



International Reporting of Adverse Drug Reactions

CIOMS Working Group Report



Geneva, 1987

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International Reporting of Adverse Drug Reactions Progress Report of CIOMS Working Group

INTRODUCTION

The Council for International Organizations of Medical Sciences (CIOMS) is an international, nongovernmental, non-profit organization established in 1949 under the auspices of the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (Unesco). Among its prime functions are: to act as a sounding-board for capturing and disseminating informed opinion on new developments in biology and medicine, and to explore their social, ethical, moral, administrative and legal implications.

In 1977 a CIOMS Round Table Conference on "Trends and Prospects in Drug Research and Development" recommended that, by offering an independent forum, CIOMS should facilitate discussion of policy matters between the research-based pharmaceutical companies and national regulatory authorities, and, when required, convene groups of experts to make recommendations on specific issues.

Over the past decade CIOMS has collaborated with WHO in a variety of matters of direct concern to manufacturers and prescribers of drugs. Notably, it has produced a set of International Guidelines for Biomedical Research Involving Human Subjects, which relate to ethical aspects of medical research and have been incorporated in statutory provisions in several countries. Also, it has issued a report on Safety Requirements for the First Use of New Drugs and Diagnostic Agents in Man, and a set of International Guiding Principles for Biomedical Research Involving Animals.

The present CIOMS Pilot Project on International Reporting of Adverse Drug Reactions is aimed at developing internationally acceptable reporting methods whereby manufacturers can report post-marketing adverse drug reactions rapidly, efficiently and effectively to regulators. This is crucial to proper interpretation of adverse reactions and follow-up for ensuring drug safety.

During the next year it is proposed to invite the participation in the project of a few more regulatory authorities and manufacturers and to assess the utility of this reporting scheme. Finally, it is expected that, in collaboration with WHO, national regulatory authorities and manufacturers, it will be possible to make this reporting system available internationally.

Comments are invited and should be addressed to:

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BACKGROUND

This is a summary report of a project aimed at coordinating and improving international reporting of post-marketing adverse drug reactions (ADR) between five countries and six pharmaceutical manufacturers. Because the project is only beginning, the report focuses on methods and procedures. It is expected that future reports will be concerned more with findings and the evaluation of the project.

In September 1985 CIOMS convened a meeting to discuss monitoring and assessment of adverse drug effects¹. It focused on pharmaco-epidemiological aspects of post-marketing surveillance, and examined the utility of follow-up studies, case-control studies and cohort studies as means of recognizing such effects. The collection and use of reports on adverse drug reactions was also discussed and it was recognized that some international means of coordinating the surveillance activities of regulating bodies and those of manufacturers would be extremely useful. For this reason a separate CIOMS ADR Working Group (see Annex I) met in Geneva in April 1986; it reached a remarkable level of agreement on procedures, format, definitions, and other aspects of a coordinated reporting system, and decided to initiate a CIOMS pilot project on international reporting of adverse reactions. The group met subsequently in Washington, D.C., in June 1986, and at Strasbourg, France, in May 1987. Early on it was agreed that there was a clear advantage to limiting the number of participants in the project in order to facilitate communication and flexibility so that proposed procedures could be tested. Because the project has made so much progress and generated so much outside interest, it was felt desirable to prepare the current report.

Concern with international reporting of adverse drug reactions is not new^{2,3,4} and reflects the global scale of the marketing of pharmaceutical products by multinational corporations and their affiliates. What is observed in one country related to a pharmaceutical product will be crucially important information to other countries. In recent years there has been an increased amount of regulation governing the submission of foreign reports to regulators. Notable examples of this are the requirements issued in the United Kingdom in 1984⁵, in the United States in 1985^{6,7} and in the Federal Republic of Germany in

1987 (oral communication, Kreutz, W., Bundesgesundheitsamt, F.R.G). Each set of requirements tends to use slightly different definitions, procedures and deadlines. The resulting mass of bureaucratic requirements imposes an enormous effort in complying with them. Thus, an international manufacturer who receives a report in one country may be required to submit it to 20 or more other countries, using 20 different forms, 20 different procedures and 20 different schedules.

The purpose of the CIOMS ADR pilot project is to develop means whereby manufacturers can report post-marketing adverse reactions rapidly, efficiently and effectively to regulators. It must be emphasized that it is not concerned with the reporting of adverse reactions observed during drug development, before the product is licensed for marketing. Neither is it intended to replace domestic reporting procedures and requirements. It refers only to the transfer of information from one country to another through the manufacturer. The WHO International Drug Monitoring Programme is quite separate from the CIOMS project in that it receives domestic reports from regulators^{3,4} (Figure 1).

