem.

3.5 Preventive Action

An action taken to prevent recurrence or pre-empt a potential deviation, issue, incident or problem.

3.6 Repeat Deviation

A deviation that re-occurs, after the identification of actions identified from a previous deviation. This would indicate that the root cause of the previous deviation had not been correctly identified and/or that the actions determined, had either not

There must be a local procedure to describe the steps to be followed to investigate and document deviations and to prevent premature batch release.

The local system must ensure that all deviations are adequately addressed according to the seriousness of the deviation and that the appropriate corrective and preventative actions are taken. The originating area and

Quality Assurance must agree the corrective and/or preventative actions. Deviations must be classified and investigated according to their seriousness as, Level 1, 2 and 3. Appendices 1 and 2 identify the minimum reporting requirements and the key steps in the lifecycle of a deviation.

For Level 1 deviations, the root cause must be identified wherever possible and a formal root cause analysis should be done if the root cause cannot be readily identified. If, following analysis, the root cause cannot be identified, the most probable root cause should be identified. The identified root cause, or the most probable root cause should be used as the basis for defining preventative actions to prevent recurrence.

For Level 1 and 2 deviations, a formal investigation should be performed and the root cause identified. Level 3 deviations are at minimum usually only documented in routine batch or test related documentation and records.

The process and timing in which agreement and approval are achieved may vary depending on the level of the deviation. The exact approach should be described in local procedures. For example, for a Level 3 deviation a retrospective review by QA in connection with batch release is acceptable. However, for a Level 1 deviation, corrective and preventative actions should be agreed with QA as soon as reasonably practicable after the incident.

5.1.1 Deviation Reporting

Electronic or paper records of all deviations must be kept, together with a record of the investigation (if applicable) and remedial action taken. The degree of documentation required may vary according to the level of the deviation. For example, minor deviations (Level 3) can be recorded in batch or other GMP documentation, whereas more significant deviations (Level 1 and 2) are usually recorded using a specific proforma. Batch related deviations must be referenced and/or filed with the relevant batch records.

The following minimum requirements must be included in the deviation documentation, as appropriate:

If the nature of the deviation raises questions about its impact on stability, then a special stability study should be considered.

These studies may be conducted as part of the postproduction surveillance program. This should not be used on a regular basis and it is important to know beforehand how to act on the results from the study. Comparison of stability data generated at accelerated conditions may be useful in predicting atypical adverse stability characteristics providing that data on typical manufacture have been generated under similar conditions. In this eventuality the person responsible for releasing the affected batches should consider appropriate corrective actions

Note: stability OOS results (or adverse stability trends) are not regarded as process deviations.

5.2 Systematic approach for the trending of deviations

In addition to the identification of specific actions identified through individual investigations, a formal periodic review of all deviations will enable the identification of any trends and the definition of improvement actions where appropriate. This pro-active approach, in addition to the re-active approach used for individual investigations and an appropriate set of Key Performance Indicators (KPIôs), should result in the elimination of specific types of deviations and on-going improvement in deviation performance (e.g. reduction in the number of deviations occurring; elimination of repeat deviations).

Depending on site size, the formal periodic review of all deviations may be a one step process looking across the whole site, or a multi step process built up from logical groupings (e.g. functional areas such as processing, packaging, distribution, quality assurance). Typically, this work is performed in cross-functional teams including Production, Quality Assurance and Process

Technology (the function with knowledge of the process). The full process and a systematic approach to classification and trending is outlined below in section 5.3 and 5.3.1.

5.3 Classification and trending, overview

The quality system covering deviations should facilitate the identification of trends (including any emerging trends), their communication to management and identification of areas for improvement. Therefore the system should include a periodic review and analysis of all deviations, to identify recurring incidents and trends. For Level 1 and 2 deviations, this formal review should be at least annual and may be performed as part of the periodic and/or annual product quality review. It may be appropriate to trend Level 3 deviations on a less formal basis.

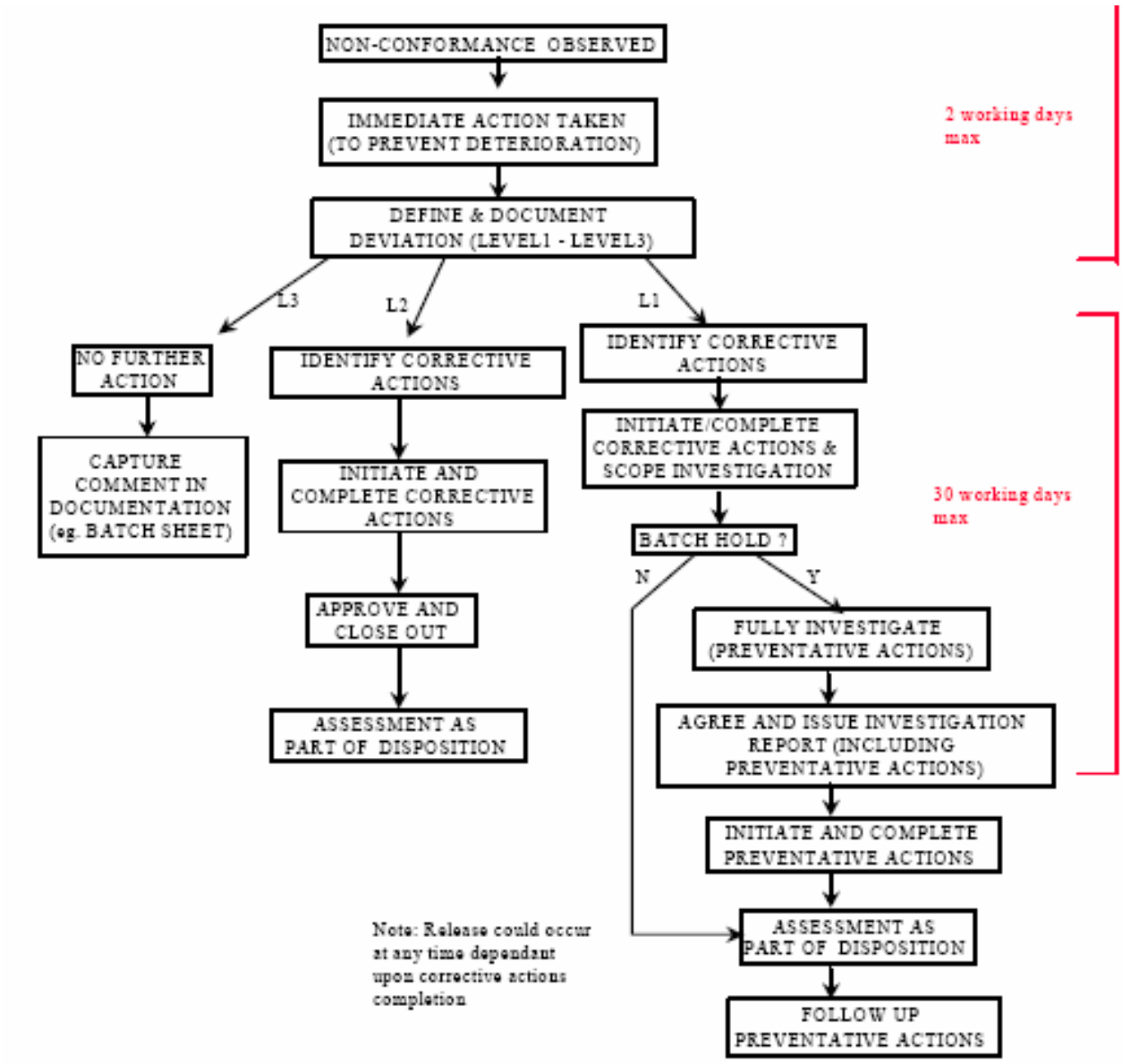
To support the formal and systematic trending of deviations, measurement and trending processes need to be in place. The review frequency should be linked to the numbers of deviations raised and other relevant factors, such as process

outcome has been achieved, ensure that the benefits are consolidated for the long term (e.g. by ensuring that any related process and procedural documents are updated and personnel trained in them). If a desired outcome has not been achieved, determine why not and define any additional actions to address this. This may require going back to Step 3, or starting again from Step 1.

Step 6
Communicate the outcome of the improvement actions across the site, to ensure that the learning is shared and can be applied elsewhere, where appropriate. As appropriate, communicate the outcome of the improvement actions with other sites, to ensure that the learning is shared and can be applied elsewhere, where appropriate. Start a new review of the deviation profile and run the process again.
See appendix 3 for process scheme.

6.2 Appendix 2

Deviation Lifecycle



6.4 Appendix 4 Tools – (Examples of common tools)

Root cause analysis:

Spider
Fishbone diagrams
5 Whyôs
Kepner-Tregoe problem solving tool

Trending tools:

Cumulative diagram
Pareto diagram
Histograms

Prioritization tool:

4-Box model

Easy but not under your control	Easy and under your control
Difficult and not under your control	Difficult but under your control

Road of choice analysis

FMEA/FMECA

