Guidelines for Preparing Core Clinical-Safety Information on Drugs

Second Edition

Report of CIOMS Working Groups III and V

Including New Proposals
for Investigator's Brochures

CIOMS
Geneva 1999

Guidelines for Preparing Core Clinical-Safety Information on Drugs

Second Edition

Report of CIOMS Working Groups III and V

Including New Proposals
for Investigator's Brochures

Geneva

ACKNOWLEDGMENTS

The Council for International Organizations of Medical Sciences is greatly indebted to the members of the Working Groups that prepared this second edition of Guidelines for Preparing Core Clinical-Safety Information on Drugs, and to the drug regulatory authorities and pharmaceutical companies they represented, for the efficient and expeditious way in which they brought this project to its successful conclusion. Special thanks are due to the co-chairs, Dr. Win Castle and Dr. Gottfried Kreutz of Working Group III, and Dr. Castle and Dr. Murray Lumpkin of Working Group V, for their capable leadership.

We wish to record our special thanks to Dr. Arnold J. Gordon who compiled and edited the second edition, to Dr. Hugh Tilson for his editorial assistance, and Mrs. Theresa Coughlan for her secretarial support.

DEDICATION

This report is dedicated to the memory of Dr. Susan Wood, former head of pharmacovigilance at the UK Medicines Control Agency, and to the contributions she has made to enhance drug safety monitoring and assessment practices. As a loyal member of the CIOMS Working Groups, she provided valuable insights to their initiatives, including the present report and its predecessor.

ISBN 92 9036 070 4

Printed in Switzerland

Reprinted 2001

TABLE OF CONTENTS

VISION

The CIOMS Working Group III envisioned that all manufacturers of pharmaceutical products will harmonize their practices regarding Company Core Safety Information (CCSI) that their internal, central Company Core Data Sheets for a marketed drug must contain. As introduced by CIOMS Working Group II on periodic safety update reporting, CCSI consists of the minimum essential information that a manufacturer requires to be listed in all countries where the drug is marketed; it excludes extraneous or inadequately substantiated information. It is believed that the principles and guidelines proposed by Working Group III for the inclusion of CCSI in Core datasheets and its modification will lead to application of consistent decision-rules on its content, to the use in common of standard terms and definitions, a standard format for the placing of information in different sections of data sheets, and to adherence to valid criteria for timely and accurate revision.

It is now also proposed that the same basic philosophy and practices be applied to the safety information provided to clinical investigators during a development program. Toward that goal, CIOMS Working Group V in this update of the initial report, has introduced the concept of Development Core Safety Information (DCSI) as a discrete, focussed section of Investigator's Brochures, which would have the same format as, and would evolve into, the CCSI at initial marketing of the product.

The absence of internationally agreed standards for the format and content of information on pharmaceutical products for investigators, prescribers and other healthcare professionals is giving rise to discrepancies and inconsistencies from country to country and manufacturer to manufacturer. Therefore, the Working Groups also envision that national regulatory authorities will harmonize their basic requirements for safety information about medical products to be contained in data sheets and Investigator's Brochures, while it acknowledges the possible need for cultural differences reflected in different forms of medical and legal practice. It is hoped that these proposals will form the basis of such harmonization. Since the standards proposed here would undoubtedly need continuous evaluation, updating and refinement, it is suggested that they be retained as guidelines and not adopted as regulations.

In an increasingly global regulatory and information environment, the Working Group foresees that widespread adoption of its suggestions will be of benefit to all by:

- minimizing confusion among investigators, prescribers and other healthcare professionals due to inconsistencies between the drug-safety information of different countries and manufacturers;
- facilitating access to important information for making rational clinical decisions; and

- eliminating the diversity of national alert/expedited reporting requirements of different regulators, which result from differences in what constitute unexpected ("unlabelled") adverse drug reactions.

Comments are invited and should be sent to Dr. Zbigniew Bankowski, Secretary-General, CIOMS, c/o WHO, Avenue Appia, 1211, Geneva 27, Switzerland

PREFACE

In 1995, the CIOMS Working Group III published its proposals for the international harmonization of practical principles and processes for producing and modifying a pharmaceutical company's core clinical safety information (CCSI) for each of its products[1]. The concept of a Company Core Data Sheet (CCDS) and the Company Core Safety Information it contains originated in the work of CIOMS Working Group II on periodic safety update reports (PSURs)[2] and was elaborated in the CIOMS III report. It was also adopted for use in the ICH guideline on periodic safety reporting for marketed drugs (ICH Topic E2C),[3] which is now making its way into health authority regulations or guidelines.

The present volume, the second edition of the widely read and endorsed CIOMS III report, is made available for two major reasons: (1) to address an important issue left unresolved in the first edition, namely, the need for clinical safety information standards for Investigator's Brochures (IBs) on a drug under development, especially when the same active ingredient is marketed in one or more countries and for which there exists a CCDS/CCSI; and (2) copies of the report are now out of print and due to significant demand, it represents an opportunity to republish the volume and include a few clarifications and pertinent additional points that have arisen since the first edition appeared. It is also worth noting that many of the concepts and practices put forth within CIOMS III are expected to be incorporated within evolving regulatory guidelines on product information ("labeling") standards.

Although most of the regulatory and industry participants in CIOMS III (which met from 1992 through 1994) are the same as those who contributed to this second edition, there were a few changes (see Appendix 2). To ensure continuity with the first edition, the basic structure and content of the original report has been maintained with the following exceptions: the material on Investigator's Brochures has been introduced as a new, separate section (Chapter 8); the Vision, Introduction, Summary of Proposals, and Unresolved Issues chapters, as well as Appendix 2, have been modified to account for the inclusion of the IB proposals; any changes or additions to the original CIOMS III text are identified as such with attribution, as appropriate, to the contributing parties within or outside the present CIOMS Working Group (V).[4]

---

[1] *Guidelines for Preparing Core Clinical-Safety Information on* Drugs. Report of CIOMS Working Group III (1995). 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] *ICH Harmonized Tripartite Guideline. Clinical Safety Data Management: Periodic Safety Update Reports for Marketed* Drugs (November 1996). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, IFPMA, Geneva.

[4] In addition to the work on this report, CIOMS Working Group V is currently addressing many aspects of good clinical safety management practices; its predecessor, CIOMS IV (1994-1997), has recently published proposals on a separate initiative [*Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals*. Report of CIOMS Working Group IV (1998). Council for International Organizations of Medical Sciences, Geneva].

With the addition of the new material, it is believed that the CIOMS III and V proposals provide a framework for development of practical and useful product safety information that begins in the Investigator's Brochure and evolves into the CCSI for a marketed drug.

1. INTRODUCTION

a. Background

One of the key obligations of both manufacturers and health authorities with respect to the regulatory approval of a medicine and its introduction for prescription or non-prescription use is the provision for healthcare professionals of the most relevant and helpful information on the drug's benefits and risks, a statutory requirement linked to a marketing license in most countries. This information is customarily provided in the form of a document variously referred to as a data sheet, product document, product characteristics, product monograph, prescribing information, package insert, and other titles. Such information is subject to change as experience is gained with regard to the balance of risks and benefits associated with the medicine, and data sheets must be altered if and when indicated.

The impetus for convening the CIOMS III Working Group, to deal with the safety aspects of data sheets, came from the CIOMS I and II projects on, respectively, international reporting of adverse drug reactions, and the periodic drug-safety update summaries for marketed products[5]. The concept of a Company Core Data Sheet (CCDS) [see diagram] had been introduced to ensure the availability of a central reference document for manufacturers, and the Company Core Data Sheet has been defined as follows:

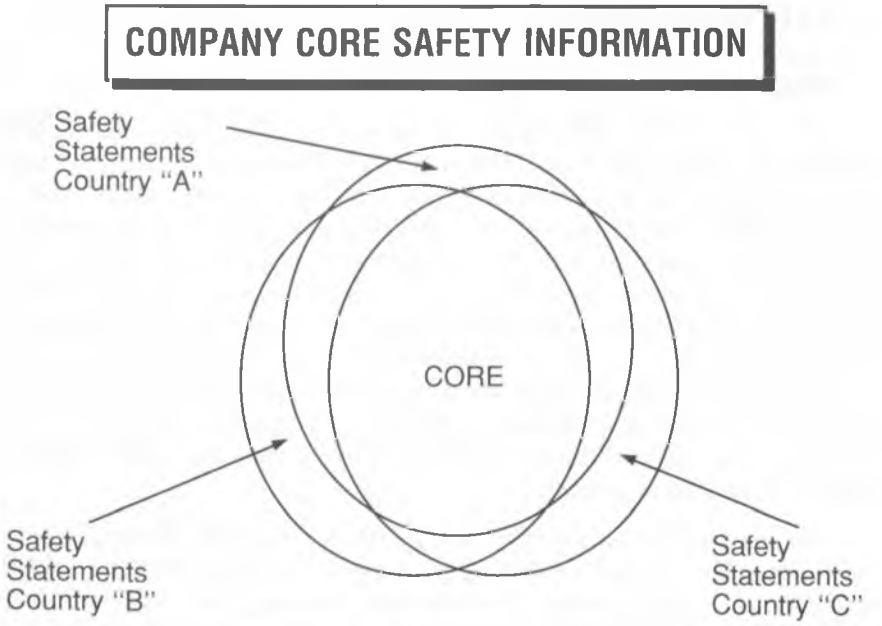
> A document prepared by the pharmaceutical manufacturer, containing [among other things] all relevant safety information, such as adverse drug reactions, which the manufacturer requires to be listed for the drug in all countries where the drug is marketed. It is the reference document by which "labelled" and "unlabelled" are determined [for the purpose of international ADR reporting]...

As shown in the diagram, additional safety information of national or local interest or need may be required beyond the CORE. "Safety information" in this report is used as a collective term covering adverse drug reactions (undesirable effects), warning, precautions, and contra-indications, but also such pharmacodynamic and pharmacokinetic information as has important bearing on the safe use of the medicine.

An exploration of the various approaches of manufacturers to such documents, and a review of the relatively few regulations or guidelines on data sheets in general, showed that no standards existed on important fundamental concepts or criteria regarding the creation or modification of those parts of a data sheet concerned with drug safety. Some of the

---

[5] *International Reporting of Adverse Drug Reactions*: Final Report of CIOMS Working Group (1990) and *International Reporting of Periodic Drug-Safety Update Summaries*: Final Report of CIOMS Working Group II (1992). Council for International Organizations of Medicinal Sciences, Geneva.



more obvious areas in need of international standards are exemplified by the following questions:

- what information should be included (or not included) in the data sheet and how may one decide?
- on what basis and when should changes, including deletions, be made to an established data sheet?
- where in the data sheet should specific types of information be placed?
- how are such commonly but inconsistently used sections of a data sheet as warnings, precautions, contraindications defined and applied?
- is there a standard nomenclature for "frequency" (rare, common, frequent, etc.) and other terms, and are there agreed definitions of such terms?