METHODS

At the first meeting of the Working Group all 11 members discussed their different international reporting requirements. From the start, the need to standardize definitions, procedures, time-frames and formats was evident. Since many of these are embedded in law and regulations, the several representatives of regulating authorities first sought to identify common ground. It was recognized that each regulating authority would have to modify its regulations or seek other means of allowing the pilot project to proceed.

For manufacturers, a key issue was communication and contractual arrangements between their representatives on the Working Group and their affiliates in the several countries participating in the project. Each manufacturer had undertaken to involve affiliates in different countries. Clearly, the project's success would depend on each

manufacturer obtaining the cooperation and agreement of his affiliates. The direct representation of the affiliates would have resulted in a group too cumbersome to function easily.

The Working Group reached some agreements in April 1986, and each participant returned home to explore their implications and to ascertain their feasibility. At its June 1986 meeting the Group agreed that there was sufficient promise to move forward to alter regulations, data systems and internal procedures. By May 1987 enough progress had occurred to justify this publication.

In the course of these several meetings it became clear that it was essential to agree on one form, in one language, and on one set of definitions in order to permit follow-up data to be linked with original reports, and to prevent corruption of the international data base by duplicate, triplicate, or multiple versions of a report of a single adverse drug reaction.

RESULTS

The Working Group has developed a common set of definitions, procedures, and formats for reporting serious unexpected adverse drug reactions between the bodies represented by its members. The Group's definition of an adverse drug reaction is "an undesirable effect suspected of being caused by a drug". This definition includes abuse, dependency and drug interactions. In contrast to domestic regulations in several countries, it does not include failure of expected pharmacological action or overdose. A *serious* ADR is taken as one that is associated with death, inpatient hospitalization, prolongation of hospitalization, or persistent significant disability or incapacity, or otherwise life-threatening. An *unexpected* ADR is one the nature or severity of which is not consistent with domestic labelling or marketing authorization.

Although the Working Group concentrated on reports of single serious, unexpected reactions, it was agreed that serious known reactions that were occurring at a rate greater than stated in domestic

labelling or marketing authorization should be brought to the attention of regulatory authorities as soon as possible, independently of the CIOMS project.

The Group addressed itself to a number of other definitional questions. Although the principal concern is about recently approved drugs, regulations in most countries set no limits on the compounds that should be monitored. For this reason it was felt that the pilot reporting scheme should include all drugs, regardless of when they came on the market. It was also agreed that the most valuable ADR reports come from a prescribing professional and not from other sources such as consumers and attorneys, whose information is often insufficiently detailed, or may be biased or second-hand. When a manufacturer receives reports from such sources, it is likely that a professional prescriber was involved if a serious reaction occurred, and this professional should be sought out.

It was also agreed that only reports that had reached some minimal standard of adequacy of information should be considered as CIOMS reports. Four pieces of information constitute this minimum: an identifiable source, an identifiable patient (even if not precisely identified by name and date of birth), an identifiable drug, and an identifiable suspect reaction. If any of these essential elements is missing then no report should be made until the missing information is obtained via follow-up inquiries. With regard to an identifiable patient, reports of the type "some patients got a rash" should be excluded until further information is obtained, while a report that said "an elderly woman and a young man who come for consultation had rashes" would be included.

It should be emphasized that eligible reports should be those that refer to a suspect reaction, not an event. The distinction between "suspect reaction" and "event" is that, in the case of a reaction, a physician or other professional health worker has made a judgement that there was a reasonable possibility that the observed clinical occurrence was caused by the drug, while for an event no such causal judgement has been made. Typically, events are recorded during a study, and rates of events of different study groups are compared. For

study events, only those adjudged by a physician to have been reasonably possibly related to drug exposure should be considered for a CIOMS report. Spontaneous reports by practising physicians are always considered reports of suspect reactions, since the act of reporting signals is a judgement of possible causality on the part of the reporter.

The Group recognized from the start that different labels are used in different countries. For this reason it is clear that manufacturers must generally collect all reports of serious adverse reactions at one central point, enter them on a form and then decide, on a country-by-country basis, whether the reactions reported are unlabelled or not. Alternatively, all these forms could be sent to all affiliates, where decisions about submission could be made, or a manufacturer might have standard international prescribing information.

