Current Challenges in Pharmacovigilance: Pragmatic Approaches

Report of CIOMS Working Group V

Geneva 2001

Current Challenges in Pharmacovigilance: Pragmatic Approaches

Report of CIOMS Working Group V

Geneva 2001

ISBN 92 9036 074 7
Printed in Switzerland

Acknowledgements

The Council for International Organizations of Medical Sciences is grateful to the members of CIOMS Working Group V, on Current Challenges in Pharmacovigilance: Pragmatic Approaches, and to the drug regulatory authorities, pharmaceutical companies and other organizations represented, for their patience and hard work in bringing this project to its successful conclusion. Special thanks are due to the co-chairs, Drs. Murray Lumpkin and Win Castle, for their capable leadership, to Ms. Susan Roden, the secretary of the group, and to the editorial committee comprised of Drs. Lumpkin and Castle along with Dr. Arnold J. Gordon and Dr. Hugh Tilson. We wish to express our special thanks to Dr. Gordon, who as chief editor of the interim and final full reports, collected, coordinated and edited the contributions of individual members and assured the quality of the document.

The Working Group is thankful for important input received on several topics from many individuals outside the Group. Particular thanks are due to Dr. James Buchanan and Ms. Linda Hostelley for their thoughtful review of the entire manuscript and for their valuable suggestions, and to Mr. Richard Kingham for his perspective on the use of the Internet; thanks are also given to more than 40 regulatory and company colleagues who completed CIOMS questionnaires whose results helped formulate the content of some of the chapters.

Dedication

This report is dedicated to the memory of the Working Group's esteemed colleague and friend, Dr. Christian Benichou, who sat on all CIOMS drug safety Working Groups from their inception as a representative from pharmaceutical companies. His experience, intelligence and commitment were indispensable to their success. His important contributions to the field of pharmacovigilance are extensive and have left an indelible mark, not only through his work with CIOMS and the ICH process, but from his many publications and participation in international meetings and educational programs. We hope that the results of CIOMS V meet the high ethical and professional standards he set for himself. He will be sorely missed by all who knew him.

Table of Contents

Vision

Over more than a dozen years of fruitful collaboration, the CIOMS Working Groups on drug safety have evolved an exciting dynamic vision: to enhance systems that advance the public health, world-wide, through better assurance of the safety of medicinal products. From the beginning, the Groups have been dedicated to focussing on the processes for detection and management of potential problems with drugs as quickly and efficiently as possible, especially in the post-approval environment. The CIOMS V Working Group, as its predecessors, was committed to finding areas for simplification, clarification, and harmonization of practices on topics that are inadequately or never addressed by regulations or guidelines.

Our vision once again is that a single set of recommended ''best practices'' will lead to enhanced public health protections in the area of drug safety by ensuring proper focus on substantive scientific and medical inquiry and by eliminating unnecessary administrative requirements.

Working Group V hopes that its proposals on pragmatic approaches to some difficult dilemmas facing regulatory authorities and companies in carrying out their daily responsibilities will be endorsed and applied by all stakeholders. Specifically, we hope that the suggestions made in the following key areas will be widely implemented:

- classification and handling of individual safety case reports from a variety of traditional as well as new sources
- some new approaches to case management and regulatory reporting practices
- improvements and efficiencies in periodic safety reporting
- determination and proper use of population exposure data
- a critical overview of worldwide regulations for safety reporting.

Even in the face of this extensive work — which to a certain extent was aimed at completing unfinished business from prior CIOMS Working Groups' efforts — a fundamental aspect of our overall vision is that the work of drug safety surveillance and public health protection is never completed. Innovations and improvements will always be needed as experience grows. Thus, we envision a world in which all who are engaged in pharmacovigilance will constantly work toward continuous learning, self-improvement, and sharing. Each of the members of the CIOMS V Working Group pledges to continue in this spirit.

Preface

Since 1986, when the first of a series of CIOMS Working Groups dedicated to important drug safety issues was established, they have been recognized for creating the theoretical platforms and pragmatic suggestions to advance the debates leading to harmonization of international pharmacovigilance practices. The initiatives over the years, identified as CIOMS Working Groups I, IA, II, III and IV, have resulted in four major published reports.[1] The nature of their membership, senior drug safety officials from many major regulatory agencies and the regulated pharmaceutical industry, and their modus operandi as a "think tank" seeking practical solutions to important problems, have facilitated their unique contributions. All members have served less as representatives of any single organization or interest and more as motivated colleagues, with day-to-day responsibility in the drug safety field. All shared a commitment to think beyond their local practices even if such thinking were in disagreement with current rules and regulations, in order to optimize drug safety procedures, particularly in an international context. Although the Working Groups did not — indeed could not — develop regulations, its work has always been intended to inform and encourage those with rule-making responsibilities.

Gratifyingly, many of their recommendations have been incorporated into regulations, not only in the countries of the participating regulators, but elsewhere as well.

The CIOMS I Working Group (1986-1990) introduced definitions, criteria and a standard form (the CIOMS I Form) for international reporting of medically important ("serious") adverse drug reactions (ADRs). It also served as a model for the development of the International Conference on Harmonization (ICH) Guideline E2A on expedited ADR case reporting for clinical trials.

The result of the CIOMS II deliberations was a set of proposed standards for the format, content and frequency of periodic safety update

[1] *International Reporting of Adverse Drug Reactions* (CIOMS I) (1990); *International Reporting of Periodic Drug-Safety Update Summaries* (CIOMS II)(1992); *Guidelines for Preparing Core Clinical-Safety Information on Drugs,* First Edition (1995) (CIOMS III) and Second Edition, *Including New Proposals for Investigator's Brochures* (1999)(CIOMS III/V); *Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals* (CIOMS IV)(1998). All published by the Council for International Organizations of Medical Sciences, Geneva.

reports (PSURs) which has been adopted by many regulatory authorities. It also formed the basis for the ICH Guideline on periodic reporting (E2C) adopted in 1996 which, since then, has been undergoing implementation internationally.

In recognition of the need for more efficient, automated techniques to document and report ADRs to regulators, beyond the paper-based techniques of CIOMS I, a subgroup of the CIOMS II group invoked the powers of modern computing. Issued as a CIOMS IA report (unpublished), it outlined a vision of a seamless, paper free system in which privacy was protected and proprietary data respected, but core information could be shared system-wide globally through computer networking. The vision was that the primary recipient of a report, whether a regulator or industry would follow up a case, as needed, and enter it directly into a universally shared database. The Group developed a comprehensive set of data fields and outlined their electronic specifications which are widely credited as aiding the development of the ICH Guideline E2b (Data Elements for Transmission of Individual Case Safety Reports, 1997).

The CIOMS III Working Group concentrated on best practices for applying the findings of the information underlying CIOMS I and II safety reporting standards to meaningful safety information (''labeling''). The concept of ''company core safety information'' (CCSI) introduced in CIOMS II was elaborated and better defined in CIOMS III with a set of what have conveniently been referred to as ''good safety information/labeling practices'' for post-approval drug safety data. This CIOMS effort has influenced the shape of new regulatory guidelines on product safety information (e.g., the Summary of Product Characteristics (SPC) in the EU). The CCSI is, in fact, an integral part of the ICH E2C Guideline. The concepts were extended to the pre-approval environment in a second edition of the CIOMS III report by the CIOMS V Group, by recommending use of Development Core Safety Information (DCSI) within Investigator's Brochures.

One of the most important aspects of marketed-drug safety monitoring is the identification and analysis of new, medically important findings (''signals'') that might influence the use of a medicine. In recognizing that there existed no guidance on a systematic approach for handling the emergence of a major safety signal, especially one that might lead to important regulatory action, CIOMS IV developed its proposals for approaches to comparative benefit-risk weighing, analysis of options for action, and good decisionmaking practices.

As acknowledged in the reports by each of the Working Groups, unresolved and unaddressed issues remained. Although each successive working group attempted to address those remaining from prior work, it was clear at the close of the CIOMS IV effort that in spite of updated and refined regulations, including those influenced by ICH initiatives, many important areas were still inadequately addressed, if at all. To confirm the Group's judgment, an informal survey of industry safety experts generated a list of the same or similar topics for which consensus and guidance were requested. Thus was born the CIOMS V Working Group which has focussed on several difficult aspects of day-to-day pharmacovigilance work that affect the management and interpretation of safety data. The proposals and their rationale are the subject of this report.

Another area deemed of high priority but outside the scope of this report, namely risk communication, was also identified and selected for parallel effort by an independent sub-group. Although a separate initiative, known as the Erice project,[2] its progress has been regularly reviewed and input provided by the CIOMS V Working Group.

Throughout the 14 years of their existence, the Working Groups have enjoyed the inspiration and support from the convening organization, CIOMS, and particularly from its Secretary-General, Dr. Zbigniew Bankowski. With great affection, upon celebration of his twenty-five years of achievements and of his retirement at the close of 1999, we pay tribute to him through the present work. The special "Zbigniew Bankowski Fund" to support lectures on ethical aspects of health policy, established in his honor by CIOMS, will serve as a lasting memory of his contributions.

Finally, we wish to express our deep sense of loss and great respect for our colleague, Dr. Christian Benichou, an invaluable member of all the CIOMS Working Groups from their inception, who died from sudden illness several months prior to our last meeting.

[2] See Appendix 1 for the "Erice Declaration on Communicating Drug Safety Information" of September 1997. For more detail, see *Effective Communications in Pharmacovigilance. The Erice Report* (1998). Uppsala Monitoring Center, Sweden. For availability of the report, see <www.who-umc.org> or request it via e-mail at <who.drugs@who.pharmasoft.se>.

I

Introduction

a. Background

Much progress has been made over the past several years in reducing unnecessary diversity in regulations and guidances among health authorities in the field of pharmacovigilance. Beginning in the late 1980's, achievements by CIOMS through its drug safety Working Groups I through IV,[1-4] by the International Conference on Harmonization (ICH),[5] and by individual drug regulatory authorities have created a solid foundation for more international consistency in rules, terminology and technology for the monitoring, reporting, analysis and use of safety information.

However, based on experience of the CIOMS V Working Group members and on the results of an informal survey of their colleagues, several topics were identified that are not — perhaps cannot be — covered by formal regulations, yet are the subject of considerable uncertainty, ambiguity and debate.

As will become clear, these topics represent many obvious as well as subtle issues that affect different aspects of drug safety work. They influence how companies and regulators design their data base systems and their Standard Operating Procedures and they generally present difficulties in day to day working practices. They also affect interpretation of regulatory guidelines and reporting obligations as well as decisions on creation and maintenance of "labeling" (e. g., local data sheets or Company Core Safety Information — CCSI). With the added consideration of new technologies applied to drug safety (such as MedDRA, ICH electronic standards for data transmission, and use of the Internet), these unaddressed aspects of pharmacovigilance practices pose increasingly difficult challenges.

---

1 *International Reporting of Adverse Drug Reactions*. Final Report of CIOMS Working Group (1990). Council for International Organizations of Medical Sciences, Geneva.

2 *International Reporting of Periodic Drug-Safety Update Summaries:* Final Report of CIOMS Working Group II (1992). Council for International Organizations of Medical Sciences, Geneva.

3 *Guidelines for Preparing Core Clinical-Safety Information on Drugs. Second Edition, Including New Proposals for Investigator's Brochures.* Report of CIOMS Working Groups III and V (1999). Council for International Organizations of Medical Sciences, Geneva.

4 *Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals*. Report of CIOMS Working Group IV (1998). Council for International Organizations of Medical Sciences, Geneva.

5 The final guidelines on expedited ADR reporting during clinical trials (ICH E2A), data elements for individual ADR cases (E2B), periodic reporting for marketed drugs (E2C), Good Clinical Practices (ICH E6), medical terminology (MedDRA, ICH M1), and electronic standards for transmission of regulatory information (ICH M2) can be found at: <www.ifpma.org/ich1.html> The documents can also be obtained from the ICH Secretariat: IFPMA, 30 rue de St.-Jean, Box 9, 1211 Geneva 18, Switzerland (tel. 41 (22) 340 1200).

The CIOMS V Working Group through this report is advocating acceptance of proposals on a wide range of issues covering terminology and definitions, common every day practices such as follow-up of individual adverse event cases, the rational scheduling and content of periodic safety update reports (PSURs), the role of the Internet, and quantification of population drug use. Many of the topics represent areas described as ''unfinished business'' or ''unresolved issues'' in CIOMS I, II, III, and IV reports but similarly address inadequately defined aspects of Good Clinical Practice and other regulatory guidelines covering pharmacovigilance.

A few topics involved some very complex and controversial issues on which consensus could not be reached with regard to recommending solutions. These and items which were not or could not be addressed might form the basis of future work.

The list of members of CIOMS Working Group V and a description of its activities are found in Appendix 2.

b. Privacy and the Protection of Personal Health Data

A recurring theme within the Working Group's discussions which has achieved considerable prominence and importance, even beyond pharmacovigilance, is the privacy and confidentiality of personal data. Legislation or rules recently enacted or in progress in the EU, US, and elsewhere[6] have introduced new data subject rights and the need for strong safeguards in the collection, processing and transfer (especially across country borders) of personally identifiable data handled via any media, electronic or physical (paper, film, etc.). This has particular relevance to health information, among the more sensitive types of data, and certainly applies to adverse event reports, which often include data that directly identify the subject and/or the reporter with name, address, national health number, or other overt identifiers. Within some legal systems, *indirect* information that might allow

[6] European Parliament and the Council of the European Union ''Directive on the Protection of Individuals with Regard to the Processing of Personal Data and on the Free Movement of Such Data,'' (Directive 95/46/EC), Official Journal of the European Communities, No. L 281, 31-50 (November 23, 1995). Also available on the Internet at: http://europa.eu.int/eur-lex/en/lif/dat/1995/en_395L0046.html The Directive has been or will be transposed into local law within the Member States of the European Economic Area. In the US, the Department of Health and Human Services (DHHS) released its final rule on Standards for Privacy of Individually Identifiable Health Information on 20 December 2000; see http://www.hhs.gov/ocr/hipaa.html

determination of an individual's identity must also be protected (i.e., reference to one or more factors specific to a person's physical, physiological, mental, economic, cultural, or other characteristics that could facilitate determination of his/her identity).

Although current practices throughout the pharmaceutical industry and by regulatory authorities reflect a commitment to protection of personal data, new laws in many countries necessitate some changes in personal-data handling practices. Increased rights for data subjects include notification on who is processing their data, for what purpose, and with whom the data may be shared, as well as the ability to access their own data and make corrections. Under appropriate circumstances, this may require enhancement of the ordinary informed consent process for activities such as clinical trials. The use of secondary databases, so important to pharmacoepidemiology and retrospective studies in general, may also be affected.

There is no intention to cover this complicated topic here in more detail and those working in pharmacovigilance, and clinical research generally, should familiarize themselves with applicable data protection laws and regulations. However, it is important to explain that the term "identifiability" does not have the same meaning under one of the CIOMS V topics, "Assessing Patient and Reporter Identifiability" (see Chapter III.b.), as it does within the context of data protection legal regimes. For adverse event reporting, an identifiable patient or reporter relates to the existence of a real person that can be verified/validated in some way. Under data protection schemes, the term refers to an ability to associate a data set with a particular person ("trace" a person from the data available).

c. Overview

As a guide to the contents of this report, the following brief description of each of the topics and the rationale for their inclusion will aid the reader. Unless indicated otherwise in the specific topic Chapters, the proposed concepts and proposals apply to pre-marketing and marketing conditions for both prescription and non-prescription products, whether they be drugs, biologics or vaccines. Although we are accustomed to dealing with prescription and non-prescription drugs in pharmacovigilance — and that is the underlying theme in this CIOMS report — it is well worth reminding ourselves to remain alert to the fact that herbal and other non-traditional treatments can cause allergic and toxic reactions, have the potential to be carcinogenic, mutagenic,or teratogenic, and can interact with concomitantly

taken medicines.[7] The principles and recommendations presented here should apply to those products as well.

All the principles and practices proposed throughout this report are summarized in Chapter VII (Summary of Proposals), which the reader may wish to consult for a convenient overview of the "take-away messages."

Sources of Individual Case Reports

(1) ***Spontaneous Reports:*** Traditionally, reports on marketed product experiences are referred to as spontaneous reports, also commonly called voluntary, unsolicited or anecdotal reports. They are handled differently from reports arising from clinical trials with regard to expedited and periodic reporting procedures. For example, by international convention, spontaneous reports are always considered to have an implied causal relationship to the subject drug(s).

There are several influences complicating the classification and handling of spontaneous reports, for which some consensus and guidance would be helpful. For example, it is believed that the regulatory authorities of only two countries (US and Canada) require the collection and reporting of direct reports from consumers, but there is considerable debate internationally about the role of such cases in pharmacovigilance. Some argue that valid reports require "medical confirmation" while others regard patient-direct reports as potentially valuable. Proposed definitions and practices for these circumstances are given.

(2) ***Literature.*** As part of good pharmacovigilance practices and regulatory reporting requirements, companies monitor various types of literature for relevant safety information on their products. However, there are many questions related to this responsibility:

- Other than the obvious sources, namely published prominent medical and scientific literature, what else should be reviewed among the thousands of journals and other published materials in many languages? Should other media be regarded as "literature" (radio, TV, the Internet)?

[7] For example, see Ernst, E and de Smet, PAGM. Risks Associated with Complementary Therapies, in Dukes, MNG, ed., *Meyler's Side Effects of Drugs,* 13th edition, Elsevier, Amsterdam, 1996. Also, see Willis, J. Drug interactions — when natural meets ethical. *SCRIP Magazine,* Issue 91, pp. 25-27, June 2000.

- What information from the literature is reportable under regulations? Who should be responsible for reporting the relevant information when there are multi-source, including generic, manufacturers?
- What is the timeline for regulatory reporting of published reports?
- What follow-up should be conducted on published safety information? Whose responsibility is it?
- Is it necessary to translate articles in a "foreign" language, in part or *in toto,* and under what circumstances? With what reporting timeline?
- What are the roles and obligations of authors and journal editors?

Recommendations for dealing with all these questions are given.

(3) ***The Internet.*** The rapid and widespread growth of the electronic communication technology commonly referred to as the Internet and e-mail presents some difficult challenges in the context of drug safety monitoring and reporting. The technology might be regarded as just another medium for facile information exchange, albeit one with unprecedented global reach and speed. However, there are many new considerations for pharmacovigilance that need debate and resolution. In addition to the confidentiality and security of the data, the validity and integrity of the information, and ascertainment of the source of the information — common concerns for any application of the technology — several special issues arise: are companies responsible for "surfing" the Web for safety information on its products? Should ADR reporting to companies and regulators via the Internet be encouraged? What use, if any, of a company's or regulator's "home page" should be made for ADR reporting? Is there an appropriate role for the Internet in disseminating product "labels," especially safety information, recognizing the usually unavoidable differences between countries' product information?

These and other questions are discussed along with specific recommendations for handling drug safety information with this now well-established new tool.

(4) ***Solicited Reports.*** The recent widespread use of special post-marketing programs, such as drug compliance support or surveys, in which patients may be contacted routinely, has blurred the line between true spontaneous reports and what have become known as "solicited"

reports from patients (''How do you feel?'' ''Well, I had a headache yesterday.''). Should they be treated differently from traditional spontaneous reports?

(5) ***Clinical Trial Reports.*** The handling of suspected ADRs from clinical studies and similar sources would appear to be fairly straightforward. However, there are many circumstances and applications for which there is a lack of regulatory guidance, which has led to considerable differences in practices among both companies and regulators. Should there be a common, global standard for how and when to inform investigators in clinical trials of expedited/alert ADR reports? How should apparent safety-related data from quality-of-life questionnaires included in studies be handled?

(6) ***Epidemiology and Observational Studies.*** What are the reporting obligations with respect to either isolated case findings or a suspected signal when conducting observational studies or in general when working with data bases (e.g., learning how to use them vs a protocol-driven project)?

(7) ***Disease Registries and Regulatory Databases.*** What and how should companies report on pertinent cases from disease-specific and other ''registries'' (e.g., pregnancy registries)? From regulatory ADR databases? Under what timeline?

(8) ***Licensor-Licensee Interactions.*** How should exchanges of ADR information between licensors and licensees be handled, especially with regard to regulatory-reporting timelines?

Good Case Management Practices

(1) ***Introduction: Clinical Evaluation of Cases.*** Especially for cases involving serious or unexpected (unlabeled/unlisted) suspected ADRs, there is a need for guidance on a systematic, thorough clinical evaluation of reports to ensure that the case has been correctly interpreted given the reported signs, symptoms and any diagnostic procedures. All action on the case depends on such an evaluation. A common complication with spontaneous reports arises when there is ancillary information associated with a case report that on review suggests an adverse event other than the intended subject of the reporter's communication. The proper interpretation and handling of such ''incidental'' events (as they have come to be known), especially with respect to regulatory reporting, pose a challenge.

(2) ***Assessing Patient and Reporter Identifiability.*** Under the ICH guideline on expedited reporting (ICH E2A) and within many country regulations or guidelines, the minimum information required to consider a case as a bona fide report is an ''identifiable patient,'' an ''identifiable reporter,'' a drug (or other suspect causative agent), and an event or outcome. Unfortunately, there are no internationally accepted definitions on what is meant by an ''identifiable'' patient or what constitutes a ''reporter.'' Does a report on ''several patients'' who are otherwise not characterized satisfy the criterion? Does a newspaper account of a medical event represent a ''reporter?'' These and many other examples frequently faced by companies and regulators are addressed and practical recommendations are made for their handling.

(3) ***Seriousness.*** Although some differences still exist between countries, the regulatory definition of a serious adverse event or reaction has been harmonized through ICH for events during clinical trials; regulators, such as the US FDA, are also adopting the same definition for spontaneous and other post-marketing events. However, some of the criteria that define a serious suspected ADR, including ''medical judgment'' for cases that do not readily fall under the usual criteria (e.g., hospitalization, death, etc.), are subject to broad interpretation, often due to differences in regional or cultural practices. Insights are provided on dealing with the diversity of situations in which case reports might be regarded as medically serious within an administrative definition. Included is a proposal for the possible use of a standard list of reaction terms/diagnoses that would always be considered ''serious,'' even in the absence of an outcome or substantiating medical details.

(4) ***Expectedness.*** In addition to classifying a case as serious or non-serious, designation of a term or diagnosis as ''expected'' or ''unexpected'' with regard to the appropriate reference safety information (RSI) determines the nature and timing of regulatory reporting and possibly other action. The RSI can be one or more documents commonly referred to as the Development Core Safety Information (DCSI) in an Investigator's Brochure, the Company Core Safety Information (CCSI) in a marketed product Company Core Data Sheet (CCDS), or the official local data sheet (e.g., US Package Insert or EU SPC). There are many complicated issues surrounding a decision on whether a new reaction represents added specificity to the description, nature, severity, mechanism, and usual outcome of a previously recorded term or diagnosis, and therefore

might require a change in, or addition to, the RSI. Insights and recommendations on these issues are provided.

(5) ***Case Follow-up Approaches.*** Spontaneous adverse reaction reports invariably lack complete information; companies have different philosophies and practices for attempting to obtain follow-up information. In order to optimize the use of resources, the nature and extent of follow-up will ordinarily depend on the medical significance of the case (e.g., serious vs non-serious), its origin (e.g., literature, physician, consumer), and other factors (e.g., "expectedness"). The proposals by the Working Group for a systematic approach to follow-up include an algorithm (that could be computer-driven) to decide on which cases and what types of information should be considered. Also discussed are the circumstances under which follow-up information, once obtained, should then be submitted to regulatory authorities for expedited and/or periodic reports.

(6) ***The Role of Narratives.*** In an era when there is a movement toward non-paper reporting of individual ADR cases which focuses on the use of established standards for data elements (ICH E2B) and electronic transmission (ICH M2), the role of a well written case narrative (the medical "story") for certain cases is still regarded as important. Appropriate uses for a narrative as well as a proposal for a standardized format and content are given; hints are provided on the use of computer-driven draft narratives. Among the ideas presented is inclusion of a specific section for the company's (or other reviewer's) comments on the case and its interpretation, including recommendations on what might be regarded as acceptable and unacceptable comments.

Good Summary-Reporting Practices: PSURs Reconsidered

The format and content of periodic safety reports on marketed products have been harmonized under ICH and many regulators have implemented or are in the process of implementing the guideline (ICH E2C). One of the key provisions is that companies conduct six-monthly safety database reviews on their products, whether or not a formal report is prepared or required. However, experience has shown that there is an important need for consensus on other aspects of periodic reporting. The required interval between submissions of PSURs usually is dependent on the time-on-market relative to a product's approval or launch date but is not the same under different country regulations. Individual countries within Europe and elsewhere may have different schedules for the same product.

Also, there are difficulties with the required content of five-year PSURs and those that cover large numbers of case reports (products with continuous high volume ADR reporting).

In addition to PSURs, there is a special requirement in the EU for five yearly and in Japan usually for six-year recertification/relicensing/reexamination reports which have their own target dates and have traditionally been handled independently from periodic safety reporting, even though the bulk of such reports deals with safety information.

The Working Group conducted a survey of companies and regulators on their workload and practices for handling the various types of periodic reports and the difficulties they can present. The results are presented and discussed.

In attempting to rationalize the various periodic safety reporting requirements so as to eliminate unnecessary preparation work (by companies) and review (by regulators), and to facilitate the practical use of PSURs, the CIOMS Working Group has generated proposals on PSUR content modification and for dealing with frequency and timing of reporting through use of the following approaches:

- ***High Case Report Volume/Long-Term Reports.*** Recommendations are made on format and content for long-term and high-ADR-volume PSURs. Mechanisms for dealing with the different due-dates for license renewal on the same drug in different EU countries, including for different formulations (which may have their own due-dates), are also discussed, with proposed approaches for unifying the two different five-year reporting requirements.

- ***Simplification of PSURs.*** For drugs associated with little or no new information during the intervals between PSURs, criteria are suggested as the basis for a highly simplified report.

- ***Summary Bridging Reports*** represent a method for tying together two or more previously prepared PSURs (e.g., six-month reports) for submission to regulators that do not require or desire receipt of reports on as frequent a schedule as other regulators. This eliminates the need to prepare yet another, separate PSUR covering the longer period.

- ***Addendum Reports*** cover supplemental data when a regulatory authority requires a safety update outside the usual schedule cycle and more than a brief time-gap (e.g., up to 6 months) has elapsed since the last scheduled PSUR.

Recommendations are made on a variety of other issues for managing PSUR preparation, including considerations involving "old" products, the need to restart the reporting schedule clock to six monthly for new dosage forms or new uses, and recommendations on several other details.

Determination and Use of Population Exposure Data

Estimates of numbers of patients who have taken a particular medicine are needed for routine periodic reporting and for special situations involving, for example, a new, important safety signal. Such estimates help to put into perspective the relative risk (and benefit) a product represents in the treated population. It is usually difficult to obtain accurate and timely exposure data, and their determination is more of an art than a science. However, there are considerably more sources and techniques for obtaining and appropriately using such data than is commonly realized. Even for clinical trials and cohort studies, where the denominators (exposure) are accurately known, there are mistakes made in their use and interpretation. A guide to data sources and analytical approaches for exposure information is given.

Clinical Safety Reporting Regulations: an Overview

Regulatory reporting requirements around the world for individual case and periodic reports have been under continuous change and it was deemed important to review them if only to determine how far we have moved toward global consistency. The Working Group has summarized its interpretation of the regulations as of 2000 in order to examine whether there has been significant progress in harmonization as a result of prior CIOMS proposals and ICH initiatives. The results demonstrate the complexity and ambiguities that still prevail. Recommendations are made for moving forward.

II

Sources of Individual Case Reports

a. Introduction

During the development and use of medicines, any communication involving a drug experience, positive or negative, can in principle form the basis of a case report on an individual patient. The exchange of information can originate with a patient, a healthcare provider or other party and it may be initially directed to a manufacturer, a health authority, or both. The CIOMS Working Group endorses use of the widely accepted term-usage (ICH, various regulations) associated with unfavorable medical effects.[1]

The source of a report can be an important factor for the evaluator; awareness of the "environmental" factors contributes to an understanding of the quality and value of the information for assessing a case. The nature, amount and even feasibility of any needed follow-up will also be highly dependent on the source.

The traditional sources of adverse experience information are clinical trials and spontaneous reports (voluntary, unsolicited communications on marketed products), with the latter ordinarily far exceeding the former in numbers and types of reports, especially serious reports, over the lifetime of a product. In addition, in some countries, adverse reaction reporting by physicians is mandatory; such reports are usually also regarded as "spontaneous." The principles and practices governing individual case reporting by healthcare professionals are generally well established and understood and are not discussed in detail here. However, there are many other media, places, and opportunities for accessing potentially useful drug safety intelligence, i.e., other "sources" and types of reports for which the procedures and obligations with respect to collection and regulatory reporting are not well established. The primary purpose of this chapter is to provide recommendations on common problems associated with the processing of adverse experience cases from these other sources, some of which represent new concepts.

Two properties or aspects of individual AE/ADR cases tend to control their handling: (1) their source — whether they are from a clinical trial setting,

[1] In brief, an adverse event or experience (AE) is any untoward/undesirable occurrence in a patient (or trial subject) administered a pharmaceutical product, an event which is not necessarily causally related to the medicine. An adverse drug reaction (ADR), or for short adverse reaction, is an adverse event for which there *is* a known or suspected causal relationship to the drug. By international convention, a spontaneous report is regarded as having implied causality. However, because it is rare that a causal relationship can be proven definitively for individual cases, they are commonly referred to as "suspected ADRs," even for clinical trial cases. As elaborated elsewhere within this report, criteria for regulatory reporting depend on whether a case is regarded as an AE or an ADR.

truly spontaneous, or the subject of solicited reporting[2] and (2) whether a causality assessment is required for drug-attribution. With rare exception, there is international consensus that spontaneous reports have implied causality (thus, they are suspected ADRs), whereas for prospective clinical studies a causality assessment by the investigator and/or the sponsor should determine whether the case represents an adverse drug reaction. It is not as clear for other case sources on whether the respective cases should be considered solicited (vs. spontaneous) and whether a causality assessment should be conducted. Examples include patient support programs,[3] patient surveys, Prescription Event Monitoring studies,[4] intensified monitoring (e.g., AB studies in Germany),[5] observational (epidemiologic) studies, disease or drug registry cases, and others. Details are discussed later in this chapter.

Many people regard literature cases as a form of spontaneous reporting (see Chapter II.c.); depending on the nature of the case, the original adverse experience reported may have occurred during a trial or been the result of a solicited response, however.

Some refer to the Internet as a "source" of adverse experience information, but it should be considered as yet another mechanism for conveying information (e.g., e-mail as a replacement for postal service). However, there are special issues with respect to its use as a medium for retrieving and handling adverse experience information; thus, a separate Chapter (II.d.) is dedicated to the topic.

It would be impossible to cover all the various sources and circumstances involved in safety monitoring and reporting. For example, how would one classify an isolated case that is sent to a manufacturer by a clinician conducting an independent Phase 4 study on one of the company's marketed drugs? Should it be treated as a spontaneous or study report? We believe that most companies would regard it as a study report, but with a presumption of attributability to the drug. What about a case received in connection with a lawsuit? Most would regard such a case as a spontaneous report. There are many such special examples, for which there may not be

---

[2] Unlike truly voluntary (unsolicited or spontaneous) reporting, solicited reporting refers to situations in which a patient is prompted by questioning or other intervention regarding the toleration of a medicine; in that sense, clinical investigators routinely "solicit" such information from trial subjects. However, there are many other circumstances, especially in postmarketing patient support programs, when prompting elicits adverse experience reports from patients. See Chapter II.e. for detailed discussion on this issue.

[3] For example, periodic communication with patients to check on medicine compliance.

[4] A retrospective examination of drug experiences conducted in the UK by the Drug Safety Research Unit in Southampton (www.dsru.org).

[5] AB (Anwendungsbeobachtung) studies are phase 4-type trials that capture experience under ordinary medical practice using a simplified case record form.

one right answer. The purpose of this Chapter is to address the most common types of circumstances.

Finally, it must be emphasized that single-case ADR monitoring and reporting should always be viewed as part of "epidemiologic intelligence." One can almost never be certain about a causal relationship between a drug exposure and an adverse event on the basis of an individual case; it is only through ongoing analysis of the collection of reported events that a potential "signal" is generated and better understood.

b. Spontaneous Reports from Persons Other than Healthcare Professionals

Introduction

Protecting the health of the patient/consumer is the purpose of any safety surveillance system. Yet the optimal way to include the consumer in the activities of this system has never been properly addressed. Therefore, the CIOMS V Working Group has considered best practices for involvement of the consumer, and particularly to consider how best to respond when a report is received by a pharmaceutical company or regulatory body directly from the consumer or someone other than a healthcare professional.

As a general guiding principle, the Working Group holds that emphasis should be placed on the quality of a report, and not on the nature of its source. Thus, the value of a report lies not in who made it, but in the care and thoroughness with which it is prepared, documented, received, recorded, followed-up, clarified, and analyzed in evaluation of possible drug-associated problems.

Internationally, adverse drug reaction reporting systems in the post-marketing environment depend primarily on voluntary reporting from healthcare professionals, especially physicians and dentists, and preferably the one directly associated with the care of the patient (i.e., the patient's primary healthcare provider or a specialist). This is appropriate, since the understanding of ADRs depends on medical knowledge and such professionals should be attuned to the subtleties of clinical differential diagnosis. Although there is no widely accepted definition of "healthcare professional," others in addition to physicians and dentists commonly included, by convention or under regulatory guidance, are pharmacists, nurses, coroners, *et al.* Reports may also be received, primarily by

companies, directly from consumers, their representatives (e.g., relatives, lawyers), and other non-healthcare parties. Reports received from people other than healthcare professionals are not routinely accepted by some regulatory authorities (e.g., in the EU) without confirmation by a healthcare professional or by the submission of medical documentation and explanatory details from a healthcare professional.

There are reasons other than an adverse effect that might prompt a patient to contact a company. These include requests for reimbursement of drug expenses, legal concerns and, most frequently, requests for further information about the product. Such communication may or may not result in a spontaneous report by the patient. A special case exists when reports are published by lay authors, e.g., in the public media or on the Internet (see Chapter II.d.). Another source of consumer reports derives from a variety of industry programs in which adverse reaction information may be solicited, but such cases are not characterized as spontaneous reports (see Chapter II.e.).

There is no international harmonization of regulations covering consumer reports. There are apparently only two regulatory authorities that explicitly require collection and reporting of consumer-direct reports. The US FDA requires companies to forward any consumer reports it receives (nearly all of which, in practice, originate within the US). Canada, on the other hand, requires submission of reports originating only within Canada. In both countries, serious unexpected ADR reports must be expedited, and information on all relevant cases is submitted with any required periodic reporting.

Little is known about the extent and nature of consumer reporting and its management. No systematic surveys or reviews of actual experiences within existing national healthcare systems could be found by the Working Group. A few careful studies have been published. Fisher *et al.*[6] in the USA (1990) found that patient causality attribution was contributory to ADR recognition. DeWitt and Sorofman[7] in a US study also examined a patient's recognition of whether a symptom is drug- or disease-related and found that their sample of 338 adult outpatients had reasonably accurate knowledge of ADR symptoms attributable to an adverse effect. Mitchell *et al.*[8] in

[6] Fisher, S. and Bryant, S. G. Postmarketing surveillance: accuracy of patient drug attribution judgements. *Clinical Pharmacology and Therapeutics,* 48: 102-107, 1990.

[7] DeWitt, J. E. and Sorofman, B. A. A Model for Understanding Patient Attribution of Adverse Drug Reaction Symptoms. *Drug Information Journal,* 33:907-920, 1999.

[8] Mitchell, A. S., Henry, D. A., Hennrikus, D. and O'Connell, D. L. Adverse Drug Reactions: Can Consumers Provide Early Warning? *Pharmacoepidemiology and Drug Safety,* 3: 257-264, 1994.

Australia (1996) were able to demonstrate that consumers who were surveyed were more likely than physicians under comparable circumstances, to report relatively mild symptoms of concern to them. The findings also suggested that early warnings of potentially more serious problems might emerge from a well-directed patient-based surveillance system. These findings have been confirmed and extended by others. However, all authors have pointed to the problems with lack of patient sophistication and the need for medical confirmation, particularly in complex cases. Thus, the authors recommended caution as to the relevance of their findings to national reporting systems.

Although there is a clear need for physicians' cooperation in ADR reporting, in general they do not usually respond well to requests for further data, especially on non-serious cases, which they consider 'trivial.' Thus, when consumers are prompted by regulators or sponsors to see their physicians, with the suggestion that they urge the doctor to send in adverse reaction reports, the doctor may not follow through. As potential epidemiologic intelligence, therefore, consumer reports deserve and should receive appropriate respect and attention. Education of physicians and other healthcare professionals is needed on this matter, particularly on the need to assess and report ADRs when the concern is initiated by the consumer/patient.

For the monitoring of non-prescription over-the-counter (OTC) products, often taken without physician involvement or advice, reports received directly from consumers may provide the only source of signals. However, it is the very nature of many newer OTC products that they are converted from prescription products only after significant amounts of safety data and marketing experience have been realized. Thus, they are, in general, expected to be relatively free of significant adverse reactions. Consumer associations in many nations have included adverse drug effects monitoring among their functions. This phenomenon has been increasing and has become more visible through extensive use of the Internet for global communication. No standard approach to such programs or reports from such associations exist. There is clearly a role for consumer reporting in the OTC setting. The community pharmacist could also play a particularly useful role in monitoring the safety of OTC products, although many such products are sold outside pharmacies as well.

The primary focus on consumers has historically been to educate the public about the problems of drug safety and encourage reporting of possible ADRs through their medical providers. The Working Group agrees that further, substantial and organized efforts should be made by all of those

responsible for improving systems of ADR reporting and monitoring to improve understanding of drug safety issues by consumers.

Pharmaceutical companies generally have policies and practices for the receipt and management of ADR reports directly from consumers. This is driven at least in part by the North American requirements for reporting such cases. In general the practice is always to acknowledge such reports, record them in a data base with a 'flag' to recognize them as consumer-direct reports, and analyze the data along with all other ADR data for signals. Follow-up practices vary; in general consumers are requested to ask their physician to make a report if appropriate, and permission is usually sought from the consumer to allow the company to obtain confirmation directly from a treating physician, particularly if the report reflects an event that may be serious[9] or unusual/unexpected.

In developing its recommendations, the CIOMS Working Group addressed four underlying challenges regarding consumer reports:

(1) How can one recognize a report from a consumer as medically important or 'serious' in the usual regulatory sense? Consumers do not use medical terminology or standard taxonomy for diseases and their complications; standard medical thesaurus sources are not equipped to handle such terms as 'scared me to death' or 'in a fog for three days' or 'pizza head,' which are examples derived from an informal survey. Such cases require in-house medical review and judgment, including the use of substitute terminology and description to characterize the case.

(2) How should one handle reports from consumers that are not strictly 'spontaneous'? A new category of reports, namely solicited reports, has been introduced to place them in proper perspective. Details are discussed in Chapter II.e.

(3) What does 'medically confirmed' for such cases mean (a term used in some regulations) and how does one obtain medical confirmation? A consumer case is generally considered 'medically confirmed' when a medically qualified person treating that patient provides confirmation on at least the usual minimal criteria for a case. Discussed elsewhere (Chapters III.a. and III.e.) are general principles of clinical evaluation and case follow-up. However, in the case of a consumer report, a

[9] In the EU, when information is received directly from a patient or a relative suggesting that a serious adverse reaction may have occurred, the marketing authorization holder is requested to attempt to obtain relevant information from a healthcare professional involved in the patient's care (Notice to Marketing Authorization Holders, Pharmacovigilance Guidelines, 2000).

'confirmation' by a healthcare professional requires not just verification (or further explication) of the patient, the exposure, the reported medical event(s), and the drug, but also the healthcare professional's opinion that the event(s) may have been causally linked to drug exposure. Thus, if the patient does not give the company permission to contact a professional, or there is no response from the professional to requests for information even when permission is granted, the case is unverified. On the other hand, if the professional is contacted and replies, he/she may not agree with the basic facts or their interpretation as presented to the company by the patient. For both situations, the case is not medically confirmed. Thus, even if the physician agrees with the facts as presented by the patient, this alone is not sufficient for medical confirmation of an ADR, since the professional may conclude that the attribution made or implied by the consumer reflects lack of understanding of the circumstances and is inappropriate.

(4) Who is best qualified to provide 'medical confirmation'? Often more than one person is involved in a patient's care. The preferred source of ADR confirmation is the primary healthcare provider. Often, however, the office nurse, hospital pharmacist, or another healthcare professional authorized to prescribe or dispense such as a nurse practitioner, will be the logical source of medical confirmation. Other expert consultation may also be advisable or required (e.g., a pathologist). If patients prefer to obtain medical or hospital records themselves and convey them to the company (or regulator), that should also be acceptable for verifying the facts of the case, but may not be adequate to determine if an ADR is ''confirmed'' unless the records also indicate a suspected causal attribution.

Conversely, if a healthcare professional is contacted and confirms that the case does not represent a suspect ADR, it should be documented as such but no further action should be necessary, including any regulatory reporting of the case. These cases should be retained in the data base in such a way that they can be excluded from formal analysis but subsequently examined if needed.*

Review and causality assessment by a company or regulatory healthcare professional do not constitute medical confirmation of the case. However,

* However, as with all situations in which a reporter's attribution must be considered, the sponsor is always encouraged to exercise medical judgment. For example, based on broader understanding from other, drug-related experiences, the sponsor may choose to over-ride an individual physician's non-attribution, and report the case as needed.

there may be some situations in the absence of medical confirmation in which a company may decide to report the case (e.g., if medical records are provided by the patient). Such cases are still regarded as spontaneous reports (i.e., with assumed causality); however, if the cases originate from "solicited" reports (see Chapter II.e.), a causality assessment would be called for.

New Proposals

The CIOMS Working Group proposes several policy approaches and practices which aim to ensure that consumer reports are treated with appropriate respect and that there is a rational approach for handling them. In general, because the treating healthcare professionals remain vital partners in understanding and managing treatment emergent adverse events, their involvement in the confirmation process should take place whenever possible. Because much time and effort are expended on the management of consumer reports, international alignment of expectations regarding the handling of consumer-cases is also needed to assure proper focus on efforts likely to add public health value. Therefore, the following principles and practices are recommended:

Definition of Medical Confirmation

A situation in which a healthcare professional, preferably one directly involved in the care of the patient (primary healthcare provider), confirms (i.e., agrees) that the circumstances as reported by or on behalf of the patient occurred and that the facts, as amended or updated in the confirmation process, constitute an adverse event case for which there is a suspicion by that healthcare professional of drug causality (thus, it should be considered an ADR).

The important point in this context is to distinguish between *verification* of the facts by the healthcare professional (things did or did not happen as described by the patient) and the professional's *confirmation* that a drug-related adverse event (i.e., an ADR) occurred.

General Policy Issues

- *Consumers should be encouraged to report personal adverse experiences to healthcare providers, but primarily to their treating physician. Companies and regulators should convey this message through educational materials or in the course of responding to consumer inquiries or complaints. Consumer advocacy groups and disease-specific patient support groups should also be encouraged to foster this practice among their constituents.*

- *Neither a company nor a regulator should refer a consumer/patient to a specific healthcare professional.*

- *Physicians and other healthcare professionals, as part of any medical education, should be sensitized to the importance of listening to their patients for circumstances which might constitute a reportable ADR. When reports about consumers are received from a third party who is not a healthcare professional (e.g., a relative or other patient advocate, traditional healer, lawyer), that party should be encouraged to have the patient contact his/her physician and request that the physician report the case, if appropriate, or alternatively (or in addition) to encourage the consumer to authorize the sponsor/authority to contact the doctor directly.*

Case Management Practices for Companies and Regulators

- **Regarding all reports directly from consumers or from their non-healthcare- professional representatives:**

  - ❑ *During all contacts, attempts should be made to obtain information sufficient to ascertain the nature and seriousness of the complaint. Based upon this understanding, the strategy for documentation and follow-up will be determined (see below).*

  - ❑ *Permission should be sought to contact the consumer's primary healthcare provider in order to obtain additional medical details when relevant; such permission should be documented. If the patient prefers to obtain and forward supporting/confirmatory medical records, attempts should still be made to obtain physician-contact permission.*

  - ❑ *All such reports should be documented as for any other types of cases and should be taken into consideration when overall safety assessments are conducted.*

  - ❑ *As with the handling of all other individual case reports, patient-specific information (personal data) should be treated confidentially (see Chapter I.b.). Identification of the case should be sufficient to permit recall and cross-linkage with any subsequently obtained medical information, with all requisite steps to assure protection of patient privacy.*

In addition to these general practices, some special considerations apply that depend on the perceived serious or non-serious nature of the case. The information provided in the initial consumer report will usually permit a

judgment as to whether the case is ''apparently'' serious or non-serious; this may be the only judgment possible in the absence of subsequent medical confirmation.

- **When the event is apparently non-serious and already labeled/expected:**
  - ❑ *No additional effort (follow-up or medical confirmation) is required by the company or regulatory recipient as long as the minimum criteria for a case are satisfied. (See Chapter III.b.)*
- **When the event is apparently serious, or is non-serious unlabeled/unexpected:**
  - ❑ *Special effort should be made to obtain permission to contact the consumer's physician. If the patient refuses, attempts should be made to encourage the consumer to provide relevant medical records on his/her own.*
  - ❑ *If permission is obtained to contact the patient's physician or other healthcare professional, who in turn is unwilling to respond to company attempts at follow-up for confirmation, it is possible that regulators in some countries may be in a better position to obtain the requisite follow-up or confirmatory data.*
  - ❑ *Even in the absence of medical confirmation, any report containing suspected ADRs with possible implications for the medicine's benefit-risk relationship should be submitted to regulators on an expedited and/or periodic basis.*

Although the U.S. and Canadian regulatory authorities appear to be the only ones currently requiring submission of consumer reports, consideration should be given to submitting such important cases to all regulators.

Considerations on Periodic Safety Reporting

- ❑ *To satisfy current European, Japanese and other countries' requirements, medically unconfirmed consumer reports should not be routinely included in official international summary reports, such as ICH Periodic Safety Update Reports (PSURs). It should be recognized, however, that others (such as the US and Canadian regulators) may require that a listing or summary of such reports be provided as an appendix to a PSUR.*

- *Nevertheless, all consumer reports regarded as ADRs should be regularly scrutinized for new 'signals' or to confirm or extend the safety experience derived from all other sources. A statement should be made in the PSUR that such unconfirmed reports have been reviewed and either add no important new information or, conversely, suggest new findings.*
- *It is possible that unconfirmed consumer reports could contribute new, important information; if so, a separate tabulation and comment within the formal PSUR should be included.*

c. Literature

Introduction

Published medical literature is a well-recognized and valuable source of information about pharmaceutical products and specifically about their safety profile. Important new types of adverse drug reactions may first appear as published individual case reports (e.g., as letters to the editor of a journal). In addition, case reports may also be found as part of a published clinical study report. The objective of this chapter is to attempt to clarify currently ambiguous areas for both types and to recommend guidance on good practices for the handling of literature with relevance to pharmacovigilance. From the regulators' and the companies' points of view, the obligations go beyond drug regulation and are founded on public health principles, medical and scientific ethics, legal liability, and business needs. Although the primary focus is usually on scientific/medical journals and publications by health authorities and regulators, lay publications and even, by extension, other media sources, e.g., television, radio and the Internet (see Chapter II.d.), may provide important new information about drug safety. Pragmatic approaches to the role of these sources must also be considered.

Monitoring and regulatory submission of relevant reports from the published literature fall under well established rules and regulations, generally similar to those covering spontaneous reports. However, special issues arise because of two critical differences: published reports have been submitted to a third party (editors) and might lack clarity with respect to drug-event attribution, particularly for publications on studies in contrast to individual case histories. A published paper may or may not specifically describe or discuss attributability; adverse events are often mentioned in passing without further discussion. Unlike ordinary spontaneous reports, which are prompted by a suspicion of drug-related harm, publications containing adverse

experience data cannot necessarily be categorized as having presumed drug-causality. Sometimes the author will not only publish his/her findings, but also submit a direct report to a company or regulator; the direct reports should be treated as spontaneous reports as usual. However, most published adverse event/reaction information is not also conveyed through direct (unpublished) reports to either companies or regulators. Therefore it is incumbent on companies to monitor the literature actively for relevant information — on safety as well as efficacy — on their drugs.

Although there were differing views on the value of literature reports among the members of the Working Group, based on their experience they agreed that:

(1) The published literature sometimes provides a drug safety signal earlier than other reports; however, because the culture for reporting has changed and there is a greater volume of spontaneous reporting today than in the past, traditional published literature may now not be the primary or major source of an initial signal.

(2) Literature sources can provide confirmation of a signal previously suspected; this confirmation sometimes occurs as a result of additional information and better medical detail and analysis (including assessments of causality and discussions of mechanisms) that are not always provided in reports from other sources.

(3) There may be a long lag time between first detection of a signal by a researcher or clinician and publication of a report. This may occur because academics often wait for a case series before publishing, presenting at meetings, or notifying anyone.

(4) Publications can sometimes be the source of false signals and must be evaluated as carefully as other reports.

Literature sources represent about 3% of reports in the US FDA database. Regulators have taken action based on a review of literature reports; piperazine and the association of nitrosamines and cancer is an example.

Although the usual minimum criteria that define a valid ADR case (identifiable patient, identifiable reporter, a suspect product, and an event or outcome — and for clinical trial cases, a reasonable causal association), apply to literature cases, there is a need for a set of "best practices" for surveillance and handling of the published literature. A number of questions are raised by the need to monitor the literature for which the CIOMS V Working Group has developed proposals. Among the issues addressed are:

- ❑ What literature is appropriate for review?
- ❑ What is reportable under regulation?
- ❑ Who is responsible for reporting among multi-source and generic manufacturers?
- ❑ What is the timeline for reporting published events?
- ❑ What translations should be performed and under what circumstances?
- ❑ What follow up should be conducted and under what circumstances?
- ❑ How can authors and editors improve their contribution to safety reporting?

Proposals

What literature is appropriate for review?

Although the answer may seem straightforward to many readers, staff in pharmaceutical companies frequently debate this practical question. The issues are both regulatory (ensuring that companies comply with the various national regulations) and practical (the need for important pharmacovigilance information and the expense and effort required to cover the vast amounts of published literature in many languages and countries of the world). Regulations and guidance documents variously refer to cases found in the "literature," "worldwide literature," "medical literature" and "medical/scientific literature."[10]

There are literally thousands of medical and scientific journals published in a large number of languages. There are published meeting abstracts, letters to editors, editorials and proceedings from conferences that may contain relevant safety information. Duplicate reports may be

[10] The ICH E2A Guideline on Expedited Reporting during clinical trials includes "publications" among the sources of potential reports. The marketed product periodic reporting guideline on PSURs, ICH E2C, includes simply "Literature" under sources of reports. Reports on safety studies in the "scientific and medical literature, including relevant published abstracts from meetings containing important safety findings (positive or negative)" must also be discussed within a PSUR. The EMEA's Notice to Marketing Authorization Holders, Pharmacovigilance Guidelines states that "the marketing authorization holder is expected to screen the world-wide scientific literature." U.S. IND regulations (21CFR312.32(b), Review of Safety Information and 21CFR314.80(b), Review of Adverse Drug Experiences) require that a sponsor promptly review all information relevant to the safety of a product from any source including "reports in scientific literature, and unpublished scientific papers." U.S. NDA regulations (21CFR314.80 (d) Scientific literature) specify that expedited reporting applies only to reports "found in scientific and medical journals either as case reports or as the result of a formal clinical trial."

published in different journals (and a published report may be a duplicate of a spontaneous report from the author or a different source). There are also local newsletters from health authorities. Review articles may re-publish previously reported cases. There are also journals covering non-human research that may contain information of importance to the clinical use of a product. All these must be considered potential sources of adverse reaction reports and of other vital safety information. Considering all the potential sources, one might ask if or when a company is culpable if a report from an ''obscure'' publication is missed. It is virtually impossible to monitor all the world's medical and scientific literature for potentially useful or important drug safety information.

Added to these are publications not traditionally thought of as medical or scientific but which may increasingly contain information about pharmaceutical products. Patients and consumers are becoming more sophisticated about diseases and their treatments, perhaps because of the large number of patient and disease advocacy groups and because drugs, both OTC and prescription, are increasingly promoted directly to patients. The result is that consumer oriented lay journals often have articles about pharmaceutical products which may contain suspected ADR information.

There are no known requirements to screen lay publications, radio and television for safety information. From time to time, a company or regulator may be directly notified about such materials, in which case they must be processed as suspected ADR cases. Reports from these sources may, on their own, provide adequate information to fulfil the criteria for a valid case. When appropriate, follow-up may be required. If so, the report is then handled as a consumer report or a health professional report dependent upon the source of the information. (See Chapter II.b.) It is important to keep in mind, however, that whether such reports are valid or not, they can be the trigger for an irrational public health scare and it may, therefore, be appropriate to inform regulators of a perceived significant issue even when the requirement for ADR reporting may not be satisfied.

Medical and scientific journals are the primary target of the pharmaceutical industry's organized efforts to obtain and report new information from the published literature. From among the multitude of journals and publications worldwide, it is usual practice for companies to target their active review to those publications that appear in internationally recognized databases such as the Index Medicus, Current Contents, The Science Citation Index, EMBASE, Reactions, etc. A description of the most prominent databases is included in Appendix 3. Companies generally search at least two

such databases. When searching them, consistent search strategies and use of the International Nonproprietary Name (INN) as a keyword for retrieval are required to ensure comparability and comprehensiveness. Such databases usually provide abstracts of full papers. To the extent they provide sufficient detail to recognize new and important drug safety information and permit an evaluation of the seriousness and the expectedness of reports, expedited reporting based on their content is reasonable.[11]

Selection of standard literature databases and publications for screening will be based mostly on their appropriateness for identifying new and important information and on the product. A company may have reason to believe a particular publication ordinarily not on the list should be added. If relevant information from other publications not actively screened come to the attention of the company, of course it should be evaluated in the same way as any other reports received by the company. Letters to the Editor, as well as full journal articles, are often sources of individual case reports or a case series. Some publications commonly present review articles and may include meta-analyses of data. These aspects must be considered in the choice of publications to be screened. Under most regulations, literature reports are no different than other reports. For instance, proceedings from conferences are often reviewed by staff from marketing, clinical research and other departments outside drug safety. As usual, any suspect reports from these sources should be forwarded to the drug safety department for appropriate review, evaluation, and possible regulatory reporting.

In summary, the CIOMS V Working Group proposes the following practices:

- *Companies should search at least two internationally recognized literature databases with consistent strategies, using the INN as a keyword for retrieval. Such searches should be conducted regularly with a frequency appropriate to the drug and any special situations, but in general not less frequently than once a month.*
- *Automated searches should be supplemented to include monitoring of special publications relevant to the drug or circumstances.*

[11] The EMEA Notice to Marketing Authorisation Holders, Pharmacovigilance Guidelines, recognizes both the utility and the limitation of these databases, stating that "the marketing authorization holder is expected to maintain awareness of possible publications by accessing a widely used systematic literature review and reference database, such as Medline, Excerpta Medica or Embase, no less frequently than once a week, or by making formal contractual arrangements with a second party to perform this task." It also states, however, that "marketing authorization holders are expected to ensure that relevant publications in each member state are appropriately reviewed."

- *Sources such as broadcast and lay media should not ordinarily be monitored; however, if information on potentially important cases from these sources is made available, attempts should be made to ascertain whether there is a valid case. If in doubt, cases satisfying the usual minimum criteria should be reported to regulators.*

What should be reported to regulators?

Under regulation, there is in principle no difference between published reports on identifiable patients with attributed reactions, and spontaneous or clinical study reports. Thus, the usual considerations on seriousness and expectedness apply with regard to expedited and periodic reporting. Publications addressing product safety fall into a number of broad categories including individual case reports or case series, letters to the editor, retrospective database reviews (e.g., reports from poison control centers), results of clinical studies, reports from registries which may solicit reports prospectively, literature reviews, etc. In addition to individual case reports, many articles contain information on identifiable patients in various forms. (For discussion of identifiable patients see Chapter III.b.) It is typical for reports on clinical trials and from registries or poison centers to list patients by age, sex, etc., usually with outcomes and sometimes with attribution, if only in terms of identifying the "suspect product(s)." Many times, such reports represent nothing new or unexpected. Also, it may be very difficult or impossible to determine whether the same cases are already represented in the company or regulatory safety database (as a result of prior direct reporting). The following is recommended:

- *In accord with most current guidelines and regulations, appropriate types of reports of adverse drug reactions (e.g., serious ADRs;positive attribution by either the author or company/regulator) should be reported to authorities, on an expedited and/or periodic basis, depending on the nature of the case (e.g., expected vs unexpected). All reports should satisfy the minimum criteria for a valid case.*

Published line listings from registries, studies and drug information centers infrequently provide sufficient details to form the basis of individual patient case reports to authorities.[12] (See Chapter II.h.) Furthermore, unless the author specifically associates an adverse event with a specific suspected drug(s), positive attribution should not be assumed; the patient may have

[12] However, aggregate safety data may have to be the subject of reporting; publication of information, clinical or non-clinical, that has an impact on the recognized safety profile of a product may relate to previously unidentified risks or a greater risk than previously recognized (see Chapters II.g. and II.h.).

been receiving many concomitant therapies. On the other hand, if the author asserts or speculates that a drug may be part of the differential diagnosis, this should qualify the drug and case as 'suspected' for the purposes of review and reporting. To assure that all recipients of the report can properly evaluate the relationship of the event to the suspect drug and reach their own conclusions about attribution, all concomitant medications should be entered in the database and recorded on any report.

Another issue reviewers of literature cases face is what to do about the list of references usually cited within an article, some of which may relate to cases similar to those that are the subject of the publication under review. This problem is magnified for review articles, in which few if any identifiable cases are discussed but extensive references are given to articles that might be relevant. Many of those references will already be known to the company (or regulator); some of the cases discussed within those ''secondary'' references may have been reported through other sources, and many if not all the cases may reflect years-old experiences. Routinely checking or tracking down all such sources is clearly unrealistic, especially if some of the reference articles are in different languages which require translation. Of course, when faced with a major safety issue all such sources should be sought and would probably be found with a literature search anyway. However, for the more general situation the following is recommended as a reasonable practice:

- ❏ *References which are cited in support of discussion on apparently* ***unexpected/unlisted and serious reactions*** *should be checked against the company's existing database of literature reports; articles not already recorded in the database should be retrieved and reviewed as usual.*

Who is responsible for reporting?

There are often multiple manufacturers and/or marketers of the same drug, operating independently or through contractual arrangements. All manufacturers, including generic companies, have the responsibility to review the literature and report appropriate information to regulators. This has the potential to greatly increase the number of duplicate reports in databases of both regulators and manufacturers, since information is often shared in many directions, between and among companies and regulators. This leads to the following recommendations:

- ❏ *Licensing agreements should identify responsibilities of the partners, including screening of databases and local publications, procedures for processing and exchange of reports, and regulatory reporting (see Chapter II.i.).*

- *If the product source or brand is not specified in a publication (i.e., only the generic name is mentioned), the manufacturer can try to determine which specific product was used by contacting the author(s), especially for an important case. However, in the absence of clarification it should be presumed that it was the company's product; the data base and any reports should indicate that the specific brand was not identified.*

What is the timeline for reporting?

Most regulations for expedited reporting of clinical trial and spontaneous reports stipulate that the regulatory clock begins with the first awareness of a valid case by anyone in a company anywhere in the world. Can or should the same rule prevail for the literature? Special considerations might apply under some circumstances, such as in the following not unusual scenario: initial awareness comes from a printout by a literature search service or from an abstract that does not provide sufficient individual patient and other details to satisfy the minimum criteria for a case; a copy of the full paper or abstract is ordered; the original paper is in a language unfamiliar to the company (e.g., Chinese) and there is no familiar-language summary; the paper (or abstract) is translated. For reports uncovered by foreign affiliates of a multinational company in a journal published in their local language, the situation is a bit more straightforward; that affiliate will still have to provide, say, an appropriate translation, typically in English, to the central safety department of the corporation.

Assuming that after all these steps, a potentially reportable ADR is found, exactly when is a company considered to have knowledge of a published report, and should that moment become the criterion for the start of a reporting 'clock'? And should the standard depend on what the language of the original report was?

The 2000 EU Notice to Applicants, Pharmacovigilance Guidelines, stipulates that "the clock starts with awareness of the publication by any personnel of the marketing authorization holder." The criterion of "awareness of the publication" leaves much uncertainty; mere knowledge of a publication does not constitute awareness of a valid case.

Journals may be circulated to staff in a number of different departments and in a number of different countries. A published report may thus become known to individuals within a company soon after a journal is received. However, individual members of a safety department with responsibility for managing such a report may or may not be the first to become aware of an article on safety or an individual case. Journals are often read for many

reasons and identification of a case report may depend on the skills of the reader. In many companies, there is a formal process for screening the literature for safety information, which may be under the responsibility of someone within the company library, within the safety department, or through an outside contractor, for example. Although others outside the safety department may come upon a relevant article, they may not bring it to the attention of the safety people, knowing that such an automatic search process is in effect. Thus, awareness of and action on pharmacovigilance information may not be possible until after the abstracting services have added the article to their databases and it is received as part of the company's search process. The drug safety unit of a company also requires adequate time to process the case(s) and conduct appropriate evaluation.

Recognizing the difficulties involved, the general recommendations on reporting timelines are as follows:

- *Companies should establish processes for timely access to and review of the literature to permit expedited reporting of relevant cases within the usual timeframe (15 calendar days from recognition of a valid case).*[13]

It is recognized that cases described in the literature may have occurred long before publication, and that a sense of urgency for reporting might be perceived as inappropriate. However, especially when the case(s) represent new information, attempts to obtain any needed follow-up should still be made promptly and the case(s) dutifully reported to regulators as necessary.

What translations should be performed?

When is translation required, to what extent, and into what language(s) should it be done? The EMEA Notice to Marketing Authorization Holders, Pharmacovigilance Guidelines requires that a "copy of the relevant published article should be provided in a language acceptable to the member state." For post-approval surveillance, Japan requires translations into Japanese, and reporting if appropriate within 30 days of a report's being received in Japan. FDA requires attachment of English translations to expedited reports (Regulatory Guidance of March 1992).

In general, for most countries other than those whose language is that of the journal, the internationally accepted standard is that translations can be in English; however, as noted, several regulators might require translation into the local language for some or all literature reports.

[13] A valid case is one that satisfies the standard minimum criteria for essential information (identifiable patient, identifiable reporter, a drug, an event or outcome).

The following are proposed as guiding practices:

- *A translation of an abstract or pertinent sections of the publication should be accepted by regulators if it captures all the necessary case information, especially when dealing with long articles whose subject matter is largely outside the scope of the case(s) in question.*
- *Unless specifically otherwise required, it is recommended that translations into English be recognized as the accepted standard.*

What follow-up should be performed?

Companies generally have in place routine mechanisms for follow-up of spontaneous adverse event reports, which usually differ from practices with the literature (see Chapter III.e.). Because experience suggests that literature reports are often sufficiently complete and detailed enough to permit evaluation, the need for follow-up may not be as important. However, caution is always appropriate to be aware of fraudulent or fictitious reports.

Additionally, the lag time between the event and publication has often resulted in the original medical records having been archived and less available than for more recent cases, making it less likely that an author will respond to requests for information; authors may be much less likely than other reporters to cooperate since they believe and often reply that all the pertinent and important information is in the publication; and, there appears to be less urgency in follow-up, since, by the time a case appears in the published literature, considerable time is likely to have elapsed since its occurrence.

Suggested follow-up guidance is as follows:

- *As emphasized elsewhere (Chapter III.e.), judgment is needed to decide on the intensity and method of follow-up, taking into consideration the need for and importance of more information.*
- *As usual, the most aggressive follow-up efforts should be directed at valid reports of serious, unexpected suspected adverse drug reactions that lack details deemed important for assessment of the case.*
- *A publication may constitute an unsolicited follow-up to a report previously received via other means (e.g., spontaneously), or it may duplicate the original publication. In either case, the publication details should be added to the case record along with any additional important medical details relevant to the case; the new information should be handled as for any other follow-up report for regulatory reporting purposes, including on an expedited basis if appropriate.*

- *Occasionally, results of company-sponsored clinical trials will be published with explicit mention of individual ADR cases. It would be highly unusual for such publications to provide information beyond what was already reported. Thus, the fact that the study results have been published should not, per se, be the subject of a follow-up report to the original case submission or study-report regulatory filings.*

How can authors and editors improve their contribution to safety reporting?

In addition to the regulatory standards against which companies and regulators manage literature safety information, there have been attempts to set publication standards for authors and editors on content guidelines for adverse experiences and on informing companies or regulators of cases on a timely basis (the Morges recommendations).[14] Unfortunately, the recommendations are not widely known or applied.

Editors of journals often do not require that adverse reaction reports be submitted to the manufacturer or regulator at or before the time of submission of a manuscript for publication. Similarly, authors all too frequently fail to report cases in a timely way, either because they are not accustomed to spontaneous reporting or prefer to wait and only publish the case or case series. As a result, information may appear in print and become 'news,' even to the public, before those in a position to provide the necessary perspective have been notified and before information can be provided to health care providers.

Changes to these unfortunate practices would help both companies and regulators fulfill their obligations and responsibilities and would ultimately help to improve the quality of case reports as a result of interactions between the authors and knowledgeable company representatives. The situation in France provides a positive model; an editor is responsible for ascertaining from the author whether an ADR submitted for publication has been reported to one of the Regional Pharmacovigilance Centers or the National Agency.

---

[14] A meeting now referred to as the Morges workshop on improving ADR publications was held in 1984. (*Drug Information Journal,* 19:357-365, 1985). Minimum information requirements for single and multiple case reports were defined, i.e., the minimum data set that would allow a "valid assessment" of the cases reported. During the workshop, it was identified that of 1379 publications in the then Ciba Geigy database which identified a suspect drug and ADR, only 21% included all of the following: the sex and age of the patient, daily dose, duration of treatment with the suspect drug, co-medications and outcome. The guidelines developed in Morges are accessible on the Drug Information Association web site: < dia@diahome.org >

Most journals now agree that prior notification of an adverse event to a company or health agency will not jeopardize publication. Additionally, when the report is sent to companies prior to publication, they can provide comments and information that the author will often find very useful in his/her interpretation of individual cases as well as in placing such cases in perspective relative to the overall safety experience. Furthermore, advanced notice to a company or regulator of a proposed publication can prepare these parties for disseminating any necessary information to the public or professionals, e.g., to preclude an inappropriate crisis.[15] While exchange of information and opinions between authors and those who receive advanced draft copies can enhance the process, clearly no parties should exercise pressure or influence against publication.

Thus, the CIOMS V Working Group strongly endorses the following:

- *All journal editors should require not only complete documentation for published ADR case reports, but also encourage prompt reporting to companies and regulators independent of any publication.*
- *Editorial standards should include a requirement that ADR cases be reported to both the company and local regulator* ***prior*** *to submission of a manuscript for publication. Such reporting should not prejudice the author's right and timing of publication.*

Editors can go even further by requiring authors to *document* that they have submitted to regulators and/or companies all ADR cases submitted for publication, while providing assurance to the authors that such prior submission does not jeopardize the right to publish.

d. The Internet

Introduction

The Internet, in particular the "world wide web" (www), is a rapidly growing medium for communication and transmission of information (e-mail and web sites). It represents a network of millions of computers throughout the world that have the ability to interconnect on a full-time or part-time basis. It is expected to transform the healthcare landscape by offering unprecedented access to information, and it will empower

[15] See Appendix 1. Also, see Effective Communications in Pharmacovigilance. The Erice Report. WHO Collaborating Center for International Drug Monitoring, Uppsala, Sweden, 1998 (www.who-umc.org).

consumers to exercise greater involvement in their care.[16] The Internet represents an opportunity in pharmacovigilance but careful thought must be given to whether and how this tool should be used for drug safety monitoring or to share objective drug safety information.[17]

Transmission and retrieval of information with the Internet is relatively fast and simple. However, the ability to search for and obtain comprehensive information on a particular subject may be difficult depending on the choice of search engine(s), data classification and selection of search-term(s). Many websites have prescribing information for healthcare professionals and an area for posing and answering questions. Depending on the website sponsor (e.g., regulatory authority, pharmaceutical company, advocacy/special interest group, an individual, etc.), the information may be accurate and reliable, based on scientific evidence; alternatively, it may be anecdotal, speculative and personal, or it may be out-of-date.

From a pharmacovigilance perspective it is important to distinguish between (1) the collection (receipt) of safety data or correspondence over the Internet by companies or regulators from healthcare professionals or consumers (e.g., inquiries, spontaneous reports), and (2) the dissemination of safety information to the public (e.g., labeling information). These two different uses of the medium do not necessarily carry the same responsibilities and processes. Another, indirect consequence of the Internet relates to prescription drug access via on-line pharmacies internationally; the possibility of inappropriate or inadequate prescribing is magnified, increasing the possibility of ADRs.

Although it is not possible to be comprehensive in coverage of the many circumstances under which the Internet may be a factor in drug safety monitoring and reporting, the CIOMS V Working Group has addressed what it believes are the most common and important questions and provides recommendations.

Some Practical Issues

Several considerations bear on the possible use of the Internet for pharmacovigilance and drug safety applications. The Internet is also playing an ever increasing role in drug development, marketing and sales of

[16] Poste, G., The Right Treatment for the Right Patient, *Scrip Magazine,* January 2000, pp. 11-14.

[17] Cobert, B. L. and Sylvey, J. The Internet, Adverse Events and Safety, *International Journal of Pharmaceutical Medicine,* 12:83-86, 1998.

medicines; although these activities can involve drug safety issues, they are beyond the scope of this discussion.[18]

Information Privacy and Security

The need for personal data protection is particularly important with a medium such as the Internet over which potentially sensitive health information is readily exchanged. Without the requisite information, it may not be possible to satisfy the minimum criteria for a valid safety case report in terms of an "identifiable" reporter or patient. (See Chapters I.b. and III.b.)

There is also a need for restricted access to data (especially personal data) and various software and other tools are available for that purpose, such as passwords, key-coding, and encryption of data. The International Conference on Harmonization (ICH), through topic M2 (Electronic Standards for Transfer of Regulatory Information (ESTRI)), has developed standards for Internet transmission of information primarily between industry and regulators or regulator to another regulator. The standard will ensure that the information transferred will be protected (i.e., secure), carry the senders "electronic signature," reaches the correct (intended) recipient(s), does not change during transmission, and that a receipt is returned to the sender certifying the action. The ESTRI system is being tested in several pilot projects in the EU, US and Japan involving the exchange of adverse reaction reports using the ICH E2B standard.[19]

However, outside the ICH environment, there are no generally agreed or established standards and there is the potential risk that Internet messages may not be secure, or be fraudulent or manipulated. Can one validate that an e-mail relating to an individual ADR is legitimate and came from the apparent sender? Can appropriate follow-up be accomplished? There is also the risk that information may by accessed by unintended parties and that the information may be deliberately altered. While these actions are not unique to the Internet, they are facilitated with such a medium and precautionary measures are advisable.

