HISTORY OF AMENDMENT
ORIGINAL DOCUMENT: MARCH 2004
AMENDMENT NO. 1: SEPTEMBER 2004
AMENDMENT NO. 2: SEPTEMBER 2007
AMENDMENT NO. 3: JUNE 2011

RATIONALE FOR AMENDMENT NO. 2

• To update the requirements for expedited safety reporting of serious and unexpected adverse drug reactions arising from clinical trials on locally registered products.

A risk-based approach stratified by local product registration status will be implemented for the submission of expedited safety reports. For clinical trials on locally registered products, we would no longer require all adverse drug reactions that are both serious and unexpected to be submitted. Only local and overseas adverse drug reactions that are both serious and unexpected and arising from that clinical trial protocol conducted in Singapore need to be submitted. This is in tandem with our scope to look at the benefit – risk balance for the indication or population type that is studied locally in order for signals that are generated to be relevant for the local clinical trial. For unregistered products, a closer monitoring of the safety of the investigational product is required and hence, this change in requirement would apply only to registered products. The flow chart and Appendix 3 have been revised.

New text in Section 3.1.1 reads: “For clinical trials on locally registered products, only local and overseas reports of adverse drug reactions that are both serious and unexpected and arising from that clinical trial protocol conducted in Singapore need to be submitted.”

• To update on the process for submission of expedited safety reports.

New text in Section 3.3 reads: “The expedited safety reports should be submitted through the Expedited Safety Reporting (ESR) online module with effect from November 2008. For ongoing trials whereby the initial clinical trial certificate application was not submitted online (i.e., before 2005), please continue to make hard copy submissions of the expedited safety reports.”

• To reflect the submission of the treatment allocation code to HSA on the online ESR form if the blind has already been broken.

New text in Section 4 reads: “For events where the treatment blind has been broken for submission to the European Medicines Agency (EMEA) or other national authorities, this information should be submitted through the online ESR form.”

• To delete Appendix 4 from this guidance document as the requirements may differ between the Institutional Review Boards (IRB) and NHG Domain Specific Review Board (DSRB). Sponsors should refer to the current safety reporting requirements of the IRB/ DSRB.

• To update the requirements for expedited safety reporting of active comparator drug reactions.

• Administrative updates to reflect organisational changes.
RATIONALE FOR AMENDMENT NO. 3

- To update that the description of SAE in MedDRA terminology is preferred for expedited safety reporting of serious, unexpected and related adverse drug reactions in clinical trials.

This change is based on ICH E2B(R2) guidelines where MedDRA is the recommended standard terminology for classifying adverse reaction/adverse event (AE/AR) information in individual case reports both on paper or electronically in the ICH region. This will also allow HSA’s safety database to be aligned with international standard used by ICH regulatory authorities and facilitate exchange and analysis of data related to the safe use of medical products between biopharmaceutical industry and regulatory authority.

New text in Section 3.3 reads: “It is recommended that the description for the serious, unexpected ADRs be reported using MedDRA (Medical Dictionary for Regulatory Activities), which is a standardised medical terminology developed by ICH to classify adverse event information associated with the use of biopharmaceuticals and other medical products."

- To update on the process for submission of expedited safety reports for locally unregistered active comparators.

New text in Section 5.1 reads: “For locally unregistered active comparators, the sponsor is encouraged to submit expedited safety reports to the Clinical Trials Branch based on the safety reporting requirements for locally unregistered products (refer to 3.1.1).”

- To provide clarification on the process for submission of expedited safety reports for compassionate use programmes.

New section added: “5.4 Compassionate Use Programme"

- Administrative updates to reflect organisational changes
# TABLE OF CONTENTS

**HISTORY OF AMENDMENT** ............................................................................................................. 2

1 **INTRODUCTION** ......................................................................................................................... 5

1.1 Purpose ......................................................................................................................................... 5

1.2 Background ................................................................................................................................... 5

1.3 Scope ............................................................................................................................................ 5

2 **DEFINITIONS AND TERMINOLOGY ASSOCIATED WITH CLINICAL SAFETY EXPERIENCE** .................................................................................................................. 6

2.1 Basic Terms .................................................................................................................................. 6

2.2 Serious Adverse Event or Adverse Drug Reaction ......................................................................... 7

2.3 Expectedness of an Adverse Drug Reaction ................................................................................. 8

3 **STANDARDS FOR EXPEDITED REPORTING** .......................................................................... 9

3.1 What Should Be Reported ........................................................................................................... 9

