MAHs should consider utilising their websites to facilitate ADR data collection, e.g., by providing ADR forms for reporting or by providing appropriate contact details for direct communication.

Unsolicited cases from the Internet should be handled as spontaneous reports. For the determination of reportability, the same criteria should be applied as for cases provided via other ways.

In relation to such cases from the Internet e.g. e-mail, identifiability of the reporter refers to the existence of a real person, i.e., it is possible to verify that the patient and the reporter exist.

3.1.4 Other Sources

If an MAH becomes aware of a case report from non-medical sources, e.g. the lay press or other media, it should be handled as a spontaneous report. For the determination of reportability, the same criteria should be applied as for other reports.

3.2 Solicited Sources

Solicited reports are those derived from organized data collection systems, which include clinical trials, registries, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or healthcare providers, or information gathering on efficacy or patient compliance. Adverse event reports obtained from any of these should not be considered spontaneous.

For the purposes of safety reporting, solicited reports should be classified as study reports, and therefore should have an appropriate causality assessment by a healthcare professional or an MAH. Further guidance on study-related issues, such as managing blinded therapy cases, can be found in the ICH E2A guideline.

3.3 Contractual Agreements

The marketing of many medicines increasingly takes place through contractual agreements between two or more companies, which may market same product in the same or different countries/region. Arrangements vary considerably with respect to inter-company communication and regulatory responsibilities. Overall, this can be a complex issue.

In such relationships, it is very important that explicit licensing/contractual agreements specify the processes for exchange of safety information, including timelines and regulatory reporting responsibilities. Safety personnel should be involved in development of any agreements from the beginning. Processes should be in place to avoid duplicate reporting to the regulatory authority, e.g. assigning responsibility to one company for literature screening.

Whatever the nature of the arrangement, the MAH is ultimately responsible for regulatory reporting. Therefore, every reasonable effort should be made between the contracting partners to minimize the data exchange period so as to promote compliance with MAH responsibilities.

3.4 Regulatory Authority Sources

Individual serious unexpected adverse drug reaction reports originating from foreign regulatory authorities are subject to expedited reporting to other authorities by each MAH. Re-submission of serious ADR cases without new information to the

originating regulatory authority is not usually necessary, unless otherwise specified by local regulation.

4. STANDARDS FOR EXPEDITED REPORTING

4.1 What Should Be Reported?

4.1.1 Serious ADRs

Cases of adverse drug reactions that are both serious and unexpected are subject to expedited reporting. The reporting of serious expected reactions in an expedited manner varies among countries. Non-serious adverse reactions, whether expected or not, would normally not be subject to expedited reporting.

For reports from studies and other solicited sources, all cases judged by either the reporting healthcare professional or the MAH as having a possible causal relationship to the medicinal product would qualify as ADRs. For purposes of reporting, spontaneous reports associated with approved drugs imply a suspected causal relationship.

4.1.2 Other Observations

In addition to single case reports, any safety information from other observations that could change the risk-benefit evaluation for the product should be communicated as soon as possible to the regulatory authorities in accordance with local regulation. Examples include any significant unanticipated safety findings from an in vitro, animal, epidemiological, or clinical study that suggest a significant human risk, such as evidence of mutagenicity, teratogenicity, carcinogenicity, or lack of efficacy with a drug used in treating a life-threatening or serious disease.

4.1.2.1 Lack of Efficacy

Evidence of lack of efficacy should not normally be expedited, but should be discussed in the relevant periodic safety update report. However, in certain circumstances and in some regions, individual reports of lack of efficacy are considered subject to expedited reporting. Medicinal products used for the treatment of life-threatening or serious diseases, vaccines, and contraceptives are examples of classes of medicinal products where lack of efficacy should be considered for expedited reporting. Clinical judgment should be used in reporting, with consideration of the local product labeling and disease being treated.

4.1.2.2 Overdose

Reports of overdose with no associated adverse outcome should not be reported as adverse reactions. Cases associated with serious adverse reactions are considered subject to expedited reporting, unless otherwise specified by local regulation. They should be routinely followed up to ensure that the information is as complete as possible with regard to symptoms, treatment, and outcome. The MAH should collect any available information on overdose related to its products.

4.2 Minimum Criteria for Reporting

It is recommended that as much information as possible be collected at the time of the initial report. However, for the purpose of regulatory reporting, the minimum data elements for an ADR case are: an identifiable reporter, an identifiable patient, an adverse reaction, and a suspect product. Lack of any of these four elements means

that the case is considered incomplete; however, MAHs are expected to exercise due diligence to collect the missing data elements.

4.3 Reporting Time Frames

In general, expedited reporting of serious and unexpected ADRs is required as soon as possible, but in no case later than 15 calendar days of initial receipt of the information by the MAH. Time frames for other types of serious reports vary among countries, depending on source, expectedness and outcome.

The regulatory reporting time clock is considered to start on the date when any personnel of the MAH first receive a case report that fulfills minimum criteria as well as the criteria for expedited reporting. In general, this date should be considered day 0.

When additional medically relevant information is received for a previously reported case, the reporting time clock is considered to begin again for submission of the follow-up report. In addition, a case initially classified as a non-expedited report, would qualify for expedited reporting upon receipt of follow-up information that indicates the case should be re-classified (e.g., from non serious to serious).

4.4 Non-serious ADRs

Cases of non-serious ADRs, whether expected or not, would not normally be considered reportable on an expedited basis. Non-serious ADRs should be included in the periodic safety update report according to the ICH E2C guideline.

5. GOOD CASE MANAGEMENT PRACTICES

Accurate, complete, and bona fide information is very important for MAHs and regulatory agencies identifying and assessing ADR reports. Both are faced with the task of acquiring sufficient information to help ensure that the reports are authentic, accurate, as complete as possible, and non-duplicative.

5.1 Assessing Patient and Reporter Identifiability[1]

Patient and reporter identifiability is important to avoid case duplication, detect fraud, and facilitate follow-up of appropriate cases. The term identifiable in this context refers to the verification of the existence of a patient and a reporter.

Local data privacy laws regarding patient and reporter identifiability might apply.

One or more of the following should automatically qualify a patient as identifiable: age (or age category, e.g., adolescent, adult, elderly), gender, initials, date of birth, name, or patient identification number. In addition, in the event of second-hand reports, every reasonable effort should be made to verify the existence of an identifiable patient and reporter.

All parties supplying case information or approached for case information should be identifiable: not only the initial reporter (the initial contact for the case), but also others supplying information.

In the absence of qualifying descriptors, a report referring to a definite number of patients should not be regarded as a case until the minimum four criteria for case reporting are met. For example, "Two patients experienced..." or " a few patients experienced" should be followed up for patient-identifiable information before regulatory reporting.