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

ICH Harmonised Tripartite Guideline draft

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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 to gather and report information. ICH E2A provides guidance on pre-approval safety data management. Although many stakeholders have applied these E2A concepts to the post-approval phase, there is a need to provide further guidance on the definitions and standards for post-approval expedited reporting. This guideline is based on the content of ICH E2A 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. Basic Terms

2.1.1. Adverse Event (or Adverse Experience)

An adverse event (AE) 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.

2.1.2. Adverse Drug Reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

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

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

2.2. Seriousness Criteria

The most internationally agreed seriousness criteria appear in ICH guideline E2A. A

serious adverse event (experience) 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/a reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/a 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 as serious such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also be considered serious.

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 hospitalisation; or development of drug dependency or drug abuse.

2.3. Unexpected Adverse Drug Reactions

An ADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the official product information should be considered unexpected.

An ADR with a fatal outcome should be considered unexpected, unless the official product information specifies a fatal outcome for the ADR. In the absence of special circumstances, once the fatal outcome is itself expected, reports involving fatal outcomes should be handled as for any other serious expected ADR in accord with appropriate regulatory requirements.

Please note that the term "listedness" is not applicable for expedited reporting (refer to ICH E2C for definition).

Additional considerations:

"Class ADRs" should not automatically be considered to be expected for the subject drug. "Class ADRs" should be considered to be expected only if described as specifically occurring with the product in the official product information, as 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 official product information:

- "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.

In the absence of sufficient documentation and in the face of uncertainty, a reaction should be regarded as unexpected.

2.4. Other Definitions

2.4.1. Healthcare Professionals

Healthcare professionals are medically-qualified persons such as physicians, dentists, pharmacists, nurses, coroners, or as otherwise specified by local regulations. Preferably, information about the case should be collected from the healthcare professionals who are directly involved in the patient's care. In some regions, the healthcare professional status of the reporter is immaterial to reporting practices.

2.4.2. Consumers

A consumer is defined as a person who is not a healthcare professional.

2.5. Sources of Individual Case Reports

2.5.1. Unsolicited Sources

2.5.1.1. Spontaneous Reports

A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a company, regulatory authority or other organization (e.g. WHO, Regional Centers, 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 may occur in certain situations, such as a notification by a "Dear Healthcare Professional" letter, a publication in the press, or questioning of healthcare professionals by company representatives. These reports should be considered spontaneous.

2.5.1.1.1. Consumer reports

Consumer adverse reaction reports should be handled as spontaneous reports irrespective of any subsequent "medical confirmation", a process required by some authorities for reportability. Even if reports received from consumers do not qualify for regulatory reporting, the cases should be retained. Emphasis should be placed on the quality of the report and not on its source.

2.5.1.2. Literature

The Marketing Authorisation Holder (MAH) is expected to regularly screen the worldwide scientific literature, by accessing widely used systematic literature reviews or reference databases. 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 once it is determined that the case meets minimum criteria for reportability. MAHs should search the literature according to local regulation or at least once a month. If the product source, brand, or trade name is not specified, the MAH should assume that it was its product, although reports should indicate that the specific brand was not identified.

2.5.1.3 Internet

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 adverse reaction and determine whether it should be reported. Unsolicited cases from the Internet should be handled as spontaneous reports.

MAHs should regularly screen their websites for potential ADR case reports. MAHs and regulators should consider utilising their websites to facilitate ADR data collection, e.g. by providing ADR forms for direct reporting or by providing appropriate contact details for direct communication. For the determination of reportability the same criteria should be applied as for cases provided via other ways.

2.5.1.4 Other Sources

If MAHs become aware of a case report from non-medical sources, it should be handled as a spontaneous report.

2.5.2. Solicited Sources

Solicited reports are those derived from organized data collection systems, which include clinical trials, 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 handled as if they were study reports, and therefore should have an appropriate causality assessment. Further guidance on study-related issues such as managing blinded therapy cases can be found in ICH E2A.