3.2 Reporting Time Frames ............................................................................................................... 11

3.3 How To Report .......................................................................................................................... 12

4 **MANAGING BLINDED THERAPY CASES** ............................................................................. 13

5 **MISCELLANEOUS ISSUES** ....................................................................................................... 14

5.1 Reactions Associated with Active Comparator or Placebo Treatment ........................................ 14

5.2 Products with More Than One Presentation or Use ...................................................................... 14

5.3 Post-study Events ...................................................................................................................... 15

5.4 Compassionate Use Programme ................................................................................................ 15

6 **INFORMING INVESTIGATORS AND ETHICS COMMITTEES (EC) / INSTITUTIONAL REVIEW BOARDS (IRB) OF NEW SAFETY INFORMATION** ......................................................................................... 15

APPENDIX 1: CIOMS-I Format .............................................................................................................. 16

APPENDIX 2: Data Elements for Inclusion in Expedited Reports of Serious Adverse Drug Reaction ................................................................................................................................. 17

APPENDIX 3: Clinical Drug Trials Serious Adverse Event (SAE) Reporting Requirements and Timelines to the Clinical Trials Branch ........................................................................................................... 19
1 INTRODUCTION

1.1 Purpose

The purpose of this document is to provide guidance to industry on the submission of safety information occurring in all phases of clinical drug trials to the Clinical Trials Branch, Health Products Regulation Group (HPRG), Health Sciences Authority.

1.2 Background

When a medicinal product is under clinical development, there is limited safety information surrounding its use. This is especially so in the early stages of clinical trials and before any marketing experience is available. It is important to obtain timely and pertinent safety information in order to have a broader picture of the clinical safety surrounding a medicinal product, and if necessary, to take action on important clinical safety information arising during clinical development. However, the sponsor is ultimately responsible for the ongoing safety evaluation of the medicinal product.

This guidance for industry on clinical drug trials safety reporting requirements in Singapore is adapted from the ICH Harmonised Tripartite Guideline E2A – Clinical Safety Data Management: Definitions And Standards For Expedited Reporting, which has been developed by the appropriate ICH Expert Working Group and subjected to consultation by the regulatory parties, in accordance with the ICH Process. This document serves to clarify the local requirements in relation to the ICH Harmonised Tripartite Guideline E2A, which is currently appended at the end of the Singapore Guideline for Good Clinical Practice.

1.3 Scope

This guidance addresses the type of documents to be submitted, the timelines and the requirements for reporting of safety information in clinical drug trials. It covers the following:

⇒ Definitions and terminology associated with clinical safety experience
⇒ Standards for expedited reporting: what to report and how to report
⇒ Timelines for expedited reporting
⇒ Minimum data set for reporting
⇒ Managing blinded therapy cases

This guidance does not cover safety reporting relating to medicinal products that do not have any ongoing clinical drug trials in Singapore.
2 DEFINITIONS AND TERMINOLOGY ASSOCIATED WITH CLINICAL SAFETY EXPERIENCE

2.1 Basic Terms

(a) Adverse Event (or Adverse Experience)

Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

(b) Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established:

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 reasonable possibility, i.e. the relationship cannot be ruled out.

(c) Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator’s Brochure for an unapproved investigational medicinal product).
2.2 Serious Adverse Event or Adverse Drug Reaction

During clinical investigations, adverse events may occur which, if suspected to be medicinal product-related (adverse drug reactions), might be significant enough to lead to important changes in the way the medicinal product is developed (e.g., change in dose, population, needed monitoring, consent forms). This is particularly true for reactions, which, in their most severe forms, threaten life or function. Such reactions should be reported promptly to the Clinical Trials Branch.

Therefore, special medical or administrative criteria are needed to define reactions that, either due to their nature (“serious”) or due to significant, unexpected information they provide, justify expedited reporting.

To ensure no confusion or misunderstanding of the difference between the terms “serious” and “severe,” which are not synonymous, the following note of clarification is provided:

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

NOTE: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, 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 usually 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 Expectedness of an Adverse Drug Reaction

The purpose of expedited reporting is to make regulators, investigators, and other appropriate people aware of new, important information on serious reactions. Therefore, such reporting will generally involve events previously unobserved or undocumented, and a guideline is needed on how to define an event as “unexpected” or “expected” (expected/unexpected from the perspective of previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product).