---

[18] For example, see P. Bleicher and G. Benghiat, Security in Web Clinical Trials, *Applied Clinical Trials,* 8:40-45, 1999.

[19] For details on the ICH guidelines for M2 and E2B, see: <http://www.ifpma.org/ich1.html> Alternatively, see <www.fda.gov/cder/m2/spechtml/specdocument022299.htm> and <www.ifpma.org/pdfifpma/e2b.pdf>

The Internet as a Spontaneous Reporting Mechanism

Despite their recognized limitations, individual spontaneous case reports from any source represent potentially important safety information, especially for rare, serious, unexpected ADRs. Currently, there does not appear to be any clear regulatory guidance for companies on how to approach information on the Internet.

There is considerable variation between companies on what their homepages say about adverse reaction reporting. Many companies receive reports, mostly from consumers, via e-mail or message fields on their website, even though companies may not encourage direct Internet reporting. To be valid, a spontaneous case report must have a subject drug, a suspected ADR, an identifiable (real) patient and also an identifiable reporter. Follow-up information is often required, ideally from a patient's treating physician; there is insufficient experience to know whether suitable follow-up is more or less difficult for Internet reports compared to those from other sources. The typical debate on whether scanty, possibly incorrect information is better than no information at all also applies to the Internet as a source; as usual, judgment will be needed on a case-by-case basis.

There have been documented instances of pharmaceutical company representatives or others sending fictitious ADR reports in an attempt to tarnish the safety profile of a competitive product (see Chapter III.b.). This temptation may well increase if the fictitious case reports were intended to be seen by persons other than the usual regulatory or company recipient (e.g., potential prescribers or patients or the media). It is therefore particularly important to check the credentials of the reporter; this is sometimes difficult if not impossible without direct contact, e.g., by telephone. It should be recognized that any abuse that can occur on the Internet also occurs now via more traditional media.

Source of Literature and Medicinal Product Information

The Internet provides access to a wealth of published literature from peer reviewed and other journals, but it also generates an enormous amount of anecdotal exchanges. Chat rooms, bulletin boards, and websites produce volumes of information that must be cautiously evaluated before acceptance. Experience to date generally indicates that spontaneous reports from chat rooms provide very scanty information. The onus is clearly on the reader to try to determine the validity and reliability of the information.

The CIOMS V Working Group also considered the suitability of the Internet to provide "labeling" information on medicinal products, especially safety-related data, to a wide audience. Although this could be achieved at relatively low cost, given the borderless nature of the Internet there is a potential for confusion, even misinformation, given the different content and requirements for labeling in different countries and in different languages, even for the same product.

Retrieving Information from the Internet

When attempting to search for relevant safety data, for example, care must be taken in accessing or retrieving information on the Internet. Regional differences in language and spelling (e.g., oesophagus versus esophagus) may produce incomplete data searches. Terminology standards and classification protocols will influence the ability to search for and retrieve the desired information. It is also important to select the appropriate search engine(s), in order to optimize data retrieval. However, it must be acknowledged that even using multiple search engines will only reach a fraction of available web sites.

Access to Web Site Information

Information posted on web sites primarily intended for persons in one country may be accessible to people in many other countries. For example, direct-to consumer advertising of prescription medicines may be accessed in countries where it is not allowed.

Companies frequently post on the Internet the approved patient information for their products. At present, this information often differs from country to country, but it would not be unreasonable to post multiple versions of the approved patient leaflet, each in the language or languages of the country in which it is approved.

Recommended Practices in Use of the Internet for Pharmacovigilance

- Should companies and regulators encourage ADR reporting via their home pages?

  It has always been a goal of pharmacovigilance to encourage and facilitate spontaneous reporting. It is recommended that companies and regulators use their "Home Page" for doing so, as long as the site

is secure. Providing an ADR form on their Website, either for direct electronic submission or as a printable form for mailing, is suggested.

To ensure sufficient case information is available via this source, allowable submissions should be made dependent on the sender's completing mandatory fields (particularly the four minimum criteria for a valid case).

Some regulatory authorities already provide AE/ADR forms on their home page. Any form should obviously be accompanied by instructions, e.g., minimum criteria for reporting, and by appropriate notices on confidentiality. It may be necessary to present the form in the local language. It will be necessary to identify the reporter and to establish that there is an identifiable patient as part of the minimum criteria for a report. There are confidentiality and authentication issues, but the form with defined minimum criteria could be downloaded and sent by e-mail. For efficiency sake, the components of any form should mimic as closely as possible the comparable data element fields for the ICH E2B standard.

- What is the responsibility for screening a company or regulatory website for safety reports?

  A procedure should be in place to ensure daily screening by a designated person(s) of the website(s) in order to identify potential safety case reports.

Care is needed in screening web site communications. For example, sometimes an ADR case will appear within a simple question from a healthcare provider or a patient (something that occurs via telephone contact or regular mail as well). To encourage more thorough communication, especially on safety matters, some companies' websites provide a "toll-free" telephone number with instructions to call the company about adverse effects or product complaints, perhaps even directly to a clinical safety office.

- What should a company's or regulator's responsibility be with regard to searching the Internet ("surfing") for spontaneous reports of individual suspected ADR cases?

  The Working Group does not believe it necessary for regulators or companies routinely to "surf" the Internet beyond their own sites for individual spontaneous reports. However, it would be appropriate to look actively for ADR information on special home pages such as those of patient support or special disease groups ***if there is a significant issue***

(for example, new important signal, off-label use, circumstances leading to misinformation).

It is also recommended that such sites be visited selectively for discussions on a significant drug safety issue in order to determine whether potentially useful safety information has been overlooked or whether information has been adequately communicated (i.e., to guard against misinformation).

Recommended Practices on Communication of Safety Information

- Should product safety information be disseminated by companies and regulators via the Internet?

The Internet could have an important role in the transmission to healthcare professionals and, as appropriate, to consumers of consistent, up to date messages concerning safety and other aspects of labeling (for example, new warnings and contraindications). Use of the Internet in this way could also accelerate the availability of key information, subsequent to approval by regulators (if needed). Official data sheets and patient leaflets are already available through the Internet.

The Working Group has specific recommendations in this area:

In principle, the message should be consistent around the world since the Internet generally does not respect geographic boundaries. However, due to local labeling and language differences, this may not be possible to accomplish for all product details.

In spite of the widespread availability of the Internet, many people do not have access to it or use it as a major source of information. Therefore, it is important that Internet and traditional sources convey the same message, including promotional material. In addition, due to the generally passive nature of Internet communication, traditional sources should be continually made available.

Important safety information, such as that conveyed in Dear Doctor Letters, should be disseminated via the Internet as well as through more traditional mechanisms.

Relevant background information (evidence) that explains the reasons for labeling changes could also be made available on a company's or regulator's website. Appropriate hyperlinks to sources of detailed information on such changes can also be provided.

e. Solicited Reports

Post-marketing regulations generally refer to two types of safety reports: those that are reported spontaneously (''spontaneous reports'') and those that are reported as part of the conduct and analysis of a clinical or non-clinical study involving the drug product (i.e., ''study reports''). There is, however, an increase in types of reports that do not fall neatly into either of these categories. Many of these newer reports are generated by marketing programs used by pharmaceutical companies and through the increasing use of methods to encourage contact between consumers and the pharmaceutical company. Pharmaceutical companies continue to struggle with determining how to handle such reports. In general, reports that are identified in any manner other than by a study are traditionally handled as ''spontaneous'' reports. However, the CIOMS V working group is not convinced that this is the most appropriate way to approach this ever-growing issue.

The underlying assumption of a spontaneous reporting system is that health care providers and others make an effort to report (i.e., voluntarily on their own initiative) to either a drug regulatory authority or to a pharmaceutical company those adverse events that the reporter believes has at least the possibility of a causal relationship to a drug product — especially when the reporter deems the information to be important. Although some reports might be generated as a result of prompting by the health authorities (and in that sense might be considered ''stimulated'' reports), they should still be regarded as spontaneous reports from a regulatory perspective. Examples include the UK Medicines Control Agency's Black Triangle program,[20] and the situation in countries where the laws or regulations require reporting by physicians.[21]

[20] An inverted black triangle usually appears on the data sheets of new drugs in the UK to prompt physicians to report any suspect ADRs to the authorities in accord with their yellow card system.

[21] To ensure clarity of concept, it is important in the current context to make a distinction between ''stimulated'' and ''solicited,'' for which there are no current definitions as to their use in pharmacovigilance. Stimulation (or inducement or prompting) to report occurs, e.g., when special attention is given to safety issues (for example, a Dear Dr. Letter or prominent notification in the lay or professional press about a suspect serious adverse reaction); new reports are thus stimulated, although they should still be considered spontaneous reports. On the other hand, as explained in more detail within the text, solicited reports do not originate with any safety issue or safety study, but invariably arise in the course of interaction with patients for unrelated purposes. As defined under ICH Guideline E2C (on periodic reporting for marketed drugs), a spontaneous report is ''An unsolicited communication to a company, regulatory authority or other organization that describes an adverse drug reaction in a patient given one or more medicinal products and which does not derive from a study or any organized data collection scheme.''

It might also be mentioned that if in the course of investigating a spontaneous report (follow-up discussions with the reporter, e.g.) additional cases of the event are identified, then these additional cases are usually also considered spontaneous reports.

On the other hand, if a reporter mentions events other than the subject of his/her communication (''By the way, the patient also had an MI.'') this ''incidental event'' information (see chapter III.a.) should not necessarily be construed as a new spontaneous report.

In recent years, there has been an increase in a variety of different programs, usually by manufacturers, that generate adverse experience reports to manufacturers that are neither truly spontaneous in origin nor a result of a prospective or retrospective clinical study:

- ❏ patient-support and disease management programs involving, for example, telephone service for patients to obtain direct advice, or nurse-initiated calls for medicine compliance management. Generally, a patient support program is one in which patients can enroll to obtain educational information and prescription reminders. Enrollment may be through a physician, a pharmacist, or directly by a patient with a company; in each case there is likely to be at least one direct contact with the patient by the company or a contract organization, and each contact has the potential for generating adverse event information (Q. ''How do you feel?'' A. ''I had a headache yesterday.'')
- ❏ survey cards collecting demographic and other patient data; follow-up calls by pharmacists to patients concerning prescription renewals; toll-free numbers for product information and for refund/rebate transactions; surveys of patient satisfaction.
- ❏ company-sponsored healthcare provider surveys
- ❏ establishment of large patient registries
- ❏ information gathering on efficacy and other follow-up information for outcomes or pharmacoeconomic studies, especially data derived from patient diaries. (See Chapter II.f. for a discussion of potential safety information derived from quality-of-life questionnaires.)

Because of these contacts with drug product prescribers, dispensers and users, a large number of reports of adverse events reach companies. These are clearly not generated in the usual spontaneous manner that is the premise upon which our spontaneous reporting systems are based; they are usually obtained incidentally to the main purpose of the program. In none of these

situations is the communication of a possible adverse reaction initiated in an unsolicited way by the reporting patient or other person. Had the company, its agent, or other party not taken the initiative to contact these people, or to solicit their communication for purposes other than safety reporting, the event would most likely not have been the subject of independent voluntary reporting to a healthcare provider or directly to a company*. For this reason, such reports are regarded as solicited in nature and one cannot infer implied causality, the convention for spontaneous reports. Indeed, they may be nothing more than incidental experiences (see Chapter III.a. for a discussion of "incidental" events).

Therefore, the CIOMS Working Group believes that such reports do not meet the standards of spontaneous reports. With the possible exception of "patient registries" which may be driven by a structured protocol, they also do not involve formal studies and so do not meet the criteria for study reports. For more discussion on registries, see Chapter II.h.

Most of the solicited reports involve non-serious events/reactions. Regarding them as "spontaneous" would undermine, possibly corrupt, the objectives and effectiveness of the spontaneous reporting system for the generation of important new safety signals, especially given the limited resources usually available. Emphasis must be placed on the processing and analysis of medically important information. Therefore, the CIOMS Working Group is advocating the introduction of a new category, solicited reports, to supplement the traditional spontaneous and study types.

To place these types of reports in proper perspective, however, it is important to draw on the experience of some companies represented within the CIOMS Working Group who have conducted programs that generate solicited adverse event reports. That experience has raised some fundamental issues on how safety-related information gathered during such exercises should be handled, which in turn should depend on the actual or expected value of such information:

- there are major differences between the various programs in what information is solicited and how (e.g., check-the-box surveys/questionnaires vs open-ended telephone or in-person interviews or discussions, which in either case can be either narrowly focused or

* In contrast to this general observation, adverse events arising from conversation between company sales representatives or clinical liaisons with physicians or pharmacists, e.g., should be regarded as spontaneous reports. For example, a sales representative might ask: "How is the product performing?" A physician might then volunteer information on a suspected ADR.

expansive); thus, the amount of detail and the ability to interpret reports varies markedly

- ❏ some programs of the types described that generate solicited reports are not initiated until after a product has been on the market for at least a year
- ❏ some programs are retrospective (with information collected as much as a year after the fact); the usual problems of recall and inability to obtain follow-up details are paramount
- ❏ for all the types of programs, it is very difficult to obtain follow-up information, which is invariably desirable in order to make sense of typically scanty, ill-defined reports; there are no ''investigators'' in such programs and the opportunity to communicate with patients or their physicians directly is very limited
- ❏ some programs inquire as to the effect of a drug on the treated indication; this automatically results in ''lack of effect'' reports which not unexpectedly leads *de facto* to a ''signal,'' misleading as it may be
- ❏ managing the data from these programs, which can involve very large populations of patients, is very resource and time intensive and must be weighed against other priorities and the relatively poor return on investment that such data provides
- ❏ some regulators have attributed little value to the data generated from such programs; considering that the information can confuse interpretation of more traditional data (e.g., spontaneous reports), they have requested that such data be removed and reports redone for some periodic or special safety submissions
- ❏ there are no known instances of the generation of a legitimate signal that has not been detected earlier through ordinary post-marketing monitoring.

The quality of solicited reports is very low and they should not be put into the same category as spontaneous reports regarding information content and potential usefulness. Doing so only floods the system with noise. The chances of learning something important and new from such sources is small, especially given the difficulty of obtaining detailed medical information. These considerations are important in trying to decide on the proper level of attention and regulatory reporting such reports should receive.

A rational approach to handling solicited reports without compromising patient safety is outlined below.

- *adverse event information obtained in the types of programs described should be collected and processed separately, and categorized in the data base as solicited reports. They should also, therefore, be identified as solicited cases in any reports or tabulations that may be required for regulatory submission.*

- *another category of reports falls under the same concept of solicited: in constructing class-action law suits, lawyers will often actively seek out (i.e., solicit) cases through personal contact or advertisements. These should also be regarded as solicited reports in terms of their processing.*

- *suspected serious, unexpected ADRs should be regarded in the same way as they would be for a clinical trial;*[22] *thus, for purposes of regulatory post-marketing drug safety reporting on an expedited basis, a causality assessment should be conducted by the manufacturer*

It is recognized that conducting a causality assessment on these types of cases will be quite difficult. If a patient provides the initial report, experience in such programs to date has shown that follow-up information, either from the patient or (with permission of the patient) from the treating physician, is not helpful or is difficult to obtain. For purposes of causality assessment, the patient should not be regarded in the same way that a reporting healthcare professional or investigator would be in terms of providing an opinion on causality (however, see Chapter II.b., especially the footnote on p. 35, for discussion on this point). Therefore, it is up to the company to evaluate the case and using the best data available decide on attribution. In many instances, the physician may not even be aware of the patient's complaint, which was casually made outside the usual medical treatment setting. Nevertheless, in the face of uncertainty, particularly for a suspected *serious, unexpected* reaction, appropriate expedited reporting should be the practice as long as the case meets the usual minimum criteria for a case.

[22] At least one drug regulatory authority (US FDA) has already adopted such a stance via a guidance. An important factor in applying this recommendation is a decision on what reference safety information should be used to determine expectedness. For consistency, it is suggested the Company Core Safety Information (CCSI) serve as the basis for this determination. Whether expedited reporting on such specific cases is required within different countries will depend on the local data sheet, as usual. See Chapter III.d. for details.

- *all other types of cases (serious-expected and non-serious) should be stored as part of the manufacturer's safety database, but made available to regulators only on request*[23].

- *notwithstanding the above, recognition of medically important information from the aggregate data of such programs may on rare occasions be possible. Therefore, a responsible party within a company should review the data on an ongoing basis, particularly at the time of periodic report preparation, to ensure that no potential signals are present.*

f. Aspects of Clinical Trial Reports

For an unapproved/unlicensed product, the only clinical safety experience derives from clinical trials or compassionate/named patient use. The rules for collecting, processing and reporting adverse experiences during clinical trials (including Phase 4 studies) are reasonably well established under regulation and Good Clinical Practice Guidelines, especially for expedited reporting to regulators of serious suspected adverse reactions. In general, non-serious events from Phase 1-3 studies will not be reported and discussed until submission of a marketing application dossier or, when applicable, with end-of-study reports. Although the requirements for safety monitoring and reporting with regard to clinical trials are fairly well established, there are many details for which standards have not been developed or agreed. Most are beyond the scope of CIOMS V and have become the subject of a new initiative, CIOMS VI.[24]

However, the CIOMS V Working Group felt it appropriate to address some issues related to aspects of clinical trial safety data management. One involves the sharing of new, important safety information with clinical trial investigators and other stakeholders, an area that has not been adequately discussed elsewhere.

---

[23] It is recognized that this represents a departure from the requirement under ICH Guideline E2C on PSURs, which asks for inclusion of *all* serious, related cases (listed and unlisted). However, this exception is regarded as consistent with the origin and nature of such cases (as discussed in the text); focus should only be placed on suspected serious unexpected/unlisted ADRs from solicited sources.

[24] The new Working Group will be addressing, among other issues involving safety: roles and responsibilities (CROs, sponsors, investigators, external committees); when, to whom and how to disseminate new important safety information; special study populations (e.g., elderly, children, organ impaired, pregnant or lactating females, etc.); connection between laboratory abnormalities and clinical findings; criteria for treating or following adverse event dropouts/discontinuations; criteria for premature study termination; statistical analysis of safety data; personal data protection (privacy); tissue sample handling and post-study reuse.

There are differences of opinion and practices within the industry regarding when and how to inform investigators of such information, especially serious, unexpected adverse reactions. The ICH "Guideline for Good Clinical Practice" (May 1996) specifies in Section 5.17.1:

> "The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the Institutional Review Board(s) (IRB)/Independent Ethics Committee(s) (IEC), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected."

Regulations in some countries do specify such reporting obligations, but many do not. As specified under the ICH Guideline for expedited reporting (E2A), there are other types of important safety information that should also be considered, such as new and significant animal study findings, or an unexpectedly high incidence of known serious adverse reactions.

Although ICH GCP does not mention it specifically, it may be necessary to inform independent data and safety management boards/committees responsible for such things as breaking the blind and assessing on an ongoing basis whether a trial should be halted or modified.

Furthermore, there are often situations in which a compound may be the subject of different research and development programs (different indications, dosage forms, formulations, administration routes), in which decisions on appropriate expedited reporting to investigators and IRBs/IECs must be made. In principle, any systemic effect of a drug can express itself through any dosage form, formulation, administration route or indication. However, questions such as the following frequently occur. Should information on a serious, unexpected reaction with an oral dosage form be conveyed to investigators working with a topical dosage form? In general, should serious unexpected ADRs within one clinical program (e.g., under an IND in the US or CTX in the UK, for a specific product or product use) automatically be reported to investigators in all other programs with the pharmacologically active compound? Should such information be conveyed to Phase 4 investigators who are studying one or more of the products and claims under ordinary prescribing conditions?

When deciding on a recommended course of action for these and other circumstances, the CIOMS Working Group took into account an overriding ethical consideration: once a new serious unexpected suspected adverse reaction is identified, whether or not it is "officially" added at that time to

the Investigator's Brochure (IB),[25] it is important for all relevant parties to be informed. It is especially incumbent on both the sponsor and the investigators to modify the informed consent information, particularly for newly recruited patients (many companies also encourage investigators to provide already enrolled patients with an addendum to the safety information). Whether and when such a new important safety finding should lead to a change in the product information for a drug that is also on the market is a separate issue (see below).

Generally, the first report of a particular serious suspected ADR would be considered a new finding (a "signal") for which the evidence is not considered strong enough to add to the DCSI/IB formally (in such cases, any subsequent cases would still be regarded as "unexpected" and be reported on an expedited basis). For example, although the investigator judges that an event is related to the study drug, the sponsor might disagree (it still must be submitted to regulators as an expedited report); the availability of subsequent research may or may not confirm the investigator's opinion. Another situation under this option arises in a blinded study. If the blind is maintained for such cases, then until it is broken by the sponsor or a safety data review board in the face of a signal, the event remains unexpected and, of course, unassigned to a particular treatment.

Many companies follow this practice; application of a high threshold standard for adding new, serious adverse experiences to the DCSI/IB as expected ADRs has been recommended in the CIOMS III/V report (see footnote 25). In principle, the same concepts apply to other types of new, important safety findings (e.g., from animal study results).

Under exceptional circumstances, it may be appropriate to add the first case of a new, serious ADR to the IB (hence, it would be "expected" from then on, and under most regulatory systems additional cases would not be reported to the authorities on an expedited basis).

Although there is a belief by some that "official" entry of an ADR in an IB or DCSI automatically leads to inclusion of that event in the marketing data sheet (labeling), in practice the final decision on safety information in a CCSI or local labeling (e.g., SPC) will be based on a comprehensive review of all data and on negotiations between the regulators and the sponsor.

---

[25] For a discussion of the Development Core Safety Information (DCSI) as a standard document for safety information in an Investigator's Brochure that defines "expectedness," and for its relationship to Company Core Safety Information (CCSI) and the official data sheet when the same compound is on one or more markets, see *Guidelines for Preparing Core Clinical-Safety Information on Drugs. Second Edition, Including Proposals for Investigator's Brochures*. Report of CIOMS Working Groups III and V. Council for International Organizations of Medical Sciences, Geneva, 1999.

The CIOMS V recommendations are as follows:

Any serious, unexpected (vis-à-vis the Investigator's Brochure/DCSI) safety information that is the subject of expedited reporting to regulatory authorities under clinical trial reporting circumstances, should generally be reported on an expedited basis to all Phase 1, 2 and 3 clinical investigators who are conducting research for any use of the product(s) and with any form of the product.

This should apply to reports from sources other than clinical trials (e.g., spontaneous reports for a drug that is also marketed in a country that is the same as or different from the study location). Expectedness is still based on the IB/DCSI; thus, even though a serious suspected ADR may be "labeled" in a local data sheet (e.g., SPC) or "listed" in the Company Core Safety Information (CCSI), if it is not likewise expected vis-à-vis the IB, it requires expedited reporting and sharing with appropriate investigators.

The addition of a new suspected ADR to the DCSI of an IB, thereby making it subsequently expected, will depend on circumstances and company practice, but the decision should be made using the guidance outlined in the CIOMS III/V report[25] on when the threshold is reached for an ADR's inclusion in the reference safety document.

An example of when informing all investigators studying a pharmacologically active substance would be unnecessary is a case of injection-site thrombophlebitis with an intravenous dosage form while the drug is under separate investigation in a non-injectable form (e.g., oral). There can be other situations in which the ADRs will be indication or dosage form specific. Obviously judgment will be needed in many circumstances, but in general the default decision should be to share the information with all parties involved in developmental research with the active substance(s).

It may be less appropriate, however, to include Phase 4 investigators in the dissemination of such expedited report information. Phase 4 studies typically use the local, official data sheet as the equivalent of an Investigator's Brochure. As mentioned above, it must be recognized that a new addition to an IB used in Phase 1-3 studies does not necessarily mean that the threshold has been reached for a similar addition to the marketed product data sheet. Any new finding within a research setting must be regarded as a signal until such time that the ADR(s) or other pertinent information are confirmed and added to both the official labeling and to the Company Core Safety Information (CCSI). Of course this does not preclude

the prompt dissemination of new, important safety information to Phase 4 investigators and it is the practice at some companies.

A different question arises, however, when one begins to see an increasing number of reports of an *expected* serious ADR during premarketing Phase 2 or 3 studies. Is there a point at which the regulators and investigators should be informed of an unusual incidence of serious cases? Perhaps awareness of an increase would lead investigators to be more alert and monitor patients more carefully; it might also lead to protocol adjustments or, in the extreme, termination of a study. The Working Group suggests the following guidance:

> *Responsible company safety and clinical experts should be reviewing safety data on an ongoing basis especially for such important findings.*
>
> *There are no established rules or objective criteria for defining an "increased frequency" of reports. Judgment will be required to determine when it is necessary to review the data with the regulatory authorities; consideration of changing the study conditions (e.g., patient entry criteria) or introducing a temporary halt to the study program may have to be considered. Even if no changes to the study conditions are made, it may be useful to update the investigators as well as ethics committees or safety/data management boards on the new findings; again, informed judgment will be required.*

There is another reporting issue confronting manufacturers when engaged in Phase 1-3 studies for a drug that is also on the market. If an unexpected serious suspected ADR occurs in a premarketing clinical trial (and an expedited report is made), under what circumstances should that same report be submitted on an expedited basis to the marketed product regulatory system if the event is not already "labeled"? Referring to the example given above (thrombophlebitis), judgment is needed if the marketed product or its use are sufficiently distinct from, or not relevant to, the activity for the experimental program. However, once again the default decision should be to report such a suspect ADR to the regulators' marketed-product file, even if it involves breaking the blind for the individual case in a blind study, as required under ICH Guideline E2A on pre-approval expedited reporting.

Finally, there is a type of study or data collection that has received little if any attention with regard to safety assessment and reporting responsibilities: quality-of-life (QOL) investigations. Answers to questions on a QOL instrument, without drug attribution, should not necessarily be considered

ADRs (e.g., answers such as "I feel sad a lot" or "Sometimes I think about suicide"). Typically, QOL questionnaires are included as part of data collection in ordinary clinical trials although they may also be used during a separate exercise with patients. For either situation, the following recommendations are made:

> *Quality-of-Life (QOL) data should be managed in the same way as other clinical trial data; an adverse event should be considered an ADR only through drug attribution by the reporter or through a causality assessment by the reviewer.*
>
> *For certain questions on a QOL instrument, especially those dealing with potentially serious outcomes (such as suicide ideation), it is recommended that an affirmative response should result in a referral to the investigator or other responsible party for further discussion and consideration as to evaluation for a possible ADR.*

In general, however, answers to QOL questions do not provide much information, and routine follow-up of responses that do not involve drug attribution is not recommended.

Depending on the study protocol, it may be preferred to present the results of comparative QOL studies in the form of summary data rather than as individual case reports, as suggested for observational or epidemiological studies (see Chapter II.g.).

Any serious, unexpected[26] *suspected ADR should be reported on an expedited basis in accord with local regulations; all other appropriate data should be submitted periodically as required.*

g. Epidemiology: Observational Studies and Use of Secondary Databases

The evolution over the past twenty years of the field of pharmacoepidemiology has added a substantial resource to the armamentarium of structured research approaches through which we learn about drug safety issues, particularly in the post-marketing environment. Pharmacoepidemiology relies on the observational method, well-suited to monitoring of extensive treatment experiences. Observational studies are sometimes

[26] Serious *expected* suspected ADRs occurring within the EU must also be filed on an expedited basis to the relevant EU country regulator(s) and/or the EMEA (see Appendix 19C).

referred to as non-interventional or non-experimental studies, in that the investigator observes and evaluates results of ongoing medical care without "controlling" the therapy beyond normal medical practice. Thus, study designs do not involve such techniques as randomization but rely on case reports, case series, analyses of secular trends, and other approaches.

Traditional epidemiologic approaches involve two basic observational study types, cohort and case control. A cohort study observes a drug-exposed population of individuals (a cohort) to ascertain the nature and extent of specified outcomes in those individuals. In a case control study, one or more groups of patients (cases) who have experienced the medical condition of interest are compared to control group(s) who did not experience the event, looking at both the cases and controls for antecedent drug exposure; patient data for these generally retrospective studies can be obtained from a variety of sources, such as case registries, medical records search, or secondary (existing) data bases such as automated multipurpose population databases (see below). Discussion of details on these and other approaches to structured epidemiologic studies is beyond the scope of this report. Interested readers are referred to one of the several published texts in the field.[27]

The use of existing data bases of many types has become commonplace, especially for pharmacoepidemiologic purposes. Retrospective studies of varying design (case control, etc.) and the use of general "data mining" techniques for detecting and examining safety signals or for other hypothesis testing purposes make use of isolated or linked data bases of varying quality and quantity of information on individual patients.[28] In addition, such databases may also be used for learning purposes (how to access and analyze data from such sources) without any specific protocol or research purpose in mind. Thus, clinical and safety personnel will be examining patient efficacy and safety data from these sources for a variety of reasons and under many circumstances.[29]

---

[27] For example, see Strom, B. L., Editor. *Pharmacoepidemiology,* John Wiley & Sons, 3rd edition, 2000.

[28] For an extensive inventory and description of such data bases, see *BRIDGE On-Line* (Benefit and Risk Information for Drug Evaluations). Information regarding its availability and use can be found at www.dgi.org (phone in the U.S. 703-276-0056).

[29] A clinical trial data base created by a manufacturer during a development or marketing program may also be the subject of "future" examination and in that sense represents a retrospective examination of an existing data base; however, it is expected that any regulatory reporting obligations with regard to safety reports would already have been met. It is still possible, as usual, that new insights or understanding may emerge from such a later examination of the data which may require additional regulatory reporting.

There is very little specific regulatory guidance on what constitutes relevant safety information in such databases from the perspective of a company's or health authority's obligations for expedited or periodic reporting. That the data are not usually current introduces special considerations (*i.e.,* as retrospective sources, they contain data that were collected and documented months or years prior to their examination). It may be difficult, if not impossible, to obtain needed follow-up information on specific cases. In addition, medical events within a database will typically have been recorded as observations without regard to considerations of whether an ADR had occurred or there were any attributability to one or more drugs.

There is no obligation to search through databases for all possible adverse reactions; spurious signals will give rise to erroneous conclusions. Rather, studies conducted with databases should have a scientifically sound protocol which will specify the kinds and amount of safety data to explore and analyze.

Observational studies introduce other questions: if database review appears to confirm a signal hypothesis, should the relevant cases be submitted as individual ADR reports? Or should only the total report be submitted, with detailed line-listings available on request, e.g.? When does the reporting clock start if an alert situation may be suspected from the aggregate data? Does the answer depend on when an analysis and conclusions are final? The process for conducting and completing an analysis is invariably iterative (follow-up for more data, reanalysis, etc.). There are also implications with regard to "labeling;" product information (labeling, data sheet, etc.) should be changed at the earliest opportunity when appropriate.

Generally, important information on safety will inevitably be inferred from the aggregate results of such studies; attribution on individual cases would ordinarily be impossible. On the other hand, it must be recognized that isolated, important cases, either those related to the event(s) under study, or to some other event, may be described with convincing evidence and opinion of causality; these must still be dealt with in order to satisfy expedited regulatory reporting obligations.

The CIOMS V Working Group believes that the same reporting rules which apply to clinical trials should generally also apply to structured epidemiologic studies that typically use secondary data bases:

- ❑ *summary reports of the findings of such safety studies included in a PSUR*

- *a prompt notification*[30] *to regulators of a study result showing an important increase in the rate of a serious suspected ADR relative to an 'expected' rate in an appropriate comparison group(s)*

- *expedited reports for individual cases which are specifically attributed to the drug by the reporter, the investigator, or the sponsor in accord with local requirements*

However, as already pointed out, observational studies differ from ordinary prospective clinical trials in one important, critical way: they examine events which occur in the study population as a whole, without attribution (causality), in order to determine on an aggregate basis whether a signal of a possible drug-attributable problem exists. If it does, then an event would occur with excess frequency in the treated group compared to one or more appropriate 'control' or comparison populations (which can also be historical or population controls). Such studies, especially those that make use of secondary data bases, do not have an investigator in the traditional sense and therefore do not involve direct evaluation of individual event cases as they occur.

The CIOMS V Working Group proposes that for epidemiologic studies, unless there is specific attribution in an individual case (for example, within the medical record), individual case reporting is generally not appropriate.

Pregnancy follow-up studies are an important case in point. Occasionally referred to (incorrectly) as Pregnancy Registries (see Chapter II.h.), such studies assemble data on cohorts of women who have been exposed inadvertently or intentionally to one or more drugs under surveillance, generally just prior to or during the first trimester of pregnancy. The woman is followed throughout her pregnancy and the eventual outcome is documented. The background rate of birth defects expected in the general population is about 3-5% of live births (depending on the specific population, ascertainment methods and definitions). Thus, the finding of a birth defect (always regarded as a serious adverse event) is expected in such a study in 3-5% of a birth cohort.[31] In order to ensure that results of the study are monitored on an ongoing basis,

[30] The expression "prompt notification" is introduced to distinguish this type of submission from the more traditional "expedited report," which refers to one or more individual case reports (e.g., CIOMS 1 forms). A prompt notification refers to a summary result based on aggregate data that represents important information that must be shared with the regulators. It is generally accepted that once it is recognized that a study result demonstrates a new, important finding (e.g, involving a serious event), the usual 15-day reporting time-frame be used.

[31] A pregnancy registry generally is a cohort of women who are known or possibly expected to be pregnant and are followed for both positive and negative outcomes. This is not the same as a congenital abnormality/birth defect registry, which is a repository of established cases of children born with defects/abnormalities.

the analysis plan should include a strategy for regular database updates and interim analyses. The finding of unusual rates or types of birth defects should lead to a prompt (15-day) notification to regulators describing the study and results; individual case reports (e.g., CIOMS 1 forms) are not appropriate. However, only under exceptional circumstances would there be a need for expedited individual case reports *as they occur,* especially if the birth defect (or other adverse finding, such as premature delivery or spontaneous abortion) were already "expected."

The CIOMS V Working Group proposes the following working practices for dealing with clinical safety information from observational studies or data reviewed during the examination and use of existing data bases:

(1) It is important to distinguish between isolated, individual cases that may have to be the subject of expedited reporting, and population-based results and conclusions that are better suited for aggregate reporting.

(2) If relevant, study results should be summarized as part of periodic reporting (PSURs). General guidance is provided in the ICH Guideline on Periodic Safety Update Reports for Marketed Drugs (E2C): all completed studies yielding safety information with potential impact on product information, as well as safety studies specifically planned or in progress, should be discussed. Positive (favorable) as well as negative results should be reported.

(3) Sponsor judgment will be required on whether and how to report more rapidly than through a PSUR any aggregate findings of medical and/or statistical significance for a drug-serious ADR association, especially when in a long-term PSUR reporting cycle (e.g., 5 years). It may be necessary to alert the regulators before a final study report has been prepared if there is a suspicion that an important signal has been confirmed; follow-up with more analysis and a final report would be in order.

(4) Cases of isolated serious, unexpected suspected adverse drug reactions, for which positive attribution is either expressed within the data base or judged by the parties reviewing the data base, should be reported on an expedited basis in accord with appropriate local regulations for the marketed or investigational status of the drug.[32] This pertains to cases reviewed as part of a specific, protocol-driven study as well as to those uncovered during any exploratory data mining or learning exercise. The reporting "clock" should start, as usual, with the first recognition of a valid case.

[32] Although there are some country or regional requirements for expedited reporting of expected as well as unexpected serious ADRs (e.g., spontaneous cases within the EU), especially in this context the CIOMS Working Group recommends the broader international standard of reporting only unexpected serious ADRs.

(5) *When retrospective databases are used only for technical/learning purposes and do not involve an a priori hypothesis or study protocol, such training/educational use should be documented. However, any clear signals arising from such use may also constitute reportable findings.*

(6) *For manufacturers, it is recommended that expedited reports only involve their own drugs; any relevant comparative data with other drugs should be forwarded to the other manufacturer(s) for their regulatory reporting as appropriate. The aggregate data summarizing all drugs would, of course, also be part of a summary report.*[33]

h. Disease-Specific Registries and Regulatory ADR Databases

The term "registry" as applied to pharmacovigilance and pharmacoepidemiology is often used with different meanings and applications. It is often misused when referring to observational study efforts that happen to use data from registries; in other words a registry per se is not a study. It is an organized collection of data on humans within a particular disease group or other special group (e.g., cancer, pregnancy, birth-defect, organ transplant, and serious skin disease registries). In that sense, a registry will have the following qualities:

- ❏ systematic collection of defined events and/or exposures
- ❏ defined population in one or more specific geographic area
- ❏ defined period of time

The CIOMS V Working Group recommends that the term "registry" be reserved for inventories of case information collected without an *a priori* research hypothesis, but held in reserve for future possible study and analysis.

Such registries are managed on an ongoing basis by public and private organizations throughout the world. They may also be created on an *ad hoc* basis; for example, for certain newly introduced medicines or vaccines, pharmaceutical companies may establish registries to collect and hold patient data (also referred to as a patient cohort) for possible future follow-up and analysis in the event a signal arises from another source. These registries actively collect data on drug exposure, but most disease-based and

[33] As usual, all concomitant medicinal and other therapies should be recorded with each case, no matter who assumes responsibility for handling the report.

other registries generally do not. Typical registries include sufficient patient identification to make possible a search of patient medical records, or linkage with other databases containing information on the same patient; with appropriate consent and human subject protections, it also makes possible direct contact with the patient and/or healthcare provider.

Under some circumstances the purpose of a registry may be to collect specified suspected ADR's, such as a serious cutaneous or ocular disease registry. However, for most registries, no such attribution to a drug or other cause is presupposed or considered.

Another common but inappropriate use of the term relates to what are sometimes called "regulatory registries," usually of spontaneous, suspect adverse reaction reports on marketed products. However, these collections of data are more properly called "regulatory ADR databases" or listings.[34] All these types of databases contain reports received by the regulators directly from healthcare providers and others, as well as those submitted by pharmaceutical companies. Ideally, the origin of each case will be indicated (direct to regulator vs from a manufacturer). In some jurisdictions, notably the US and Canada, certain reports by patients themselves are also received by the regulators, and these too will be part of their databases. (See Chapter II.b.)

Although there are important differences between them in their content, availability and use, both registries and regulatory ADR databases share the following issues in common for pharmaceutical manufacturers with regard to safety monitoring and reporting obligations; recommendations by the CIOMS V Working Group are given:

- **active vs. passive monitoring:** except for a company-sponsored patient registry, should manufacturers actively seek out and review the multitude of registries and regulatory ADR databases to determine whether they contain ADR information on their drugs? Under what circumstances are individual suspect ADR cases within such sources reportable (expedited or periodic) and for what types of cases? And when does the reporting clock start?

[34] Examples include the printouts or electronic databases available from the US FDA (www.fda.gov/cder/ and www.fda.gov/cber/index.html), the MCA Adroit system in the UK (www.gtnet.gov.uk/mca/csm/yellow.htm), the SWEDIS system in Sweden (www.pharmasoft.se/index2.html), the WHO's multi-regulatory ADR database in Uppsala, Sweden (www.pharmasoft/se/who), and the periodic publications of some regulatory bodies (e.g., New Zealand , Australia) that summarize the suspected ADR reports (usually spontaneous reports) they have received over a particular time period for specific drugs. The UK, Australian and German authorities routinely send reports that they receive to the manufacturers of the relevant products.

It is recommended that if a company is in possession of data from a registry or a regulatory database, the data should be reviewed promptly for unexpected suspected ADRs, both serious and non-serious. For any required expedited reporting, as usual the clock starts once a valid case is identified. For periodic reporting, as required under ICH E2C (PSURs), only serious (expected and unexpected) suspected ADRs from registries and regulatory databases need be included. Even if no relevant cases are found, it is advisable to mention in the PSUR that the registry(ies)/databases at hand had been examined but with no reportable findings.

It is regarded as impractical and unnecessary to actively collect routinely the many and varied registries and databases for review. On the other hand, when dealing with a signal of importance, attempts should be made to obtain as much information as possible from all sources, including available registries and databases.

Although attempts to seek out and examine the possibly hundreds of registries and regulatory ADR databases from around the world on a routine basis would be virtually impossible, for specific problems or hypotheses (e.g., a known class effect), appropriate sources should be identified and monitored. Since the focus of most disease-based registries relates to disease epidemiology, and they do not necessarily search for signals involving medicines, there does not appear to be a tradition or opportunity for such registries to inform pharmaceutical companies of any potential signals that arise from the data they collect. Nevertheless, those that do detect potential drug-related problems should have an obligation to share the information with the relevant companies as well as the health authorities.

There is a somewhat related and important issue with regard to the sharing of information from regulatory agency ADR databases. Whether companies actively request case information from the regulators or the regulators routinely send their data to companies, the question always arises as to whether such information should be entered into the company's own database; a decision also must be made on which of those cases, if any, should be reported to other regulators. Indeed, some regulators do require at least expedited reports from other regulatory sources; also, the standard PSUR calls for inclusion of all serious cases from regulatory ADR databases. Assuming one can isolate cases that were unique to the regulatory database (i.e., cases only received by the regulator with any duplicate reports eliminated, as discussed below), cross-reporting of these data by companies

to multiple regulators is an inefficient and outdated process. It would not be necessary if all regulators provided their data promptly to the WHO Collaborating Center for International Drug Monitoring (see footnote 34), from which they have ready access to each others' data. The CIOMS Working Group vision has always been that all suspect ADR cases received by regulators and companies would be maintained in a "shared" database environment with appropriate secure access. The opportunity for such a mechanism increases with the introduction of electronic reporting systems under ICH standards. However, until such a system is available, companies will have to use judgment in how to handle such cases. For additional discussion and recommendations, see Chapter VI.

- **case duplication:** particularly with regulatory databases, it is often difficult to ascertain whether they contain cases that represent the same ones already received directly by the manufacturer.

  Appropriate methods should be used to screen any registry or regulatory database case listings for the possibility of duplicate cases, especially for cases relevant to an important situation (e.g., serious ADRs). If unable to rule out possible duplicates, such cases, if and when reported to regulators, should be identified as suspected duplicates.

- **how should suspect ADRs from registries and regulatory databases be classified?** Ordinarily, cases found in regulatory databases will be of spontaneous origin (thus, will have implied causality), although clinical trial cases may also be included; if properly documented, they will be identified accordingly. However, cases from disease or special-interest registries, especially targeted-purpose registries established by manufacturers, are more like "solicited reports;" such reports in other contexts are meant to be treated like study reports, in that they require assignment of drug-attribution either by the "reporter" or through the manufacturer's causality assessment. (See Chapter II.e.) However, sufficient information or opportunity for follow-up are frequently not available to enable such an assessment. (See Chapter III.e. for a discussion on follow-up obligations — by companies and regulators — with respect to registries and regulatory databases.)

  Individual adverse event cases from disease and other special purpose registries, should be treated as solicited reports and managed in the same way as study cases (causality assessment required). In addition to individual cases, if the weight of the evidence from data collected (e.g., through a company-sponsored special registry) suggests an important signal, the aggregate findings should be reported in the same

way as discussed for observational studies, i.e., without multiple, individual case reporting.

- **characterization of the case:** although cases within registries and regulatory databases of all sorts may include a diagnosis or description of signs and symptoms, unless other details such as outcome are also included it can be very difficult to determine whether a case is "serious" in the usual regulatory sense (fatal, life-threatening, etc.). Without sufficient details or follow-up, it may also be difficult to decide whether the suspected ADR is expected or unexpected, an important criterion for a decision on expedited reporting. See Chapter III.a. for further guidance.

i. Licensor-Licensee Interactions

The development and/or marketing of many medicines increasingly take place through contractual agreements between two or more companies, each of which conducts research on or markets the same product, or perhaps the same pharmacologically active entity but in different dosage forms or for different indications. Two or more companies may market the same product in the same or different countries. The arrangements can vary considerably with respect to inter-company communication and regulatory responsibilities. This can be a very complex issue and it is crucial that safety personnel be involved in the development of any agreements from the beginning.[35]

One of the major challenges in such relationships is arranging the process for exchange of important safety (and other) information, especially with regard to timelines and regulatory reporting obligations.[36] Any properly crafted contract between the parties will include details for the timely exchange and management of safety and other data. It may also be important to develop agreements on how changes to product safety information (e.g., labeling) will be handled. For both the companies' and the regulators' sake, the goal should be to avoid duplication and confusion. However, special problems arise with regard to ADR cases that may have to

[35] There are many possible types of contractual arrangements. Among the more common are co-development (joint pre-marketing research and development), co-marketing (each partner company markets the same drug in competition using different trademarks), and co-promotion (partners market the same drug using the same trademark, packaging and labeling). These terms, their definitions, and associated legal requirements may differ between countries. Also, see footnote 37.

[36] For one company's approach, see Fieldstad, L. M., Kurjatkin, O. and Cobert, B. L. A Template for Adverse Event Reporting in Licensing Agreements, *Drug Information Journal,* 30:965-971, 1996.

be submitted on an expedited basis to one or more regulator. Many of the issues may be covered in a contract, but it is worth discussing them for reasons that will become evident.[37]

To illustrate the types of situations that arise, assume the agreement stipulates that one partner (P-1) in a two company arrangement handles all global reporting (expedited and periodic) on behalf of both parties. [This would be appropriate when both partners hold licenses/NDAs in the same countries; it would not if the partners develop or market the product alone in one or more countries, in which case each partner would have to be responsible for its own, exclusive-country requirements.] If P-2 first receives a case report that is suspected to be serious, it must transmit it "immediately" (presumably as defined by contract) to P-1 for processing, decisionmaking and any 7- or 15-day reporting. What if follow-up information is required (before or after an initial submission to regulators)? Who should attempt to obtain it? The CIOMS Working Group recommendation is as follows:

> *The original recipient party (P-2) of a suspect adverse reaction report should be asked to conduct any necessary follow-up. It is in the best position to interact and maintain a relationship with the reporter. However, it is recognized that some contractual relationships call for one company (or a CRO) to manage all aspects of case follow-up, no matter which company first received the report; such arrangements should be honored.*
>
> *Follow-up information sent to regulators should be submitted by the same company that sent the initial report.*

Although P-1 receives case reports "second-hand" from P-2, when a single company is responsible for all reporting, it is reasonable that the usual reporting deadlines (7- or 15-day) be met. Copies of any such reports would be sent to all partners for their information and records, but not for their regulatory reporting. It would also be prudent for P-1 to mention that its submission is on behalf of all relevant license holders/partners, who may have their own marketing license or NDA-file, and therefore reporting obligations.

However, the situation changes when different companies retain local or regional regulatory reporting obligations. Thus, partnering companies may arrange to "divide the regulatory world" for safety reporting responsibilities. It is also possible that each company would report all relevant data independently

[37] A 1997 working party of the Society of Pharmaceutical Medicine has published a report on issues with respect to pharmacogvigilance requirements in the EU arising as a result of commercial licensing arrangements: Monitoring Drug Safety in Commercial Licensing Situations in Europe: A Commentary, *International Journal of Pharmaceutical Medicine,* Volume 12, No. 2, pp. 1255-1270, 1998.

to all appropriate regulators, but this obviously introduces duplicate reporting and possibly confusion, especially for the regulators. Under this new scenario, P-2 receives an ADR report it deems serious and unexpected and a copy is forwarded to P-1; it is submitted as required by P-2 in the local country (and possibly elsewhere depending on the contract). The difficult issue here is whether P-1 can or should meet the 7- or 15-day clock (from the date P-2 first received notice of the ADR) for its reporting obligations.

There are several factors influencing this process: the initial, "raw" report will be sent by P-2 to P-1 within a time period specified by contract, typically within one or two days of receipt; but it will often be incomplete, may be in a different language than P-1's home language, and will invariably differ from the actual report sent by P-2 to its local regulatory body (due to clarifications, with or without follow-up during the period up to actual local submission by P-2). It therefore may be very difficult for P-1 to submit an accurate, meaningful report consistent with the report submitted by P-2, within the currently required 7- or 15-day window from the typical clock-start date, especially for cases requiring 7-day reporting under clinical trial rules. This becomes even more difficult in multiple company licensing or co-marketing arrangements in which company A has a contract with company B, but company B has a separate contract on the same product with company C, such that company C has no contact with A; thus, there may have to be a cascade of communications between and among various partners.

This issue has been considered within the current EU Pharmacovigilance Guidelines which state: "where the MAH [Marketing Authorization Holder] has entered into relationships with a second company..... the clock starts as soon as any personnel of the MAH receives the minimum information; *wherever possible* [emphasis added], the time frame for regulatory reporting should be no longer than 15 days from the first receipt by the second company and explicit procedures and detailed agreements should exist between MAH and the second company to facilitate achievement of this objective." The same Guidelines call for the establishment of "practical arrangements" for co-marketing relationships.

It is unclear whether US FDA regulations allow such flexibility. Under 21 CFR 314.80 (C)(1)(i): "The applicant shall report each adverse experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant." However, in a separate guidance issued in March 1992, reference was made to the applicant [i.e., NDA holder] and to

"affiliates;" the meaning of affiliates is not defined but can be interpreted as local country offices/divisions within the same company or to contractual partners, or both.

Under the scenario described, the case will have been reported to at least one regulatory authority within the usual strict time limits; however, in trying to meet the same time limits possibly in several other countries, P-1 as the second (or further removed) recipient may be put in the position of submitting an inaccurate or incomplete report.

In view of these and similar circumstances, the CIOMS Working Group recommends the following:

> *The EU formulation should be accepted by all regulators, namely, partner companies that are the secondary or tertiary recipients of reports should make all reasonable efforts to meet 7-day and 15-day reporting requirements; nevertheless, regulators should also allow reasonable flexibility for companies to fulfill their reporting requirements in unusual situations.*

All companies entering license agreements should take on the responsibility for ensuring that all reporting time-lines are met.[38]

> *All arrangements should be specified by contract and SOP in order to hold the relevant parties accountable, in accord with local legal and regulatory requirements for applicable pre- and post-marketing situations.*
>
> *In order to avoid duplication and potential confusion, only one company should submit safety reports to regulators in each country where there are product contractual arrangements among two or more companies. When the responsibility for reporting is so delegated, it is advisable to inform regulators about relevant license agreements.*

It must be remembered that delegation of reporting responsibility does not relieve each Marketing Authorization Holder from its legal responsibility, which makes it especially important to ensure that all contracts are appropriately drawn.

[38] It should be noted that there may be different regulatory definitions of clock start-dates for expedited reporting in different countries.

III

Good Case Management Practices

a. Introduction: Clinical Evaluation of Cases

Many steps are involved in the processing of individual adverse event/suspected adverse reaction report cases, all requiring varying degrees of technical skill and judgment to ensure that the information is properly documented, assessed, understood, and placed in proper perspective relative to an already established benefit-risk profile for the product. Decisions on expedited and periodic safety reporting to regulatory authorities, and on whether changes or additions should be considered for product information (e.g., Investigator's Brochure or marketed product data sheet), are also highly dependent on the application of rational and consistent processes. The introduction in recent years of some new concepts and rules in drug surveillance and reporting (e.g., through ICH) has complicated the characterization and handling of case reports. That, and the generally incomplete guidance on defining some of the key factors (such as serious vs non-serious, expected vs. unexpected) that describe a case report, led to the development of the present proposals by the Working Group.

This Chapter addresses five topics of considerable importance: validity of a case report in terms of an "identifiable" patient and reporter; determination of "seriousness," including discussion of how to define disability and incapacity; determination of "expectedness" relative to appropriate reference safety information; a rational approach to seeking follow-up information; and the proper use and style of case narratives.

Underlying all the steps in the process to describe and manage a case adequately, however, is another topic that has received little if any attention: the proper clinical evaluation of the information provided by the reporter. Has a diagnosis been assigned? Are the reported signs and symptoms consistent with the diagnosis? Is the medical information sufficient for an adequate classification of the case and for an adequate causality assessment?

Whatever the source of a safety case report, the recipient, whether a company or a regulator, must evaluate the medical information provided by the reporter. A clinical evaluation should be an integrated process aimed at: identification of a diagnosis; ascertainment that the relevant diagnostic procedures have been performed; consideration of alternative causes of the event(s); and, generally, a causality assessment for the suspected drug(s). This process is dependent on reference to standard medical guidelines or textbooks and should be conducted by a qualified healthcare professional.

Not all reports necessitate such detailed, in-depth attention but it is justified for all serious (expected or unexpected) cases and non-serious

unexpected cases, in view of their importance for regulatory reporting and labeling. As established in the ICH guideline on expedited reporting and in some regulatory definitions, "medically important" has been added to the criteria for serious. Medical judgement must be exercised for correct case categorization and early signal detection. Also, the ICH Guideline on Periodic Safety Update Reports suggests that important or unusual unlisted ("unlabeled") cases, especially serious reports, be discussed individually as to their nature, medical significance, mechanism, reporting frequency, etc.; thus, careful clinical evaluation of such cases is important. Unfortunately, particularly with reporting sources outside clinical trials, there often remains considerable uncertainty with regard to the serious/non-serious, expected/unexpected nature of a case, factors critical to decisions on expedited reporting. Especially in the absence of follow-up information, considerable judgment is required. Some companies and regulators make use of a list of medical diagnoses/conditions that are always regarded as "serious." (See Chapter III.c.) As usual, one should err on the side of reporting in the face of uncertainty.

Some examples will illustrate the problems that arise with cases that have not been adequately investigated or are not well documented by the reporters:

- ❏ it is not unusual to receive a report mentioning jaundice; even if total bilirubin is provided, without at least minimum information on liver function tests and blood count it will not be possible to distinguish between cholestatic liver injury and hemolysis.

- ❏ a case reported simply as pseudomembranous colitis without further clinical detail may not provide information on the results of a colonoscopy or on attempts to detect the toxin secreted by *clostridium difficile;* until the case is discussed with the reporter for the confirming evidence, it cannot be considered fully documented.

- ❏ a case of purpura might be reported with a full description of the skin lesion but without results on platelet count; it will not be possible to classify the case correctly: is it due to thrombocytopenia or to vasculitis? The clinical consequences and prognosis of these two diseases are quite different.

A collection of signs and symptoms cannot always be converted into a known diagnosis or syndrome, of course; in such cases, enumeration of the reported terms and results of any special examinations will have to suffice.

In view of the importance of this issue, the CIOMS Working Group offers the following points to consider and recommendations for carrying out proper clinical evaluation of individual case reports:

- in the absence of sufficient information and lack of evidence that the reporter has evaluated and interpreted the case thoroughly and accurately, follow-up is especially important (see Chapter III.e.).

- when the clinical pattern and/or results of diagnostic procedures do not fit the reporter's assigned diagnosis in the opinion of the company or the regulatory recipient, they can propose to the reporter alternative term(s) which might best describe the medical condition. As appropriate, these terms could be recorded in addition to those initially presented by the reporter, in order to facilitate case retrieval and ensure consistency and uniformity in the database. It must be clear, however, that the reporter's original term(s) must be retained and coded. If differences of opinion prevail, they can be expressed and identified as such within the case narrative (see Chapter III.f.). If the original reporter has changed his/her opinion and is prepared to document it in writing, only then should the database be amended.

- ADR terms should be used consistently and in accord with recommended standards for diagnosis to ensure the recommended diagnostic criteria are satisfied[1] and the appropriate data elements for the medical details of the case are considered.[2] The terminology used should reflect careful evaluation by the manufacturer or regulator and not merely be vebatim quotation from the report received.

- When a case is reported by a consumer, any information from a healthcare professional should be added but the original consumer-reporter's description should be retained.

Because many spontaneous reports suffer from poor documentation, several benefits are envisioned by adopting good clinical evaluation practices: data quality will be enhanced through dialogue with the reporter

---

[1] Venulet, J. and Bankowski, Z. Harmonizing Adverse Drug Reaction Terminology, *Drug Safety*, 19(3): 165-172 (1998) and *Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for their Use,* Edited by Z. Bankowski *et al.,* Council of International Organizations of Medical Sciences (CIOMS), Geneva, 1999.

[2] *Adverse Drug Reactions — A Practical Guide to Diagnosis and Management*. Edited by C. Benichou. John Wiley and Sons Ltd., Chichester, England, 1994.

(or, if a different person, with the healthcare professional who has examined the patient); diagnosis will be based on a clear description of the events and supported by appropriate procedures; coding of ADR terms will be medically rational, facilitating data base searches and signal detection.

Although drug causality is assumed in spontaneous reports, one would like to have sufficient documentation for validation of the reporter's presumed attributability, especially for serious cases. Searching for drug and non-drug causes of an event will benefit from an exchange of information with the reporter. When many drugs are involved in the same case, differences in the time to onset and previous knowledge of the drugs could help to differentiate or to rank the drugs according to their likelihood of causation. It might also be necessary to consult an outside expert in the system organ class involved who may produce a specific report, as needed.

There is a particular example of a situation that has not previously been addressed that exemplifies the need for careful case evaluation — the distinction between suspected adverse drug reactions and "incidental events." The principle purpose of a spontaneous reporting system is to generate signals that may lead to the identification of previously unrecognized, suspected adverse drug reactions (ADRs), especially those that have serious outcomes. These systems were not designed for, nor are they intended to be, complete collections of every adverse event that occurs to every person taking every drug. In order for such a system to be most useful for its intended purpose, those events that are reported should be defined in a way that allows maximization of the signal-to-noise ratio and a focus on truly important information.

In ICH guideline (E2C) on periodic post-marketing safety reporting, a spontaneous report of a suspected adverse drug reaction is defined as "any unsolicited communication to a company, regulatory authority, or other organization that describes an adverse drug reaction in a patient given one or more medicinal products and which does not derive from a study or any organized data collection scheme." Reports that fulfill this definition emanate from many different sources (see Chapter II).

A basic principle upon which spontaneous reporting systems have been built and analyzed over the past decades is the assumption of at least a "possible" causal relationship between the event(s) reported and one or more specified drug products (i.e., it is a suspected ADR). In other words, the voluntary nature of the initial communication reflects an index of suspicion on the part of the reporter regarding the role of one or more products. Follow-up information may indeed rule out the role of a medicinal product in an

adverse event; however, it is understood that all initial reports will at least be entered into the database of the recipient (company or regulator).

One of the more difficult, common problems drug safety personnel encounter with spontaneous reports is in trying to differentiate "adverse events" from "suspected adverse drug reactions." By definition, a suspected ADR implies at least some level of suspicion of causation between a noted event and the use of one or more drug products. An AE, on the other hand, only refers to an unwanted event that has occurred without regard to attribution (to any cause). An ADR is always an adverse event but an AE is not always an ADR. Because of the confusion this distinction sometimes engenders, it has not been uncommon for some companies to report to regulators post-marketing "adverse events" rather than ADRs and even to list "adverse events" in their product information — although there may be little, if any, biological plausibility of a causal relationship. While some regard this practice as "ensuring complete compliance with reporting requirements," it has quite the opposite effect, because it makes it inherently more difficult for those working within the spontaneous reporting system to use it most effectively on behalf of public health. Rather than fulfilling or enhancing reporting regulations, such practices actually undermine the post-marketing surveillance system.

The following fictitious examples are provided for illustration:

Example 1: A physician contacts a pharmaceutical company to inquire as to whether or not Drug X can cause anosmia. During the discussion, the doctor volunteers that he has a patient who has been on Drug X for several years for the treatment of hypertension and who recently developed anosmia. Anosmia is already listed as a possible ADR to Drug X in the product information sheet. It is clear from the conversation with the reporting physician that the patient has not had a serious outcome because of the anosmia. In accord with the company's standard procedures, a letter with a reporting form is sent to the reporting physician, asking for further information. In the information returned from the physician, the "medical history" includes reference to a hospitalization because of a myocardial infarction that occurred about one year after starting Drug X. There is no indication that the reporting physician suspects a possible causal relationship between Drug X and the myocardial infarction. The company safety reviewer has no reason to suspect a possible causal relationship; there have been no previous reports of such an association. Clearly a myocardial infarction is an adverse event with

a serious outcome (hospitalization/life-threatening) and, were it suspected to be possibly related to the drug, it would be "unexpected." But does this situation meet the definition of a suspected ADR? Is this report subject to expedited (i.e., 15-day) reporting to regulators?

Example 2: A physician contacts a pharmaceutical company to report a gastrointestinal bleed that is believed by the reporter to be causally related to Drug Y. The patient who suffered the gastrointestinal bleed required hospitalization for its treatment. On follow-up, the company obtained a copy of the medical record for the hospitalization. Gastrointestinal bleeding is already listed as a possible ADR to Drug Y in the product information sheet. In reviewing the medical record, a company safety reviewer notes the results of an abdominal radiological examination. The radiologist notes in the report the presence of renal calculi. A consultant urologist had suggested further testing, prolonging the hospitalization. There is no indication that the reporting physician or any other physician caring for this patient suspects the possibility of a causal relationship between the renal calculi and Drug Y. The company reviewer also has no reason to suspect a possible causal relationship between the renal calculi and Drug Y. Nephrolithiasis is not listed as a possible ADR in Drug Y's product information sheet. Clearly, the development of renal calculi is an adverse event which, in this case, resulted in a serious outcome (prolongation of hospitalization). Were this adverse event suspected to be possibly related to the use of Drug Y, it would be considered "unexpected." But does this situation meet the definition of a suspected ADR? Is this report subject to expedited (i.e., 15-day) reporting to regulators?

Arguably, the myocardial infarction and the renal calculi in the examples should be considered "incidental" events, as they are not the adverse events that were the subject of the original contacts with the company by the physicians. In other words, it was not those events that raised the suspicion of a possible causal relationship with the drug and prompted the physicians to contact the company. Expedited reporting of serious, unexpected adverse but incidental *events* does nothing to enhance the ability to detect new and important safety signals. Rather, reporting such events most likely detracts from the efficiency of a spontaneous reporting system to generate important signals by adding to the already significant background "noise" in these systems. Therefore, the CIOMS V Working Group proposes the following definition to help eliminate the reporting of truly incidental adverse events as spontaneous suspected ADRs:

*An **incidental** event, adverse or otherwise, is one that satisfies the following criteria: although it occurs in reasonable clinical temporal association with the use of a drug product, it is not the intended subject of a spontaneous report (i.e., it did not prompt the contact with the pharmaceutical company or the regulator) and there is no implicit or explicit expression of possible drug causality by the reporter, other parties cited in the medical record, or the company's safety review staff.*[3]

In practice, the qualified personnel and review process for deciding whether events in the medical record qualify as incidental events should be consistent within an organization. Incidental events should not ordinarily be the subject of expedited or periodic safety reporting. They should be captured as medical history or concurrent conditions, and therefore retrievable at a later date if necessary, but should not be described as suspected ADRs on which reporting decisions are based. Given sufficient information on the case, there may be good reasons to regard incidental findings as possible ADRs, but medical judgment should be exercised in making the decision.

There is always the possibility for a change in perspective on a possible causal relationship between an incidental event and a drug product; retrievable information from a database, as well as source documents, may then have to be accessed.

The important conclusion for manufacturers and regulators is that the receipt and processing of adverse event reports should not be a passive activity but must be part of a systematic process that for appropriate cases might involve an open exchange of medical information with the reporter. Such dialogue, based on scientific grounds, can serve as a mechanism for improving case documentation and ideally lead to the collection of information on a possible mechanism for the reaction, as well as prognostic or risk factors that suggest new lines of inquiry through, e.g., animal research, clinical trials or epidemiological studies.[4]

---

[3] When assessing incidental events (or any adverse events), it is inappropriate to assume that just because a patient took a drug at some time prior to the appearance of an adverse event there is a "temporal relationship," and therefore an automatic suspicion of causality. Such a strict interpretation fails to consider whether there is a reasonable, medically sound time-relation, taking into account the clinical course of the signs, symptoms or diagnosis and therefore sufficient plausibility to make an association to a drug.

[4] Case reviewers should also remain alert to the possibility that a suspected ADR was caused by inappropriate or mis-prescribing of a drug (see the Introduction to Chapter III.e. for more discussion on this point).

b. Assessing Patient and Reporter Identifiability

Introduction

The need for accurate, complete and *bona fide* information is critical for pharmaceutical companies and regulatory agencies to identify and assess ADR reports. Companies and some regulatory agencies are faced with the task of acquiring sufficient information to help ensure that the reports are authentic, accurate, as complete as needed, and non-duplicative.

Minimum criteria for a valid ADR case have been established by ICH and individual regulatory agencies:

an identifiable reporter
an identifiable patient
a reaction/event
a suspected medicinal product

Unfortunately, there are no clear definitions or guidelines on what is meant by "identifiable" patients or reporters. Such information is important not only to provide at least some assurance that the case can be regarded as valid (real people), but to assist a company or regulatory agency to ensure that the case does not represent duplicate reporting on the same patient from the same or other sources. It is also important should there be a need to contact the reporter or patient for routine follow-up or for special medical reasons appertaining to the circumstances of the case.

The goal of this chapter is to provide guidance on what constitutes an "identifiable reporter" and an "identifiable patient" in the context of any adverse experience case. It must be made clear that "identifiable" as used here does not refer to issues of personal data privacy and confidentiality but to the existence of a real person (can one reasonably verify or validate that the patient and reporter exist); for more discussion on this point, see Chapter I.b.

A case meeting minimal criteria is considered sufficient to inform a company or a regulator to the possibility that an adverse reaction to a drug has occurred. However, that does not necessarily mean the information is sufficient for assessing the case adequately or for adding insight to the safety profile of a product. Clearly, whenever possible and appropriate, follow-up details should be sought (see Chapter III.e.). Nevertheless, regulators consider that cases meeting minimal criteria do qualify for expedited and/or periodic reporting and might be sufficient to form the basis for changes to product information.

Some companies treat reports without all four minimum case criteria as ''incomplete cases'' that are tracked in a database; follow-up efforts attempt to obtain further information to confirm the existence of a valid case. When follow-up attempts yield no information (and the minimum case criteria remain unfulfilled), they need not be reported but should be kept in the database as ''incomplete cases.''

The Concept of an Identifiable Reporter

It is generally assumed that a reporter is a person who describes a suspected ADR to a pharmaceutical company (usually a marketing authorization holder), to a health care system (government agency), or to an institution authorized to handle ADR information for pharmacovigilance purposes. Ideally, the reporter will have the most knowledge about the patient, has observed or diagnosed the suspected adverse reaction and has access to the medical details. In most instances, this is likely to be a health professional involved in the care of the patient. However, the consumer/patient or other non-healthcare professional may also be a reporter of such case information, sometimes with access to medical details, although he/she may not necessarily be able to make a medical judgment about the information. In addition, companies receive reports from health professionals who may have no direct healthcare responsibility for the patient and have no direct knowledge of medical details.

A clarification and further specification of the reporter is thus needed. ICH Guideline E2B refers to the ''primary source'' of a report as the person who provides the facts of the case (E2B section A.2); for a publication, this would be the investigator or first author. However, any party that provides useful information on a case should be considered a ''reporter.'' Given the passive nature of the spontaneous reporting system with its considerable underreporting, no source of information should be ignored or discouraged.

By way of illustration, it is useful to delineate the various possible participants in a reporting chain. The first contact to the company or regulatory agency with a report of a suspected adverse reaction may be a health professional or a consumer/patient, with or without direct knowledge about the medical details of the case. Unless this first notifier is the treating healthcare professional, he/she may only be able to provide minimal case details but also details on how to contact a more knowledgeable person.

All parties supplying case information (or approached for case information) are subject to the notion of identifiability. Thus, there may be an initial identifiable reporter (the initial contact for the case) as well as

other reporters (e.g., the main source of medical information on the case or other, secondary sources who provide relevant information).

Recently the EU (Appendix 1 in Notice to Marketing Authorization Holders Pharmacovigilance Guidelines, January 2000) has defined an identifiable reporter to be a healthcare professional who can be identified by either name, initials, address or qualification (e.g., physician, dentist, pharmacist, nurse). Cases reported by consumers/lay persons are not considered to be valid cases unless confirmed or verified by a health professional (see Chapter II.b.). In the EU the health professional who medically confirms the report is considered to be the primary reporter, while the consumer/lay person would be the initial notifier. However, at least the US FDA and the Canadian authorities consider consumers/lay persons to qualify as primary reporters as well; although medical confirmation is desirable, it is not a pre-requisite for reporting in those countries. Thus, under FDA regulations, the reporting time-clock starts with the first contact by the initial notifier (a patient, e.g.) while in the EU the reporting time-clock begins at the first contact with the primary reporter (healthcare professional).

The Concept of an Identifiable Patient

With respect to adverse event reporting, some level of patient identifiability is necessary in order (1) to be certain that the same patient is not the subject of duplicate reports or is recorded in multiple files, (2) to help establish authenticity of a case report in order to avoid scientific errors or fraud, and (3) to allow follow-up communication with the health professional or patient if more evidence of confirmation is warranted, or out of medical treatment necessity.

From a scientific point of view, it is desirable ideally to have reports based on verifiable data, i.e., by contact with a primary care physician. However, criteria for patient identifiability as a pre-requisite for entry into a pharmacovigilance database should not be too demanding, since a high threshold might exclude ADR reports of medical importance. Thus, judgment for accepting a case should always be based on the credibility of the source and nature of the purported event.

To protect patient privacy and to ensure that potential reporters do not neglect reporting because of insufficient identifiability of a patient, the identification threshold for ADR reporting in the European Union and the US is set at a low level. In the January 2000 EU Notice to Marketing Authorization Holders — Pharmacovigilance Guideline, Annex 1, the threshold is stated as: ''The patient can be identified by initials or patient

number, or date of birth (or age information if date of birth is not available) or sex. The information should be as complete as possible.'' In the FDA ''Guidance for Industry, Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report'' (August 1997), the following examples appear: ''With regard to *an identifiable patient,* reports of the type 'some patients got anaphylaxis' should be excluded until further information about the patients is obtained; a report stating that 'an elderly woman had anaphylaxis' or 'a young man experienced anaphylaxis' should be included because there is enough information to suspect that specific patients were involved. Patients should not be identified by name or address; instead the applicant, manufacturer, and licensed manufacturer should assign a code (e.g., patient initials) to each report.''

There are other considerations to keep in mind when trying to develop appropriate criteria for ''identifiable'' patients, as well as ''identifiable'' reporters. It is generally assumed that the majority of reporters convey potentially helpful information to assist a company or regulator to improve its understanding of a drug's safety profile. On rare occasions, however, company employees or other parties, in trying to damage the reputation of a competitor product, have been known to report fictitious cases to companies under a false name so that the recipient company would submit them to regulatory agencies. This practice may be facilitated with use of the Internet (see Chapter II.d.). Other potentially fraudulent activities have been identified when lawyers and/or media personnel have contacted a company on the pretext of reporting an ''unexpected'' ADR, with the intention of determining such things as the number of cases in a company's data base.

