POST-APPROVAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING

1. INTRODUCTION

It is important to establish an internationally standardized procedure in order to improve the quality of post-approval safety information and to harmonise the way of gathering and reporting information. The ICH E2A guideline provides guidance on pre-approval safety data management. Although many stakeholders have applied ICH E2A concepts to the post-approval phase, there is a need to provide further guidance on definitions and standards for post-approval expedited reporting, as well as good case management practices. This guideline is based on the content of ICH E2A guideline, with consideration as to how the terms and definitions can be applied in the post-approval phase of the product life cycle.

2. DEFINITIONS AND TERMINOLOGY ASSOCIATED WITH POST-APPROVAL DRUG SAFETY EXPERIENCE

2.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

2.2 Adverse Drug Reaction (ADR)

Adverse drug reactions, as established by regional regulations, guidance, and practices, concern noxious and unintended responses to a medicinal product.

The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (refer to the ICH E2A guideline).

A reaction, in contrast to an event, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse drug reaction.

2.3 Serious AE/ADR

In accordance with the ICH E2A guideline, a serious adverse event or reaction is any untoward medical occurrence that at any dose:

* results in death,
* is life-threatening
  (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe),
* requires inpatient hospitalisation or results in prolongation of existing hospitalisation,
* results in persistent or significant disability/incapacity,

* is a congenital anomaly/birth defect,
* is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

2.4 Unexpected ADR

An ADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the local/regional product labeling (e.g. Package Insert or Summary of Product Characteristics) should be considered unexpected. When a Marketing Authorisation Holder (MAH) is uncertain whether an ADR is expected or unexpected, the ADR should be treated as unexpected.

An expected ADR with a fatal outcome should be considered unexpected unless the local/regional product labeling specifically states that the ADR might be associated with a fatal outcome.

"Class ADRs" should not automatically be considered to be expected for the subject drug. "Class ADRs" should be considered expected only if described as specifically occurring with the product in the local/regional product labeling. This is illustrated in the following examples:

- "As with other drugs of this class, the following undesirable effect occurs with Drug X."
- "Drugs of this class, including Drug X, can cause..."

If the ADR has not been documented with Drug X, statements such as the following are likely to appear in the local/regional product labeling:

- "Other drugs of this class are reported to cause..."
- "Drugs of this class are reported to cause..., but no reports have been received to date with Drug X."

In these situations, the ADR should not be considered as expected for Drug X.

NOTE: The term "listedness" is not applicable to expedited reporting but should be used to characterize the ADR according to the Company Core Safety Information (refer to ICH E2C guideline for definitions).

2.5 Healthcare Professional

Healthcare professional is defined as a medically-qualified person such as a physician, dentist, pharmacist, nurse, coroner, or as otherwise specified by local regulations.

2.6 Consumer

Consumer is defined as a person who is not a healthcare professional such as a patient, lawyer, friend, or relative of a patient.

3. SOURCES Of INDIVIDUAL CASE SAFETY REPORTS

3.1 Unsolicited Sources

3.1.1 Spontaneous Reports

A spontaneous report is an unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organization (e.g. WHO, Regional Center, Poison Control Center) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

Stimulated reporting can occur in certain situations, such as notification by a "Dear Healthcare Professional" letter, publication in the press, or questioning of healthcare professionals by company representatives. These reports should be considered spontaneous.

Consumer adverse reaction reports should be handled as spontaneous reports irrespective of any subsequent "medical confirmation". Regulatory Authorities might require medical confirmation for the purpose of expedited reporting. Emphasis should be placed on the quality of the report and not on its source. Even if reports received from consumers do not qualify for regulatory reporting, the cases should be retained.

3.1.2 Literature

Each MAH is expected to regularly screen the worldwide scientific literature by accessing widely used systematic literature reviews or reference databases. The frequency of the literature searches should be according to local requirements or at least every two weeks. Cases of ADRs from the scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, might qualify for expedited reporting. A regulatory reporting form with relevant medical information should be provided for each identifiable patient. The publication reference(s) should be given as the report source; additionally a copy of the article might be requested by the local regulatory authority to accompany the report. All company offices are encouraged to be aware of publications in their local journals and to bring them to the attention of the company safety department as appropriate.

The regulatory reporting time clock starts as soon as the MAH has knowledge that the case meets minimum criteria for reportability.

If the product source, brand, or trade name is not specified, the MAH should assume that it was its product, although the report should indicate that the specific brand was not identified.

If multiple products are mentioned in the article, a report should be submitted only by the applicant whose product is suspected. The suspect product is that identified as such by the article's author.

3.1.3 Internet

MAHs should regularly screen websites under their management or responsibility for potential ADR case reports. MAHs are not expected to screen external websites for ADR information. However, if an MAH becomes aware of an adverse reaction on a website that it does not manage, the MAH should review the case and determine whether it should be reported.