INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

CLINICAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING

E2A

Recommended for Adoption

at Step 4 of the ICH Process

on 27 October 1994

by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

CLINICAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING

ICH Harmonised Tripartite Guideline

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I. INTRODUCTION

It is important to harmonise the way to gather and, if necessary, to take action on important clinical safety information arising during clinical development. Thus, agreed definitions and terminology, as well as procedures, will ensure uniform Good Clinical Practice standards in this area. The initiatives already undertaken for marketed medicines through the CIOMS-1 and CIOMS-2 Working Groups on expedited (alert) reports and periodic safety update reporting, respectively, are important precedents and models. However, there are special circumstances involving medicinal products under development, especially in the early stages and before any marketing experience is available. Conversely, it must be recognised that a medicinal product will be under various stages of development and/or marketing in different countries, and safety data from marketing experience will ordinarily be of interest to regulators in countries where the medicinal product is still under investigational-only (Phase 1, 2, or 3) status. For this reason, it is both practical and well-advised to regard pre-marketing and post-marketing clinical safety reporting concepts and practices as interdependent, while recognising that responsibility for clinical safety within regulatory bodies and companies may reside with different departments, depending on the status of the product (investigational vs. marketed).

There are two issues within the broad subject of clinical safety data management that are appropriate for harmonisation at this time:

(1) the development of standard definitions and terminology for key aspects of clinical safety reporting, and

(2) the appropriate mechanism for handling expedited (rapid) reporting, in the investigational (i.e., pre-approval) phase.

The provisions of this guideline should be used in conjunction with other ICH Good Clinical Practice guidelines.

II. DEFINITIONS AND TERMINOLOGY ASSOCIATED WITH CLINICAL SAFETY EXPERIENCE

A. Basic Terms

Definitions for the terms adverse event (or experience), adverse reaction, and unexpected adverse reaction have previously been agreed to by consensus of the more than 30 Collaborating Centres of the WHO International Drug Monitoring Centre (Uppsala, Sweden). [Edwards, I.R., et al, Harmonisation in Pharmacovigilance. *Drug Safety* 10(2): 93-102, 1994.] Although those definitions can pertain to situations involving clinical investigations, some minor modifications are necessary, especially to accommodate the pre-approval, development environment.

The following definitions, with input from the WHO Collaborative Centre, have been agreed:

1. Adverse Event (or Adverse Experience)

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

An adverse event (AE) can therefore be any unfavourable 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.

2. 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 products" 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.

Regarding *marketed medicinal products*, a well-accepted definition of an adverse drug reaction in the post-marketing setting is found in WHO Technical Report 498 [1972] and reads as follows:

A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

The old term "side effect" has been used in various ways in the past, usually to describe negative (unfavourable) effects, but also positive (favourable) effects. It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction.

3. 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). (See section III.C.)

B. 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 regulators.

Therefore, special medical or administrative criteria are needed to define reactions that, either due to their nature ("serious") or due to the 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.

After reviewing the various regulatory and other definitions in use or under discussion elsewhere, the following definition is believed to encompass the spirit and meaning of them all:

> *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 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.
>
> * *requires inpatient hospitalisation or prolongation of existing hospitalisation,*
>
> * *results in persistent or significant disability/incapacity, or*
>
> * *is a congenital anomaly/birth defect.*

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.

C. 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 (II.A.3.), an "unexpected" adverse reaction is one, 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:

1. For a medicinal product not yet approved for marketing in a country, a company's Investigator's Brochure will serve as the source document in that country. (See section III.F. and ICH Guideline for the Investigator's Brochure.)

2. 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.

III. STANDARDS FOR EXPEDITED REPORTING

A. What Should be Reported?

1. Single Cases of Serious, Unexpected ADRs

All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting. This applies to reports from spontaneous sources and from any type of clinical or epidemiological investigation, independent of design or purpose. It also applies to cases not reported directly to a sponsor or manufacturer (for example, those found in regulatory authority-generated ADR registries or in publications). The source of a report (investigation, spontaneous, other) should always be specified.

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 subject to *expedited* reporting.

Information obtained by a sponsor or manufacturer on serious, unexpected reports from any source should be submitted on an expedited basis to appropriate regulatory authorities if the minimum criteria for expedited reporting can be met. See section III.B.

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.

2. Other Observations

There are situations in addition to single case reports of "serious" adverse events or reactions that may necessitate rapid communication to regulatory authorities; 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 represents 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).

B. Reporting Time Frames

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 investigations program. Fatal or life-threatening, unexpected ADRs occurring in *clinical investigations* qualify for very rapid reporting. Regulatory agencies should be notified (e.g., by telephone, facsimile transmission, or in writing) 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 must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products.

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.

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; 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. Follow-up information should be actively sought and submitted as it becomes available.

C. How to Report

The CIOMS-I 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. The listing in Attachment 1 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. (See section III.B.)

All reports must be sent to those regulators or other official parties requiring them (as appropriate for the local situation) in countries where the drug is under development.

D. 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 data bases 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.

However, 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 regulatory authorities in advance concerning serious events that would be treated as disease-related and not subject to routine expedited reporting.

E. Miscellaneous Issues

1. Reactions Associated with Active Comparator or Placebo Treatment

It is the sponsor's responsibility to decide whether active comparator drug reactions should be reported to the other manufacturer and/or directly to appropriate regulatory agencies. Sponsors must report such events to either the manufacturer of the active control or to appropriate regulatory agencies. Events associated with placebo will usually not satisfy the criteria for an ADR and, therefore, for expedited reporting.

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 overreporting 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.

3. Post-study Events

Although such information is not routinely sought or collected by the sponsor, serious adverse events that occurred after the patient had 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, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

F. INFORMING INVESTIGATORS AND ETHICS COMMITTEES/ INSTITUTIONAL REVIEW BOARDS OF NEW SAFETY INFORMATION

International standards regarding such communication are discussed within the ICH GCP Guidelines, including the addendum on "Guideline for the Investigator's Brochure." In general, the sponsor of a study should amend the Investigator's Brochure as needed, and in accord with any local regulatory requirements, so as to keep the description of safety information updated.

Attachment 1

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-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 (speciality)

6. Administrative and Sponsor/Company Details

Source of report: was it spontaneous, from a clinical investigation (provide details), from the literature (provide copy), other?

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

Identifying regulatory code or number for marketing authorisation dossier or clinical investigation process for the suspected product (for example IND or CTX number, NDA 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).