Steps are also needed to ensure that companies do not fail to collect sufficient identification information initially or on follow-up, leading to a rationale not to report ADR information to regulatory agencies. For this reason, many companies use quality assurance inspections on safety data using electronic or in-person audits to enhance data collection and follow-up. Additionally, some regulatory agencies (notably the US FDA) audit the safety functions of companies for the same reason. The importance must be emphasized of ensuring that the many potential portals of entry for safety information into a company be staffed by adequately trained personnel with appropriate dedication to pharmacovigilance.

Illustrative Examples for Guidance

Many sample cases have been compiled by the CIOMS V Working Group based on the collective experience of both pharmaceutical company

and regulatory agency pharmacovigilance personnel. They illustrate general principles for determining identifiability, but also show that judgment is needed when less than adequate information is provided. In many instances, but not all, follow-up will clarify the case sufficiently. However, when given *only* the information in the examples, the key question is whether the case satisfies the minimum criteria for a valid case report. There are no international standards in this area, and few specific regulatory guidelines. If there are doubts with regard to criteria for individual cases, as usual the default decision should be to report them.

(1) Dr. Isabella Queen reports that her patient, a 34 year old white male (initials A.V.) experienced hair loss after taking drug X. Dr. Queen's address and phone number are available.

This is a clear-cut case of an identifiable reporter and an identifiable patient.

(2) Dr. Isabella Queen reports her patient, a male, was reported to have experienced hair loss after taking drug X. Dr. Queen's phone number is available.

This is another example of an identifiable reporter and patient with somewhat less, but nevertheless sufficient, patient-identifiable information.

(3) Dr. Feelgood reports that 2 patients were reported to have given birth, to a premature female infant in one case and a premature male infant in another, while on drug X. Dr.'s phone number and address are available.

This is an example of an identifiable reporter. The patients would be presumed to be female and therefore be considered identifiable.

(4) Dr. Bones reports via e-mail that her patient (initials X.X.) developed a melanoma after taking drug Z. While the physician's e-mail address is available, attempts to reach her yielded no response. Address and phone number are not available.

This is an example where both physician and patient would be considered identifiable, but unfortunately the lack of information diminishes the usefulness of the case.

(5) Dr. Bones reports via e-mail that her patient developed a melanoma after taking drug X. Dr. Bone's address and phone number are not available, but she does respond by e-mail.

This is an example in which the primary reporter is identifiable, and there is sufficient information to believe that there is a real patient, even given the paucity of information.[5]

(6) An employee of a drug company is at a barbecue at the house of pediatrician, Dr. Wiener, his neighbor. He hears from Dr. Wiener about his patient who developed hepatitis three weeks after one injection of the company's drug X. The employee sends a memo to the drug safety department with the clinical details he remembered on the patient and also includes Dr.Wiener's address and phone number.

The neighbor (Dr. Wiener) is the initial reporter of the information and would be considered an identifiable reporter. It is apparent from the clinical details that the patient is real, although age or sex or initials have not been specifically mentioned.

(7) Dr. Lindbergh on a commercial airplane flight from Paris to New York is seated next to an employee from a drug company. Dr. Lindbergh talks about his patient who experienced severe depression after taking the company's drug A (an oral contraceptive). The company employee, a marketing manager, reports the case to his drug safety department and provides the physician's business card.

The initial reporter is a health professional and would be considered to be identifiable. The patient would be considered to be identifiable.[5]

(8) The safety department of pharmaceutical company A sends to company B a report it received of a 23 year old female who developed Stevens Johnson Syndrome after taking drug A (a company A product) and drug B (a company B product). On follow-up with the reporting physician, Company A is told that their drug is not considered as a suspect causal agent. Company A sends the contact information on the identifiable physician to company B.

The company A employee would be considered to be the initial reporter to company B. Company B would contact the prescriber to verify the case and to obtain case details relevant to Drug B, unless there was a formal data exchange agreement between the two companies, e.g., as part of a co-marketing agreement. In the latter instance, follow-up might be done by company A on behalf of company B.

[5] This case would not currently be acceptable in the EU, given its requirement that some sort of patient descriptor be available (one or more of age, sex, initials, etc.).

(9) Professor Messer presents a paper at a medical convention (either orally or as a poster presentation) on a patient that developed thyroiditis after long-term therapy with Drug X. The paper is seen (or heard) by a company employee who reports it to the drug safety department.

This is another example of an identifiable reporter (the speaker) who would need to be contacted to obtain additional clinical data. If specific patient details were made available during the course of the talk or in the poster presentation, the patient would be considered to be identifiable also. In the absence of a given patient age, sex or initials, the mere fact that Professor A presented this case in a paper would suggest that an identifiable patient exists.

(10) The International Herald Tribune publishes an article describing a 5 year old patient who died after Drug Y ingestion. There is no physician mentioned and no author is listed for the article. The editor of the IHT (or, for example, a reader of the paper) forwards the article to the company.

While no by-line is available for this report, the editor can be considered to be the initial reporter of the case. This would be a valid case even though it is not medically confirmed; clearly, follow-up should be initiated, however. Similar considerations apply for potential cases recognized through other media, such as radio and TV.

(11) A company employee reads in a newspaper that several patients at Massachusetts General Hospital have given birth prematurely while taking drug X.

The initial reporter is not considered immediately identifiable without a by-line or other identifiers (see example (10)). Additionally, while the patients are presumably female, details as to the number of patients have not been given; therefore, these patients would be considered indistinguishable and thus not identifiable. Additional follow-up would be prudent with the newspaper or the hospital in order to ascertain whether there were a valid case or cases.

(12) Pharmacist Gene Type reports that a neighbor told him that a female taking drug Z had dyspepsia at that neighbor's house last week. Only the pharmacist's address and phone number are available. Further information is not forthcoming despite rigorous follow-up.

The initial reporter is a health professional (pharmacist) who was not involved in the care of the patient. The information is based on second-hand or hearsay information. Unless the pharmacist provides the means of

contact to either the patient's healthcare provider, the neighbor, or the patient herself, a reporter can be considered to be unidentifiable and the report unconfirmed.

(13) Dr. NoRed Cell reports that 6 patients developed aplastic anemia while on drug X. Dr.'s address and phone number are not available, but his/her e-mail address is given.

This is an example of an identifiable reporter and presumably 6 identifiable patients.

It is recommended that multiple patients should be treated individually in a database and for the purposes of regulatory reporting when there are details on each case. However, judgment about the credibility of a notification should be exercised in cases of multiple patients. For example, if this reporter were a hematologist, 6 cases of aplastic anemia would not be unrealistic. On the other hand, if the physician were a general practitioner, one might question the accuracy of the number of cases. Rigorous follow-up would be needed to verify the reports and to obtain further information in either instance. A company might consider entering the report into its safety database as one case until further details on the individual patients were obtained. This would enable the case to be tracked and reported, but would not give undue weight to cases for which only minimal detail is available. Although the information provided does not qualify for reports on 6 individual cases, it is cause for a prompt notification letter (15-day)[6] to the regulators in view of the seriousness and importance of the event (even if aplastic anemia is labeled, due to the unusual number of cases). If and when further follow-up yields individual data on the 6 patients, 6 individual case records should be created with appropriate cross-referencing among them.

(14) Dr. Onko Gene communicates to a company that 50 patients developed ovarian cancer while on drug X. The Dr.'s address, phone number and e-mail address are available, but attempts to reach her by the usual means are unsuccessful.

While the reporter would be considered identifiable, the number of female patients stretches the limits of credibility. Rigorous efforts should be

[6] The expression "prompt notification" is introduced to distinguish this type of submission from the more traditional "expedited report," which refers to one or more individual case reports (e.g., CIOMS 1 forms). A prompt notification refers to a summary result based on aggregate data that represents important information that must be shared with the regulators. Once a new, important finding is recognized (e.g, involving a serious event), the usual 15-day reporting time-frame should be used.

expended to follow these potential cases up by phone, mail and/or site visit by the company. One company with a similar experience even enlisted the help of the local regulatory agency to "encourage" the physician to report. As in the aplastic anemia example presented above (13), the company could store the report as one "case", clearly indicating the number of potential patients in a notification letter to the regulators until such time as individual patient data are obtained.

General Recommendations

There probably can never be absolute rules regarding patient or reporter identifiability. Individual judgment will be needed at times to decide whether or not a patient or a reporter should be considered identifiable for purposes of considering a suspect ADR case as valid. It must be emphasized that follow-up efforts should be made to establish patient and reporter identifiability in cases where this is not clear. As part of all follow-up procedures, a record of attempts to determine patient identifiability or reporter identifiability should be kept available for internal audit and regulatory agency review. Furthermore, the amount of effort exerted should be commensurate with the nature of the adverse event reported (see Chapter III.e.).

The following proposals are made by the CIOMS V Working Group in an attempt to provide some guidance to manufacturers and regulators who receive data on adverse events/reactions.

- *Availability of data on one or more of the following automatically qualify a patient as identifiable: age (or age category), sex, initials, date of birth, name, or patient number.*
- *Even in the absence of such qualifying descriptors, a report referring to a definite number of patients should be regarded as legitimate as long as the other criteria for a valid case are met. For example, "Two patients experienced...." but* ***not*** *"A few patients experienced...." would constitute "identifiable" patients for reporting purposes prior to any follow-up. On the other hand, the information falls short of individual (two separate) cases for reporting but would still warrant a prompt notification letter to meet 15-day reporting requirements.*[7]
- *Whenever possible, each patient included in a multiple patient report should be identified by at least one of the usual data elements (age, sex, etc.). When individual patient information is unavailable, the report*

[7] It is recognized that this minimum criterion standard may not currently be acceptable by some regulators.

can be treated as one "case" in the form of a "notification letter." However, the case narrative or other description must clearly state the potential number of patients involved and indicate that they cannot be individually identified.

- *It is especially important that care be taken to avoid acceptance of reports based on hearsay or rumor ("My neighbor told me that a friend of his heard...."). Clearly judgment for accepting a case must always be based on the credibility of the source and the nature of the purported event. Attempts should be made to obtain more details whenever possible. However, particularly for serious, unexpected suspected reactions, the threshold for reporting in the absence of confirmatory identifiability should be lowered.*

c. Criteria for Seriousness

Introduction

One of the main objectives of ADR monitoring is to avoid any delay in decisions affecting the public health with regard to the use of medicines. However, for products under development as well as for marketed drugs, the typically large volume of clinical safety information precludes the ability to document, validate, evaluate and report all experiences with the same degree of priority. It is necessary to select information which might require urgent decisions, i.e., information regarding events that create a threat for patients' life or function ("seriousness criteria" in this chapter), especially events previously undocumented ("expectedness criteria" are discussed in Chapter III.d.).

To ensure that detection of such events is made as early as possible, regulators and industry collect extensive amounts of case data from all parties involved in drug safety monitoring in all countries where the drug is marketed or under investigation. Criteria defining seriousness in the regulatory sense need harmonization so as to be:

- **sensitive enough** to avoid loss or delay of information regarding medically important events,
- **specific enough** to prevent dilution of important information and inclusion of extraneous information,
- **logical enough** to make the selection reproducible, i.e., understood by all the parties involved even when their medical qualifications are different.

It is also important that terminology be consistent. For example, the terms "serious" and "severe" are not synonymous but are often used interchangeably. To ensure no confusion or misunderstanding of the difference between the terms, the CIOMS Working Group endorses the statements provided in the ICH E2A Guideline on expedited case reporting:[8]

> "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 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."

The most recent internationally agreed seriousness criteria appear in ICH guideline (E2A) which covers products under investigation:

> "A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:
>
> - ❏ results in death,
> - ❏ is life-threatening,
> - ❏ 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 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 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."

[8] Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. ICH Harmonised Tripartite Guideline E2A, in *Proceedings of the Second International Conference on Harmonisation* (Orlando, 1993), Appendix 4, pp. 603-618. P.F.D'Arcy, D.W.G. Harron, Eds., Belfast 1994. See also Gordon, A. J. ICH Guideline E2A Recommendations and Reasoning, *idem,* pp. 380-389.

The phrase "at any dose" was included since the ICH E2A guideline focuses on clinical trials before marketing, when the optimal dose had not been determined. This definition has also been adopted with minor modification for post-marketing use by the Japanese MHLW[9] and by the US FDA. In the EU, for post-marketing situations there are two differences from the ICH definition:

- a reaction is defined as occurring "at doses normally used in man" (and not "at any dose") in Directive 75/319, as amended, as well as in the most recent Pharmacovigilance Guidelines;

- the seriousness criteria include "medical judgement" in the Pharmacovigilance Guidelines of January 2000 but not in the above-mentioned EU Directive, which has been incorporated in all the EU Member States regulations.[10]

The new contribution of the ICH definition beyond previously used criteria is in the last paragraph devoted to "medical judgement." It illustrates the difficulty of including the diversity of situations that might be regarded as medically serious within an administrative definition: for example, the occurrence of severe neutropenia with a count of polymorphonuclear neutrophils below 100/μl is a potentially "serious" abnormality which may or may not be associated with clinical signs or symptoms; this count result may only be made available to the treating physician a few days after blood were drawn, while the patient is in good condition (asymptomatic). If a new count were performed and the results reverted to normal, the patient would not be hospitalized and the case would not fulfill any of the usual seriousness criteria. However, if a drug origin could not be ruled out for this finding, this information might be a signal justifying a prompt and close monitoring of the consequences of this drug on the white blood cell count.

Among the specified criteria, two, death and hospitalization, are considered "hard" and objective, supposedly easy to define.

---

[9] In Japan, the MHW specifies detailed "Severity Grading Criteria" for identifying common adverse events in terms of laboratory and clinical data, as: Grade I (mild), Grade II (moderate) and Grade III ("serious"). Difficulties can arise with this classification which may conflict with ICH definitions. It is possible, for example, that a case categorized as Grade II in Japan would be "serious" elsewhere; conversely, reporting Japanese cases internationally could be delayed. Company guidelines are needed to ensure that suspected serious ADRs, in the ICH-sense, are reported internationally when appropriate.

[10] The CIOMS Working Group advocates for the ICH definition as *the* standard for seriousness without local modifications.

- **Death** in this context is an outcome that does not need definition. The only issue is the role of the drug in a fatality. An AE or ADR may be the direct cause of death, or may have been contributory to the fatal outcome of an underlying condition. On the other hand, a death may be totally incidental to the appearance of a suspected ADR.[11]
- **Hospitalization,** however, requires discussion:
  - ❑ The definition of hospitalization and even of a hospital is different in different countries. It may vary according to the nature of the center, to the unit (e.g., Emergency Room, Casualty Departments) where care is provided, or to the duration of the hospital stay.
  - ❑ Initial hospitalization as a direct result of an ADR is easier to ascertain than the prolongation of hospitalization due to an ADR.
  - ❑ Some hospitalizations are related more to the anxiety of the patient or that of the physician than from the actual medical importance of the event.
  - ❑ In some medical cultures, patients are hospitalized for what might be regarded elsewhere as conditions treatable on an outpatient basis.
  - ❑ In the reverse situation, a patient who should be hospitalized may not be because he/she cannot afford to pay or the hospital is full or inaccessible.

Another seriousness criterion that could benefit from some quantification is **disability/incapacity.** To qualify as serious, it would be useful if one could standardize to what extent of alteration of function or of quality of life, and for what minimal duration (hours, days, weeks?) such an outcome must be. Should a headache lasting 24 hours or partial deafness in one ear be considered as inducing ''persistent or significant disability''? One regulatory authority, the US FDA, uses the following definition: ''a substantial disruption of a person's ability to conduct normal life function.'' However, this still leaves to the evaluator the responsibility for deciding when the disruption becomes substantial, usually taking into account the person's occupation.

[11] An extreme example would be a patient who had experienced a documented ADR but died as a passenger in an airplane accident; while any follow-up on the case would include information about the accident, the death would not be connected to the ADR.

Congenital anomaly/birth defect in principle could also benefit from some classification of degree.

Yet another criterion, **life-threatening,** can leave much room for interpretation. The usual application of the term in association with an adverse event implies an immediate risk of death at the time of the event. However, the reporting healthcare professional or other reporter, as well as the recipient of a case report (a company or regulatory agency), is placed in the position of inferring what could or would have happened if, for example, no treatment had been administered. This evaluation does involve the "medical judgment" invoked by ICH, which is by definition subjective, may not be reproducible, and which usually relies more on potential risks than on observed effects.

Other criteria have been or are still used by some regulators to define serious: cancer; frequently observed misuse; overdose; drug abuse or dependency. Cancer is not mentioned specifically in the ICH E2A guideline definition, since it is but one of many diagnoses that are generally considered medically serious; there is no need to single it out. In most cases, cancer induces hospitalization or disability, and would be classified as serious anyway. Furthermore, ICH E2A focused on clinical trials before registration, whose duration is usually not long enough to observe development of cancers.

Regarding drug abuse and dependency, they are given as examples of important medical events by ICH.

Lack or diminution of expected efficacy could result in event(s) fulfilling one or more of the seriousness criteria, particularly for drugs used in treating serious and/or life-threatening conditions. Such findings should be discussed in periodic reports, as outlined in the ICH E2C (PSUR) guideline.

Is it Necessary or Desirable to Modify the Criteria?

In order to help gauge whether the current criteria serve their purpose adequately, two retrospective unpublished reviews have been conducted by two members of the CIOMS Working Group, one from a regulatory agency (1,950 serious ADRs attributed to marketed drugs) and one from a company (1,319 serious ADRs comprising 723 spontaneous reports and 596 from pre-marketing clinical trials, plus an additional 443 spontaneous reports classified as non-serious).

The objectives of these reviews were to determine the proportion of the different seriousness criteria that were used to categorize the expedited

reports; and in the review from industry, to identify the least reproducible criteria as determined by a second assessment of the same cases performed by a medically qualified industry member of the CIOMS Group.

In both reviews, most cases had been reported after January 1995 and had been classified according to the criteria proposed by ICH E2A.

The results for the first objective are presented in the following table:

	Regulator (N=1,950)	Industry (N=1,762)
Death	19%	20%
Life-threatening	10%	15%
Hospitalization	60%	62%
Disability/Incapacity	3%	2%
Other	8%	1%

- death and hospitalization represented 80% of the reported cases
- life-threatening (15% for industry, 10% for the agency) and other medically important events (1% for industry and 8% for agency) represented together 16% to 18% of cases. Regarding the differences between the two surveys, the case narratives provided an explanation: many cases reported as ''other important medical event'' to the agency could have been reported under the ''hospitalization'' or ''life-threatening'' criterion, because the latter two classifications also fit the cases.

A reproducibility test was undertaken by applying an independent new review of all 1,762 industry cases. Only 2% of the cases originally classified as serious were regarded as non-serious in the new review. The survey did not show any disagreement regarding hospitalization, and in only 2% of cases was there disagreement regarding the role of the adverse reaction in a fatal outcome.

Conversely, regarding the three other criteria (life-threatening, disability, other medical event), in about 10% of cases there was a disagreement regarding the evaluation of the medical significance of the reaction (e.g., angioedema, behavior disturbances, laboratory abnormalities).

In summary, most issues and discrepancies were related to the evaluation of disability, life-threatening condition or medical significance. Therefore, it would appear to be useful to find ways to increase the reproducibility related to decisions on these seriousness criteria.

A different type of survey was conducted among attendees at Drug Information Association meetings on drug safety and with pharmaceutical company physicians in 1993.[12] Details are shown in Appendix 4. Its purpose was to assess some of the potential sources of differences among people in determining "seriousness" as well as "expectedness" and to determine whether guidelines aimed at standardizing such decisions could be considered. In the absence of standardized guidelines, the same case history could be subject to different expedited or periodic reporting behavior, even though based on the same reference data.

Test cases were given to 90 attendees at a DIA Safety Monitoring Workshop held in Europe, 70 who attended an equivalent workshop in the United States, and 22 full-time physician monitors employed in the pharmaceutical industry. For none of the cases was a unanimous view achieved. The following summary sample data illustrate the results:

Would You Consider the Following Reported Events Serious? (N = 176)

	Yes	No
Total blindness for 30 minutes	70%	30%
Suicide threat	17	83
"Mild" anaphylaxis	61	39
Spontaneous abortion	95	5

For some cases, there was a marked difference between European and American respondents; however, the differences could not be ascribed to the commonly perceived "extra" reporting in the US. For example: 89% of Europeans vs 44% of Americans said yes for the blindness case, whereas the figures were 37% and 96%, respectively, for the anaphylaxis case.

Proposals

(1) *The CIOMS Working Group recommends the universal adoption of the ICH E2A definition for both the pre- and post-approval definition of seriousness.*

From a pharmacovigilance perspective, it is irrelevant whether a drug is used "at doses normally used in man" (i.e., within labeling recommendations), the currently used phraseology in some regulations; a drug may

[12] Castle, W. and Phillips G. Standardizing Expectedness and Seriousness for Adverse Experience Case Reporting, *Drug Information Journal,* 30: 73-81, 1996.

inadvertently or purposely be administered at less than or more than the recommended dosing. Thus, in addition to the other changes the ICH definition introduces, an event/reaction occurring at any dose should be reviewed for seriousness.

(2) ***Death*** *as a seriousness criterion is only relevant for reporting purposes if it represents the outcome of a drug-associated ADR.*

A problem with using "death" as a criterion for seriousness could be over-reporting of fatal outcomes unrelated to an adverse reaction. Death should be considered as a seriousness criterion for reporting purposes only if the ADR results in or contributes to the death. In some cases a patient may die coincidentally due to causes unrelated to the ADR which led to the initial report (e.g., underlying illness, surgical procedure, etc.). When a relationship between the death and the drug or ADR can be ruled out, death should not be used as a criterion to define/classify the case. However, for a report of a death without any information as to possible cause, such as an underlying suspect ADR, the death would be reportable as a serious suspect ADR (as well as an outcome) if there is a possible drug-association; such cases are often referred to as "death NOS," (i.e., not otherwise specified or explained, or perhaps as "sudden death").

(3) *It is useful to consider* ***hospitalization*** *as an admission to any hospital, casualty center, emergency room, or health care center as an inpatient as opposed to an examination and/or treatment on an outpatient basis.*

One of the difficulties with this seriousness criterion is that there is no universal definition or understanding of "admission" to a hospital or what constitutes an "in-patient." Being seen in an emergency room or otherwise treated as an out-patient, is not generally considered as hospitalization. Even if the patient is admitted (kept overnight, e.g.), this does not necessarily mean that the event is indeed medically serious or that the admission was medically justified; on the other hand, the consequences of hospitalization to the patient and his/her family make it an important (if not strictly a "serious") event. The focus should always be on the adverse event and its treatment, not necessarily where the patient is treated or if he/she is an "in-patient." As usual, when in doubt, the case should be considered as serious.

(4) *All* ***congenital anomalies and birth defects*** *should be considered as serious.*

It is difficult to predict the near and long term consequences, and any attempt to classify or introduce degrees of severity for such reactions is considered inappropriate.

(5) *It is too difficult to develop a standardized quantification for* ***disability/incapacity****; the decision should be left to "medical judgement" of the reporting physician and/or other relevant reviewers for each case.*

Quantification would be necessary for the proportion and duration of the loss of ability in order to make an evaluation reproducible. However, this criterion was referenced in only 2 to 3% of the cases in the surveys discussed. Any attempts at quantification would undoubtedly be very difficult, given the often subjective nature of the situation.

(6) Because of the lack of objective standards associated with ***life-threatening*** *and* ***medical judgment*** *as criteria, and to avoid unnecessary delay in reporting potentially serious reactions, it is recommended especially for post-marketing reports that a list of terms be considered for use by a company that will always characterize a case as serious if one or more of those terms define the case. Although a standard list of diagnoses/terms would help minimize such discrepancies if consistently applied, the Working Group emphasizes the list should never be considered comprehensive.*

The terms life-threatening and medical judgment both require individual, professional evaluation, which might be very different depending on medical qualification and experience, leading to lack of reproducibility (inter- and intra-individual).

Use of a standard list of terms would be useful but any such list will be expected to evolve because new cases and occasionally medical knowledge will introduce additions or modifications. It is important to emphasize, however, that no list should substitute for medical judgment in the evaluation of each individual case. It is possible that the presence of a list-term may not necessarily render the case "serious" in the regulatory sense; conversely, the absence of a term should not be an automatic default for not reporting on an expedited basis.

One of the most commonly used lists is the WHO Critical Terms.[13] When reviewing this list, there are very few preferred terms which do not correspond to events usually regarded as medically serious (e.g., hyporeflexia, hypokinesia, or dyskinesia other than tardive dyskinesia); however, quantified threshold values for seriousness are not defined even for the most

[13] WHO Adverse Reaction Terminology — Critical Term List, WHO Collaborating Center for International Drug Monitoring, Uppsala, Sweden. The List is updated six-monthly and is available by subscription (www.who-umc.org). It consists of reported medical terms which warrant special attention because of their possible association with serious disease states. (Such a term may not itself be a serious medical condition, but may be a part of, or might lead to, a serious medical condition.)

important laboratory abnormalities (increases in aminotransferases, hypercreatininaemia, hyper- or hypokalaemia, hyper- or hyponatremia, neutrocytopenia, thrombocytopenia, anemia).[14] Since MedDRA is expected to become the most commonly used reference terminology, an example of a list of Preferred Terms contained within the MedDRA coding dictionary, correlated with the same or similar WHO-ART terms, is given in Appendix 5 as a possible starting point.

(7) *Whether or not a standard list is used, in order to improve consistency among all parties, the published medical definitions and basic requirements for the use of ADR terms developed by groups of experts should be considered as a basis.*[15]

There will always be room for medical debate about which terms, diagnoses or entire cases should be regarded as clinically serious, or serious from an administrative/regulatory perspective. However, application of recognized medical criteria for establishing diagnoses and descriptions would be advantageous.[16] Recognize, however, that ordinary prescribers or other providers of case reports will not be familiar with or have access to the compendia recommended for use by the industry and regulators. Thus, it is important to remember that the terms and/or diagnoses given by the reporter of a case must also be recorded and included in any case submission to regulators.

(8) *It is recommended that the decisionmaking process and tools used to determine seriousness be harmonized globally within a company so that they can be applied consistently when the same debate arises with additional cases.*

---

[14] Any single laboratory value outside the normal range for a laboratory should always be considered in the context of the clinical state of the patient, other abnormal laboratory values, and the degree of variation from the norm. Clinically consistent patterns of laboratory test abnormalities are of more importance than isolated values. The most significant situation of all is when there is a chronological trend in an abnormality. The ultimate judgment of seriousness is a clinical one, taking all these considerations into account as well as the nature of the pathophysiological disturbance reflected by the particular abnormal test or tests.

[15] For example, International Consensus Meeting on Criteria of Drug-induced Liver Disorders, *J. Hepatol.,* 11: 272-276, 1990 and Basic Requirements for the Use of Terms for Reporting Adverse Drug Reactions (VIII): Renal and Urinary System Disorders, *Pharmacoepidemiology and Drug Safety,* 6: 203-211, 1997. For recent compilations, see Venulet, J. and Bankowski, Z. Harmonizing Adverse Drug Reaction Terminology, *Drug Safety,* 19(3): 165-172 (1998) and the currently comprehensive *Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for Their Use,* Edited by Z. Bankowski *et al.,* Council of International Organizations of Medical Sciences (CIOMS), Geneva, 1999. The latter book comes with a CD-ROM.

[16] See *Adverse Drug Reactions — A Practical Guide to Diagnosis and Management*. Edited by C. Benichou. John Wiley and Sons Ltd., Chichester, England, 1994.

d. Criteria for Expectedness

Introduction

There are two principal criteria that control the priority for documenting, validating, evaluating and regulatory-reporting of ADR cases: seriousness (Chapter III.c.) and "expectedness." The concept of expectedness refers to events that may or may not have previously been observed and documented. It does **not** refer to what might be anticipated (expected in a different sense) from the known pharmacological properties of the medicine. Nor does it refer to what may occur in the course of the treated disease such as in the case of disease progression and/or lack of drug effect.

An adverse reaction will be unexpected in the regulatory sense unless it is mentioned in the appropriate reference safety information (RSI) document(s) for the drug, even if it is a medical occurrence expected for the disease being treated. Depending on the status and circumstances of the drug, RSI may be one or more of the following:[17] a component of an Investigator Brochure (Development Core Safety Information, e.g.), a company's core safety information (CCSI) within its internal core data sheet, or the official local data sheet (e.g., Package Insert in the US, Summary of Product Characteristics (SPC) in the EU).

To ensure proper classification and specificity of ADR terms, ideally three conditions should be fulfilled:

- ❏ case reports must be sufficiently well documented,
- ❏ there must be no ambiguity regarding the nature, severity and outcome of the event, and
- ❏ there must be no ambiguity regarding the section(s) in the RSI where the appropriate information is placed.

Much safety information may be contained in various sections of the RSI; this may actually create confusion or ambiguity about what should or should not be considered 'expected.' Thus, the CIOMS Working Group takes the position that expectedness should be based on inclusion of a drug-associated experience in the ADR section (also called Undesirable Effects section by some) of the RSI; as an ADR, the experience therefore is regarded

[17] ***Guidelines for Preparing Core Clinical Safety Information on Drugs. Second Edition.*** Report of CIOMS Working Groups III and V (1999). Council for International Organizations of Medical Sciences, Geneva.

as at least possibly causally related to use of the drug (i.e., an adverse reaction, not an adverse event). Even when an ADR is mentioned in the clinical pharmacology, contraindications, warnings, precautions, or other sections of a data sheet or label (e.g., an ADR in connection with an overdose or a drug interaction), it should also be included in the ADR section, which is the comprehensive repository of *expected* ADRs. This principle applies to any RSI, whatever the stage of development or marketing of a drug.[18]

Many different terms are currently used to indicate expected or unexpected. The CIOMS Working Group endorses the following distinctions established under ICH:

- **listed** or **unlisted** are the terms used to refer to ADRs in association with the Company Core Safety Information (CCSI) within a company's Core Data Sheet for a marketed product, as recommended by CIOMS, and in ICH Guideline E2C on Periodic Safety Update Reports.[19] Similarly, these terms are recommended by the CIOMS Working Group to describe expectedness of ADRs in association with the Development Core Safety Information (DSCI) in an Investigator's Brochure.
- **labeled** or **unlabeled** (i.e., expected or unexpected) are terms that should be used only in connection with official product information for marketed medicines, such as a US package insert, an EU SPC, or other country data sheets.

Current Concepts of Expectedness

Determining whether a reported reaction is expected or not involves two levels of inquiry:

(1) Is the reaction mentioned in the appropriate section of the reference safety information (RSI)? Any reaction which is not mentioned is supposedly new and therefore unexpected.

[18] It is acknowledged that by advocating placement of all ADRs in the ADR section of the Reference Safety Information, there is the possibility of significant duplication of information between sections. For example, ADRs resulting from drug-drug interactions may appear in the clinical pharmacology or other section(s) of the RSI. Therefore, to avoid unnecessary duplication, the ADR section itself could contain a brief statement about the particular ADR with a cross-reference to the other relevant section(s) containing the more comprehensive information.

[19] *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. ICH Harmonised Tripartite Guideline E2A* in Proceedings of the Second International Conference on Harmonisation. Orlando 1993. Appendix 4. Ed. P.F. D'Arcy, D.W.G. Harron, Belfast 1994; pp 603-618.

(2) From the medical data provided in the case report(s), is the adverse reaction different regarding its nature, severity, specificity or usual outcome relative to the term or description used in the RSI? In order to answer this question it is important to analyse the way the RSI is prepared and interpreted.

The purpose of RSI is, of course, not limited to the determination of expectedness. The main objective of RSI is to inform the parties involved in using medicines (investigators, prescribers, other healthcare providers, regulators and patients) of the most current expression possible of clinical safety experience. The threshold for inclusion of information in RSI may be viewed differently by regulators (and between regulators) than by industry, potentially leading to disagreements on the proper safety information. The relative weight of the criteria for inclusion may also vary during the life cycle of a drug.

The Investigator's Brochure (IB) should provide a description of the possible risks anticipated on the basis of prior experience with the product under investigation and with related products. The CIOMS V Working Group has already recommended that a standard safety data sheet (development core safety information, DCSI) be included in the IB, to be used both to summarise the information contained within the document and to determine "expectedness" of reactions for regulatory reporting purposes during development programs.

Investigators of a drug in early development need details concerning animal toxicology, anticipated class effects, kinetics, pharmacodynamics, laboratory data, vital signs, etc. When initiating the first clinical studies (Phase 1), obviously nothing has been previously observed in humans with the medicine. Therefore, none of the reactions that might be predicted from preclinical data or from class effects should be considered expected. However, for adverse reactions that might be anticipated, greater importance is usually given to their detection and monitoring in the safety section of the study protocols.

As soon as relevant clinical safety information on the new medicine becomes sufficiently well established throughout the development process, it should be included in the adverse reactions section within the DCSI and thereafter considered expected.

For marketed products also, a CIOMS report[17] gives details on the philosophy and practical considerations for the preparation and updating of Company Core Safety Information (CCSI).

Regulatory Definitions of Expectedness and Reference Safety Information (RSI)

Examples of definitions used for expectedness and RSI as under ICH [20] and in the regulations of the US FDA[21] and the European Union[22] are given in Appendix 6.

The concept of expectedness is similar for ICH, USA, Japan and Europe. There is also agreement that the safety information used as a reference should differ according to a drug's regulatory status (development vs marketed) and depends on the nature of the regulatory reporting.

For investigational products, the Investigator's Brochure, if available, is the reference document for expedited reporting and for any pre-approval periodic reporting (e.g., IND annual reports in the US).

For expedited reporting to individual country regulators on marketed drugs, the locally approved product information (e.g., SPC) is the reference document on which expectedness is based, for reports from all sources, including clinical trials. On the other hand, for periodic reporting, ICH recommends that the information prepared under the medical responsibility of the companies (Company Core Safety Information, CCSI) be used.

The situation becomes more complex when a drug is already on the market in one or more countries but is still under investigational status in others — or if a marketed drug is also under investigational status for new uses (indications, populations) or for a new dosage form. In such cases, reliance on the DCSI, CCSI and/or the local data sheet will depend on the specific circumstances.

In the absence of standardised guidelines, opinions and decisions on expectedness for a given adverse reaction can differ greatly between and

---

[20] *Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs. ICH Harmonised Tripartite Guideline E2C* in Proceedings of the Fourth International Conference on Harmonisation. Brussels 1997. Appendix 4. Ed. P.F. D'Arcy, D.W.G. Harron, Belfast 1998; pp. 613-634.

[21] *Expedited Safety Reporting Requirements for Human Drug and Biological Products*. Federal Register, Vol. 62 N 194, October 7, 1997, Part 312 — Investigational New Drug Application — 52250: *Expedited Safety Reporting Requirements for Human Drug and Biological Products*. Federal Register, Vol. 62 N 194, October 7, 1997, Part 314 — Applications for FDA Approval to market a New Drug or an Antibiotic Drug — 52251; and Federal Register , Vol. 62 (96): 27470-27476, May 19, 1997. The Code of Federal Regulation documents are: 21CFR312.32 and 312.33 (INDs); 21CFR314.80 and 314.81 (NDAs-drugs); 21CFR600.80 and 600.81 (NDAs-biologics and vaccines).

[22] Official Journal of European Communities, October 8, 1997, C306/9.15 and Note for Guidance on Clinical Safety Data Management. Periodic Safety Update Reports for Marketed Drugs. CPMP/ICH/288/95.

among companies and regulators and even between professionals within the same organisation.[23]

If RSI is to serve its purpose as a useful and meaningful source of safety knowledge and as a valid reference for regulatory reporting, then approaches are needed to ensure that:

- A sign, symptom or diagnosis that already appears in the list of adverse reactions in an RSI is not classified as "unexpected" if reported using another term which means the same thing; and
- a sign, symptom or diagnosis is not regarded as "expected" when it is different from reactions already included in the RSI with respect to their nature, specificity, mechanism, severity, or outcome.

Recommendations and Proposals

As already mentioned, there are two perspectives to keep in mind when classifying expectedness, one regarding the choice of terms (semantics) and the other the validity of the terms given the clinical evidence on a case.

Is the term for the adverse reaction used by the reporter (the "verbatim" language) already listed in the ADR section of the RSI? If not, is there a synonym or medically equivalent term that is contained within the coding terminology employed by the organisation? When a report is inadequately documented, this "semantic" evaluation may be the only possible recourse for a decision on expectedness.

The most difficult and important consideration is whether the clinical information contained in the report is consistent with the description, nature, severity, mechanism and usual outcome associated with the information listed in the ADR section of the RSI. Thus, is there a clinically significant difference discernible between the data reported and the information already covered in the RSI? This evaluation requires well documented cases.

The CIOMS Working Group has developed a series of proposals intended to improve accuracy and consistency in the process for classifying expectedness. Following the recommendations, several examples of their application are presented.

In the absence of sufficient documentation and in the face of uncertainty, a reaction should be regarded as unexpected.

[23] For a recent detailed discussion from the perspective of one company, see: Brown, K., Sykes, R.S., and Phillips, G. Is that Adverse Experience Really Expected? Guidelines for Interpreting and Formatting Adverse Experience Information in the United States, Drug Information Journal, 35: 269-284, 2001.

This rather obvious suggestion reflects the need to strive always for improved quality of reporting. The ability generally to assess and characterise a case and particularly to assign expectedness with accuracy and reproducibility relies on the quality and completeness of individual reports. This is especially important for suspected serious and/or new ADRs. (See Chapters III.a. and III.e. for further discussion on this point.)

Inclusion of safety information in the adverse reactions/undesirable effects section of the RSI should be strictly limited to reactions which have been observed and documented in humans, and for which the causal role of the drug has been reasonably established or inferred.

Special types of reactions, such as those occurring under conditions of overdose, drug interaction or pregnancy should also be included in this section, with a cross-reference to other relevant RSI sections for details.[24]

If an ADR has been reported only in association with an overdose, then that same ADR at ordinary (usual) doses should be considered unexpected.

Clear, unambiguous wording is required in the Reference Safety Information[25] *in which the list of terms is:*

complete, *covering all the drug-induced situations which may be encountered;*

mutually exclusive, *such that each term would cover medical conditions with comparable clinical properties , namely, their nature, severity, specificity or usual outcome; situations with different clinical attributes would be ascribed different terms.*

Although a standard coding terminology might be used for term selection (e.g., MedDRA), caution must be exercised to avoid the use of unclear or uncommon terms; the focus must be on medically meaningful, understandable terms and concepts. The Working Group does not support the unconditional use of MedDRA (or other coding dictionary) terms for product data sheets.

One approach to enhance the choice and inclusion of proper terms is to apply standard medical definitions for the terms. In other words, what are

[24] Terminology in use by some refer to Type A reactions, *viz.,* those that tend to be common, dose-related ADRs that are predictable pharmacological effects of the drug, and Type B reactions, which tend to be more serious, uncommon, not dose-related, and unpredictable (idiosyncratic, e.g., hypersensitivity reactions).

[25] Benichou C. and Castle W. Points of view on adverse drug reactions terminology, *Thérapie,* 53: 145-149, 1998.

the accepted diagnostic criteria for a condition or diagnosis and are those criteria satisfied to allow the term (e.g., hepatic necrosis) to be used appropriately in the RSI? Such definitions for a variety of important medical conditions associated with ADRs have been published.[15]

However, not all terms need to be defined. Relevant definitions are needed mostly when there are discrepancies between medical dictionaries, or when the available definitions are not readily applicable in the face of incomplete information. An example of a system-organ class terminology that correlates terms with the newly developed definitions with terms derived from older medical definitions has been published.[26]

Examples to Illustrate the Problems and Recommended Solutions

Reference has been made earlier (Chapter III.b.) to a survey that examined people's decisionmaking behavior for seriousness and expectedness of ADR reports.[27] The examples given below are derived from that survey; details are provided in Appendix 4.

- **When is additional specification of an expected ADR needed?**

  A case report may include details that imply further specification of an ADR (anatomical or histological details, or information related to severity and prognosis, duration, frequency, etc.). However, not all such clarifications should result in a change to the RSI.

*Further **anatomical** specification:*

- ❏ left-sided chest pain is equivalent to chest pain; it should not be assessed as unexpected if chest pain is expected;
- ❏ if arteritis is expected, temporal arteritis should be considered unexpected due to the associated additional risks and poorer prognosis.

*Further **histological or diagnostic** specification does* not *per se* make an expected ADR unexpected [e.g., a liver biopsy shows hepatic necrosis (expected) with the presence of eosinophils (not mentioned in labeling)].

---

[26] Edwards, IR *et al*. Proposed Improvement to the WHO Adverse Reaction Terminology, *Pharmacoepidemiology and Drug Safety*, 2: 177-184, 1993.

[27] Castle W. and Phillips G. Standardizing Expectedness and Seriousness for Adverse Experience Case Reporting. *Drug Information Journal* 30: 73-81, 1996.

- ❏ however, an example of greater diagnostic specification: cerebral thromboembolism and cerebral vasculitis would both be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents;
- ❏ interstitial nephritis should be considered unexpected when only acute renal failure is expected.

Medical judgement should be used in these and other decisions which are based on whether the extra specificity is clinically important.

*Further specification regarding **severity:***

- ❏ fulminant hepatitis should not be considered expected if "liver injury" is mentioned in the reference information; fulminant hepatitis is defined, for example, by time to onset and specific signs of severity, and deserves to be identified as such, owing to the known high incidence of fatal outcome.
- ❏ rash does cover morbilliform rash but not Stevens Johnson Syndrome.
- ❏ rash should be used for coding of cases that have no other specification regarding their nature or severity or when cases of rash have been documented as either isolated events, or associated with other signs or symptoms which could not be recognised as a specific syndrome.

When a term mentioned in the reference information encompasses situations with distinguishable and recognised levels of severity, a significantly more serious case should be considered unexpected.

*Further specification regarding **duration:***

A case will usually be considered "unexpected" if the RSI lists an ADR which is specified as transient or acute, but it persists in the new case.

E.g., if the label refers to acute elevated liver function tests, a raised level lasting three months would be unexpected. Thus, prolonged cholestatic liver injury should not be considered expected when acute cholestatic liver injury is mentioned in the RSI, since prolonged forms may not be reversible.

- **Do additional signs and symptoms necessarily infer unexpectedness?**

  Mention of any additional symptoms or signs usually associated with an expected ADR does not always merit upgrading the event to unexpected. Petechia associated with labeled thrombocytopenia, or dehydration associated with labeled pseudomembranous colitis, are not unexpected.

If an expected ADR is not usually accompanied by or complicated by a sign, the ADR should not be considered expected. Melena, a complication of labeled gastrointestinal irritation, is unexpected because gastrointestinal irritation *per se* does not usually cause bleeding. On the other hand, melena would be expected if the label includes "gastrointestinal bleeding."

- **How should signs and symptoms of a diagnosis or syndrome be handled?**

  If a diagnosis is an expected ADR, then the signs and symptoms which comprise the diagnosis are also considered to be expected, when they are reported as associated. For example, if anaphylactic reaction is labeled, then a report of a patient who experienced hypotension, wheezing, and urticaria together would be considered an expected event.

  The reverse is not true however; a diagnosis relating to a group of symptoms or signs which are each individually labeled would not usually be considered expected. A reported anaphylactic reaction is unexpected if only isolated hypotension, or wheezing, or urticaria are labeled.

  However, even though a diagnosis or syndrome is expected, if the usually accompanying signs and symptoms are reported in the absence of a clear diagnosis (i.e., as one or more isolated signs and symptoms), those terms should not be considered as expected unless already in the RSI. It is impossible to ascertain that their appearance alone or together necessarily reflects a mechanism similar to that of a labeled diagnosis (e.g., isolated nausea, or asthenia, or gastralgia, when liver injury is labeled; or isolated pallor, or hypotension or pruritus when anaphylactic reaction is labeled).

- **Death as an Outcome: A Difficult Labeling Issue**

  If a labeled ADR is known to represent a life-threatening condition or often results in death, does a fatal outcome in a particular case make the ADR unexpected if death is not specifically mentioned in the RSI as a possible outcome?

  The survey on which the examples in this Chapter were taken showed that 46% of participants in Europe but only 1% of those in the US would consider a case of "death from hepatic necrosis" as expected if hepatic failure was listed in the RSI without mention of

fatal outcome. It is unknown whether the difference reflects, at least in part, different regulatory traditions.

The possibility was considered of establishing a list of adverse events for which death might be anticipated, i.e., current medical knowledge teaches that at least some fatal cases for certain conditions would not be unexpected. However it was considered that the evidence-base for such a list is inadequate, that the ability to determine cut-offs and compile an exhaustive list is implausible, and that it would be difficult to apply such a list consistently across therapeutic areas. Furthermore, given the importance and sensitivity associated with cases involving death, some members of the Working Group felt that until and unless death (or life-threatening) is explicitly mentioned in product information (i.e., it is "expected"), each case should be reported on an expedited basis. On the other hand, it is generally accepted that it is not the purpose of product information, specifically the RSI, to "teach" medical practice[17] (in this context, e.g., that an MI as an ADR can result in death). In that sense, one must distinguish between useful, practical product information and regulatory reporting considerations.

A minority of the Working Group suggested that, even though all expected (labelled, listed) drug-related death cases are routinely covered in periodic safety reports, there may be a public health argument for *expedited* reporting of all drug related deaths. Such expedited reporting would be required even if the adverse event causing the death is labeled and whether or not the RSI specifically mentions that there is a possibility of death from that ADR. All parties agreed that possibly drug associated fatalities or life-threatening episodes (like any medically serious ADRs) are always a matter of professional and public concern. The debate revolves around whether individual reports of deaths should be regarded as an exception, and in that sense be the subject of over-reporting, relative to the generally accepted practices for regulatory reporting of serious, expected suspected ADRs.[28]

[28] The minority view held that the "public" is always interested and concerned about drug-associated deaths and that they turn to the regulators and perhaps academia to keep them abreast of this most serious and tragic outcome. Thus, constant alert through expedited reporting of deaths, even if already labeled, was believed important for public health and would provide confidence to the public that systems are in place for controlling such important drug safety issues. On the other hand, there is always the concern, as expressed by others, that this would detract from the needed prioritization of resources, time and effort for investigation and assessment of new signals. It is worth commenting that the anticipated future use of electronic ADR report submission on an ongoing basis will probably make most of this discussion moot.

The question that must always be asked is whether such reporting adds value to pharmacovigilance. It should be noted that under the ICH Guideline E2A on expedited reporting during clinical trials, once "expected" in the Investigator's Brochure, expedited reporting for fatalities is not required.[29] Another argument against routine expedited reporting, particularly for spontaneous reports on marketed drugs, relates to the complexity of attribution of the death (an outcome, not an AE/ADR per se). Because all spontaneous reports generally have implied causality, routine prompt reporting can generate a false impression; other than the rare cases involving sudden death or "death NOS," it is an ADR which generates the spontaneous report. It is also suggested that the difference between a life threatening medical situation resulting in survival of the patient and an outcome of death may depend merely on the availability of appropriate medical care and expertise; in that sense, any distinction made for expedited vs periodic reporting between "life threatening" and "death" is artificial. The majority felt that in the absence of special circumstances, a more deliberate, periodic assessment is necessary for proper perspective.[30]

Obviously, this is a difficult and complex issue. Although complete consensus was not reached, a majority of the CIOMS V Working Group favoured the following practices:

- *Unless the RSI specifies a fatal outcome, then the case should be considered as unexpected as long as there was an association between the adverse reaction and the fatality.*
- *A fatal outcome to a suspected ADR should not be mentioned in the RSI unless it has been reported to occur and is thought to be causally related to the ADR.*
- *In the absence of special circumstances, once the fatal outcome is itself expected (labeled/listed), reports involving fatal outcomes should be handled as for any other serious suspected ADR in accord with appropriate regulatory requirements.*

[29] Clearly, any suspicion of an increased frequency of fatality reports, or of a change in the nature or specificity associated with the underlying ADR leading to a death, should always be the subject of expedited reporting to the regulators. However, the focus here is on individual suspected ADR reports involving death that is already "expected" or implied.

[30] All fatal or life-threatening cases should receive particularly careful medical review for causality. See Chapter III.c. for more discussion on this point.

- **How Should Various Sections of a Core Data Sheet or Other RSI-Containing Document Inter-relate with Regard to Safety Information?**

  Recommendations for the definitions and use of the traditional sections of product information (data sheets, CCSI, DCSI) have been published by CIOMS. However, there remains some uncertainty as to how the various sections relate when ADR or other safety information are covered in more than one place. The following three recommendations illustrate the situation.

  ❑ *The existence of concurrent medical disorders or abnormalities may be given as a reason for a contraindication or precautions-for-use. This does not imply, of course, that such concurrent conditions are ADRs, unless they are specifically mentioned as such in the adverse reaction section. Otherwise, they are not expected.*

  The general and obvious point made here is that the mere mention somewhere within RSI of a medical condition is not by itself grounds for regarding that condition as an "expected" ADR.

  ❑ *If it is specified (for example in the dosing section of CCSI), that dosage should be reduced in case of renal insufficiency, then renal insufficiency is not an expected ADR unless it is also included in the ADR section.*

  ❑ *When renal insufficiency is mentioned as a finding from animal studies but has never been observed in patients or, if observed as an adverse event but judged unrelated to the drug in question, then renal insufficiency is not expected.*

- **Is There a Role for Provisional/Uncertain Causality Statements in RSI?**

  As emphasised throughout this Chapter, the evaluation of expectedness should be based on whether or not an event was previously observed and documented, and that the causal role of the drug was sufficiently reasonably established so as to include the event in the ADR section of RSI.

  ❑ *It is generally regarded as inadvisable (CIOMS III)*[17] *to include a disclaimer for causality (e.g., "acute liver injury has been reported but the relationship with the drug has not been established"). Even if such a statement were to be used, the reaction (in this case "acute*

liver injury'') remains unexpected until and unless it appears in the ADR section of the RSI.

- ❑ *Events cited in data from clinical trials are not considered ''expected,'' unless the same events have been included in the ADR section for the marketed product.*

A distinction must always be made between the pre-marketing clinical trial data (often including placebo as a comparison) typically presented as general background information in tabular form in the CCSI or a product data sheet, and the 'official' listing of expected ADRs in the separate ADR/undesirable effects section of the Reference Safety Information.

- **What is the Role, if any, of "Class Labeling" in RSI**

Data sheets in some countries, particularly in the US, include a section related to adverse drug reactions for the class of drugs to which the product belongs.

''Class ADRs'' should not automatically be expected for the subject drug. The discussion in the RSI depends on the circumstances.

Class ADRs will be expected only if the product is itself implicated, as illustrated with the following fictional sample statements: ''As with other antiwhiskey receptors, the following undesirable effect occurs with X'' or ''Antiwhiskey receptors, including X, can cause...'' If the ADR has not been documented for drug X, the more appropriate statements would be: ''Other anti-whiskey receptors are reported to cause —'' or ''Antiwhiskey receptors, as a class, cause — but no reports have been received to date with X.'' Thus, the class effect(s) would still be unexpected for Drug X.

- **Should RSI Deal With Lack of Expected Clinical Effect?**

Lack of expected effect, although important, does not strictly belong to the same discussion of considerations about whether or not an adverse (safety) event is expected. Indeed, no drug can be expected to cure 100% of patients. For example, an oncology drug may not cure a hospitalised patient's cancer, which results in a prolongation of hospitalisation, e.g., but this lack of effectiveness does not make the case unexpected (or serious) from the perspective of safety reporting.

However, what if the treatment exacerbates the ''target'' disease (the indication for the medicinal product)? An example of such a

paradoxical observation is asthma exacerbation caused, albeit rarely, by some asthma therapies. In this case, the asthma exacerbation would be unexpected unless detailed in the prescribing information. Similarly, if an anti-migraine treatment were followed by an increase in frequency or intensity of migraine attacks above baseline, then unless listed in the safety information, this adverse consequence would be unexpected.

Another significant concern is detection of an "unusual" lack of expected therapeutic effect for medicines used in life-threatening diseases, which may have life or death consequences. While individual reports are not *per se* unexpected, reports of unusual numbers of treatment failures may constitute a signal of a problem and should be handled as other changes in frequency are. (See below).

As recommended by CIOMS III,[17] adverse medical consequences of lack of expected efficacy should be included in product information but should be distinguished and separated from the usual safety information. Whether such information should be located within contraindications, precautions, a section on special populations, or elsewhere will depend on circumstances; the details were considered beyond the scope of the CIOMS V initiative.

- **How Should Changes in Frequency of ADRs Be Handled?**

  Although this and other chapters focus on individual ADR cases, there is a need to consider multiple-case expectedness, especially for a known (expected) ADR. Does the appearance of an "unusual" incidence of reports from one or more sources indicate a signal of importance?

  Standard categories of known or estimated frequency of ADRs have been proposed by CIOMS Working Group III:

[very common	$\geqslant 1/10$ ($\geqslant 10\%$)]
common (frequent)	$\geqslant 1/100$ and $<1/10$ ($\geqslant 1\%$ and $<10\%$)
uncommon (infrequent)	$\geqslant 1/1000$ and $<1/100$ ($\geqslant 0.1\%$ and $<1\%$)
rare	$\geqslant 1/10{,}000$ and $<1/1000$ ($\geqslant 0.01\%$ and $<0.1\%$)
[very rare	$<1/10{,}000$ ($<0.01\%$)]

  [Very common and very rare suggested as optional]

  In evaluating clusters of cases as opposed to individual cases, the newly observed (estimated) frequency of occurrence may be "unexpected" relative to the information in the RSI (e.g., RSI may

state an ADR is "rarely" observed but the new information signals the possibility that the frequency may have changed by at least one category, say, to "uncommon"). It must be recognized, however, that such changes are very difficult to detect and evaluate from only spontaneous reporting of a cluster of cases; there is considerable uncertainty inherent in estimating the denominator (actual patient use/exposure) and the numerator (which is associated with a typically high, but unknown degree of under-reporting). More discussion on these points is found in Chapter V. Nevertheless, it is possible that changes in labeled frequency could be based on the receipt of a well documented cluster of reports from one or two reporters who state that they are seeing an increasing number or incidence of such events.

An epidemiological study may be necessary to confirm an increase of frequency. For this reason the criterion of "increased frequency" of spontaneous cases is generally no longer a prescribed, routine requirement for expedited reporting to regulatory agencies. One or more clusters of cases in localised areas or during a short period of time will lead to a search for an explanation (e.g., it might be a product defect) and depending on the particulars may necessitate an expedited regulatory notification. A special situation arises when a series of individual cases may not have initially been considered drug-related, but upon separate analysis (e.g., from a blinded study), the treatment is shown to have a much higher rate than a comparator. That constitutes a signal as well and may require prompt notification to regulators.

In general, statements involving frequency in product information should be considered carefully and developed with full consideration of the difficulties in establishing denominators (exposure). (See Chapter V)

Conclusion

The determination of whether an ADR is or is not expected is not an exact science; there are many grey areas. A decision in many instances will have to be based on clinical evaluation of inadequate case information.

Evaluation of expectedness will probably remain subject to high variability between assessors. It is believed, however, that more widespread use of the DCSI and CCSI concepts and practices as articulated in the CIOMS III/V report, along with the concrete suggestions and examples provided here, will lead to more consistency and reproducibility in the process.

e. Case Follow-up Approaches

Introduction

The information from adverse event cases when first received will generally be incomplete. Ideally, comprehensive information would be available on all cases, but in practice efforts are needed to seek additional information on selected reports. This is especially true for spontaneous reports. The extent and nature of follow-up is driven by the nature of the case and consideration of the value of learning more detail, tempered by insight into the likelihood of success at such attempts.

Although procedures are already in place within companies and regulatory authorities, guidance is needed to ensure that resources for case follow-up are focussed on the most relevant data elements for the most important cases for both marketed and investigational drugs. Busy professionals will be more willing to offer further details if questions are asked on important information in clinically important cases and if they are not approached with redundant queries.

In addition to the nature of the case, there are many other influences and factors to consider when deciding on the appropriate type of follow-up:

- ❏ source of the report: literature, newspaper or other media, consumers, pharmacists, physicians, dentists, other healthcare professionals,[31] company representatives, or from the patient's lawyers. (If there is a case with legal implications, it is advisable to involve the legal department.)
- ❏ the most appropriate or effective method (site visit, letter, fax, e-mail, telephone) and how many attempts should be made
- ❏ for consumer reports, the need for medical confirmation in some countries adds another dimension to the process (see Chapter II.b.)
- ❏ the methods available for follow-up may be driven by the local culture
- ❏ the "age" of the drug: is there a possibility of diminishing returns on investing efforts on well established products ("enough is enough")? But other factors probably outweigh such considerations (e.g., serious unexpected cases and new drug interactions)

[31] In the EU, when reports originate from healthcare professionals other than physicians or dentists it is requested that, if possible, further information about the case be obtained from a medically qualified person. (Notice to Marketing Authorization Holders, Pharmacovigilance Guidelines, 2000)

Another aspect of case follow-up which is hardly ever addressed by either the regulators or companies involves instances of misprescribing (for example, where a prescriber inadvertently has given a drug contraindicated in a particular patient leading to a serious adverse reaction or even death, such as a beta-blocker mistakenly prescribed to an asthmatic child). Should any action be taken and by whom? Following extensive discussion, and because there are different mechanisms for dealing with misprescribing in individual countries, the Working Group was not able to reach consensus on this important matter. There are several factors to consider, including the legal implications. There is, however, an obvious public health need to address this risk communication issue, which is beyond the scope of the Working Group.

General Considerations for Follow-up Practices

In any scheme to optimize the value of follow-up, the first consideration is prioritization of case reports as they are brought to the attention of the companies and regulators. Once they are classified in order of importance, decisions must be made on the minimal amount of information that should be sought for the different categories of cases; thus, not all reports warrant the same effort to obtain follow-up nor is it necessary that the same type and depth of information be sought for all types of cases that are followed-up. For example, because a good narrative description is required for, among others, expedited reports to regulators, more information is needed for those cases than, for example, non-serious expected cases. However, if deciding not to seek follow-up data on non-serious events (e.g., abdominal pain), it is important to be reasonably assured that a serious medical event (e.g., pancreatitis) is not involved. If there is any level of doubt, which will depend on the information received with the case, follow-up is in order.

Well documented serious expected cases are potentially of epidemiological interest in helping to identify risk factors. Non-serious unexpected cases are also of potential interest for detecting a new signal.

It is suggested that once a case is entered into a database, triage by computer can be used to indicate, based on the case content, whether it should be handled on an urgent basis (requiring a telephone call or a visit, for example), whether it might need a letter requesting follow-up information (which could be computer generated as well), or whether the case information is sufficient. For some spontaneous cases, especially those which are not serious, are already expected (labeled), and are the subject of many previous reports, a computer generated acknowledgement letter to the reporter may be

all that is needed provided the original information is adequate (see below). However, such letters should also invite additional relevant information.

Proposals are also needed on the best methods for follow-up and the proper frequency (how many attempts) with respect to the various parties in the communication link (original case reporters, companies, regulators). The challenge is to obtain as much useful information as possible without pestering reporters, such that he or she might be disinclined to cooperate and be discouraged from future reporting. Partly for this reason, three levels of case information (data elements) have been developed that are tailored to the specific types of cases according to priority and importance (see below and Appendix 7).

Finally, the Working Group considers it important to develop a position on whether and under what circumstances rechallenge or re-exposure should be considered as part of a follow-up routine.

Specific Recommendations

What are the criteria for case prioritization?

Highest priority for follow-up are cases which are both serious and unexpected. At a slightly lower priority are serious, expected and non-serious, unexpected cases. In general, any cases for which additional detail might lead to a labeling change decision should be considered at a high priority level. However, in addition to seriousness and expectedness as criteria, cases "of special interest" also deserve extra attention.

Cases of "special interest" include those which the company is actively monitoring as a result of a previously identified signal (even if non-serious and expected). For instance: concern over excessive drowsiness which could possibly lead to accidents; drug interactions; drug misuse; or a contra-indication. Events of special interest, especially if they concern a new indication, new dosage regimen, or new dosage form, should be given the same attention as serious, unexpected reactions.

How should companies handle case reports received from a regulator?

The extent to which regulatory authorities themselves follow up cases varies widely. On occasion, regulators may request the manufacturer to follow up a case; if so, the same algorithms and logic proposed here for cases received directly by companies should be used. With permission, a regulator can divulge the name and address of the reporter to enable any necessary company-initiated follow-up. If required, a regulator may also be able to

assist the company if requests for information have been rejected by the reporter. If assistance from the regulators is requested — for cases received directly by companies or by regulators — it is suggested that the company provide specific questions it would like answered. The roles of the company and regulatory authority should be complementary.

It must be recognized, however, that in some instances, the reporter's identity will be unavailable and follow-up not possible (e.g., cases from independent databases). There are also circumstances in which, even though the reporter's identity is known, detailed efforts at case follow-up are not expected or required under conditions of a post-marketing surveillance study protocol.

For case reports forwarded from regulators to companies, it should not be assumed that regulators will conduct any needed follow-up. Therefore, especially for serious, unexpected cases received by the headquarters of, for example, a US company from a country authority in Europe, it is recommended that the local affiliate be relied on for assistance in determining whether the follow-up were conducted; if it were not, the affiliate could be asked to do so.

What Reference Safety Information (RSI) should be used when trying to decide whether follow-up is needed to clarify expectedness?

Companies often receive partial reports from many sources such as published line listings; the information provided may be insufficient to characterize the event for purposes of ascertaining expectedness, an important determinant for priority of handling and possible regulatory reporting. However, expectedness may be country-specific in view of differences between local data sheets. The Company Core Safety Information (CCSI) contains the minimum information a company insists be included on all data sheets. The use of a more inclusive RSI, such as the US Package Insert, could result in failure to follow up cases of reactions that might be unlabeled in data sheets elsewhere.

To facilitate the decision and ensure that the case is properly treated on behalf of all parties, the following is recommended:

> *The Company Core Safety Information (CCSI) should be used as the RSI against which expectedness is classified with regard to any follow-up decisions.*[32]

[32] As usual, regulatory reporting on all cases will be driven by the local official data sheet (e.g., SPC in the EU).

What specific follow-up information should be sought for the various types of cases?

In addition to decisions on which cases should receive priority for handling (i.e., the relative urgency of follow-up), it is also important to delineate the types of information that should be sought for the various types of cases. As already mentioned, the extent of detail needed for a given case should be driven by its seriousness and expectedness.

The Working Group has developed what it believes to be rational and practical sets of data elements, specifically targeted for different categories of cases, that should be considered sufficient to characterize the cases. Any missing information should thereby be sought through follow-up efforts. The lists of data elements are referred to as Lists A, B and C, with A containing the least and C the most called-for information. Of course any data obtained that are not on the lists should also be recorded and reported as appropriate; however, follow-up is recommended only when the data elements on the Lists are missing or incomplete.

The ICH E2B guideline for individual safety case reports contains an extensive list of data elements. However, it is not expected that all such information would be available for most cases; indeed, it would be rare. For convenience, the data elements contained in Lists A, B and C have been mapped to the corresponding ICH E2B items and specifications (see Appendix 7).

Although the items in the Lists are regarded as reasonable and sufficient for the purpose of characterizing different types of cases, the data elements are not expected to serve as automatic check-lists against which, for example, regulatory compliance is assessed. They are presented here as a practical expediency to assist in the follow-up process.

For non-serious, expected cases: no follow-up recommended if all of the following are available (**List A**):

- ❏ country of occurrence
- ❏ an identifiable reporter (see Chapter III.b.)
- ❏ an identifiable patient (see Chapter III.b.)
- ❏ source type (e.g., physician, lawyer, regulatory authority, etc.)
- ❏ a suspect drug or drugs
- ❏ one or more adverse event.

For serious expected **and** ***non-serious unexpected cases:*** the data elements contained in a standard ICH E2C (PSUR) line listing generally cover most of the necessary information and could be regarded as sufficient. However, other items of potential importance may also be needed. Thus, in addition to the items in List A, the following should be available (**List B**):

List A Plus:

- ❏ Daily dose of suspected medicinal product and regimen
- ❏ Route of administration
- ❏ Indication(s) for which suspect medicinal product was prescribed
- ❏ Starting date (and if relevant, time of day of treatment; e.g., acute hypersensitivity reaction)
- ❏ If serious, criterion or criteria for regarding the case as serious
- ❏ Full description or reaction(s) including body site and severity
- ❏ Starting date of onset of reaction (or time to onset)
- ❏ If not available, best available date or treatment duration
- ❏ Time lag if ADR occurred after cessation of treatment
- ❏ Patient outcome (at case level and, when possible, at event level): Information on recovery and any sequalae.
- ❏ Dechallenge information (if any)
- ❏ Rechallenge information (if any)
- ❏ For a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction(s)
- ❏ Causal relationship assessment
- ❏ Other relevant etiological factors

For serious unexpected, **and** ***"special interest" cases:*** everything in Lists A and B plus the following (**List C**):

Lists A and B plus:

- ❏ Stopping date and time or duration of treatment
- ❏ For concomitant medications:
  Daily dose and regimen
  Stopping date and time or duration of treatment

- ❑ Specific tests and or/treatment required and their results
- ❑ Setting (e.g., hospital, outpatient clinic, home, nursing home)
- ❑ Any autopsy or other post-mortem findings
- ❑ Whether or not the hospital discharge summary is available if the patient was hospitalized.
- ❑ Anything relevant to facilitate assessment of the case such as medical history, relevant drug history including allergies, drug or alcohol abuse, family history.

Other information that might be important to capture for reports in this category includes the investigator's causality opinion for clinical trial cases as well as other possible etiologic factors besides a drug; such items will be needed to complete a proper narrative for the case (see Chapter III.f.). Autopsy and hospital discharge summaries need not be submitted but the obligatory narrative should highlight the findings and state whether or not the detailed reports are available on request. (See Chapter III.f.).

When laboratory or other tests are conducted specifically to investigate the case, results should be obtained for all such tests. Specific investigative tests should be the focus and must not be confused with routine tests conducted independently of the adverse event. Medical confirmation should be sought from a medically qualified healthcare professional involved in the patient's care if the report originates from other than a physician if the case is serious or medically significant.

How long should a case be followed by a company to determine the outcome?

There are no guidelines on how long a company should continue to obtain information on the clinical course of an ADR and on what constitutes a reasonable effort. This is obviously a matter of clinical judgement, but for important cases the following approach is recommended:

In general, when the case is serious, especially if also unexpected (therefore with possibly important labeling consequences), if the ADR has not resolved at the time of the initial report, it is important to continue follow-up until the outcome has been established or the condition is stabilized (e.g., acute renal failure, with the patient still on dialysis).

Because each clinical situation will be unique and require judgment, more specific guidance on how long to follow-up is not appropriate.

Under what circumstances does follow-up information on a previously reported case warrant a follow-up report to the regulatory authorities?

Only if the fields identified in the Lists A, B and C are updated should the new information be submitted. Conversely, it is unnecessary to send a follow-up regulatory report if non-significant data elements *not* included in the Lists (such as height) subsequently become known or require correction. If a follow-up report with pertinent information **is** sent to regulators, then all available information should be submitted (even height, for example). In general, the follow-up information would be incorporated into a revised narrative (see Chapter III.f.).

As part of follow-up procedures, is it appropriate to request that a patient be rechallenged with a drug suspected of causing the reported event(s)? In general, with or without a company's or regulator's involvement, should physicians conduct rechallenge experiments?

It is commonly believed that one of the most powerful pieces of evidence to ascertain drug causality for an adverse event is the subsequent readministration of the medicine, a technique commonly referred to as ''rechallenge.''[33] The term ''re-exposure'' is often used in the same context, but there is confusion as to whether the two terms have different meaning; both have been used to indicate either intentional or inadvertent exposure to a suspect drug (or other cause). A decision to readminister a drug that is suspected of causing an adverse reaction is dependent on many factors (e.g., is the suspected reaction reversible, idiosyncratic, etc.).[34]

Obviously, careful judgment by the treating physician will be needed on a decision to carry out a rechallenge procedure; referral to an ethics review committee (for clinical trials) and patient-informed consent are advised, particularly if the suspect reaction is serious or otherwise medically important. Rechallenge for scientific interest alone is inappropriate.

The CIOMS Working Group believes that the one overriding factor is an ethical one and subscribes to the following principle:

Intentional rechallenge *should be carried out only when there is likely to be clinical benefit to the patient. Thus, only if in the judgment of the treating*

[33] The reappearance of an adverse event after a drug is given again does not necessarily represent proof of causality, however. See Rothman, K. J. Causal Inference in Epidemiology, in *Modern Epidemiology,* Little, Brown and Company, Boston, 1986 (pp. 7-21).

[34] Stephens, M. D. B. Deliberate drug rechallenge, *Human Toxicology,* 2:573-577, 1983.

physician the anticipated result is directly relevant to the patient's treatment and well being should that individual be rechallenged.

Some General Good Follow-up Practices

Beyond the specific recommendations made above, the Working Group offers several practical suggestions to facilitate the follow-up process.

Regulators and companies should collaborate to ensure that only one party conducts follow-up on a case in accord with the requirements or practice within individual countries. Regulators are expected to share cases they receive directly with the relevant manufacturer(s), especially serious, unexpected reports; therefore, any follow-up obtained by the regulators should also be transmitted to the manufacturer(s).

Follow-up information should be obtained in writing, via a telephone call, and/or a site visit as appropriate. Written confirmation of details supplied verbally should be obtained whenever possible.

If it is not possible to obtain full details by telephone or through a site visit, follow-up information should be requested in writing (for example, by supplying a partially completed regulatory or company form that includes a draft narrative, when appropriate, with a cover letter identifying the additional key information sought).

Every effort should be made to follow-up ***unexpected*** *deaths or life-threatening events within 24 hours of ascertainment by a company that such a case exists.*

All attempts to obtain follow-up information (whether or not successful) should be documented as part of the case file.

Acknowledgement letters should be sent to providers of follow-up information which should include relevant feedback, whenever possible (e.g., a planned labeling change).

Follow-up encounters should optimally take place only once; therefore, plans should be made to obtain as much information as possible the first time around.

Collaborative follow-up may be necessary if more than one company's drugs are involved.

If the first written follow-up attempt on a serious unexpected case or a non-serious unexpected case fails to generate a satisfactory response, a second follow-up letter should be sent no later than four weeks after the first letter. In

general, when the reporter does not respond or is incompletely cooperative, the two follow-up letters should reflect sufficient diligence.

A two-letter standard refers to written (including electronic) communication; of course, in addition, there may also have been telephone contact(s) or perhaps a site visit along the way.

For non-serious expected cases requiring follow-up (List A), only one letter (or equivalent communication) should suffice. However, for cases falling under Lists B and C, two letters or other communication should be the rule; for List C cases, a site visit may be needed or advisable.

Consideration should be given to informing regulators, particularly on important cases, if all attempts to obtain follow-up information have failed. This allows them to "close out" the case within their files.

f. Role of Narratives

Introduction

Case narratives are written by companies for different purposes, but primarily as part of regulatory reports on ADRs for a medicinal product. Such narrative statements are required by regulatory authorities to describe the details of cases (*i.e.,* the 'medical story') particularly for those involving serious cases, especially expedited reports. The concept of company case narratives should not be confused with the statements or descriptions of the specific reaction (the text narratives, if you will) received from a reporter by a company, e.g., in a letter describing a spontaneous report. Although parts of such statements may be included verbatim within a company's narrative report to the regulatory authorities, they should clearly be attributed to the specific reporter. Regulators may also find it useful to prepare case narratives on reports received directly (not from companies).