2.5.3. Licensor-Licensee Interaction

When companies co-develop, co-market, or co-promote products, it is considered very important that explicit contractual agreements specify the processes for exchange of safety information, including timelines and regulatory reporting responsibilities. Whatever the contractual arrangement, the MAH is ultimately responsible for regulatory reporting.

It is particularly important to ensure that processes are in place to avoid duplicate reporting to the regulatory authority, e.g. assigning responsibility to one company for literature screening. The time frame for expedited regulatory reporting should normally

be no longer than 15 calendar days from the first receipt of a case meeting minimum criteria by any of the partners, unless otherwise specified by local regulation. Any subsequent follow-up information sent to the regulators should be submitted by the same MAH that reported the case originally.

2.5.4. Regulatory Authority Sources

Individual serious unexpected adverse drug reaction reports originating from foreign regulatory authorities are always subject to expedited reporting. Re-submission of serious ADR cases without new information to the originating regulatory authority is not usually required, unless otherwise specified by local regulation.

3. STANDARDS FOR EXPEDITED REPORTING

3.1. What Should Be Reported?

3.1.1. Single Cases of Serious ADRs

Cases of adverse drug reactions from all sources 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 qualify as ADRs. For the purposes of reporting, spontaneous reports associated with approved drugs imply a possible causality.

3.1.2. Reporting Guidelines for 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 promptly communicated to the regulatory authorities.

3.1.2.1. Lack of Efficacy

Reports of lack of efficacy should not normally be expedited, but should be discussed in the relevant periodic safety update report. However, in certain circumstances reports of lack of efficacy should be treated as expedited cases for reporting purposes. 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 approved product labeling/prescribing information.

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301 **3.1.2.2 Overdose**
302 Reports of overdose with no associated adverse outcome should not be reported as
303 adverse reactions. They should be routinely followed up to ensure that information is as
304 complete as possible with regard to symptoms, treatment, and outcome. The MAH
305 should collect any available information related to its products on overdose, and report
306 cases of these that lead to serious adverse reactions according to expedited reporting
307 criteria.
308
309 **3.2. Reporting Time Frames**
310 In general, expedited reporting of serious and unexpected ADRs refers to 15 calendar
311 days. Time frames for other types of reports vary among countries.
312
313 **3.2.1.Minimum Criteria for Reporting**
314 Minimum required data elements for an ADR case are: an identifiable reporter, an
315 identifiable patient, an adverse reaction, and a suspect product. Lack of any of these four
316 elements means that the case is incomplete; however, MAHs are expected to exercise due
317 diligence to collect the missing data elements. It is recommended that as much
318 information as possible be collected at the time of the initial first report.
319
320 **3.2.2. Time Clock Start Point**
321 The regulatory reporting time clock (in calendar days) starts on the date when any
322 personnel of the MAH first receive a case report that fulfills minimum criteria as well as
323 the criteria for expedited reporting. In general, this date should be considered as day 0.
324 When additional medically significant information is received for a previously reported
325 case, the regulatory reporting time clock begins again for submission of the follow-up
326 report.
327
328 **3.2.3 Non-serious ADRs**
329 Cases of non-serious ADRs are not normally reportable on an expedited basis. The
330 spontaneous reports of non-serious ADRs should be reported in the periodic safety update
331 report.
332
333 **4. GOOD CASE MANAGEMENT PRACTICE**
334 Accurate, complete and bona fide information is very important for MAHs and regulatory
335 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.

4.1. Assessing Patient and Reporter Identifiability

Patient and reporter identifiability is necessary 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.

One or more of the following automatically qualifies a patient as identifiable: age (or age category, e.g., adolescent, adult, elderly), sex, initials, date of birth, name, or patient identification number. Additionally, in the event of second-hand reports, every effort should be made to verify the report source. All parties supplying case information (or approached for case information) are subject to the notion of identifiability: 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.

4.2. The Role of the Narratives

The objective of the narrative is to summarize all relevant clinical and related information, including patient characteristics, therapy details, medical history, clinical course of the event(s), diagnosis, and ADR(s) (including the outcome, laboratory evidence and any other information that supports or refutes an ADR). The narrative should serve as a comprehensive, stand-alone “medical story”. The information should be presented in a logical time sequence; ideally this should be presented in the chronology of the patient’s experience, rather than in the chronology in which the information was received. In follow-up reports, new information should be clearly identified.

Abbreviations and acronyms should be avoided, with the possible exception of laboratory parameters and units. Key information from supplementary records should be included in the report, and their availability should be mentioned in the narrative and supplied on request. Any autopsy or other post-mortem findings (including a coroner’s report) should also be provided when available if allowed by local privacy protection laws. Terms in the narrative should be accurately reflected by appropriate coding.

4.3. Single Case Evaluation

The purpose of careful medical review is to ensure correct interpretation of medical information. Regardless of the source of an ADR report, the recipient should carefully review the report for the quality and completeness of the medical information. This should include, but is not limited to, consideration of the following:

- Is a diagnosis possible?
- Have the relevant diagnostic procedures been performed?
- Were alternative causes of the reaction(s) considered?
- What additional information is needed?

ADR terms should be used consistently and in accord with recommended standards for diagnosis. The report should include the verbatim term, which quotes the reporter. Staff receiving reports should provide an unbiased and unfiltered report of the information from the reporter. While the report recipient is encouraged to actively query the reporter to elicit the most complete account possible, inferences and imputations should be avoided in report submission. However, clearly identified evaluations by the MAH are considered acceptable and, for some authorities, required.

Encouraging good communication on medical information with the reporter will serve to improve the quality of case documentation.

When a case is reported by a consumer, his/her description of the event should be retained, although confirmatory or additional information from any relevant healthcare professionals should also be sought and included. Ideally, supplemental information should be obtained from the healthcare professional directly involved in the care of the patient.

4.4. Follow-up Information

The information from ADR cases when first received is generally incomplete. Ideally, comprehensive information would be available on all cases, but in practice efforts should be made to seek additional information on selected reports (see Attachment). 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 which are 1) both 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., ADRs under active surveillance at the request of the regulators), as well as any cases that might lead to a labeling change decision.

Follow-up information should be obtained, via a telephone call and/or site visit and/or via a written request. Efforts should be tailored toward optimising the chances to obtain the new information. Written confirmation of details given verbally should be obtained whenever possible. In exceptional circumstances, a regulatory authority might be able to assist an MAH to obtain follow-up data if requests for information have been refused by the reporter. The company should provide specific questions it would like to have answered.

In order to facilitate the capture of clinically relevant and complete information, use of a targeted questionnaire is encouraged, preferably at the time of the initial report. Ideally, healthcare professionals with thorough pharmacovigilance training and therapeutic expertise should be involved in the collection and the direct follow up of reported cases (particularly those of medical significance). For serious ADRs, it is important to continue follow-up and report new information until the outcome has been established or the condition is stabilized. How long to follow-up such cases will require judgment.

MAHs should collaborate on follow-up if more than one MAH's drug is suspected as a causal agent in a case.
It is important that, at the time of the original report, sufficient details about the patient and reporter be collected and retained to enable future investigations, within the constraints imposed by local data privacy legislation.

4.4.1. Follow-up Related to Pregnancy Exposure

MAHs are expected to follow up all reports, from healthcare professionals or consumers, of pregnancies where the embryo/foetus could have been exposed to one of its medicinal products. When an active substance, or one of its metabolites, has a long half-life, this should be taken into account when considering whether a foetus could have been exposed (i.e. medicinal products taken before the gestational period need to be considered). If a pregnancy results in an abnormal outcome that the reporter considers might be due to the drug, this should be treated as an expedited report if the criteria for expedited reporting are met.

