



Practical addenda

Addendum 2: Reporting ADEs to health authorities

Pharmaceutical companies have a duty to study what is happening with their medicines in the market. Health authorities have a right to know what is going on. In many Western countries, including the EC and the USA, there is a legal obligation for drug manufacturers and licence holders to submit post-marketing ADEs to the national health authorities. For that purpose, each incoming ADE is to be classified according to its newness (“expected” versus “unexpected”, the latter meaning that it is not consistent with the nature or severity described in the national data sheet) and seriousness. The criteria used to consider an ADE serious are rather well defined and are similar in the USA and in the EC: basically, these criteria refer to ADEs that are fatal or life-threatening, ADEs that require or prolong hospitalisation, and ADEs that cause persistent or otherwise significant disability.

There are two types of reports to health authorities in most of these countries:

(1) Reports on individual ADEs

Relevant details on serious unexpected ADEs must be reported to the health authorities within a predetermined time interval: this interval is not identical across countries, but is always less than 1 month.

In the USA, domestic ADEs that are serious and unexpected must be submitted to the FDA within 15 working days.

In addition, many health authorities require that details on foreign ADEs that are serious and unexpected be reported within the above relatively short time interval.

Foreign serious and unexpected ADEs must also be submitted to the FDA within 15 working days. According to the FDA, these 15 days should be calculated from the moment the company hears about the ADE for the first time, wherever in the world. This is very stringent and at times very hard, if not impossible, to adhere to.

(2) *Periodic surveys*

Serious expected ADEs and non-serious ones are allowed to accumulate for a sizeable time interval before a survey of their main features is reported to the health authorities. This time interval may vary from something like 6 months, for newly introduced drugs, to 5 years, for older medicines.

In the USA, periodic reports are required for domestic serious expected and non-serious ADEs and for foreign serious expected (but not non-serious) ADEs. The interval between two periodic reports varies with the length that the product has been on the market. If it appears from the periodic analysis or from other information that the frequency of a serious expected adverse effect is increased in the USA or elsewhere, the FDA requires a separate, specific report on this finding within 15 working days.

Reporting format

(1) *Reports on individual ADEs*

Many health authorities have developed their domestic form for reporting serious unexpected ADEs, which is often identical to the one that health professionals are requested to use when they want to report an ADE to those same health authorities. CIOMS has been very instrumental by developing a form for the international reporting of foreign serious unexpected ADEs, regardless of the health authorities to whom the reports are going. This form is shown in Fig. 1. This form is also accompanied by a couple of useful definitions, likewise developed by the CIOMS group, as follows:

— The title of the reporting form refers to an **adverse “reaction”**. In its publication on the form, CIOMS has wisely defined what it meant by “reaction” namely:

“Reactions” is to be distinguished from “events”. CIOMS reports always refer to a suspect reaction, which implies that a physician or other professional health care worker has judged it a reasonable possibility that an observed clinical occurrence had been caused by a drug. CIOMS reports do not relate to events or “experience”, where some level of causal judgement has not been made. Note, however, that the group did not decide on any particular method of assessing causality. To the contrary, it interprets the fact that a physician makes a spontaneous report as evidence indicating that he suspects that the event may be due to the drug. Hence, CIOMS feels that all spontaneous reports of serious unlabelled ADEs made by a medical professional should be considered as CIOMS reports. As another corollary, it also implies that the submission of such a report does not necessarily constitute acceptance of causality by the manufacturer.

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT											
I. REACTION INFORMATION											
1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION <input type="checkbox"/> PATIENT DIED <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)											
II. SUSPECT DRUG(S) INFORMATION											
14. SUSPECT DRUG(S) (include generic name)								20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA			
15. DAILY DOSE(S)				16. ROUTE(S) OF ADMINISTRATION				21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA			
17. INDICATION(S) FOR USE											
18. THERAPY DATES (from/to)				19. THERAPY DURATION							
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											
24a. NAME AND ADDRESS OF MANUFACTURER											
24b. MFR CONTROL NO.											
24c. DATE RECEIVED BY MANUFACTURER			24d. REPORT SOURCE <input type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input type="checkbox"/> HEALTH PROFESSIONAL								
DATE OF THIS REPORT			25a. REPORT TYPE <input type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP								

Fig. 1.

— As labelling status may differ between countries, certain ADEs may be “labelled” or “expected” in some countries but “unlabelled” or “unexpected” in others. It is the labelling status of a country that determines whether a certain ADE should be submitted in that country.

(2) Periodic surveys

CIOMS has similarly made proposals for this type of routine compilations of

ADEs, as well as for their timing. Unlike the above “CIOMS I” reports, the “CIOMS II” reports are meant to cover all appropriate ADEs, i.e. foreign as well as domestic.

The following are guidelines that CIOMS has proposed in this context:

— Applicability: all new chemical entities licensed for the first time in 1992 or later.

— Frequency: every 6 months.

— ADEs covered: those reported in the latest 6 months.

— Proposed contents:

- I. Introduction.
- II. Core data sheet. Defined by CIOMS as: “A document prepared by the pharmaceutical manufacturer, containing all relevant safety information, such as adverse drug reactions, which the manufacturer stipulates should be listed for the drug in all countries where the drug is marketed. It is the reference document by which “labelled” and “unlabelled” are determined, and is therefore always included in a report.”
- III. The drug’s licensed status for marketing.
- IV. Update of regulatory or manufacturer actions taken for safety reasons.
- V. Patient exposure. This information (sales experience) should match as far as possible the period covered by the interim safety data. The method used to estimate patient exposure should always be outlined.
- VI. Individual case histories. The individual histories of the unlabelled, serious ADEs that are considered attributable to the drug and that have been received during the 6-month period of review. The information should be presented in a proposed line-listing format.
- VII. Studies. New important studies that pertain to the safety of the drug.
- VIII. Overall safety evaluation. A concise critical analysis and opinion.
- IX. Important information received after data lock-point. The data lock-point is the cut-off date for data to be incorporated into the safety summary.

Full references of CIOMS publications

(1) Reports on individual ADEs

Final Report of CIOMS Working Group: “International Reporting of Adverse Drug Reactions.” The Council for International Organizations of Medical Sciences (CIOMS), Geneva, 1992. [ISBN 92 9036 042 9]

(2) Periodic surveys

Final Report of CIOMS Working Group II: “International Reporting of Periodic Drug-Safety Update Summaries.” The Council for International Organizations of Medical Sciences (CIOMS), Geneva, 1992. [ISBN 92 9036 053 4]