The objective of the narrative is to summarize all relevant clinical and related information, including patient characteristics, therapy details, prior medical history, clinical course of the event(s), laboratory evidence and any other information that supports or refutes a diagnosis for an ADR. The information should be presented in a logical time sequence. If the narrative is to stand alone, it needs to be comprehensive. If pertinent, it is customary to discuss alternative causes of adverse events within a narrative as part of a considered overall evaluation as a conclusion.

Narratives, especially on significant individual cases, are important and useful for case assessment by company physicians and other staff,

investigators, ethics review committees/investigational review boards, data and safety study-monitoring boards, and regulatory authorities. They are considered valuable by those reviewers who want to read the 'story' rather than review line-listed data to obtain information. They may also help the reviewer to assess both the quality of the report and how well documented the case is. Nevertheless, when looking across cases to identify whether a signal exists, many reviewers prefer to examine line-listed information (summary case-data tabulations), at least initially, while others prefer to assess the weight of the evidence from the collection of narratives.

Thus, in addition to their routine preparation for submitting individual case reports to regulators, reviewing a group of narratives may be helpful when investigating a signal of a potential new adverse reaction, clarifying the diagnosis and/or the association to different drugs, or identifying or delineating risk factors and risk groups.

Current Regulatory Perspectives on Narratives

The ICH guideline (E2B) on data elements and specifications for electronic reporting of individual ADR cases states that company narratives are required for all serious reactions. Narrative length is currently constrained to 10,000 characters but enlargement of the narrative field is planned. Narratives are expected to be submitted for all cases reported expeditiously to any regulatory authority, but are useful and should be made available when needed for other types of reports and purposes.

There are regulatory requirements in Japan, Germany, and Austria for the company to provide its overall clinical evaluation for each case, generally from the perspective of whether the new report changes the benefit-risk relationship for the product; it is important that such an evaluation (which can be part of the case narrative) be the same for all regulators who receive them.

Proposals for Format and Content of Narratives

The Working Group considered several issues for which little or no guidance is available with regard to the use and preparation of narratives. The recommendations given apply not only to narratives for marketed products but also for drugs in development.

When should narratives be written?

It is recommended that narratives be prepared for all serious cases and for non-serious unlisted (unexpected) cases. It is not considered useful to do so for non-serious listed (expected) ADRs.

The CIOMS Working Group believes that for purposes of narrative preparation, the Company Core Safety Information (CCSI) should be the Reference Safety Information (RSI) of choice for determining "listedness," recognizing that a decision on reporting to regulators on an expedited basis is always based on local data sheets/labeling. See Chapter III.d.

What are the stylistic and editorial considerations?

Whenever possible, the reporter's exact (verbatim) words for the suspected adverse reaction(s) should be used, supplemented if necessary with clarifying or complementary descriptions.

Narratives should be written in the third person using the past tense.

In general, abbreviations and acronyms should not be used. Relevant laboratory assays and units are an exception but it is important that values be quoted in Système International (SI) units, with an option to include additional units as well.

Time to onset of an event from the start of treatment should generally be given in the most appropriate time units (e.g., days or hours or weeks), but actual dates can also be included if considered helpful to the reader.

If detailed supplementary records are important to a case (e.g., an autopsy report), their availability should be mentioned in the narrative.

Information may be provided by more than one person (e.g., original reporter plus supplementary information from a specialist); all source(s) of additional material should be specified.

When there is conflicting information provided from different sources, this should be mentioned and the sources identified.

If it is suspected that an adverse reaction resulted from misprescribing (e.g., wrong drug or wrong dose) or other medication error, judgmental comments should not be included in the narrative due to the legal implications. However, it is important to state the facts (e.g., "four times the normal dose had been administered," "prescription was misread and a contraindicated drug for this patient was given," etc.).

What should the format of a narrative be?

It is proposed that a standard narrative consist of eight discrete paragraphs in the following order:

1. *source of report and patient demography*
2. *medical and drug history*
3. *the suspect drug(s), timing and conditions surrounding the onset of the reaction(s)*
4. *the progression of the event(s) and its(their) outcome in the patient*
5. *if outcome is fatal, relevant details*
6. *rechallenge information, if applicable*
7. *the original reporter's clinical assessment*
8. *the narrative preparer's medical evaluation and comment.*

ICH Guideline E2B specifies the structure of a case report for electronic messaging. Paragraphs 1 through 6 should be entered in the ICH narrative field (B.5.1) which calls for a focused, factual and clear description of the case. Paragraph 7 should be separated and captured in the ''Reporter's comments'' field (B.5.2). Paragraph 8 may include two different types of information: a suggested reclassification by the company or regulator of the diagnosis made by the original reporter of the case, which should populate field B.5.3, and the sender's (i.e., usually a company's) concluding medical evaluation and comments in field B.5.4.

A sample narrative using the recommended format is shown in Appendix 8. For demonstration purposes, the information that would be obtained directly from the elements within a database are underlined.

A report that is obtained from the literature may already have a well written case summary (narrative) prepared by the author(s). In such circumstances, consideration might be given to using the published summary rather than having to prepare a new one. However, if computer-assisted narratives are in use (see below), this may not be suitable.

Appendix 9 gives some examples of company clinical evaluation comments regarded as either acceptable or unacceptable in the opinion of the CIOMS V Working Group. Often more than one relevant comment would be included at the end of each report in paragraph 8. The contents of this paragraph, as for all others, should not be dependent on the intended recipient of the narrative. This will ensure that the company expresses the same opinion on the case to all regulatory authorities. Its purpose is to provide an opportunity for a company to highlight important issues, e.g., stating why in its opinion the event may not be causally related to the

"suspect" drug. Such interpretations and opinions should always be based on the best evidence available and not on speculation. This section should be clearly identified as an in-house perspective.

In anticipation of using computer-assisted narrative preparation, at least two companies are known to have developed a similar list of standard comments for use in Paragraph 8; staff can choose the appropriate statements to use for the medical evaluation comments.

There is some legal opinion, particularly in the US, that liability issues are possible if such comments are used, which commit a company in writing to an opinion on the case. However, the Working Group is of the view that to have non-harmonized company assessments of the same case anywhere within a narrative or other documentation is potentially a much greater liability concern. Furthermore, with additional information or experience, the company or individual reviewer's opinion on individual or collective cases may change. Consideration should be given under such circumstances, particularly for serious ADR cases, to revising the narrative(s) and informing regulators of such a change (see Chapter III.e. on follow-up reporting).

Some discussion of individual paragraphs will help to explain the process; see Appendix 8 for a complete example.

Paragraph 1 might read, for example: "This case, reference number 517689, is a report from Israel referring to a male, age 42 years, reported by a physician from clinical study 9846, an uncontrolled observational study sponsored by [name of company]."

The underlined information (517689, Israel, male, 42 years, physician, study 9846, uncontrolled observational study) would be derived from the database. The rest is, of course, connecting text. It is important to keep in mind that this information and the rest of the narrative may have to be translated into, for example, French, German, Spanish and Japanese; therefore, insofar as possible, the text should be reasonably standardized and consistent across cases.

Paragraph 7 should contain the causality assessment, if any, made by the original reporter. It is also important to describe other etiological factors which could possibly be relevant. An example might be: "The investigator considers the event possibly related to treatment with drug X. In his opinion, other possible etiological factors are a, b, c." This information could also be derived from the database. For clinical trial cases, the CIOMS III report

recommended a standard Case Record Form (CRF) format for soliciting and collecting this type of information.[35]

How Can the Narrative be Keyword-Indexed?

> *It is recommended that coded adverse reaction terms be placed above the narrative in order of reaction importance, as judged by the preparer.*

All coded terms should be medically rational and derived from the preparer's standard coding terminology, such as MedDRA. Keywords should not include non-medical terms that may have been used by the patient or reporter, even though such terms should be included in the narrative itself (e.g., ''pizzahead,'' an actual example). If possible, use diagnoses whenever known rather than the signs and symptoms comprising the diagnosis; however, the latter should be described in the narrative if part of the reporter's case description. Because death is an outcome and not an adverse event/reaction *per se,* in principle death or fatality should not be a keyword in this context unless the case involves death with no underlying cause provided.

How Should Follow-up Information be Incorporated Into a Revised Narrative?

When relevant new information becomes available, a follow-up narrative may need to be written depending on the amount and importance of the information. There are three obvious options for incorporating the new information: prepare an entirely new narrative; add new information in a separate additional paragraph; or highlight in some way (e.g., bold or underline) the newly added follow-up material interspersed within the original narrative. The Working Group's preference is as follows:

> *Every effort should be made to blend the follow-up details into the original narrative, as usual in chronological order, to avoid repetition and contradictions. However, follow-up information should be identified in some way (e.g., italics or underlining); for multiple follow-up alterations, the dates and/or sequence for each should be documented.*[36]

As a technical detail, it will be important to ascertain whether special markings (such as italics) will be detected after electronic transmission.

---

[35] *Guidelines for Preparing Core Clinical-Safety Information on Drugs,* 2nd edition, Council for International Organizations of Medical Sciences, Geneva, 1999, p. 56.

[36] It should be noted that this approach has met with some difficulty by some companies that have tried it. They found quality control (QC) and administrative tracing cumbersome, especially when multiple updates were involved. Some QC software does not permit tracing different fonts; problems arose in tracing what information came in on what date, and in incorporating conflicting information.

Can the Computer be Used to Help Draft a Narrative?

One area in which modern computer technology can facilitate work in pharmocovigilance is assistance in narrative preparation, which is a resource intensive activity.

> *If done correctly, computer-assistance can have many advantages; it obviously can save time for the preparer to have a first draft produced at the press of a button.*
>
> *Advances in automated (computerized) translation into different languages might also be tried to facilitate case review by all concerned parties.*

The use of such techniques is optimized when as much information for the narrative as possible is extracted directly from the database fields and any extra annotations within or between the data fields are minimized and standardized across cases. No doubt regulatory authorities would also find use of computer-assisted narrative preparation an advantage for summarizing and communicating clinical details of spontaneous cases that are received directly by the agencies, *e.g.,* from physicians.

No matter how a narrative is prepared, there is always the need to reconcile the information between its contents and the data base fields from which it is derived (part of a quality assurance process).

> *Computer-assisted narratives have the additional advantage that they obviate the manual reconciliation step, thereby allowing more focus by the reviewer on case evaluation.*

An effective computer-assisted narrative program will automatically account for phrases or sections not relevant to a particular patient (e.g., deletion of a standard paragraph about death if the patient remains alive or a paragraph about rechallenge if the patient is not rechallenged).

For purposes of clarity and improved understanding, extra information beyond the data stored in the database might be added to a narrative. However:

> *Any alteration to the basic data included within a narrative should be made first and foremost to the underlying database (e.g., an initially incorrect patient's age is corrected); otherwise, the advantages of automated reconciliation are lost.*

It is important to ensure consistency between the data field in the safety or clinical trial data base and the information in the narrative. It may be possible to do so with suitable software applications.

IV

Good Summary Reporting Practices: PSURs Reconsidered

a. Introduction

The periodic summarization and analysis of post-marketing drug safety experience by manufacturers is one of the most useful and important functions for assessing whether a product's safety profile has remained the same or has undergone change. CIOMS Working Group II published proposals for the harmonization of periodic safety reporting by pharmaceutical manufacturers to health regulators in 1992.[1] Its purpose was to define a format and content for Periodic Safety Update Reports (PSURs) that were practical and achievable, would reassure regulators that current safety data had been reviewed, and would preclude the need to produce multiple versions of report formats, contents and periods covered. By its nature, a PSUR is an integrated summary assessment; important acute safety issues are brought to the attention of healthcare regulators, and ultimately providers when appropriate, through expedited reporting and other defined procedures. CIOMS II recommended that companies review their interval (as opposed to cumulative) safety data every six months and that its proposals be initiated for new chemical entities (NCEs) approved during and after 1992.

More recently and significantly, the proposals formed the basis for ICH Guideline E2C ("Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs") which was approved by the Steering Committee in November 1996. The ICH Guideline includes several minor modifications to the CIOMS II format, including a requirement to explain to local regulators any differences between the local product information (data sheet) and the Company Core Safety Information (CCSI), the reference document against which listedness (expectedness) is assessed (see Chapter III.d).

The ICH E2C Guideline is being implemented within individual countries. It was adopted in principle by the EU (CPMP/ICH/288/95; September 1996) and has been incorporated in the "Notice to Marketing Authorization Holders: Pharmacovigilance Guidelines"(June 2000). It was also adopted by the Ministry of Health in Japan in April 1997 and is undergoing implementation over a transition period. In the US, the FDA was expected to publish proposed rules reflecting the guideline early in 2001. Pending implementation in the US, companies are allowed, with waivers, to submit PSURs in lieu of the usual NDA quarterly or annual reports; however, individual case reports (e.g., MedWatch or CIOMS 1 forms) still

[1] *International Reporting of Periodic Drug-Safety Update Summaries* (CIOMS II). Council for International Organizations of Medical Sciences, Geneva, 1992.

must be submitted. The Canadian authorities have proposed adoption of ICH E2C and made it part of their pending post-approval reporting requirements (Product Licencing Framework, Draft IV, May 1999). Regulators in several other countries now accept reports following ICH E2C standards, even though their regulations have not yet been changed.

PSURs and other safety updates require significant time and resources by pharmaceutical companies in their preparation and by regulators in their review. Adding to the complexity are any contractual company arrangements (such as co-marketing of the same product); careful attention is needed to ensure agreements on responsibilities and proper process for PSURs, similar to those discussed in Chapter II.i. for individual case reporting.

In order to assess current company practices and experiences in preparing PSURs, the CIOMS V Working Group undertook a survey during 1999 of 29 multinational companies in the US, Europe and Japan. The results are summarized later in this chapter and presented in full in Appendix 11. The experience gained over the past several years has led to the recognition of several problem areas that were not foreseen and for which the process might benefit from change or enhancement. The primary focus of the CIOMS V Working Group was to develop recommendations for the following problem areas:

- Concerns on format and content for reports covering long-terms (e.g., five years) or generally for high ADR-volume reports. For example, are individual case line-listings necessary or desirable for hundreds or thousands of cases? How should exposure data, publications, and other data be handled? What version of the Company Core Safety Information (CCSI) is best suited for an effective analysis? Modifications to PSUR content are proposed.

- The ICH PSUR guideline specifies that regulators wishing to receive reports less frequently than others should be prepared to accept, for example, multiple six-month reports that cover the longer period. However, a method is needed to tie together (bridge) such multiple reports for ease of understanding. A brief "Summary Bridging Report" is described to accommodate this need.

- Although ICH introduced the concept of a single International Birth Date (IBD) that would define the PSUR data cut-off dates globally for all parties, for various reasons some authorities do not accept reports (e.g., six-month or one-year) if the data are "out of date" vis-à-vis the product's local birthdate (approval anniversary). For

example, a standard PSUR covering the period 1 December 1999 to 30 November 2000 may not satisfy a regulator insisting on coverage from 1 March 2000 to 28 February 2001. A proposal is made for a simplified "Addendum Report" to cover the desired new data (1 December 2000 to 28 February 2001 in the example).

- For old drugs with a well established safety profile and even for recently approved drugs, there may be little or no new information to report for a PSUR review period. Recommendations are given for simplifying such PSURs.

In addition to these four broad concepts, there are several related details for which proposals are made. The aims of any solutions to the current difficulties are that they be practical and achievable with the focus on safety assessment rather than on merely satisfying sometimes divergent or arbitrary regulatory requirements. The options considered require that both companies and regulators be flexible. Focus is placed on suitable solutions for report content, format and frequency which undoubtedly should depend on the stage a drug has reached in its life cycle — whether the product is new with a rapidly evolving safety profile, has an established profile which has changed little over several years, or lies somewhere in between. The need for new approaches also depends on the volume of ADR reports received during the review period.

To assist in understanding the recommendations developed by the CIOMS V Working Group, it may be useful to review some of the fundamental principles and practices underlying CIOMS II and ICH E2C reports, and some of the associated problems (see Appendix 10). In addition, the special reports required for product license renewal and re-examination/re-evaluation required, respectively, in the EU and Japan introduce some interrelated difficulties which are also explained in Appendix 10.

The Working Group has attempted to articulate many of the vexatious problem areas associated with PSURs; however, some were beyond its capacity to provide adequate solutions.

b. Results of a Survey on PSUR Workloads

A questionnaire was sent to the pharmacovigilance departments of 50 multinational companies in May 1999 to assess the practices and burdens associated with the preparation of periodic safety reports during the year 1998. The companies were based in Europe, US and Japan. Each company

was asked to respond on behalf of their entire corporation by obtaining data from their affiliates, if appropriate. Responses were received from 29 companies (48%), 6 based in Europe, 12 in Japan, and 11 in the U.S. The entire questionnaire and the results are provided in Appendix 11. An overall summary is presented below.

Table 1 shows that in 1998, companies prepared periodic reports for an average of 47 active compounds covering 86 different products; ICH PSURs and US NDA reports dominated, but many companies prepared CIOMS II reports and other formats to satisfy special individual country requirements (Table 2). Further breakdown of the types of reports, including license-renewal reports, is found in Table 3. The actual number of all types of reports averaged 87 for U.S., 115 for EU, and 7 for Japanese companies (Table 4). As shown, some companies prepare over 200 different reports per year; the numbers for Japanese companies were surprisingly low and may reflect the fact that they dealt only with local reports.

Table 1. Number of Products Covered Per Company

	a. Mean number moieties [range]	b. Mean number products [range]
Europe	96 [30-150]	221 [100-308]
Japan	6 [2-11]	10 [4-27]
US	59 [3-148]	99 [3-250]
Overall	**47** [2-150]	**86** [3-308]

Table 2. Types of Reports Prepared by Companies (Number of Companies)*

	a. CIOMS-II	b. ICH PSUR	c. US NDA	d. Other**
Europe	3	6	5	1
Japan	3	8	1	6
US	2	10	8	2
Total	**8**	**24**	**14**	**9**

* Some companies prepared more than one type.

** Local requirements or PSUR variations.

Table 3. Different Types of Reports: Range in Number of Reports by Location of Companies

	US	EU	Japan
US NDA Quarterly	1-46	4-82	–
US NDA Annual	2-109	2-109	1
6-Month PSUR	2-50	5-30	1-6
CIOMS II or ICH E2C:			
One-Year PSUR	1-48	5-25	1-5
Five-year relicensing (for EU)	1-13	1-27	1
Six-year relicensing (for Japan)	1-20	22-27	5-16

Table 4. Mean Total Number (Range) of Reports Prepared in 1998
(Four non-responders)

US (N=10)	87 (6-222)
EU (N= 5)	115 (41-224)
Japan (N=10)	7 (1-23)
Total (average)	**60 (1-224)**

Among the many responses to the different types of survey questions, the following represent some of the key findings:

- ❏ 22 companies (76%) prepare combined reports for different dosage forms/formulations and/or indications
- ❏ EU regulators have rejected or criticized reports prepared according to ICH E2C for 21% of respondent companies; among reasons given were inappropriate inclusion of medically unconfirmed (consumer) reports within the core PSUR (E2C does specify that such reports be relegated to a PSUR addendum if their submission is required by a regulator)
- ❏ 90% of companies preparing them use the same 5-year (EU) or six-year (Japan) relicensing report for different countries even though time periods are not in complete accord with anniversary dates. However, 7/19 (34%) companies report initial rejection of the submissions as a result (including Belgium, Finland, Germany, Ireland, Italy, Sweden)

- ❑ 9/23 companies believe the PSUR process (including labeling review) led to detection of an important safety signal not identified through expedited reporting; some companies indicate that the PSUR process merely confirms trends
- ❑ 80% of companies indicated that the redundancy incurred in preparation of multiple reports on the same product(s), due to different anniversary date requirements by different regulators, was "bothersome" (40%) or "extensive" (40%)
- ❑ about one-third of companies indicated they had prepared PSURs or five(six)-year license renewal reports that contained more than 500 ADR cases; the time to prepare a PSUR more than doubles as case volume increases from less than 100 to greater than 500
- ❑ most companies indicated they were able to prepare a "typical" 6-month PSUR within the required 60 days from data lock point.

The details in Appendix 11 should be consulted for a more extensive perspective on the many issues and ideas raised by the survey respondents.

c. Proposals for PSUR Content Modification

The CIOMS V Working Group agrees that the full ICH E2C format should be used for most PSURs. However, two situations have been identified that might benefit from alterations to the standard content prescribed under the ICH Guideline: (1) long-term reporting periods and/or high ADR volume and (2) little or no new information during a reporting period. Not all 10 of the ICH PSUR standard sections will be affected, but they are listed as a convenient reminder:

1. Introduction
2. World-wide Marketing Authorization Status
3. Update on Regulatory Authority or Marketing Authorization Holder (MAH) Actions for Safety Reasons
4. Changes to Reference Safety Information
5. Patient Exposure Data
6. Individual Case Histories: Line Listings and Summary Tabulations (including discussion of individual cases as necessary)
7. Studies

8. Other Information (efficacy-related; late-breaking important safety data)
9. Overall Safety Evaluation
10. Conclusion

Some reports may require supplemental information (usually as appendices) to satisfy specific local regulatory requirements (e.g., line listings and/or summary tabulations on spontaneous consumer reports).

Suggestions for PSURs with a High Volume of Reports and/or Long-Term Coverage

For reports that cover long periods of time, especially those with very large numbers of ADR cases, the required line listing is voluminous and unwieldy (tens or hundreds of pages). Other practical problems arise that reflect on the necessity and utility (or lack of utility) of the typical information in a standard PSUR. More streamlined inclusion and presentation criteria for the data are desirable under such circumstances. The following modifications to specific ICH PSUR sections are recommended:

Section 4. When producing a full five-year report it is often impractical to base the analysis of listedness on the CCSI which was in effect at the beginning of the 5 year period unless there have been very few changes. There can be considerable variations in listedness over 5 years depending on when the classification is made (i.e., on an ongoing basis, such as at ADR case entry, or when a PSUR is compiled). Flexibility is proposed depending on the company process.

When listedness is classified at the time of PSUR preparation it should be acceptable to use the then current version of the CCSI as the reference document as long as that choice is made clear in the PSUR text.

Companies allocating listedness at case entry throughout the five year period may also find it helpful to include the most current version of the CCSI and comment on the reasons for the change in listedness assessment over time. In both cases, changes added since the previous PSUR should be explained in sections 4 and/or 9, as needed.

This will have an impact on Section 6 of the PSUR. Non-serious unlisted ADRs that are added to the CCSI over the five year period become listed, and therefore no line listing would be needed if the then current version of the CCSI is used and accepted as the reference safety information by the regulators.

Section 5. Especially for many older products, clinical trial exposure may be minimal over a 5 year period and in any event will be far exceeded by market exposure. It is proposed that:

Clinical trial data should only be included if the data suggest a signal or are relevant to any suspected changes in the benefit-risk relationship for the product.

Section 6. When several hundred or more individual case histories have been received in the period covered by a PSUR, the line listing will be extensive and its value in any form questionable.[2] Currently, line listings *per se* are not entered into the databases of any known regulator; furthermore, review of extensive line listings on paper is highly impractical. It is proposed, therefore, that:

For all PSURs containing more than 200 individual case histories, the line listing be omitted and only summary tabulations submitted.[3] If a company does not submit a line listing, it must provide one within 10 working days of a regulatory request.

The standard line listing in an ICH PSUR contains all serious (listed and unlisted) and non-serious unlisted ADR cases. When the number of individual case reports fulfilling ICH E2C line listing criteria exceeds 200, the individual cases will not be line-listed, but will only be included as summary tabulations. Furthermore, the serious unlisted cases will have already been reported to most or all regulators (depending on the local data sheet) on an expedited basis, and will be discussed specifically within Section 9 of the PSUR.

A statement that a line listing can be made available promptly should be included in the PSUR. It must be emphasized that companies must still review and analyze all the case histories received in the time period to search for safety signals.

When the line listing is omitted, presentation and analysis of the case reports through the summary tabulation(s) becomes especially im-

[2] In principle, company-generated line listings may become moot in the future for those regulators able and willing to receive individual case reports electronically, especially on an ongoing basis. Thus, they will be able to create their own line listings as needed. However, it is uncertain when such a situation will prevail and furthermore there will presumably always be some authorities requiring that line listings be submitted.

[3] For widely used products, MAHs may receive many hundreds or thousands of ADR case reports, not only over long periods such as five years , but during shorter PSUR intervals. There is no magic number that qualifies as defining a very large, unwieldy volume for a line listing; 200 is chosen arbitrarily as a reasonable cut-off. Clearly, for any event involving a signal or key safety issue, all relevant cases should be line-listed independent of any cut-off number.

portant and should be included as usual (e.g., by system organ class (SOC) and other informative breakdowns such as dosage form, indication, etc., as necessary). ADR terms used for the tabulations should be at a relatively high level (e.g., MedDRA preferred-terms) which can then be expanded in Section 9 if a safety signal is apparent. However, care must be taken to ensure that medically important distinctions are not overlooked by using terms at too high a level (e.g., kidney disorders vs acute renal tubular necrosis). Also, it is important that when possible, diagnoses rather than (or in addition to) signs and symptoms be identified in summary tabulations.

Depending on individual company processes, sorting of thousands of individual case histories by seriousness and listedness may be complex and time consuming, especially if the CCSI has changed in the 5 year period or there were recent changes in working practices to accommodate the ICH E2C requirement. Presentation and assessment in terms of listedness (rather than by serious vs non-serious) under each system organ class may be the most meaningful approach. Seriousness can be addressed in section 9 when a signal is discussed.

With regard to the utility of follow-up information on individual cases:

When there is a five year gap since the previous PSUR, any follow-up information on cases described in the ***previous*** *PSUR should be limited to cases associated with safety issues that are new or still under consideration.*

Section 7. A large number of clinical or non-clinical studies may have been conducted during a five-year reporting period. Similarly, a comprehensive literature search for an active drug could potentially produce several hundred papers. Therefore:

As usual, only those studies related to safety, including Prescription Event Monitoring (PEM) and epidemiology studies (see Chapter II.g.), should be listed, with any final or interim results discussed.

The inclusion and discussion of literature reports should be selective and focus on publications relevant to safety findings, independent of listedness. (See Chapter II.c.)

Section 9. *For reports with extensive amounts of ADR case data, discussion and analysis for the Overall Safety Evaluation should be partitioned by system organ class (SOC), rather than by listedness or seriousness; the latter properties would, of course, still be covered under each SOC.*

Suggestions for Simplification of PSURs with Minimal Information

Under circumstances when only a few adverse reaction cases have been reported during the time period covered and if no or only non-significant changes in the safety profile have emerged, the content specified for ordinary PSURs may be more extensive than the data can support. The CIOMS V Working Party is not suggesting a new format but simply an approach when there are little or no new safety data. An abbreviated content PSUR can be prepared more easily, thus saving time and resources for both companies and regulators, while still providing all relevant information. The key question, of course, is how to define little or no new information or findings. The following criteria are suggested, all of which ought to be considered:

(1) No serious unlisted cases have been received, there are very few serious listed cases (e.g., 10 or less) and all the remaining cases are non-serious.[4]

(2) No significant regulatory actions have been taken for safety reasons during the time period reviewed.[5]

(3) No major changes have been made to the core safety information. A proposed definition of a major change would include the addition of a serious ADR, including drug abuse and dependence, or an addition or modification to the contraindications, warnings, precautions, pregnancy/lactation or drug interactions sections.

(4) No findings have led to any other action (e.g., initiation of new targeted safety studies). As usual, a list of any completed studies that focussed on safety should be mentioned. If such studies had been initiated or analyzed for the first time, a full-length PSUR would generally be expected.

When there is little or no new information to report, the Marketing Authorization Holder should be permitted to submit an abbreviated version of the standard PSUR that reassures regulators that all relevant data had been reviewed and that no meaningful changes to product information or use was required.

---

[4] Judgment will be needed in deciding what kinds of cases and how many represent the basis for "simplification." The example of a simplified PSUR in Appendix 12 illustrates the practical complexities.

[5] It is not uncommon for local regulators to request changes to safety information in a data sheet. Such label changes may not result in changes to the company's CCSI. Therefore, it is incumbent on the company to use its judgment on whether local label alterations constitute "regulatory actions for safety reasons."

Under this scheme, inclusion of the full inventory of locations where the drug is marketed (ICH PSUR Section 2) would be unnecessary, but any new approvals should be specified. An example of a simplified PSUR is presented in Appendix 12. While the example is for an annual report, the same format could be used for 6 month and 5 year reports as well. Please note that the example purposely does not technically satisfy all the suggested criteria but is included to illustrate how a special situation can be handled.

It is recommended that there should be no simplification of PSURs for the first two years following the first introduction of a new chemical entity in an ICH country.

d. Proposals Relating to Frequency and Timing of Reporting

As already discussed, there are circumstances in which the usual reporting schedule as designated by many regulators does not or cannot readily apply. For example, regulators who do not wish to receive 6-month reports but prefer only annual reports are, under ICH E2C provisions, expected to accept two 6-month reports that a company may have already prepared. In order to avoid the need for a company to prepare a separate one-year report when the product is still under a 6-monthly reporting cycle, a need has been expressed by regulators for some other way to tie together (''bridge'') the two 6-month reports (thus, a Summary Bridging Report). Another key issue relates to the situation in which an already prepared PSUR may be considered out of date relative to a particular regulator's requirements for report submission. In order to avoid the necessity of preparing yet another report covering a different calendar period, interval information covering periods beyond the closing date for a PSUR would be a rational solution (thus, an Addendum Report).

A final topic under this heading deals with difficulties associated with five-year license renewal reports in the EU. Some ideas are advanced to help overcome the problems.

One possible practical approach to help overcome the difficulty associated in general with timing and frequency of reporting for new drugs would be to continue with a six-monthly or annual schedule indefinitely, especially if new indications or formulations are likely to be introduced over the years. A series of 6-month or annual reports can then be submitted, as

needed, with a summary bridging report (see below) to serve as the basis for 5 year reports, including those needed for license renewal in the EU (or reexamination in Japan). However, whether such an approach is suitable will depend on the number and types of products a company sells, business processes, resources, and other factors. Although companies should regularly review their safety data on an ongoing basis (typically six-monthly), unless required to do so as part of the PSUR reporting schedule, written reports (PSURs) summarizing the data need not be prepared routinely.

Summary Bridging Reports

The summary bridging report is a concise document integrating the information presented in two or more PSURs, which is submitted to a regulatory authority to cover a specified period over which a single report is required.

It does not contain any new information. The primary purpose of the summary bridging report is to use existing PSURs along with a suitable bridging summary so as to avoid unnecessary effort. For example, it may be used to cover four six-month reports in lieu of a separate two-year report, or five separate annual reports for a new, cumulative 5-year report, including reports for license renewal in Europe. The bridging report would obviously cross reference the covered individual reports and, although some of them may have been previously submitted as part of a shorter reporting cycle, the actual reports should be appended.

The submission of a summary bridging report should not by itself indicate a need for a new review of the data. Usually, it should only cover the information in the appended PSURs and not update them. Neither is it intended to be a cumulative report. Its main function is to assist the reviewer, usually the regulator, by providing a helpful overview of the appended PSURs. Details of each PSUR do not need to be repeated in the bridging report provided there is consistency between the appended PSURs with regard to presentation and interpretation of information (e.g., method for estimating exposure data). The MAH can simply cross-reference the relevant sections of the appropriate PSUR, usually the most recent in the series.

If a substantial interval has passed since the data-lock point of the most recent appended PSUR, it may be necessary to produce an addendum report (see below) as an update to describe the intervening experience. This report would also be appended and referenced in the bridging report. The summary bridging report itself, however, is not the tool for such interim (addendum) reporting.

It is logical that the outline of a Summary Bridging Report follow the same format/outline as an ICH E2C PSUR, as shown in the following sample template:

- **Introduction** — a brief description of the purpose of the document specifying the time periods covered and cross-referencing the appended PSURs.
- **Worldwide Market Authorization Status** — a simple statement on the number of countries which have approved the product and a cross-reference to the appropriate tabulations of the most recent PSUR appended.
- **Update on Regulatory Authority or MAH Actions for Safety Reasons** — an integrated summary of actions taken. It may not be appropriate to structure this chronologically but according to issues and the most recent measures taken to manage them.
- **Changes to the CCSI** — a listing, with appropriate cross-references, of significant changes made over the entire period. It may be useful to present this by body system (SOC) if there have been several changes.
- **Exposure data** — an estimate of the total number of patients exposed in the time period covered by the bridging report (including from clinical trials if appropriate). This is particularly important if different methods of calculation have been applied from one PSUR period to another. The method used for the bridging report should be clearly stated.
- **Individual case histories** — a brief statement giving the total number of cases presented in the series of PSURs appended. In general, it is not necessary to produce new line-listings or summary tabulations even though inevitably, due to the dynamic structure of databases, numbers of cases and some details may have changed subsequent to preparation of the most recent PSUR. An exception would be when there is an important specific safety issue that has not already been adequately discussed in one or more of the covered PSURs; then it would be appropriate to include a cumulative line listing or summary tabulation for the types of cases of concern, pointing out any differences from prior listings or tabulations.
- **Studies** — a brief summary of any important targeted clinical safety studies mentioned in the PSURs may be useful, with appropriate cross-referencing.

- **Other information** — only highly significant safety information received after the last data-lock point for the most recent PSUR should be included.
- **Overall Safety Evaluation and Conclusion** — mention only key unresolved issues and possible measures to address the problem.

An example of a summary bridging report is presented in Appendix 13.

Addendum Reports

The concept and use of an International Birthdate (IBD) for PSURs have not been fully accepted by all regulators. As a result, some authorities are not prepared to accept PSURs perceived to be out of date relative to the local approval date (see Appendix 10 for details). Furthermore, even if the IBD is honored, some authorities may request data for a period outside the routine reporting cycle; for example, when a drug is the subject of five-year PSUR reporting, an authority may request data covering four years. The CIOMS V Working Group strongly advocates that all regulators strive to adopt the IBD and a standard PSUR reporting cycle. Until then, an expedient approach is needed to manage the inconsistencies in harmonization without adding an undue burden for both companies and regulators in the preparation and review of extra reports. In that spirit, an "Addendum Report" is recommended.

An addendum report is an update to the most recently completed scheduled PSUR when a regulatory authority (or the company) requires a safety update outside the usual reporting cycle, and more than a brief amount of time has elapsed since the most recent PSUR.

It will summarize the safety data received between the data-lock point of the most recent PSUR and the authority's due date. Addendum reports will usually supplement either annual or five-year PSURs. They should not be required routinely but should be prepared only on special regulatory request.

Depending on circumstances and the volume of additional data since the last scheduled report, an update (addendum) may follow the ICH E2C format or a simplified report (see above). However, recognizing the limitations of pharmacovigilance resources, the Working Group proposes the following minimum information for inclusion in an addendum report:

- **Introduction** — a brief introduction to the report giving its purpose and a cross-reference to the last scheduled PSUR (and any previous addenda if relevant).

- **Changes to the CCSI** — details of the changes to the core safety information since the last scheduled PSUR and a copy of the most recent CCSI if it is different from the one within the PSUR.
- **Significant regulatory actions bearing on safety** — new information subsequent to the most recent PSUR
- **Line listing and/or summary tabulations** — inclusion of the new cases in the usual format. If the volume of reports is high, as already recommended consideration should be given to excluding the line-listing.
- **Conclusion** — a brief overview of the new cases included and a comment on whether or not they are in line with the known safety profile of the product.

In summary, the purpose of an addendum report is to supplement, not replace, the basic reporting cycle. For example, if an addendum has been produced three years following the most recent five year PSUR, the next scheduled five year report will be prepared relative to its usual anniversary date and will include the data in the addendum plus the data for the following two years.

License Renewal Reports in the EU: Special Problems

Some EU countries accept a company's previously submitted PSUR reports through month 48 (i.e., four six-month and two annual reports) as satisfying most of the safety component of the license renewal requirements; to complete the renewal application, supplemental data must cover the 6 month period from the 48-month data-lock point through month 54. (See Appendix 10) However, *cumulative* 5-year safety updates (in reality 4.5 years for the first such report) are still required for license renewal by some countries, which necessitates the preparation of a whole new report beyond those already submitted as PSURs.

Subsequent five-year license renewal reports would be submitted at five year intervals following the submission of the first "five year" report (that really covers, as stated, 4.5 years). It was agreed that it should be acceptable to provide multiples of six-monthly or annual reports that have already been prepared by the company to cover the period requested by individual regulatory authorities to comply with their own local requirements. However, it was considered necessary that the reports be accompanied by a document chronologically summarizing the information contained in the series of reports (a Summary Bridging Report as described above). This same concept is applicable for all five-year license renewals subsequent to the first one.

Another general improvement in the overall system would be for the EU regulators to consider allowing synchronization of the license renewal date for each formulation of each product across countries.

e. Miscellaneous Proposals for Managing PSURs

The Working Group discussed several items of technical detail that do not fit neatly into the above discussions but are of practical importance in managing the preparation of PSURs. Several relate to the need for adjustments for "older" products to the newly emerging PSUR system. Individual regulators may define what is meant by "old" products; there is no general definition.

Synchronization of International Birthdates (IBDs)

Ideally, it would be a great advantage to synchronize the international birthdate for all formulations of all drugs in all EU countries. This would facilitate regulatory review of PSURs and relicensing reports, especially if the regulators wish to cooperate mutually in the review process. However, it must be recognized that such a conversion for existing drugs is time consuming, expensive and not very practical especially for global companies with extensive portfolios and line extensions; each attempt requires a variation application within each country. Nevertheless, it may be possible for companies with fewer products.

Scheduling the preparation of PSURs for a company's entire portfolio of drugs is ordinarily dictated by each product's "birthdate." However, the international birthdate is frequently unkown for very old products and has little relevance; even if such a date could be determined, it is not known whether individual regulatory authorities would accept it under the new PSUR system in place of the original anniversary date. It is proposed that:

Manufacturers should be allowed to select their own IBDs for "old" products, and therefore the data cut-off (review) dates for such products, to allow synchronization of reports to all regulators and optimization of PSUR workload scheduling. Once the IBD is chosen, it should be adhered to thereafter.

Approval and Launch Dates for Old Products

The dates of approval and launch in various countries called for in ICH PSUR Section 2 are not always readily available for old drugs.

If the product is already marketed in several countries, and there have been no new approvals in the period since the last report, or in the last five years

if no previous PSUR exists, it is recommended that only a list of countries where the drug is marketed (in alphabetical order) be required.

Naturally, this modification will not be appropriate if the data were available and already presented in full ICH E2C format in a previous PSUR.

It is also necessary, as usual, to indicate which countries, if any, have refused approval or license renewal, or in which the product has been withdrawn for safety reasons, along with an explanation.

CCSI (Reference Safety Document) for Older Products

If there is no CCSI for an old product it will be necessary to generate one. This could be accomplished *de novo*. However, it might be useful to review the available local data sheets for the product and select the most suitable one as a basis for the CCSI. It would not be considered acceptable to use data from a standard textbook or monograph for the CCSI, although useful data could be obtained from such sources.

Types of ADR Case Reports and the Overall Safety Evaluation

The evaluation in any PSUR should focus especially on unlisted ADRs and it is suggested that analyses be organized primarily by body system (System Organ Class) rather than by seriousness and listedness; the latter will of course be discussed within each body system. It is also important to indicate that all the cases received during the period, including medically unconfirmed cases (see Chapter II.b.), have been reviewed and that no issues related to them have been identified. Although solicited reports should also be examined as part of a general data review for any possible contribution to the analysis, data from those sources should not be commingled with standard spontaneous and study data (see Chapter II.e). It is also important to remember that discussion of serious unlisted cases should cover cumulative data.

When is it Appropriate to Restart the PSUR Clock?

There are two general situations for which regulators must consider whether it is necessary to ask companies to revert to a six-month reporting interval when a longer period (one or five years, e.g.) is already routinely covered: (a) when a new use (indication, population) or dosage form is introduced to the market and (b) when a relatively mature drug with a well established safety profile enters a new market for the first time.

The need to reset the clock under any circumstances should be driven by the data available to support the product's safety profile and the relative

stability of that profile, not by regulatory approval dates. The safety profile of a product is best characterized according to the number and types of patients treated; reporting frequency should be influenced by the extent of clinical knowledge of the product.

(a) For products with a well characterised safety profile, renewed annual or semi-annual reporting should apply only after important changes in clinical use are first approved (e.g., for a new clinically dissimilar indication, or in a previously unexposed patient population, such as children or pregnant women). Even then, the analyses in the PSUR should focus on the newly-exposed population by identifying and characterising any differences from the established safety profile.

(b) Products with a well established safety profile based on a long market history and extensive patient exposure that are approved for the first time in a new market should not automatically require frequent (annual or semi-annual) PSURs, something that is now required (in Japan, e.g.). For such products, it is recommended that regulators in the new market accept a summary tabulation (with or without supporting line listings) of spontaneously reported adverse events over the shorter periods in the new market (say every 6 months for a reasonable length of time, perhaps two years). MAH comment on whether the experience reflects the established suspected ADR profile would also be appropriate. For such short-interval data submissions, review of the worldwide literature is not considered necessary, especially for older products already available generically in major markets.

For both (a) and (b), in any event, consideration for restarting the clock should be discussed between the regulators and the company preferably prior to but certainly no later than time of approval of the relevant application dossier.

Are 60 Days Sufficient to Prepare PSURs?

Currently, all PSURs must be submitted within 60 days from the data lock-point date. There is a need for a greater degree of flexibility in the time-line to ensure that not only all the relevant safety data are covered (line-listings, tabulations, literature, studies) but appropriate analysis and interpretation of the data are made (overall analysis and conclusions).

The length of time to complete a PSUR should be based on one or more of the following factors:

- Period covered by the report (i.e., six-months, one year, five years)

- Number of reports for the reporting period (high volume versus low volume)
- Drug activity (e.g., issues raised by Health Authorities that may require subset analysis)
- Complication of the treated disease(s) (e.g., cancer with cytotoxic drugs, AIDS with multiple antiretroviral agents)
- Nature of product information (CCSI, data sheets); if there is a relatively small number of ADRs listed in the CCSI, especially for a new, very active product, the drug safety evaluation may be more complicated
- Whether safety issues had been raised in previous PSURs (e.g., is a cumulative safety evaluation for unlisted suspected ADRs needed).

For a well-established product, without any specific safety issues and a low volume of adverse event reports, 60-days for completion of the PSUR is relatively easy. However, for a recently introduced product with multiple safety issues that is indicated for a complicated disease syndrome and is associated with a high volume of adverse event reports, a longer preparation time (e.g., 90 days) would be more appropriate, regardless of the period covered by the report.

The goal of PSURs as a means for maintaining diligent pharmacovigilance is better satisfied by permitting additional time for preparation when warranted; in this sense, flexibility is called for. When a company realizes that 60 days may not suffice, it should alert regulators to a possible delay and provide an explanation; this will allow the regulators to facilitate their own review planning, especially if it involves multiple agencies (e.g., CPMP in the EU).

An Executive Summary for PSURs

The Working Group recommends that companies consider preparing a brief overview (executive summary) of each PSUR. It would provide the reader, especially the regulators, with a description of the basic content and most important findings as a guide to the full document.

A fictitious example is shown in Appendix 14. It is recommended that the Executive Summary preface the PSUR but should not be used as the usual cover letter for submission of PSURs, because that is typically generated locally.

V

Determination and Use of Population Exposure Data

a. Introduction

Obtaining and understanding patient exposure information (the "denominator") is important for both manufacturers and regulatory authorities to help assess the benefits and risks of any medicinal product and to place such information in proper perspective.[1] The need to evaluate the benefit-risk relationship spans the continuum of a product's lifecycle, from early in clinical development through its use in the marketplace. Not only are exposure data required for routine regulatory reporting purposes (as part of a PSUR, for example), but used properly they are essential for addressing special problems (or opportunities). In general, appropriate use of denominator data is part of good epidemiological and public health practices.

There are many difficulties associated with obtaining and using the relevant data, particularly from sources outside the relatively controlled environment of clinical trials or other studies in which the size and characteristics of the treated populations are known with considerable accuracy. Estimating person-use for marketed drugs usually relies on gross approximations, especially for non-prescription products, and represents more of an art than a science. Of course, there are exceptions for which accurate counts are possible, such as administration of a single-dose treatment in hospital or clinic under direct supervision, or in vaccination programs. However, these represent the exception.

The level of detail and accuracy required for exposure statistics will depend on the intended use of the data. A simple denominator that defines broad exposure, useful for routine periodic safety reporting, might need only a count or estimate of all exposed subjects, without regard to their characteristics. On the other hand, an analysis of a subgroup, defined by age and/or gender, for example, might require considerably more effort. Although it may be useful, even important, to obtain breakdowns of patient exposure according to the many covariates that define user groups (see below), it is usually very difficult to obtain such detailed and extensive data outside a clinical trial environment.

The CIOMS V Working Group conducted a survey of manufacturers and regulators in 1998 to help gain insight on their knowledge of this topic

[1] The word "exposure" is often used to represent an individual patient's treatment experience. However, in this context, the word should be regarded as synonymous with "denominator," a measure of the number of patients in a population that are treated with a medicine. The dimension of time on drug is obviously important in any real measure of drug-exposure.

and on their practices. It was designed to collect information on sources of denominator information, exposure metrics, time period covered by exposure information, processes for compiling exposure data, circumstances surrounding the determination of exposure data, and regulatory experience with exposure data; the questionnaire and results are presented in Appendix 15 but are summarized here. Four agencies (Canada, EU (EMEA), Germany, US), the WHO Collaborating Center (Uppsala) and 19 companies (14 in Europe, 5 in US) provided replies.

Sales statistics (e.g., amounts sold) are the main source of exposure data for 63% of companies; only one of the regulators reported access to and use of such data. Only 20% of the companies agreed that marketing data were sufficiently complete and accurate for the purpose of estimating drug exposure. Information on particulars such as duration of treatment, age or gender of exposed population, or the medical specialty of the prescriber, were not available through traditional sales information and when needed had to be obtained from other sources. Although the majority of companies were aware of one or more of the various non-company databases mentioned in the questionnaire (e.g., various IMS Health products), surprisingly only 7/19 were using one or more of them. In contrast, 3/4 of the regulators and WHO reported using at least one. The most commonly used type of unit for describing marketed drug use was patient-time (e.g., patient-days), used by 17 of 19 companies and 4 of 5 of the regulators/WHO.

Most (16/19) companies and one of the regulators routinely attempt to assess whether the reporting pattern of ADRs changes over defined reporting periods. However, most companies did not or were unable to routinely stratify patient exposure by age or gender. Estimates of off-label use were made by 5 (19%) companies but by three of the four regulators. However, most respondents did report attempts to collect and assess data relevant to overdose.

The survey revealed that the regulators were generally dissatisfied with the amount and type of exposure data supplied by Companies, describing the data received in PSURs as "good" (1/4) or "poor" (3/4). They also regarded the use and interpretation of exposure data by Companies as "good" (1/4) or "poor" (3/4).

In covering this topic, the CIOMS V Working Group believes that (i) there are more extensive data available and techniques for accessing them than generally believed and (ii) there is a need for guidance on analytical methods for using denominator data, especially for monitoring and assessing drug safety profiles.

The approaches described here focus on the post-marketing environment and are generally applicable to both prescription and non-prescription medicines. For clinical trials and other studies in which the treated populations are usually well characterized by their nature and size, there are established methods for calculating and representing "drug exposure" (something that is deceptively simple, but can actually be quite complicated);[2] this topic will be discussed briefly.

There is another aspect to the concepts of numerator and denominator, particularly when attempting to use spontaneous report data for signal detection. One important statistic that is always valuable is the background rate for a condition within a specific population (e.g., gender or age group). For example, when faced with a case series involving a new, especially unusual, adverse medical condition, an estimate of the background rate for the type of population exposed to the drug can be very useful. Such data, when available, can be found in compilations of national health statistics databases. Several cases of an unusual adverse event in a population in which that event is very rare would suggest at least the possibility of a drug signal.

b. Periodic Safety Update Reports and Exposure Data Sources

PSURs represent one of the most common and routine circumstances for which an estimate of patient exposure is needed. In addition to helping place into perspective the numbers and types of safety reports over time, the data also are useful for detecting trends in drug use. The ICH Guideline on PSURs (E2C) describes the types of data needed and how they might be used.[3] In summary:

- ❑ an estimate of patient-use should be provided along with a description of the method used to derive the data
- ❑ the estimate should cover as closely as possible the same period as the interim safety data

---

[2] O'Neill, RT. Statistical analyses of adverse event data from clinical trials. Special emphasis on serious events. *Drug Information Journal*. 21: 9-20, 1987 and Lee, M-L T and R Lazarus. Meta-analysis of drug safety data with logistic regression. *Drug Information Journal*. 31:1189-1193, 1997. Also, see Gait, J. E., Smith, S. and Brown, S. Evaluation of Safety Data from Controlled Clinical Trials: The Clinical Principles Explained. *Drug Information Journal,* 34: 273-287, 2000.

[3] *Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs. ICH Harmonised Tripartite Guideline E2C* in Proceedings of the Fourth International Conference on Harmonisation. Brussels 1997. Appendix 4. Ed. P.F. D'Arcy, D.W.G. Harron, Belfast 1998; pp. 613-634.

- ❑ when possible, and particularly if needed to understand and interpret the safety information, the data should be divided by age and/or gender.

Even for routine use, it would be advantageous to have exposure data in terms of other variables, such as duration of exposure, indication, dose and dosage form; however, it may be very difficult to obtain such breakdowns, especially within the timeframe needed to prepare and submit a PSUR. One particular gap is the absence of hospital-based (inpatient exposure) statistics from the major use-monitoring sources. Thus, in the absence of special situations (important safety signal, for example), an overall estimate expressed in customary terms and units (see below) is adequate. The general CIOMS V recommendation is:

> *For a PSUR, detailed calculations on exposure (the denominator) are ordinarily unnecessary; especially given the unreliability of the actual numbers of cases (numerator),*[4] *order of magnitude estimations should suffice.*

Available sources of data and methods for estimating drug use depend on the setting (e.g., studies vs marketed drug use) and are highly variable with regard to their level of accuracy, geographic coverage, and degree of detail (re covariates of interest or need). In clinical trials, compassionate treatment (named-patient) programs, observational studies and other situations in which a cohort of subjects is readily defined, the number of patients treated with a drug is easily obtained. However, the proper measure of patient-exposure as a function of time, demographics, and other parameters requires care. It should also be remembered that for complete estimates of drug use, data covering generic products and non-prescription use (when the same product is sold over-the-counter and by prescription in different locations) may have to be considered. The data on marketed products do not appear to follow a normal distribution, which could be due to a variety of causes (e.g., geographic variability, ascertainment bias, etc.). For marketed drugs, data sources and services can be classified as follows:

> **The Manufacturer (or Distributor):** amount sold or put into commercial circulation; results of sponsored surveys by companies are also useful

[4] For details on the various confounders and biases associated with both numerators and denominators, see: Sachs, R. M. and Bortnichak, E. A. An Evaluation of Spontaneous Adverse Reaction Monitoring Systems, *American Journal of Medicine,* supplement 5B, 81:49-55, 1986; Baum, S., Kweder, S. and Anello, C. The Spontaneous Reporting System in the United States, in Strom, B. L., ed., *Pharmacoepidemiology,* 2nd edition, John Wiley and sons, 1994, pp. 125-137; and Wiholm, B. Olsson, S., Moore, N. and Wood, S. Spontaneous Reporting Systems Outside the United States, *ibid.,* pp. 139-155.

Government Authorities: pharmacy-prescription databases (usually based on documentation for reimbursement purposes)

Independent Monitoring and Survey Services: international (e.g., IMS Health), regional or local (e.g., in the US the NDC Health Information Services, National Prescription Audit, and National Drug and Therapeutic Index)

Information on various sources is covered in Appendix 16.

Also of interest are the many private and public secondary databases or collections of medical records that can provide patient-use data as well as offer the opportunity to evaluate hypotheses or generally to conduct retrospective studies on a designated population (e.g., Pharmaceutical Benefits Management companies, General Practice Research Database of the NHS in the UK, Medicaid Management Information Systems in the US, managed care linked data bases, etc.).[5] These sources often contain extensive data on very large populations (up to a few million patients); retrospective studies of various designs may permit the attainment of accurate exposure data for a variety of therapeutic interventions on the desired population subset(s).[6] (See Chapter II.g.)

c. Technical Considerations

Covariates Defining a Treated Population

The amount of data necessary to characterize a treated population depends on the circumstances and intended use of the information: from a crude overall estimation (order of magnitude) to specifically defined and highly detailed subsets. Ideally, it would be possible to characterize a treated population in terms of many properties (see Table 1). In practice, even in clinical trials, such degrees of detail are inaccessible. Typically, the level of complexity for defining a population is highly dependent on the disease(s) or condition(s) treated, the number and types of dosage forms, doses and dosing regimens in use, and other general factors.

---

[5] For an extensive inventory and description of such data bases, see *BRIDGE On-Line* (Benefit and Risk Information for Drug Evaluations). Information regarding its availability and use can be found at www.dgi.org . Or you may inquire by phone (U.S., 703-276-0056).

[6] For example, see West, S. L. A Comparison of Data Sources for Drug Exposure Ascertainment in Pharmacoepidemiologic Studies with Emphasis on Self-Reported Information, *Pharmacoepidemiology and Drug Safety,* 6:215-218, 1997.

Table 1. Some Possible Covariates for Defining Treated Populations

Demographics: age, gender, race, ethnicity, geography (e.g., region, country, climate, season), socioeconomic class
Disease/Condition: indication treated, disease severity, acute/chronic, outpatient/inpatient
Relevant Medical History: risk factors, diet, alcohol use, tobacco use, concomitant therapy/ treatment
Product/Administration: dosage form, dose strength, dose (single/multiple), regimen, route, acute/ chronic use, self- vs other-administered, OTC vs Rx, source (e.g., name, formulation, generic vs brand, batch number), treatment duration, compliance level
Pharmacology-Related: blood or tissue levels; pharmacodynamic, pharmacokinetic and pharmacogenetic information
Miscellaneous: prescriber (generalist vs specialist), pregnancy/nursing status, organ impairment

Under most circumstances, there will be no need for most of these covariates, even if the information were available. However, when investigating major safety signals, medication errors, product defects and other special situations, several of these parameters will be important and attempts may be necessary to gather as much information on them as possible.

As already pointed out, on a more routine basis, as when assessing the results of clinical development programs, or during periodic review of the safety profile of a marketed drug, it may be prudent to examine the data on exposure as a function of such parameters as age and gender, possibly geographic origin and race, if such data are readily available. This will help to ensure that differentiable safety (or generally benefit-risk) profiles do not go undetected.

Units of Measurement

The representation of patient exposure in terms of quantifiable measurements will depend on the types of data available. At the lowest end of the spectrum is a company's gross estimate of total quantity placed into distribution or sold during a given period (''tonnage''); this would serve as a crude proxy for patient exposure. It may also be possible to express such estimated exposure data from economic data (''cash'' sales, e.g.). At the other extreme will be extensive breakdowns of actual patient numbers sorted according to one or more of the covariates discussed above (e.g., geographic location, age, sex, indication, dosage form, dose, duration and other factors that might contribute to an understanding of the drug's use and benefit-risk relationship).

Table 2 lists the types of measurements and units that can be used, from the most indirect representation to actual numbers of patients. The measure and unit chosen will depend not only on the availability of the data but on the use and application of the information. For ongoing, routine applications (e.g., PSURs), even crude approximations used consistently can be helpful as long as the measure and unit are kept the same for the various analyses or presentations done over time.

Table 2. Measures and Units of Population Exposure

Total quantity sold (e.g., tons, kilograms, liters)
Number of prescriptions
Number of packages/packs (e.g., boxes, bottles)
Number of units (e.g., tablets, vials, inhalers)
Defined Daily Doses (DDDs)
Number of treatments x time (e.g., patient-days, -months, or -years)
Number of patients

If there is more than one dose strength for a given dosage form, or there is more than one dosage form, data for each of the various preparations might be available, depending on circumstances and data sources. If there is more than one manufacturing source for the same drug(s), including branded and generic versions, ideally the data would be accessible for each source, but under spontaneous reporting conditions, such details are usually difficult to obtain.

It should be emphasized that invariably most expressions of drug exposure, no matter how determined, represent at best an *approximation* of actual drug use by the patients (i.e., the data reflect "as prescribed, given or purchased" conditions, not "as used or administered"). Exposure data can not take into account therapeutic compliance in the absence of controlled administration (e.g., in hospital or by vaccination) or through special monitoring efforts, and the figures must ordinarily be regarded as an overestimation. Although assumptions can be made to account for compliance, it is well to remember that it will vary across therapeutic classes and indications for use; for example, compliance with oral contraceptives and insulin is expected to be very high, relative to antihypertensives or lipid lowering agents.

The Defined Daily Dose (DDD) is "the assumed average maintenance dose per day for a drug used on its main indication in adults." [7] It is initially

derived from premarketing experience, refined with sales statistics or pharmacy inventories (numbers of packages, tablets or other dosage forms) and decided by a group of experts. The DDD is a suggested standard unit (e.g., tablets per day) for assessing market penetration of a drug and for making comparisons between countries. The unit allows crude estimates of the number of patients exposed to a specific drug or class of drugs. Nearly all companies and regulators in the CIOMS survey (Appendix 15) reported familiarity with the WHO-originated DDD concept. However, 10 of 17 (59%) Companies and three of the four regulators indicated that they did not routinely use DDD in estimating population exposure.

The DDD may differ from the average daily amount of drug actually prescribed, referred to as the Prescribed Daily Dose (PDD), which is derived from prescription studies, medical or pharmacy records and patient interviews. It is important to relate the PDD to a particular indication.[7] If the number of DDD's sold and the PDD are known, it is possible to calculate a rough estimate of person-time exposure. Thus, a crude ADR incidence can be expressed as number of cases per patient exposure-time (however, see below). Because the recommended dose range may differ across countries, the DDD and the PDD may be influenced; thus, care must be taken in using the DDD across countries and over time without first checking the PDD.

In general, when dosing is simple and straightforward (a known dose of a single dosage form taken by all patients for the same duration, for example), expressing the exposure data in terms of numbers of patients can be relatively straightforward. However, for drugs taken for different lengths of time whether for the same or different indications, then in the absence of a detailed breakdown of the relevant subgroups, it may be necessary or convenient to summarize exposure in terms of units such as total patient-days. However, interpretation of such units is difficult without additional information; to take an extreme example, 1,000 patient-days could mean 1,000 patients each on a drug for one day or one patient taking a drug for 1,000 days.

Uses of Denominator Data: Calculations and Caveats

In addition to general estimates of total exposure to marketed drugs, attempts are often made to estimate the incidence of various adverse reactions from the collection of spontaneous reports received by a company or regulator (the "numerator"). This becomes particularly important when

[7] See *Guidelines for ATC Classification and DDD Assignment,* WHO Collaborating Centre for Drug Statistics Methodology, Oslo 1996 and *Pharmacoepidemiology,* 2nd Edition, B. L. Strom, Editor, John Wiley and Sons, NY, 1996, pp. 149-150 and 379-393.

conducting comparative benefit-risk evaluations when the suspected ADR is serious and rare. However, such calculations can be very inaccurate and misleading and great caution is advised in attempting to use reporting numerators and estimated denominators for incidence calculations.[4] Nevertheless, as covered later in this Chapter, with careful use of appropriate methodologies reasonable estimates can be made.

It is beyond the scope of this work to discuss in detail the analytical approaches to risk estimations or benefit-risk evaluations from various sources of data on marketed drugs (e.g., spontaneous reports, registries, literature).[8] However, a discussion is provided here of important points to consider when trying to obtain and use both numerator and denominator data.

- ***Prescription Considerations:*** The lack of information on use-compliance by patients has already been discussed (something that applies especially to non-prescription products); however, unless exposure data are based on prescriptions actually filled, there is the added uncertainty as to whether patients have indeed obtained the assigned medication from the pharmacist. Also, good prescription survey data will allow differentiation between first-time prescriptions for new patients, and refills of old prescriptions; this obviously will influence any estimate of patient-numbers. For drugs with more than one indication, or for which there may be considerable off-label prescribing (unapproved indications), it may be particularly difficult to interpret the numerator-denominator relationship. Finally, care must be taken in using "numbers of prescriptions," e.g., as a measure of exposure; a prescription may be defined differently in different settings (one-month's drug supply vs three-month's supply, for example).

- ***Drug Distribution Issues:*** Exposure estimates based on amounts produced or distributed ("tonnage") are subject to biases related to company supplying practices. For example, manufacturers may place into distribution unusually large amounts of drug supplies at the launch of a new product ("stock-building") or at the end of a fiscal period for already marketed products ("end-of-period stocking").

- ***Time Lag Between Numerator and Denominator:*** Accurate numerator data based on numbers of suspected ADR reports received and processed are readily available as of a cut-off date. However, exposure data, especially from outside survey sources (e.g., IMS

[8] See *Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals*. Report of CIOMS Working Group IV (1998). Council for International Organizations of Medical Sciences, Geneva.

Health), usually lag by about three months. To meet regulatory deadlines for periodic reporting, one is therefore often obligated to pair numerator data for a specific time period (such as 6 months) with denominator data from an earlier time window. In practice, this lack of synchrony will usually not have an important influence on data interpretation but there may be special circumstances when this issue is important. It is possible to obtain weekly updates from IMS Health on numbers of prescriptions issued for selected drugs; however, those data cannot provide the more meaningful information on filled prescriptions (and derived standard units such as tablets) until they obtain data from pharmacies.

- ***Special Problems for Over the Counter (OTC) Products:*** Often for the same active ingredient(s), especially for combinations (e.g., cough/cold remedies), there will be many different formulations by the same or different manufacturers; such differences may exist within the same country and/or between countries. This can introduce great difficulty in associating the "drug" or its producer to suspected ADR reports. When using OTC products, compliance with use instructions is highly variable, many products are meant to be used prn (on demand), and consumers may share their medications with family or friends; these make any estimates of "true" exposure extremely difficult.

- ***Denominators in Clinical Trials:*** The number of subjects receiving a specific treatment is known with great accuracy and the data can be subdivided by as many covariates as long as the data are available and the numbers are large enough to make such a subdivision appropriate. However, merely using the number of patients to calculate the incidence of events (adverse or beneficial) can be highly misleading, especially for medium- to long-term exposure. Time-to-onset among other variables must be factored into any analysis of adverse event rates; life-table analyses similar to those used in assessing comparative survival rates in cancer trials, for example, are appropriate in this context as well. These and other considerations are discussed in the papers cited in footnote 2.

The remainder of this chapter deals with specific approaches to the determination and use of denominator data from marketing-based exposure and some special situations. Complementing these discussions is a bibliography of references covering a wide variety of techniques and applications to drug exposure measurements and use (Appendix 17).

d. Spontaneous Reporting and Patient Exposure[9]

Introduction

Calculations of the rate at which new cases occur in the exposed population, often referred to as an incidence rate, is the prerequisite for any risk assessment. The numerator is the number of new (i.e., "incident") cases that occur during a defined period and the denominator is the number of exposure units for this period (e.g., exposed patients, treatments, months of exposure or other relevant units). Calculation of a rate from spontaneous report data is difficult because this method of surveillance (i) does not identify all cases which have occurred ("underreporting" phenomenon) and (ii) rarely provides any direct information on the size and characteristics of the exposed population. Both numerator and denominator are subject to a host of other potential biases (see footnote 4).

Thus, the CIOMS Working Group strongly recommends that this statistic always be referred to as a "reporting rate." Under most conditions, the denominator can be estimated from sales and/or prescription data. A reporting rate should only be considered a lower bound of the true incidence of the concerned reaction; it is inappropriate to call it an incidence.

Two fundamental principles should be kept in mind when dealing with drug-exposure data:

(i) each unit (e.g., patients, treatments, etc.) considered for the denominator should reflect populations at risk for the event. Therefore, one should attempt to exclude patients or treatments which are not at risk for the event, e.g., because of an exposure which is too short or a dose which is too low.

(ii) some events may occur only after a long period of treatment, in which case the denominator should be calculated using only data on the cohort of patients corresponding to that treatment period.

However, whenever a selected subset is used, it is also important to indicate the total estimated exposed population along with an explanation of how the subset was derived.

---

[9] For more detailed coverage of this topic, see B. Begaud, J.-C. Pere and G. Miremont, Estimation of the denominator in spontaneous reporting, in *Methodological Approaches in Pharmacoepidemiology* by ARME-P (Association for Research in Methodology for Pharmacovigilance), Elsevier, Amsterdam, 1993, pp. 51-70. Also published in the Elsevier journal *PostMarketing Surveillance,* Vol. 7, 1993 (journal discontinued but merged with *Pharmacoepidemiology and Drug Safety* in 1994).

Selecting the Unit of Measurement

Number of packages sold: Although this figure is often the most readily available, it is a rather crude measure of exposure. Only in special situations will it be of interest. For example, (i) when a package corresponds to a unit-dose of exposure (infusion vials, single dose treatments with an antibiotic, etc.), or (ii) when the patient determines dosage and administration frequency, which makes any estimation of average dosage or duration of treatment extremely difficult (e.g., inhaled beta-2-agonists).

Number of units sold: The calculation for units is straightforward — the number of packages sold during the reference period multiplied by the number of units (tablets, capsules, etc.) per package, taking into account, of course, packages of various sizes.

As with numbers of packages, this mode of expression is not particularly accurate or useful for reflecting actual patient exposure and has limited use. However, it is appropriate (i) if the risk potential is acute and is apt to occur with any administration of a dose (anaphylactic reaction, cardiac arrest during an IV injection, haematoma after an IM injection, etc.), (ii) in case of intermittent use (e.g., analgesics) or (iii) when treatment consists of a single dose (certain antibiotics, contrast media, local or general anesthetics, etc.).

Person-time: A denominator expressed in person-time units (e.g., treatment-months, person-months, person-years) corresponds, for a given period, to the sum of the durations of exposure for the whole exposed population. Such a denominator is frequently used in epidemiology (incidence density). Under certain conditions, the total exposure time may be estimated from sales and prescription data:

$$\text{Number of treatment — months} = \frac{\text{number of packages sold} \times \text{number of units per package}}{\text{average daily dose} \times 30.4}$$

where 30.4 is the average number of days in one month (i.e., 365/12).

The average daily dose (ADD) may be derived from drug utilization studies, surveys, databases or, if none of these is available, the dosage recommended in the relevant product information/data sheet(s). For purposes of the calculation, it is the average number of drug-units taken per day for a treatment indication (e.g., 1.5 tablets).

Example: 12 cases of hepatic injury were reported with a given drug for which 144,000 packages of 20 tablets each were sold during the same period.

The ADD was determined as 1.4 tablets per day. The number of treatment-months is:

$$\frac{144{,}000 \times 20}{1.4 \times 30.4} = 67{,}669$$

from which the calculated ADR reporting rate is 12 out of 67,669 or 18 in 100,000 treatment-months or patient-months.

As already mentioned, for this and most exposure units, poor compliance may lead to overestimation of the denominator. The same caution applies to the first few months of marketing, especially when compared to later periods; a significant part of manufacturer's initial sales is derived from volume-stocking to wholesale-distributors and pharmacists. The estimation using the above techniques is valid only if the number of packages sold is reasonably consistent over time.

Another limitation relates to drugs with different indications for which the durations of treatment and the average daily doses are different. Estimations from sales figures can then be extremely misleading unless reliable information on the relative proportion of sales, daily dose, and duration of treatment for each indication is available from prescriber panels or databases. Without appropriate detailed information, one approach is to provide the extremes, i.e., assume all patients were on the regimen providing the lowest exposure, and then that providing the highest exposure; the reality will fall somewhere in between.

A person-time denominator is a good compromise if, and only if, each treatment time interval can be considered as an independent exposure unit that can produce the event of interest. If not, one must be very cautious in converting such a reporting rate into a risk or in comparing the safety of two drugs. As already pointed out, for effects occurring only after long-term treatment, the risk could be underestimated due to the fact that short-term periods which would not generate the adverse event are included in the denominator. Nevertheless, person-time denominators can be considered useful when comparing, for the same adverse event, drugs belonging to the same therapeutic class, where it can be expected that non-compliance and other biases are similar.

Number of Prescriptions or Treatments: If available, number of prescriptions or treatment courses is especially informative because it expresses the risk in a practical, common unit. In some countries, surveys, population-based databases or reimbursement systems can provide on-line

and reliable information on such figures except for over-the-counter drugs for which one should use estimations based on sales.

In the case of single and short-term treatments (e.g., a course of antibiotics), the number of prescriptions, treatment courses and patients are equal. In other cases, treatment may necessitate several consecutive prescriptions for the same patient. If the risk can be considered the same during each treatment course (prescription), the total number of treatments is a better representation of the risk; thus, for a patient treated 10 times, he/she can be considered as having been at risk 10 times. On the other hand, treatments may not be independent with regard to the risk (e.g., cumulative toxicity, allergic reactions) in which case the risk will be a result of a combination of treatment episodes; then it is preferable to use the actual number of patients.

The number of treatments can be estimated by using sales and prescription data:

$$\text{Number of treatments} = \frac{\text{number of packages} \times \text{number of units per package}}{\text{average daily dose} \times \text{average duration of treatment}}$$

The average daily dose is expressed in units (e.g., number of tablets). The average duration of treatment (ADT) may be difficult to obtain, although for some drugs (e.g. antibiotics), a good estimate can be made. Ordinarily, the average duration of exposure derived from reported adverse event cases should not be used as the ADT, since this value reflects only the time-to-onset of the considered effect, and may be significantly different from the ADT in the overall population treated. The only exception might be when the risk is independent of treatment time.

When sales are stable, the ADT can be estimated from a panel of prescribers which supplies, for a given drug, the average duration of a prescription as a function of prescribed number of units (tablets, etc.) and dosage, as well as the average proportion of first prescriptions:

$$\text{ADT} = \frac{\text{average duration of a prescription}}{\text{proportion of first prescriptions}}$$

The proportion of new prescriptions is the number of new prescriptions divided by total prescriptions for the period. For never-renewed prescriptions (proportion of new prescriptions = 1), then the duration of treatment equals the duration of a prescription.

For instance, if a prescription covers 31 days and the proportion of first prescriptions is 12%, ADT is 31/0.12 = 258 days.

Guidelines for Presentation of Data

When it is not possible to obtain directly the number of patients or treatments as a function of duration, many different units as described can be used. Such derivative units may even be more appropriate for describing the considered risk. The following units are recommended for expressing the denominator:

- ❏ for single or intermittent short-term treatments: number of units or packages
- ❏ for continuous treatment with a constant or small range of durations: number of treatments or patients whenever possible
- ❏ intermittent treatments with variable duration: person-time units, mainly when the risk is assumed to be constant over time.