As stated in the definition, an “unexpected” adverse reaction is one where the nature or severity of which is not consistent with information in the relevant source document(s). Until source documents are amended, expedited reporting is required for additional occurrences of the reaction.

The following documents or circumstances will be used to determine whether an adverse event/reaction is expected:

(a) The Investigator's Brochure will serve as the source document for a medicinal product that is not yet approved for marketing;

(b) The local product information leaflet for a medicinal product that has been approved for marketing;

(c) Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered “unexpected”. Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.
3 STANDARDS FOR EXPEDITED REPORTING

3.1 What Should Be Reported

3.1.1 SINGLE CASES OF SERIOUS, UNEXPECTED ADRS

All adverse drug reactions (ADRs) that are both serious and unexpected arising from ongoing clinical drug trials in Singapore on pre-marketed and marketed products are subjected to expedited reporting. Such expedited safety reports should be sent to the Clinical Trials Branch when the minimum criteria for expedited reporting are met. The source of these expedited safety reports should always be specified.

Locally unregistered products

Reports from the following sources should be submitted:

- Any type of clinical investigation, independent of design or purpose (including other protocols with the same study drug);
- Cases not reported directly to a sponsor or manufacturer, for example, those found in regulatory authority-generated ADR registries;
- Overseas spontaneous reports. Please refer to section 3.2.3 to ensure that the minimum criteria are met for regulatory reporting.

Locally registered products

For clinical trials on locally registered products, only local and overseas reports of adverse drug reactions that are both serious and unexpected and arising from that clinical trial protocol conducted in Singapore need to be submitted. Any additional information may be requested as needed.

Expedited reporting of reactions, which are serious but expected, will ordinarily be inappropriate. Expedited reporting is also inappropriate for serious events from clinical investigations that are considered not related to study product, whether the event is expected or not. Similarly, non-serious adverse reactions, whether expected or not, will ordinarily not be subjected to expedited reporting. Figure 1 is a flow chart of the safety reporting decision process for clinical drug trials.
Figure 1: Flow Chart of Safety Reporting Decision Process for Clinical Drug Trials
Causality assessment is required for clinical investigation cases. All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs. For purposes of reporting, adverse event reports associated with marketed drugs (spontaneous reports) usually imply causality.

Many terms and scales are in use to describe the degree of causality (attributability) between a medicinal product and an event, such as certainly, definitely, probably, possibly or likely related or not related. Phrases such as “plausible relationship,” “suspected causality,” or “causal relationship cannot be ruled out” are also invoked to describe cause and effect. However, there is currently no standard international nomenclature. The expression “reasonable causal relationship” is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

### 3.1.2 OTHER OBSERVATIONS

There are situations in addition to single case reports of “serious” adverse events or reactions that may necessitate rapid communication to the Clinical Trials Branch; appropriate medical and scientific judgement should be applied for each situation. In general, information that might materially influence the benefit-risk assessment of a medicinal product or that would be sufficient to consider changes in medicinal product administration or in the overall conduct of a clinical investigation represent such situations. Examples include:

- a. For an “expected,” serious ADR, an increase in the rate of occurrence which is judged to be clinically important.
- b. A significant hazard to the patient population, such as lack of efficacy with a medicinal product used in treating life-threatening disease.
- c. A major safety finding from a newly completed animal study (such as carcinogenicity).

### 3.2 Reporting Time Frames

#### 3.2.1 FATAL OR LIFE-THREATENING UNEXPECTED ADRS

Certain ADRs may be sufficiently alarming so as to require very rapid notification to regulators in countries where the medicinal product or indication, formulation, or population for the medicinal product are still not approved for marketing, because such reports may lead to consideration of suspension of, or other limitations to, a clinical investigation programme. Fatal or life-threatening, unexpected ADRs occurring in clinical investigations qualify for very rapid reporting.

The Clinical Trials Branch should be notified as soon as possible but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by as complete a report as possible within 8 additional calendar days. This report may include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products. Any subsequent follow-up reports should be filed as it becomes available.
3.2.2 ALL OTHER SERIOUS, UNEXPECTED ADRS

Serious, unexpected reactions (ADRs) that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting. Follow-up information should be actively sought and submitted as it becomes available.

3.2.3 MINIMUM CRITERIA FOR REPORTING

Information for final description and evaluation of a case report may not be available within the required time frames for reporting outlined above.

Nevertheless, for regulatory purposes, initial reports should be submitted within the prescribed time as long as the following minimum criteria are met:

- An identifiable patient;
- A suspect medicinal product;
- An identifiable reporting source;
- Event or outcome that can be identified as serious and unexpected;
- In clinical investigation cases, there is a reasonable suspected causal relationship.

3.3 How To Report

The CIOMS-I form (Appendix 1) is a widely accepted standard for expedited adverse event reporting. However, no matter what the form or format used, it is important that certain data elements described in Appendix 2, when available, be included in any expedited report (although some items may not be relevant depending on the circumstances).

It is recommended that the description for the serious, unexpected ADRs be reported using MedDRA (Medical Dictionary for Regulatory Activities), which is a standardised medical terminology developed by ICH to classify adverse event information associated with the use of biopharmaceuticals and other medical products.

All reports must be sent to the Clinical Trials Branch, and other official parties requiring them (e.g., Investigators and Institutional Review Boards). Please refer to Appendix 3 for a summary of the safety reporting requirements for clinical drug trials to the Clinical Trials Branch.

The expedited safety reports should be submitted through the Expedited Safety Reporting (ESR) online module with effect from November 2008. For ongoing trials whereby the initial clinical trial certificate application was not submitted online (i.e., before 2005), please continue to make hard copy submissions of the expedited safety reports.
4 MANAGING BLINDED THERAPY CASES

When the sponsor and investigator are blinded to individual patient treatment (as in a double-blind study), the occurrence of a serious event requires a decision on whether to open (break) the code for the specific patient. If the investigator breaks the blind, then it is assumed the sponsor will also know the assigned treatment for that patient. Although it is advantageous to retain the blind for all patients prior to final study analysis, when a serious adverse reaction is judged reportable on an expedited basis, it is recommended that the blind be broken only for that specific patient by the sponsor even if the investigator has not broken the blind. It is also recommended that, when possible and appropriate, the blind be maintained for those persons, such as biometrics personnel, responsible for analysis and interpretation of results at the study’s conclusion.

There are several disadvantages to maintaining the blind under the circumstances described, which outweigh the advantages. By retaining the blind, placebo and comparator (usually a marketed product) cases are filed unnecessarily. When the blind is eventually opened, which may be many weeks or months after reporting to regulators, it must be ensured that company and regulatory databases are revised. If the event is serious, new, and possibly related to the medicinal product, then if the Investigator’s Brochure is updated, notifying relevant parties of the new information in a blinded fashion is inappropriate and possibly misleading. Moreover, breaking the blind for a single patient usually has little or no significant implications for the conduct of the clinical investigation or on the analysis of the final clinical investigation data.

For events where the treatment blind has been broken for submission to the European Medicines Agency (EMEA) or other national authorities, this information should be submitted through the online ESR form. For events where the treatment blind has been broken and reveals placebo, and no expedited report has been filed to the Clinical Trials Branch yet, expedited safety reporting is not required. On the other hand, if a report has already been submitted and subsequently, the blind is broken, the Clinical Trials Branch must be updated on this new information by sending the safety report and highlighting this information for the database to be updated.

When a fatal or other “serious” outcome is the primary efficacy endpoint in a clinical investigation, the integrity of the clinical investigation may be compromised if the blind is broken. Under these and similar circumstances, it may be appropriate to reach agreement with the Clinical Trials Branch in advance concerning serious events that would be treated as disease-related and not subjected to routine expedited reporting.
5 MISCELLANEOUS ISSUES

5.1 Reactions Associated with Active Comparator or Placebo Treatment

Local reports of locally registered active comparator adverse drug reactions that are both serious and unexpected arising from the clinical trial protocol conducted in Singapore should be submitted to the Clinical Trials Branch. Adverse drug reactions of locally registered active comparators arising from overseas reports need not be submitted. Events associated with placebo will usually not satisfy the criteria for an ADR and, therefore, for expedited reporting.

For locally unregistered active comparators, the sponsor is encouraged to submit expedited safety reports to the Clinical Trials Branch based on the safety reporting requirements for locally unregistered products (refer to 3.1.1).

5.2 Products with More Than One Presentation or Use

To avoid ambiguities and uncertainties, an ADR that qualifies for expedited reporting with one presentation of a product (e.g., a dosage form, formulation, delivery system) or product use (e.g., for an indication or population), should be reported or referenced to regulatory filings across other product presentations and uses.

It is not uncommon that more than one dosage form, formulation, or delivery system (oral, IM, IV, topical, etc.) of the pharmacologically active compound(s) is under study or marketed; for these different presentations there may be some marked differences in the clinical safety profile. The same may apply for a given product used in different indications or populations (single dose vs. chronic administration, for example). Thus, “expectedness” may be product or product-use specific, and separate Investigator’s Brochures may be used accordingly. However, such documents are expected to cover ADR information that applies to all affected product presentations and uses. When relevant, separate discussions of pertinent product-specific or use-specific safety information will also be included.

It is recommended that any adverse drug reactions that qualify for expedited reporting observed with one product dosage form or use be cross referenced to regulatory records for all other dosage forms and uses for that product. This may result in a certain amount of over-reporting or unnecessary reporting in obvious situations (for example, a report of phlebitis on IV injection sent to authorities in a country where only an oral dosage form is studied or marketed). However, underreporting is completely avoided.
5.3 Post-study Events

Although such information is not routinely sought or collected by the sponsor, serious adverse events that occur after the patient has completed a clinical study (including any protocol-required post-treatment follow-up) will possibly be reported by an investigator to the sponsor. Such cases should be regarded for expedited reporting purposes as though they were study reports.

Therefore, causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

5.4 Compassionate Use Programme

Unregistered medicinal products may be made available through an approved clinical trial protocol, compassionate use programmes or via named-patient basis. Compassionate use programmes are intended for a group of patients to facilitate the availability of new treatment options under development.

For a compassionate use programme which is an extension of a completed clinical trial, where patients are provided continued treatment with the unregistered product, all serious and unexpected adverse drug reactions should be reported to the Clinical Trials Branch (refer to 3.1.1).

The product licence holder importing locally unregistered medicinal products not for use in clinical trials or compassionate use programmes (as detailed above), should report all suspected local adverse reactions to the Vigilance Branch in accordance to the reporting requirements on unregistered medicinal products in their guidance, ‘Guidance for Industry: Safety Reporting Requirements for Registered Medicinal Products’.

6 INFORMING INVESTIGATORS AND ETHICS COMMITTEES (EC) / INSTITUTIONAL REVIEW BOARDS (IRB) OF NEW SAFETY INFORMATION

In general, the sponsor of a study should amend the Investigator’s Brochure as needed, so as to keep the description of safety information updated. Sponsors should refer to the current safety reporting requirements of the IRB/DSRB.
## CIOMS-I Format

### SUSPECT ADVERSE REACTION REPORT

#### I. REACTION INFORMATION

<table>
<thead>
<tr>
<th>1. PATIENT INITIALS (first, last)</th>
<th>1a. COUNTRY</th>
<th>2. DATE OF BIRTH</th>
<th>2a. AGE</th>
<th>3. SEX</th>
<th>4-6 REACTION ONSET</th>
<th>B-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day</td>
<td>Month</td>
<td>Year</td>
<td>Day</td>
<td>Month</td>
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</tbody>
</table>

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

#### II. SUSPECT DRUG(S) INFORMATION

<table>
<thead>
<tr>
<th>14. SUSPECT DRUG(S) (include generic name)</th>
<th>20 DID REACTION ABATE AFTER STOPPING DRUG?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>15. DAILY DOSE(S)</th>
<th>16. ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
</table>

| 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? |
| YES | NO | NA |

<table>
<thead>
<tr>
<th>17. INDICATION(S) FOR USE</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>18. THERAPY DATES (from/to)</th>
<th>19. THERAPY DURATION</th>
</tr>
</thead>
</table>

#### III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

#### IV. MANUFACTURER INFORMATION

<table>
<thead>
<tr>
<th>24a. NAME AND ADDRESS OF MANUFACTURER</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>24b. MFR CONTROL NO.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>24c. DATE RECEIVED BY MANUFACTURER</th>
<th>24d. REPORT SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>REPORT SOURCE</td>
<td>STUDY</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>25a. REPORT TYPE</th>
<th>DATE OF THIS REPORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>INITIAL</td>
<td>FOLLOWUP</td>
</tr>
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</table>
APPENDIX 2
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-I, the WHO International Drug Monitoring Centre, and various regulatory authority forms and guidelines. Some items may not be relevant depending on the circumstances. The minimum information required for expedited reporting purposes is: an identifiable patient, the name of a suspect medicinal product, an identifiable reporting source, and an event or outcome that can be identified as serious and unexpected and for which, in clinical investigation cases, there is a reasonable suspected causal relationship. Attempts should be made to obtain follow-up information on as many other listed items pertinent to the case.

