3.3 Follow-up of Adverse Events

There are different scenarios in which it is necessary to obtain follow-up information. These are described below.

3.3.1 Information to validate a case

The criteria for a valid case are:

- an identifiable patient;
- a suspect drug;
- a suspect reaction;
- an identifiable HCP reporter.

When one or more of these criteria are missing, it is expected that the MAH attempts to follow the case up in order to validate the report. The MAH should also consider the way in which these cases are collated and collated; for example, if the MAH uses a computerised database for recording pharmacovigilance data, should this type of case also be entered?

With regard to consumer reports, it is expected that the MAH seeks the consumer's consent to contact their HCP so that medical confirmation of the suspect reaction can be obtained. This applies to reports from all territories, for example US affiliates may not routinely follow up consumer reports for medical confirmation as the US Food and Drug Administration accepts reports from patients. Attempts at follow-up should not just be directed at the patient's doctor, as there may be many situations in which the patient did not need to consult their doctor but spoke with a pharmacist, nurse or other HCP about the reaction. It should be noted that review of a report by a HCP employed by the MAH does not constitute medical confirmation of the suspected reaction. There are circumstances whereby HCP confirmation of a report could be supplied by a consumer, for example in medical notes relating to the event and the specific patient.

In the context of expedited reporting, day zero should be considered the day on which the minimum criteria for a reportable adverse reaction report becomes available to the MAH. In order to be in receipt of the minimum criteria for a case in the shortest timeframe, personnel should have a clear understanding of what makes a case valid (as detailed above). This would then provide an opportunity to attempt to obtain this information on first notification. Personnel should, however, not delay reporting a non-valid case to the pharmacovigilance department if the minimum criteria are not initially available.

3.3.2 Information relevant for case evaluation

When a report of an AE is made, the information made available may be minimal and insufficient to form an accurate opinion of whether there is a suspected causal relationship between the drug and the event. The MAH is expected to make attempts to obtain additional information relevant to the evaluation of the case. The information requested may be general in nature (e.g. past medical history, concomitant medications) or more specific to the event being reported. The type of information required to understand an event adequately could be a diagnosis (when only signs and symptoms are reported), a cause of death (postmortem results), an outcome or dechallenge/rechallenge information. For example, a report of neutropenia would warrant a request for details of blood test results.

For ICSRs published in the worldwide literature, it is expected that the MAH attempts to obtain follow-up information if it would provide information relevant to the assessment of the case. For example, in a publication listing multiple medications it may be unclear whether all of the medications are considered to be causally related to the reaction. It may, therefore, be useful to attempt to obtain follow-up information to clarify which of the drugs was specifically thought to be causally related. Publications often provide the contact details of the author(s) for correspondence, such as an email address.

The need to request follow-up information should not affect expedited reporting activities: an initial report should be made as soon as the minimum criteria for a reportable adverse reaction report become available. Any follow-up information received should be reported within 15 days of receipt if it adds to or changes the case information.

3.3.3 Reports of drug exposure during pregnancy

Volume 9A states that the MAH should follow up all reports relating to pregnancies where the fetus may have been exposed to one of its medicinal products; this can be the result of either maternal exposure or transmission of a medicinal product via semen following paternal exposure. The MAH should gather information relating to both normal and abnormal outcomes. Consequently, a mechanism is required to ensure that reports of use of a drug during pregnancy are followed up at suitable intervals, for example following the initial report and also around/after the expected delivery date.

3.3.4 Reports of overdose, abuse and misuse

Volume 9A discusses the need to follow up reports of overdose, abuse and misuse to obtain details of any associated clinical effects. Reports of overdose, abuse and misuse that are associated with serious adverse reactions (SARs) qualify for expedited reporting (Section 3.5) and so information received in response to a request for follow-up will contribute to the assessment of whether or not the case requires expedited reporting.

Reports of overdose, abuse and misuse that are not associated with SARs should be recorded in the pharmacovigilance system as they provide useful information relevant to the risk–benefit assessment of a product. These issues should be considered in PSURs and RMPs.

In terms of overdose, a HCP may submit a report of an adverse reaction where the patient has received a larger than approved dose, but not explicitly use the term "overdose". The MAH should consider how to record such an event in the pharmacovigilance database to aid retrieval of such cases. This is particularly important for products that have a narrow therapeutic margin. For example, if such an event is not coded as overdose in the MAH's database, will it still be retrieved when running a query to identify all cases where patients have received a larger than approved dose?

3.3.5 Additional considerations regarding follow-up attempts

Consideration should be given to the types of report that should be followed up (serious versus non-serious, expected versus unexpected), the number of attempts to obtain follow-up information per report, the frequency of requests and the method of obtaining the information. These details should be recorded in procedural documents.

This is discussed in ICH E2D: "In any scheme to optimize the value of follow-up, the first consideration should be prioritization of case reports by importance. The priority for follow-up should be as follows: cases that are 1) serious and unexpected, 2) serious and expected, and 3) non-serious and unexpected. In addition to seriousness and expectedness as criteria, cases "of special interest" also deserve extra attention as a high priority (e.g. adverse reactions under active surveillance at the request of the regulators), as well as any cases that might lead to a labelling change decision."

All attempts at follow-up should be documented: for example, if a letter was sent, a copy should be retained; if an attempt was made to follow up via telephone, a record of the call should be made. In this way the MAH can demonstrate due diligence in attempting to obtain follow-

up information. The availability of reporter contact details (telephone or fax number, postal or email address) will to a great extent determine the method used to obtain follow-up information. When urgent information is required, it may be more appropriate to attempt to follow up by telephone rather than sending a letter.

For routine follow-up requests, use of standard forms may facilitate collection of standard data elements. Including a reference number on the form will make it easier to link the original report to the follow-up information when it is returned. The success rate for obtaining follow-up is often quite low, and time constraints may affect whether or not a HCP fulfils a request for follow-up information. Therefore, consideration should be given to pre-populating some data fields to make completion of the form less burdensome. This is also useful when a case was initially reported by a consumer, thus enabling the HCP to provide further information about the report.

Even when standard follow-up questions or reporting forms are used, there should always be consideration of additional follow-up requirements and questions on a case-by-case basis.

3.4 Case Assessment

The requirements for expedited reporting depend upon several criteria, including:

- seriousness of the reaction;
- causality;
- expectedness of the reaction (in terms of the local Summary of Product Characteristics (SPC) for the product);
- country of origin of the report;
- method of marketing authorisation.

In addition, Competent Authorities may lay down expedited reporting requirements over and above the standard requirements for specific issues, either at the time of licensing or at any point during the life-cycle of the product when there is cause for concern.

The company's assessments of seriousness, expectedness and causality should be documented. If additional information relevant to these assessments becomes available, the MAH should:

- reassess the case;
- document the reassessment and the reason for any changes from the original assessment;