experience is available. Conversely, it must be recognized 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 premarketing and postmarketing clinical safety reporting concepts and practices as interdependent, while recognizing that responsibility for clinical safety within regulatory bodies and companies may reside with different departments, depending on the status of the product (investigational versus marketed).

There are two issues within the broad subject of clinical safety data management that are appropriate for harmonization 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., preapproval) 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 Centers 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 preapproval, 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 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.

2. Adverse Drug Reaction (ADR).

In the *preapproval 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 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 postmarketing 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 (unfavorable) effects, but also positive (favorable) 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 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 that no confusion or misunderstanding exist 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 hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect. Medical and scientific judgment 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 hospitalization but may jeopardize 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 hospitalization; 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 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 ADR's $\,$

All ADR's that are both serious and unexpected are subject to expedited reporting. This applies to reports from spontaneous sources and from any type of