In order to facilitate the interpretation and comparison of data, whenever possible the denominator should be given as number of treated patients (or number of treatments). A whole number for the denominator is always preferable when expressing an event incidence (e.g., *k* reports per 1,000 or 5,000 or 10,000 treated patients). Thus, 22 cases per 182,000 treated patients should be expressed as 12 cases per 100,000 rather than 1 case per 8,273. Similarly, a whole number is also preferable for the numerator (e.g., 12 cases per 100,000 is preferred to 1.2 per 10,000 or 0.12 per 1,000).

e. Real Examples of Denominator Determination and Use

The following example describes the practical aspects of how exposure data are obtained and presented for typical PSURs by one company. Data in standard units (e.g., tablets or capsules) are requested from IMS Health for all sales information/market usage data on a particular drug product for a specified reporting period (e.g., 6-months, 1-year, or 5-years). IMS Health provides the requested information for all of their data-collection panels (i.e., retail pharmacies, and hospitals where available) for all formulations. The data are provided on an Excel spreadsheet, by route of administration and formulation, sorted by country and dosage form (and strength if more than one); the data are usually presented for calendar

quarters. For PSUR reporting purposes, an estimate of the total market exposure is made by adding all the available information provided by IMS Health.

Lag time is an unavoidable factor. For example, PSURs are due 60 days from the data lock point (cut-off date). For a PSUR covering a period from 1 January 2000 to 30 June 2000, the submission due date would be would be 30 August 2000. Given the time available to prepare the report, the exposure data may only be available up to and including 31 March 2000 since it may take IMS Health between two and four months to update all its data-panels. Thus, the exposure data reported in the PSUR will only be for the 3-month period for which drug use data are available. Or one could request and use exposure data covering the period from 1 October 1999 through 30 March 2000 as an approximation to the six month period covering the ADR period of interest. Alternatively, one could extrapolate the three month data to six months (by just doubling the three month data) assuming there were no reason to suspect major differences in use from one quarter to another. In the unusual event that exposure data are not available from IMS Health (or another commercial source), in-house distribution data would be used.

In the case described, a PSUR was needed for Drug X covering the time period 01 November 1999 through 31 October 2000. IMS provided all available data covering 1 October 1999 through 30 June 2000 (three calendar quarters). The exposure data are presented in the PSUR for that period, showing the total units worldwide and the figures for the five largest user-countries:

Worldwide sales in standard units for Drug X (4Q99-2Q00)

Worldwide sales	1,855,000
Egypt	382,000
Poland	286,000
Japan	262,000
Pakistan	142,000
United States	115,000
All others	668,000

The data were presented as shown without attempting to extrapolate to 12 months. Although the estimated exposure does not cover the full period

over which ADR cases were received, it does provide an order of magnitude approximation that can be used. Should any special safety issues arise during the 12 month period covered, more effort would be needed to ascertain the relevant exposure breakdown (e.g., age, gender, or location).

A more comprehensive description of the use of IMS Health data as applied to signal detection and assessment can be found in a report on the "ADR Signal Analysis Project" (ASAP) conducted by the WHO Collaborating Center for International Drug Monitoring.[10] The global WHO adverse reaction database for the period December 1994 through 30 November 1996 was used along with drug sales information (IMS), drug utilization and disease monitoring data, and demographic information to investigate safety signals for some 17 products. The analyses covered single compounds, groups of products and therapeutic classes. Sales data were often used to calculate DDDs, which were checked for their applicability. Among the outcomes of the study was to demonstrate how reporting rates can be expressed as ADR reports per standard-doses-sold over time and also be used for detailed cross-country comparisons (including use distribution by indication, dose, co-prescriptions, age, and gender).

f. Patient-Exposure and Measurements of Risk

From a clinical safety perspective, denominator data ultimately translate into practical use if and when the data can be used to estimate and convey information on the risk of adverse reactions. A prescriber would like to know the risk of gastrointestinal bleeding for a 16 year old girl if she uses aspirin or a non-steroidal anti-inflammatory drug four days a month to prevent and treat painful menstruation. Here the preferred expression of risk would be per treatment course. Similarly, what is the risk for an 83-year-old man or woman using the same drugs continuously for the treatment of osteoarthrosis? Such specific, absolute risk estimates are not routinely available but relative measurements of risk may be.[11] The best estimates of risk for marketed drugs, especially for rare adverse reactions, are obtained not from spontaneous reporting data but from observational studies (e.g.,

[10] For a copy of the ASAP Final Report contact the Uppsala Monitoring Center (www.who-umc.org; e-mail: ralph.edwards@who.pharmasoft.se; tel. 46-18-656060: FAX. -656080). See Appendix 17 (Specific Applications) for citations of publications reporting work on specific drugs and drug issues under the ASAP project.

[11] *Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals* (CIOMS IV). Council for International Organizations of Medical Sciences, Geneva, 1998.

case control; see Chapter II.g.). A detailed discussion of this complex topic is beyond the scope of this CIOMS V report, but some general points to consider are provided in the context of relating patient-exposure (denominators) data to reports of adverse events (numerators).

Several typical risk situations can be described which attest to the important fact that risk is seldom independent of treatment-time; therefore, each specific type of situation requires different calculations of risk: [12]

1. First dose reactions like hypotension with alpha-blocking drugs
2. Early reactions like mucosal microbleedings from aspirin that disappear after about one week of continuous treatment
3. Type 1 allergic reactions that usually develop during the first two weeks of treatment
4. Other immunologic reactions that usually develop during the first three months
5. Reactions due to accumulation of toxic metabolites that can develop during the first two to six months
6. Fibrotic reactions which rarely appear before six months
7. Cancer induction that can take years.

Another factor involving exposure that influences apparent drug risks is the "channeling effect." Often when a new product of a class is introduced the first patients to receive it are those that have not fully tolerated older products (thus, they are "channeled" or "switched" (converted) to the new drug). This may be especially important if a claim for increased safety is made for the new product. For example, a claim of increased gastrointestinal safety for a new NSAID introduced several years ago was followed by an unusually high spontaneous reporting rate of gastro-intestinal ulcers and bleedings.[13] Controlling for previous exposures and differentiating between first time users and so called switchers (or channelers) is important.

Recently, a new expression for risk derived from case-control studies has been proposed that provides an intuitive quantity related to exposure:

[12] Personal communication from Lise M. Bjerre (McGill University) and Jacques LeLorier (Montreal University Hospital Center).

[13] Van Staa TP, Abenhaim L, Leufkens HGM. Switching patterns of non-steroidal anti-inflammatory drugs. *Journal of Pharmacoepidemiology,* 4:37-47, 1995.

number of people exposed to a treatment for a specified time such that, on average, one person experiences a treatment-related adverse event (NNH = number needed to harm).[14] It expresses the additional absolute risk of an adverse reaction and might be a practical metric for practicing physicians. This unit is consistent with the parallel concept of "number needed to treat" to gain an additional unit of benefit (e.g., number of myocardial infarction patients needed to treat with a thrombolytic agent to gain an additional life saved). Performing a benefit-risk assessment is facilitated since the same unit of measure is used for both benefits and risks. The number needed to treat for an additional life saved minus the number needed to harm could be considered a measure of net clinical benefit. This converts a benefit-risk evaluation into a single unit of measure with an intuitive quality.

Many other approaches to risk calculations using patient exposure determinations are described in the references collected in Appendix 17.

[14] Bjerre LM and LeLorier J, Expressing the magnitude of adverse effects in case-control studies: "the number needed to be treated for one additional patient to be harmed." *British Medical Journal,* 320:503-506, 2000.

VI

Clinical Safety Reporting Regulations: an Overview

a. Introduction

It has been over a decade since the first successful international harmonization of a drug safety reporting procedure, namely the development and introduction of the CIOMS I form in 1990 for foreign serious, unexpected adverse reactions on marketed products. At that time, not only were the regulations different between countries, but the contents of the reporting forms varied; the requirements for reporting of individual cases on marketed drugs within the Federal Republic of Germany (then the BGA, now BfArM), United Kingdom (MCA), and United States (FDA) when CIOMS I was initiated are summarized in Appendix 18.[1] Throughout the 1990s, many other initiatives were undertaken under CIOMS (CIOMS II, III and IV) and ICH (Guidelines E2A, B and C) which have led to some convergence in regulations for expedited and periodic reporting. Although regulations continue to change in many countries throughout the world, partly to incorporate such international agreements, the CIOMS V Working Group felt it was important to take stock of the global situation in 2000. Have we in practice achieved significant harmonization? Is there more consistency in regulations and their implementation today than during the 1980s? Given known differences in regulations and local product information (''labeling''), is it still possible for a company to submit systematically the same individual case report to all regulators that require such a report? If not, and if harmonization to date is deemed insufficient generally, are there some steps worth considering that might help us move forward?

The pre-marketing regulations as of the beginning of 2000 are shown in Appendix 19A for 43 countries around the world. The post-marketing regulations for individual case expedited reporting are presented for 58 countries in Appendix 19B, excluding the EU due to the differences in regulations associated with the drug approval scheme (national or mutual recognition vs centralized through the EMEA). The post-marketing requirements for the EU countries are presented separately (Appendix 19C).

[1] For a comprehensive review of expedited and periodic reporting regulations as of 1990-1991, see Gordon, A. J. and Petrick, R. Worldwide Regulations for Manufacturers on Clinical Safety Surveillance of Drugs, *Drug Information Journal,* 26:1-15, 1992.

Although focus here is on individual cases, the presence or absence of regulations for periodic safety update reports (PSURs) is also specified for the national agencies in 62 countries (Appendix 20).[2]

There have been some technical advances recently proposed under ICH that are intended to facilitate international harmonization, such as the introduction of MedDRA (standard coding dictionary for medical terms, ICH topic M1) and electronic reporting standards (ICH E2B and M2). Differences in plans for adoption and implementation of these tools by the various regulators are beyond the scope of this discussion.

b. Basis for Comparison of Regulations

There are many factors that determine the requirements for case reporting to regulators. The compilations under consideration here focus at a high level, primarily on seriousness, expectedness, case origin (local vs foreign), and whether the case arises during pre- or post-marketing drug use. It would be extremely unwieldy to include the host of other factors that control what, how and when individual case reports must be submitted. Therefore, the summary tables do not reflect details such as the following:

- ❏ differences in time schedule for reporting
- ❏ although countries accept the CIOMS I form for foreign reports, some prefer or require a special form for reports of local origin (*e.g.,* MedWatch form in US); neither forms nor any language requirements are covered
- ❏ possible differences in definitions (e.g., for the terms serious/non-serious and expected /unexpected)

[2] The summary compilation of recent regulations on expedited and periodic reporting is based partly on information from Arnold, B. *Global ADR Reporting Requirements,* 2nd edition, Scrip Report BS 980, PJB Publications, London, 1999 (with assistance of the author) and for EU regulations, from *Notice to Marketing Authorization Holders — Pharmacovigilance Guidelines,* EMEA (London, June 2000). In addition, help was obtained directly from individual regulators (e.g., Milan Smidt, Czech Republic, covering information on Eastern European countries) and from the published review, *National Pharmacovigilance Systems,* 2nd Edition, WHO Collaborating Center for International Drug Monitoring (Uppsala, Sweden), 1999. To our knowledge, the data are accurate and up to date (as of early 2000 to late 2000); however, it must be recognized that different people may interpret or apply the same regulations differently, in part due to translation problems but also as a result of *ad hoc* discussions with regulators on specific questions or issues. The difficulties are exemplified by wording in some regulations that state ''serious and unexpected'' without clarifying whether that refers to serious, unexpected cases or to all cases that are serious (whether expected or not) and all cases that are unexpected (whether serious or not).

- ❏ any differences that might relate to sources of reports (literature, solicited vs spontaneous, consumer vs. professional, etc.)
- ❏ any requirements for unusual lack of efficacy reports or for an increased frequency of known (expected), serious ADRs; such findings are normally based on case series or clusters (as required, for example, under ICH Guideline E2A on expedited reporting for clinical trials)
- ❏ specific requirements related to reports of drug abuse
- ❏ no details are provided on the required format, content or timing of PSURs (many countries currently accept or require PSURs according to a CIOMS II or ICH E2C format and content; see Appendix 20).

There are also various administrative requirements covered in regulations which may differ from country to country, including obligations for reporting to investigators, ethics committees, or safety management boards, and responsibilities involving licensing agreements between companies. These are not covered either.

However, as developed in previous chapters, several assumptions are made; in addition, other factors are covered in the presentation and interpretation of the regulations for this discussion:

- A spontaneous report is always assumed to have at least a "possible" relationship between a drug and an event(s). However, it is assumed that if there is insufficient information (e.g., case does not meet minimum criteria for a valid case), such a case should not be reported to regulators.
- There are countries that request submission of clinical trial adverse *event* cases, which is taken into account.
- In the absence of regulations specifically addressing cases from post-marketing surveillance studies, it is assumed that they would be treated as for any other study; if either the investigator or the sponsor company suspects a drug relationship, the event would be considered a suspected ADR.
- In countries requiring direct reporting to the authorities by clinical trial investigators, it is assumed that sponsor companies would oversee/monitor this activity and may assist the investigator to fulfill this responsibility.

- For expedited reporting of individual cases on marketed drugs, expectedness is based on the local data sheet (*e.g.,* SPC in the EU, Package Insert in the US); however, in accord with ICH E2C, for PSURs expectedness is based on the Company Core Safety Information (CCSI), viz., the "listedness" of an ADR.
- Independent of any special local form that might be required, it is assumed that all countries will accept the same report. In some countries, the same report may have to be submitted to different offices of the same regulatory body. For example, in the US, depending on circumstances, duplicate reports on a case may have to be submitted to both an NDA (marketed product) file and an IND (pre-approval) file.

c. Current State of Affairs

It is clear from an examination of the tables that there remain considerable differences in reporting requirements between countries (even within EU countries, depending on the drug approval process). Some specific examples will highlight the diversity of approaches taken by some authorities:

- Hungary, Poland and Switzerland appear to require submission of local pre-marketing cases of serious adverse *events,* not just reactions
- In Japan, reports on cases of "serious infections" are specifically required both pre- and post-marketing
- Some countries require expedited reporting of non-serious, unexpected local cases (Greece, Japan, New Zealand, Poland, South Africa and Switzerland)
- Expedited reports of serious *expected* cases are required pre-marketing in several places, with specifics (local and/or foreign cases, *e.g.*) depending on the country (for example, Austria, Canada, Denmark, Estonia, Norway, Spain, etc.)
- EU Member States require expedited reporting of local (within the EU) postmarketing spontaneous cases that are serious *expected.*

There is commonality across most countries for requirements covering expedited reports of suspected serious unexpected adverse reactions, whether they be of local or foreign origin. Therefore, multinational companies should be able to prepare centrally a standard report for such

cases; the submission of such reports will still depend on local requirements based on the local data sheet. There are many differences in both pre- and post-approval requirements for other types of reports, however, especially cases of local origin. It is obvious that in spite of attempts to standardize safety reporting criteria and procedures over the past decade, there remains considerable divergence for which there does not appear to be a scientific or public health rationale.

d. Recommendations

The Working Group offers some thoughts on both company practices and broader considerations involving the regulatory "system."

Previous chapters have outlined strategies for the handling and interpretation of individual cases. Through proper case evaluation techniques (see Chapter III.a.), standard lists (e.g., medically serious conditions; see Chapter III.c.) and algorithms (e.g., classification of expectedness; see Chapter III.d.), companies can enlist the computer to store a consistent logic for characterization of case types. Furthermore, for those companies operating centrally, the same automation can be used to prepare and deliver to their subsidiaries case reports that will satisfy the various regulatory requirements.

Therefore, based on its understanding and interpretation of the various local regulations, a company could create a computerized algorithm that would automatically indicate what cases had to be reported on an expedited basis to which regulators. It is believed that some commercial vendors of clinical safety data management software systems have designed such tools. However, given the current differences as shown in the Appendix tables and the complexity involved, as well as the seemingly frequent changes to such regulations, any algorithm would have to be updated and validated carefully on an ongoing basis to ensure its utility and accuracy.

From a system-wide perspective, there are some practical steps that regulators can take to help rationalize a more consistent, internationally-based approach to safety reporting requirements, based on good science and public health needs:

- Even if the regulatory reporting requirements continue to vary, it is important that standard terminology and definitions be used. Those developed under ICH should be adopted as early as possible.

- Although it may be necessary or advantageous to have some regional- or country-specific safety reporting requirements, there are compelling arguments for achieving consistency on the nature, amount and timing of clinical safety report information (individual case or aggregate data) received by different regulators around the world. ICH has set the standards for pre-approval individual case reporting and for post-marketing periodic reporting. At a minimum, these standards should be adopted universally.

- The emerging tools and technologies, such as MedDRA and electronic reporting, show great promise not only for standardization of key aspects of safety reporting, but also for efficiencies in data management and communication. However, it is vital that regulators make the requirements for implementation and application of such techniques by companies as consistent as possible.

- In spite of the advent of electronic ADR submissions to regulators, safety reporting still involves extensive redundancy, multiple reporting, avoidable delays and the possibility of double counting and misinterpretation.[3] Thus, we reiterate the vision put forth by the CIOMS 1A Working Group on "Harmonization of Data Fields" for individual ADR reports.[4] In the interest of public health and efficiency, the ideal situation would be to enter a case only once into a single database with worldwide access, something already feasible with distributed-database technology. Using ICH E2B and MedDRA, for example, all parties can process cases with uniform standards. CIOMS 1A proposed the following:

  - ❑ a specified data set (fields) for spontaneous and study cases with emphasis on their utility for signal detection

[3] For example, safety data received by a regulator (e.g., from a physician) in one country might be entered into its national database and shared with the local manufacturer. The manufacturer in turn reenters the case into its own database for dissemination to its worldwide sites, as needed. Those local company offices may then have to submit the same case to their local regulators (e.g., a serious, unexpected CIOMS 1 report) who may enter the data into their own databases, and so on. In addition, one or more of those same regulators will forward the same case to the WHO Collaborating Center (Uppsala, Sweden). The same repetitiveness prevails independent of the report source and chain of transfer (e.g., healthcare professional to manufacturer to regulator).

[4] The CIOMS 1A initiative, completed at the end of 1994, produced an unpublished report that proposed data fields and their specifications for an international paperless submission and access system for individual suspected ADR reports. Most of the technical suggestions formed the basis for the more elaborate ICH Guideline E2B, now the standard for single case electronic reporting.

- ❏ creation of a single, global shared data set for all ADR cases submitted to regulators which would contain as much information as possible on each case, commensurate with confidentiality and utility
- ❏ continual access to this "shared area" by all appropriate parties; multiple regulators and product license holders will need agreed levels of read-only access in various ways to various portions of the data set
- ❏ data entry should be decentralized but data management centralized with agreed rules for updates and editing
- ❏ the party first receiving a report (regulator or company) would be responsible for case follow-up and data entry.

It is hoped that efforts will be taken to make the availability of a single, shared database a reality.

e. Conclusion

Considerable progress has been made over the past decade in achieving harmonization for many aspects of drug safety surveillance and reporting. However, much remains to be done in order to eliminate unnecessary differences and inefficiencies that command resources and time but add no real value to pharmacovigilance. The standards introduced under ICH and the proposals made by the various CIOMS Working Groups set an excellent precedent and should serve as a stimulus for better rationalization of international safety reporting requirements.

Monitoring drug safety is a shared responsibility and the focus must always be on the collection, reporting, interpretation and any necessary action on important safety information on behalf of patients and the healthcare professionals that serve them. The CIOMS V Working Group hopes that there will be expeditious movement towards more complete harmonization of regulatory requirements to satisfy those needs.

VII

Summary of Proposals

Sources of Individual Case Reports

Spontaneous Reports from Persons Other than Healthcare Professionals

- Traditionally, reports on marketed product experiences are spontaneous reports, also commonly called voluntary or unsolicited.
- Spontaneous reports are always considered to have an implied causal relationship to the subject drug(s).
- Emphasis should be placed on the quality of a report and not on its source. There are several examples of consumer-identified signals.
- As potential epidemiological intelligence, consumer reports should receive appropriate attention and should be regularly scrutinized for new "signals."
- Remember that reasons which might prompt a patient to contact a company include reimbursement, legal concerns and requests for information.
- Personal data collected should be sufficient to permit recontacting the patient and cross-linkage whilst protecting patient privacy.
- Consumer reports are spontaneous reports irrespective of any subsequent "medical confirmation," a process required by some authorities for reportability.
- Medical confirmation means that the patient exists, that the event occurred and is considered to be drug related by a healthcare professional.
- The term "healthcare professional" includes physician, dentists, pharmacists, nurses, coroners, and others.
- When consumers contact a company or a regulator, they should be encouraged to report personal adverse experiences to their treating physician but they should not be referred to any specific healthcare professional.
- If the report is received from a third party, that party should be asked to encourage the consumer to report the information to their physician or to authorize the sponsor/authority to contact the doctor directly.

- Permission should be sought to contact the consumer's treating physician in order to confirm the complaint; such permission should be documented.
- All efforts should be made to obtain medical confirmation of serious unexpected consumer reports, preferably from the primary healthcare provider.
- It is possible that regulators may be in a better position to obtain confirmatory data from healthcare professionals and can be asked to do so when companies are unsuccessful.
- If the event is not considered to be drug-related, the case should be retained in the database but not reported.
- Even in the absence of medical confirmation, any ADR with significant implications for the medicine's benefit-risk relationship should be submitted on an expedited and/or periodic basis.
- Only two regulatory authorities require routine reporting of consumer reports from the sponsor: US (reports from any country) and Canada (only those originating in Canada).
- Include consumer reports in PSURs as a separate appendix or include a statement within the PSUR that they had been received and reviewed and either suggest or do not suggest new findings.
- Efforts should be expended to improve understanding by the public and patients regarding drug safety.

Literature

- Letters to the editor often describe serious ADRs.
- The published literature sometimes provides a signal earlier than other reports.
- Literature reports can also confirm a previously suspected signal.
- However, there may be a long lag time between first detection of a signal by a researcher and his/her publication of a report.
- Publications can sometimes be the source of false information and signals.
- Companies should search at least two internationally recognized literature databases, using the International Normalized Nomenclature (INN) name as a keyword, not less frequently than once a month.

- Also monitor special publications relevant to the drug or its current circumstances.
- Broadcast and lay media should not ordinarily be monitored; however, if important information from these sources is specifically made available to a company, attempts should be made to ascertain whether there is a valid case.
- All staff in all countries have a responsibility to be aware of publications in their local journals and bring them to the attention of the safety department as appropriate.
- Case reports described in the literature should be checked against the company's existing database; previously undocumented articles should be reviewed as usual.
- Companies should have processes and procedures in place for ensuring literature reports are dealt with appropriately.
- Judgment is needed on the intensity and method of follow-up for literature cases. The most aggressive follow-up efforts should be directed at valid reports of serious, unexpected adverse drug reactions that lack details for case assessment.
- If the product source or brand is not specified, until clarified a company should assume that it was their product although reports should indicate that the specific brand was not identified.
- When companies are involved in contractual arrangements for a product (e.g., co-marketing), it is recommended that the legal agreement specify responsibility for literature searches and reporting.
- It is recommended that English be the accepted standard language for literature report translations.
- Regulators should accept translation of an abstract or pertinent sections of a publication.
- The clock starts when the MAH first receives a copy of the pre-published or published paper and the case is reportable.
- Relevant literature cases should be reported to the appropriate regulatory authorities within 15 calendar days of being recognized as a valid case.
- Editors of medical journals have a responsibility to encourage authors to make regulators and companies aware of important drug

safety issues promptly and prior to publication, without prejudicing the author's right to publish the information.

The Internet

- It is important to distinguish between the dissemination of drug safety information over the Internet by companies and regulators, and the collection (receipt) of safety information from healthcare professionals or consumers.
- The need for personal data protection is particularly important with a medium such as the Internet.
- For adverse event reporting, an "identifiable" patient or reporter relates to the existence of a real person that can be validated. Under data protection law, however, the term refers to an ability to "trace" a person from the data available.
- Provide an ADR form on a website, either for direct electronic submission or as a printable form for mailing. It may be necessary to have local company websites with forms in the local language.
- There are confidentiality and authentication issues as with any media; however, allowable e-mail submissions should be made dependent on completion by a reporter of mandatory fields (at least the four minimum criteria for a valid case).
- Fraud and potential abuse are easier on the Internet than via other media.
- A procedure should be in place to ensure daily screening of a company's or regulator's website in order to identify potential case reports.
- It is not necessary for regulators or companies routinely to surf the Internet beyond their own sites other than to actively monitor relevant special home pages (e.g., disease groups) if there is a significant safety issue.
- The Internet can have an important role in transmitting consistent up-to-date messages in labeling, especially important information such as contraindications and new warnings.
- Official data sheets and patient leaflets are being made available over the Internet.

- It is important that Internet and traditional sources (e.g., paper-based) of information convey the same message and that traditional sources continue to be made available.
- In principle, the message should be consistent around the world especially because the Internet does not respect geographic boundaries.
- Relevant and appropriate background information (evidence) that explains the reasons for labeling changes could also be made available on a company's or regulator's website.

Solicited Reports

- Solicited ADR reports arise in the course of interaction with patients for purposes often unrelated to safety or a safety study. They should be regarded as distinct from spontaneous (unsolicited) reports.
- Solicited reports should be processed separately and identified as solicited reports in any expedited or periodic regulatory reporting.
- To satisfy post-marketing drug safety regulations, solicited reports should be handled in the same way as study reports: causality assessments are needed and if necessary follow-up information should be sought.
- Serious, unexpected ADRs should be reported on an expedited basis.
- All other types of cases (serious-expected and non-serious solicited reports) should be stored in the safety database, but made available to regulators only on request.
- It is possible that a signal based on aggregated solicited reports may arise; therefore, a designated responsible party within a company should review the data on an ongoing basis.

Aspects of Clinical Trial Reports

- Generally, safety information reported expeditiously to regulatory authorities should be reported to all Phase 1, 2 and 3 clinical investigators who are conducting research with any form of the product and for any indication.
- It is less important to notify Phase IV clinical trial investigators of expedited reports; they will ordinarily use the available up to date local official data sheet as part of the Investigator's Brochure.

- Quality-of Life (QOL) data should be managed like clinical trial data; an adverse event should be considered an adverse drug reaction only if the reporter or reviewer judges a causal relationship.
- It may be preferable to report results of comparative QOL studies as summary data rather than as individual case reports, as recommended for observational studies.

Epidemiology: Observational Studies and Use of Secondary Databases

- Studies conducted by reviewing databases should have a scientifically sound protocol. If retrospective databases are used for training and do not involve an *a priori* hypothesis, such use should be documented.
- The same reporting rules on suspected ADR cases for clinical trials apply to structured epidemiologic studies.
- For epidemiological studies, unless there is specific attribution in an individual case, its expedited reporting is generally not appropriate.
- If relevant, study results should be summarized as part of periodic reporting (PSURs).
- Promptly notify regulators (within 15 days) if a study result shows an important safety issue (e.g., a greater risk of a known serious ADR for one drug vs another).
- For manufacturers, expedited reports from comparator drug data should be forwarded to the relevant manufacturer(s) for their regulatory reporting as appropriate.

Disease-Specific Registries and Regulatory ADR Databases

- A "registry" per se is not a study. It is a systematic collection of defined events and/or exposures in a defined population over a defined period of time that can be used for study and analysis of hypotheses.
- Although there are numerous ADR case databases/listings created by regulatory authorities, it is unnecessary to attempt to routinely collect them for regular review; however, if a company is in possession of data from regulatory databases it should review them promptly for any required expedited reporting.
- Even if no relevant cases are found, it is advisable to mention in the PSUR that the database(s) had been examined.

- Care should be taken to screen any regulatory-derived case listings, as well as data from registries, for duplicate cases relevant to a potential signal.
- Individual adverse event reports from disease and other registries should be treated as solicited reports (causality assessment required, as appropriate).

Licensor-Licensee Interactions

- When companies co-develop, co-market, or co-promote products, it is critical that explicit contractual agreements specify processes for exchange of safety information, including timelines and regulatory reporting responsibilities.
- The time frame for expedited regulatory reporting should normally be no longer than 15 calendar days from the first receipt of a valid case by any of the partners.
- The original recipient of a suspected adverse reaction case should ideally conduct any necessary follow-up; any subsequent follow-up information sent to the regulators should be submitted by the same company that reported the case originally.

Good Case Management Practices

Clinical Case Evaluation

- Whatever the source of a safety case report, the recipient, whether a company or a regulator, should ideally evaluate the medical information through a clinical evaluation process: is a diagnosis possible; have the relevant diagnostic procedures been performed; were alternative causes of the event(s) considered); has a causality assessment for the suspected drug(s) been made?
- The purpose of careful medical review is to ensure correct interpretation of medical information.
- ADR terms should be used consistently and in accord with recommended standards for diagnosis. The terminology used should reflect careful evaluation by the manufacturer or regulator and not merely be verbatim quotation from the report received.
- For appropriate cases, open exchange of medical information with the reporter will serve to improve the quality of case documentation.

- The company or regulatory authority staff can propose alternate clinical terms and interpretation of the case from those of the reporter, but unless the original reporter alters his original description in writing, the original terms must also be reported.
- When a case is reported by a consumer, his/her clinical description of the event should be retained, although confirmatory or additional information from any healthcare professionals with whom the case is discussed should be added. Ideally, supplemental information should be obtained from the person directly involved in the care of the patient.
- There is an important distinction between a suspected adverse drug reaction and an "incidental" event.
- An incidental event is one that occurs in reasonable clinical temporal association with the use of a drug product, but is not the intended subject of a spontaneous report (i.e., it did not prompt the contact with the pharmaceutical company or the regulator); in addition, there is no implicit or explicit expression of possible drug causality by the reporter or the company's safety review staff.
- "Incidental events" should be included as part of the medical history but not be the subject of expedited reporting to regulatory authorities.
- Because there is always the possibility for a change in perspective on a possible causal relationship between an incidental event and a drug product, incidental event information should be captured and stored in the database for possible future retrieval.

Assessing Patient and Reporter Identifiability

- The standard minimum criteria for a valid ADR case (ICH) are an identifiable patient, an identifiable reporter, a suspected medicinal product and a reaction.
- The term "identifiable" in this context does not refer to issues of personal data privacy and confidentiality but to the existence and verification of a real patient and reporter.
- When follow-up attempts leave the minimum case criteria unfulfilled, keep the case in a database as an "incomplete" case.
- All parties supplying case information (or approached for case information) are subject to the notion of identifiability, not only the initial reporter (the initial contact for the case) but others supplying information.

- In the EU, the regulatory reporting clock begins at the first contact with a healthcare professional but in the US and Canada, which require submission of consumer-direct reports, it starts when the case is initially reported to the company, even by a consumer/lay person.
- Patient identifiability is necessary to avoid case duplication, detect fraud and facilitate follow-up of appropriate cases.
- One or more of the following automatically qualify a patient as identifiable: age (or age category), sex, initials, date of birth, name, or patient number.
- Even in the absence of such qualifying descriptors, a report referring to a definite number of patients should be regarded as a case as long as the other criteria for a valid case are met. For example, "Two patients experienced...." but **not** "A few patients experienced...."
- However, until information on the individual patients is obtained, and the ADR is suitable for expedited reporting, all the cases should be covered in a single *prompt notification letter* to Regulatory Authorities, rather than as individual cases.
- Particularly for serious, unexpected suspected reactions, the threshold for reporting in the absence of confirmatory identifiability should be lowered.

Criteria for Seriousness

- The CIOMS Working Group recommends the universal adoption of the ICH E2A definition of serious for both pre- and post-approval use.
- Death as a seriousness criterion is, of course, only relevant for reporting purposes if it represents, or contributes to, the outcome of a drug associated ADR.
- "Hospitalization" includes only admission as an in-patient as opposed to an examination and/or treatment on an outpatient basis.
- All congenital anomalies and birth defects, without regard to their nature or severity, should be considered serious
- There is a lack of objective standards for "life threatening" and "medical judgment" as seriousness criteria; both require individual, professional evaluation which invariable introduce a lack of reproducibility.

- A list of medical terms developed by a company which always will count as serious, although never totally comprehensive, will aid reproducibility by minimizing internal discrepancies, and can facilitate expedited reporting decisions.
- An example of a recommended list, based on the WHO Critical Terms adapted to the MedDRA Coding Dictionary, is given in an Appendix.
- In order to improve consistency among all parties, the use of published medical definitions, such as those developed under CIOMS by organ-disease experts, is recommended (whether or not a standard list of serious terms is used).
- Within a company, the tools, lists and decisionmaking processes should be harmonized globally in order to facilitate consistency of interpretation and reporting decisions on potentially serious cases.

Criteria for Expectedness

- The terminology associated with expectedness depends on the relevant reference safety information (RSI):
  - ❑ **listed** or **unlisted** refer to the ADRs contained within the Company Core Safety Information (CCSI) for a marketed product, or within the Development Core Safety Information (DCSI) in an Investigator's Brochure.
  - ❑ **Labeled** or **unlabeled** should only be used in connection with official product safety information for marketed products (e.g., Summary of Product Characteristics (SPC) in the EU).
- Inclusion in the RSI should be strictly limited to reactions observed in humans for which the causal role of the drug has been reasonably established.
- Determining whether a reported reaction is expected or not is a two-level process: (1) is the reaction term already included in the RSI, and (2) is the ADR different regarding its nature, severity, specificity or outcome?
- Expectedness should strictly be based on inclusion of a drug-associated experience in the ADR section (also called Undesirable Effects) of the RSI.

- Special types of reactions, such as those occurring under conditions of overdose, drug interaction or pregnancy, should also be included in this section, with a cross-reference to other relevant RSI sections for details.
- Patient disorders mentioned in "contraindications" or "precautions" as reasons for not treating with a drug are not expected ADRs unless they also appear in the ADR section of RSI.
- If an ADR has been reported only in association with an overdose, it should be considered unexpected if it occurs at a normal dose.
- For a marketed drug RSI, events cited in data from clinical trials are not considered "expected" unless the same events have been included in the ADR section.
- The ADR terms included in RSI should be both complete and clearly specified to ensure clarity and avoid ambiguity.
- Although a standard coding terminology might be used for term selection, the focus must be on medically meaningful terms and not the unconditional use of a controlled coding vocabulary such as MedDRA.
- For expedited reporting on marketed drugs, local approved product information is the reference document upon which expectedness (or labeledness) is based.
- For periodic reporting the CCSI is the information upon which expectedness (or "listedness") is based.
- Disclaimer statements for causality (e.g., "X has been reported but the relationship with the drug has not been established") are discouraged; however, even if used, the reaction X is still unexpected.
- Class labeling does not count as "expected" unless the concerned event(s) are also observed and included in the ADR section of the specific drug's RSI.
- Lack of expected efficacy, although important, is not relevant as to whether an adverse event is expected or not.
- If the treatment exacerbates the target indication for the medicinal product (e.g., asthma), it would be unexpected unless already detailed in the RSI.

- Mention in ADR reports of any additional symptoms or signs usually associated with an already expected diagnosis (ADR) does not qualify the new report(s) as unexpected.

- However, an ADR will usually be considered unexpected if the RSI lists an ADR which is specified as transient or acute, but the new case indicates persistence of the reaction.

- A case report may include further specifications (anatomical, histological or related to severity, prognosis, duration, or frequency) but will usually remain expected, depending on the particular situation.

- Unless the RSI specifies a fatal outcome for an ADR, the case is unexpected as long as there was an association between the adverse reaction and the fatality.

- In the absence of special circumstances, once the fatal outcome is itself expected (labeled/listed), reports involving fatal outcomes should be handled as for any other serious suspected ADR in accord with appropriate regulatory requirements.

- Statements in RSI involving expected frequency of occurrence of an ADR (e.g., rare) should be considered carefully, as should a contemplated change in such a designation.

Case Follow-Up Approaches

- In any scheme to optimize the value of follow-up, the first consideration is prioritization of case reports by importance.

- The challenge is to obtain as much useful information as possible during the first follow-up encounter, without future requests of reporters, such that they might be disinclined to cooperate and be discouraged from future reporting.

- A regulatory authority may be able to assist a company to obtain follow-up data if requests for information have been refused by the reporter. The company should provide specific questions it would like answered.

- Regulators and companies should collaborate to ensure that only one party conducts follow-up on a case in accord with the requirements or practice within individual countries.

- Follow-up information should be obtained in writing, via a telephone call and/or site visit, as appropriate. Written confirmation of details given verbally should be obtained where possible.
- Highest priority for follow-up are cases which are both serious and unexpected, followed by serious, expected and non-serious, unexpected cases.
- In addition to seriousness and expectedness as criteria, cases "of special interest" also deserve extra attention as a high priority (e.g., ADRs under active surveillance at the request of the regulators), as well as any cases that might lead to a labeling change decision.
- For non-serious expected cases no follow-up is recommended if all four of the usual minimum criteria for a valid case are present plus country location and source of the report (physician, literature, patient's lawyer, etc.).
- For any cases with legal implications, the company's legal department should be involved.
- For a systematic approach to follow-up, an algorithm is proposed that could be computer driven to decide which cases should be followed-up and what types of information should be sought.
- The extent of follow-up detail needed should be driven primarily by seriousness and expectedness case criteria.
- It is recommended that the CCSI be used to determine expectedness in applying the follow-up triage algorithm.
- The triage algorithm contains three levels of data elements based mainly on ICH E2C data field requirements. The three lists increase in data required from non-serious expected to serious expected/non-serious unexpected to serious unexpected/special interest cases.
- The absence in a case report of data cited in the lists drives the need for follow-up; however, if data not called for in the lists are obtained, they should also be recorded.
- A regulatory authority should similarly require follow-up information on a previously submitted report by a company only if one or more of the data elements in the algorithm fields has been completed or changed as a result of follow-up.

- When the case is serious, especially if also unexpected, and if the ADR has not resolved at the time of the initial report, it is important to continue follow-up until the outcome has been established or the condition is stabilized. How long to follow-up such cases will require judgment.
- Collaborate with other companies if more than one company's drug is suspected as a causal agent in a case.
- Every effort should be made to follow up unexpected deaths or life-threatening events within 24 hours.
- If a case reporter fails to respond to the first follow-up attempt, reminder letters should be sent as follows:
  - ❑ A single follow-up letter for any non-serious expected case.
  - ❑ If the first written follow-up reminder on all other types of cases fails to generate a satisfactory response, a second follow-up letter should be sent no later than four weeks after the first letter.
  - ❑ In general, when the reporter does not respond or is incompletely cooperative, the two follow-up letters should reflect sufficient diligence.
- Acknowledgement letters should be sent to suppliers of follow-up information and they should be given any relevant feedback (e.g., that the company is currently updating product information).
- Intentional rechallenge as part of a follow-up procedure should be carried out only when there is likely to be clinical benefit to the patient.

Role of Narratives

- A company case narrative is different from the reporter's clinical description of a case, although the latter should be an integral part of the former.
- It is recommended that narratives be prepared for all serious (expected and unexpected) and non-serious unexpected cases, but not for non-serious expected cases. It is suggested that expectedness be based on the CCSI (listed vs unlisted ADRs).
- It is proposed that a standard narrative consist of eight discrete paragraphs (sections) that serve as a comprehensive, stand-alone "medical story."

- It is recommended that coded adverse reaction terms be placed as keywords above the narrative in order of reaction importance as judged by the preparer.
- If non-medical terms are used by the case reporter, they should be included in the narrative but not coded. All codes should be medically rational terms.
- Editorial recommendations include: write in the third person past tense; present all relevant information in a logical time sequence; avoid abbreviations and acronyms with the possible exception of laboratory parameters and units.
- If supplementary records are important (e.g., an autopsy report), their availability should be mentioned in the narrative and supplied on request.
- It is important that any alternative cause(s) to that given by the reporter be described and identified as a company opinion; a considered company overall evaluation should be given under such circumstances.
- It is not appropriate to comment judgmentally that the reaction has resulted from misprescribing but it is acceptable to state the facts (e.g., that four times the normal dose had been administered).
- There are regulatory requirements in Japan, Germany and Austria for a company to provide an assessment on the influence of individual cases on the benefit–risk relationship for the drug; it can be part of the narrative but it is important that the evaluation be consistent for all regulators.
- A list of appropriate medical evaluation comments which can be selected as appropriate to the case has been recommended.
- Computer-assisted narrative preparation, which links safety database elements to text preparation, should be considered. There are several advantages: eliminates the need for manual reconciliation between written narrative and database; automatic deletion of phrases or sections not relevant to a particular case; and possibly automated translation into different languages.
- Before any changes are made to a narrative as a result of follow-up information, the database should be corrected first.

- Follow-up information on cases reported to regulatory authorities should be incorporated within the original narrative structure but identified in some distinguishing way (e.g., underlining or bolding).

Good Summary Reporting Practices: PSURs Reconsidered

PSUR Content Modification

High Volume of Case Reports and/or Long-Term Coverage

- For reports covering long periods (e.g., 5 years), it is more practical to use the CCSI current at the time of PSUR preparation to classify expectedness, rather than the document in effect at the beginning of the period (the usual requirement).
- Clinical trial data should only be included if the data suggest a signal or are relevant to any suspected changes in the benefit-risk relationship.
- If there are more than 200 individual case reports, submit only summary tabulations and not line-listings. If subsequently requested by a regulator, however, a line listing should be provided within 10 working days.
- For a five year gap between reports, follow-up information on cases described in the previous report should only be provided for cases associated with ongoing or new safety issues.
- Inclusion and discussion of literature reports should be selective and focus on publications relevant to safety findings, independent of listedness.
- For reports with extensive numbers of case reports, discussion and analysis for the Overall Safety Evaluation should be partitioned by system organ class, rather than by listedness or seriousness.

PSURs With Minimal New Information

- When little or no new information is generated during a reporting period, an abbreviated PSUR will save time and resources for companies and regulatory reviewers.
- In general, the criteria that should be considered for an abbreviated report are: no serious unlisted cases and few (e.g., 10 or less) serious

listed cases; no significant regulatory actions for safety reasons during the review period; no major changes to the CCSI; no findings that lead to new action (e.g., safety study).

- In an abbreviated report, it should be unnecessary to include the usual full inventory of locations where the drug is marketed.
- There should be no simplification/abbreviation of PSURs for the first two years following first introduction of a new chemical entity in an ICH country.

Proposals Relating to Frequency and Timing of Reporting

A Summary Bridging Report

- A Summary Bridging Report is a concise document that integrates two or more PSURs to cover a specified period over which a single report is required by those regulators not requiring or desiring PSURs on a more frequent basis.
- It does not contain any new information but provides a brief, bridging summary of two or more previously prepared PSURs.
- The concept is applicable for the initial and subsequent 5-year license renewals report requirements in the EU and reexamination procedures in Japan.
- The format/outline should follow that of an ordinary PSUR but the content should consist of summary highlights from the full PSURs to which it refers.

An Addendum Report

- An Addendum Report is designed to satisfy regulators who may request data covering a period outside the routine PSUR reporting cycle (for example, those who rely on the product's local approval date rather than the International Birthdate (IBD)).
- It serves as an update to the most recently completed scheduled PSUR and summarizes data received since the most recent data-lock point.
- It will ordinarily supplement annual or five year reports and should not be required routinely but only on special regulatory request.
- An Addendum Report could follow the ordinary ICH PSUR format, depending on circumstances and the volume of additional data since the most recently prepared PSUR. However, the minimum informa-

tion suggested is: changes to the CCSI; significant regulatory actions on safety issues; line listing and/or summary tabulations; conclusions.

Miscellaneous Proposals for Managing PSURs

- Companies should consider preparing a brief (e.g., one page), stand-alone overview (Executive Summary) of each PSUR to provide the reader with a brief description of the content and the most important findings.
- Manufacturers should be allowed to select the IBDs (International Birthdates) for their ''old'' products to facilitate synchronization of reports to all regulators and optimization of PSUR workload scheduling.
- For old products, in general if there have been no new approvals in any country since the last PSUR (if any were prepared), include only an alphabetical list of countries in which the product is marketed.
- If there is no CSSI for an old product, the most suitable local data sheet could be considered for use.
- The evaluation of cases in a PSUR should focus on unlisted ADRs with analyses organized primarily by system organ class (body system).
- Remember that the discussion of serious unlisted cases should include cumulative data.
- Complicated PSURs and those with extensive new data may require more than 60 days to prepare adequately, and flexibility on the part of regulators is recommended; a company should alert the regulators of any likely delay to the usual 60 day deadline.
- The possibility of ''resetting'' the PSUR clock (e.g., from annual to six-monthly as a result of a new indication or dosage form) should be discussed between a company and the regulators prior to, or at the time of, approval of the new application dossier.

Determination and Use of Population Exposure Data

- For a PSUR, detailed calculations on exposure (the denominator) are ordinarily unnecessary, especially given the unreliability of the numerator; rough estimates usually suffice, but the method and units used for the determination should be explained clearly.

- Data sources for exposure estimates in PSURs can be derived from the amount of the product sold or distributed, sponsored surveys, local and international survey services (e.g., IMS Health), and pharmacy or prescription databases.
- Most drug exposure data are an approximation and represent an overestimate; for example, therapeutic compliance is rarely measurable and not all prescriptions are filled by patients.
- Although numbers of treated patients are readily available from clinical trial and other controlled cohort situations, that statistic by itself is not an accurate measure of patient-exposure; time-on-drug, patient discontinuations and other factors must be considered carefully and special approaches are needed.
- For special situations, such as when dealing with an important safety signal, attempts should be made to obtain exposure information as a function of as many relevant covariates as possible (e.g., age, gender, race, indication, dosing details).
- In evaluating numbers of spontaneous reports against patient exposure, different options are possible for the appropriate units; each has advantages and disadvantages.
- The following denominator units are generally recommended: single or intermittent short-term use — units or packages; continuous treatment — numbers of treatments or patients; intermittent treatments with variable duration — person-time.

Clinical Safety Reporting Regulations: An Overview

- A summary of premarketing regulations on expedited ADR reporting for 43 countries and postmarketing regulations for 58 countries covered in the report indicates considerable differences between countries, especially for local suspected ADR cases.
- However, there is commonality across many countries for expedited reporting of serious unexpected cases, whether of local or foreign origin.
- In 62 countries whose requirements were reviewed and presented, some 29 now accept or require ICH E2C PSURs for periodic postmarketing safety reports.

- To enhance international harmonization in pharmacovigilance, the CIOMS Working Group advocates the following:
  - ❑ standard terminology and definitions developed under ICH should be used by all
  - ❑ agreement by all regulators on the nature, amount and timing of individual or aggregate safety reports
  - ❑ it is important that different regulators establish consistent requirements for implementation and application of MedDRA and electronic case reporting
  - ❑ movement toward establishing a single worldwide database (the "shared area"), into which each suspected ADR case is entered only once by the initial company or regulatory recipient, and in which accessibility is limited to appropriate parties, a vision espoused by the CIOMS 1A Working Group.
- Although considerable progress has been made toward international harmonization of requirements and practices, considerable work remains to eliminate inefficiencies and unnecessary differences so as to optimize the contributions of pharmacovigilance.

VIII

Appendices

Appendix 1

The Erice Declaration on Communicating Drug Safety Information

The following declaration was drawn up at the International Conference on Developing Effective Communications in Pharmacovigilance, Erice, Sicily, 24-27 September 1997. It was attended by health professionals, researchers, academics, media writers, representatives of the pharmaceutical industry, drug regulators, patients, lawyers, consumers and international health organizations.

PREAMBLE:

Monitoring, evaluating and communicating drug safety is a public-health activity with profound implications that depend on the integrity and collective responsibility of all parties — consumers, health professionals, researchers, academia, media, pharmaceutical industry, drug regulators, governments and international organisations — working together. High scientific, ethical and professional standards and a moral code should govern this activity. The inherent uncertainty of the risks and benefits of drugs needs to be acknowledged and explained. Decisions and actions that are based on this uncertainty should be informed by scientific and clinical considerations and should take into account social realities and circumstances.

Flaws in drug safety communication at all levels of society can lead to mistrust, misinformation and misguided actions resulting in harm and the creation of a climate where drug safety data may be hidden, withheld, or ignored.

Fact should be distinguished from speculation and hypothesis, and actions taken should reflect the needs of those affected and the care they require. These actions call for systems and legislation, nationally and internationally, that ensure full and open exchange of information, and effective standards of evaluation. These standards will ensure that risks and benefits can be assessed, explained and acted upon openly and in a spirit that promotes general confidence and trust.

The following statements set forth the basic requirements for this to happen, and were agreed upon by all participants, from 30 countries at Erice:

1. Drug safety information must serve the health of the public. Such information should be ethically and effectively communicated in terms

of both content and method. Facts, hypotheses and conclusions should be distinguished, uncertainty acknowledged, and information provided in ways that meet both general and individual needs.

2. Education in the appropriate use of drugs, including interpretation of safety information, is essential for the public at large, as well as for patients and health-care providers. Such education requires special commitment and resources. Drug information directed to the public in whatever form should be balanced with respect to risks and benefits.

3. All the evidence needed to assess and understand risks and benefits must be openly available. Constraints on communication parties, which hinder their ability to meet this goal, must be recognised and overcome.

4. Every country needs a system with independent expertise to ensure that safety information on all available drugs is adequately collected, impartially evaluated, and made accessible to all. Adequate nonpartisan financing must be available to support the system. Exchange of data and evaluations among countries must be encouraged and supported.

5. A strong basis for drug safety monitoring has been laid over a long period, although sometimes in response to disasters. Innovation in this field now needs to ensure that emergent problems are promptly recognised and efficiently dealt with, and that information and solutions are effectively communicated.

These ideals are achievable and the participants at the conference commit themselves accordingly. Details of what might be done to give effect to this declaration have been considered at the conference and form the substance of the conference report.

Erice September 27, 1997

The Conference was organised by:
the Uppsala Monitoring Centre
The Clinical Pharmacology Unit
Institute of Pharmacology of Verona University
with the support of IUPHAS's division of Clinical Pharmacology
The Ettore Majorana Centre for Scientific Culture
International School of Pharmacology
The World Health Organisation

and supported by EQUUS Communications, London

Further information from:
Professor I Ralph Edwards +46 18 65 60 60
or Bruce Hugman, EQUUS +44 171 274 8724

Appendix 2

Membership and Process of CIOMS Working Group V

The CIOMS V Working Group met in a series of 8 formal meetings from April 1997 through August 2000. Listed below, followed by a chronology of their work, are the participants.

Name	Organization*	Part time/full time
Peter Arlett	MCA (UK)	Part time
Zbigniew Bankowski	CIOMS	Part time
Christian Benichou	Synthelabo	Full time
Win Castle	SmithKline Beecham	Full time – Co-Chair
Ann Castot	Agence du Medicament (France) and CPMP	Full time
Diane Chen	CKW Consulting	Full time
Mary Couper	WHO	Part time
Gaby Danan	HMR/Aventis	Full time
Ralph Edwards	WHO Collaborating Centre	Full time
Peter Folb	University of Cape Town (South Africa)	Full time
Arnold Gordon	Pfizer	Full time (Editor)
Juhana Idanpaan-Heikkila	WHO	Part time
Gottfried Kreutz	BfArM (Germany)	Full time
Edith LaMache	EMEA	Full time
Murray Lumpkin	FDA	Full time – Co-Chair
John Milander	Novartis, Glaxo Wellcome	Full time
Norbert Paeschke	BfArM (Germany)	Full time
Sue Roden	GlaxoWellcome	Fulltime – Secretary
Bruce Rowsell	HPB (Canada)	Full time
Jens Schou	University of Copenhagen and CPMP	Full time
Barbara Sickmueller	BPI (Germany)	Part time – Observer
Wendy Stephenson	Wyeth-Ayerst Research, AHP	Full time
Martijn Ten Ham	World Health Organization	Full time
Hugh Tilson	GlaxoWellcome/University of North Carolina	Full time
Ernst Weidmann	Hoechst, Bayer	Full time
Bengt-Erik Wiholm	MPA (Sweden), Pharmacia	Full time

* Some members had more than one affiliation during the project.

At its first official meeting (Philadelphia, April 1997), the Group agreed on topics for the CIOMS V project based on unfinished/unresolved matters emanating from CIOMS I, II and III and from an informal survey of industry and regulatory colleagues outside the CIOMS Group. Its first initiative was to prepare the second edition of CIOMS III which was completed in November 1998 (for details, see *Guidelines for Preparing Core Clinical-Safety Information on Drugs*, 2nd edition. Report of CIOMS Working Groups III and V, CIOMS, Geneva 1999).

In addition, individual topic chapters or issues for this CIOMS V report were assigned to subgroups early in the project, with most participants serving on multiple subgroups. Throughout the various meetings, concepts were presented and debated, drafts of proposals were reviewed and discussed, and two surveys of the industry were carried out (one on practices and experience in preparing periodic safety update reports (see Chapter 4) and the other on knowledge and use of patient exposure information (see Chapter 5)). The meetings subsequent to April 1997 were as follows: July 1997 (Geneva), November 1997 (New York), April 1998 (Paris), November 1998 (Philadelphia), March 1999 (Amsterdam), July 1999 (Berlin), and August 2000 (Barcelona). In May 1999 and February 2000, the appointed editorial committee for the report (A. Gordon, W. Castle, H. Tilson and M. Lumpkin) held meetings to resolve outstanding issues and design the overall report. A. Gordon as chief editor compiled and edited draft consolidated reports for the editorial board and for the entire Group at its August 2000 meeting; he also prepared the final manuscript for publication by CIOMS.

Appendix 3

Available Bibliographic Databases Suitable for Identifying Reports of Adverse Drug Reactions

[Note: The CIOMS V Working Group is not endorsing any particular data base source or publication. However, it is common practice to rely on at least two such sources for literature searches.]

Introduction

There is a wide variety of bibliographic databases suitable for identifying reports of adverse drug reactions. Perhaps the two most widely used general biomedical databases for this purpose are Medline and Embase. In addition there are several more general biological and scientific databases such as SciSearch, Biosis, and the Derwent Drug File. SEDBASE is a specialist database derived from Meyler's Side Effect of Drugs, which specialises in drug reactions and interactions. There are also specialized databases which deal with specific disease areas (such as CancerLit and AidsLine), or with the toxicological effects of drugs (ToxLine).

All these databases are available on major online hosts such as Dialog, and many are available in other formats such as CD-ROM or magnetic tape. Several are available for free searching on the World Wide Web.

Further details on the databases mentioned above are given below.

1. Medline

Medline is a vast source of medical information, covering the whole field of medicine including dentistry, veterinary medicine and medical psychology. The database covers clinical medicine, anatomy, pharmacology, toxicology, genetics, microbiology, pathology, environmental health, occupational medicine, psychology, and biomedical technology, etc. The database corresponds to the printed publications: Index Medicus, Index to Dental Literature, International Nursing Index and various bibliographies. Over 3,900 journals from more than 70 countries are regularly indexed.

Producer

National Library of Medicine (NLM)
8600 Rockville Pike
Bethesda, Maryland 20894
USA
http://www.nlm.nih.gov/databases/medline.html

It is available on most major online hosts such as Dialog, and in various CD-ROM and tape formats. It is also available in many manifestations on the World Wide Web, several of which are free to use. One of the best is the official NLM Internet version called PubMed at http://www.ncbi.nlm.nih.gov/PubMed/

2. EMBASE

EMBASE, the Excerpta Medica database, is a current and comprehensive pharmacological and biomedical database containing over 7.5 million documents from 1974 to date, with approximately 415,000 records added annually. It features unique international journal coverage and includes many important journals from Europe and Asia not found in other biomedical database; overall coverage is approximately 4,000 journals published in 70 countries.

EMBASE covers the whole world's biomedical literature whilst concentrating in particular on European sources. The emphasis of the database is on the pharmacological effects of drugs and chemicals. Over 40% of current data are drug-related. Additional areas of coverage are human medicine and biological sciences relevant to human medicine, health affairs (occupational and environmental health, health economics, policy and management), drug and alcohol dependence, psychiatry, forensic science, pollution control, biotechnology, medical devices and alternative medicine.

Producer

Elsevier Science B.V.
Secondary Publishing Division
Molenwerf 1
1014 AG Amsterdam
The Netherlands
http://www.elsevier.nl/inca/publications/store/5/2/3/3/2/8/index.htt

It is available on most major online hosts such as Dialog, and in various CD-ROM and tape formats.

3. SciSearch

SciSearch® (Cited Reference Science Database) is an international, multidisciplinary index to the literature of science, technology, biomedicine, and related disciplines produced by the Institute for Scientific Information® (ISI).

It indexes all significant items (articles, review papers, meeting abstracts, letters, editorials, book reviews, correction notices, etc.) from approximately 4,500 major scientific and technical journals. Some 3,800 of these journals are further indexed by the references cited within each article, allowing for citation searching. An additional 700 journals indexed have been drawn from ISI Current Contents® series of publications.

Producer

Institute for Scientific Information (ISI)
3501 Market Street
Philadelphia, PA 19104
http://www.isinet.com/products/citation/citsci.html

It is available on most major online hosts such as Dialog, and in various CD-ROM and tape formats. SciSearch is also available directly from ISI on the World Wide Web, where it is marketed as the Web of Science®

4. Biosis Previews

BIOSIS Previews is the electronic format of the respected print publications, Biological Abstracts® and Biological Abstracts/RRM® (Reports, Reviews, Meetings). BIOSIS Previews supplies comprehensive coverage of international life science journal and meeting literature. BIOSIS Previews covers approximately 5,500 life science journals, 1,500 international meetings, as well as review articles, books, and monographs.

Producer

BIOSIS
2100 Arch Street
Philadelphia, PA 19103-1399
http://www.biosis.org/htmls/common/bp.html

It is available on most major online hosts such as Dialog, and in various CD-ROM and tape formats.

5. Derwent Drug File

The Derwent Drug File (DDF) presents information on all aspects of drug research and usage. It selectively covers the worldwide pharmaceutical literature; papers chosen may cover the chemistry, analysis, pharmaceutics, pharmacology, metabolism, biochemistry, interactions, therapeutic effects and toxicity of a drug. Each document in DDF contains a detailed abstract written by a Derwent subject specialist and is accompanied by extensive drug oriented indexing allowing highly specific retrieval. Papers from over 1,150 scientific and medical journals and conference proceedings are included.

Producer

Derwent Information Ltd
Derwent House
14 Great Queen Street
London, WC2B 5DF
UK
http://www.derwent.com/prodserv/pharm/drug_file.html

It is available on many major online hosts such as Dialog, and in CD-ROM and tape formats.

6. SEDBASE

SEDBASE — derived from Meyler's Side Effects of Drugs — contains synopses of relevant drug reactions and interactions. Each year approximately 9,000 articles on adverse drug reactions are published in the scientific literature. These are identified and collected for SEDBASE from over 3,500 journals published in 110 countries, using the resources of the Excerpta Medica database, EMBASE. All articles are sent to recognised authorities who critically assess the information and distil the key elements for inclusion. Speculative or unsubstantiated statements on the side effects of ethical drugs are not included.

Producer

Elsevier Science B.V.
Secondary Publishing Division
Molenwerf 1
1014 AG Amsterdam
The Netherlands
http://www.elsevier.nl/

It is available on many major online hosts such as Dialog.

7. CancerLit

CANCERLIT® is produced by the International Cancer Research DataBank Branch (ICRDB) of the U.S. National Cancer Institute. The database consists of bibliographic records referencing cancer research publications dating from 1963 to the present. CANCERLIT includes indexing for articles from more than 3,500 journals; approximately 200 core journals contribute a large percentage of the citations. Selected records are taken from the MEDLINE database beginning in June 1983. In addition, proceedings of meetings, government reports, symposia reports, selected monographs, and theses are also abstracted for inclusion in the database.

Producer

CANCERLIT is produced by the U.S. National Cancer Institute (NCI): http://cancernet.nci.nih.gov/nci.htm. Questions concerning file content should be directed to:

National Library of Medicine
8600 Rockville Pike
Bethesda, MD 20894
http://www.nlm.nih.gov/

It is available on many major online hosts such as Dialog, and directly on the World Wide Web from the National Cancer Institute at
http://cnetdb.nci.nih.gov/cancerlit.shtml

8. AidsLine

AIDSLINE®, produced by the U.S. National Library of Medicine (NLM), contains citations to literature covering research, clinical aspects, and health policy issues concerning AIDS (Acquired Immunodeficiency Syndrome). The citations are derived from Medline, CancerLit and HealthStar. In addition, the file includes the meeting abstracts from the International Conferences on AIDS, the Symposia on Non-human Primate Modes of AIDS, and AIDS-related abstracts from the Annual Meetings of the American Society of Microbiology.

Producer

National Library of Medicine
8600 Rockville Pike
Bethesda, MD 20894
http://www.nlm.nih.gov/

It is available on many major online hosts such as Dialog, and directly on the World Wide Web via Internet Grateful Med (IGM): http://igm.nlm.nih.gov/

9. ToxLine

TOXLINE covers the toxicological, pharmacological, biochemical, and physiological effects of drugs and other chemicals. It is composed of a number of sub-files, several of which are unique to TOXLINE. TOXLINE includes primarily English-language items with international coverage of journal articles, monographs, technical reports, theses, letters, meeting abstracts, papers, reports, research project summaries, and unpublished material.

Producer

National Library of Medicine
8600 Rockville Pike
Bethesda, MD 20894
http://www.nlm.nih.gov/

It is available on many major online hosts such as Dialog, and directly on the World Wide Web via Internet Grateful Med (IGM).
http://igm.nlm.nih.gov/

Appendix 4

Standardizing "Expectedness" and "Seriousness" for Adverse Experience Case Reporting*

Win Castle, MD, FFPM
Retired Vice-President, International Drug Surveillance, Glaxo Inc.,
Consultant, "Safety First", Cary, North Carolina

George Phillllips, PharmD
Director, International Drug Safety Reporting, Glaxo Inc.,
Research Triangle Parc, North Carolina

Recent harmonization initiatives have led to the idia of a core safety data sheet. Even with a single company statement, however, there can well be debate and sometimes discrepant views between personnel within an organization as to what a safety data mean. Such a nonstandardized company view can lead to the same adverse event (AE) case history being reported to some authorities and not to others, even when assessed aganst the same source reference document, or similar regulations.

The opportunity was, therefore, taken to informally survey views on some selected borderline AE cases from attendees at Drug Information Association (DIA) Safety Monitoring Workshops held in Europe and the United States. In addition, 22 physician monitors enployed by either Glaxo or SmithKline Beecham Pharmaceuticals completed the exercise.

The results of the survey are analysed and guidelines proposed. Whether or not the reader agrees with all of these suggestions, the authors recommend an agreed company position with regard to assessing "expectedness" and "seriousness".

Key words: Harmonization; Adverse experience; Expectedness; Seriousness; Regulatory reporting; Labeledness

Introduction

It would be unfortunate if manufacturers failed to capitalize on the many ongoing harmonization initiatives for AE reporting. Most notable are the

* Extracted from *Drug Information Journal*, Vol. 30, pp. 73-81, 1996.

Council for International Organization of Medical Sciences (CIOMS) and International Conference on Harmonization (ICH) initiatives. Despite these efforts, reporting discrepancies within and between organisations are ocurring. These are felt to be not only due to cultural differences between organizations and regulatory agencies.

The purpose of conducting the small informal survey reported in this article was to assess some of the potential sources of differences in determining ''expectedness'' and ''seriousness'' and based on this, to propose guidelines aimed at standardizing and decisions reached. In the absence of standardized guidelines, such opinions caused by a nonstandardized view can lead to the same case history being reported to some regulatory authorities but not to others, even though reporting is based on the same reference data and similar regulations.

Methods

Based on experience from recent ''in-house'' debates, a list of 10 borderline examples relating to ''labeledness'' (Table 1) and six relating to ''seriouseness'' (Table 2) were identified. In order to determine whether there were transatlantic differences or differences from medically qualified personnel, the examples were given to 90 attendees at a DIA Safety Monitoring Workshop held in Europe (1993), 70 of whom attended the equivalent workshop in the United States, plus 22 full-time physician monitors employed either by Glaxo or SmithKline Beecham Pharmaceuticals. No attempt was made to compare responses from regulators attending the meeting with the others, although it would have been interesting. In addition, 97 of the above agreed to review desk copies of 14 ''cases,'' each selected on the basis of there being a potential issue relating to the decision of whether or not to report to a regulatory authority (Table 3).

Results

Table 1 was designed to elicit opinions regarding whether a reported AE and a labeled AE were considered to be one and the same for regulatory reporting purposes. As can be seen, there appears to be a different philosophy between Europe and the United States in the way the events are interpreted, particularly where the outcome is death (examples 6 and 9). Individuals in the United States would tend to report a fatality as an unlabeled event, whereas in Europe this is generally viewed as an outcome rather than a factor relevant to labeledness. For example, in Europe, 97% of the respondents accept that if myocardial infarction is to be labeled, death

due to myocardial infarction is also labeled. Only 43% of the respondents in the United States, however, would accept fatal myocardial infarction to be labeled if only myocardial infarction appeared in the labeling. Also of interest is that in Europe, rather than the United States, cyanosis secondary to hypoventilation was equated with respiratory depression (Example 8).

The responses from the company medical monitors were not examined, other than to compare how physicians responded when compared to the diverse backgrounds of industry and regulatory individuals who attended at the DIA meetings. As can be seen, medical opinion was unanimous among 22 medical monitors in only one example (Example 1) where the greater anatomical specificity did not affect the labeledness of lung fibrosis. In general, the example in which there was the most debate about labeledness was between "vertigo" and "dizziness" where between 50% and 72% of those in any category (63% in total) considered them to be equivalent, but 37% did not.

Table 2 was designed to gather responses on whether certain medical events should be considered to be serious. As in Table 1, the responses seem to show transatlantic differences. For instance, in Example 1, total blindness for 30 minutes was considered to be serious in Europe, whereas in Example 3, mild anaphylaxis was thought to be serious in the United States. Medical opinion, more so than general DIA opinion, considered as more serious a threat of suicide, a stomach washout procedure (even though negative for the patient supposedly having taken the drug), and in particular, a laboratory test result above a level specified in the protocol to warrant fast tracking to the company.

An interesting unofficial observation relating to whether or not a "spontaneous abortion" was considered serious in the regulatory sense was that of the seven DIA meeting attendees (United States and Europe) who considered it not to be serious in the regulatory sense, six were themselves regulators. This is in contrast to the overall total of 95% who consider this event to be serious.

The information found in Table 3 was designed to determine whether the respondents felt, based on the available case details, the case should be reported to regulatory authorities. The results suggest a fairly uniform transatlantic view about whether or not a case should be reported. Fewer in Europe than in the United States, however, would report a case where the reporter could not remember the age or even the sex of a patient (Example 167). Also, in Europe rather than in the United States, more would consider that if pseudomembranous colitis was labeled, the label also covered "dehydration" (Example 168).

On the other hand, more in Europe would report a medically serious case (respiratory collapse in Example 169) even if the investigator failed to identify the case as serious by not ticking the appropriate "seriousness" box on the case record form. Company medical opinion also seems to support the majority DIA view for each issue, although only 30% would advocate reporting "eight cases of..." (Example 185) as compared with more than 50% of attendees at the workshop.

Discussion

None of the 30 examples surveyed achieved a totally unanimous view and so the guidelines presented below are all based on a majority verdict. To some extent the non-uniform opinion is surprising because of the relatively small number of individuals who took part in the survey, with many having a substantial amount of expertise in the area of drug safety.

It appears that in many situations reporting is practiced according to medical common sense (e.g., abnormal laboratory findings highlighted as a possible signal in a clinical trial protocol — Case 6 in Table 2). It is believed that the newly proposed United States regulations, in the wake of fialuridine experience, should serve to move general opintion further toward reporting based on medical opinion.

There also appears to be an American/European divide which is not surprising. Worthy of comment is that the extra reporting is not always within the United States. For example, blindness for 30 minutes, respiratory collapse, and respiratory depression would be more frequently viewed as medically serious and would be reported more often in Europe. The United States reporting practice is more to view fatalities as unlabeled unless death is specifically mentioned in the label. Individuals in the United States would also tend to report anaphylaxis (even when the presentation is described as "mild") to the regulatory authorities (96%), whereas in Europe, the majority (63%) would not view the case as "serious" in the regulatory sense.

Before suggesting a pragmatic way forward to best benefit from the harmonization initiatives, the following 20 guidelines are proposed.

Proposed guidelines

(Numbers in brackets or parentheses indicate the percentage of those individuals surveyed who are in agreement with the proposed guidelines — see tables.)

Labeledness

1. *Further anatomical specification* of a labeled AE does not make it unlabeled (e.g., fibrosis of the left upper lobe is equivalent to lung fibrosis [99%]; leftsided chest pain is equivalent to chest pain [87%]).

2. *Extra histological specification* does not make, per se, a labeled AE unlabeled (e.g., a liver biopsy shows hepatic necrosis [labeled] with the presence of eosinophils [not mentioned in labeling] [74%]). It should be noted, however, that the Food and Drug Administration (FDA) states, as an example of greater diagnostic specification that cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents.

3. If a labeled *AE is not normally accompanied by an additional sign or symptom*, the AE should not be considered labeled (e.g., the labeling mentions gastrointestinal irritation and a report is received of gastrointestinal irritation associated with melena [98%]).

4. Mention of any *additional symptom or sign usually associated* with an already labeled AE does not merit upgrading the event to unlabeled (e.g., the labeling mentions thrombocytopenia, and a report is received of thrombocytopenia associated with petechia [90%]; labeling mentions pseudomembranous colitis, and a report is received of pseudomembranous colitis associated with dehydration [69%]).

5. In general, the medical view is that if a *labeled AE is often life-threatening or often results in death*, a fatal outcome in a particular case does not make the AE unlabeled, even if death is not mentioned in the labeling as a possible outcome (e.g., myocardial infarction is mentioned in the labeling, but fatal myocardial infarction is not) [72%]. Pragmatically, however, the FDA states that if the labeling does not specifically mention death as a possible outcome of an AE, and a report is received where a patient died from the AE, the AE should be reported as unlabeled. Thus, if a fatality is considered unlabeled in the United States and is reported to the FDA, it makes sense to report the case internationally.

6. If a reported AE is *significantly more severe than the labeled AE*, it should be considered unlabeled (e.g., circulatory collapse when hypotension is labeled [97%]). This is probably particularly true if the outcome of the AE is fatal (death from hepatic necrosis when hepatic failure is labeled [74%]). As an additional example, the FDA states that a report of hepatic necrosis would be unlabeled (by virtue of greater

severity) if the labeling only referred to elevated hepatic enzymes or hepatitis.

7. If an AE is *not medically more important* than a labeled adverse event, the case need not be considered unlabeled (e.g., vertigo when dizziness is labeled [63%]; raised liver function tests when hepatitis is labeled [85%]).

8. Although it is suggested that any AE with a fatal outcome, whether or not labeled, should be reported internationally, *death from a condition diagnosed prior to treatment* is not a reportable event (91%) — in fact, it is not an event at all. This is assuming that death is a possible normal outcome of the condition (e.g., bronchogenic carcinoma). The exception would be where there is an exacerbation of the condition following treatment leading to death (authors' comment).

9. An *unlabeled diagnosis which relates to a group of symptoms or signs which are labeled*, the new case is not in itself labeled (e.g., anaphylaxis when hypotension, wheezing, and urticaria are all labeled [86%]). In other words, the diagnosis must be expressly stated in the labeling. The reverse however, is not true — see guideline 10 immediately below.

10. If a *diagnosis is a labeled AE, then the signs and symptoms which comprise the diagnosis are also considered to be labeled*. For example, if anaphylaxis is labeled, then a report of a patient who experienced hypotension, wheezing, and urticaria would be considered to be labeled (69%).

11. If the label lists an *AE which is specified to be transient*, but it persists in the new case, the case is unlabeled and should be reported (e.g., prolonged elevated liver function tests when the labeling states transient elevated liver function tests [95%]).

Seriousness

12. If a report is *serious in the medical sense*, even though it is not serious in the regulatory sense (e.g., the outcome of the AE is not death, hospitalization, disability, etc.) the case should be considered serious for regulatory reporting purposes (authors' comment). The majority view was that a spontaneous abortion (95%), total blindness for 30 minutes (70%), and anaphylaxis (even if described as "mild" (61%)) are serious in the medical sense. On the other hand, a threat of suicide is not considered to be serious (83%), nor in itself is an emergency room or outpatient department visit (97%).

Miscellaneous

13. Medically serious cases from clinical trials should be reported to the regulatory authorities even if the *''seriousness'' box is not checked* by the investigator (76%). Similarly, for spontaneous case reports, the authors believe that the same rule should hold where a regulatory box for ''seriousness'' may not be checked.

14. If the *investigator persists in specifying a case is drug-related*, even though this view is medically nonsensical, the case should be considered drug-related and reported to the regulatory authorities (e.g., anaphylaxis one year after starting treatment (91%)).

15. Whenever there is a *known class effect*, an AE in a new drug in that class should be considered to be possibly drug-related or suspected, even if the reporter states the event is ''definitely not drug-related'' (79%).

16. *Spontaneously reported cases should always be considered to be possibly drug-related*, even if an alternative explanation is given by the reporter (72%). See reference case 182.

17. If a patient should not have received the drug, (i.e., *contraindicated*), and the patient experiences an adverse event, the case should still be reported according to usual practices (85%), although it would seem appropriate to mention the fact that the patient should not have received the drug in the first place. The same guideline would hold for a drug prescribed for an unapproved indication or in a heroic dose (authors' comment).

18. The overall majority of individuals surveyed would not report to regulatory authorities a case where the details of a specific patient could not be recalled (e.g., *neither age nor sex could be remembered* [59%]), and would not submit individualized case reports based on a report that a physician *''Had eight cases of...''* (52%). In the United States, however, 72% would report the unidentified patient and 59% the series of eight cases. Thus, a pragmatic view would be to report these cases internationally if medically warranted and the individual case(s) are reported within the United States (authors' comment).

19. In those instances where the *brand name of a generic drug is stated to be unknown*, the case should be processed and reported to regulatory authorities by the company which becomes aware of the adverse event (70%). In the United States, this obligation generally falls to the original brand name manufacturer of the drug.

20. *If in any doubt*, report! (authors' comment).

Conclusion

Recent harmonization initiatives have led to the idea of a core safety data sheet or core label. Even with a single company statement, however, there is often debate and sometimes discrepant views between personnel within the organization. Such a nonstandardized company view can lead to the same adverse event case report being reported to some authorities and not reported to others elsewhere, even when judged against the same source reference document. Regulators, partly due to their position, seem to be more pragmatic in their views (previously cited example regarding spontaneous abortion). Often the problem is within the company itself where sometimes (particularly in the United States) there is a need to adhere to a legalistic interpretation of the regulations.

When one examines the diverse responses received to the examples presented in this informal survey (Tables 1, 2, and 3), it is quite apparent that there is indeed a need to develop standardized approaches in determining "expectedness" or "labeledness" and seriousness.

Despite slight differences between the regulations (e.g., Europe and United States), the level of harmonization presently reached is now probably sufficient for a company to either submit or not submit a single case report in a systematic manner to regulatory authorities worldwide.

If one accepts the last guideline, that if in doubt report, and bears in mind that the core safety data sheet contains the central elements pertinent to safe use of the drug, wherever in the world the drug is marketed, it should be easy to determine the company stance for labeledness equivalence, and the company can then generate a universal list of adverse events which would always be viewed as medically, and consequently regulatory, serious by that organization. If this information is stored in the company's computerized database, an automated regulatory reporting algorithm can indicate those cases to be reported to the regulatory authorities worldwide, thus saving debate, and possible company embarrassment.

Whether or not the reader agrees with each guideline presented above, and recognizing that there will always be medical "gray" areas, the authors recommend a unified within-company position now for standardizing "expectedness" and "seriousness" for adverse event case reporting, and hopefully, a unified between-company position in the future.

Table 1. Summary of Responses as to whether Reported Events were Considered Labeled

"Labeled" Event	Reported Event	DIA Europe N = 90			DIA US N = 70			Company Medical Monitors N = 22			Total N = 182		
		Yes	(%)	No	Yes	(%)	No	Yes	(%)	No	Yes	(%)	No
1. Lung Fibrosis	Fibrosis of the left upper lobe	90	100%	0	68	97%	2	22	100%	0	180	99%	2
2. Transient Raised LTFs	One LFT still raised after 3 months	1	1%	89	5	7%	65	4	18%	18	10	5%	172
3. Hypotension	Circulatory collapse	1	1%	89	1	1%	69	3	14%	19	5	3%	177
4. Gastrointestinal Irritation	Melena	2	2%	88	0	0%	70	1	5%	21	3	2%	179
5. Dizziness	Vertigo	65	72%	25	35	50%	35	14	64%	8	114	63%	68
6. Hepatic Failure	Death from hepatic necrosis	41	46%	49	1	1%	69	5	23%	17	47	26%	135
7. Thrombocytopenia	Thrombocytopenia with petechia	83	92%	7	62	89%	8	18	82%	4	163	90%	19

"Labeled" Event	Reported Event	DIA Europe N = 90 Yes	(%)	No	DIA US N = 70 Yes	(%)	No	Company Medical Monitors N = 22 Yes	(%)	No	Total N = 182 Yes	(%)	No
8. Respiratory Depression	Cyanosis secondary to hypoventilation	86	96%	4	23	33%	47	17	77%	5	116	64%	66
9. Mycoardial Infarction	Fatal MI with raised CPK	87	97%	3	30	43%	40	14	64%	8	131	72%	51
10. Hypotension, Wheezing, and Urticaria	Anaphylaxis	16	18%	74	2	3%	68	8	36%	14	26	14%	156

Table 2. Summary of Responses as to whether Reported Events were Considered Serious, N = 176

Reported Event	DIA Europe N = 90			DIA US N = 70			Company Medical Monitors N = 16			Total N = 176		
	Yes	(%)	No	Yes	(%)	No	Yes	(%)	No	Yes	(%)	No
1. Total Blindness for 30 Minutes	80	89%	10	31	44%	39	13	81%	3	124	70%	52
2. Suicide Threat	17	19%	73	2	3%	68	7	44%	9	26	17%	150
3. "Mild" Anaphylaxis	33	37%	57	67	96%	3	8	50%	8	108	61%	68
4. Spontaneous Aborion	85	94%	5	68	97%	2	14	88%	2	167	95%	9
5. Stomach Washout in Emergency Room/OPD (-ve for drug)	0	0%	90	0	0%	70	5	31%	11	5	3%	171
6. Lab Test Result above a level requiring fast tracking in protocol	2	2%	88	6	9%	64	12	75%	4	20	11%	156

Table 3: Summary of Responses as to whether Cases would be Reported, N = 79

Point for Debate	Europe N = 45			US N = 32			Company Medical Monitors N = 20			Total		
	Yes	(%)	No	Yes	(%)	No	Yes	(%)	No	Yes	(%)	No
167 Age and sex not remembered	17	38%	28	23	72%	9	10	50%	10	40	41%	57
168 Pseudomembaranous colitis labeled. but not dehydration	9	20%	36	16	50%	16	5	25%	15	30	31%	67
169 A clinical trial case in which for respiratory collapse, no seriousness box was checked	37	82%	8	19	59%	13	18	90%	2	74	76%	23
171 Chest pain specified in label but this case specified left-sided chest pain	7	16%	38	5	16%	27	1	5%	19	13	13%	84
172 More histological specificity. (A liver biopsy which showed hepatonecrosis (labeled) was described as having a large number of eosinophils present)	17	31%	31	7	22%	25	4	20%	16	25	26%	72
173 Anaphylaxis in study, but on that treatment for a year on code break	42	93%	3	29	91%	3	17	85%	3	88	91%	9
174 Stroke unlabeled but patient contra-indicated for treatment	32	71%	13	30	94%	2	20	100%	0	82	85%	15

Point for Debate	Europe N = 45			US N = 32			Company Medical Monitors N = 20			Total		
	Yes	(%)	No	Yes	(%)	No	Yes	(%)	No	Yes	(%)	No
181 Death due to preexisting disease which had not exacerbated 32 days post study	4	9%	41	3	9%	29	2	10%	18	9	9%	88
182 Anaphylasis spontaneously reported by locum, but food considered more likely by the patient's doctor	28	62%	17	28	87%	4	16	80%	4	70	72%	27
185 "A doctor had 8 cases of..."	23	51%	22	18	59%	14	6	30%	14	47	48%	50
193 Generic: brand unknown	32	71%	13	20	63%	12	16	80%	4	68	70%	29
194 Trial. Investigative drug not implicated by investigator but a known class effect	36	80%	9	22	69%	10	19	95%	1	77	79%	20
197 Hepatitis in label and reported event in a trial is raised LFT	8	18%	37	5	16%	27	2	10%	18	15	15%	84
198 Anaphylaxis is labeled but not the 3 individual symptoms (hypotension, wheezing, and urticaria)	15	33%	30	10	31%	22	5	25%	15	30	31%	67

Appendix 5

List of Adverse Event/Reaction Terms to be Considered Always 'Serious': Explanation

Special attention must be paid to a decision on whether a case report fulfils the usual criteria for seriousness, and therefore its eligibility for expedited and/or periodic reporting to regulatory authorities. Difficulties often emerge in the case evaluation process, particularly in the absence of clear criteria such as hospitalization, life-threatening, death; in such cases, medical judgement is called for. It is suggested that a list of terms that would always be considered "serious" could be developed to provide some guidance and to reduce uncertainty in what should be reportable to regulators.

Such a list is not meant to be a substitute for case-by-case review and decisionmaking; however, it can provide a mechanism for assigning medical seriousness in the absence of detailed and confirming information. Moreover, any terminology (controlled vocabulary/coding dictionary) such as MedDRA will undergo continuous development leading to the introduction of new terms or changes to old ones. As a result, the sample list presented should not be regarded as thorough or definitive, but rather a starting point. Different users may wish to develop their own custom-designed list to serve their special needs related to the medical aspects of their products and the diseases they treat.

The starting point for the proposed sample list is the 'WHO-Critical-Terms-List' (version of 1998). The terms given do not necessarily refer to a serious condition *per se*, but may be indicative of a serious syndrome.

The 'WHO-Critical-Terms-List' comprises only preferred-terms in WHO-ART which means that all included-terms (lower level terms) that are assigned to these preferred-(critical-) terms also fulfil the criteria. MedDRA lowest-level-terms are linked to MedDRA preferred-terms in the same general way as with other terminologies (e.g., WHO-ART).

Based on the WHO-Critical-Terms-List and according to the pathways described, it was thus possible to create a list of MedDRA-preferred

(critical)-terms that are ''mapped'' to similar terms in WHO-ART. Version 3.1 of MedDRA and the first-quarter 2000 version of WHO-ART were used.

The attached table provides four columns:

1. MedDRA primary SOC (System Organ Class): Name of the primary SOC to which a preferred-term is assigned.
2. MedDRA preferred term (PT): name of the MedDRA-preferred-term that is considered 'critical' (serious). The number of preferred-terms for the proposed list is 836 (out of a total number of about 12,000 PTs).
3. WHO: critical-term: list of corresponding WHO-ART critical terms, including those terms that are defined as ''included-terms,'' which are linked to a preferred-term.
4. WHO: PT/IT: designation of WHO-ART-terms, whether they are preferred- (PT) or included-terms (IT).

List of MedDRA Preferred-Terms to be Considered 'Serious' Based on WHO-ART Critical-Terms

(All WHO-ART Critical-Terms Mapped to MedDRA Preferred-Terms by Primary System-Organ-Class in MedDRA)

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
blood and lymphatic system disorders	agranulocytosis	agranulocytic angina	IT
blood and lymphatic system disorders	agranulocytosis	agranulocytosis	PT
blood and lymphatic system disorders	aplastic anaemia	anaemia aplastic	PT
blood and lymphatic system disorders	blast cell proliferation	blast cell proliferation	PT
blood and lymphatic system disorders	bone marrow depression nos	aplasia bone marrow	PT
blood and lymphatic system disorders	bone marrow depression nos	bone marrow depression	IT
blood and lymphatic system disorders	bone marrow depression nos	bone marrow hypocellular	IT
blood and lymphatic system disorders	bone marrow depression nos	haematopoiesis decreased	IT
blood and lymphatic system disorders	bone marrow depression nos	haematopoiesis impaired	IT
blood and lymphatic system disorders	bone marrow depression nos	haematopoiesis suppressed	IT
blood and lymphatic system disorders	bone marrow depression nos	marrow depression	PT
blood and lymphatic system disorders	bone marrow depression nos	marrow hypoplasia	IT
blood and lymphatic system disorders	bone marrow depression nos	panmyelophthisis	IT
blood and lymphatic system disorders	coagulation disorder neonatal	coagulation disorder neonatal	PT
blood and lymphatic system disorders	coagulation disorder nos	coagulation disorder	PT
blood and lymphatic system disorders	coombs negative haemolytic anaemia	anaemia haemolytic dcn	PT
blood and lymphatic system disorders	coombs negative haemolytic anaemia	haemolytic autoimmune anaemia dcn	IT
blood and lymphatic system disorders	coombs positive haemolytic anaemia	anaemia haemolytic dcp	PT
blood and lymphatic system disorders	coombs positive haemolytic anaemia	anaemia haemolytic icp	PT
blood and lymphatic system disorders	coombs positive haemolytic anaemia	haemolytic autoimmune anaemia dcp	IT
blood and lymphatic system disorders	coombs positive haemolytic anaemia	haemolytic autoimmune anaemia icp	IT
blood and lymphatic system disorders	disseminated intravascular coagulation	dic	IT
blood and lymphatic system disorders	disseminated intravascular coagulation	dissem. intravasc. coagulation	PT
blood and lymphatic system disorders	haemoglobinaemia	haemoglobinaemia	IT
blood and lymphatic system disorders	haemolysis aggravated	haemolysis aggravated	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
blood and lymphatic system disorders	haemolysis nos	haemolysis	PT
blood and lymphatic system disorders	haemolysis nos	haemolytic reaction	IT
blood and lymphatic system disorders	haemolytic anaemia drug induced	anaemia primaquine sensitivity	IT
blood and lymphatic system disorders	haemolytic anaemia enzyme specific	anaemia haemolytic, enzyme spec.	PT
blood and lymphatic system disorders	haemolytic anaemia nos	anaemia haemolytic	PT
blood and lymphatic system disorders	heinz bodies	heinz bodies	IT
blood and lymphatic system disorders	histiocytosis haematophagic	histiocytosis haematophagic	IT
blood and lymphatic system disorders	hypoplastic anaemia	anaemia hypoplastic	PT
blood and lymphatic system disorders	idiopathic thrombocytopenic purpura	purpura thrombocytopenic	PT
blood and lymphatic system disorders	intravascular haemolysis	haemolysis intravascular	IT
blood and lymphatic system disorders	leucoerythroblastic anaemia	anaemia leukoerythroblastic	IT
blood and lymphatic system disorders	leucopenia nos	leucopenia	PT
blood and lymphatic system disorders	leukaemoid reaction	leukaemoid reaction	PT
blood and lymphatic system disorders	lymphadenopathy	lymphadenopathy massive	IT
blood and lymphatic system disorders	lymphocytopenia neonatal	lymphocytopenia neonatal	IT
blood and lymphatic system disorders	neutropenia	granulocytopenia	PT
blood and lymphatic system disorders	neutropenia	granulocytopenia severe	IT
blood and lymphatic system disorders	neutropenia	neutropenia	IT
blood and lymphatic system disorders	neutropenia aggravated	neutropenia aggravated	IT
blood and lymphatic system disorders	neutropenia neonatal	granulocytopenia neonatal	IT
blood and lymphatic system disorders	pancytopenia	pancytopenia	PT
blood and lymphatic system disorders	pancytopenia aggravated	pancytopenia aggravated	IT
blood and lymphatic system disorders	platelet destruction increased	platelet destruction increased	IT
blood and lymphatic system disorders	platelet production decreased	platelet production decreased	IT
blood and lymphatic system disorders	sideroblastic anaemia nos	anaemia sideroblastic	PT
blood and lymphatic system disorders	spherocytic anaemia (exc congenital)	anaemia spherocytic	PT
blood and lymphatic system disorders	thrombocytopenia	thrombocytopenia	PT
blood and lymphatic system disorders	thrombocytopenia	thrombopenia	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
blood and lymphatic system disorders	thrombocytopenia aggravated	thrombocytopenia aggravated	IT
blood and lymphatic system disorders	thrombocytopenia neonatal	thrombocytopenia neonatal	PT
blood and lymphatic system disorders	thrombotic thrombocytopenic purpura	purpura thrombopenic thrombotic	PT
cardiac disorders	angina pectoris	angina pectoris	PT
cardiac disorders	angina pectoris	anginal attack	IT
cardiac disorders	angina pectoris	anginal pain	IT
cardiac disorders	angina pectoris	anginal syndrome	IT
cardiac disorders	angina pectoris	effort angina	IT
cardiac disorders	angina unstable	angina unstable	IT
cardiac disorders	arrhythmia nos	arrhythmia	PT
cardiac disorders	arrhythmia nos	cardiac arrhythmia nos	IT
cardiac disorders	arrhythmia nos	conduction delayed transient	IT
cardiac disorders	arrhythmia nos neonatal	arrhythmia neonatal	PT
cardiac disorders	atrial flutter	atrial flutter	IT
cardiac disorders	atrial tachycardia	tachycardia atrial	IT
cardiac disorders	atrioventricular block complete	av block complete	PT
cardiac disorders	atrioventricular block complete	heart block complete	IT
cardiac disorders	atrioventricular block first degree	av block first degree	IT
cardiac disorders	atrioventricular block first degree	heart block first degree	IT
cardiac disorders	atrioventricular block first degree	pr interval prolonged	IT
cardiac disorders	atrioventricular block nos	atrioventricular block	IT
cardiac disorders	atrioventricular block nos	av block	PT
cardiac disorders	atrioventricular block nos	av dissociation	IT
cardiac disorders	atrioventricular block nos	heart block	PT
cardiac disorders	atrioventricular block nos	heart block av	IT
cardiac disorders	atrioventricular block second degree	av block second degree	IT
cardiac disorders	atrioventricular block second degree	heart block second degree	IT
cardiac disorders	cardiac arrest	asystolia	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
cardiac disorders	cardiac arrest	cardiac arrest	PT
cardiac disorders	cardiac arrest neonatal	cardiac arrest neonatal	PT
cardiac disorders	cardiac failure chronic	cardiac failure chronic	IT
cardiac disorders	cardiac failure congestive	congestive heart failure	IT
cardiac disorders	cardiac failure nos	cardiac failure	PT
cardiac disorders	cardiac failure nos	heart failure	IT
cardiac disorders	cardiac failure nos	myocardial decompensation	IT
cardiac disorders	cardiac fibrillation nos	fibrillation cardiac	PT
cardiac disorders	cardiac fibrillation nos	fibrillation cardiac nos	IT
cardiac disorders	cardiogenic shock	shock cardiogenic	IT
cardiac disorders	cardiomegaly nos	cardiac hypertrophy	IT
cardiac disorders	cardiomegaly nos	cardiomegaly	PT
cardiac disorders	cardiomyopathy acute	cardiomyopathy acute	IT
cardiac disorders	cardiomyopathy nos	cardiomyopathy	PT
cardiac disorders	congestive cardiac failure aggravated	congestive cardiac failure aggr.	IT
cardiac disorders	cor pulmonale nos	cor pulmonale	PT
cardiac disorders	coronary artery disease nos	coronary insufficiency	IT
cardiac disorders	coronary artery occlusion	coronary artery occlusion	IT
cardiac disorders	coronary artery spasm	coronary spasm	IT
cardiac disorders	coronary artery thrombosis	thrombosis coronary	PT
cardiac disorders	extrasystoles nos	ectopic beats	IT
cardiac disorders	extrasystoles nos	extrasystoles	PT
cardiac disorders	extrasystoles nos	extrasystoles multifocal	IT
cardiac disorders	grey baby syndrome	grey syndrome neonatal	IT
cardiac disorders	haemopericardium	hemopericardium	PT
cardiac disorders	left ventricular failure	cardiac asthma	IT
cardiac disorders	left ventricular failure	cardiac failure left	PT
cardiac disorders	myocardial infarction	heart attack	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
cardiac disorders	myocardial infarction	myocardial infarction	PT
cardiac disorders	myocardial ischaemia	myocardial ischaemia	PT
cardiac disorders	myocarditis nos	myocarditis	PT
cardiac disorders	nodal arrhythmia	arrhythmia nodal	PT
cardiac disorders	nodal arrhythmia	tachycardia nodal	IT
cardiac disorders	pericardial effusion	pericardial effusion	PT
cardiac disorders	pericarditis constrictive	pericarditis constrictive	IT
cardiac disorders	pericarditis nos	pericarditis	PT
cardiac disorders	pulmonary oedema aggravated	pulmonary oedema aggravated	IT
cardiac disorders	pulmonary oedema nos	lung oedema	IT
cardiac disorders	pulmonary oedema nos	oedema pulmonary	IT
cardiac disorders	pulmonary oedema nos	pulmonary oedema	PT
cardiac disorders	pulmonary oedema nos	pulmonary oedema cardiac cause	IT
cardiac disorders	pulsus bigeminus	bigeminy	IT
cardiac disorders	pulsus bigeminus	coupled beats	IT
cardiac disorders	pulsus bigeminus	pulsus bigeminis	IT
cardiac disorders	right ventricular failure	cardiac failure right	PT
cardiac disorders	sick sinus syndrome	sick sinus syndrome	PT
cardiac disorders	stokes adams syndrome	adams stokes syndrome	PT
cardiac disorders	stokes adams syndrome	av block complete with syncope	IT
cardiac disorders	stokes adams syndrome	stokes adams syndrome	IT
cardiac disorders	supraventricular arrhythmia nos	arrhythmia atrial	PT
cardiac disorders	supraventricular arrhythmia nos	arrhythmia supraventricular	IT
cardiac disorders	supraventricular extrasystoles	extrasystoles supraventricular	IT
cardiac disorders	supraventricular tachycardia	tachycardia supraventricular	PT
cardiac disorders	tachycardia supraventricular aggr	tachycardia supraventricular aggr	IT
cardiac disorders	torsade de pointes	torsade de pointes	PT
cardiac disorders	ventricular arrhythmia nos	arrhythmia ventricular	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
cardiac disorders	ventricular asystole	ventricular asystolia	IT
cardiac disorders	ventricular extrasystoles	extrasystole ventricular	IT
cardiac disorders	ventricular fibrillation	fibrillation ventricular	PT
cardiac disorders	ventricular fibrillation	ventricular fibrillation paroxysm	IT
cardiac disorders	ventricular tachycardia	paroxysmal vt	IT
cardiac disorders	ventricular tachycardia	tachycardia ventricular	PT
cardiac disorders	wandering pacemaker	wandering pacemaker	IT
cardiac disorders	withdrawal arrhythmia	withdrawal arrhythmia	PT
congenital and familial/genetic disorders	adrenogenital syndrome nos	adrenogenital syndrome congenital	PT
congenital and familial/genetic disorders	anophthalmos	anophthalmia	PT
congenital and familial/genetic disorders	congenital cerebrovascular anomaly nos	vascular malformation cerebral	PT
congenital and familial/genetic disorders	cystic fibrosis nos	cystic fibrosis	PT
congenital and familial/genetic disorders	duodenal atresia	duodenal atresia	PT
congenital and familial/genetic disorders	glucose-6-phosphate dehydrogenase deficiency	anaemia haemolytic g6pd	PT
congenital and familial/genetic disorders	muscular dystrophy nos	muscular dystrophy	IT
ear and labyrinth disorders	auricular swelling	swelling auricular	IT
ear and labyrinth disorders	deafness conductive (exc otosclerosis)	deafness middle ear	IT
ear and labyrinth disorders	deafness neurosensory	cochlear nerve damage	IT
ear and labyrinth disorders	deafness neurosensory	cochlear nerve deafness	IT
ear and labyrinth disorders	deafness neurosensory	deafness nerve	PT
ear and labyrinth disorders	deafness nos	deafness	PT
ear and labyrinth disorders	deafness transitory	deafness temporary	IT
ear and labyrinth disorders	hearing impaired	hearing decreased	PT
ear and labyrinth disorders	hearing impaired	hearing impaired	IT
ear and labyrinth disorders	hearing impaired	hearing reduced	IT
ear and labyrinth disorders	hearing impairment aggravated	hearing impairment aggravated	IT
ear and labyrinth disorders	hypoacusis	auditory hypoacuity	IT
ear and labyrinth disorders	inner ear disorder nos	labyrinthine disorders	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
ear and labyrinth disorders	inner ear disorder nos	labyrinthine dysfunction aggrav.	IT
ear and labyrinth disorders	labyrinthitis nos	labyrinthitis	IT
ear and labyrinth disorders	meniere's disease	meniere's syndrome	IT
ear and labyrinth disorders	meniere's disease aggravated	meniere's disease aggravated	IT
ear and labyrinth disorders	sensation of block in ear	sensation of block in ear	IT
ear and labyrinth disorders	vestibular ataxia	ataxia vestibular	IT
ear and labyrinth disorders	vestibular disorder nos	vestibular disorder	PT
ear and labyrinth disorders	vestibular neuronitis	vestibular nerve damage	IT
endocrine disorders	adrenal cortex dysplasia	adrenal cortex dysplasia	IT
endocrine disorders	adrenal haemorrhage	adrenal haemorrhage	PT
endocrine disorders	adrenal insufficiency nos	adrenal cortex dysfunction	IT
endocrine disorders	adrenal insufficiency nos	adrenal cortex hypofunction	IT
endocrine disorders	adrenal insufficiency nos	adrenal cortical insufficiency	IT
endocrine disorders	adrenal insufficiency nos	adrenal hypofunction	IT
endocrine disorders	adrenal insufficiency nos	adrenal insufficiency	PT
endocrine disorders	adrenal insufficiency nos	hypoadrenalism	IT
endocrine disorders	adrenal storm	adrenal storm	IT
endocrine disorders	adrenal suppression	adrenal suppression	IT
endocrine disorders	adrenocortical insufficiency acute	adrenal crisis	IT
endocrine disorders	adrenocortical insufficiency chronic	addison's disease	IT
endocrine disorders	hypopituitarism	hypopituitarism	IT
endocrine disorders	hypopituitarism	pituitary insufficiency	PT
endocrine disorders	hypothalamo-pituitary disorders nec	pituitary disorder	PT
endocrine disorders	steroid withdrawal syndrome	steroid withdrawal syndrome	IT
eye disorders	angle closure glaucoma	angle closure glaucoma acute	IT
eye disorders	cataract nec	cataract	PT
eye disorders	cataract nec	cataract lenticular	IT
eye disorders	cataract nos aggravated	cataract aggravated	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
eye disorders	cataract subcapsular	cataract subcapsular	PT
eye disorders	corneal lesion nos	corneal lesion	IT
eye disorders	corneal opacity	corneal opacity	PT
eye disorders	corneal ulcer nec	corneal desquamation	IT
eye disorders	corneal ulcer nec	corneal ulceration	PT
eye disorders	eyelid ptosis	eyelid ptosis	IT
eye disorders	eyelid ptosis	ptosis	PT
eye disorders	glaucoma aggravated	glaucoma aggravated	IT
eye disorders	glaucoma nos	glaucoma	PT
eye disorders	glaucoma nos	secondary glaucoma	IT
eye disorders	keratitis nec	corneal inflammation	IT
eye disorders	keratitis nec	keratitis	PT
eye disorders	keratopathy nos	keratopathy	IT
eye disorders	lenticular opacities	lens opacity	IT
eye disorders	lenticular opacities	lenticular deposits	IT
eye disorders	lenticular opacities	lenticular opacity	IT
eye disorders	macular degeneration	macula lutea degeneration	PT
eye disorders	macular degeneration	macular degeneration	IT
eye disorders	maculopathy	macula lutea abnormality	IT
eye disorders	ocular hypertension	hypertension ocular	IT
eye disorders	optic atrophy	optic atrophy	PT
eye disorders	optic atrophy	optic disc pallor excessive	IT
eye disorders	optic discs blurred	optic discs blurred	IT
eye disorders	optic neuritis nec	neuritis bulbar	PT
eye disorders	optic neuritis nec	optic neuritis	PT
eye disorders	optic neuritis retrobulbar	retrobulbar neuritis	PT
eye disorders	optic papillitis	optic papillitis	IT
eye disorders	papilloedema	papilloedema	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
eye disorders	retinal artery thrombosis	retinal artery occlusion	IT
eye disorders	retinal artery thrombosis	thrombosis retinal artery	PT
eye disorders	retinal detachment	retinal detachment	PT
eye disorders	retinal disorder nos	retinal damage	IT
eye disorders	retinal disorder nos	retinal disorder	PT
eye disorders	retinal haemorrhage	retinal haemorrhage	PT
eye disorders	retinal microaneurysms	retinal microvascular aneurysm	IT
eye disorders	retinal pallor	retinal pallor	IT
eye disorders	retinal vascular disorder nos	retinal vascular disorder nos	IT
eye disorders	retinitis nec	retinitis	PT
eye disorders	retinopathy nos	retinopathy	IT
eye disorders	vitreous detachment	vitreous detachment	PT
gastrointestinal disorders	abdominal rigidity	abdominal rigidity	PT
gastrointestinal disorders	colitis aggravated	colitis aggravated	IT
gastrointestinal disorders	colitis haemorrhagic	colitis haemorrhagic	PT
gastrointestinal disorders	colitis nos	colitis	PT
gastrointestinal disorders	colitis ulcerative	colitis ulcerative	PT
gastrointestinal disorders	colonic obstruction	colon obstruction	IT
gastrointestinal disorders	diarrhoea haemorrhagic	diarrhoea bloody	PT
gastrointestinal disorders	duodenal ulcer	duodenal ulcer	PT
gastrointestinal disorders	duodenal ulcer haemorrhage	duodenal ulcer haemorrhagic	PT
gastrointestinal disorders	duodenal ulcer perforation	duodenal ulcer haemper	PT
gastrointestinal disorders	duodenal ulcer perforation	duodenal ulcer perforated	PT
gastrointestinal disorders	duodenal ulcer reactivated	duodenal ulcer reactivated	PT
gastrointestinal disorders	enteritis	enteritis	PT
gastrointestinal disorders	enterocolitis	enterocolitis	PT
gastrointestinal disorders	faeces discoloured	stool black	IT
gastrointestinal disorders	gastric atony	gastric atony	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
gastrointestinal disorders	gastric dilatation	gastric dilatation	PT
gastrointestinal disorders	gastric dilatation	stomach dilatation	IT
gastrointestinal disorders	gastric haemorrhage	haemorrhage gastric	IT
gastrointestinal disorders	gastric perforation	gastric perforation	IT
gastrointestinal disorders	gastric ulcer	gastric ulcer	PT
gastrointestinal disorders	gastric ulcer	stomach ulcer	IT
gastrointestinal disorders	gastric ulcer	ulcus ventriculi	IT
gastrointestinal disorders	gastric ulcer haemorrhage	gastric ulcer haemorrhagic	PT
gastrointestinal disorders	gastric ulcer haemorrhage	haematemesis gastric ulcer	IT
gastrointestinal disorders	gastric ulcer haemorrhage	melaena gastric ulcer	IT
gastrointestinal disorders	gastric ulcer perforation	gastric ulcer haemper	PT
gastrointestinal disorders	gastric ulcer perforation	gastric ulcer perforated	PT
gastrointestinal disorders	gastric ulcer perforation	perforation and haem gast ulcer	IT
gastrointestinal disorders	gastritis haemorrhagic	gastritis haemorrhagic	PT
gastrointestinal disorders	gastritis haemorrhagic aggravated	gastritis haemorrhagic aggravated	IT
gastrointestinal disorders	gastrointestinal haemorrhage nos	gastrointestinal tract bleed nos	IT
gastrointestinal disorders	gastrointestinal haemorrhage nos	gi haemorrhage	PT
gastrointestinal disorders	gastrointestinal necrosis	intestinal necrosis	PT
gastrointestinal disorders	gastrointestinal obstruction nos	gi tract obstruction	IT
gastrointestinal disorders	gastrointestinal stenosis nos	gi tract stenosis any site	IT
gastrointestinal disorders	haematemesis	haematemesis	PT
gastrointestinal disorders	haematemesis	vomiting blood	IT
gastrointestinal disorders	haemoperitoneum	haemoperitoneum	PT
gastrointestinal disorders	ileal ulcer	ileal ulcer	IT
gastrointestinal disorders	ileal ulcer perforation	ileal ulcer perforation	IT
gastrointestinal disorders	ileus	ileus	PT
gastrointestinal disorders	ileus paralytic	ileus paralytic	PT
gastrointestinal disorders	ileus spastic	ileus spastic	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
gastrointestinal disorders	impaired gastric emptying	gastroparesis	IT
gastrointestinal disorders	intestinal dilatation	intestinal dilatation	IT
gastrointestinal disorders	intestinal gangrene nos	intestinal gangrene	PT
gastrointestinal disorders	intestinal ischaemia	intestinal ischaemia	PT
gastrointestinal disorders	intestinal obstruction nos	bowel obstruction	IT
gastrointestinal disorders	intestinal obstruction nos	intestinal obstruction	PT
gastrointestinal disorders	intestinal perforation nos	bowel perforation	IT
gastrointestinal disorders	intestinal perforation nos	intestinal perforation	PT
gastrointestinal disorders	intestinal stenosis nos	intestinal stenosis	PT
gastrointestinal disorders	intestinal ulcer	intestinal ulceration	PT
gastrointestinal disorders	intestinal ulcer perforation nos	intestinal ulceration perforated	PT
gastrointestinal disorders	intra-abdominal haemorrhage nos	haemorrhage intraabdominal	PT
gastrointestinal disorders	intra-abdominal haemorrhage nos	intra-abdominal haemorrhage nos	IT
gastrointestinal disorders	intussusception	intussusception	IT
gastrointestinal disorders	large intestinal obstruction nos	large bowel obstruction	IT
gastrointestinal disorders	meconium ileus	ileus paralytic neonatal	PT
gastrointestinal disorders	megacolon acquired	megacolon acquired	PT
gastrointestinal disorders	melaena	melaena	PT
gastrointestinal disorders	melaena	stool tarry	IT
gastrointestinal disorders	mesenteric artery embolism	embolism mesenteric	PT
gastrointestinal disorders	mesenteric occlusion	mesenteric artery thrombosis	IT
gastrointestinal disorders	mesenteric occlusion	thrombosis mesenteric vessel	PT
gastrointestinal disorders	mesenteric vein thrombosis	mesenteric vein thrombosis	IT
gastrointestinal disorders	mesenteric vein thrombosis	thrombophlebitis mesenteric vein	PT
gastrointestinal disorders	necrotising enterocolitis	enterocolitis necrotising	IT
gastrointestinal disorders	oesophageal haemorrhage	oesophageal haemorrhage	IT
gastrointestinal disorders	oesophageal perforation	oesophageal perforation	PT
gastrointestinal disorders	oesophageal stenosis	oesophageal stricture	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
gastrointestinal disorders	oesophageal stenosis	oesophageal stricture	PT
gastrointestinal disorders	oesophageal ulcer	oesophageal ulceration	PT
gastrointestinal disorders	oesophageal ulcer haemorrhage	oesophageal ulceration haemorrhag	PT
gastrointestinal disorders	oesophageal varices nos	oesophageal varices	PT
gastrointestinal disorders	oral mucosal petechiae	petechiae oral mucosa	IT
gastrointestinal disorders	pancreatitis acute	pancreatitis acute	IT
gastrointestinal disorders	pancreatitis acute on chronic	pancreatitis acute on chronic	IT
gastrointestinal disorders	pancreatitis aggravated	pancreatitis aggravated	IT
gastrointestinal disorders	pancreatitis chronic	pancreatitis chronic	IT
gastrointestinal disorders	pancreatitis haemorrhagic	pancreatitis haemorrhagic	IT
gastrointestinal disorders	pancreatitis necrotising	pancreatitis necrotising	IT
gastrointestinal disorders	pancreatitis nos	pancreatitis	PT
gastrointestinal disorders	pancreatitis relapsing	pancreatitis relapsing	IT
gastrointestinal disorders	peptic ulcer	peptic ulcer	PT
gastrointestinal disorders	peptic ulcer aggravated	peptic ulcer aggravated	PT
gastrointestinal disorders	peptic ulcer haemorrhage	peptic ulcer haemorrhagic	PT
gastrointestinal disorders	peptic ulcer perforation	peptic ulcer haemper	PT
gastrointestinal disorders	peptic ulcer perforation	peptic ulcer perforated	PT
gastrointestinal disorders	peptic ulcer perforation	peptic ulcer perforation and haem	IT
gastrointestinal disorders	peptic ulcer reactivated	peptic ulcer reactivated	PT
gastrointestinal disorders	peritoneal effusion bloody	peritoneal effusion bloody	IT
gastrointestinal disorders	peritoneal haemorrhage	peritoneal haemorrhage	IT
gastrointestinal disorders	peritonitis	peritonitis	PT
gastrointestinal disorders	peritonitis sclerosing	peritonitis sclerosing	PT
gastrointestinal disorders	proctitis nos	proctitis	PT
gastrointestinal disorders	proctitis ulcerative	proctitis ulcerative	PT
gastrointestinal disorders	pyloric ulcer	pyloric ulcer	IT
gastrointestinal disorders	rectal haemorrhage	haemorrhage rectum	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
gastrointestinal disorders	rectal haemorrhage	rectal bleeding	IT
gastrointestinal disorders	retroperitoneal fibrosis	retroperitoneal fibrosis	PT
gastrointestinal disorders	retroperitoneal haemorrhage	haemorrhage retroperitoneal	PT
gastrointestinal disorders	small intestinal gangrene nos	small intestine gangrene	IT
gastrointestinal disorders	small intestinal obstruction nos	small intestine obstruction	IT
gastrointestinal disorders	small intestinal ulcer nos	small intestinal ulcer nos	IT
gastrointestinal disorders	small intestinal ulcer nos	small intestine ulcer	IT
gastrointestinal disorders	stomatitis necrotising	stomatitis necrotising	PT
gastrointestinal disorders	tongue spasm	spasm tongue	IT
gastrointestinal disorders	toxic dilatation of intestine	intestine dilatation toxic severe	IT
general disorders and administration site conditions	crepitations nos	crackles	IT
general disorders and administration site conditions	death nos	death	PT
general disorders and administration site conditions	drug withdrawal syndrome neonatal	withdrawal syndrome neonatal	PT
general disorders and administration site conditions	hyperpyrexia	hyperpyrexia	PT
general disorders and administration site conditions	hyperpyrexia malignant	hyperpyrexia malignant	PT
general disorders and administration site conditions	hyperpyrexia malignant	hyperthermia malignant	IT
general disorders and administration site conditions	neuralgia nos	nerve pain	IT
general disorders and administration site conditions	neuralgia nos	neuralgia	PT
general disorders and administration site conditions	neuroleptic malignant synd. aggr.	neuroleptic malignant synd. aggr.	IT
general disorders and administration site conditions	neuroleptic malignant syndrome	neuroleptic malignant syndrome	PT
general disorders and administration site conditions	oedema nos	oedema generalised	PT
general disorders and administration site conditions	pain nos	angina	IT
general disorders and administration site conditions	sluggishness	sluggishness	IT
general disorders and administration site conditions	sudden death unexplained	sudden death	PT
general disorders and administration site conditions	sudden infant death syndrome	sudden infant death syndrome	PT
hepato-biliary disorders	bile duct stricture	bile duct stricture	PT
hepato-biliary disorders	cholangiolitis	cholangiolitis toxic	IT
hepato-biliary disorders	cholestasis	cholestasis intrahepatic	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
hepato-biliary disorders	hepatic cirrhosis nos	hepatic cirrhosis	PT
hepato-biliary disorders	hepatic disease nos	hepatic disease	IT
hepato-biliary disorders	hepatic failure	hepatic failure	PT
hepato-biliary disorders	hepatic haemorrhage	hepatic haemorrhage	PT
hepato-biliary disorders	hepatic infarction	hepatic infarction	PT
hepato-biliary disorders	hepatic necrosis	hepatic necrosis	PT
hepato-biliary disorders	hepatitis aggravated	hepatitis aggravated	IT
hepato-biliary disorders	hepatitis cholestatic	hepatitis cholestatic	PT
hepato-biliary disorders	hepatitis cholestatic	hepatitis toxic obstructive	IT
hepato-biliary disorders	hepatitis fulminant	hepatitis fulminant	IT
hepato-biliary disorders	hepatitis granulomatous nos	hepatitis granulomatous	IT
hepato-biliary disorders	hepatitis neonatal	hepatitis neonatal	PT
hepato-biliary disorders	hepatitis nos	hepatitis	PT
hepato-biliary disorders	hepatitis nos	hepatitis nos	IT
hepato-biliary disorders	hepatitis nos	hepatitis toxic	IT
hepato-biliary disorders	hepatocellular damage	hepatic damage	IT
hepato-biliary disorders	hepatocellular damage	hepatocellular damage	PT
hepato-biliary disorders	hepatocellular damage	liver cell damage	IT
hepato-biliary disorders	hepatocellular damage neonatal	hepatocellular damage neonatal	PT
hepato-biliary disorders	hepatorenal syndrome	hepatorenal syndrome	PT
hepato-biliary disorders	hepatotoxicity nos	hepatotoxic effect	IT
hepato-biliary disorders	hyperbilirubinaemia	bilirubinaemia newborn	IT
hepato-biliary disorders	jaundice cholestatic	jaundice cholestatic	IT
hepato-biliary disorders	jaundice haemolytic	jaundice haemolytic	PT
hepato-biliary disorders	jaundice hepatocellular	jaundice hepatocellular	IT
hepato-biliary disorders	liver fatty	hepatic steatosis	IT
hepato-biliary disorders	liver fatty	liver fatty	PT
hepato-biliary disorders	liver fatty	liver fatty change	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
hepato-biliary disorders	liver fatty	liver fatty degeneration	IT
hepato-biliary disorders	liver fatty	liver fatty deposition	IT
hepato-biliary disorders	liver fatty	liver fatty infiltration	IT
hepato-biliary disorders	liver fatty	liver fatty metamorphosis	IT
hepato-biliary disorders	liver fatty	liver fatty phanerosis	IT
hepato-biliary disorders	portal hypertension	hypertension portal	PT
hepato-biliary disorders	reye's syndrome	reye's syndrome	PT
immune system disorders	amyloidosis nos	amyloidosis	PT
immune system disorders	anaphylactic reaction	anaphylactic reaction	IT
immune system disorders	anaphylactic reaction	anaphylaxis	IT
immune system disorders	anaphylactic shock	anaphylactic shock	PT
immune system disorders	anaphylactoid reaction	anaphylactoid reaction	PT
immune system disorders	graft versus host disease	graft versus host disease	PT
immune system disorders	hypersensitivity nos	red neck syndrome	IT
immune system disorders	polyarteritis nodosa	panarteritis nodosa	IT
immune system disorders	polyarteritis nodosa	periarteritis nodos with necrosis	IT
immune system disorders	polyarteritis nodosa	periarteritis nodosa	IT
immune system disorders	polyarteritis nodosa	polyarteritis nodosa	PT
infections and infestations	colitis pseudomembranous	colitis pseudomembranous	PT
infections and infestations	croup aggravated	croup aggravated	IT
infections and infestations	croup infectious	croup	IT
infections and infestations	epiglottitis nos	epiglottitis	PT
infections and infestations	herpes gestationis	herpes gestationnis	PT
infections and infestations	keratoconjunctivitis	keratoconjunctivitis	PT
infections and infestations	meningitis bacterial nos	meningitis bacterial	IT
infections and infestations	meningitis meningococcal	meningitis meningococcal	IT
infections and infestations	meningitis nos	meningitis	PT
infections and infestations	meningitis pneumococcal	meningitis pneumococcal	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
infections and infestations	meningitis viral nec	meningitis viral	IT
infections and infestations	poliomyelitis nec	polio-like paralysis	IT
infections and infestations	tetanus	tetanus-like	IT
injury and poisoning	asbestosis	asbestosis	PT
injury and poisoning	asphyxiation	asphyxiation	IT
injury and poisoning	berylliosis	berylliosis	PT
injury and poisoning	corneal perforation	corneal perforation	IT
injury and poisoning	haemothorax	hemothorax	PT
injury and poisoning	medication error	drug maladministration	IT
injury and poisoning	meningitis chemical	meningitis chemical	IT
injury and poisoning	metal poisoning	acrodynia	PT
injury and poisoning	metal poisoning	burton's lines	IT
injury and poisoning	metal poisoning	gums blue line	PT
injury and poisoning	metal poisoning	lead line	IT
injury and poisoning	metal poisoning	lead poisoning	PT
injury and poisoning	metal poisoning	saturnism	IT
injury and poisoning	nephropathy toxic	nephropathy toxic	PT
injury and poisoning	neurotoxicity nos	neurotoxicity	IT
injury and poisoning	non-accidental overdose	non-accidental overdose	IT
injury and poisoning	ototoxicity	ototoxicity	PT
injury and poisoning	peripheral nerve injury	nerve damage	IT
injury and poisoning	peripheral nerve injury	peripheral nerve injury	IT
injury and poisoning	pneumoconiosis	baritosis	PT
injury and poisoning	pneumoconiosis	pneumoconiosis	PT
injury and poisoning	silicosis	silicosis	PT
injury and poisoning	subdural haematoma	haemorrhage subdural	IT
injury and poisoning	subdural haematoma	subdural haematoma	IT
injury and poisoning	sunburn	sunburn	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
investigations	albuminuria present	albuminuria	PT
investigations	anion gap abnormal	anion gap abnormal	PT
investigations	arterial pressure nos increased	arterial pressure high	IT
investigations	bence jones proteinuria present	bence jones proteinuria	IT
investigations	blood alkaline phosphatase nos increased	alkaline phosphatase serum incr	IT
investigations	blood alkaline phosphatase nos increased	alp increased	IT
investigations	blood alkaline phosphatase nos increased	phosphatase alkaline increased	PT
investigations	blood amylase increased	amylase increased	PT
investigations	blood bicarbonate decreased	bicarbonate reserve decreased	IT
investigations	blood calcium decreased	calcium blood decreased	IT
investigations	blood calcium increased	calcium increased serum	IT
investigations	blood glucose decreased	blood sugar decreased	IT
investigations	blood in stool	blood in stool	IT
investigations	blood in stool	faeces bloodstained	IT
investigations	blood insulin increased	insulin value increased	IT
investigations	blood lactic acid increased	lactate blood increase	IT
investigations	blood ph decreased	ph reduced	IT
investigations	blood potassium decreased	potassium serum decreased	IT
investigations	blood potassium increased	potassium retention	IT
investigations	blood potassium increased	potassium serum increased	IT
investigations	blood pressure increased	blood pressure increased	IT
investigations	blood pressure increased	pressure blood increased	IT
investigations	coagulation factor decreased	coagulation factor decreased	PT
investigations	coagulation time nos prolonged	clotting time increased	IT
investigations	coagulation time nos prolonged	clotting time lengthened	IT
investigations	coagulation time nos prolonged	clotting time prolonged	IT
investigations	coagulation time nos prolonged	coagulation time increased	PT
investigations	coagulation time nos prolonged	hypocoagulable state	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
investigations	creatinine renal clearance decreased	creatinine clearance decreased	PT
investigations	drug specific antibody present	antibodies drug specific	PT
investigations	drug specific antibody present	develop antibodies to drugs	IT
investigations	electrocardiogram qt prolonged	qt prolonged	PT
investigations	faecal occult blood positive	faecal occult blood positive	IT
investigations	haptoglobin increased	haptoglobin increased	PT
investigations	heart rate irregular	pulse irregularity nos	IT
investigations	intraocular pressure increased	intraocular pressure increased	IT
investigations	intraocular pressure increased	ocular tension increased	IT
investigations	ketonuria present	acetonuria	IT
investigations	le test abnormal	le cells present	IT
investigations	le test abnormal	le test abnormal	PT
investigations	lymphocyte morphology nos abnormal	pseudo monomucleosis	IT
investigations	osmolar gap abnormal	osmolar gap abnormal	PT
investigations	pancreatic enzymes nos increased	pancreas enzymes increased	PT
investigations	proteinuria aggravated	proteinuria aggravated	IT
investigations	proteinuria present	proteinuria	IT
investigations	prothrombin level decreased	factor ii deficiency	IT
investigations	prothrombin level decreased	hypoprothrombinaemia	IT
investigations	prothrombin level decreased	prothrombin activity decreased	IT
investigations	prothrombin level decreased	prothrombin consumption increased	IT
investigations	prothrombin level decreased	prothrombin decreased	PT
investigations	prothrombin level decreased	prothrombin deficiency	IT
investigations	prothrombin level increased	prothrombin activity increased	IT
investigations	prothrombin level increased	prothrombin increased	PT
investigations	prothrombin time prolonged	prothrombin time prolonged	IT
investigations	prothrombin time shortened	prothrombin time shortened	IT
investigations	pulse abnormal nos	pulse abnormal	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
investigations	raised intraocular pressure aggr.	raised intraocular pressure aggr.	IT
investigations	renal clearance nos decreased	renal clearances low	IT
investigations	renal concentrating power decreased	hyposthenuria	IT
investigations	renal concentrating power decreased	renal concentrating power decr	IT
investigations	smear cervix abnormal	cervical smear pos class iii to v	IT
investigations	smear cervix abnormal	cervical smear test positive	PT
investigations	specific gravity urine abnormal	urine specific gravity fixed	IT
metabolism and nutrition disorders	acetonaemia	acetonaemia	IT
metabolism and nutrition disorders	acidosis nos	acidosis	PT
metabolism and nutrition disorders	calcium deficiency	calcium deficiency	IT
metabolism and nutrition disorders	calcium deficiency	calcium depletion	IT
metabolism and nutrition disorders	diabetic coma nos	coma diabetic	PT
metabolism and nutrition disorders	diabetic hyperglycaemic coma	coma hyperglycaemic	IT
metabolism and nutrition disorders	diabetic ketoacidosis	diabetic ketoacidosis	IT
metabolism and nutrition disorders	hypercalcaemia	calcium repletion serum	IT
metabolism and nutrition disorders	hypercalcaemia	hypercalcaemia	PT
metabolism and nutrition disorders	hypercalcaemia aggravated	hypercalcaemia aggravated	IT
metabolism and nutrition disorders	hyperkalaemia	hyperkalaemia	PT
metabolism and nutrition disorders	hyperkalaemia	hyperpotassaemia	IT
metabolism and nutrition disorders	hypermagnesaemia	hypermagnesaemia	PT
metabolism and nutrition disorders	hypocalcaemia	hypocalcaemia	PT
metabolism and nutrition disorders	hypoglycaemia aggravated	hypoglycaemia aggravated	IT
metabolism and nutrition disorders	hypoglycaemia neonatal	hypoglycaemia neonatal	PT
metabolism and nutrition disorders	hypoglycaemia nos	hypoglycaemia	PT
metabolism and nutrition disorders	hypoglycaemia nos	hypoglycaemic reaction	PT
metabolism and nutrition disorders	hypoglycaemic coma	coma hypoglycaemic	PT
metabolism and nutrition disorders	hypokalaemia	hypokalaemia	PT
metabolism and nutrition disorders	hypokalaemia	hypopotassaemia	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
metabolism and nutrition disorders	hypokalaemia	potassium deficiency	IT
metabolism and nutrition disorders	hypokalaemic syndrome	low potassium syndrome	IT
metabolism and nutrition disorders	ketoacidosis	acetone breath	IT
metabolism and nutrition disorders	ketoacidosis	ketoacidosis	IT
metabolism and nutrition disorders	ketosis	ketosis	PT
metabolism and nutrition disorders	lactic acidosis	acidosis lactic	PT
metabolism and nutrition disorders	metabolic acidosis nos	acidosis metabolic	IT
metabolism and nutrition disorders	shock hypoglycaemic	insulin shock	IT
metabolism and nutrition disorders	tetany	tetany	PT
musculoskeletal, connective tissue and bone disorders	aseptic necrosis bone	aseptic necrosis bone	PT
musculoskeletal, connective tissue and bone disorders	aseptic necrosis bone	avascular necrosis femoral head	PT
musculoskeletal, connective tissue and bone disorders	drug induced lupus erythematosus	hydralazine le type reaction	IT
musculoskeletal, connective tissue and bone disorders	joint stiffness	jaw stiffness	IT
musculoskeletal, connective tissue and bone disorders	muscle atrophy	muscle atrophy	PT
musculoskeletal, connective tissue and bone disorders	muscle atrophy	muscle degeneration	IT
musculoskeletal, connective tissue and bone disorders	muscle atrophy	muscle wasting	IT
musculoskeletal, connective tissue and bone disorders	muscle disorder nos	muscle disorder	IT
musculoskeletal, connective tissue and bone disorders	muscle haemorrhage	muscle haemorrhage	PT
musculoskeletal, connective tissue and bone disorders	muscle necrosis	muscle necrosis	IT
musculoskeletal, connective tissue and bone disorders	muscle spasms	spasm generalized	PT
musculoskeletal, connective tissue and bone disorders	muscle spasms	spasms	IT
musculoskeletal, connective tissue and bone disorders	muscle stiffness	muscle stiffness	IT
musculoskeletal, connective tissue and bone disorders	myopathy	myopathy	PT
musculoskeletal, connective tissue and bone disorders	myopathy aggravated	myopathy aggravated	IT
musculoskeletal, connective tissue and bone disorders	myositis	myositis	PT
musculoskeletal, connective tissue and bone disorders	myositis-like syndrome	myositis-like syndrome	IT
musculoskeletal, connective tissue and bone disorders	osteolysis	acroosteolysis	PT
musculoskeletal, connective tissue and bone disorders	polyserositis	polyserositis	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
musculoskeletal, connective tissue and bone disorders	rhabdomyolysis	rhabdomyolysis	PT
musculoskeletal, connective tissue and bone disorders	sle arthritis	le arthritis	IT
musculoskeletal, connective tissue and bone disorders	systemic lupus erythematosus	disseminated lupus erythematosus	IT
musculoskeletal, connective tissue and bone disorders	systemic lupus erythematosus	le syndrome	PT
musculoskeletal, connective tissue and bone disorders	systemic lupus erythematosus	le type reaction	IT
musculoskeletal, connective tissue and bone disorders	systemic lupus erythematosus	lupus erythematosus systemic	IT
musculoskeletal, connective tissue and bone disorders	systemic lupus erythematosus	sle-like symptoms	IT
musculoskeletal, connective tissue and bone disorders	systemic lupus erythematosus	systemic lupus erythematosus synd	IT
neoplasms benign and malignant (including cysts and polyps)	acute leukaemia nos	leukaemia acute	PT
neoplasms benign and malignant (including cysts and polyps)	acute myeloid leukaemia aggravated	acute myeloid leukaemia aggravat.	IT
neoplasms benign and malignant (including cysts and polyps)	angiofibroma	angiofibroma	PT
neoplasms benign and malignant (including cysts and polyps)	angiofibroma	angiofibromatous hyperplasia	IT
neoplasms benign and malignant (including cysts and polyps)	astrocytoma	astrocytoma	PT
neoplasms benign and malignant (including cysts and polyps)	benign breast neoplasm nos	breast neoplasm benign female	PT
neoplasms benign and malignant (including cysts and polyps)	benign ovarian tumour	ovarian tumour benign	IT
neoplasms benign and malignant (including cysts and polyps)	benign vaginal neoplasm	vaginal neoplasm benign	PT
neoplasms benign and malignant (including cysts and polyps)	bowen's disease	bowen's disease	IT
neoplasms benign and malignant (including cysts and polyps)	breast cancer aggravated	breast cancer aggravated	IT
neoplasms benign and malignant (including cysts and polyps)	breast cancer female nos	breast cancer	IT
neoplasms benign and malignant (including cysts and polyps)	breast cancer female nos	breast neoplasm malignant female	PT
neoplasms benign and malignant (including cysts and polyps)	breast cancer male nos	breast neoplasm malignant male	PT
neoplasms benign and malignant (including cysts and polyps)	breast neoplasm nos	breast neoplasm female	PT
neoplasms benign and malignant (including cysts and polyps)	breast neoplasm nos male	breast neoplasm male	PT
neoplasms benign and malignant (including cysts and polyps)	cervical cancer stage 0	cervix carcinoma in situ	PT
neoplasms benign and malignant (including cysts and polyps)	cervical carcinoma nos	cervix carcinoma	PT
neoplasms benign and malignant (including cysts and polyps)	degeneration of uterine fibroid	degeneration of uterine fibroid	IT
neoplasms benign and malignant (including cysts and polyps)	endometrial cancer nos	endometrial adenocarcinoma	IT
neoplasms benign and malignant (including cysts and polyps)	endometrial cancer nos	endometrial neoplasm malignant	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
neoplasms benign and malignant (including cysts and polyps)	endometrial stromal sarcoma	endometrial stromal sarcoma	IT
neoplasms benign and malignant (including cysts and polyps)	epithelioma	epithelioma	IT
neoplasms benign and malignant (including cysts and polyps)	erythroleukaemia	di guglielmo's syndrome	IT
neoplasms benign and malignant (including cysts and polyps)	erythroleukaemia	erythraemic myelosis	IT
neoplasms benign and malignant (including cysts and polyps)	fibroadenoma of breast	breast fibroadenosis	PT
neoplasms benign and malignant (including cysts and polyps)	fibrocystic breast disease	breast cystic fibrosis	IT
neoplasms benign and malignant (including cysts and polyps)	fibrocystic breast disease	breast fibrocystic change	IT
neoplasms benign and malignant (including cysts and polyps)	fibrocystic breast disease	breast fibrocystic disorder	IT
neoplasms benign and malignant (including cysts and polyps)	fibroma nos	fibroids	IT
neoplasms benign and malignant (including cysts and polyps)	hairy cell leukaemia	hairy cell leukaemia	PT
neoplasms benign and malignant (including cysts and polyps)	leukaemia granulocytic nos	leukaemia granulocytic	PT
neoplasms benign and malignant (including cysts and polyps)	leukaemia monocytic nos	leukaemia monocytic	PT
neoplasms benign and malignant (including cysts and polyps)	leukaemia nos	leukaemia	PT
neoplasms benign and malignant (including cysts and polyps)	lymphocytic leukaemia	leukaemia lymphatic	IT
neoplasms benign and malignant (including cysts and polyps)	lymphocytic leukaemia	leukaemia lymphocytic	PT
neoplasms benign and malignant (including cysts and polyps)	lymphocytic leukaemia	leukaemia lymphoid	IT
neoplasms benign and malignant (including cysts and polyps)	lymphoma nos	lymphoma malignant	PT
neoplasms benign and malignant (including cysts and polyps)	malignant histiocytosis	histiocytosis	PT
neoplasms benign and malignant (including cysts and polyps)	marrow hyperplasia	haematopoiesis increased	IT
neoplasms benign and malignant (including cysts and polyps)	marrow hyperplasia	marrow hyperplasia	PT
neoplasms benign and malignant (including cysts and polyps)	marrow hyperplasia	panmyelosis	IT
neoplasms benign and malignant (including cysts and polyps)	mycosis fungoides nos	mycosis fungoides	IT
neoplasms benign and malignant (including cysts and polyps)	myelodysplastic syndrome nos	myelodysplastic syndrome	IT
neoplasms benign and malignant (including cysts and polyps)	myelofibrosis	myelofibrosis	PT
neoplasms benign and malignant (including cysts and polyps)	myeloid leukaemia nos	leukaemia myelogenous	IT
neoplasms benign and malignant (including cysts and polyps)	myeloid leukaemia nos	leukaemia myeloid	IT
neoplasms benign and malignant (including cysts and polyps)	myeloid metaplasia	myelosis non-leukaemic	IT
neoplasms benign and malignant (including cysts and polyps)	myeloproliferative disorder nos	myeloproliferative disorder	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
neoplasms benign and malignant (including cysts and polyps)	neonatal leukaemia	leukaemia neonatal	PT
neoplasms benign and malignant (including cysts and polyps)	nonhodgkin's lymphoma nos	non-hodgkin's lymphoma	PT
neoplasms benign and malignant (including cysts and polyps)	ovarian cancer nos	ovarian carcinoma	PT
neoplasms benign and malignant (including cysts and polyps)	pseudo lymphoma	hodgkin's-like	IT
neoplasms benign and malignant (including cysts and polyps)	pseudo lymphoma	lymphoma-like disorder	PT
neoplasms benign and malignant (including cysts and polyps)	pseudo lymphoma	lymphoma-like reaction	IT
neoplasms benign and malignant (including cysts and polyps)	pseudo lymphoma	lymphomoid	IT
neoplasms benign and malignant (including cysts and polyps)	pseudo lymphoma	lymphosarcomoid	IT
neoplasms benign and malignant (including cysts and polyps)	pseudo lymphoma	pseudo lymphoma	IT
neoplasms benign and malignant (including cysts and polyps)	squamous cell carcinoma	carcinoma squamous	PT
neoplasms benign and malignant (including cysts and polyps)	testis cancer (exc germ cell)	testis neoplasm malignant	PT
neoplasms benign and malignant (including cysts and polyps)	uterine cancer nos	uterine carcinoma	PT
neoplasms benign and malignant (including cysts and polyps)	uterine fibroids	uterine fibroid	PT
neoplasms benign and malignant (including cysts and polyps)	uterine fibroids	uterine fibromyoma	IT
neoplasms benign and malignant (including cysts and polyps)	uterine fibroids aggravated	uterine fibroids aggravated	IT
neoplasms benign and malignant (including cysts and polyps)	uterine neoplasm nos	uterine neoplasm	PT
neoplasms benign and malignant (including cysts and polyps)	vaginal cancer nos	vaginal neoplasm malignant	PT
nervous system disorders	akathisia	akathisia	IT
nervous system disorders	akathisia aggravated	akathisia aggravated	IT
nervous system disorders	akinesia	activity motor retarded	IT
nervous system disorders	akinesia	akinesia	IT
nervous system disorders	akinesia	motor activity retarded	IT
nervous system disorders	akinesia	movements reduced	IT
nervous system disorders	akinesia	responses voluntary reduced	IT
nervous system disorders	akinetic mutism	akinetic mutism	IT
nervous system disorders	amnesia aggravated	amnesia aggravated	IT
nervous system disorders	amnesia nec	amnesia	PT
nervous system disorders	amnesia nec	memory loss	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
nervous system disorders	amyotrophy nos	amyotrophy	IT
nervous system disorders	arachnoiditis	arachnoiditis	PT
nervous system disorders	areflexia	areflexia	IT
nervous system disorders	areflexia	reflexes absent	IT
nervous system disorders	athetosis	athetosis	IT
nervous system disorders	atonic seizures	atonic seizures	IT
nervous system disorders	benign intracranial hypertension	intracranial pressure inc. benign	IT
nervous system disorders	benign intracranial hypertension	pseudotumor cerebri	IT
nervous system disorders	bulbar palsy	bulbar palsy	IT
nervous system disorders	bulbar palsy	paralysis bulbar	PT
nervous system disorders	cataplexy	cataplexy	IT
nervous system disorders	cataplexy aggravated	cataplexy aggravated	IT
nervous system disorders	central nervous system stimulation nos	cns stimulation nos	IT
nervous system disorders	cerebellar syndrome	dysmetria	IT
nervous system disorders	cerebral atrophy	cerebral atrophy	PT
nervous system disorders	cerebral oedema	oedema cerebral	PT
nervous system disorders	cervical spasm	cervical spasm	IT
nervous system disorders	chorea aggravated	chorea aggravated	IT
nervous system disorders	chorea nos	chorea	IT
nervous system disorders	choreoathetosis	choreoathetoid movements	IT
nervous system disorders	choreoathetosis	choreoathetosis	PT
nervous system disorders	coma nec	coma	PT
nervous system disorders	complex partial seizures	complex partial seizures	IT
nervous system disorders	convulsion neonatal	convulsions neonatal	PT
nervous system disorders	convulsions nos	convulsions	PT
nervous system disorders	convulsions nos	convulsive disorder	IT
nervous system disorders	convulsions nos	epileptiform attacks nos	IT
nervous system disorders	convulsions nos	epileptiform fits nos	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
nervous system disorders	convulsions nos	fits nos	IT
nervous system disorders	convulsions nos	seizures cerebral	IT
nervous system disorders	convulsions nos aggravated	convulsions aggravated	PT
nervous system disorders	convulsive threshold lowered	convulsive threshold lowered	IT
nervous system disorders	coordination abnormal nos	asynergia	IT
nervous system disorders	dementia due to creutzfeld-jacob disease	creutzfeldt-jakob disease	PT
nervous system disorders	dementia nos	dementia	PT
nervous system disorders	dementia nos	dementia acquired	IT
nervous system disorders	dementia nos aggravated	dementia aggravated	IT
nervous system disorders	dementia of the alzheimer's type nos	alzheimer's disease	PT
nervous system disorders	developmental coordination disorder nos	psychomotor development impaired	PT
nervous system disorders	drug withdrawal convulsions	withdrawal convulsions	PT
nervous system disorders	dyskinesia aggravated	dyskinesia aggravated	IT
nervous system disorders	dyskinesia nec	dyskinesia	PT
nervous system disorders	dyskinesia nec	dyskinesia acute	IT
nervous system disorders	dyskinesia nec	dyskinetic syndrome	IT
nervous system disorders	dyskinesia nec	head-face-neck syndrome	IT
nervous system disorders	dyskinesia nec	involuntary movement oral	IT
nervous system disorders	dyskinesia nec	movements involuntary	IT
nervous system disorders	dyskinesia nec	movements spastic involuntary	IT
nervous system disorders	dyskinesia nec	tongue protrusion spastic involun	IT
nervous system disorders	dyskinesia neonatal	dyskinesia neonatal	PT
nervous system disorders	dystonia	dystonia	PT
nervous system disorders	dystonia aggravated	dystonia aggravated	IT
nervous system disorders	encephalitis nos	encephalitis	IT
nervous system disorders	encephalitis nos	encephalitis toxic	IT
nervous system disorders	encephalitis nos	encephalomyelitis	PT
nervous system disorders	encephalopathy allergic	encephalopathy allergic	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
nervous system disorders	encephalopathy neonatal	encephalopathy neonatal	PT
nervous system disorders	encephalopathy nos	encephalopathy	PT
nervous system disorders	encephalopathy nos	encephalopathy toxic	IT
nervous system disorders	epilepsy nos	epilepsy	IT
nervous system disorders	epilepsy nos	epilepsy equivalent	IT
nervous system disorders	epileptic aura	epileptic aura	IT
nervous system disorders	extensor plantar response	babinski sign positive	IT
nervous system disorders	extensor plantar response	reflex babinski positive	IT
nervous system disorders	extensor plantar response	reflex plantar extensor	PT
nervous system disorders	extensor plantar response	reflex plantar upgoing	IT
nervous system disorders	extraocular muscle paresis	extraocular muscle paresis	IT
nervous system disorders	facial palsy	facial palsy	IT
nervous system disorders	facial palsy	paralysis facial	IT
nervous system disorders	facial palsy aggravated	facial palsy aggravated	IT
nervous system disorders	fontanelle bulging	fontanelle bulging	IT
nervous system disorders	grand mal convulsion	convulsions grand mal	PT
nervous system disorders	grand mal convulsion	tonic/ clonic convulsions	IT
nervous system disorders	grand mal epilepsy	epilepsy grand mal	IT
nervous system disorders	guillain barre syndrome	guillain-barre syndrome	IT
nervous system disorders	guillain barre syndrome	paralysis ascending	PT
nervous system disorders	haemorrhagic stroke	cerebral haemorrhage	PT
nervous system disorders	haemorrhagic stroke	haemorrhage brain stem	PT
nervous system disorders	haemorrhagic stroke	haemorrhage cerebellar	PT
nervous system disorders	hemianopia nos	hemianopia	PT
nervous system disorders	hemianopia nos	hemianopsia	IT
nervous system disorders	hemiparesis	hemiparesis	PT
nervous system disorders	hemiplegia	hemiplegia	PT
nervous system disorders	hemiplegia transient	hemiparesis transient	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
nervous system disorders	hepatic encephalopathy	coma hepatic	PT
nervous system disorders	hydrocephalus nos	hydrocephalus acquired	PT
nervous system disorders	hydrocephalus nos	hydrocephaly hypertensive	PT
nervous system disorders	hydrocephalus nos	hydrocephaly obstructive	PT
nervous system disorders	hyperactivity syndrome aggravated	hyperactivity syndrome aggravated	IT
nervous system disorders	hyperkinesia neonatal	hyperkinesia neonatal	PT
nervous system disorders	hyperkinetic syndrome	activity motor exaggerated	IT
nervous system disorders	hyperkinetic syndrome	hyperkinesia	PT
nervous system disorders	hyperkinetic syndrome	hyperkinetic reaction	IT
nervous system disorders	hyperkinetic syndrome	hyperkinetic syndrome	IT
nervous system disorders	hyperkinetic syndrome	motor activity exaggerated	IT
nervous system disorders	hyperkinetic syndrome	muscular hyperactivity	IT
nervous system disorders	hyperkinetic syndrome	psychomotor hyperactivity	IT
nervous system disorders	hypertonia	hypertonia	PT
nervous system disorders	hypertonia	hypertonus	IT
nervous system disorders	hypertonia	muscular tone excessive	IT
nervous system disorders	hypertonia	muscular tone increased	IT
nervous system disorders	hypokinesia	hypokinesia	PT
nervous system disorders	hypokinesia	mobility decreased	IT
nervous system disorders	hypokinesia neonatal	hypokinesia neonatal	PT
nervous system disorders	hyporeflexia	hyporeflexia	PT
nervous system disorders	hypotonia neonatal	hypotonia neonatal	PT
nervous system disorders	iiird nerve paralysis	cranial third nerve paralysis	IT
nervous system disorders	iiird nerve paralysis	cranial third nerve paresis	IT
nervous system disorders	iiird nerve paralysis	oculomotor nerve paralysis	PT
nervous system disorders	iiird nerve paralysis	oculomotor paralysis	IT
nervous system disorders	increased activity	behaviour hyperactive	IT
nervous system disorders	increased activity	hyperactivity	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
nervous system disorders	intracranial pressure increased nos	hypertension intracranial	PT
nervous system disorders	intracranial pressure increased nos	intracranial pressure increased	IT
nervous system disorders	intracranial pressure increased nos	subarachnoid pressure increased	IT
nervous system disorders	locked-in syndrome	locked-in syndrome	IT
nervous system disorders	loss of consciousness nec	unconsciousness	IT
nervous system disorders	lower motor neurone lesion	lower motor neurone lesion	PT
nervous system disorders	lower motor neurone lesion	paralysis lower motor neurone	IT
nervous system disorders	memory impairment	forgetfulness	IT
nervous system disorders	memory impairment	memory disturbance	IT
nervous system disorders	memory impairment	memory impairment	IT
nervous system disorders	meningism	meningeal irritation	IT
nervous system disorders	meningism	meningism	PT
nervous system disorders	meningism	meningismus	IT
nervous system disorders	meningism	meningitis-like reaction	IT
nervous system disorders	meningitis aseptic	meningitis aseptic	IT
nervous system disorders	mental impairment nos	mental deterioration	IT
nervous system disorders	meralgia paraesthetica	meralgia paraesthetica	IT
nervous system disorders	mononeuritis	mononeuritis	PT
nervous system disorders	monoplegia	monoplegia	PT
nervous system disorders	multiple sclerosis	ms-like syndrome	PT
nervous system disorders	multiple sclerosis aggravated	ms aggravated	PT
nervous system disorders	multiple sclerosis aggravated	multiple sclerosis aggravated	IT
nervous system disorders	multiple sclerosis relapse	multiple sclerosis relapse	IT
nervous system disorders	muscle rigidity	muscle rigidity	IT
nervous system disorders	muscle spasticity	muscle spasticity	IT
nervous system disorders	muscle spasticity aggravated	muscle spasticity aggravated	IT
nervous system disorders	mutism nec	mutism	IT
nervous system disorders	myasthenia gravis	myasthenia gravis-like syndrome	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
nervous system disorders	myelitis nos	myelitis	PT
nervous system disorders	myelitis transverse	myelitis transverse	IT
nervous system disorders	myelopathy nec	myelopathy	IT
nervous system disorders	narcolepsy	narcolepsy	IT
nervous system disorders	narcolepsy aggravated	narcolepsy aggravated	IT
nervous system disorders	nerve root lesion nos	polyradiculitis	IT
nervous system disorders	neurasthaenia	neurasthenia	IT
nervous system disorders	neurasthaenia	neurocirculatory asthenia	IT
nervous system disorders	neuritis cranial	neuritis cranial	PT
nervous system disorders	neuritis nos	neuritis	PT
nervous system disorders	neuritis nos	neuritis motor	PT
nervous system disorders	neuritis nos	neuronitis	IT
nervous system disorders	neurological disorder nos	brain stem disorder	PT
nervous system disorders	neurological disorder nos	brain stem dysfunction	IT
nervous system disorders	neurological disorder nos	neurologic complication	IT
nervous system disorders	neurological disorder nos	neurologic disorder nos	IT
nervous system disorders	neurological findings abnormal nos	neurologic findings abnormal	IT
nervous system disorders	neurological symptoms nos	neurologic reaction	IT
nervous system disorders	neurological symptoms nos	neurologic symptoms	IT
nervous system disorders	neuromuscular blockade	neuromuscular block	IT
nervous system disorders	nodding of head	nodding of head	IT
nervous system disorders	ophthalmoplegia nos	oculomotor paresis	IT
nervous system disorders	opisthotonus	back arched backward	IT
nervous system disorders	opisthotonus	opisthotonos	PT
nervous system disorders	opisthotonus	spine rigidly extended	IT
nervous system disorders	opisthotonus	trunk bowed back	IT
nervous system disorders	paralysis flaccid	paralysis flaccid	PT
nervous system disorders	paralysis nos	paralysis	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
nervous system disorders	paralysis nos	paralysis muscle general skeletal	IT
nervous system disorders	paralysis nos	paralysis muscle local skeletal	IT
nervous system disorders	paralysis nos	skeletal muscle paralysis	IT
nervous system disorders	paralysis spastic (exc congenital)	paralysis spastic	PT
nervous system disorders	paraplegia	paraplegia	PT
nervous system disorders	paresis	paresis	PT
nervous system disorders	parkinsonism aggravated	parkinsonism aggravated	PT
nervous system disorders	peripheral motor neuropathy	peripheral motor neuropathy	IT
nervous system disorders	peripheral neuropathy nec	neuropathy	PT
nervous system disorders	peripheral neuropathy nec	neuropathy peripheral	PT
nervous system disorders	peripheral neuropathy nec	peripheral neuritis	IT
nervous system disorders	peripheral sensory neuropathy	peripheral sensory neuropathy	IT
nervous system disorders	petit mal epilepsy	petit mal	IT
nervous system disorders	polyneuropathy nos	polyneuritis	IT
nervous system disorders	pupil fixed	fixed pupils	PT
nervous system disorders	pupil fixed	pupils fixed	IT
nervous system disorders	quadriplegia	quadriplegia	PT
nervous system disorders	quadriplegia	tetraplegia	IT
nervous system disorders	radial nerve palsy	radial nerve palsy	IT
nervous system disorders	restless leg syndrome	restless legs	IT
nervous system disorders	sciatic nerve lesion nos	sciatic nerve palsy	IT
nervous system disorders	scotoma	scotoma	PT
nervous system disorders	scotoma	scotoma central	IT
nervous system disorders	scotoma	scotoma peripheral	IT
nervous system disorders	scotoma	teichopsia	IT
nervous system disorders	seizure anoxic	seizure anoxic	IT
nervous system disorders	serotonin syndrome	serotonin syndrome	PT
nervous system disorders	simple partial seizures	simple partial seizures	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
nervous system disorders	somnolence neonatal	somnolence neonatal	PT
nervous system disorders	speech disorder developmental	speech disorder developmental	IT
nervous system disorders	status epilepticus	status epilepticus	IT
nervous system disorders	subacute myeloopticoneuropathy	smon	IT
nervous system disorders	subacute myeloopticoneuropathy	subacute myeloopticoneuropathy	PT
nervous system disorders	supranuclear palsy	supranuclear palsy	IT
nervous system disorders	tardive dyskinesia	dyskinesia tardive	PT
nervous system disorders	temporal lobe epilepsy	epilepsy temporal lobe	IT
nervous system disorders	temporal lobe epilepsy	psychomotor epilepsy	IT
nervous system disorders	tonic seizures	tonic convulsion	IT
nervous system disorders	trismus	lockjaw	IT
nervous system disorders	trismus	trismus	IT
nervous system disorders	tunnel vision	tubular vision	IT
nervous system disorders	tunnel vision	vision tubular	IT
nervous system disorders	uncinate fits	uncinate fits	IT
nervous system disorders	upper motor neurone lesion	pyramidal tract lesion	IT
nervous system disorders	upper motor neurone lesion	upper motor neurone lesion	PT
nervous system disorders	uraemic encephalopathy	coma uremic	PT
nervous system disorders	viiith nerve lesion nos	eighth nerve lesion nos	IT
nervous system disorders	visual field defect nos	vision peripheral decreased	IT
nervous system disorders	visual field defect nos	visual field constriction	IT
nervous system disorders	visual field defect nos	visual field defect	PT
pregnancy, puerperium and perinatal conditions	abortion missed	abortion missed	PT
pregnancy, puerperium and perinatal conditions	abortion missed	foetus macerated	IT
pregnancy, puerperium and perinatal conditions	abortion nos	abortion	PT
pregnancy, puerperium and perinatal conditions	abortion spontaneous nos	miscarriage	IT
pregnancy, puerperium and perinatal conditions	antepartum haemorrhage	antepartum haemorrhage	IT
pregnancy, puerperium and perinatal conditions	antepartum haemorrhage	haemorrhage in pregnancy	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
pregnancy, puerperium and perinatal conditions	blighted ovum	blighted ovum	IT
pregnancy, puerperium and perinatal conditions	death neonatal	death neonatal	PT
pregnancy, puerperium and perinatal conditions	ectopic pregnancy	extrauterine pregnancy	IT
pregnancy, puerperium and perinatal conditions	ectopic pregnancy	pregnancy ectopic	PT
pregnancy, puerperium and perinatal conditions	foetal distress syndrome	foetal distress	PT
pregnancy, puerperium and perinatal conditions	foetal movements decreased	foetal movements decreased	IT
pregnancy, puerperium and perinatal conditions	haemorrhage nos neonatal	haemorrhage nos neonatal	PT
pregnancy, puerperium and perinatal conditions	intra-uterine death	death foetal	PT
pregnancy, puerperium and perinatal conditions	intra-uterine death	death intrauterine	IT
pregnancy, puerperium and perinatal conditions	jaundice neonatal	icterus neonatorum	IT
pregnancy, puerperium and perinatal conditions	jaundice neonatal	jaundice neonatal	PT
pregnancy, puerperium and perinatal conditions	jaundice neonatal	jaundice of newborn	IT
pregnancy, puerperium and perinatal conditions	leucopenia neonatal	leucopenia neonatal	PT
pregnancy, puerperium and perinatal conditions	placenta praevia	placenta praevia	PT
pregnancy, puerperium and perinatal conditions	polyhydramnios	hydramnios	PT
pregnancy, puerperium and perinatal conditions	postmature baby	birth postmature	PT
pregnancy, puerperium and perinatal conditions	premature baby	baby 28 weeks plus under 2.5 kg	IT
pregnancy, puerperium and perinatal conditions	premature baby	birth premature	PT
pregnancy, puerperium and perinatal conditions	premature baby	prematurity syndrome	IT
pregnancy, puerperium and perinatal conditions	premature labour	labour premature	PT
pregnancy, puerperium and perinatal conditions	ruptured ectopic pregnancy	ruptured ectopic pregnancy	IT
pregnancy, puerperium and perinatal conditions	small for dates baby	birth weight low	IT
psychiatric disorders	agitation	hyperexcitability extreme	IT
psychiatric disorders	anorexia nervosa	anorexia nervosa	PT
psychiatric disorders	anxiety disorder nec	neurosis gi	IT
psychiatric disorders	anxiety disorder nec	psychoneurosis	IT
psychiatric disorders	anxiety disorder nec	psychophysiologic reaction	IT
psychiatric disorders	bipolar affective disorder aggravated	bipolar affective disorder aggr.	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
psychiatric disorders	bipolar disorder nec	bipolar affective disorder	IT
psychiatric disorders	bipolar i disorder	psychosis manic-depressive	PT
psychiatric disorders	cardiac neurosis	effort syndrome	IT
psychiatric disorders	cardiac neurosis	neurosis cardiovascular	IT
psychiatric disorders	catatonia	catatonia	IT
psychiatric disorders	catatonia	catatonic reaction	PT
psychiatric disorders	catatonia	catatonic state	IT
psychiatric disorders	childhood disintegrative disorder	childhood disintegrative disorder	PT
psychiatric disorders	completed suicide	suicide	IT
psychiatric disorders	decreased activity	hypoactivity	IT
psychiatric disorders	delirium	brain syndrome acute	IT
psychiatric disorders	delirium	delirium	PT
psychiatric disorders	delirium	delirium toxic	IT
psychiatric disorders	delusion nos	delusion	PT
psychiatric disorders	delusion nos	delusion unsystematized	IT
psychiatric disorders	delusion nos	delusional jealousy	IT
psychiatric disorders	delusional disorder, paranoid type	paranoid psychosis	IT
psychiatric disorders	depression post-partum (exc psychosis)	depression puerperal	PT
psychiatric disorders	disinhibition	disinhibition	IT
psychiatric disorders	dissociative disorder nos	dissociative disorder	IT
psychiatric disorders	drug dependence	addiction any drug	IT
psychiatric disorders	drug dependence	drug addiction	IT
psychiatric disorders	drug dependence	drug dependence	PT
psychiatric disorders	drug dependence	drug dependence physical	IT
psychiatric disorders	drug dependence	drug dependence psychic	IT
psychiatric disorders	drug dependence	drug habit	IT
psychiatric disorders	drug dependence	drug habituating	IT
psychiatric disorders	hallucination nos	hallucination	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
psychiatric disorders	hallucination nos	sensory hallucinations	IT
psychiatric disorders	hallucination, auditory	hallucination auditory	IT
psychiatric disorders	hallucination, visual	hallucination visual	IT
psychiatric disorders	hallucinations aggravated	hallucinations aggravated	IT
psychiatric disorders	hypervigilance	hyperalertness	IT
psychiatric disorders	hypochondriasis	hypochondriasis	IT
psychiatric disorders	hypomania	hypomania	IT
psychiatric disorders	illusion	false sensation	IT
psychiatric disorders	illusion	illusion	PT
psychiatric disorders	mania	mania	IT
psychiatric disorders	mania	mania acute	IT
psychiatric disorders	mania	manic excitement	IT
psychiatric disorders	mania	manic psychosis	IT
psychiatric disorders	mania	manic reaction	PT
psychiatric disorders	mood disorder nos	affective disorder nos	IT
psychiatric disorders	mood disorder nos	psychosis affective	IT
psychiatric disorders	neurosis nos	neurosis	PT
psychiatric disorders	neurosis nos	neurotic reaction	IT
psychiatric disorders	obsessional neurosis aggravated	obsessional neurosis aggravated	IT
psychiatric disorders	obsessive-compulsive disorder	compulsive reaction	IT
psychiatric disorders	obsessive-compulsive disorder	obsessional neurosis	IT
psychiatric disorders	obsessive-compulsive disorder	obsessive reaction	IT
psychiatric disorders	obsessive-compulsive personality disorder	obsessional personality	IT
psychiatric disorders	paranoia	paranoid reaction	PT
psychiatric disorders	paranoia aggravated	paranoia aggravated	IT
psychiatric disorders	phobias nec	phobic disorder	IT
psychiatric disorders	phobias nec	phobic reaction	IT
psychiatric disorders	phobic disorder aggravated	phobic disorder aggravated	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
psychiatric disorders	psychosis aggravated	psychosis aggravated	IT
psychiatric disorders	psychotic disorder nos	psychosis	PT
psychiatric disorders	psychotic disorder nos	psychotic reaction nos	IT
psychiatric disorders	psychotic disorder nos	psychotic state	IT
psychiatric disorders	restlessness	muscular unrest	IT
psychiatric disorders	restlessness	psychomotor restlessness	IT
psychiatric disorders	schizophreniform disorder	schizophrenic reaction	PT
psychiatric disorders	schizophreniform disorder	schizophreniform illness	IT
psychiatric disorders	somatic delusion	delusion somatic	IT
psychiatric disorders	suicidal ideation	suicidal tendency	IT
psychiatric disorders	suicidal ideation	thoughts of self harm	IT
psychiatric disorders	suicide attempt	suicide attempt	PT
psychiatric disorders	waxy flexibility	catalepsy	IT
renal and urinary disorders	anuria	anuria	PT
renal and urinary disorders	anuria	urinary output arrest of	IT
renal and urinary disorders	anuria	urine formation failure of	IT
renal and urinary disorders	fluid retention	extracellular fluid increased	IT
renal and urinary disorders	fluid retention	fluid retention in tissues	IT
renal and urinary disorders	fluid retention	interstitial fluid increased	IT
renal and urinary disorders	fluid retention	tissue fluid increased	IT
renal and urinary disorders	fluid retention	water retention in tissues	IT
renal and urinary disorders	glomerulonephritis acute	glomerulonephritis acute	IT
renal and urinary disorders	glomerulonephritis nos	glomerulitis	IT
renal and urinary disorders	glomerulonephritis nos	glomerulonephritis	PT
renal and urinary disorders	glomerulonephritis proliferative	glomerulonephritis focal	IT
renal and urinary disorders	glomerulonephritis proliferative	glomerulonephritis proliferative	IT
renal and urinary disorders	goodpasture's syndrome	goodpasture's syndrome	PT
renal and urinary disorders	haemolytic uraemic syndrome	haemolytic-uraemic syndrome	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
renal and urinary disorders	isosthenuria	isosthenuria	IT
renal and urinary disorders	kidney small	kidney contracted	PT
renal and urinary disorders	nephritis haemorrhagic	nephritis haemorrhagic	IT
renal and urinary disorders	nephrogenic diabetes insipidus	diabetes insipidus nephrogenic	PT
renal and urinary disorders	nephropathy nos	nephropathy nos	IT
renal and urinary disorders	oliguria	decreased fluid output	IT
renal and urinary disorders	polyuria	diuresis excessive	IT
renal and urinary disorders	polyuria	polyuria	PT
renal and urinary disorders	polyuria	urine volume increased	IT
renal and urinary disorders	renal failure acute	renal failure acute	PT
renal and urinary disorders	renal failure acute	renal failure acute hypotensive	IT
renal and urinary disorders	renal failure acute	renal failure acute ischaemic	IT
renal and urinary disorders	renal failure acute	renal shutdown acute	IT
renal and urinary disorders	renal failure aggravated	renal failure aggravated	IT
renal and urinary disorders	renal failure chronic	kidney failure chronic	IT
renal and urinary disorders	renal failure chronic	renal failure chronic	IT
renal and urinary disorders	renal failure chronic aggravated	renal failure chronic aggravated	IT
renal and urinary disorders	renal failure nos	azotemia of renal origin	IT
renal and urinary disorders	renal failure nos	renal failure nos	IT
renal and urinary disorders	renal failure nos	uraemia	PT
renal and urinary disorders	renal failure nos	uraemia of renal origin	IT
renal and urinary disorders	renal failure nos	uraemic syndrome	IT
renal and urinary disorders	renal hypertension nos	hypertension renal	IT
renal and urinary disorders	renal hypertrophy	kidney enlargement	PT
renal and urinary disorders	renal impairment nos	kidney dysfunction	IT
renal and urinary disorders	renal impairment nos	renal function abnormal	PT
renal and urinary disorders	renal impairment nos	renal function abnormal glomer	PT
renal and urinary disorders	renal impairment nos	renal function tests nos abnormal	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
renal and urinary disorders	renal tubular necrosis	lower nephron nephrosis	IT
renal and urinary disorders	renal tubular necrosis	renal tubular necrosis	PT
renal and urinary disorders	renal vasculitis	renal vasculitis	IT
renal and urinary disorders	urinary casts	cylinduria	IT
renal and urinary disorders	urinary casts	urinary casts	PT
reproductive system and breast disorders	genital leukoplakia	leukoplakia genital	PT
reproductive system and breast disorders	genital leukoplakia	vulval leukoplakia	IT
reproductive system and breast disorders	haematometra	haematometra	IT
reproductive system and breast disorders	malignant ovarian cyst	ovarian cyst malignant	IT
reproductive system and breast disorders	mastitis	mastitis chronic	IT
reproductive system and breast disorders	ovarian cyst	ovarian cyst	PT
reproductive system and breast disorders	post-menopausal bleeding	post-menopausal bleeding	PT
reproductive system and breast disorders	uterine enlargement	myometrial increase	PT
reproductive system and breast disorders	uterine haemorrhage	endometrial bleeding	IT
reproductive system and breast disorders	uterine haemorrhage	uterine haemorrhage	PT
reproductive system and breast disorders	uterine perforation	uterine perforation	PT
respiratory, thoracic and mediastinal disorders	adult respiratory distress syndrome	adult respiratory stress syndrome	PT
respiratory, thoracic and mediastinal disorders	adult respiratory distress syndrome	shock lung	IT
respiratory, thoracic and mediastinal disorders	allergic granulomatous angiitis	allergic granulomatous angiitis	IT
respiratory, thoracic and mediastinal disorders	allergic granulomatous angiitis	churg strauss syndrome	PT
respiratory, thoracic and mediastinal disorders	alveolitis allergic	alveolitis allergic	PT
respiratory, thoracic and mediastinal disorders	alveolitis allergic	pneumonitis hypersensitivity	IT
respiratory, thoracic and mediastinal disorders	alveolitis fibrosing	alveolitis fibrosing	PT
respiratory, thoracic and mediastinal disorders	alveolitis nos	alveolitis nos	PT
respiratory, thoracic and mediastinal disorders	apnoea	apnoea	PT
respiratory, thoracic and mediastinal disorders	asphyxia	asphyxia	PT
respiratory, thoracic and mediastinal disorders	asthma aggravated	asthma aggravated	IT
respiratory, thoracic and mediastinal disorders	asthma nos	asthma	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
respiratory, thoracic and mediastinal disorders	bronchospasm nos	bronchoconstriction	IT
respiratory, thoracic and mediastinal disorders	bronchospasm nos	bronchospasm	PT
respiratory, thoracic and mediastinal disorders	bronchospasm paradoxical	bronchospasm paradoxical	PT
respiratory, thoracic and mediastinal disorders	cheyne-stokes respiration	cheyne-stokes respiration	PT
respiratory, thoracic and mediastinal disorders	diaphragmatic paralysis	respiratory paralysis	PT
respiratory, thoracic and mediastinal disorders	epistaxis	epistaxis	PT
respiratory, thoracic and mediastinal disorders	epistaxis	haemorrhage nasal	IT
respiratory, thoracic and mediastinal disorders	epistaxis	nasal bleeding	IT
respiratory, thoracic and mediastinal disorders	epistaxis	nosebleed	IT
respiratory, thoracic and mediastinal disorders	haemoptysis	coughing blood	IT
respiratory, thoracic and mediastinal disorders	haemoptysis	haemoptysis	PT
respiratory, thoracic and mediastinal disorders	haemoptysis	sputum bloody	IT
respiratory, thoracic and mediastinal disorders	laryngeal oedema	glottic oedema	IT
respiratory, thoracic and mediastinal disorders	laryngeal oedema	laryngeal oedema	IT
respiratory, thoracic and mediastinal disorders	laryngeal oedema	larynx oedema	PT
respiratory, thoracic and mediastinal disorders	laryngeal oedema	subglottic oedema	IT
respiratory, thoracic and mediastinal disorders	laryngeal oedema	vocal cord oedema	IT
respiratory, thoracic and mediastinal disorders	laryngospasm	glottic spasm	IT
respiratory, thoracic and mediastinal disorders	laryngospasm	laryngismus	PT
respiratory, thoracic and mediastinal disorders	laryngospasm	laryngospasm	IT
respiratory, thoracic and mediastinal disorders	laryngotracheal oedema	laryngotracheal oedema	IT
respiratory, thoracic and mediastinal disorders	mediastinal fibrosis	fibrosis mediastinal	PT
respiratory, thoracic and mediastinal disorders	neonatal apnoeic attack	apnoea neonatal	PT
respiratory, thoracic and mediastinal disorders	neonatal asphyxia	asphyxia livida of newborn	IT
respiratory, thoracic and mediastinal disorders	neonatal asphyxia	asphyxia neonatal	PT
respiratory, thoracic and mediastinal disorders	neonatal asphyxia	asphyxia pallida of newborn	IT
respiratory, thoracic and mediastinal disorders	neonatal respiratory arrest	neonatal respiratory arrest	IT
respiratory, thoracic and mediastinal disorders	neonatal respiratory depression	respiratory depression neonatal	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
respiratory, thoracic and mediastinal disorders	neonatal respiratory distress syndrome	resp distress syndrome neonatal	PT
respiratory, thoracic and mediastinal disorders	oropharyngeal spasm	spasm oropharyngeal	IT
respiratory, thoracic and mediastinal disorders	pharyngeal haemorrhage	haemorrhage pharyngeal	IT
respiratory, thoracic and mediastinal disorders	pleural fibrosis	pleural fibrosis	PT
respiratory, thoracic and mediastinal disorders	pleural fibrosis	pleurisy obliterative	IT
respiratory, thoracic and mediastinal disorders	pulmonary fibrosis	lung fibrosis interstitial	IT
respiratory, thoracic and mediastinal disorders	pulmonary fibrosis	pulmonary fibrosis	PT
respiratory, thoracic and mediastinal disorders	pulmonary haemorrhage	pulmonary haemorrhage	PT
respiratory, thoracic and mediastinal disorders	pulmonary infarction	pulmonary infarction	PT
respiratory, thoracic and mediastinal disorders	pulmonary vasculitis	vasculitis pulmonary	IT
respiratory, thoracic and mediastinal disorders	respiratory arrest (exc neonatal)	breathing arrested	IT
respiratory, thoracic and mediastinal disorders	respiratory arrest (exc neonatal)	respiratory arrest	IT
respiratory, thoracic and mediastinal disorders	respiratory depression	respiratory depression	PT
respiratory, thoracic and mediastinal disorders	respiratory failure (exc neonatal)	respiratory failure	IT
respiratory, thoracic and mediastinal disorders	respiratory failure (exc neonatal)	respiratory insufficiency	PT
respiratory, thoracic and mediastinal disorders	respiratory gas exchange disorder nos	resp gas exchange disorder nos	IT
respiratory, thoracic and mediastinal disorders	respiratory tract haemorrhage neonatal	resp tract haemorrhage neonatal	PT
respiratory, thoracic and mediastinal disorders	respiratory tract haemorrhage nos	respiratory tract haemorrhage	PT
respiratory, thoracic and mediastinal disorders	status asthmaticus	status asthmaticus	IT
respiratory, thoracic and mediastinal disorders	stridor	stridor	PT
respiratory, thoracic and mediastinal disorders	stridor	stridor inspiratory	IT
respiratory, thoracic and mediastinal disorders	throat oedema	throat swelling non-specific	IT
respiratory, thoracic and mediastinal disorders	vocal cord thickening	vocal cord thickening	IT
respiratory, thoracic and mediastinal disorders	wheezing	wheezes	IT
respiratory, thoracic and mediastinal disorders	wheezing	wheezing expiratory	IT
respiratory, thoracic and mediastinal disorders	wheezing	wheezing inspiratory	IT
skin & subcutaneous tissue disorders	angioneurotic oedema	angioedema	PT
skin & subcutaneous tissue disorders	angioneurotic oedema	angioneurotic oedema	IT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
skin & subcutaneous tissue disorders	angioneurotic oedema	giant hives	IT
skin & subcutaneous tissue disorders	angioneurotic oedema	giant urticaria	IT
skin & subcutaneous tissue disorders	angioneurotic oedema	quincke's oedema	IT
skin & subcutaneous tissue disorders	angioneurotic oedema aggravated	angioedema aggravated	IT
skin & subcutaneous tissue disorders	angioneurotic oedema aggravated	angioneurotic oedema aggravated	IT
skin & subcutaneous tissue disorders	cutaneous amyloidosis	cutaneous amyloidosis	IT
skin & subcutaneous tissue disorders	dermatitis exfoliative aggravated	dermatitis exfoliative aggravated	IT
skin & subcutaneous tissue disorders	dermatitis exfoliative nos	dermatitis exfoliative	PT
skin & subcutaneous tissue disorders	dermatitis exfoliative nos	skin erythema desquamative	IT
skin & subcutaneous tissue disorders	dermatitis exfoliative nos	skin exfoliation	PT
skin & subcutaneous tissue disorders	discoid lupus erythematosus	dle	IT
skin & subcutaneous tissue disorders	discoid lupus erythematosus	le-like discoid rash	IT
skin & subcutaneous tissue disorders	discoid lupus erythematosus	lupus erythematosus discoid	IT
skin & subcutaneous tissue disorders	discoid lupus erythematosus aggravated	discoid lupus erythematosus aggr.	IT
skin & subcutaneous tissue disorders	ecchymosis	bruise	IT
skin & subcutaneous tissue disorders	ecchymosis	ecchymosis	IT
skin & subcutaneous tissue disorders	epidermal necrolysis	dermatitis necrotising	IT
skin & subcutaneous tissue disorders	epidermal necrolysis	epidermal necrolysis	PT
skin & subcutaneous tissue disorders	epidermal necrolysis	lyell syndrome	IT
skin & subcutaneous tissue disorders	epidermal necrolysis	toxic epidermal necrolysis	IT
skin & subcutaneous tissue disorders	erythema annulare	erythema annulare	IT
skin & subcutaneous tissue disorders	erythema multiforme	erythema multiforme	PT
skin & subcutaneous tissue disorders	erythema multiforme	erythema multiforme severe	IT
skin & subcutaneous tissue disorders	eyelid oedema	eyelid oedema	IT
skin & subcutaneous tissue disorders	face oedema	face oedema	PT
skin & subcutaneous tissue disorders	face oedema	lips swelling non-specific	IT
skin & subcutaneous tissue disorders	idiopathic capillaritis	idiopathic capillaritis	IT
skin & subcutaneous tissue disorders	leukocytoclastic vasculitis	vasculitis allergic	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
skin & subcutaneous tissue disorders	leukocytoclastic vasculitis	vasculitis neutrophilic	IT
skin & subcutaneous tissue disorders	localised exfoliation	skin peeling	IT
skin & subcutaneous tissue disorders	mucocutaneous ulceration	mucocutaneous ulceration	IT
skin & subcutaneous tissue disorders	nodular vasculitis	vasculitis nodular	IT
skin & subcutaneous tissue disorders	oedema mouth	oedema mouth	PT
skin & subcutaneous tissue disorders	pemphigoid	cicatricial mucous mem. pemphig.	IT
skin & subcutaneous tissue disorders	pemphigoid	pemphigoid reaction	PT
skin & subcutaneous tissue disorders	petechiae	petechiae	IT
skin & subcutaneous tissue disorders	petechiae	rash petechial	IT
skin & subcutaneous tissue disorders	photosensitivity allergic reaction	photosensitivity allergic react	PT
skin & subcutaneous tissue disorders	photosensitivity reaction nos	photosensitivity reaction	PT
skin & subcutaneous tissue disorders	photosensitivity reaction nos	photosensitivity toxic reaction	PT
skin & subcutaneous tissue disorders	purpura neonatal	purpura neonatal	PT
skin & subcutaneous tissue disorders	purpura nos	purpura	PT
skin & subcutaneous tissue disorders	purpura senile	purpura senile	IT
skin & subcutaneous tissue disorders	rash erythematous	erythema exudativum	PT
skin & subcutaneous tissue disorders	red man syndrome	red man syndrome	IT
skin & subcutaneous tissue disorders	skin vasculitis nos	skin vasculitis nos	IT
skin & subcutaneous tissue disorders	solar urticaria	solar urticaria	IT
skin & subcutaneous tissue disorders	stevens johnson syndrome	stevens johnson syndrome	PT
skin & subcutaneous tissue disorders	systemic lupus erythematosus rash	le rash	PT
skin & subcutaneous tissue disorders	systemic lupus erythematosus rash	le-like butterfly rash	IT
skin & subcutaneous tissue disorders	systemic lupus erythematosus rash	systemic erythematosus rash	IT
skin & subcutaneous tissue disorders	tongue oedema	tongue swelling non-specific	IT
skin & subcutaneous tissue disorders	vascular purpura	purpura vascular	IT
social circumstances	drug abuse	drug abuse	PT
surgical and medical procedures	ectopic pregnancy termination	ectopic pregnancy termination	IT
surgical and medical procedures	vaccination complication	vaccination complication	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
vascular disorders	acute circulatory failure	cardiovascular collapse	IT
vascular disorders	acute circulatory failure	circulatory failure	PT
vascular disorders	acute circulatory failure	collapse circulatory	IT
vascular disorders	acute circulatory failure	shock	IT
vascular disorders	acute circulatory failure	shock circulatory	IT
vascular disorders	aortic aneurysm	aortic aneurysm	IT
vascular disorders	aortic aneurysm rupture	aortic aneurysm rupture	IT
vascular disorders	aorto-duodenal fistula	aorto-duodenal fistula	PT
vascular disorders	arterial aneurysm nos	aneurysm	PT
vascular disorders	arterial embolism nos	embolism arterial	PT
vascular disorders	arterial spasm nos	arteriospasm	IT
vascular disorders	arterial thrombosis limb	axillary artery thrombosis	IT
vascular disorders	arterial thrombosis limb	brachial artery thrombosis	IT
vascular disorders	arterial thrombosis limb	femoral artery thrombosis	IT
vascular disorders	arterial thrombosis limb	thrombosis arterial arm	PT
vascular disorders	arterial thrombosis limb	thrombosis arterial leg	PT
vascular disorders	arterial thrombosis limb	tibial artery thrombosis	IT
vascular disorders	arterial thrombosis nos	thrombosis arterial	PT
vascular disorders	arteritis nos	arteritis	PT
vascular disorders	arteritis nos	endarteritis	IT
vascular disorders	arteritis nos	inflammatory artery reaction	IT
vascular disorders	arteritis nos	panarteritis	IT
vascular disorders	brain stem infarction	brain stem infarction	IT
vascular disorders	brain stem ischaemia	brain stem ischaemia	IT
vascular disorders	carotid artery thrombosis	thrombosis carotid	PT
vascular disorders	cerebellar artery thrombosis	thrombosis cerebellar arterial	PT
vascular disorders	cerebellar infarction	cerebellar infarction	PT
vascular disorders	cerebral artery embolism	embolism cerebral	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
vascular disorders	cerebral artery thrombosis	thrombosis cerebral	PT
vascular disorders	cerebral haemorrhage neonatal	cerebral haemorrhage neonatal	PT
vascular disorders	cerebral venous thrombosis	thrombophlebitis cerebral vein	PT
vascular disorders	cerebral venous thrombosis	thrombosis cerebral vein	IT
vascular disorders	circulatory failure neonatal	circulatory failure neonatal	PT
vascular disorders	cranial arteritis	cranial arteritis	IT
vascular disorders	gangrene neonatal	gangrene neonatal	PT
vascular disorders	gangrene nos	gangrene	PT
vascular disorders	gangrene nos	peripheral gangrene	PT
vascular disorders	hypertension nos	blood pressure high	IT
vascular disorders	hypertension nos	hypertension	PT
vascular disorders	hypertension nos	hypertension arterial	IT
vascular disorders	hypertension nos	hypertension diastolic	IT
vascular disorders	hypertensive encephalopathy	encephalopathy hypertensive	PT
vascular disorders	iliac artery embolism	iliac artery embolus	IT
vascular disorders	iliac artery thrombosis	iliac artery thrombosis	IT
vascular disorders	intracranial haemorrhage nos	haemorrhage intracranial	PT
vascular disorders	intraventricular haemorrhage nos	intraventricular haemorrhage	IT
vascular disorders	malignant hypertension nos	hypertension malignant	IT
vascular disorders	necrosis ischaemic	necrosis ischaemic	PT
vascular disorders	pelvic venous thrombosis	pelvic venous thrombosis	IT
vascular disorders	peripheral coldness	peripheral coldness	IT
vascular disorders	peripheral embolism nos	embolism limb	PT
vascular disorders	peripheral ischaemia nos	ischaemia peripheral	IT
vascular disorders	peripheral ischaemia nos	peripheral ischaemia	PT
vascular disorders	peripheral ischaemia nos	poor peripheral perfusion	IT
vascular disorders	peripheral vascular disease nos	peripheral vascular disease	IT
vascular disorders	phlebitis deep	phlebitis deep	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
vascular disorders	phlebitis nos	phlebitis	PT
vascular disorders	phlebitis nos	phlebitis alone	IT
vascular disorders	phlebitis nos	phlebitis arm	IT
vascular disorders	phlebitis nos	thrombophlebitis	PT
vascular disorders	phlebitis nos	thrombophlebitis arm	PT
vascular disorders	phlebitis nos	thrombophlebitis leg	PT
vascular disorders	phlebitis nos	thrombophlebitis multiple	PT
vascular disorders	phlebitis superficial	phlebitis superficial	PT
vascular disorders	pulmonary embolism	embolism pulmonary	PT
vascular disorders	pulmonary hypertension nos	hypertension pulmonary	PT
vascular disorders	pulmonary hypertension nos aggravated	hypertension pulmonary aggravated	IT
vascular disorders	pulmonary thrombosis nos	thrombosis pulmonary	PT
vascular disorders	raynaud's phenomenon	raynaud's phenomenon	IT
vascular disorders	raynaud's phenomenon	raynaud-like disorder	IT
vascular disorders	raynaud's phenomenon aggravated	raynaud's phenomenon aggravated	IT
vascular disorders	spinal haematoma	spinal haematoma	PT
vascular disorders	subarachnoid haemorrhage nos	subarachnoid haemorrhage	PT
vascular disorders	thromboembolism nos	embolism — blood clot	PT
vascular disorders	thromboembolism nos	thromboembolism	PT
vascular disorders	thrombophlebitis deep	thrombophlebitis arm deep	PT
vascular disorders	thrombophlebitis deep	thrombophlebitis deep	PT
vascular disorders	thrombophlebitis deep	thrombophlebitis leg deep	PT
vascular disorders	thrombophlebitis deep	thrombophlebitis multiple deep	PT
vascular disorders	thrombophlebitis neonatal	thrombophlebitis neonatal	PT
vascular disorders	thrombophlebitis of vena cava	thrombophlebitis vena cava	PT
vascular disorders	thrombophlebitis pelvic vein	thrombophlebitis pelvic vein	PT
vascular disorders	thrombophlebitis superficial	thrombophlebitis arm superficial	PT
vascular disorders	thrombophlebitis superficial	thrombophlebitis leg superficial	PT