The Group also agreed that a single common reporting form, in English, should be used (Annex II). The report form has all the usual elements of some patient and demographic information, a description of the suspected reaction and its severity, and a description of the drugs involved.

Lastly, it was agreed that manufacturers should submit completed CIOMS report forms to the several regulating bodies as soon as they receive them, and in no case later than 15 working days after their receipt.

CURRENT STATUS

The United States, the United Kingdom and the Federal Republic of Germany have moved actively to modify requirements to make them compatible with the CIOMS proposal. In the United States, regulations are being modified, for example to alter the definition of "serious", so that it is now totally compatible with that of the CIOMS Group⁸. In the United Kingdom all manufacturers (whether or not they are members of the CIOMS Working Group) are now required to use the CIOMS form and procedures for reporting⁹. In the Federal Republic

of Germany regulations are being changed but the CIOMS form is provisionally acceptable for the reporting of foreign adverse reactions. France has agreed to accept the form instead of other forms for reporting of foreign adverse reactions. Sweden has indicated that it is willing to accept summaries based on the CIOMS form, but emphasizes that it does not wish to receive single case reports unless specifically requested. Most of the manufacturers represented in the Group are at varying stages of project implementation¹⁰. With six manufacturers each covering five countries, there are 30 information transfer points; over half of these are operational.

SUMMARY

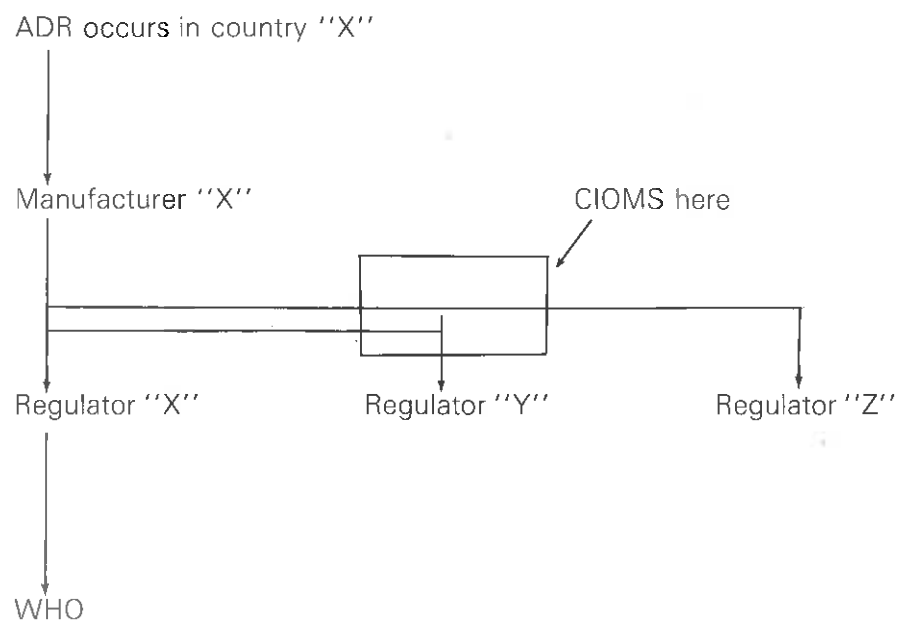
In a period of one year the CIOMS Working Group has made remarkable progress in the development of a pilot project seeking to coordinate reporting of adverse drug reactions. A common set of definitions and procedures, and a report form, have been developed and implemented. Over the next year the Group should have data to assess the volume and utility of this reporting method. In the future it will be important to consider how to expand this work to bring about an even greater improvement in international reporting. Rapid collection and transmission of post-marketing ADR reports are crucial to interpretation and follow-up for ensuring drug safety and proper use. It is expected that the CIOMS project will greatly contribute to this.

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FIGURE I

CIOMS in relation to WHO and domestic reporting



WORKING GROUP PARTICIPANTS

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Also participating in one or more of the Working Group meetings
were:

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SUSPECT ADVERSE REACTION REPORT												

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1 a. COUNTRY	2. DATE OF BIRTH			2a. AGE Years	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 OF SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING
		Day	Month	Year			Day	Month	Year	
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 REINTRO- DUCTION? <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

24 a. NAME AND ADDRESS OF MANUFACTURER	
24 b. MFR CONTROL NO.	
24 c. DATE RECEIVED BY MANUFACTURER	24 d. REPORT SOURCE <input type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input type="checkbox"/> HEALTH PROFESSIONAL
DATE OF THIS REPORT	25 a. REPORT TYPE <input type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP