1 Purpose

To provide requirements in addition to recommendations for the performance of investigations in response to an incident, problem or deviation that may affect the safety, identity, strength, purity or quality of an active pharmaceutical ingredient (API) or drug product.

2 Scope and Applicability

This Guideline is applicable to all Operations and Research and Development (R&D) sites, functions and departments undertaking work, or providing support services, required to meet Good Manufacturing Practice (GMP) or International Organization for Standardization (ISO) standards.

It applies to investigations performed as a result of an incident, problem or deviation identified in the manufacture, testing, control and distribution of active pharmaceutical ingredient (API) and drug product.

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 Corrective Action

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

3.3 Preventive Action

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

4 Responsibilities

4.1 Management

It is the responsibility of management to:

- Ensure the establishment and maintenance of investigation procedures
- Ensure that investigations are performed as a matter of urgency and priority
- Ensure adequate resource allocation to perform investigations and associated actions
- Ensure timely completion of corrective and preventive actions (CAPA)
- Maintain awareness of trends in incidents, problems, deviations and root causes
- Maintain awareness of overdue investigation reports

Once an incident, problem or deviation is identified, immediate corrective action may be necessary (e.g. to hold batches from further distribution). Upon investigation, further corrective action should be outlined to isolate the problem, to minimize impact on compliance and to ensure the safety of consumers and/or study participants, (e.g. product recall).

Actions should also be identified to prevent reoccurrence of the problem. These are considered preventive actions and may include such things as revision of processes or procedures, creation of new systems, training or re-training of personnel.

An implementation plan for corrective and preventive action (where necessary) must be established with identified actions, persons or groups responsible, and timing for completion of the actions. The timing for implementation must be agreed and take into account the relative risk to ongoing and future activities. Any preventive actions must be completed as soon as possible. In the event that a preventive action may take some time to implement (e.g. purchase and commission a new piece of equipment), the corrective actions identified must take into account such things as additional oversight to minimize the occurrence of similar incidents while the preventive action is being completed.

5.8 Investigation Conclusions and Approval

An investigation must include documented conclusions. Conclusions should include identified or probable root cause(s), scope of the incident, problem or deviation, recommendations for disposition of the product batch(es), including any actions taken on other related product batches identified as a result of the investigation.

The investigation, conclusions, corrective and preventive actions taken and/or proposed must be approved by management and by the Quality Assurance function.

5.9 Investigation Closure

Investigation procedures must outline requirements that must be met to allow an investigation to be closed. Investigations must involve a formal step for closure. Investigation closure should be performed at the point where conclusions have been drawn, dispositions made, corrective actions taken and preventive actions taken or identified. In the case of longer term preventative action identified (i.e. beyond 30 working days to implement), the investigation may be considered closed, with agreement of the approving parties, provided outstanding actions are included in an action plan or compliance improvement plan (or similar system), with identified completion dates, and that follow up is monitored to completion.

5.10 Preventive Action Follow Up

Although an investigation may be considered closed, additional, longer-term preventive actions may have been identified.

A process must be in place to monitor the preventive action plan and ensure documented closure of actions. If, through the course of the implementation, it is

6 Appendices

Appendix 1 - Recommended Process for Conducting Investigations