MedDRA: primary soc name	MedDRA: pt name	WHO: critical-term	WHO (PT/IT)
vascular disorders	thrombophlebitis superficial	thrombophlebitis multiple superfi	PT
vascular disorders	thrombophlebitis superficial	thrombophlebitis superficial	PT
vascular disorders	thrombosis nos	thrombosis	PT
vascular disorders	vasculitis cerebral	vasculitis cerebral	IT
vascular disorders	vasculitis gastrointestinal	vasculitis gastrointestinal	IT
vascular disorders	vasculitis nos	vasculitis	PT
vascular disorders	vasculitis nos aggravated	vasculitis aggravated	IT
vascular disorders	vena cava embolism	thrombosis vena cava inferior	IT
vascular disorders	venous thrombosis deep limb	thrombosis venous deep	IT
vascular disorders	venous thrombosis nos	phlebothrombosis	IT
vascular disorders	venous thrombosis nos	venous thrombosis	IT
vascular disorders	venous thrombosis superficial limb	thrombosis venous superficial	IT

Appendix 6

Some Regulatory Definitions of Expectedness

	ICH	USA	EUROPE
Definition of Expectedness	Unexpected adverse drug reaction: [ICH Guideline E2A] ... 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)... An adverse reaction, the nature or severity of which is not consistent with the applicable product information or labeling.	Unexpected adverse drug experience (for investigational new drug application): [21CFR312.32 and 21CFR312.33] Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended... ''Unexpected'', as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product. Unexpected adverse drug experience (for a marketed drug): Any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. [21CFR314.80 and 21CFR314.81]	Investigational Medicinal Products in Clinical Trials: Unexpected adverse reaction: an adverse reaction not mentioned in the Investigator's Brochure or in the Summary of Product Characteristics, if any. For marketed drugs (Notice to Marketing Authorization Holders — Pharmacovigilance Guidelines, June 2000): An unexpected adverse reaction is an adverse reaction which is not mentioned in the relevant Summary of Product Characteristics (SPC). This includes any adverse reaction whose nature, severity, specificity or outcome are inconsistent with the information of the SPC. Under Commission Directive 2000/38/EC: An adverse reaction, the nature, severity or outcome of which is not consistent with the Summary of Product Characterisitcs. *Continued*

	ICH	USA	EUROPE
Reference Safety Information			
1. Pre-marketing	For a drug not yet marketed, a company's Investigator's Brochure will serve as the source document. [ICH Guideline E2A]	Investigator's Brochure, or risk information described in the general investigational plan or elsewhere in the current application, as amended.	Investigator's Brochure
2. For marketed drugs Expedited reporting	[ICH Guideline E2C] ''...the local approved product information continues to be the reference document upon which labeledness/expectedness is based for the purpose of local expedited post-marketing safety reporting.''	Current labeling for the drug product. [21CFR314.80 and 21CFR314.81]	The relevant Summary of Product Characteristics (SPC): For products authorised nationally, the relevant SPC is that approved by the competent authority in the member state to whom the reaction is being reported. For centrally authorised products, the relevant SPC is the SPC authorised by the European Commission.
Periodic reporting	Reference safety information (ICH E2C): 'It is a common practice for MAHs to prepare their own ''Company Core Data Sheet'' (CCDS) which covers material relating to safety, indications, dosing, pharmacology, and other information concerning the product. A practical option for the purpose of periodic reporting is for each MAH to use, as a reference, the safety information contained within its central document (CCDS), which will be referred to as ***''Company Core Safety Information''*** (CCSI). For purposes of periodic safety reporting, CCSI forms the basis for determining whether an adverse drug reaction is already **Listed** or is still **Unlisted**, terms which are introduced to distinguish them from the usual terminology of ''expectedness'' or ''labeledness'' which is used in association with official labeling.' [See CCSI definition under EU]	**US Package Insert.** **However,** ICH E2C guideline has been published in Federal Register; the new Rule for PSURs was pending as of end-2000; it will include the CCSI as the reference safety information document.	**Company Core Safety Information (CCSI)** All relevant safety information contained in the company core data sheet (CCDS) prepared by the marketing authorisation holder (MAH) and which the MAH requires to be listed in all countries where the company markets the drugs, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.

Appendix 7

Lists of Data Elements that Determine whether Follow-up Information is Needed for Particular Types of Adverse Event Reports

[Next to each data element is the corresponding specified field within ICH Guideline E2B]

LIST A: Case neither serious nor unexpected

• Country in which the event occurred	A .1.2
• Reporter ID	A .2.1.1
• Source of report	A.2
• Identifiable Patient	B.1.1 or B.1.2 or B. 1.5
• Suspected Medicinal Product	B.4.k.1 and B.4 k.2
• Adverse Event (s)	B.2.i.2

LIST B: Case serious-expected or non-serious unexpected

List A above, PLUS:

• Daily dose of suspected medicinal product and regimen	B 4.k.5
• Route of administration	B.4.k.8
• Indication(s) for which suspect medicinal product was prescribed	B 4.k.11
• Starting date (and if relevant, time of day of treatment; e.g., acute hypersensitivity reaction)	B 4.k.12
• Full description or reaction(s) including body site and severity	B.2.i.1

• If serious, criterion or criteria for regarding the case as serious	A.1.5.2
• Starting date of onset of reaction (or time to onset)	B.2.i.4
• If not available, time interval between drug administration and start of event/reaction	B.2.i.7
❑ If not available, treatment duration.	B.4.k.15
❑ Time lag if ADR occurred after cessation of treatment	B.4.k.13.2
• Patient outcome (at case level and, when possible, at event level). Information on recovery and any sequelae.	(No ICH E2B field)[1]
• Dechallenge information	B.4.k.16 and B.2.i.8
• Rechallenge information	B.4.k.17
• For a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction(s)	B.1.9.2, B.2.i.8 and B.4.k.18
• Causal relationship assessment	B.4.k.18
• Other relevant etiological factors	B.5

LIST C: Case serious-unexpected or of "special interest"

Lists A and B, PLUS:

• Stopping date and time or duration of treatment	B.4.k.14 or B.4.k.15
• For concomitant medications:	B.4.k.1
❑ Daily dose and regimen	B.4.k.5
❑ Stopping date and time or duration of treatment	B.4.k.14 or B.4.k.15
• Specific tests and or/treatment required and their results	B.3

[1] Information on outcome or sequelae at the case level can be included in the free-text field B.5.1.

• Setting (e.g., hospital, outpatient clinic, home, nursing home)	B.5.1 or B.1.7.2
• Any autopsy or other post-mortem findings.	B.1.9.3 and B.1.9.4
• Whether or not the hospital discharge summary is available if patient were hospitalized.	A.1.8.2
• Anything relevant to facilitate assessment of the case such as medical history, relevant drug history including allergy, drug or alcohol abuse, family history.	B.1.7 and B.1.8

Appendix 8

Example of a Standard Narrative Template

[Note: Underlining is used for illustration purposes only, to indicate information that can be extracted directly from the database on the case. Paragraph numbering is also used for demonstration purposes to highlight the order proposed for the template.]

Coded terms: Myocardial infarction. Rash. Nausea.

1. Case reference number 16041938 is a spontaneous case report sent by a hospital pharmacist which refers to a male aged 84 years.

2. The patient's past medical history included gastric ulcer, asthma, and hypertension. At the time of the event the patient had Lyme Disease and severe headache. The following drugs are known to have been taken by the patient prior to the event (start date in parentheses): cimetidine (1996), steroids (1990) and tetracycline (September 9, 1999). The patient has a history of allergy to penicillin and gin.

3. On 1 January 2000 at 1:00 PM, the patient started taking qweasytrol for vomiting. Some 12 hours later, and 10 minutes following the latest dose, the patient developed rash, dyspnea and queasiness. Over the period of the next two days, the patient also developed chest pain and later unconsciousness. Relevant laboratory test results include elevated CK-MB and relevant physical signs were hypertension, fourth heart sound and bradycardia. The patient was hospitalized. Hospital records are available on request. The eventual diagnosis made on the 10 January 2000 was myocardial infarction.

4. The patient was treated for the event with a beta-blocker; qweasytrol was discontinued on 8 January 2000.

5. The patient died on 12 January 2000 from myocardial infarction; no autopsy was done. Death occurred approximately 12 days after the treatment with qweasytrol began and 4 days after it was discontinued.

7.* The cardiologist cited in the pharmacist's report considers the myocardial infarction possibly related to qweasytrol. In his opinion,

other possible etiological factors include hypertension and the patient's age.

8. The company believes the following facts are also relevant in this case: as a highly selective epsilon — G2 receptor antagonist, there is no known plausible mechanism by which the drug would cause a myocardial infarction.

* Paragraph 6 is not used since it is reserved specifically for results of a rechallenge. However, if there were a rechallenge, a typical paragraph might read: Qweasytrol was subsequently reintroduced and the event did/did not recur. When qweasytrol was again discontinued, the event abated/did not abate/had an unknown outcome.

Appendix 9

Examples of Acceptable and Unacceptable Company Clinical Evaluation Comments in Case Narratives

A. Examples of Acceptable Company Clinical Evaluation Comments for Possible use in Paragraph 8 of a Standard Narrative

1. The available pre-clinical data did not suggest a possibility that the subject drug would induce —.
2. As only limited information has been obtained so far, it is difficult to assess a cause and effect relationship.
3. The temporal relationship (6 weeks) between the onset of the event and administration of drug x, which has a one-hour half-life, makes any causal relationship unlikely.
4. The reported event is a well-known class effect (specify drug class here). However, this is the first reported case with —.
5. There is no plausible mechanism to implicate the subject drug.
6. It is of interest to note that the patient was subsequently rechallenged at the same dose without recurrence of the adverse effect.
7. The skin test with drug x, performed immediately after the event, was negative.
8. The following important information is lacking —, thus the causal relationship to drug x is not assessable.
9. The event resolved while drug x was continued at the same dose which makes any relationship to the drug unlikely.
10. The co-medications y and z should also be considered causative; the reported event is labeled for both drugs.
11. The company is currently reviewing the label.
12. The company's view is that the event is not due to the drug for the following reasons — (e.g., probably unrelated due to pre-existing —).

13. This adverse event is not reflected in the prescribing information, but will be monitored closely in the future.
14. The medication was not administered according to the dosage recommendation for the drug.
15. The investigator on follow-up has changed his assessment from ''probably'' to ''probably not'' for the following reasons —.
16. This case has also been forwarded to (name of the other manufacturer) as — (drug name) is the primary suspect drug.
17. No further details were received. Further information has been requested.
18. This case was found to be a duplicate of case xxx and has been logically deleted.
19. The patient's medical history provides an alternative explanation for the reported event.
20. The benefit-risk relationship of drug x is not affected by this report.

B. Examples of Unacceptable Company Clinical Evaluation Comments for Paragraph 8 of a Standard Narrative

1. The investigator changed his assessment from ''probably'' to ''probably not'' on follow-up. [Without a reason, such a statement should not be made.]
2. The company view is that the event is not due to the subject drug. [Inadequate without a reason given].
3. No comment. [Under some regulatory requirements, such as in Germany, Austria and Japan, some company opinion is expected; for example, see #20 above.]

Appendix 10

Basic Requirements for PSURs

1. Periodicity (Frequency of Data Review and Reporting)

Both CIOMS II and ICH Guideline E2C call for companies to review their safety data every 6 months even if they do not produce PSURs. Under the ICH Guideline, as was proposed in the CIOMS II recommendations, each product should have one international birthdate (IBD), namely, the first approval date for the product anywhere in the world. Furthermore, for products with subsequent additional regulatory approvals (new indications, new dosage forms, etc.), the original birthdate would still serve as the basis for establishing the two dates per year for the data lock points that define the data covered. When feasible, all forms and uses of a product would be covered in the same PSUR. This has significant implications with regard to database cut-off dates (data lock-points), analysis and presentation of data, as well as for preparation and submission of reports (which is required no more than 60 days beyond the data lock-point date.

Although the format and contents for a PSUR have been described under ICH E2C, there is no standard across regulators for the frequency of production and submission of actual reports on individual drug products. This was not part of the original ICH remit and would have been difficult to achieve given the fact that most drugs receive approval and reach the marketplace in different countries at different times, sometimes years apart.

The June 2000 EU Pharmacovigilance Guidelines call for a schedule of six-monthly PSURs for the first two years after EU approval, annual reports for the next two years, a report to coincide with the first 5-year license renewal application (more discussion on this later), then 5-year reports thereafter, regardless of the product approval process (centrally through the EMEA, by mutual recognition, or nationally). However, this schedule will mean that for older products not approved through the centralized or mutual recognition procedures, reports on a single drug covering different time periods (6 months, one year or 5 years of data) may be required, possibly at different times, in different countries, depending on the approval dates in those countries. The European Guidelines also suggest that variations for data sheet changes following the identification of safety signals during the PSUR process should be submitted at the same time as the PSUR.

In Japan, a new chemical entity requires a PSUR every six months for 2 years and annually for the next four years. A line extension or new formulation requires a PSUR every 6 months for two years and annually for two years. An orphan drug requires a PSUR every 6 months for two years and annually for 8 years.

The US FDA is expected to require the same PSUR reporting periodicity as in the EU, at least for the first five years following U.S. approval. Companies are expected to have the option of retaining the current, annual post-marketing NDA periodic report format and schedule for older products (to be defined by FDA). For the five-year report, FDA has indicated its intention to exercise flexibility in required timing of submission to enable synchronization of reporting schedules with the EU, and it is hoped, with Japan and other countries adopting ICH standards.

A few regulatory authorities are not prepared to accept reports which are perceived to be out of date with reference to the product's local birthdate. For example, the Finnish and Belgian agencies demand that the cut-off date (data lock-point) for a five year report be within 6 months prior to the renewal date. Thus, in practice the concept of a true IBD has yet to be accepted by all regulators.

Theoretically, if an international birthdate acceptable in all countries could be established for all formulations of a drug, the five-year report could be compiled only once every 5 years when the product had reached maturity in all relevant countries; regulators would have to agree to permit flexibility in earlier submissions relative to the local birthdates to allow synchronization of reports for all regulators. At present, companies are dealing with this situation in a number of different ways. The size of their product portfolio, the number of line extensions and formulations marketed for each drug, and the number of postmarketing spontaneous ADR reports received during the reporting period are important determinants. Some companies supplement their already prepared five-year updates with line listings of reports covering the time between the cut-off for the five-year report and the later submission (e.g., to Finland or Belgium). Others produce a series of five-year reports that cover overlapping 5 year periods. Neither approach is ideal — they are very time consuming and defeat the objective of having harmonized, integrated and consistent analyses for all regulators at the same time.

The situation becomes even more complicated if the reporting clock is set back to six-monthly when a new formulation or new indication is approved for a drug already on or near a 5 year reporting schedule. Similarly, six-monthly reports may be required by a country when its first

approval is obtained several years beyond the original international birthdate, even for a drug with a well established safety profile.

2. License Renewal in EU and Japan

An added complication for companies, particularly in scheduling five-year PSURs for EU countries and Japan, is a separate license renewal requirement.

Five-year safety (and efficacy) updates are required for the renewal of product licenses throughout the EU, and more recently within CADREAC (Collaboration Agreement between Drug Regulatory Authorities in European Union Associated Countries).[1] These requirements are often specific to different formulations of the same active ingredient, based on their different approval dates not only in the same country but in different countries. While some companies currently use their PSURs as the safety component of the license renewal package, these reports are not synonymous from a regulatory or legal perspective. As with PSURs, legal requirements currently oblige companies to adhere to specific, often divergent time intervals for submission of license renewal data. For non-centralized EU approvals, these differ between countries and may be implemented under national acts of Member States so that there is little flexibility.

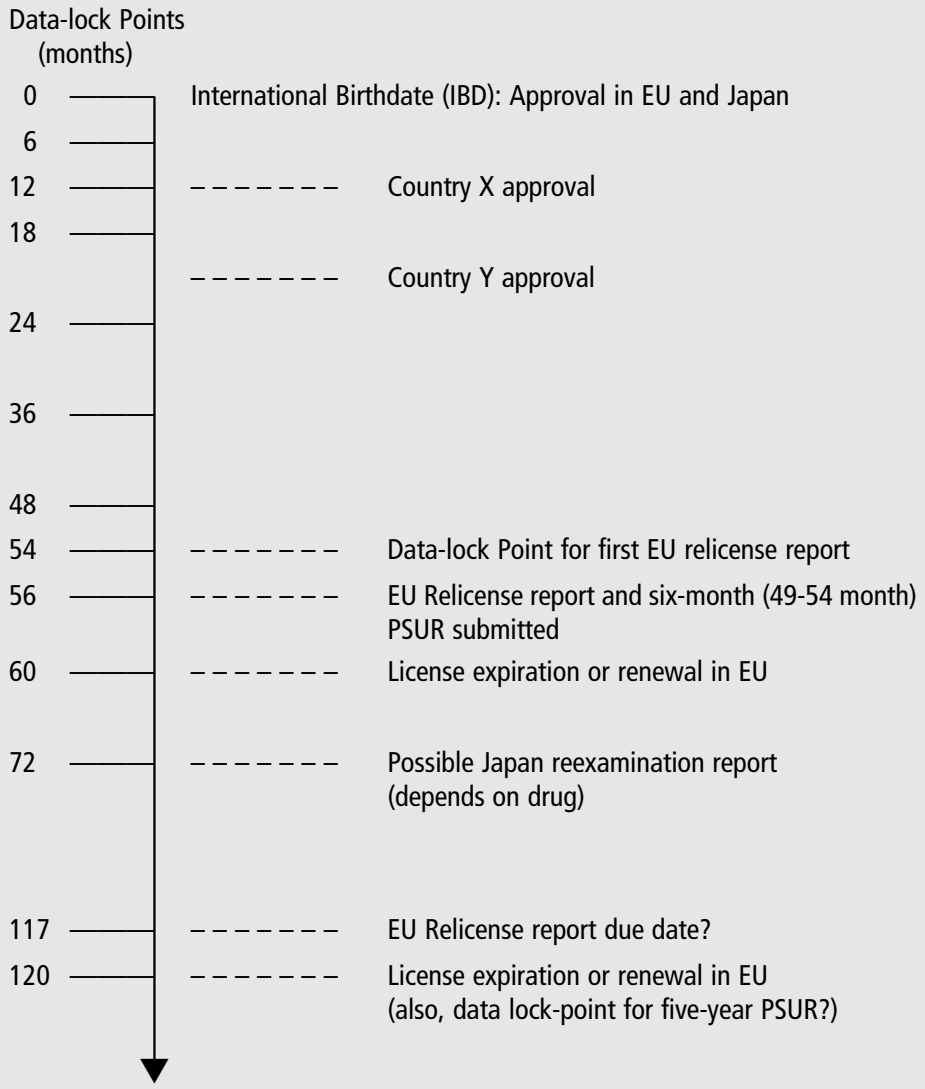
Japan, like the EU, has a drug reexamination/reevaluation separate from routine periodic safety reporting requirements; however, the process occurs only once after initial approval. PSURs are used in association with the formal reexamination process, even for ''older'' drugs that have not yet undergone the process, which is conducted after 4 years, 6 years, or 10 years depending on the category of the drug.

The Figure below is an attempt to illustrate the overall PSUR and license renewal report preparation cycle. It shows a hypothetical situation in which a drug is first approved at the same time in Japan and centrally in the EU, both of which currently require similar PSUR reporting schedules. If a third country/region (Country X) approves the drug one year after the IBD, then if that regulator accepts the already established IBD, it could in fact receive PSURs according to the same schedule as the EU and Japan; whether it wants a full two years of six-monthly reports (through month 36) would depend on the local PSUR reporting requirements. For Country Y, however, with an approval date 21 months after the IBD, its local

[1] Bulgaria, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia and Slovenia.

anniversary date would be three months out of sync with the ordinary data lock-points; in that situation it would be hoped that the regulator would exercise flexibility in allowing the company to maintain its already established data cut-off and calendar reporting schedule.

Figure 1
Hypothetical Report Schedule for PSURs and Relicensing Submissions*



* PSURs must be submitted within 60 days of the data-lock points shown.

The first "five-year PSUR report" (really the fifth-year report) should theoretically cover the one year period after the end of the four-year (48 month) data lock-point. Ideally, it would cover all dosage forms and uses. Subsequent reports (in the EU and Japan) would then cover five-years' worth of data. However, there are some difficulties with this apparently straightforward schedule, particularly in the EU.

EU regulations specify that a PSUR must be submitted within 60 days of the data lock-point. On the other hand, the first license renewal application must be submitted at least three months before the expiration date of the marketing license (60 months after approval); in practice, because it takes about three months to prepare a renewal report, the first license renewal submission will cover only 4.5 (not 5) years of post-marketing data, as shown in the Figure. However, in practice, companies are permitted to submit a PSUR covering the period from the 49th through the 54th months (a six month rather than the annual or fifth-year PSUR) to coincide with the license renewal report. However, in order to comply with the 60-day post-data lock-point submission requirement for PSURs, the license renewal application would also be submitted at the same time (end of month 56), or four months before license expiration. The license renewal package is supposed to be specific for each drug formulation (and include an analysis of efficacy as well as safety). For practical purposes, most pharmaceutical companies try to produce and use a single "4.5-year" report for the EU, which includes all formulations of the same product, for both PSUR and license renewal submissions. However, this is not always appropriate or achievable, especially for the first license renewal in the EU.

One way some companies facilitate their submissions at 56 months is to submit a summary bridging report that covers all the PSURs previously submitted over the four year period plus the new six-month report (covering months 49 through 54), all of which are appended.

As a result of these circumstances, there is still uncertainty with regard to the timing and coverage of the next license renewal submission within the EU, and of the first full five-year PSUR. Thus, although the original intent was to have a five-year PSUR that covers the period from month 60 through month 120, that cycle is out of sync with the license renewal/PSUR submission whose data lock-point was month 54. Whether the EU will request (or accept) a separate six-month report covering months 54 through 60, thus allowing restoration of the five-year PSUR cycle, is not known. Nor is it clear whether the second and subsequent license renewal applications will be allowed to coincide with the restored PSUR cycle.

Report Format and Content

The ICH guideline suggests that the E2C format is considered particularly suitable for comprehensive reports covering short periods (e.g., 6 months and one year) and that it might also be applicable for longer term reporting intervals. However, it was also recognized that other options for long-term reporting may be appropriate. No special recommendations have been issued by the EU or other regulators on the format for five-year reports. However, there is now evidence that regulatory authorities are expecting to receive them in ICH E2C format and also that they be submitted within the 60 day time frame from the last data-lock point, as with six-monthly or annual reports.

Some practical issues present themselves for five-year PSUR reports beyond the end-of-year-five report. For example, with a report covering from end of year 5 to end of year 10, is it meaningful to use as the reference safety information the version of the Company Core Safety Information (CCSI) in effect at the beginning of the reporting interval, as called for in the E2C Guideline? When the report concerns widely used products which generate many spontaneous ADR reports and extensive literature coverage during a 5 year period, there may be many changes to the CCSI (and data sheets) throughout the period. If the ADR case volume is "large," would endless pages of line listings serve any purpose? Is it unrealistic to expect that, without some pragmatic approaches, such a voluminous report should be prepared and submitted within the currently required 60 days from data-lock point?

Some other aspects of PSUR content that may also require new thinking and suggestions are provided in Chapter IV.

Appendix 11

Results of a Survey of Companies on Periodic Safety Reporting

CIOMS V SURVEY ON PERIODIC SAFETY REPORTING WORKLOAD: ACTUAL QUESTIONNAIRE, AS SENT, AND SUMMARY OF RESPONSES

[Note: Numbers next to quoted comments from responders refer to the code used to identify the specific companies for record-keeping purposes; the responses, however, are anonymous to their origin in this report.]

I. Background

The CIOMS Working Group V is in the process of preparing proposals on many aspects of ''good safety reporting'' practices, including some difficult issues regarding the nature, timing and content of periodic safety reports for marketed products (e.g., CIOMS II-type reports or ICH E2C PSURs). In addition to the ''routine'' periodic reporting that companies face, in EU countries and in Japan there is the added burden of preparing special 5-year (6-year in Japan) re-licensing (re-examination) applications, composed mostly of clinical safety information that must cover the specific five or six year period relative to the original approval date in each license-granting country.

The regulators and industry representatives in the Working Group recognize the extensive amount of work involved and the volume of reports generated. However, there do not seem to be any reliable statistics on just what the burden really is. As the working Group grapples with preparing guidance on ways to minimize unnecessary work and maximize the utility of periodic safety reporting, it is seeking basic information on company practices and workloads.

Your completing the questionnaire would be greatly appreciated — and valuable to our deliberations. We realize that some of the questions may be difficult to answer precisely (such as numbers of products or reports); however, your best estimate is acceptable. Individual replies will be kept confidential, and no company will be identified in any presentation of the results. A summary of the results will be provided to you as soon as it is prepared.

[Note: Ideally, we would like to have information that covers your entire corporation; if you believe that someone else within your company at the same or different site from yours would be in a better position to provide such complete information, please forward this questionnaire to that person. However, please arrange to have your reply sent to Dr. Gordon no later than 14 June 1999.]

II. Questionnaire

A. Contact information

Your Name .....

Your Company .....

Your Company Location (City/Country) .....

Your telephone number .....

Your E-mail address .....

	Number responses received*	Complete responses (number of business entities)
Europe	6	5
Japan	12	9
US	11**	9
Total	**29****	**23**

* Participating companies: Amgen, Astra AB, Biogen, Chugai Pharmaceutical Co., Ltd, Daiichi Pharmaceutical Co., Ltd, Dainippon Pharmaceutical Co., Eisai Co., Ltd., Glaxo Wellcome, Eli Lilly & Co, Merck & Co., Mochida Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Orion Corporation, Pfizer Inc., PPD Development, Procter & Gamble Pharmaceuticals, Rhone-Poulenc Rorer, Hofmann-La Roche, Sankyo Co., Ltd., Shionogi & Co., Ltd., Solvay Pharmaceuticals, SmithKline Beecham, Sumitomo, Takeda Chemical Industries, Ltd., Tanabe Seiyaku Co., Ltd., Warner-Lambert, Yoshitomi Pharmaceutical Ind., Zeneca

** Number includes two responses (one drugs, one biologicals) from one company, which are included as separate entries in the tabulations below. Also, two companies included as separate entries in the tabulations have recently merged into one corporate entity. Data from incomplete questionnaires were processed when possible. Likewise, a single participant may have included multiple responses to individual questions; all were processed. Rounding was applied, when appropriate, to calculated numbers in the tables.

B. Administrative information

1. To allow us to interpret your replies to this questionnaire correctly, please indicate whether you are answering for: Your Location Only or Entire Company

[As mentioned above, it is preferred that your replies cover your entire company if at all possible.]

	Your location only	Entire company	No response
Europe	1	4	1
Japan	2	7	3
US	2	8	1
Total	**5**	**19** (79%)	**5**

2. Check one or more of the following descriptions of how the responsibility for preparing reports is organized within your company:

   a. All reports are prepared centrally at one location for the entire company.

   b. **Except** for reports prepared for the US FDA (quarterly and/or annual safety reports prepared by our US location), all other reports are prepared centrally.

   c. Different divisions/locations of our company prepare reports, depending on the products or other factors.

	a. Central*	b. Central, except US	c. Non-centralized
Europe	2	1	3
Japan	3	3	4
US	5	2	4
Total	**10**	**6**	**11** (41%)

* Supplemental comments for question 2.a. (central report preparation):

Yes, except when local requirements require preparation of local reports (example France). [30] For reference purposes, the number in brackets following a supplemental comment identifies (anonymously) the code given to a company.

3. An active substance (or substances for a combination) may be used in many different formulations/products. For all the different products (both Rx and OTC) that your company sells in one or more countries **for which periodic safety reports are actually prepared by your company,** please estimate the following:

   [Note: for licensing arrangements on a product with other companies, in which you do not prepare the report(s), do not count such reports in your answer. Questions D.1. and E.5. deal specifically with this issue.]

a. Number of pharmacologically active substances .....

b. Total number of products (all dosage forms, combinations, etc.) .....

	a. Mean number moieties [range]	b. Mean number products [range]
Europe	96 [30-150]	221 [100-308]
Japan	6 [2-11]	10 [4-27]
US	59 [3-148]	99 [3-250]
Overall	**47** [2-150]	**86** [3-308]

4. Indicate in what format(s) you prepare your various periodic safety reports; circle all that apply:

   a. CIOMS-II

   b. ICH PSUR

   c. US NDA quarterly/annual

   d. Other (comment/describe briefly).....

	a. CIOMS-II	b. ICH PSUR	c. US NDA	d. Other*
Europe	3	6	5	1
Japan	3	8	1	6
US	2	10	8	2
Total	**8**	**24**	**14**	**9**

* Supplemental comments for question 4.d. (other):

a, b, or c, depending on locale. [25]
Line listings only; abbreviated reports. [22]
Country-specific requirements — Swiss specifically. [17]
We submit ICH PSURs to FDA — we do not prepare [US NDA] periodics at all. [16]
Japanese domestic format for 6 products. We have to prepare both ICH PSUR and Japanese domestic report for one product that we are selling in European countries. [13]
Japanese Drug-Safety Periodic. [12]
Similar to ICH PSUR but some modification and/or abridgement made. [10]
Other: (1) Safety Periodic Report using formats designated by MHW and to be submitted to MHW. (2) Report including summary of Safety Periodic Report to MHW plus other safety information. (3) Periodic Report including CIOMS I, II and other safety information, etc. [07]
Other, Japanese "Anzenseiteiki Hokoku" which is a local addition to the PSUR. [04]

C. *Volume of reporting*

1. How many of each of the following types of reports did you prepare in 1998 for all relevant products? If you used the same product-report for more than one submission/regulator, count such a report only once.

   a. US NDA quarterly .....

   b. US NDA Annual .....

   c. Six-month (CIOMS or ICH) .....

   d. One year (CIOMS or ICH) .....

   e. Five-Year relicensing reports for Europe .....

   f. Six-year re-examination reports for Japan .....

   g. Other (e.g., 2-year reports for BfArM or IKS) (specify).....

   .....

   .....

   .....

	Mean number of indicated type of reports [range]						
	a. US NDA quarterly	b. US NDA annual	c. 6-month CIOMS/ICH	d. one-yr CIOMS/ICH	e. 5-yr re-licensing	f. 6-yr re-licensing	g. Other*
Europe	24 [4-82]	43 [2-109]	14 [5-30]	9 [5-25]	15 [1-27]	0	25 [22-27]
Japan	4	1	2 [1-6]	3 [1-5]	1	3 [1-6]	11 [5-17]
US	19 [1-46]	46 [2-109]	19 [2-50]	29 [1-48]	7 [1-13]	11	9 [1-20]
Overall	**20** [1-82]	**42** [1-109]	**11** [1-50]	**9** [1-48]	**9** [1-27]	**4 [1-11]**	**14** [1-27]

	Number of responses	Mean total number of reports (all types) per company [range]
Europe	5	115 [41-224]
Japan	10	7 [1-23]
US	10	87 [6-222]
Overall	**25**	**60** [1-224]

* Supplemental comments for question 1.g. (other):

All reports prepared in Europe, cannot answer. [06]
12 5-yr reports in 1998, but in 1999 will prepare approx. 35 and in 2000 we know that 50 are due. [01]

Other reports: Addendum, 11; Line listings, 10; Abbreviated, 1. Two-year reports were covered by submitting a series of 6-month reports (number not available.) [22]
One- or 5-year PSUR in ICH format or similar (4 reports). [10]
Other: (1) Safety Periodic Report to MHW, 12. (2) Report including summary of Safety Periodic Report to MHW plus other safety information. (3) Periodic Report including CIOMS I, II and other safety information, etc., 4. [07]
Other: One 2-year report for Germany. [30]

2. How many of these reports contained the indicated number of ADR cases in your line listings and/or summary tabulations, or, as required by FDA, copies of the individual cases (e.g., MedWatch or CIOMS forms):

Number of Individual Cases	No. of Periodic Reports	No. of 5-and 6-Year Reports
Less than 100	.....	.....
100 to 499	.....	.....
500 or more	.....	.....

	Mean number of indicated type of report, by volume of individual cases [range]					
	<100 cases		100-499 cases		>= 500 cases	
	Number periodic reports	Number 5-yr & 6-yr reports	Number periodic reports	Number 5-yr & 6-yr reports	Number periodic reports	Number 5-yr & 6-yr reports
Europe	55 [17-152]	57 [10-144]	24 [11-46]	9 [6-12]	7 [3-11]	8 [7-8]
Japan	3 [1-10]	2 [1-6]	2 [1-3]	2 [1-2]	5 [1-5]	2 [1-3]
US	29 [1-113]	6 [3-10]	16 [1-66]	5 [1-14]	11 [1-22]	10 [7-14]
Overall	**24** [1-152]	**17** [1-144]	**14** [1-66]	**5** [1-14]	**9** [1-22]	**6** [1-14]

In one instance, percentages were reported. The table above includes calculated numbers based on these estimates derived from available information: 188 periodics, 34 renewals. [17]

3. For products with different dosage forms/formulations and/or different indications (e.g., pediatric and adult; injectable and oral; hypertension and angina), circle all that apply:

   a. We combine all formulations/uses into one report whenever possible and practical.

   b. We usually prepare separate reports for different dosage forms and different major indications.

c. Other (specify) . . . . . .

. . . . . .

. . . . . .

	a. Combine	b. Separate	c. Other*
Europe	5	2	3
Japan	9	0	0
US	8	1	1
Total	**22** (76%)	**3**	**4**

* Supplemental comments for question 3.c. (other):

Combination of the above, depending on locale. [25]
Although "a" applies practically always, in certain rare cases in which there is a great difference with regard to the ADR profile (or otherwise between the dosage forms) formulations, we separate the PSURs. [23]
Combine (a.) for PSURs, usually separate reports for NDAs. [22]
It depends on the indication, type of report, formulations, date of registration. We try to combine as much as possible all formulations in the same report, but for some drugs it is not possible. [21]
Combine, except for US NDA reports, where one report per NDA. [17]
Combine, although some exceptions exist. [05]

4. For reports containing line-listings (data elements that describe individual ADR cases), how are the line listings submitted? Check all that apply.

   a. On paper only (e.g., as Appendix 3 of the ICH PSUR format)

   b. Electronic version only (e.g., as a disk)

   c. For the same report, both paper and electronic

   d. Paper and/or electronic, depending on the product or on the regulatory authority to whom the report is sent.

	a. Paper only	b. Electronic only	c. Both	d. Either or both
Europe	4	0	0	2
Japan	8	0	0	0
US	10	0	0	0
Total	**22** (92%)	**0**	**0**	**2**

5. Focussing only on five-year (six-year) relicensing reports:

   a. In your preparation of such reports for a given product: (circle one answer)

      ❑ we *always* prepare separate reports for each country requiring them, based on each country's official anniversary date

      ❑ depending on circumstances, we may use the same report for different countries even though the time periods covered may not be exactly in accord with the official anniversary dates

   b. If you circled the second choice, have such "off-date" submissions been rejected by any regulators? Yes No

      If Yes, please indicate which countries: .....

      .....

      .....

	a. For a given product		b. Off-date submissions rejected?	
	Report always separate	May use same report, even for off-dates	Yes	No
Europe	0	6	4	2
Japan	2	5	1	4
US	0	8	2	6
Total	**2**	**19** (90%)	**7**	**12** (63%)

* Supplemental comments for question 5.a. (same report, differing time periods):

We always use the same report for all countries. [30]

* Supplemental comments for question 5.b. (rejected):

No, not yet. [29]
No, but we have used bridging reports to supplement. [01]
[In order to be acceptable,] Finland and Belgium need to be within 6-months of last datalock point. [22]
Ireland, Sweden. [21]
Italy [20]
Italy required information to its country-specific cut-off. Therefore, we supplement existing PSURs with a post-datalock line listing to Italian cut-off date and this satisfies MOH. [17]
Finland, Belgium. [16]
Germany [05]
Italy [08]
Currently only preparing for Japan because our international products are less than 5 years old. [04]

D. Resource requirements

Please indicate here whether the following answers cover the entire company or only your location: (circle one) Entire company Local site

	Entire company	Local site	No response
Europe	5	1	0
Japan	6	3	3
US	8	2	2
Total	**19** (76%)	**6**	**5**

1. Estimate how many full-time-equivalent employees are involved in the preparation of all your various periodic safety reporting obligations. Include in your count any systems, data processing, regulatory, QA/QC, etc., personnel in addition to ''safety'' people.

   [Note: It is recognized that in a licensing partnership, for example, another company may actually prepare the periodic report on behalf of both (or all involved) companies (see question E.5). Nevertheless, considerable work may be required to provide a licensing partner with appropriate data. If possible, include that effort in your estimate here.]

	Mean number FTEs [range]
Europe	15 [5-19]
Japan	16 [2-50]
US	8 [1-18]
Overall*	**12** [1-50]

* Supplemental comments for question 1:
2 FTEs for NDAs, extra 3 recruited in 1999. [22]

2. Estimate the time it takes to prepare a ''typical'' 6-month CIOMS-II type report that contains the indicated number of individual ADR cases:

Number of Cases	Time to Prepare Report (weeks)
Less than 100	.....
100 to 499	.....
More than 500	.....

	Mean time (weeks) to prepare report, by case volume [range]		
	<100 cases	100-499 cases	> = 500 cases
Europe	3 [1-5]	5 [1-9]	9 [5-13]
Japan	4 [2-8]	5 [2-8]	6 [3-8]
US	3 [1-8]	5 [1-8]	6 [4-10]
Overall	**3** [1-8]	**5** [1-9]	**7** [3-13]

* Supplemental comments for question 2:

Except products in first two years of marketing which may have low volume but high commercial interest and therefore extensive review. [17]
Time to prepare report is 60 days from the cutoff, regardless of the number of cases. [28]

E. Special questions

1. In your opinion, has the preparation of periodic safety update reports led to the detection of what you would regard as important safety signals that:

   a. Were not identified through expedited reporting?
   Yes No

   b. Could not have been identified through expedited reporting?
   Yes No

	a. New signal?		b. Periodic reporting essential to detect new signal?	
	Yes	No	Yes	No
Europe	3	3	3	3
Japan	2	6	3	6
US	4	5	3	6
Total	**9**	**14** (61%)	**9**	**15** (63%)

* Supplemental comments for question 1:

Signal probably not detected by expedited reporting. [22]
No, but it has confirmed trends and committed us to focus on an issue. [17]
Our label review process, which happens during PSUR production, detects signals. [28]

2. In the absence of any regulatory guidelines on details for the format and content of an ICH E2C PSUR, have any EU regulators criticized or rejected your reports, even though they were prepared according to the principles of the E2C Guideline?

a. No

b. Yes. If Yes, please provide description below.

c. Not applicable

Description .....

.....

.....

.....

	EU criticism of E2c PSUR?		
	a. No	**b. Yes***	**c. Not applicable**
Europe	4	1	1
Japan	4	1	3
US	7	2	1
Total	**15** (79%)	**4**	**5**

* Supplemental comments for question 2.b. (Yes):

Initial PSUR submitted to EMEA (centrally approved) having consumer reports included since they represented 90% of reports received (based upon "implied causality" of postmarketing reports). The report was rejected and a re-write requested excluding cases NOT confirmed by HCP. Decision to submit initial report including consumer cases was based upon the concern over not reporting the vast majority of cases. [27]

No, but there is evidence that they are using the PSUR as a vehicle for obtaining additional data from companies which may have been requested as ad hoc regulatory questions in the past. This is especially so for NCEs approved by the centralised procedure in Europe. [22]

France: Format has been criticized by French agency. Complementary information has been requested from time to time by European countries. [21]

They have criticized aspects of the analysis in some reports but not the format of the report. [04]

We have gotten requests for discussions of additional safety issues. [28]

3. Because of different approval or launch anniversary dates for the same product in different countries, and possibly because of other factors driven by regulatory requirements, companies may be faced with preparing multiple reports on the same product within a fairly short time span (e.g., a few months). Such different reports may in fact contain only slightly different data (e.g., due to slightly different cut-off dates). Please indicate what degree of redundancy and extra work you believe this represents for your company (circle one):

   a. Very little or none

   b. Bothersome but not excessive

   c. Extensive

	a. Little / none	b. Bothersome	c. Extensive
Europe	0	4	2
Japan	2	4	3
US	3	2	5
Total	**5**	**10** (40%)	**10** (40%)

* Supplemental comments for question 3:

Bothersome but not excessive because we strongly resist requests for individualized reports. [22]
Very little or none, because we do not prepare separate reports for separate countries. All PSURs are prepared according to International Birthdate. Previously (> 3 yrs ago) we prepared separate reports for each country and this had extensive resource implications and led to inconsistencies between what was submitted to different agencies. [17]

4. According to ICH Guideline E2C, regulators should be prepared to accept multiple six-month PSURs to satisfy a requirement for longer interval reporting periods (e.g., two six-month reports submitted for a one-year reporting schedule). This would avoid having to prepare yet another, separate report for the longer period if a company had already prepared six-month reports.

   a. Have you submitted "bundled" six-month reports to any regulators? Yes No

   b. If Yes, has this approach been **rejected** by any regulators when you have attempted to satisfy a reporting requirement covering multiples of six months (e.g., one year)? Yes No

   c. If Yes to b., please provide details .....

   .....

   .....

   .....

	a. Bundled 6-mo reports?		b. Bundling rejected?	
	Yes	No	Yes*	No
Europe	3	3	1	2
Japan	1	8	0	1
US	7	3	1	5
Total	**11**	**14** (56%)	**2**	**8** (80%)

* Supplemental comments for question 4.b. (Yes):

France, in particular has complained about the bundling of 6-month reports. It has also been reported that the Swedish agency is unhappy with this approach. [28]
When submitting a bundle of several shorter period PSURs to cover 5 years at a renewal, the RA required one 5-year PSUR. [23]
Not applicable at present, but we tentatively plan to submit multiple 6-month reports at 6-month intervals when this situation arises. [04]
FDA accepted PSUR covering 6-month period in lieu of quarterly report but with the appropriate large appendix based upon the quarter. [27]

5. When there are multiple-company marketing arrangements for a product (co-marketing, various licensing relationships, etc.), there are several ways periodic reporting responsibilities are handled. Examples include: one company prepares the ''global'' PSUR, or the partner companies independently prepare non-overlapping regional PSURs, or a combination of these two.

   a. Do you have any marketing or licensing arrangements for any products with one or more company? Yes No

   b. If Yes, circle one of the following statements:

      (1) We ordinarily try to have only one company prepare all the relevant periodic safety reports on behalf of the other partner(s).

      (2) We usually prefer to prepare our own reports even if the other partner(s) incorporate our data into their reports.

      (3) The arrangements for periodic report preparation depend on the specific product/contractual agreement and may be according to (1) or (2) or other method.

	a. Marketing/licensing agreements?		b. For marketing/licensing arrangements:		
	Yes	No	1. One company prepares	2. Prepare our own	3. Depends on terms
Europe	6	0	2	0	4
Japan	8	1	3	1	4
US	9	1	3	2	5
Total	**23** (92%)	**2**	**8**	**3**	**13** (54%)

* Supplemental comments for question 5:

We prefer b.1. (one company prepares), but in some cases the company we have licensed from has been unable to supply a PSUR at the appropriate interval. [04]

F. General comments

Please provide any information or ideas that bear on the issues raised in this questionnaire or on other matters of concern related to periodic safety reporting.

Comments from questionnaire respondents located in Europe:

None [05, 06, 21]

This company is comfortable within current periodic reporting requirements based on use of ICH E2c. [16]

We write all sections of the PSUR, obtaining raw data from other departments. Reports are to full ICH E2c criteria but the sorting of cases and the construction of the summary tabulations is mainly manual. All reports are recoded at the time of writing the PSUR, they are assessed for seriousness, listedness and the comments written at this time, too. [22]

[Our off-date submissions have not been rejected.] "No" applies [to question c.5.b] most likely because we prepare a statement to cover the gap period [from] the DLD of the actual, but somewhat (6-12 months) old, PSUR. [We] submit these together. [23]

Comments from questionnaire respondents located in Japan:

None [02, 03, 07, 09, 12, 13, 15]

I find our major problem is that after a new approval in a new country, we must go back to 6-monthly intervals (or worse in the US). Another problem is that the US format is very different from ICH. [04]

In spite of having decided on one globally unique periodic report, some countries' authorities require additional reports based on the approved date in that country. Furthermore, there is also at least one authority that requires the PSUR be translated. We strongly hope to harmonize the rules for periodic safety report worldwide to minimize redundancies. We appreciate your effort in this matter. [08]

We have started to comply with Japanese requirements for PSUR to be submitted to MHW in relating to re-examination procedure, but our experience to prepare so-called global PSUR is still very limited. Since our overseas collaborative companies began to require global PSUR of our original product, we anticipate an enormous amount of work if to completely meet all local requirements. Therefore, we welcome an efficient

simplification of PSUR submission (e.g., no multiple work to meet different local birth date). [10]

We are not in a position to answer your questionnaire because we are not selling such products in foreign countries and do not have experience of preparing PSUR as Marketing Authorization Holder. However, we have a big workload in the PSUR submission to the Japanese Health Authority, translating the PSUR to Japanese which we receive from the MAH. Therefore, we have to submit the PSUR to the Japanese Health Authority with the Periodic Safety Reports that are prepared for ADRs occurring in Japan. Again, we are sorry that we cannot answer your questionnaires since we are not a MAH. However, as we explained we have a heavy workload in the processing of CIOMS and PSUR in our Pharmacovigilance Department, so we have made some comments in section "H. General Comments." [11]

We have not drawn up any PSURs for our marketed products so far, therefore unfortunately we can not reply to your request at this stage. [14]

Comments from questionnaire respondents located in the US:

None [17, 20, 25, 26, 27, 28, 29]

Our biggest issues are the difficult date requirements; among the countries and the changing date ranges of the reports. We also have the challenge for writing reports with up to 4 actives per drug product. We can reference info on the individual actives if we have already prepared a PSUR (works occasionally). Then again, if the date ranges of the individual actives' PSURs differ significantly from the dates of the combination product report, it's a stretch to use them as reference documents. We do not have global harmonization of our formulas. They can differ slightly in the levels of actives from country to country — example, a cough syrup with the same trade name can have 12 mg/5mL, 14mg/5mL, 12.5 mg/5mL — the excipients (flavors & colors) can also vary. We have had conflicting guidance on whether the products are the same or different and whether they should be lumped together in a report or evaluated separately. We also have products with the same ingredients & same level of ingredients, but some ingredients are registered as actives while others are registered as inactives from country to country. Same issue: Do we include all in a PSUR? (Our common sense says yes, but some of our affiliates are challenging this.) [01]

Our PhV group also provides output for the clinical portion (IND portion) of the annual report. In 1998, we provided information for approximately 125 IND reports. We also provide information regarding

OTC and non-NDA products. In 1998, we provided information for approximately 35 reports. The specific Italian regulations and national license renewals are usually not in line with the periodicity of multiples of 6 months data sets following IBD, and therefore result in a significant extra workload (additional and/or modified reports). [18]

1) Because of clock re-start in many countries, we have not been able to get from 6-month to 1-year [reports] then to 5-year reports, and we have had to prepare 6-month and 5-year reports for the same drugs;

2) Need more clear guidelines and consistency between guidelines to be used for the preparation of these reports, especially regarding 5-year reports;

3) Difficulty in trying to respond to special requests from regulators, especially as some requests may contradict each other;

4) Harmonization should be encouraged and local country regulations not ''contradict'' the ''harmonized'' guidelines [30]

Until recently, the focus of our safety reporting has been in the preapproval area. Historically, our postapproval safety activities did not include actual preparation and regulatory submission of periodic safety reports. [24]

END OF QUESTIONNAIRE

Appendix 12

Sample of a Simplified PSUR

ANDSON RESEARCH LTD QWEASYTROL SAFETY UPDATE
1 October 1998 — 30 September 1999
ARDS/99/037

[Explanatory note for this sample report: You will note that this example includes a discussion of a serious unlisted case (severe sedation), a category that is suggested might rule out a ''simplified report.'' However, sedation was already included in the CCSI as a very common ADR that ''usually occurs only on starting qweasytrol and resolves within a few days on continued therapy. It may occasionally limit dose escalation.'' The reported new case, which remained severe on continued low dose therapy, was regarded as ''serious'' by the reporter, and therefore was a serious unlisted case (greater severity) when received. On receipt of the case, the CCSI was amended (see 4. below) and details would have been submitted with a variation application in the EU. Thus, at the time of the report preparation severe sedation would be regarded as serious listed relative to the updated CCSI. It was the judgment of the company that a full, detailed PSUR was unnecessary under the circumstances.]

1. **Introduction**
   This report includes safety data for all formulations of qweasytrol in all indications.

2. **Worldwide market authorization status**
   Approved in 96 countries with no change since the last PSUR.

3. **Update on regulatory or manufacturer actions taken for safety reasons**
   None.

4. **Changes to reference safety information**
   The core safety information current at the beginning of the reporting period is presented in Appendix 1. The only change relates to sedation (see case A98765), which is highlighted.

5. **Patient exposure**
   About 800,000 patients using a standard oral dose of 30mg daily.

6. **Individual case histories**
   Only 9 cases were received (all spontaneous) during the review period. See Appendix 2.

Reports	No. of cases
Serious Unlisted	1
Serious Listed	2
Non-Serious Unlisted	3
Non-Serious Listed	3
Total (Serious + Non-Serious Cases)	**9**

7. **Studies**
   The prospective cohort monitoring study (10,000 patients) is now completed. There was no increase relative to comparators in gastro-intestinal bleeding. Details available on request. No other targeted safety studies are planned, ongoing or completed.

8. **Other information**
   None.

9. **Overall safety evaluation**
   The serious unlisted report (A98765) received in the time period resulted in an amendment of the CCSI to reflect that qweasytrol alone may cause severe sedation. The 3 non-serious unlisted cases are disparate and do not add any further evidence to establish a causal relationship with qweasytrol.

10. **Conclusion**
    No actions required.

Signed: ..... Date: .....

Appendix 1

CORE SAFETY INFORMATION FOR QWEASYTROL
(Issue Number 3)

Undesirable Effects

- Neurological

Very Common	Sedation — usually occurs only on starting qweasytrol and resolves within a few days on continued therapy. It may occasionally limit dose escalation.
Common	Headache, drowsiness
Rare	Seizures — predominantly in patients with a history of epilepsy or structural brain lesion. **Severe sedation on continued low dose therapy.**

The Effects on Ability to Drive Vehicles and Operate Machinery

The statement has been modified from:

"When starting therapy, qweasytrol may affect reactivity to the extent that the ability to drive vehicles or operate machinery is impaired. This may also occur with high-dose prolonged therapy (over 45mg daily) and at all doses after alcohol consumption."

To:

"Sedation has been reported in patients receiving qweasytrol usually when starting therapy, on high-dose prolonged therapy (over 45mg daily), or when taken with alcohol. Patients should exercise caution before driving, using machinery or participating in dangerous activities."

Appendix 2

LINE LISTING (of all cases)

Appendix 13

Sample of a Summary Bridging Report

ANDSON RESEARCH LTD.
BRONCHOTEROL
FIVE YEAR SUMMARY BRIDGING REPORT

1. **Introduction**

This summary bridging report integrates the information presented in 7 Bronchoterol periodic safety update reports (PSURs) covering the 5-year period from 01 April 1995 to 30 March 2000 as detailed below.

Report number	Dates of report	Period	Format
ARDS/95/034	01 April 1995 — 30 September 1995	6 months	CIOMS II
ARDS/96/015	01 October 1995 — 31 March 1996	6 months	CIOMS II
ARDS/96/040	01 April 1996 — 30 September 1996	6 months	CIOMS II
ARDS/97/017	01 October 1996 — 31 March 1997	6 months	ICH E2C
ARDS/98/021	01 April 1997 — 31 March 1998	1 year	ICH E2C
ARDS/99/023	01 April 1998 — 31 March 1999	1 year	ICH E2C
ARDS/00/025	01 April 1999 — 31 March 2000	1 year	ICH E2C

2. **World-wide market authorisation status**

Bronchoterol has now been approved in 117 countries (see Appendix 1, ARDS/00/025).

During the 5-year time period of this bridging report, the following new formulations have been approved:

- Multidose powder for inhalation containing 300mcg Bronchoterol per inhalation capsule. First approved 25 October 1997 (UK).
- CFC-free Multidose inhaler containing either 150mcg or 300 mcg Bronchoterol per actuation. First approved by Mutual Recognition in the EU on 7 September 1999 and now approved in 14 EU countries.

3. **Update on regulatory authority or manufacturer actions taken for safety reasons**

- In December 1995, the FDA proposed class labelling for all beta-2 agonists including statements regarding cardiovascular effects such as arrhythmias and ECG changes. (ARDS/96/015).
- In October 1996, the US data sheet was amended and Dear Doctor and Dear Health Care Provider letters were issued to health care professionals in the US to emphasise the appropriate use of Bronchoterol in the management of asthma. This followed the receipt of several case reports of asthma exacerbations in the US. As a result the FDA requested that a large, prospective study be set up to characterise the safety of Bronchoterol (ARDS/97/017).
- Following the changes to the US label, the wording of the company core safety information (CCSI) was amended in November 1996 and a Dear Doctor letter was issued world-wide (ARDS/97/017).

4. **Changes to reference safety information**

The following changes have been made to the CCSI during the last 5 years:

- The wording of the CCSI was amended in November 1996 to clarify the role of Bronchoterol in the management of asthma (see Section 3). Existing statements were revised and new statements added. Issues considered to be of particular importance included the need for monitoring of **deteriorating asthma**, and recognition of increasing use of short acting bronchodilators as a sign of deteriorating asthma (ARDS 97/017).
- Hypersensitivity reactions, excluding skin rash, were first reviewed in ARDS/95/034. Data from clinical trials and an on-going Prescription Event Monitoring study (UK) did not support a causal association with non-cutaneous reports (oedema and angioedema). However, following a review of the spontaneous adverse event data in ARDS/97/017, the Undesirable Effects section of the CCSI was amended to read 'hypersensitivity reactions, including rash, **oedema and angioedema.'** No reports of anaphylaxis have been received.
- Following a request in November 1995 from a regulatory authority to add **arthralgia** to the Side Effects section of their local data sheet, all available data relating to this adverse event were reviewed and

presented in ARDS/96/015. At this time there was no strong evidence for a causal relationship. The topic continued to be closely monitored and, following the receipt of more convincing cases, arthralgia was added to the Undesirable Effects section of the CCSI in March 1998 (ARDS/98/021).

- A review of **arrhythmias** was reported in ARDS/96/015. This concluded that the majority of spontaneous and serious clinical trial reports of arrhythmias received in association with Bronchoterol did not suggest a direct causal relationship. However, a very small number of reports, particularly of supraventricular tachycardias and extrasystoles, suggested that on very rare occasions, bronchoterol may be a contributing factor. The Undesirable Effects section of the CSI was later amended to include the following statement:
  Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles) have been reported, usually in susceptible patients (ARDS/97/017).

5. Patient exposure

5.1 *Clinical Trials*

It is estimated that approximately 3,000 patients have received Bronchoterol as the MDI in corporate studies during the period of this report, 60% as the CFC-free formulation. There were no studies using the dry powder inhalation capsules.

5.2 *Market Experience*

It is estimated that there have been approximately 4.7 million patient-years of exposure to Bronchoterol as metered dose inhalation world-wide during the 5 year period of this summary report. This was calculated using available sales volume data and assuming that one MDI represents one month's treatment. Almost 80% of exposure was with the metered dose inhaler (CFC), and 20% with the CFC- free MDI.

Using a standard daily dose of two dry powder inhalation capsules, it is estimated that there have been approximately 500,000 patient-years of exposure to this formulation.

6. Individual case histories

During this time period, approximately 3,400 suspected ADR cases were received as spontaneous reports and from clinical trials. The latter

included serious, related cases and serious cases but with unknown causality. Criteria for inclusion of individual adverse event cases in periodic safety update reports changed from those under CIOMS II guidance to ICH E2C during this time period; the total number of reports included in line listings and/or summary tabulations under ICH E2C throughout the 7 reports is 2,438.

7. **Studies**

- At the request of the FDA, a large randomised, controlled trial is underway in the US to characterise the safety profile of Bronchoterol. Asthma-related mortality and asthma-related life-threatening events are the primary endpoints of this study (ARDS/97/017). This study is ongoing and an interim analysis of the results was presented in ARDS/00/025.
- A UK study investigating drug use and pulmonary death rates in increasingly symptomatic asthmatics using the GPRD database, was completed in July 1997 and published in September 1998. The aim of the study was to compare the characteristics and short term respiratory mortality rates in first time users of Bronchoterol, ipratropium bromide or theophylline. One of the conclusions was that Bronchoterol use was not associated with an increase in short-term mortality, compared with ipratropium bromide and theophylline (results presented in WPSP/98/021).
- The results of a prescription event monitoring (PEM) study undertaken by the Drug Safety Research Unit in the UK were presented in ARDS/99/023. This confirmed the statements in the CCSI and no new safety signals were identified. It was suggested that advanced age and severity of disease were the most likely factors contributing to asthma mortality in the population studied. There was no evidence to suggest that Bronchoterol contributed to the deaths. A publication is currently in preparation.

8. **Other information**

Following the introduction of the CFC-free MDI formulation there was an increase in the proportion of lack of efficacy reports received. An analysis of reporting trends by country and time on the market is presented in ARDS/99/023. On-going monitoring has confirmed that the reports peak at 8 months after introduction of the formulation and then rapidly decline. (ARDS/00/025)

9. **Overall safety evaluation and conclusion**

The safety profile of Bronchoterol is under regular review and the core safety information is updated as new adverse reactions are identified. There are no outstanding, unresolved issues from this series of safety updates. Reports of lack of efficacy of the CFC-free MDI will continue to be monitored.

Signed: ..... Date: .....

Appendix 14

Sample PSUR Executive Summary

The following is an example of a summary that could be used to provide a high-level overview of the contents of a PSUR. An appropriate heading/title relevant to the company and product should be placed on the top of the page. It is recommended that the summary be attached to the front of the PSUR or to the cover letter that might be used to submit the PSUR at the local level.

This is the third PSUR for Drug X. It includes ADR case reports and other data obtained from our license partner, Company Z. This report is being submitted on behalf of both companies.

The product was recently approved in Utopia for treatment of obsessive-compulsive disorder in children. The authority in Babaland has banned its use in adults for seasonal affective disorder. The drug is now on the market in 47 countries for one or more of three indications in adults and/or children. Only one dosage form, a tablet in three strengths (1, 2 and 5 mg), is available.

Nearly 800 thousand containers of 30 tablets each were distributed during the last period. No clinical trials or post-marketing observational studies were conducted or planned.

Overall, 798 spontaneous case reports were received from 21 countries; 19 cases, involving four different suspected ADRs, were regarded as serious and unlisted. Subsequent to the completion of this report, and within the past three days, 8 cases of overdose associated with nausea and vomiting were received. An investigation is underway.

There were no new major findings bearing on the established overall safety profile of the product. The Core Safety Information has been updated to include hypertension and nausea as new non-serious suspected ADRs.

Appendix 15

Results of a Survey on Patient Exposure (Denominator) Data

CIOMS Working Group V

Questionnaire on Regulatory and Industry Practices in Determining and Using Patient Exposure (Denominator) Data on Marketed Drugs for Pharmacovigilance Applications

Questionnaire and Tabulated Responses

(Original questionnaire dated 20 February 1998)

A. Administrative Information

Name: .....

Title or Job Description: .....

Affiliation: .....

Telephone number: .....

Fax number: .....

E-mail address: .....

Participants: Astra AB, Boehringer Ingelheim, BfArM (Germany), DuPont-Merck, European Agency for the Evaluation of Medicinal Products (EMEA), Food and Drug Administration (US), Fujisawa USA, Glaxo-Wellcome, Health Canada, Hoechst-Marion-Roussel (France), Hofmann-La Roche, Institut de Recherches Int'l Servier, Lilly, Merck (Germany), Merck & Co (US), Novartis, Organon, Pfizer, Pharmacia & Upjohn, Sanofi, SmithKline Beecham, Synthelabo, WHO Collaborating Center for International Drug Monitoring (Uppsala, Sweden), Yamanouchi Europe

B. Sources of Information

Although you may be aware of and have access to certain sources of patient exposure data, you may not use them routinely. Thus, access, use and other features are covered separately in the following question.

Sources and types of information on drug exposure: check affirmative replies only for each item regarding whether you (a) know about/are aware of, (b) have access to, and (c) use in any context (e.g., periodic safety reporting or safety signal analysis). In addition, please indicate (d) whether the data in your judgment are as complete and accurate as you need.

(check only affirmative replies)

	Know about/ Aware of		Have Access to		Use		Complete/ Accurate?	
1. COMPANY SALES INFORMATION broken down by:	reg.	co.	reg.	co.	reg.	co.	reg.	co.
– total ''tonnage''	2	10	1	11	1	12	1	4
– location of use (e.g., country)	1	10	1	12	1	14	1	3
– dosage form	1	10	1	13	1	11	1	5
– unit strength (e.g. 1 mg vs. 2 mg tablets)	1	11	1	12	1	11	1	3
– indication treated	1	6	1	4	1	4	1	0
– duration of treatment	1	7	1	6	1	3	1	0
– population (e.g., adults vs. pediatrics)	1	9	1	4	1	2	1	0
– age	1	6	1	4	1	2	1	1
– sex	1	6	1	4	1	2	1	1
– medical specialty of prescriber	1	5	1	3	1	0	1	1

(check only affirmative replies)

	Know about/ Aware of		Have Access to		Use		Complete/ Accurate?	
2. Data from other sources (NON-COMPANY) broken down by:	reg.	co.	reg.	co.	reg.	co.	reg.	co.
– total ''tonnage''	1	4	1	2	1	1	0	0
– location of use (e.g., country)	1	7	1	3	1	1	0	0
– dosage form	1	6	1	4	1	2	0	0
– unit strength (e.g. 1 mg vs. 2 mg tablets)	1	6	1	3	1	2	0	0
– indication treated	1	9	1	6	1	3	0	0
– duration of treatment	1	6	1	2	1	3	0	0
– population (e.g., adults vs. pediatrics)	1	9	1	4	1	2	0	0
– age	1	8	1	5	1	5	0	0
– sex	1	7	1	5	1	5	0	0
– medical specialty of prescriber	1	8	1	5	1	1	0	0
3. IMS Hospital Audits	3	8	3	8	3	3	0	2
4. IMS Medical Audits	2	10	2	7	2	4	0	2
5. IMS Medical MIDAS/NDTI	2	9	2	7	2	5	1	1
6. IMS National Prescription Audit Plus (NPA-Plus)	2	8	1	5	1	3	1	0
7. IMS Pharmacy Cash Audits	1	6	0	3	0	0	0	0
8. IMS Sales MIDAS	1	8	1	3	1	1	0	1
9. IMS Xponent/Xplorer	1	5	0	0	0	0	0	0

	Know about/ Aware of		Have Access to		Use		Complete/ Accurate?	
	reg.	co.	reg.	co.	reg.	co.	reg.	co.
10. IMS Xtrend	1	3	1	1	1	0	0	0
11. NDC Health Information Services	0	4	0	1	0	1	0	0
12. Sergeant System	0	2	0	0	0	0	0	0
13. Public or Private Population Data Bases (e.g., Medicaid, Saskatchewan, Medi Plus, GPRD (''VAMP''), etc.)	3	13	2	6	2	7	0	2
14. One or More National or Regional Governmental Prescription Data Sources (e.g., UK Prescription Pricing Authority; Apoteksbolaget, (National Corporation of Swedish Pharmacies), Linfa AB (Drug Information Inc., Sweden)	3	8	2	2	2	1	1	1
15. Co-prescription data (concomitant drug use) from any source or service	0	4	1	4	1	4	0	0
16. Other (specify)	1	1	1	0	1	1	0	0

C. Exposure Metrics

1. Are you familiar with the WHO-originated concept of Defined Daily Dose (DDD)?

	Yes	No	No response
Company	16	3	0
Regulator	4	0	1

If Yes, do you use DDD routinely in estimating population exposure to any of your drugs?

	Yes	No	No response
Company	7	10	2
Regulator	1	3	1

2. Are you familiar with the term Prescribed Daily Dose (PDD)?

	Yes	No	No response
Company	14	5	0
Regulator	3	1	1

If Yes, do you use PDD routinely in estimating population exposure to any of your drugs?

	Yes	No	No response
Company	3	12	4
Regulator	1	3	1

3. Which of the following types of units do you customarily use to describe marketed drug use? Circle all appropriate answers.

Company	Regulator	
17	4	a. patient-time (e.g. patient-days)
12	3	b. patient-courses or -cycles (e.g., for oral contraceptives)
14	2	c. number of patients treated
8	3	d. number of prescriptions
3	2	e. number of DDD's
2	1	f. number of PDD's
3	0	g. other (specify)

4. When relevant, do you attempt to estimate off-label use?

	Yes	No	No response
Company	5	12	1
Regulator	3	1	1

5. Do you attempt to collect and assess data relevant to overdose?

	Yes	No	No response
Company	12	5	1
Regulator	2	2	1

D. Time Period Covered by Exposure Information

Ideally, exposure data will cover the same period of interest over which adverse experiences (AE) actually occur, i.e., the same start and stop cut-off dates should be used for the "numerator" and the "denominator" (e.g., when preparing a periodic safety update report). In practice, it may be difficult.

Are you generally able to match the AE and exposure periods? Although your answer may depend on the particular source used for denominator data, indicate the best match (narrowest gap).

(check only one of the following)

Company	Regulator	
4	1	Exactly
5	1	Within one month
1	0	Within two months
6	1	Within three months
–	–	Other (specify)*

* **Company comments on other:**

- Varies
- Exposure period coincides with report cycle period, but AE may have had onset date prior to report cycle
- Sales data do not exactly match exposure for semiannual and annual reports. Less problems with 5-year reports.

* **Regulator comment on other:**

- Annual

E. Process for Compiling Exposure Data

1. Who in your organization actually determines/derives the estimated ''denominator'' for marketed drugs for use in clinical safety applications? If more than one answer, please explain.

Company	Regulator	
15	4	Safety/epidemiology staff
7	0	Marketing research staff
1	0	Clinical department
0	0	Biometrics department
–	–	Other (specify)*

* **Company comments on other:**

- Sales staff/network staff
- Product manager in marketing & sales

- Clinical and market research staff. Algorithm.
- Data held by Finance in Kg sold or dose unit sold
- Business information and research
- MR staff provides data from some services (i.e., IMS, etc.)

2. When needed, are you generally able to obtain dissection of exposure data broken down by:

Company	Regulator	Breakdown Category
15	4	Location of use (e.g. country)
8	4	Age
8	4	Sex
9+1*	3	Indication treated
6	4	Specialty of prescriber

* sometimes

Company comments:

- Program is designed to collect by product by month by location
- Only in special cases (from market research)

Regulator comments:

- From survey data & IMS
- US — by region (not valuable)
- On request and as far as the company is able to provide these data

3. If you deal with non-prescription products (OTC), what is your approach to estimating population exposure?

Company	Regulator	
5	2	Same as for prescription products
0	0	Special techniques
–	–	Explain*

* **Company comment:**

- Do not deal

* **Regulator comments:**

- We have no accurate means to estimate OTC pressure
- Survey data

4. This Question Applies Only To Manufacturers

   In most companies, the marketing research departments compile data from sales statistics and other sources (e.g. IMS), mainly for business purposes. How would you describe the relationship between the safety/epidemiology and marketing research operations with regard to provision of needed exposure data?

(check only one of the following)

Company	
5	Regular interaction and consulting
10	Confer only on an ad hoc basis
4	Interaction very infrequent
0	Almost no interaction

F. Circumstances Surrounding the Determination of Exposure Data

Depending on circumstances and your practice, for the submission of a periodic safety report on a marketed drug involving no known major safety (or efficacy) issues, it may be sufficient to provide a gross, overall estimate of the exposed population. However, in the event of a safety problem, for example, it may be necessary or useful to attempt a finer dissection of the data (see items in question B.1., e.g.).

1. Do you draw such a distinction between these two circumstances or do you attempt to obtain detailed breakdowns of exposure data routinely?

	Distinguish	Don't Distinguish
Company	13	6
Regulator	2	1

2. As part of ongoing safety monitoring and assessment, it might be possible to use different levels of exposure data to evaluate various

aspects of a product's safety profile. For each of the following sample "scenarios," indicate whether you routinely perform the indicated assessments, on either a periodic (interval) or cumulative data basis?

a. Examine whether the pattern of ADR reports (type and proportion of ADRs, e.g.), and thus the ADR reporting profile, has changed over defined periods.

	Yes	No	No Response
Company	16	3	0
Regulator	1	2	2

b. Estimate patient exposure as a function of duration of treatment to examine whether there is a pattern related to ADR onset for a specific ADR(s).

	Yes	No	No Response
Company	10	9	0
Regulator	2	1	2

c. Evaluate patient exposure by age and/or gender to determine whether the benefit-risk relationship is different (or has changed) for special populations.

	Yes	No	No Response
Company	7	12	0
Regulator	2	1	2

d. Comparison of use of a drug alone to the drug in combination with specific concomitant therapy in order to evaluate the possibility of drug interactions.

	Yes	No	No Response
Company	11	8	0
Regulator	1	2	2

e. Evaluation of the effectiveness of a label change from one period to another (e.g., as means of assessing whether prescribing practices/patterns have been modified appropriately).

	Yes	No	No Response
Company	8	11	0
Regulator	1	2	2

G. Regulatory Experience with Exposure Data. This Question is to be Answered ONLY BY THE REGULATORY RESPONDENTS.

The purpose of this question is to determine the nature of "denominator" data you receive or obtain yourself and your perspective on the adequacy of those data for pharmacovigilance purposes. It is recognized that the quantity and quality of such data may vary greatly from circumstance to circumstance, even company to company. However, we are interested in your general, overall impressions.

1. In general, how would you describe the type and amount of exposure data you receive in manufacturers' periodic safety reports:

	Excellent	Good	Fair	Poor	No Response
Regulator	0	1	0	3	1

2. In general, how would you describe the manufacturers' use and interpretation of the exposure data they provide.

	Excellent	Good	Fair	Poor	No Response
Regulator	0	1	0	3	1

3. Briefly describe the principle improvements you would like to see in the types, amounts, and uses of exposure data submitted by manufacturers.

Regulator comments:

- Standard format. Breakdown by age, sex, country, dose.

- Some description of user population demographics. Age/gender would be useful. Also, consideration of how a product is used and in what populations, when assessing safety profiles of a drug.
- Additional needs: see last question.
- To be able to get down to deeper levels when indicated.
- The method used should always be explained as required. Data should be more often provided broken by country, sex, age and used in the interpretation of the reported ADR.

4. If you make your own estimations of exposure data, independent of manufacturers, please describe what sources and methods you use for (a) routine, general purposes and (b) for special safety problem situations.

   (a) Routine:

   Regulator comments:

   - Information provided by RAKs only
   - IMS
   - Publications on prescription data from health insurances
   - IMS, NDA, NDTI, PP, RP
   - Survey data — NPHS, IMS

   (b) Special:

   Regulator comments:

   - Ad hoc studies, Industry data
   - Record linked databases. Use of HMO type record link data base to examine prevalence of use of 2 drugs in combination; duration of repeat prescriptions in real word setting — life table — compare to IMS new and useful estimates.
   - IMS

H. Comments

Please provide whatever questions, suggestions and concerns you believe are important in addressing the issue of denominator determination and application. Any special situations for which you have experience would be particularly helpful. For example: exposure data in developing countries; data on drugs that are used in two or more distinct indications or populations (pediatrics vs adults, different dosage forms, etc.); any key publications dealing with this topic. Your comments will be valuable in assisting the CIOMS Working Group to develop practical guidance on this topic.

Company comments:

Additional estimates of exposure should be provided for

- ❏ Known risk populations
- ❏ Children
- ❏ Off-label use

Estimation of denominators remains a challenging area. Any guidance from CIOMS V would be valuable.

In general, it would seem that only Pharmacovigilance is interested in patient denominator data. Other departments request this information from us (although we don't have access to the raw data) to put their data into context (e.g., Press releases). In some commercial therapeutic areas denominator data are estimated for isolated key products but the methods used are based on changing experimental data and the estimates vary accordingly from 6-month period to 6-month period (unsuitable for PSUR estimates). Also the data obtained this way are at significant variance with our estimates using kg sold or unit doses sold.

In our opinion, accurate denominator data are more important for issues arising from specific safety signals than for routine PSURs.

For spontaneous report data the numerator is terrible, but the denominator is clearly worse. The ratio is more often meaningless than of any real value. Please recognize that IMS data does not take into account anything regarding intake of either prescribed or bought medications.

In collaboration with sales and network staff, developed a program that extracts units sold on a monthly basis by code which combines all

formulations of a product and factors in a "constant" to correct for how the raw data are input into a master table. This has worked well and has been executed by safety. We have attempted to build precision into an imprecise measurement!

Recommendations of the CIOMS V group on the possible "best" practice (an algorithmic approach) would be very useful.

Regulator comments:

As regulators we would be interested in the comparison of time periods including trend analysis where appropriate.

Denominator determination is often unique for a specific situation and it is difficult to generalize. In general it should be easier and less expensive to get even basic exposure data.

Relating time windows for ADR and exposure data.

Technical problems in concatenating data.

In-hospital drug use.

There exist multiple sources of marketing data dealing with usage and patterns; these data are not being used by pharmaceutical industry in safety assessment even though it is available.

Appendix 16

Sources of Denominator Data

This Appendix contains selected information on sources of national and international denominator data. In general, these sources represent drug utilization information that has been compiled using consistent methodology and on a continuous basis. Continuity and consistency of methodology allow wide international comparisons of drug utilization.

Contact information for some major sources of denominator data:[1]

Apoteksbolaget
131 88 Stockholm
Sweden
Phone: + 08-466 10 00
Fax: + 08-466 15 15

General Practice Research Database
Freepost, LON 10978
London
SW8 5YY
United Kingdom
Phone: +44 (0)20 7273 0206
Fax: +44 (0)20 7273 0041

Health Information Designs, Inc.
1550 Pumphrey Ave.
Auburn, AL 36832
Phone Us: (334) 502-3262
Fax Us: (334) 502-6589
http://www.hidinc.com/ext_home.php3

IMS Health — Europe & World-Wide
IMS Global Services
7 Harewood Avenue
London, NW1 6JB
UK
Phone: +44 (0)171 393 5757
Fax: +44 (0)171 393 5900

IMS Health — Japan/Pacific Rim
IMS Global Services
Aobadia Hills
7-7, Aobadai 4-chrome
Meguro-ku
Tokyo 153
Japan
Phone: +81 (0)3 3481 3586
Fax: +81 (0)3 3481 3590

[1] For an extensive inventory and description of many clinical data bases that can provide good, detailed denominator data, see *BRIDGE On-Line* (Benefit and Risk Information for Drug Evaluations). Information regarding its availability and use can be found at www.dgi.org. Or you may inquire by phone (U.S., 703-276-0056).

IMS Health — United States
660 W. Germantown Pike
Plymouth Meeting, PA USA 19462
Phone: +(800) 523-5333

Medical Products Agency (Sweden)
Box 26, Husargatan 8
S-751 03 Uppsala
Sweden
Phone: +46 18 17 46 00
Fax: +46 18 54 85 66

National Data Corporation (NDC)
Health Information Services
National Data Plaza
Atlanta, GA 30329-2020
Phone: 215-860-4920
http://www.simatics.com/
businesssolutions/marketresearch.asp

Prescription Pricing Authority (UK)[2]
Bridge House
152 Pilgrim Street
Newcastle upon Tyne
England
NE1 6SN
Phone: +0191 232 5371
Fax: +0191 232 248

Saskatchewan Health Research Services
Epidemiology, Research,
& Evaluation Unit
Population Health Branch
1st Floor East, 3475 Albert Street
REGINA, Saskatchewan
CANADA S4S 6X6
Phone.: +(306) 787-2923
Fax: +(306) 787-2936

Swedish Centre for Epidemiology
The National Board of Health and
Welfare
S-106 30 Stockholm
Sweden
Phone: + 46 8 783 3000
Fax: + 46 8 783 3327

Synergy
Quintiles Transnational Corp.
1050 Winter Street, Suite 3200
Waltham, MA, USA 02451
Phone: +(781) 890-1717
Fax: +(781) 890-1818

[2] This is but one example of prescription-related databases managed by national health services in many countries, especially in Europe. The data are available from the similar pricing authorities (e.g., in Nordic/Scandinavian countries).

Selected examples of denominator data sources, with brief descriptions:

Health Information Designs, Inc. — Serves ten US state Medicaid programs and several national healthcare management companies; currently covers over five million lives under various drug review programs.

IMS Hospital Audits — estimated national consumption of pharmaceutical products within hospitals in some 40 countries, providing cash and units.

IMS Medical Dynamics (formerly IMS Medical Audits) — tracks country-specific prescriptions by diagnosis. Covers Argentina, Brazil, Canada, France, Germany, Italy, Japan, Mexico, Spain, UK, USA., which together represent over 75% of all prescriptions written.

IMS MIDAS — electronic database of summary cash (sales) data and treatment units in over 60 countries. Facilitates analysis across countries using international linkages for pharmacologically active substance, brand names, manufacturers, and the ATC (Anatomical Therapeutic Chemical) classification. Standard units sold for each dosage form are derived.

IMS Medical MIDAS — electronic database of medical audit data from over 40 countries that links information on diagnosis to prescribing (treatment). Data from major countries with greater detail on patient demographics, physician specialty, treatment regimens, and costs. In the US, this service is referred to as NDTI (National Disease and Therapeutic Index).

IMS National Prescription Audit Plus (NPA Plus) — audits and tracks data on dispensed prescriptions from retail pharmacies, mail order sales, and long-term care facilities, projected to the national level. It covers the rate at which drugs move from these facilities/pharmacies to consumers. Among other information, it provides data on average daily consumption, days of therapy, and prescription substitution.

IMS Pharmacy Cash Audits — tracks prescription and OTC drug sales to pharmacies by country in the local currency (usually converted to dollars).

IMS Xponent — is a service that monitors prescription activity in the retail and mail order segment in the United States. Xponent links and projects prescriptions for over 700,000 prescribers each month (prescriber level data). Available information: NDC code, quantity dispensed, days of supply, payment type, etc). Aggregate data provide geographic patterns of prescribing.

IMS Xtrend — data from Europe only, on doctor-based prescribing activity in great detail used for targeting, profiling, competitive analysis, etc; covers brand, generic, and parallel import prescriptions.

NDC Health Information Services (Phoenix, Arizona, USA) — formerly known variously as PDS (Prescription Data Services), Walsh America, and Source Informatics. Provides prescription data from 36,000 US retail pharmacies. Includes dispensing data, NDC code, quantity, pay method (cash, third party, etc.), a link between prescription and prescriber (specialty, etc.), encrypted patient identifier to follow for drug use (e.g., compliance).

Sergeant System — software that enables the user to manipulate IMS Health data to analyze parameters such as market rank, share, and growth. Allows subscribers to customize and conduct their own breakdown and analysis of IMS data.

DataView — software similar to Sergeant that supports analysis of IMS Health data, but with greater analytical flexibility than the Sergeant system. ViewPlus — software that enables web-based distribution of IMS Health information.

General Practice Research Database (GPRD; formerly the VAMP database) — a large computerized database of anonymized longitudinal patient records from general practice in the United Kingdom, containing more than 30 million patient years of data from 2.1 million patients (1987-1999). The GPRD is the largest database on general practice morbidity and prescribing in England and contains data from 1987 up to the present. In 1994 covered 5.6% of the population of England and Wales. The GPRD records all prescriptions events, significant morbidity and, important consultation outcomes. Participating practices follow agreed guidelines for the recording of clinical data and submit anonymized information on physician-diagnosed illness, prescriptions and out-patient referrals for each patient in the database. The data are available for research uses approved by an independent Scientific and Ethical Advisory Group (SEAG) established by the Department of Health.

Rx Market Monitor (Synergy, Waltham, Massachusetts, USA) — a web-based, interactive tool that can display aggregated patient trends, demographics, diagnoses, and disease treatment patterns. The database contains information, including indication-specific use based on medical diagnosis, that is drawn from patient-level medical and pharmacy transactions on prescription drugs in at least 20 therapeutic classes.

Rx Dosage Insight (Synergy, Waltham, Massachusetts, USA) — focuses on detailed dosage dynamics and can provide customized analyses with detailed information on how a drug and its competitors are utilized with respect to dosage and compliance patterns. Users select either ''Prescriptions'' or ''Patients'' as the focus and obtain detailed information on a variety of metrics, including total prescriptions or patients, average days of supply, average quantity dispensed, and average daily dose. In addition, patient-focused information regarding compliance, concomitant prescription drug use, and dose titration are available.

Saskatchewan Health Research Services databases (Saskatchewan Health Research Services, Regina, Saskatchewan, Canada) — a series of highly detailed databases, which are not integrated; considerable linkage and refinement are required for each exposure-outcome study. Specific data elements from various databases can be made available following approval of a written research protocol. Linkable databases include those containing outpatient prescription drug data, hospitalization data, physician services data, cancer registry data and vital statistics.

Source^{TM} Payer Geographic Level (NDC Health Information Services) — provides managed care prescription volume by custom-defined sales areas (territories); links prescriptions from retail pharmacies nationwide (US) to the prescriber.

Examples of sources of denominator data, grouped to indicate whether exposure data can be linked to clinical diagnosis

See footnote 1 for additional collections of data sources and their descriptions.

Not diagnosis-linked (North America)

IMS: National Prescription Audit (NPA) — retail pharmacy sales (dispensed)
IMS: US Pharmaceutical Market Drugstores — retail invoices, 840 pharmacies
IMS: US Pharmaceutical Market Hospitals — invoices, 350 hospitals

Not diagnosis-linked (Europe)

All Nordic countries — national drug sales figures
Apoteksbolaget sales counts
United Kingdom's Prescription Pricing Authority
Drug Data Bank — Spanish National Institute of Health

Diagnosis-linked (North America)

IMS: National Disease and Therapeutic Index (NDTI):
    Rotating sample of office-based physicians; records all patient encounters & drug mentions for 2-day periods, four times per year
Harvard Pilgrim Health Plan (US)
Kaiser Permanente Medical Plan (US)
Group Health Cooperative of Puget Sound (US)
COMPASS (Health Information Designs) — Medicaid population (US)
DURbase II (Health Information Designs) — Medicaid population (US)
Med-MetRx (Health Information Designs) (US)
Saskatchewan Health Research Services databases (Canada)
Rx Market Monitor

Diagnosis-linked (Europe)

Diagnosis and Therapy Survey (Sweden) — similar to NDTI, but cooperative effort:
    Swedish Pharmaceutical Data, Ltd
    National Corporation of Pharmacies (Apoteksbolaget)
    Swedish Medical Association
    National Board of Health and Welfare (Sweden)
    Community of Tierp Project (Sweden)

Appendix 17

Selected Bibliography on Patient Exposure Data

General

Methodological Approaches in Pharmacoepidemiology. ARME-P (Association for Research in Methodology for Pharmacovigilance), Elsevier, Amsterdam, 1993, pp. 51-70. Also published in the Elsevier journal *PostMarketing Surveillance*, Vol. 7, 1993 (journal discontinued but merged with *Pharmacoepidemiology and Drug Safety* in 1994).

Bate, A, M Lindquist, IR Edwards, S Olsson, R Orre, A Lansner, and RM De Freitas. 1998. A Bayesian neural network method for adverse drug reaction signal generation. *European Journal of Clinical Pharmacology*. 54: 315-321.

Edwards, IR, B-E Wiholm, and C Martinez. 1996. Concepts in risk-benefit assessment. *Drug Safety.* 15: 1-7.

Inesta, A. 1992. Drug utilization on community pharmacy. *Journal Clinical Pharmacy Therapeutics.* 17: 353-355.

Serradell, J, DC Bjornson, and AG Hartzema. 1987. Drug utilization study methodologies: National and international perspectives. *Drug Intelligence Clinical Pharmacy,* 21: 994-1001.

Strom, BL (ed). Pharmacoepidemiology, 3rd edition. J Wiley & Sons, 2000.

Van Staa TP, Abenhaim L, Leufkens HGM. Switching patterns of non-steroidal anti-inflammatory drugs. *Journal of pharmacoepidemiology* 1995; 4: 37-47.

West, SL. 1997. A comparison of data sources for drug exposure ascertainment in pharmacoepidemiologic studies with emphasis on self-reported information. *Pharmacoepidemiology & Drug Safety.* 6: 215-218.

Defined Daily Dose Applications

ATC Index with DDD's. *WHO Collaborating Centre for Drug Statistics Methodology,* 1997.

Clarke, KW and D Gray. 1995. The defined daily dose as a tool in pharmacoeconomics. Advantages and limitations. *Pharmacoeconomics.* 7: 280-83.

Guidelines for ATC Classification and DDD Assignment. *WHO Collaborating Centre for Drug Statistics and Methodology,* 1996.

Maxwell, M, D Heaney, JG Howie, and S Noble. 1993. General practice fundholding: Observations on prescribing patterns and costs using the defined daily dose method [published erratum appears in BMJ 1993, 307: 1407]. *British Medical Journal.* 307: 1190-94.

Merlo, J, Wessling, A and Melander, A. 1996. Comparison of dose standard units for dug utilization studies. *European Journal of Clinical Pharmacology,* 50(1-2): 27-30.

Truter, I, IC Wiseman, and TJ Kotze. 1995. The defined daily dose as a measure of drug consumption in South Africa. A preliminary study. *South African Medical Journal.* 86: 675-79.

Wertheimer, AI. 1986. The defined daily dose system (DDD) for drug utilization review. *Hospital Pharmacy.* 21: 233-34, 239-41, 258.

Wessling, A and G Boethius. 1990. Measurement of drug use in a defined population. Evaluation of the defined daily dose (DDD) methodology. *European Journal of Clinical Pharmacology.* 39: 207-10.

Specific Applications

Beghi, E, ML Monticelli, G Monza, A Sessa, M Zarrelli, and The Group for the Study of Epilepsy in General Practice. 1991. Antiepileptic drugs as 'tracers' of disease. A calculation of the prevalence of epilepsy through an analysis of consumption. *Neuroepidemiology.* 10: 33-41.

Benitez, J, AM Puerto, and JA Diaz. 1992. Differences in antidiabetic drug utilization between three different health systems in the same national region. *European Journal Clinical Pharmacology.* 42: 151-54.

Bergman, U G Boman, and B-E Wiholm. 1978. Epidemiology of adverse drug reactions to phenformin and metformin. *British Medical Journal.* 2: 464-466.

Bro, F and CE Mabeck. 1986. Use of antibiotics in general practice in Denmark. Prescribed daily dose, duration of treatment and number of treatments in general practice. *Scandinavian Journal Primary Health Care.* 4: 101-104.

Cohen, R, A Fontbonne, S Weitzman, and E Eschwege. 1990. Estimation of the prevalence of diabetes mellitus in Israel based on hypoglycemic drug supply and consumption. *Diabete Metabolisme.* 16: 59-63.

De Jong van den Berg, LT, PB Van den Berg, FM Haaijer-Ruskamp, MN Dukes, and H Wesseling. 1991. Investigating drug use in pregnancy. Methodological problems and perspectives. *Pharmaceutisch Weekblad Scientific Edition.* 13: 32-38.

Keisu, M, B-E Wiholm, A Ost, and O Mortimer. 1990. Acetazolamide-associated aplastic anaemia. *Journal Internal Medicine.* 228: 627-632.

Keisu, M, B-E Wiholm, and J Palmblad. 1990. Trimethoprim-sulphamethoxazole-associated blood dyscrasias. Ten years' experience of the Swedish spontaneous reporting system. *Journal Internal Medicine.* 228: 153-360.

Lindquist, M and IR Edwards. 1997. Risks of non-sedating antihistamines. *Lancet.* 349-1322.

Tansella, M and R Micciolo. 1992. Trends in the prescription of antidepressants in urban and rural general practices. *Journal Affective Disorders.* 24: 117-25.

The ADR Signals Analysis Project (ASAP). M Lindquist, M Pettersson, IR Edwards, J Sanderson, N Taylor, P Fletcher, J Schou, and FT Frauenfelder. 1996. Omeprazole and visual disorders: Seeing alternatives. *Pharmacoepidemiology and Drug Safety.* 5: 27-32.

The ADR Signals Analysis Project (ASAP). M Lindquist, M Pettersson, IR Edwards, J Sanderson, N Taylor, P Fletcher, J Schou, and R Savage. 1997. How does cystitis affect a comparative risk profile of tiaprofenic acid with other non-steroidal antiinflammatory drugs? An international study based on spontaneous reports and drug usage data. *Pharmacology and Toxicology.* 80: 211-217.

The ADR Signals Analysis Project (ASAP). M Lindquist, M Pettersson, IR Edwards, J Sanderson, N Taylor, P Fletcher, J Schou, and MMS Stahl. 1997. Withdrawal reactions with selective serotonin reuptake inhibitors (SSRIs) as reported to the WHO system. *European Journal of Clinical Pharmacology.* 53: 163-169.

Wiholm B-E, and M Myrhed. 1993. Metformin-associated lactic acidosis in Sweden 1977-1991. *European Journal Clinical Pharmacology.* 44: 589-591.

Begaud, B, Y Moride, and F Haramburu. 1994. Quality improvement and statistical calculations made on spontaneous reports. *Drug Information Journal.* 28: 1187-1195.

Hallas, J and A Nissen. 1994. Individualized drug utilization statistics. Analyzing a population's drug use from the perspective of individual users. *European Journal Clinical Pharmacology.* 47: 367-72.

Kiivet, RA, U Bergman, and F Sjoqvist. 1992. The use of drugs in Estonia compared to the Nordic countries. *European Journal Clinical Pharmacology.* 42: 511-15.

Lee, M-L T and R Lazarus. 1997. Meta-analysis of drug safety data with logistic regression. *Drug Information Journal.* 31: 1189-1193.

McGavock, H, CH Webb, GD Johnston, and E Milligan. 1993. Market penetration of new drugs in one United Kingdom region: Implications for general practitioners and administrators. *British Medical Journal.* 307: 1561.

O'Neill, RT. 1987. Statistical analyses of adverse event data from clinical trials. Special emphasis on serious events. *Drug Information Journal.* 21: 9-20.

O'Neill, RT. 1988. Assessment of safety. In *Biopharmaceutical Statistics for Drug Development,* pp. 543-604. KE Peace (ed), Marcel Dekker (New York).

Temple, R. 1999. Meta-analysis and epidemiologic studies in drug development and postmarketing surveillance. *Journal American Medical Association.* 281: 841-844.

Appendix 18

Information Required for Expedited Individual Case Reporting in the Mid-1980's by Regulatory Authorities of the Federal Republic of Germany (BGA), the United Kingdom (CSM) and the United States of America (FDA)

a) Required by all three regulatory authorities

Patient ''identification,'' sex, weight
Observed unwanted effect, date of onset, outcome
Identification of suspected drug(s)
Drugs given, mode and dates of administration, indication
Name of reporting doctor, address, date of report

b) Required (if available) by only one or two of the three regulatory authorities

Date of birth (BGA, CSM)	Previous tolerance (BGA)
Age (FDA)	Rechallenge results (BGA, FDA)
Race (BGA, FDA)	Past medical history (BGA, FDA)
Height (BGA, FDA)	History of allergy (BGA, FDA)
Occupation (BGA)	Smoking/drinking habits (BGA)
Parity (FDA)	Progress and treatment of observed unwanted effect (BGA)
Month of pregnancy (BGA)	Cause of death (FDA)
Week of pregnancy (FDA)	Date of death (FDA)
Duration of effect (BGA)	Assessment of causality (BGA)
Laboratory tests (FDA)	
Drug brand name (CSM, FDA)	Information about who has been informed (BGA)
Dosage form (BGA)	Whether information may be released (FDA)
Laboratory tests (FDA)	
Duration of treatment (FDA)	Specialty of reporting doctor (BGA)
Prior exposure to suspected drug (BGA, FDA)	Company reporter's signature (BGA, CSM)

Appendix 19

Summary of Regulations for Expedited Reporting as of 2000

This Appendix consists of three different sections as follows:

19A Regulations for Pre-Marketing Expedited Case Reports

19B Post-Marketing Expedited Case Reporting Requirements (excluding European Union Countries)

19C Post-Marketing Expedited Case Reporting Requirements in the European Union

(1) Medicinal Products With National Marketing Authorization Including Mutual Recognition

(2) Expedited Reporting for Suspected Serious ADRs for Centrally (EMEA) Approved Products

For all the tables, the following abbreviations are used:

SUL = serious unexpected local

SUF = serious unexpected foreign

SEL = serious expected local

SEF = serious expected foreign

NUL = non-serious unexpected local

EU = European Union countries

MS = Member State(s) (within the EU)

Non-EU = any country outside the EU

Appendix 19A

Regulations for Pre-Marketing Expedited Case Reports

Country	Requirements
Australia	SUL
Austria	SUL + SEL + new information possibly affecting conduct of local trials
Belgium	None, until marketing application submitted when they require SUL + SUF + SEL + SEF
Brazil	No legal requirements
Brunei	No legal requirements
China	SEL + SUL
Canada	SUL + SUF + SEL if not in IND study
Czech Republic	SUL + animal study updates
Denmark	SUL + SEL by investigator + SUF by company
Estonia	SUL + SEL only if fatal or life threatening
Finland	SUL
France	SUL + SUF + serious events having potential affect on trial design if studies in France
Germany	SUL + SEL + foreign S cases if multinational trials include Germany; SUL + SEL + SUF + SEF after marketing application submitted
Greece	SUL + SEL + NUL + SUF (outside EU)
Hungary	All serious ADEs
Iceland	SUL + SEL + SUF
India	SUL
Ireland	SUL + SEL + SUF (outside Ireland)
Italy	SUL + SUF
Japan	SUL + SEL + SUF; also SEF if fatal or life threatening (Serious includes reports of infection; ''probably not related'' cases should also be reported as though they were suspected cases)

Country	Requirements
Korea	SUL +SUF + SEL + SEF; to use ICH E2A as of 1/2001
Lithuania	SUL (events)
Luxembourg	No apparent legislation
Maylasia	SEL + SUL
Netherlands	SUL + SUF + those of unusually high frequency
New Zealand	SUL + SEL (if require unblinding)
Norway	SUL (investigators) + SUF + SEL (when sufficient information)
Peru	SEL + SUL
Poland	All serious local adverse events
Portugal	SUL + SEL +SUF + SEF if Portuguese centers in study or + SUF if marketing application pending
Romania	SUL + SEL (events)
Singapore	SUL + SEL
Slovakia	SUL (events)
Slovenia	SUL
South Africa	SUL + SEL + NUL + foreign if they have an impact on benefit-risk assessment
Spain	SUL + SEL + SUF + SEF if Spanish Centers in study
Sweden	SUL plus any others if safety issues arise
Switzerland	SUL (Events)
Taiwan	SUL + SUF +SEL + SEF
UK	SUL plus animal reports
US	SUL + SUF
Venezuela	SEL + SUL (SEF + SUF monthly)[1]
Vietnam	No legal requirements

[1] For cases derived from the same study conducted within Venezuela. Will also accept ''moderate'' and non-serious drug related cases within, respectively, 15 and 30 days, but they can be submitted instead with the final study report.

Appendix 19B

Post-Marketing Expedited Case Reporting Requirements (Excluding European Union Countries)

Country	Requirements
Argentina	SUL
Armenia	Not formally required
Australia	SUL plus all other local ''in due course''
Brazil	SUL + SEL
Brunei	No legal requirements
Bulgaria	SUL + SEL
Canada	SUL + SEL + SUF
Chile	No legal requirements but SUL ''recommended''
China	SUL + ''rare'' SEL
Colombia	SUL + NUL[2]
Costa Rica	No legal requirements
Croatia	''Particularly those of a serious nature''
Cuba	No legal requirements
Cyprus	No legal requirements for industry
Czech Republic	SUL
Egypt	Not described
Estonia	''Serious + unexpected'' local
Guatemala	No legal requirements
Hong Kong	No legal requirements
Hungary	SUL + SEL + SUF
Iceland	SUL + SEL + SUF
India	No legal requirements for industry
Indonesia	No legal requirements

[2] Every 6 months first year post-approval, yearly thereafter.

Country	Requirements
Iran	No legal requirements
Israel	All ''unknown'' ADRs post-registration; legislation pending on serious ''known'' ADRs
Japan	SUL + SEL + SUF + NUL including serious infections
Korea	SUL + SEL
Lithuania	''serious and unexpected'' local
Macedonia	No legal requirements
Malaysia	SUL + ''all non-serious local periodically''
Mexico	SEL + SUL
Morocco	Send to the regulators
New Zealand	SUL + SEL + NSUL
Norway	SUL + SEL
Oman	No legal requirements
Pakistan	Not described
Peru	SEL + SUL +NEL + NUL (periodic lists of foreign)
Philippines	''Post marketing surveillance data'' said to be mandatory but agency does not receive individual cases
Poland	SUL + SEL + NUL
Romania	SUL + SEL
Russia	All reactions to newly approved drugs and all serious and unexpected to other drugs
Saudi Arabia	No legal requirements
Singapore	SUL
Slovakia	SUL + SEL
Slovenia	SUL + SEL
South Africa	SUL + SEL + NUL + SUF
Sri Lanka	No information
Switzerland	SUL + SEL + NUL + SUF
Taiwan	SEL + SUL
Tanzania	No legal requirements
Thailand	SEL + SUL
Tunisia	''All cases of ADRs that come to their knowledge''

Country	Requirements
Turkey	No legal requirements
US	SUL + SUF
Venezuela	SEL + SUL + ''moderate'' Local[3]
Vietnam	No legal requirements
Yugoslavia	No mandatory reporting
Zimbabwe	Mandatory for industry ''on demand''

[3] Reports of SEF + SUF on monthly basis; non-serious local cases required monthly also.

APPENDIX 19C

Post-Marketing Expedited Case Reporting Requirements in the European Union

(1) Medicinal Products with National Marketing Authorization Including Mutual Recognition

	Spontaneous			Post-Authorization Studies		
	Within MS	From Other EU	Non-EU	Within MS	From Other EU	Non-EU
Austria	SUL + SEL	SUF	SUF	SUL + SEL	SUF	SUF
Belgium	SUL + SEL	–	SUF	SUL + SEL	–	SUF
Denmark	SUL + SEL	–	SUF	SUL + SEL	*	*
Finland	SUL + SEL	–	SUF	SUL + SEL	–	SUF
France	SUL + SEL	–	SUF	SUL + SEL	*	SUF + SEF*
Germany	SUL + SEL	SUF + SEF	SUF + SEF	SUL + SEL	SUF + SEF	SUF + SEF
Greece	SUL + SEL	–	SUF	SUL + SEL	–	SUF
Italy	SUL + SEL	–	SUF	SUL + SEL	SUF + SEF	–
Ireland	SUL + SEL	–	SUF	SUL + SEL	–	SUF
Luxembourg	SUL + SEL	–	SUF	SUL + SEL	*	SUF + SEF*
Netherlands	SUL + SEL	–	SUF	SUL + SEL	–	SUF
Portugal	SUL + SEL	SUF	SUF	SUL + SEL	SUF	SUF
Spain	SUL + SEL	–	SUF	SUL + SEL	–	SUF
Sweden	SUL + SEL	–	SUF	SUL	*	SUF
UK	SUL + SEL	SUF + SEF	SUF	SUL + SEL	SUF + SEF	SUF + SEF

* Expedited reports are required on cases that might have an impact on a protocol or study design, whether or not active therapy was administered (e.g., an MI during the washout period in a cardiovascular study).

(2) Expedited ADR Reporting for *Suspected Serious ADRs for Centrally Authorized Medicinal Products**

For Spontaneous Reports and Cases from Post-Authorization Studies				
	EU Cases: Where to Report them		**Non-EU Cases: Where to Report them**	
	Unexpected	**Expected**	**Unexpected**	**Expected**
Member States	To MS in which it occurs	To MS in which it occurs	To all MS	Not required
EMEA	–	–	Yes	Not required

* There are no requirements for expedited reporting of suspected non-serious ADRs.

Appendix 20

Existence of PSUR Requirements in 62 Countries as of 2000

[Note: ''Fully Implemented'' indicates that ICH E2C PSURs are required or accepted. In EU countries, for centrally authorized products (EMEA), the PSUR requirement is fully implemented; meaningful differences between the company CCSI and the safety information in the EU SPC must be addressed in a cover letter or addendum. Entries under individual EU Member States in the table refer to national/mutually authorized products.]

Argentina	Not required
Armenia	Not required
Australia	Not required but PSUR format accepted if submitted
Austria	Not required
Belgium	Fully implemented plus conclusion required written in Flemish or French
Brazil	Fully implemented
Bulgaria	Not required
Canada	Under implementation; PSURs on request
Chile	Not required
China	Six-monthly updates of expedited reports
Costa Rica	Not required
Croatia	Implementation in progress
Cuba	Not required
Cyprus	Not required
Czech Republic	Fully implemented
Denmark	Fully implemented
Egypt	No information available
Estonia	Fully implemented
Fiji	No information available
Finland	At time of license renewal
France	Fully implemented plus supplement describing French experience

Germany	Fully implemented including serious and non-serious cases presented in line listings
Greece	Fully implemented
Hungary	Fully implemented
Iceland	Not mentioned
India	Not required
Indonesia	Not required
Iran	Not required
Israel	Not mentioned
Italy	Fully implemented plus local update including PMS recruitment
Japan	Fully implemented (report in Japanese)
Korea	Annual report (reexam. study + S and N spont. repts.)[1]
Lithuania	No information available
Luxembourg	Not clear
Malaysia	Fully implemented
Netherlands	Fully implemented
New Zealand	Will accept ICH PSURs
Norway	Fully implemented
Oman	Not required
Pakistan	No information available
Philippines	Implemented to a major extent
Poland	Foreign ADR reports on a periodic basis
Portugal	Fully implemented
Romania	Implemented to a major extent
Russia	Not referenced
Singapore	Not required but PSURs accepted
Slovak Republic	Fully implemented
South Africa	May be required on an individual drug basis
Sri Lanka	No information available
Sweden	Fully implemented

[1] Vaccine suspected ADR reports required quarterly.

Switzerland	Required until authorities say ''sufficient''
Taiwan	PSUR every 6 months for 7 years (official PMS period)
Tanzania	Implemented to a limited extent
Thailand	Not required
Tunisia	Not required
Turkey	Implemented to a limited extent
UK	Fully implemented (also SAMM guidelines: Safety Assessment of Marketed Medicines, relating to PMS studies)
US	Currently all US ADRs + SUF but ICH PSURs soon[2]
US (vaccines)	Implemented to a small extent
Venezuela	Not mentioned
Vietnam	Not required
Yugoslavia	Implemented to a small extent
Zimbabwe	Not mentioned

[2] Pending official implementation of ICH PSURs, they are accepted by FDA in lieu of the usual NDA periodic report; companies must apply for a waiver to the existing (as of end-2000) regulation.

Index

D

E

F

G

H

I

J

L

M

N

O

P

Q

R

S

T

U

V

W

Adverse Reactions*

There once was a man who had little hair,
He said 'I want something growing up there.'
He called his doctor, 'so hard to reach ya,
Please send a prescription to me for Propecia.'

He was quickly hirsute, it was really pleasant,
But lo and behold he could not be tumescent.
So he called up the doc, 'I'm going to Niagara,
Please fix me up with a dose of Viagra.'

He was back on the scene when a pill he did take,
But he got paraesthesias and a wicked headache.
This was not good, he didn't feel right,
So he took 5 or 6 Motrin, in the heat of the night.

His headache just vanished, he felt good indeed,
Until he developed a gastro-oesophageal bleed.
He called up the doctor, 'I feel like a wreck;'
A prescription was written for some Prilosec.

His stomach felt better, but now something scarier,
Erythema and pruritus; it was urticaria.
He was getting real mad, was his doctor a quack?
His itching resolved with a Medrol Dose Pack.

He got much less itchy, but matter of factly
His face was soon covered with purulent acne.
He called once again, was he going insane?
He called in 'script, so he took Accutane.

His acne abated, his face smooth without doubt,
But his drains got all clogged when his hair all fell out.
We are who we are, so here's my benediction.
You can't change your life with a simple prescription.

James S. Newman
Galveston, Texas, USA

* Reproduced with the permission of the author and the *Journal of the Royal Society of Medicine,* Volume 92, June 1999, p. 327.

CIOMS publications may be obtained directly from CIOMS, c/o World Health Organization, Avenue Appia, 1211 Geneva 27, Switzerland or by e-mail to cioms@who.int

Both CIOMS and WHO publications are distributed by the World Health Organization, Marketing and Dissemination, Avenue Appia, 1211 Geneva 27, Switzerland and are available from booksellers through the network of WHO sales agents. A list of these agents may be obtained from WHO by writing to the above address.

Price: CHF 30.–