4.5. How to Report

The CIOMS I (Council of International Organisations for Medical Sciences) form has been a widely accepted standard for expedited adverse event reporting. However, no matter what the form or format used, it is important that certain basic information/data

elements, when available, be included with any expedited report, whether in a tabular or narrative presentation. It is recommended that the Medical Dictionary for Regulatory Activities (MedDRA) be used for coding medical information. The standards for electronic submission of Individual Case Safety Reports (ICSR), according to ICH E2B/M2, should be implemented.

The listing in the Attachment addresses those data elements regarded as desirable; if all are not available at the time of expedited reporting, efforts should be made to obtain them.

Reference Sources

1. Current Challenges in Pharmacovigilance: Pragmatic Approaches (CIOMS V), 2001
2. Rules Governing Medicinal Products in the European Union, Volume 9, PHARMACOVIGILANCE: Medicinal Products for Human Use
3. Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines, Food and Drug Administration, March 2001 (draft)
4. Safety Reporting Requirements for Human Drug and Biological Products, Proposed Rule, Food and Drug Administration, March 2003
5. Notifications #421 on the Enforcement of Revised Pharmaceutical Affairs Law, the Director General, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, March, 1997

Attachment

RECOMMENDED KEY DATA ELEMENTS FOR INCLUSION IN EXPEDITED REPORTS OF SERIOUS ADVERSE DRUG REACTIONS

The following list of items has its foundation in several established precedents, including those of CIOMS Ia; the WHO Collaborating Centre for International Drug Monitoring, Uppsala; and various regulatory authority forms and guidelines. Some items might not be relevant depending on the circumstances. Attempts should be made to obtain follow-up information on as many other listed items as are pertinent to the case.

1. Patient Details

- Initials

- Other relevant identifier (patient number, for example)
- Sex
- Age, age category (e.g., adolescent, adult, elderly) or date of birth
- Concomitant conditions
- Medical history
- Relevant family history

2. Suspected Medicinal Product(s)

- Brand name as reported
- International Non-Proprietary Name (INN)
- Batch number
- Indication(s) for which suspect medicinal product was prescribed or tested
- Dosage form and strength
- Daily dose (specify units - e.g., mg, ml, mg/kg) and regimen
- Route of administration
- Starting date and time
- Stopping date and time, or duration of treatment

3. Other Treatment(s)

The same information as in item 2 should be provided for the following:

- Concomitant medicinal products
- (including non-prescription, over-the-counter medicinal products, herbal remedies, dietary supplements, complementary and alternative therapies, etc.) .
- Relevant medical devices

4. Details (all available) of Adverse Drug Reaction(s)

- Full description of reaction(s), including body site and severity
- The criterion (or criteria) for regarding the report as serious
- Description of the reported signs and symptoms
- Specific diagnosis for the reaction
- Onset date (and time) of reaction
- Stop date (and time) or duration of reaction
- Dechallenge and rechallenge information
- Relevant diagnostic test results and laboratory data
- Setting (e.g., hospital, out-patient clinic, home, nursing home)
- Outcome (recovery and any sequelae)

- For a fatal outcome, stated cause of death
- Any autopsy or other post-mortem findings (including a coroner's report)

5. Details on Reporter of an ADR

- Name
- Mailing address
- Electronic mail address
- Telephone and/or facsimile number
- Reporter type (consumer, healthcare professional, etc.)
- Profession (specialty)

6. Administrative and MAH Details

- Source of report (spontaneous, epidemiological study, patient survey, literature, etc.)
- Date the event report was first received by manufacturer/company
- Country in which the event occurred
- Type (initial or follow-up) and sequence (first, second, etc.) of case information reported to authorities
- Name and address of MAH
- Name, address, electronic mail address, telephone number, and facsimile number of contact person of MAH
- Identifying regulatory code or number for marketing authorisation dossier
- Company/manufacturer's identification number for the case (this number must be the same for the initial and follow-up reports on the same case).