1. Patient Details
   - Initials
   - Other relevant identifier (clinical investigation number, for example)
   - Gender
   - Age and/or date of birth
   - Weight
   - Height

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 and regimen (specify Units - e.g., mg, ml, mg/kg)
   - Route of administration
   - Starting date and time of day
   - Stopping date and time, or duration of treatment

3. Other Treatment(s)
   For concomitant medicinal products (including non-prescription/OTC medicinal products) and non-medicinal product therapies, provide the same information as for the suspected product.
4. **Details of Suspected Adverse Drug Reaction(s)**

   Full description of reaction(s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious should be given. In addition to a description of the reported signs and symptoms, whenever possible, attempts should be made to establish a specific diagnosis for the reaction.

   Start date (and time) of onset of reaction
   
   Stop date (and time) or duration of reaction
   
   Dechallenge and rechallenge information
   
   Setting (e.g., hospital, out-patient clinic, home, nursing home)

   **Outcome:** information on recovery and any sequelae; what specific tests and/or treatment may have been required and their results; for a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction should be provided. Any autopsy or other post-mortem findings (including a coroner's report) should also be provided when available. Other information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations.

5. **Details on Reporter of Event (Suspected ADR)**

   Name
   
   Address
   
   Telephone number
   
   Profession (specialty)

6. **Administrative and Sponsor/Company Details**

   Source of report
   
   Date event report was first received by sponsor/manufacturer
   
   Country in which event occurred
   
   Type of report filed to authorities: initial or follow-up (first, second, etc.)
   
   Name and address of sponsor/manufacturer/company
   
   Name, address, telephone number, and Fax number of contact person in reporting company or institution
   
   HSA-HPRG clinical trial application/ reference number
   
   Sponsor/ manufacturer’s identification number for the case (this number must be the same for the initial and follow-up reports on the same case).
Unregistered Products: Local and overseas adverse drug reactions that are both serious and unexpected (including other protocols of the SAME study drug)

Locally Registered Products: Only local and overseas adverse drug reactions that are both serious and unexpected and arising from that clinical trial protocol that is studied in Singapore need to be submitted

<table>
<thead>
<tr>
<th>Nature of Report</th>
<th>Report? (Y/N)</th>
<th>Timeframe of Report</th>
<th>Form Preferred</th>
<th>Content of Submission</th>
<th>Responsibility for Reporting to CTB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious, and Unrelated</td>
<td>NO</td>
<td>Not Applicable</td>
<td></td>
<td></td>
<td>Sponsor</td>
</tr>
<tr>
<td>Serious, Related, and Expected</td>
<td>NO</td>
<td>Not Applicable</td>
<td></td>
<td></td>
<td>Sponsor</td>
</tr>
<tr>
<td>Serious, Related, and Unexpected Death * / Life Threatening Events</td>
<td>YES</td>
<td>Expedited Reporting:</td>
<td>CIOMS-I</td>
<td>Where applicable:</td>
<td>Sponsor</td>
</tr>
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<td></td>
<td></td>
<td>• Initial report by 7 calendar days</td>
<td></td>
<td>• Dear Healthcare Professional Letter</td>
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<td></td>
<td></td>
<td>• Follow-up report as complete as possible within 8 additional calendar days</td>
<td></td>
<td>• Company’s comments</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Subsequent follow-up reports: As it becomes available</td>
<td></td>
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<tr>
<td>Serious, Related, and Unexpected Non Fatal/ Non Life Threatening Events</td>
<td>YES</td>
<td>Expedited Reporting:</td>
<td>CIOMS-I</td>
<td>Where applicable:</td>
<td>Sponsor</td>
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<tr>
<td></td>
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<td>• Initial report: 15 calendar days</td>
<td></td>
<td>• Dear Healthcare Professional Letter</td>
<td></td>
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<tr>
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<td></td>
<td>• Follow-up report: As it becomes available</td>
<td></td>
<td>• Company’s comments</td>
<td></td>
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</table>

* For reported deaths, the investigator should supply HSA as well as the IRB/DSRB and Sponsor with any additional requested information.

Please note that only serious, unexpected adverse drug reactions qualify for expedited reporting as reflected in this guidance. The information provided in this Appendix is only a summary. It is important for readers to refer to the entire guidance for clinical drug trials safety reporting.

Reference: Singapore Guideline for Good Clinical Practice, section 5.17. Please also see section 5.16.
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