The absence of agreed standards on these and other topics often leads to significant discrepancies in the content and interpretation of data sheets used in different countries, or prepared by different manufacturers, even for the same medicinal product or class of product. Some local variation in data sheets may be necessary, even for the same product used for the same indications, but to inform physicians and other professionals of important risks, standards must be developed in an increasingly international medical, regulatory and marketing environment.

Thus, CIOMS Working Group III was established to develop proposals for international harmonization of the practical aspects of producing and modifying those components of a company's Core Data Sheet (CCDS) now referred to as Company Core Safety Information (CCSI). It is important to make clear the distinction between a Company Core Data Sheet (and the Company Core Safety Information it contains)

and the "medico-legal" product information or documents (data sheets) covering safety and efficacy which are required or approved by health authorities for use by prescribing physicians, pharmacists and others.

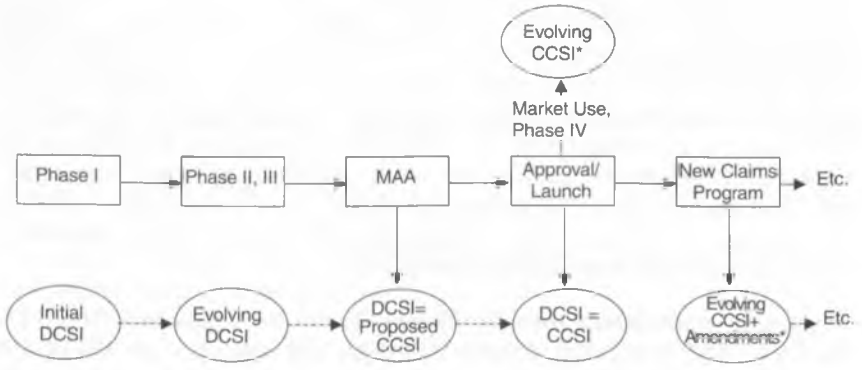
The intent is that the CCDS contain essential or Company Core Safety Information (CCSI) about the clinical safety of the medicinal product, including relevant pharmacological properties and information from non-clinical investigations. All the information must be based on and reflect the proper interpretation of valid scientific or medical data. All the companies represented in the Working Group have some type of international document containing product information that could be considered "Core" of which the CCSI would then be an integrated component.

Such company documents are to be distinguished from the "official" complete data sheets in use for approved medicines and reflected in the documents contained in such volumes as the Association of British Pharmaceutical Industries (ABPI) Data Sheet Compendium in the United Kingdom (with abbreviated versions in the MIMS series), *Farmaceviska Specialiteter I Sverige* (FASS) in Sweden, *Rote Liste* in Germany, Dictionnaire Vidal in France and the *Physician's Desk Reference* (PDR) in the United States. Clearly, it is expected that the safety information contained in the manufacturer's CCDS (an internal document so to speak) will be reflected as closely as possible in the "external" documents, particularly with regard to the more important risk information on an approved medicine. In this way, the necessary information for the safe use and handling of a medicine by prescribers and others will be as complete as possible.

One of the important unresolved and unaddressed topics recognized in the first edition of this report (CIOMS III) was the handling and presentation of clinical safety information for clinical investigators during a development program, whether for a new chemical entity or for new indications, dosage forms, or populations (i.e., new claims) for an already marketed product. This issue is usually covered in a general way under Good Clinical Practice Guidelines, especially with reference to the contents of an Investigator's Brochure. However, the lack of standards in this area creates considerable uncertainty and discrepancies with regard not only to the nature and amount of information for investigators and ethics committees, but also to regulatory safety reporting requirements faced by study sponsors. For these and other reasons, the CIOMS Working Group V, as part of a broader initiative, undertook for this second edition the development of proposals for the creation and use of Development Core Safety Information (DCSI). In general, the same principles and concepts presented through Chapter 7 for a marketed product CCSI apply to the DCSI as well. However, there are special features that require additional consideration, such as the situation when a drug is already on the market (with its CCSI and local data sheet (label)), while under investigation for unapproved claims. Details on the DCSI and its connection to the CCSI are covered in Chapter 8.

The diagram below summarizes the role and evolution of both the DCSI and the CCSI throughout a product's life. The initial DCSI at the beginning of a development program evolves into the proposed CCSI at the time of Marketing Authorization Application (MAA) submission; that document as part of the Investigator's Brochure would then be used for studies underway or begun between the time of MAA submission and approval. Subsequently, the DCSI would be equivalent to the company's CCSI, especially as it evolves with marketing and Phase IV study experience. When a new development program is undertaken with the marketed product, the evolving CCSI would be amended as needed to incorporate any special information pertinent to the new initiative (e.g., relative to a new dosage form or indication).

Role and Evolution of DCSI and CCSI Throughout a Product's Life



* In addition to the CCSI, the Investigator's Brochure would usually contain the local data sheet for the approved product/claim(s) in the country where studies are conducted.

b. Historical Perspective

In spite of the importance of data sheets and their continuous evolution in different parts of the world, there is a surprising paucity of information or literature on their actual utility from the **users'** perspective (what do ***they*** need and want?). Over the past some 25 years, individual critics have expressed dissatisfaction with the lack of consistency between data sheets and their poor quality and presentation with regard to clinically relevant and useful information. It is worth citing some of their points and proposals, which bear directly on the issues addressed by the CIOMS III Working Group.

Klein,[6] a hospital-based psychiatrist, in proposing a radical revision of data sheets, referred to the categorization of adverse reactions with regard

[6] Klein, D.F. What Should the Package Insert Be? *Arch. Gen. Psychiatry*, 31:735-41, 1974.

to importance and frequency as a "hodgepodge that offers no guidance to physicians." LittleJohn,[7] a general practitioner, suggested that doctor's comparisons of frequencies of adverse reactions of different drugs are rendered invalid by the fact that the frequencies are determined in many different ways. Denominators may represent pre-marketing clinical trial experience or may include post-marketing data or there may be lack of control for duration of exposure to the drug. She recommended that quantitation of frequency be limited to serious adverse reactions. Among the various attempts to define frequency terminology, Hollister,[8] as long ago as 1973, suggested a categorization scheme. However, there are still no accepted standards in use.

From the perspective of a physician of a multinational pharmaceutical company with many prior years as a medical practitioner, Graham[9] argued that the data sheet was not a substitute for a textbook of medicine and, by implication, with appropriate exceptions, should not teach diagnosis and management of adverse reactions. He also pointed out important ambiguities in use of the contraindications section in contrast to the warnings section and referred to the difficult decisions on the inclusion of signs and symptoms of adverse experiences rather than, or in addition to, syndromes and diagnoses. For example, most, if not all healthcare professionals are expected to be familiar with anaphylaxis but a diagnosis of neuroleptic malignant syndrome is much less familiar and inclusion of manifestations of the condition may be more informative than the name of the syndrome.

This sampling of critical comments from individual physicians is echoed by some more recent, larger scale reviews. The advisability of establishing international labelling standards among regulatory bodies and industry has been independently raised by the U.S. Office of Technology Assessment. It released a report in May 1993[10] on a study requested by the Congress and begun in 1986 which sought to compare prescribing information contained in data sheets in the U.S., Brazil, Kenya, Panama and Thailand for 241 products sold by nine U.S.-based multi-national pharmaceutical companies. The study, based on data gathered mostly in 1987 and 1988, reported medically important differences between the information contained in U.S. data sheets and that of the other countries and recommended the establishment of international rules for drug "labels." Health Action International,[11] an independent audit group, reported similar findings for European-based companies in four countries and also supported the establishment of national and international labelling standards.

---

[7] LittleJohn, J.K. Package Insert: View of a Rural Town Practitioner. *Drug Information Journal*, 21,:63-5, 1987.

[8] Hollister, L.E. New Ideas About Drug Labels. *Clin. Pharmacol. Therap.*, (3): 309-12, 1973.

[9] Graham, G.K. Labeling: What Should It Say And How Should It Say It?. *Drug Information Journal*, 25: 211-16, 1991.

[10] Drug Labeling in Developing Countries, Office of Technology Assessment Report OTAH464, 102nd Congress of the United States, February, 1993.

[11] HAI to Use OTA Labeling Report, SCRIP, No. 1830, June 18, 1993, p.17.

It is also worth noting that even outside the pharmaceutical arena, the concept of standardized safety information is taking hold. In view of a history of confusing, inconsistent and incomplete safety data on chemicals, U.S. government agencies now require standardized Material Safety Data Sheets (MSDS) developed by the American National Standards Institute and the Chemical Manufacturers Association[12]. In the European Union, there is a directive requiring the provision of data sheets that have to be submitted when a new chemical substance is registered. These data sheets contain information on the trade name, the characteristics and the labelling of the substance, safety measures and measures in case of accidents.

c. Basic Principles

At the outset, the CIOMS III Working Group defined the scope of its intentions and deliberations, indeed its whole approach to safety information in data sheets. The following agreed positions should be borne in mind when reviewing the proposals:

- Company Core Safety Information should be prepared and used to guide the preparation of national data sheets, designed to provide doctors and other healthcare professionals with the most relevant information possible to assist in the selection and use of a medicine.
- The standards developed for preparation and maintenance of CCSI should apply to all manufacturers of prescription and non-prescription medicines.
- While data sheets may have legal implications,[13,14] especially in countries with a culture of litigation, such implications are of secondary importance in providing information to healthcare professionals.
- Marketing considerations should not play a major role in the preparation of the CCSI.
- It is recognized that data sheet sections covering indications, action, dose and information on clinical safety influence one another relative to balance between benefit and risk; however, standard setting for sections not dealing directly with safety information was, for the most part, not included in the work of CIOMS III.
- The mechanisms and timing of distribution to health professionals of modified data sheets that result from changes to the CCSI are outside the scope of CIOMS III proposals.
- Although direct-to-patient information (leaflets, package inserts for patients, etc.) is receiving increasing attention and importance,[15] this topic was considered outside the scope of CIOMS III.

---

[12] Standard on Material Safety Data Sheets Upheld. Chemical and Engineering News. November 15, 1993, p. 51.

[13] Young, A. L. and Rave, N.L. Jr., Product Liability Considerations in Prescription Drug Labeling. Drug Information Journal, 27, 915-20, 1993.

[14] Weber, R.C. Product Liability: Trends Heard Round the World. Pharmaceutical Executive, September 1992, pp. 82-86.

[15] *Improving Patient Information and Education on Medicines*. A report from the International Medical Benefit/Risk Foundation (IMBRF), 12 rue Jean-Calvin, CH1204 Geneva, Switzerland, October 1993.

- Difficult choices arise with regard to the structure and content of data sheets on drugs with multiple formulations (dosage forms; combinations) and uses (indications, populations, routes of administration); this may be associated with differential safety experience. There are no known guidelines available on whether there should be: (a) one basic data sheet with subsections for different formulations/uses, (b) a separate data sheet for each brand or formulation, (c) separate data sheets for different indications associated with different safety data (how different?), or (d) other options. The Working Group did not address this complex issue but expected that the choices would require judgment based on experience with the specific drug and the circumstances.

"Good labeling practices" require flexibility. It is in the spirit of balancing idealism and pragmatism that the Working Group presents these proposals.

The CCSI must be regarded as serving medical, not regulatory or legal, purposes; therefore, the focus for its preparation and use must ultimately be the health professions, primarily doctors and pharmacists, and the goal for its use must be the well-being of the people who take medicines.

d. Objectives and Strategies

The task of the CIOMS Working Group III was, therefore, to develop proposals for standard principles and guidelines addressing the following general aspects which influence the What, When, How and Where of Company Core Safety Information:

- What evidence is needed and how should it be used to influence a decision on whether an adverse experience should be included, excluded or removed from Company Core Safety Information (CCSI)?
- At what point in the accumulation and interpretation of information is the threshold crossed for inclusion or change in a data sheet?
- What "good safety-labelling practices" can be specified regarding judgment of the relevance of information (clinical significance to the prescribers), the use of suitable language (how to say, how not to say things) and such matters as the appropriateness of "class labelling" statements?
- What should the discrete sections containing CCSI be called, how should they be defined and where in the data sheet should specific information be located? As a part of this remit, the general issue of nomenclature and definitions of commonly used terms is addressed.

Although there are many similar data sheet formats in different countries, the Working Group elected to use as its model the Summary of Product Characteristics (SPC), the official document of the European Union (111/9163/90-EN) [see Appendix 1]. It is noteworthy that the CPMP intends to issue a guidance update to the SPC (latest draft as of this report was dated October 1998) that incorporates proposals from the first edition

of this report (CIOMS III). The U.S. requires a similar classification of safety-related product information ("labelling"); a summary of the provisions contained in 21 CRF § 201.56 and § 201.57 is also found in Appendix 1. Specifically, the following headings within SPC section 4 were identified as "safety related" for CIOMS III purposes, but this report also address aspects of section 5, on Pharmacological Properties:

Cross Reference Between Section Headings of the Safety Information discussed in this Report and SPC (Europe) and FDA (U.S.) Specifications

SECTION	SPC	FDA	This Report
Clinical Particulars			
Posology (dosing) and administration	4.2	j	6b
Contraindications	4.3	d	6c
Special warnings and special precautions for use	4.4	e and f	6d
Interactions with other medicaments and other forms of interaction	4.5	f	6e
Pregnancy and lactation	4.6	f	6f
Effects on ability to drive vehicles and operate machinery	4.7	f	6g
Undesirable effects (adverse reactions)	4.8	g	6h plus 3,4 and 5
Overdose	4.9	i	6i
Drug abuse and dependence	—	i	—
Pharmacological Properties	5	b and l	6j
Pharmacodynamic Properties	5.1	b and l	6j
Pharmacokinetic Properties	5.2	b and l	6j
Preclinical safety data	5.3	l	6k

e. Membership and Process of CIOMS Working Group III

The members of the Working Group III were representatives of three United States and five European multi-national pharmaceutical companies; of regulatory authorities in Canada, Denmark, France, Germany, Italy, Sweden, the United Kingdom and the United States of America; of the WHO Collaborating Centre for International Drug Monitoring (Uppsala, Sweden); and, as observers, of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) and the

Bundesverband der Pharmazeutischen Industrie (BPI, Germany). They met as a group on five occasions between April, 1992 and April, 1994, and in special subgroups through August, 1994. CIOMS Working GroupV began its efforts in April, 1997 and completed its work on the DCSI and other updates for the present report in November 1998. Details on membership and procedures are given in Appendix 2.

As is customary in CIOMS Working Group activities, its members from both industry and regulatory authorities worked on studies of actual cases from their personal and institutional experience in order to develop and test the concepts that evolved into the proposals contained in this report. Some of the cases which led to the reasoning behind the proposals made by the Working Group are presented in Appendix 3. Finally, a fictitious, simplified CCSI document is presented to exemplify the general proposals (Appendix 4).

2. GENERAL GUIDELINES

a. The Life Cycle of a Drug and its Company Core Safety Information*

- *All pharmaceutical manufacturers must prepare Company Core Safety Information (CCSI) for each of their marketed products.*
- *The content of the CCSI for marketed products depends partly on the stage of development and the life cycle of a drug.*
- *There are two stages of CCSI, reflecting the life cycle of a marketed drug: the initial CCSI and the evolving CCSI.*

Working Group III agreed at its first meeting that all manufacturers need to provide Company Core Safety Information (CCSI) for each of their marketed products, that the CCSI should serve as the clinical safety reference information for the manufacturer and that its focus must be the essential or "Core" safety information that will permit the intelligent choice and optimum use of a medicinal product by the practicing physician or other healthcare provider anywhere in the world.

The contents of the CCSI depend partly on the stage of development of a drug. The answer to the question of what to include in the CCSI or add to it depends on whether the drug is new (the first CCSI) or already on the market. It also depends on the information. For example (Figure 1), a substantial amount of information on relatively frequent pharmacologically predictable adverse drug reactions (Type A) will usually be known when the initial CCSI is prepared, but the focus of subsequent monitoring efforts shifts towards rarer, unpredictable patient idiosyncratic (Type B) reactions. From a theoretical perspective, the approach

* Topic headings throughout this report are followed by summary proposals (slogans) intended to convey the main message of the text that follows them. All the proposals are collected in one place in Chapter 9.

changes from hypothesis generation during drug development more to hypothesis testing in the post-marketing phase, but there is also a need of methods of generating hypotheses, post-marketing.

The CIOMS III Working Group defined two stages of CCSI in the life cycle of a prescription drug:

- The initial CCSI — that which is prepared in conjunction with the first market authorization submission, review and approval.
- The evolving CCSI — that which is modified as new information accumulates, including the identification of new uses (indications) or treatment populations.

When there is extensive information from broad marketing experience, the CCSI may become stable and consistent ("mature" CCSI), but will always be subject to modification.

When the rationale and experience are sufficient to permit conversion from prescription to over-the-counter (OTC) status, different CCSI, with considerable revision, is needed, but this is beyond the scope of the present work.

The remainder of this section focuses on the general recommendations regarding the initial "Core" safety information and subsequent updates from marketing experience, and additional development of the product. As mentioned, specific considerations regarding Development Core Safety Information (DCSI) for investigators are found in Chapter 8.

To ensure use of consistent terminology, the presence or absence of adverse reaction terms in the CCSI or DCSI should be referred to as "listed" or "unlisted," in line with the recommendation in the ICH guideline (E2C) on periodic safety update reports. Thus, the terms labeled or unlabeled should be reserved for official documents such as SPCs, package inserts or product data sheets.

b. The First CCSI

- *Unless subsequently shown to be misleading or incorrect, the data in the initial CCSI should remain and be updated from additional experience.*

The CCSI at the time of first marketing approval for a drug (in the initial Company Core Data Sheet) will be based on pre-marketing findings from non-clinical and clinical studies. The former include data from pharmacology, standard and reproductive toxicology, teratology and genotoxicity studies as well as from *in vitro* tests. Clinical data originate from: human volunteer (Phase I) studies, which are ordinarily of limited value for Company Core Safety Information in view of the small numbers and short exposure to a new medicine; controlled studies (Phase II) against placebo and/or comparator(s), which generally include homogeneous, carefully selected populations; and Phase III studies which enlarge the nature and size of the safety data base population. However,

most pre-approval studies are neither designed nor powered to detect statistically significant differences in toleration and toxicity from placebo or established therapies. Nor do they help detect possibly rare but serious reactions, most often uncovered through spontaneous case reports from marketing experience, which are not available when the first CCSI is prepared.

However, extensively documented safety information may be available for pharmacologically or chemically related agents on the market; such information may be relevant to "class labelling" statements, as described elsewhere in this report.

Therefore, pivotal, well-controlled clinical studies are the most useful for identifying and evaluating the absolute and relative rates of the more frequent adverse reactions. Proposals are presented elsewhere in this report on how to decide what the CCSI should contain. Generally, the inclusion of an adverse effect in the initial CCSI may be influenced by whether it occurs at a higher rate, or different severity or greater specificity, than that observed or expected from background/placebo experience. It may also depend on pharmacological plausibility and other criteria.

c. Updating the CCSI

- *Important conclusions from special studies aimed primarily at safety evaluation should be cited, whether positive or negative.*

There will always be a need to update the CCSI regularly, on the basis of newly emerging safety information. Once a drug is marketed, there will usually be a continuing programme of post-approval (Phase IV) studies as well as trials in respect of new indications or new populations. There may also be large post-marketing surveillance (PMS) studies aimed primarily at safety evaluation as well as special, smaller studies specifically undertaken to investigate a safety issue, such as a new adverse drug reaction or a drug interaction. Important conclusions from special studies designed to investigate safety issues should be specified, whether positive or negative. This does not mean that the CCSI should contain conclusions of all studies.

With increasing numbers of patients exposed to a drug once it is marketed, and with a drug used in ways and populations different from those used in trials, events that are relatively infrequent or specific to a subgroup of patients are expected to occur. Rare but often quite serious adverse events are most commonly signaled after close scrutiny of spontaneous reports from this broader post-marketing experience. The full evaluation of such signals will often have to be based on observational studies, because randomized clinical trials would take too long and be extremely costly. The optimal study design and method of ascertaining information must be geared to the problem in hand. Therefore, depending on the seriousness of an event and the possible

alternative "treatment" strategies, the CCSI may have to be changed in the absence of extensive or definitive documentation.

d. Different Presentations and Uses of Medicinal Products

- *Information specific to different dosage forms or uses of products should be clearly identified.*

There may be circumstances in which warnings or other safety information apply only to certain formulations or dosage-forms of products or to certain indications or populations. Since a drug may not be marketed in all its dosage forms or for all its uses in all countries, it is important that information related to such variations be clearly identified in the CCSI and other sections of that drug's data sheets. More than one CCSI may be needed for the same active substance, depending on the extent of differences in adverse drug reaction profiles between different products or uses. Case 1 (Appendix 3), which involves a benzodiazepine-antibiotic interaction, illustrates the point. Under such circumstances, care must be taken to include all relevant facts, but reference made from one data sheet to another should avoid the suggestion of promoting, for example, one formulation above another.

e. Excipients and Other Substances

- *Include adverse effects due to excipients.*

All drugs can have pharmacologically active excipients and other materials, such as colouring and flavouring agents. Any adverse effects associated with such materials must be listed in the appropriate section(s) of the CCSI. Often, it is not clear to which excipient an adverse event may be attributable. However, because CCSI is intended to facilitate the safe use of a drug (including its excipients), the relevant safety findings associated with its use should be included, irrespective of attribution to one or more of its components. (see also Hypersensitivity, section 4.i.).

Metabolites or degradation products of the pharmacologically active component or excipients can also be associated with adverse reactions. Any available information on such effects must also be provided.

f. National Differences in Data Sheets

- *National data sheets may contain safety information that differs slightly from the CCSI; particularly they may contain additional information pertinent to a particular country.*

The CCSI forms the basis for the preparation of all official national data sheets, package inserts and product labels and other official statements about the product made by the manufacturer. However, the specific indications, treatment patterns in the country and medical practice and other legal and regulatory considerations may govern the

inclusion of safety information beyond that included in the CCSI; there may also be differences in wording compared to the CCSI.

Thus, in any given country, the official safety information content may be very close to that in the CCSI, but may differ from it. The outcomes of possible national decisions, and their consequences for expedited and periodic safety reporting are depicted in Figure 2, which shows the evolution of the CCSI from the first DCSI (see Chapter 8). Variants include:

- full congruence with CCSI — i.e., the "label" in the country contains information identical to that in the CCSI
- full inclusion of the CCSI plus supplementary comments or mention of additional adverse experiences for which, in the manufacturer's opinion, the relationship has not been sufficiently well substantiated
- less information than in the CCSI.

The last of these variants, in which a national authority is unwilling to accept the manufacturer's minimum Company Core Safety Information and requires selective removal of certain items, is expected to occur rarely.

3. WHAT?

a. Introduction

- *Company Core Safety Information should be determined by the needs of healthcare professionals in the context of a regulatory and legal environment.*
- *Include what is practical and important to enable the prescriber or investigator to balance risks against benefits and to act accordingly.*

The decision to include safety information in the CCSI must in all instances be determined by the usefulness of that information in enabling health professionals to balance risks against benefits in making good therapeutic decisions. In general, the CCSI is not a substitute for a textbook of medicine; it is not intended to direct the practice of medicine. It is intended, rather, to make it possible for pharmaceutical manufacturers to provide practitioners with essential information about the safe administration of a medicine, and when deemed necessary (e.g., because of great importance and for a patient's well-being) to give instruction on clinical precautions or care. Thus, decisions about what to include (and, as addressed below, When, How and Where to include) as safety information are determined by the specific attributes of the medicine, the situations in which it to be used and thus the relevance and usefulness of the information to the prescriber. The CCSI is, of course, not itself a regulatory document, but as the full summary of critical safety information it forms the basis for regulatory discussions.

In its early deliberations, CIOMS Working Group III agreed that the CCSI, directed as it is primarily to supporting communication to the practising physician, should contain "all relevant or essential informa-

tion" for the safe use of the medication. However, on further analysis, several other important dimensions surfaced. What information a physician "requires" is highly dependent on several considerations relating to the drug itself, the availability of alternative therapies and the conditions of treatment. When the Working Group developed a list of rules to guide inclusion of information in the CCSI (see description of process in Appendix 2), no fewer than seven related to the concept of relevance and usefulness.

An individual regulator's requirements are addressed in national labelling or prescribing discussions and are beyond the scope of the CCSI, yet they must be guided by and build upon the "core" embodied in the CCSI (see 2.f., National Differences in Data Sheets). Additionally, inclusion of information for purposes of legal defense should clearly not be the intent of the CCSI. The Working Group emphasized the need to limit inclusions in the CCSI to essential information and developed the concept of "advisability not to warn" (see section 3c.) as a complement to the usual "duty to warn" in the provision of safety information. Ultimately, good medicine and common sense are more important than legal, regulatory or other considerations.

b. What Not to Include

- *Avoid including events, especially minor events, that have had no well-established relationship to therapy.*

The purpose of the CCSI is to provide a summary of information necessary and useful to healthcare providers and patients, its principal ultimate "customers". Thus, one should firmly avoid including information regarding events, especially minor events, that have been incompletely examined or are not considered reasonably associated with therapy. Rare events should not be listed simply because they may have been the subjects of spontaneous adverse drug reaction reports, when such listings will not assist in medical care or awareness for additional case monitoring. There will be situations where the causal relationship of an event to the medicine is unclear; as a general rule, such an event should be included only when, even in the face of such doubt, its inclusion is potentially more valuable for weighing the benefit-risk relationship, or for taking proper action should the event occur, than its exclusion would be (e.g., a very serious, unusual or easily treatable event).

Routine inclusion of an extensive, indiscriminate list of adverse events (e.g., all the events that have been mentioned in trials or spontaneous reports) is ill-advised for several reasons:

- ***Differentiation***: Information included uncritically makes it more difficult to distinguish disease-related events or events that may be related to concomitant therapy from those that are due to the subject drug.
- ***Dilution***: Over-inclusion can obscure or devalue the truly significant adverse experiences, thereby diluting the focus on important safety information.

- ***Mistakes***: By including "unsubstantiated" information, the physician may be led to do the "wrong" thing. For example, inclusion of an incompletely studied or ill-documented weak signal of a possible birth defect could lead to unjustified abortion; overwarning for an important medical product could result in a change to a different medication not carrying the same type of warning, yet be less safe or less effective.
- ***Diversion***: The inclusion of ill-substantiated information may discourage further spontaneous reporting of problems, which might have confirmed or clarified the extent and nature of the adverse event.
- ***Clutter***: Ease of reading and understanding is critical; the fewer words and the less extraneous information the better.

In some countries, full disclosure (of "all" known information) occurs in official data sheets for the legal protection of the marketer. Therefore, one might consider including such a statement as: "The following adverse events have been reported in association with the drug, but a causal relationship has not been established." However, if such a statement were to be used (if permitted) it is recommended that reports of adverse events included under such wording in the CCSI should be considered "unexpected" for purposes of international adverse-event-alert reporting. Case 2 (Appendix 3), which deals with an antibiotic and the possibility of behavioural disturbances, illustrates these points.

The Working Group considered the possible advantages of including special wording relating to adding adverse events in which a causal relationship has not yet been generally or well established. These advantages might include:

- stimulation of additional reports
- alerting physicians to rare but serious events with which a causal relationship to a drug is not established
- clarification of the difference between well-established and less well-established relationships

The possible disadvantages include:

- the company and the regulator should be able to decide and not vacillate
- confusion on the part of prescribers
- difficulty or uncertainty in deciding not only when but also where to include the special wording

After debate, the Working Group proposal was to avoid including in the CCSI events that have no well-established relationship to therapy.

c. Legal Considerations: "Duty to Warn" and Advisability not to Warn

- *There is a legal duty to warn but this must be balanced against the need to include only substantiated conclusions in the CCSI.*

In one form or another, the legal concept of duty to warn is found in many countries, imposing upon a pharmaceutical company the legal duty to warn a physician as a "learned intermediary." Under this

concept, it is the treating physician who must thoroughly consider risks as well as benefits and, depending upon country and culture, as the intermediary between the manufacturer and the patient, "warn" the patient. A company incurs this duty when notified of a real or potential problem in association with the use of its products. It must consider this when deciding the content of, or change in, the CCSI. Thus, there is a temptation to add to the CCSI, erring on the side of inclusion rather than exclusion, to avoid even the appearance, much less the reality, of withholding information necessary for the physician's proper care of the patient. However, the company also has an obligation to maximize the usefulness and accuracy of the CCSI and must prevent the potential adverse consequences associated with a "false alarm" based on information included without good reason or on the basis of unsubstantiated risks.

d. The CCSI and General Medical Knowledge

- *The CCSI should include important information which physicians are not generally expected to know.*

The Working Group agreed that product information should not be used for basic medical training since it is expected that physicians will be properly trained to practice medicine. However, with the advent of a new pharmacological product, it is not reasonable to expect that the physician will know its proper or unique properties and its unique place in medical practice. Thus, the Working Group drew a distinction between education about a specific drug, which could be included in the CCSI where appropriate, and instruction in general medical diagnosis and care, which should not. The following are examples of material which is often appropriate to include in the CCSI:

- Requisite training or experience in the use of a drug (e.g., drugs used as anaesthetics or in cancer chemotherapy). Statements such as "...should be administered under the supervision of a specially qualified physician, experienced in the use of..."
- Need for emergency resuscitative equipment (e.g., for highly allergenic drugs). Such statements as "...serious anaphylactic reactions require immediate emergency treatment with epinephrine, oxygen, etc." should be considered.
- Management of overdose, use of antidotes, or general information (e.g., dialysis or charcoal). Specific antidotes may be stated in generic terms if there is an approved indication for their use.
- Use with another product or during a concurrent medical condition when there may be serious consequences (e.g., drugs for Parkinsonism concomitantly with neuroleptics, or β-blockers in asthmatics).
- Guidance on starting and stopping a medication if there may be safety issues (e.g., problems of addiction, withdrawal or rebound).
- Guidance on adjusting infusion speed or management of tachyphylaxis.

- Any specific need for therapeutic monitoring (e.g., of renal function, therapeutic plasma levels, etc.) or of laboratory monitoring for toxicity.
- Route preference - especially if there are route-specific problems or improper methods of application or administration.
- Danger of exceeding the recommended dose, or escalating the dose, if there is a specific reason for not doing so.
- Early discontinuation at the first sign or emergence of an adverse event that could become more serious with continued exposure.
- Safe handling and administration (e.g., of toxic and irritant compounds).

In general, the Working Group recommended inclusion in the CCSI of information which the treating physician could not reasonably be expected to know routinely, especially when the information relates to relatively dangerous consequences that are preventable or treatable.

e. Lack of Efficacy

- *Lack of efficacy should be considered apart from safety.*

The Working Group agreed unanimously that adverse medical consequences of lack of efficacy should be included but should be distinguished, and included separately, from other safety information. This topic was not discussed in detail.

4. WHEN?

a. Introduction

As soon as relevant safety information becomes sufficiently well established, it should be included in the CCSI.

The Working Group agreed to this principle, while acknowledging the difficulty of specifying when that time is reached. It inevitably varies with each situation. There is a need to achieve a balance between the requirement that associations be well established and the possible need for expeditious action. A manufacturer, on notice of a possibly important reaction, should therefore clarify the situation as quickly as is reasonably possible and decide on an informed basis whether or not to make changes or additions to the CCSI.

An inventory of desired types and sources of evidence needed to establish drug-event associations was developed. The process for doing so and a description of how the relative contribution of each of the components was scored are described in Appendix 2 and in Chapter 4.c. Although there is not a single "correct" method or philosophy for deciding which adverse events/experiences should be listed as adverse drug reactions in the CCSI (or DCSI; see Chapter 8), it is recommended that each company adopt consistent practices across the organization;

some companies have developed Standard Operating Procedures (SOPs) for this purpose.

b. The Concept of Threshold

- *The specific time when safety information must be included in the CCSI is determined by the concept of "threshold."*
- *Safety information will cross the "threshold" for inclusion if it is judged that it will influence physicians' decisions on therapy.*

A decision to include information in the CCSI depends strongly on the quality of the information, the accumulated body of the information, and the strength of the evidence, all of which may lead to the threshold for inclusion. If it is clear that a change will eventually have to be made, the sooner it is made, the better. Safety information accumulates from a series of convergent and supportive (or occasionally conflicting) sources — e.g., from Phase I studies (i.e., in volunteers) as well as from randomized, controlled clinical trials. After initial marketing, additional information may become available from clinical trials with other formulations, groups of patients and indications from large population-based epidemiological studies, and from spontaneous adverse-reaction reports from field experience. While it is recognized that a lack of reports is never a guarantee that there is no problem, for a mature product the absence of new safety-signals becomes, in itself, important.

The specific time when safety information must be included in the CCSI is determined by the concept of "threshold". At a minimum, routine consideration for changes to CCSI should be made on the occasion of the preparation of periodic safety update reports. On balance, for any single item of safety information, the decision to include is governed by certain standard criteria, but the exact decision point depends on circumstances and cannot be precisely defined. Safety information will cross the "threshold" for inclusion sooner if it is judged that it will influence the physician in making decisions about treatment or clinical management.

c. Threshold Criteria and Their Order of Importance

- *It is not possible to specify exactly when an association becomes well established but all relevant factors should be considered.*
- *Relevant factors can be identified and ranked for weighing the evidence for inclusion of new information in the CCSI.*

Working Group III identified 39 relevant factors or criteria that may be useful in determining the threshold for adding an adverse event to the CCSI and ranked them in order of importance. The range of ranking in the appended Table highlights the difficulty of the exercise. The most important criteria included positive rechallenge, a positive outcome in a specifically designed safety study, statistically significant differences (especially in comparison with placebo), recognized effect of overdosage, pharmacokinetic evidence, corroborative evidence from different methods

THRESHOLD CRITERIA GROUPED

I. According to the Source

1a. Evidence from Individual Cases

Positive rechallenge
Definitive [i.e., clearly defined specific case histories]
Time to onset plausible

Positive dechallenges
Lack of confounding factors in the spontaneously reported cases
Amount and duration of exposure plausible [appropriate]
Corroboration of the accuracy of case histories
Cases clear-cut, easily evaluated
Lack of alternative explanation

Co-medication unlikely to play a role
It is reported to occur in such as healthy children, or no other confounding risk factor is present

1b. Evidence from Clinical Trials/Studies

Positive outcome in targeted studies
Statistically significant difference

Corroborative evidence from various studies
Relative increase in frequency over placebo
Evidence from trials rather than spontaneous reports
Evidence from observational PMS studies

Consistent trend in studies

Studies are well-designed
Although there is no other corroborative evidence, there is no contrary evidence
Positive dose response

II. Supportive Evidence for Both the Above Sources

Consistency of pattern of presenting symptoms
Consistency of time to onset

Identifiable subgroup at risk

High frequency of reported cases

III. Previous Knowledge of the Adverse Event or the Drug/Class, Including the Metabolites

Recognized consequence of overdosage
Pharmacokinetic evidence [interactions]
Known mechanism

Recognized class effect

Similar findings in animal models
Closeness of drug characteristics to those of other drugs known to cause ADR

Similar reactions already recognized

Biological plausibility

Event in normal clinical practice is usually drug-related
Drug known to affect same body system in some other way
Low background incidence of event
Positive specific laboratory or *in vitro* test

IV. Other Factors

Considered drug-related by those reporting the cases
The data are objective rather than subjective

Outside turbulence (publicity) surrounding drug
Status/credibility of reporter

of investigation, or a known mechanism. The most useful categories or sources of evidence are from controlled clinical trials, knowledge of the class of drug, and the strengths of association within cases. Although many of the criteria (factors) contributing to strength of evidence are often associated with traditional causality assessment of individual case-reports, it is the application of all the relevant factors shown by the collective evidence that helps determine the threshold for inclusion.[16]

Some of the 39 factors, plus an additional two identified by the Working Group after the ranking exercise, are related to evaluating more frequent and dose-related adverse reactions which are more likely to emerge in clinical trial data, and some are more relevant to evaluating rarer and idiosyncratic reactions from spontaneously reported cases. As shown below, all 41 factors can be usefully divided into categories according to, first, the source of the data (spontaneous reports or clinical trials); second, supportive evidence for both sources, such as consistency among cases; third, supplementary information such as previous knowledge of the adverse event; and other factors.

It is interesting to note that an independent survey using the same 39 criteria initially identified by the CIOMS III Working Group has been conducted with drug safety, clinical research, legal, and marketing staff of a large pharmaceutical company, which showed a very high correlation ($r = 0.79$) with the results of the CIOMS Group's ranking.[17]

d. The Importance of Well-Documented Cases

- *It is difficult to interpret spontaneous reports of poorly researched and inadequately described cases.*
- *The status of the reporters and their attribution of causality to individual cases are less important than other factors.*

The previous sections highlight the importance of detailed and well-researched information such as positive rechallenge, definitively defined case histories, consistent patterns of symptoms between patients, and consistency of time to onset. Conversely, it is always difficult to interpret spontaneous reports of poorly researched and inadequately described and documented cases. Therefore, it is important that prescriber's spontaneous case-reports be as full and accurate as possible. Well investigated, definitive cases are relatively rarely available from spontaneous reporting, but well-documented case-histories are invaluable for deciding whether and when to add an adverse drug reaction to the CCSI.

---

[16] For results of a survey on the use of causality assessments for data sheet (labeling) changes, see Stephens, M.D.B.. From Causality Assessment to Product Labeling, Drug Information Journal, 31, 849-856, 1997.

[17] Cobert, B.L. The CIOMS III Criteria for Labeling Changes: A Survey at Schering-Plough, *Drug Information Journal*, 32, 1149-1151, 1998.

The Working Group ranked very low the cases judged by reporters as "probably due to the drug" (ranked 30 in Table 1) and cases whose validity depended mainly on reporters considered to be of high status or credibility (ranked 38).

As suggested by a reader of the first edition, there is a related consideration with regard to the medical specialty of the reporter. For example, the quality and completeness of a psychiatrist's report on a potentially complicated cardiovascular adverse event associated with administration of an antidepressant are unlikely to be as good as if the case were described by an internist or cardiologist.

e. The Threshold and Clinical Utility

- *The more the applicability and usefulness of new safety information, the sooner it should be included — i.e., the lower the threshold.*

In general, information should be added to the CCSI whenever it is likely to help the physician make a differential diagnosis related to an adverse event, spare extra tests, lead to the use of a specific targeted test, and facilitate early recognition of an event. This means that the decision when to include should take into account the potential clinical consequences of the information.

f. Considerations of Seriousness of an Adverse Drug Reaction

- *Lower the threshold and add the information earlier if an ADR is medically serious or irreversible.*

If a reaction is medically serious — for instance, life-threatening — one should be prepared to include it at a lower threshold of evidence. Thus, if the cases are well documented and the condition is serious, there need not be many before it is included.

It is also important to add information early if there is a possibility that the event represents a mild form of a potentially more serious problem (for example, erythema multiforme), or in the case of reports of serious, life-threatening events in patients who tend to have no known risk factors other than drug exposure (for example, in children).

There may also be events that are not considered serious in the regulatory or medical sense that deserve consideration for earlier addition (lower threshold) to the CCSI if they might be especially important to patients, such as hair loss; this new point was suggested by a member of CIOMS Working Group V.

g. Availability of Other Treatments

- *Add the information especially early if good alternative drugs are available.*

Case 3 (Drug A and hypoglycaemia) presented in Appendix 3 emphasizes the need to add information to the Company Core Data Sheet especially early if good alternative drugs are available. Also, if the alternative drugs differ significantly in their safety, the CCSI must reflect this to allow prescribers to differentiate between them and so influence their prescribing. Controlled comparative trials would normally be the source of this information and their results could be summarized in the CCSI.

h. Role of Indication for Treatment and Extent of Use

- *The threshold should be lower if the condition being treated is relatively trivial, or the drug is being used to prevent rather than treat a disease, or the drug is widely used.*

Although it is important to update the CCSI whenever an association is well established, any adverse reactions to drugs commonly used for relatively trivial conditions or for symptomatic treatment should be included particularly early. Likewise, for drugs indicated for the prevention of disease, the threshold for inclusion of adverse reactions should be lower.

Although the number of reports received through spontaneous ADR reporting schemes usually depends on the number of patients exposed, this relationship usually fails for older and over-the-counter medicines. Hence, whenever sporadic but serious adverse reactions are reported they should not be dismissed purely because of extensive use (low reporting rate). Instead, even if the event is not totally confirmed as an ADR, there may be a need to lower the threshold for inclusion in the CCSI because of the implications for the patient population.

The benefit-to-risk balance should always be reassessed as new information becomes available; this is particularly true for medicines used widely in otherwise normal individuals, such as over-the-counter or preventive medicines (e.g., vaccines). Widely used over-the-counter medicines, in particular, need proper elucidation of the frequency of ADRs of concern. Very rare but very serious ADRs may signify the need for reconsideration of a medicine's over-the-counter status or may lead to other action, e.g., limitation of pack size or specification of maximum dosage.

i. When to Add Hypersensitivity Reactions

- *It is important to add hypersensitivity reactions early to avoid re-exposure. If an excipient could be the cause, investigate, but until the excipient is removed, add information to the CCSI.*

If the evidence is sufficient to characterize them as such, it is important to add hypersensitivity reactions as early as possible so as to prevent re-exposure. There is often little doubt about causality when the adverse

event occurs immediately and is clinically identifiable as hypersensitivity, particularly if only one drug was given in the relevant time-frame. One well-described patient-case may be sufficient to drive inclusion of such an allergic reaction, because in such cases numbers are less important than how complete and compelling the case details are. It should be remembered that dose relationship is of minimal importance in evaluating hypersensitivity reactions.

If an excipient of a marketed drug could be the cause, investigate, but until that excipient is removed from the product it is necessary to describe the problem in the CCSI.

Hypersensitivity to any ingredient or component should constitute a standard Contraindication or at least a Warning. It seems appropriate to have standardized wording for all hypersensitivity reactions, such as: "the drug is contraindicated in patients who have shown hypersensitivity to any of its components."

j. When to Delete or Downgrade Safety Information

- *Substantial evidence is required to remove or downgrade safety information.*

As products mature and more experience is gained from broader use, results of further clinical trials, epidemiological studies, and laboratory analyses emerge. Associations which were felt necessary to include early because of their possible importance in medical practice may not be supported or may even be shown to be incorrect. The body of evidence to remove information from the CCSI would at least include failure to substantiate the information in probably two subsequent, well-controlled, randomized trials of sufficient power to detect a clinically meaningful difference or association, or in a large epidemiological study. Failure to record an event in a large body of spontaneous reports during extensive and long-term clinical use, or from laboratory, pharmacological or toxicological investigation, would rarely suffice to disprove a suggested association. In reality, strong negative evidence is likely to be required from all possible sources. This may be especially true when the issue involves the Contraindication, Warnings or Precaution sections of the CCSI.

Removal of a warning in the CCSI, although not frequent, does occur. One example is the lens-opacity warning which was removed from the lovastatin product-information after two targeted randomized placebo-controlled clinical trials with sufficient power to detect small differences provided strong evidence against an association.

Rarely, a cautionary statement may be downgraded, e.g., by changing a Contraindication to a Warning.

5. HOW? — GOOD SAFETY INFORMATION PRACTICES

a. General Formatting Principles

There are two general principles:

- *Keep ADRs identified in the initial CCSI separate from those identified subsequently.*
- *ADRs should be listed by frequency in body system order.*

Adverse drug reactions coming to light after marketing should be listed separately from those discovered during pre-marketing clinical studies (i.e., in the initial CCSI).

Adverse drug reactions should be listed preferably by body system and in order of decreasing frequency. If of the same frequency, they should be listed by seriousness or clinical importance.

b. Class Labelling

- *Although a specific "class label" section of CCSI is not recommended, the CCSI may contain statements relative to classes of drugs.*

Often adverse experiences are known to occur in similar drugs of the same "class" of chemical or pharmacological agent. If the effects are substantial, such information may help alert physicians to such ADRs. However, unless an ADR has been associated with and is included in the CCSI for a drug, it is still regarded as "unexpected" (unlisted), irrespective of any "class labelling".

If drugs in a defined class have the same tendency to cause particular adverse reactions, then the class statement should be uniform for each drug. Where possible, therefore, known reactions to drugs of the same class should have the same statements in all CCSI, within and among companies. In practice, any class effect statements that appear in official labeling (data sheets) will no doubt be decided with the cooperation of the authorities, who are expected to ensure uniformity among different companies' labeling. The class effect should be incorporated for all drugs in the class unless there is specific evidence for excluding a particular drug.

The Working Group agreed that there was a need to establish logical rules for defining classes of drugs, such as non-steroidal anti-inflammatory drugs (NSAIDS).

As already discussed, the threshold should also be lower for inclusion of ADRs in the CCSI of a new drug if there is already a known and important class-effect.

c. Format of Initial Company Core Safety Information (CCSI)

- *The initial CCSI should include information derived from pre-marketing clinical trials.*

As previously noted, the primary focus of the CCSI should be the description of **adverse reactions**. However, the Working Group felt that it could be useful to include a tabulation of the most frequently reported **adverse events** by drug compared with placebo. Such a tabulation could put into perspective for the health professional the occurrence during treatment of events that have a high background incidence. If such a tabulation were included, it would, of course, be important to describe adequately the dosage and duration of therapy for the included population, as well as any other pertinent characteristics (e.g., age/sex distribution; indication, if more than one).

Tests of statistical significance alone cannot suffice for inclusion of ADRs. There is also possibly some value in tabulating or presenting common adverse events for placebo as it may help a practising physician decide on the likelihood that an event may be drug-related in a particular patient. However, the CCSI must not contain lengthy lists. On balance, it was felt that only the most important information from core pivotal studies should be presented clearly and concisely. Tabulation may thus be useful.

Since the purpose of a table would be to show relative rates of occurrence of events, and since methods of assigning drug-relatedness vary, the tabulation should include incidence rates of the most frequent adverse events, whether or not categorized as "possibly drug related." Generally, the cut-off for inclusion would be 1% or greater. However, it is recognized that, especially for studies of long duration, it may be appropriate to use a higher cut-off value — e.g., 2% or 5%.

Since clinical trials rarely have sufficient power to detect infrequent ADRs or to detect moderate differences between treatments, statistical significance should not be a prerequisite for inclusion. While it may be useful to include confidence intervals or cite statistical significance, it is important to remember that especially when comparisons of adverse experiences entail multiple comparisons, statistical significance may occur by chance alone.

The following example is provided as guidance. Of course such summary statistics combine data from many different studies in which the comparative treatment(s) are not always the same; such data should be regarded, therefore, as overall observations and should be interpreted as such:

Adverse experiences reported among patients treated with PRODUCT during controlled clinical trials are shown in the table below. Included are all adverse experiences occurring with an incidence of 1% or greater in any treatment group. A dash represents an incidence of less than 1%. Note that entry in such a table does not necessarily mean that the adverse experiences are ADRs. Unless they also appear in the list of attributable undesired effects/adverse reactions, they would normally be considered unlisted.

	PRODUCT (N = 600) %	Placebo (N = 80) %	Control 1 (N = 90) %	Control 2 (N = 100) %
Gastrointestinal				
constipation	6.9	—	34.1	2.1
diarrhoea	6.5	4.9	8.0	10.3
dyspepsia	5.9	—	13.6	3.1
flatus	5.4	2.4	21.6	2.1
abdominal pain	4.7	2.4	5.7	5.2
heartburn	4.6	—	8.0	—
nausea	2.7	3.7	9.1	6.2
Musculoskeletal				
myalgia	3.1	1.2	1.1	—
Nervous System				
dizziness	1.3	1.2	—	1.0
headache	—	—	1.5	1.2
Skin				
rash	5.2	—	4.5	—

Whether or not a tabulation of adverse events is included in the CCSI, any adverse event (AE) considered as an adverse reaction (ADR) identified during pre-marketing studies should be included regardless of frequency, according to the threshold criteria described earlier.

d. Frequency of Adverse Drug Reactions

- *Whenever possible, an estimate of frequency should be provided, expressed in a standard category of frequency.*

It is always difficult to estimate incidence on the basis of spontaneous reports, owing to the uncertainties inherent in estimating both the denominator and the numerator (e.g., degree of under-reporting). However, the Working Group felt that, whenever possible, an estimate of frequency should be provided and in a standard way. The following standard categories of frequency are recommended:

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

* Optional categories.

Precise rates will inevitably be based on studies and limited to the more common reactions. For reactions that are less frequent than "common," estimates of frequency will inevitably be based on spontaneous reports or on very large post-marketing studies or other special studies, and the numbers will not be precise; therefore, the source of the estimates (spontaneous or clinical trial) should be indicated and it must be recognized that when the estimate is derived mainly from spontaneous reports, the statistics represent *reporting* rates. Stating the absolute numbers of cases reported may be misleading since they inevitably will become outdated.

e. Good Safety Information: Ten General Principles

As Working Group III discussed the sample case histories and formulated its proposals, it developed ten general principles governing the overall content of CCSI and the use of suitable language.

- *In general, statements that an adverse reaction does not occur or has not yet been reported, should not be made.*
  If an adverse effect is predictable pharmacologically or has been observed with other drugs in the same class it may be mentioned, even if it has not occurred despite extensive exposure in a susceptible population. In general, however, statements that an adverse reaction does not occur or has not yet been reported could be misleading and should be avoided. Often there has been inadequate exposure on which to base a decision.
- *As a general rule, clinical descriptions of specific cases should not be part of the CCSI.*
  Even though a single case report of high quality may carry more weight than many of poorer quality, it is usually not appropriate to include in the CCSI clinical descriptions of specific cases.
- *If the mechanism of a reaction is known, it should be stated, but speculation about the mechanism should be avoided.*
  If the mechanism of a reaction is known, it should be described as it could alert prescribers to identify other related reactions. If unknown, speculation about a possible mechanism should be avoided. In addition, care should be taken not to use terms that imply that the pathophysiology is known unless it is known. For example, reports of pancytopenia should not be listed as bone-marrow suppression unless there is a biopsy-proven diagnosis and the mechanism is known.
- *As a general rule, secondary effects or sequelae should not be listed.*
  It is not the purpose of the CCSI to state general medical knowledge. There are, however, special circumstances in which secondary effects may be included, such as: (1) the secondary effect may be unusual in some way (for example, there may be an increased likelihood of a fatal outcome); (2) the secondary effect may be the presenting or identifiable event and may, therefore, lead to an earlier diagnosis and influence the action taken by the physician.

- *In general, a description of events expected as a result of the progression of the underlying treated disease should not be included in the CCSI.*
  Although it is important to take into account the underlying indication for treatment as a possible confounder in the assessment of possible adverse drug reactions, it is generally not advisable to include in the CCSI a description of the events expected as a result of the progression of the disease. In special circumstances, e.g., treatment of AIDS, a warning that the drug is not a cure and that the disease may progress despite the treatment may be included. However, if a statement on lack of efficacy is needed, it should be in the efficacy section. If the drug treatment could worsen the underlying condition, this should be included in the CCSI.
- *Unlicensed or "off-label" use should be mentioned only in the context of a medically important safety problem.*
  If there is an adverse reaction which occurs only when the drug is prescribed outside of the approved, recommended use, and if it is serious or otherwise medically important, such information should be included in the CCSI and the associated off-label use should be specified. However, care should be taken to avoid indirect support of unlicensed use or an implication that these are the only risks associated with such use.
- *The wording used in the CCSI to describe adverse reactions should be chosen carefully and responsibly to maximize the prescriber's understanding. For example, if the ADR is part of a syndrome, this should be made clear.*
  It is important that the information provided, while specific, is not so detailed that the main point may be missed. The presentation of the information should help the prescriber to identify the most important issues, e.g., by structuring of the text with the use of sub-headings, bold print, italics, etc. If the ADR is part of a syndrome (e.g., arthritis as a part of serum sickness) this should be made clear and care should be taken to place the information under the appropriate body system(s) (a syndrome may affect different body systems). While specific recommendations on medical terminology were beyond the scope of the Working Groups, it was agreed that terms should be used consistently and in line with recognized standards of diagnosis [18]. Terminology should reflect careful evaluation by the manufacturer and not merely verbatim quotation from spontaneous reports.
- *The terms used should be specific and medically informative.*
  For example, if a drug may cause hallucinations, use of the term "CNS symptoms" is too vague to be of any value to the prescriber. Use of the term "hallucinations" is more informative and thus more helpful. However, if too many terms are included in the CCSI, doctors may not read them. Hence, similar terms (e.g., decreased white-blood-cell

[18] Venulet, J and Bankowski, Z. Harmonizing Adverse Drug Reaction Terminology. *Drug Safety*, 19(3):165-172, 1998.

count, neutropenia, leukopenia) may be condensed into "leukopenia," and related terms should be used individually but grouped together (e.g., nausea, vomiting and diarrhoea).

- *The use of modifiers or adjectives should be avoided unless they add useful important information.*
  In exceptional circumstances, where the characteristics of an adverse reaction may be remarkable or unusual, modifying adjectives may be used, such as "transient", "irreversible", "asymptomatic", "mild" or "severe", especially if their use may aid in the physician's decision to withdraw or continue treatment. Otherwise, the use of such modifiers should be avoided.
- *A special attribute (e.g., sex, race) known to be associated with an increased risk should be specified.*
  Many biological factors may influence the safety and efficacy of a medicinal product. Insofar as this variability may be related to a specific attribute (e.g., sex, age, race) which could be used to define a sub-population at risk, such information should be presented. A separate section of the CCSI may be used for "special populations," e.g., children or elderly. In the initial CCSI, it is useful to point out that little is known about the safety of the drug in populations in which it has not been widely tested. In subsequent revisions/updates of the CCSI, the manufacturer should amend such a statement to reflect evolving knowledge.

6. WHERE?

a. Introduction

- *Company Core Safety Information is located in different sections of a Company Core Data Sheet but the same information may be repeated in more than one place.*

Company Core Safety Information is located in different sections of a Company Core Data Sheet under separate topic headings for conceptual clarity. The Working Group considered several generally accepted section headings and underscored their inherent similarity to one another. Although the focus here is on the specific safety sections of the Summary of Product Characteristics of the European Union, information on drug safety can appear in many places in a full data sheet depending upon the urgency (e.g., highlighted at the very beginning, which could save a life) and the source (e.g., in the pharmacology section if from animal studies). Also, the same information may be repeated in more than one place. The presentation should reflect the information's importance (italics, bold face, possibly a black box).

b. Posology (Dosing) and Method of Administration

- *Specific medical interventions to prevent problems with administration of drugs should be mentioned in the section: Posology (Dosing) and Method of Administration*

Such interventions include dose titration, methods of terminating treatment, and monitoring advice (e.g., "if the drug is discontinued, the patient should be regularly monitored for clinical evidence of recurrent heart failure..."); also mention should be made of populations (e.g., the elderly, or renally impaired patients) that require special dosing.

c. Contraindications

- *If the drug should not be used under any circumstances, this should be indicated clearly in the Contraindications section.*

Some members of Working Group III were of the opinion that only absolute contraindications should be mentioned in this section (a logical interpretation of the term "contraindications"). However, in actual practice there are extreme situations where the use of the drug may still be justified (for example, when no other treatment is available in a life-threatening condition); such considerations of "relative contraindications" can be covered under "Special warnings and special precautions for use," as recently proposed by a CPMP multidisciplinary group on SPC wording.

The European Union's Summary of Product Characteristics (SPC) Guideline II/9163/89 describes contraindications as: "Situations where patients should NEVER or GENERALLY NOT be treated. In rare cases where the medicinal product should NEVER be given, this must be specifically outlined."

As suggested in the U.S. FDA Requirements for Labeling, if no contraindications are known, "None known" may be stated in this section.

It has also been suggested by some members of CIOMS V, that if other medicines (or classes of medicines) should specifically be avoided for concomitant or consecutive use, this should be stated if a contra-indication is needed (e.g., on the basis of clinical experience or strong theoretical grounds, such as from pharmacokinetic or pharmacodynamic evidence).

d. Special Warnings and Special Precautions for Use

- *"Special Warnings" should help physicians avoid the occurrence of serious adverse reactions, while allowing them to use a drug in patients who could benefit from it.*
- *"Precautions" should alert physicians to exercise special care in particular circumstances to ensure safe and effective use of a drug.*

Warnings highlight serious adverse reactions and potential safety hazards occurring under normal conditions for use or in particular situations (e.g., in patients with organ failure, in the elderly or young, in slow metabolizers or in the case of other special predispositions of patients). They also describe the limitations on use imposed under such circumstances, individual signs and symptoms, advice on early recognition of the adverse effects, if there are particular risks associated with starting a medicine (first-dose effects, e.g.) and steps to be taken should an adverse reaction occur. The types of reaction included are generally those which do not meet the more strict limitations under Contraindications, but require special attention to ensure proper use of the drug. Depending on the seriousness and importance of the risk, such as death or serious injury, the warning can be prominently displayed (e.g., bold type within a box). Any ADRs discussed under Warnings will, of course, also be listed under the Undesirable Effects (ADRs) section of the CCSI along with available information on frequency; it may also be useful, as suggested by the FDA, to indicate, if known, incidence rates of patients sustaining the reaction, when such information will contribute to the safe and effective use of the drug.

Precautions generally refer to information about special care and advice on safe and effective prescribing of a drug by the physician and its proper use by the patient. For example, under the U.S. FDA guidelines for product information, included under this heading are precautions regarding driving motor vehicles, practical guidance on drug interactions, and use during pregnancy and nursing. For the European SPC, the model adopted for the CCSI by Working Group III, these particular precautionary items are covered under their own, separate sections. Other items covered by Special Precautions might include: laboratory tests of possible use by the physician to monitor a patient's response to a drug or to help identify important adverse reactions; and practical advice on the significance of findings of carcinogenicity or mutagenicity potential from animal studies. Evidence from human data that a drug may be carcinogenic or mutagenic should be included under "Warnings."

e. Interaction with Other Medicaments and Other Forms of Interaction

- *Information on drug-drug and other interactions, including their nature and importance, should be clearly stated.*
- *It is important that manufacturers of interacting drugs communicate promptly with each other to ensure consistency of information and advice.*

Any drug interaction known at the time of first marketing is included in the initial CCSI; signs and symptoms of the drug interaction, particularly if they differ from the effects of the individual interacting drugs, should be listed here. If it is advisable to discontinue one drug in the event of the suspected interaction, such medical intervention must be discussed.

The information given should reflect the magnitude and nature of the risk and how it should be handled. It should focus on clinically important effects and be guided by:

1. the frequency of the co-administration of the interactive drugs or the frequency of the administration of the drug in the presence of the other interacting factors;
2. the clinical significance of the ADR due to the interaction;
3. the extent of relevant evidence including that available from pharmacokinetic and pharmacodynamic studies.

Interactions with drugs should be listed first and separated from those involving other factors (diet, alcohol, illicit drugs, interference with diagnostic or laboratory tests).

It is important to attempt to anticipate the most frequently administered co-medications and describe available experience, rather than to give a detailed account of erratic individual experiences in rare circumstances. Well-established interactions with co-medications should be mentioned, even if such co-administration with the subject drug is expected to be infrequent, as long as the threshold for inclusion is reached.

Drug interactions should be described in the CCSI for the different drugs. Manufacturers of newly marketed drugs must remain on the alert for drug interactions. It is strongly recommended that companies manufacturing the interacting drugs communicate with each other and that each updates its CCSI in a consistent manner and as promptly as possible.

There were two suggestions made by readers of the first edition of this report that ought to be mentioned: (1) substantiated mechanisms for interactions (e.g., involvement of P450 enzymes or isoenzymes) should be mentioned in the CCSI, information which would then be relevant to any co-administered drugs undergoing metabolism by that enzymatic route; (2) if one drug affects the pharmacokinetics and/or pharmacodynamics of a concomitant medicine or metabolites, especially if there are clinical manifestations, the information should be discussed. See Chapter 6j for additional discussion on aspects of pharmacology.

f. Pregnancy and Lactation

(i). Use During Pregnancy

- *The Company Core Safety Information section on Pregnancy is intended to help decide whether a (potentially) pregnant woman can be treated safely with a drug.*

Unless a drug is not absorbed or is known to carry no risk of indirect harm to a fetus, this section must contain information relating to possible teratogenic and non-teratogenic effects. Also, for drugs used during

labour and delivery (vaginal or abdominal), this section should describe available information on their effects on the mother and the fetus.

Major sources of safety information on a drug's effects on pregnancy are, in principle, of the same types as for the other populations: animal studies in different species, controlled clinical and epidemiological studies involving pregnant women, and individual case histories of exposure to a drug during pregnancy and its consequences. However, for ethical reasons, experimental experience in pregnant women is rarely available and is usually limited to vital indications or those related specifically to pregnancy. This may change with increasing use of a drug but, generally, such information relies heavily on animal studies and individual case reports. Pregnancy experience from individual case reports is evaluated relative to any available estimate of the number of women exposed to the drug. While results of animal studies carry higher weight in this specific area, the difficulties of extrapolation to humans are well known.

The section dealing with pregnancy must include not only pertinent findings (whether positive or negative) on pregnant women who were exposed to a certain drug and followed up for the outcome of the pregnancy (prospective monitoring). It must also present information on malformations associated retrospectively with drug exposure (retrospective analysis), data admittedly less reliable than information obtained from prospective monitoring. The CCSI should contain all the information about a drug, including circumstances of inadvertent drug exposure, which a physician needs to know to manage pregnant patients as well as all women patients of childbearing potential.

Regulatory authorities in many countries use similar, but not necessarily identical, classification schemes to categorize the level of knowledge and potential risk regarding possible teratogenic effects in various stages of pregnancy (e.g., Pregnancy Categories A, B, C, D, X). Until a worldwide standard is developed, the use of such schemes in the CCSI is at the discretion of the manufacturer and subject to national product-information requirements. It should be noted that the Teratology Society[19] has advised "that use of such a categorization rating scheme should be abandoned and replaced with narrative statements that summarize and interpret available data regarding hazards of developmental toxicity and provide estimates of potential teratogenic risk."

Nevertheless, it may be useful to consider a classification scheme for conveying the amount of data available from experience (exposure) with a drug, such as the following:

Wide exposure:	> 1,000 pregnancies
Limited exposure	< 1,000 pregnancies
Very limited exposure:	Individual cases only, without reliable data on size of population at risk

[19] FDA Classification of Drugs for Teratogenic Risk, Teratology 49: 446-7, 1994

Effects on the newborn other than malformations (fetotoxicity) should also be described: functional (e.g., disturbance of electrolyte balance by diuretics); permanent (e.g, discolouration of teeth by tetracyclines); effects on the placenta; or such effects as tendency to increased bleeding.

In view of the importance of this topic and to update information regularly, every effort must be made to follow up as many drug exposures as possible, intentional or accidental, in a collaborative effort with treating physicians, medical-care and research organizations, patients and manufacturers.

(ii). Use During Lactation

- *The same principles as those applied to use during pregnancy apply to the use of a drug while nursing.*

During pre-approval clinical testing, a drug is usually not administered to lactating, nursing women. As a consequence, information on excretion of the drug in human breast milk is rarely available. Occasionally, animal experiments provide information which may be helpful, but differences in the composition of the milk, both between and within species, diminish the validity of such information. Information about the likelihood of a drug's excretion in the milk may also be derived from its biochemical properties, in particular its lipophilicity and acid-base properties. Information regarding this point, however, may not become available until post-marketing (Phase IV) studies have been carried out.

The extent to which the infant is at risk of adverse reactions owing to the mother's ingestion of a drug depends primarily on the quantity of the drug excreted with the milk. This, in turn, depends on the absorption into the maternal circulation, the duration of therapy and variables such as binding to milk proteins and subsequent absorption by the infant. The metabolic and excretory capacity of the infant plays an important role as well.

When it has been established that use of a drug is incompatible with breast-feeding because of the likelihood of inducing adverse effects in the infant, this should be indicated in the CCSI. Depending on the severity and seriousness of the adverse effects, advice should be included that either breast-feeding should be discontinued or not started or another drug selected, if available. It should be borne in mind that advice to refrain from breast-feeding should not be given lightly, particularly in developing countries where alternative nourishment for the baby may be prohibitively expensive or unavailable.

For many drugs, no reliable data are available. In such cases, the CCSI should state that safe use during lactation has not been established. When possible, it may be helpful to include information based on theoretical

considerations (e.g., involving pharmacokinetic characteristics) on the probability of adverse effects. Statements that could convey a false sense of security, such as "no adverse effects due to maternal intake of the drug have been reported in infants" should be avoided.

g. Effects on Ability to Drive Vehicles and Operate Machinery

- *If a drug may impair the ability to drive vehicles or operate machinery, appropriate information should be given, depending on the type of drug (e.g., sedative, antihypertensive, hypoglycaemic drug).*

In deciding on the information to be included, the overall adverse reaction profile may have to be taken into account; consideration should be given to restating the relevant adverse reactions (e.g., somnolence, drowsiness, visual disturbances). If the product has a significant effect in this area, consideration should be given to mentioning it in, and cross-referencing it to, the warnings and precautions section.

The following examples provide guidance for standard, uncomplicated statements:

- *For sedatives, hypnotics*
  "This drug may affect reactivity to the extent that the ability to drive vehicles or to operate machinery is impaired. This applies, in particular, to interaction with alcohol."
- *Drugs containing alcohol*
  "This drug contains more than 3g of alcohol per single oral dose. The alcohol content must be taken into account when assessing the ability to drive vehicles or to operate machinery."
- *Drugs regulating blood pressure*
  "The treatment of hypertension with this drug requires regular medical check-ups. As a result of different reactions in individual cases, the ability to drive vehicles or to operate machinery may be impaired."
- *Hypoglycaemic drugs*
  "The treatment of diabetes with this drug requires regular medical check-ups. Until optimal control has been reached, when changing therapies or in case of irregular use of this drug, the ability to drive vehicles or to operate machinery may be impaired."
- *Local anaesthetics*
  "When using this drug during surgery, in dental treatment or over large areas of the body, the physician must decide in each individual case how soon the patient may drive vehicles or operate machinery."
- *Systemic anaesthetics*
  "After anaesthesia with this drug, the patient must not be permitted to drive motor vehicles or operate machinery for a time to be decided by the physician in each individual case. The patient should be accompanied home and be instructed not to consume alcohol."

h. Undesirable Effects (Adverse Reactions)

The location and presentations of ADRs within the CCSI has been treated extensively in sections 3, 4 and 5 to which the reader is referred. One possible general structure that could be considered for this CCSI section has been proposed by a CPMP working party on SPC wording, as follows: (1) a brief, general description based on the more detailed data presentations (overall statistics on percent of patients expected to experience ADRs, the most frequently occurring ADRs, whether ADRs are dose-related, etc.); (2) a listing of ADRs organized by a standard system organ class, ranked by frequency of occurrence within each class using the standard frequencies proposed by CIOMS III (see Section 5.d.), and by decreasing medical seriousness within each frequency; (3) information on differences between dosage forms, characterization of individual serious and/or frequently occurring ADRs (e.g., mechanism, time of onset, reversibility, dose relationship, etc.), and for combination products mention of which ADRs are usually attributable to which component when known; and (4) special considerations that may pertain to class effects.

i. Overdose

- *The overdose section must include information concerning both observed and theoretical signs and symptoms of overdose.*
- *The overdose section should also include recommendations for clinical management including the provision of antidotes and proper supportive therapy.*

The most common signs and symptoms of overdose of a drug should be described in such a way that a typical physician would recognize them and be able to react properly.

First-aid measures should be described. It must be indicated whether treatment should be symptomatic, both supportive and symptomatic, or specific. Specific treatment would depend largely on the availability of specific antidotes or other treatment which should be identified. Data on dialysability of the drug may be available as well as information on the plasma half-life. Some indication of the doses at which toxic symptoms may be expected should be given. Information on the possibility and methods of accelerating the elimination of the drug should also be provided.

j. Pharmacological Properties

- *Direct and indirect safety-effects of a drug, as observed in pharmacological and pharmacokinetic studies, should be included in the CCSI.*

Insofar as the pharmacological actions include dose-related adverse effects, these may be mentioned in the pharmacology section, but they need to be included also in the section(s) on adverse reactions/undesirable effects. There is also a need to interpret key toxicological observations.

As usual, the pharmacology section will contain details on absorption, distribution, metabolism and excretion, and will address factors influencing these properties. If there is a known or potential safety problem in persons with organ disorders (e.g., renal or hepatic disorder) this should be specified. Where there are implications for dosage and administration, a cross reference should be made to that section of the CCSI (see Section 6.i.).

k. Preclinical Safety Data

If animal data suggest possible mutagenesis, carcinogenicity or teratogenicity, this must be explicitly mentioned whether or not there is available information on human experience.

7. WHO? — SUGGESTED RESPONSIBILITIES

a. The Company

- *A company should have a diligent and assertive approach towards the CCSI.*
- *When indicated, a company should undertake a scientific study to investigate quickly any possibly serious problem.*

A company is responsible for critically assessing all available data from animal toxicology, volunteer studies, clinical trials, spontaneous reporting and the medical literature and for assiduously following signals. The balance must be maintained when making the decision on whether and when to amend the CCSI. Where an established relationship is clear, the adverse reaction should be added quickly. It is just as important, where a causal association is not strong (owing to confounding factors, poor quality reports, etc.) or when a definitive study to evaluate signals is in progress, to wait; adding potentially erroneous information only serves to mislead or confuse the prescriber.

- *It is important that the CCSI reflect the company's interpretation of all available scientific evidence.*

The manufacturer should reach decisions on the basis of a clear, scientific approach and should use a consistent threshold whenever possible. Accordingly, the CCSI is determined by the company; local regulatory demands should supervene only with appropriate evidence and arguments. Listing an adverse experience in the data sheet of any one country should require re-evaluation of the CCSI for worldwide use.

- *The company should attempt to achieve labelling consistency whenever a formulation is marketed for a particular indication. However, there are legitimate exceptions to this general rule, justified, for example, by pharmacogenetics or regional variations in disease patterns.*

- *Where practical, definitions of ADRs should be those agreed internationally.*

Some internationally developed definitions of adverse drug reactions have been published, such as those prepared under the auspices of CIOMS[20], and where possible the company should use them.

- *Apart from the areas already discussed (controlled clinical trial data) a company should not normally make any statements in the CCSI about another company's drug, with the exception of drug-drug interactions (which should be described in the CCSI for all concerned drugs), or of specific antidotes recommended for treatment of overdose.*

b. Shared Responsibility

- *Investigators should read the core information conscientiously and help the company keep it up to date by suggesting any new signals.*
- *Healthcare providers need to read data sheets conscientiously and report full and accurate case details on patients with significant adverse reactions.*
- *Patients have a role in helping to provide detailed and accurate medical histories which can lead to better advice for the benefit of subsequent patients.*

Healthcare providers are important partners of regulatory authorities and industry in maintaining quality CCSI. While maintaining the confidentiality of individual patients, there must be cooperation in follow-up for important medical information. In addition to providing information about adverse events, practitioners contribute reports to medical journals. High quality reports demand that case details and clinical evaluation be thoroughly and accurately documented and communicated.

- *Editors of medical journals have important responsibilities.*

If described well, a case report can be vitally important and in itself can serve as a signal worthy of assiduous follow-up. Quality case reports are much more valuable than a number of poorly described spontaneous reports. Editors of medical journals, before accepting correspondence or articles for publication, should ensure that case descriptions are of high quality. As publication can often take some weeks, it is strongly recommended that the editor check with the reporter as to whether a report has been sent to the regulatory authority or the manufacturer.

- *Regulators are responsible for monitoring the information provided by pharmaceutical companies and ensuring that they focus on information that is critical to the proper clinical use of the medicine.*

---

[20] Venulet, J and Bankowski, Z. Harmonizing Adverse Drug Reaction Terminology. *Drug Safety*, 19(3):165-172, 1998.

Regulatory authorities are responsible for protecting the public health. Therefore, they must ensure that pharmaceutical companies provide adequate information on the quality, efficacy and safety of their products to justify their licensing and marketing. They must also ensure that the product information provided to all drug users is accurate and informative and evolves as experience is collected with the drug in clinical practice. Product information needs to be up to date and accurate in accordance with new information from a variety of sources. There has been a tendency for product information to become overloaded with information for the legal protection of pharmaceutical companies rather than in the interests of doctors and their patients. Regulators and pharmaceutical companies have a responsibility to ensure that this does not occur and that the focus is placed on information that is crucial to the proper use of the drug. There should always be sufficient evidence to support inclusion on clinically important grounds.

Conclusion

In summary, thoughtful clinical analysis, clear and thorough documentation, accurate and full communication, careful scientific analysis of individual cases and evolving bodies of evidence, all contribute to the creation and evolution of the CCSI. In that sense, the CCSI is truly a shared responsibility.

8. DEVELOPMENT CORE SAFETY INFORMATION (DCSI)

a. Introduction

Companies usually have one Investigator's Brochure for each drug in clinical development which is intended to provide researchers with all relevant clinical and non-clinical information. Ethics Review Committees (ERCs)/Investigational Research Boards (IRBs) in the course of their study approval and monitoring responsibilities use such information for assessment of the benefits and risks to clinical trial subjects. The format and content of an Investigator's Brochure have been defined in the ICH "Guideline for Good Clinical Practice (May 1996);" a copy of the section on IBs is reproduced in Appendix 5.

As a broad guideline, it is not very specific regarding practical approaches to the assessment and presentation of safety information. It suggests, for example, that "where a number of clinical trials have been completed, the use of summaries of safety and efficacy may provide a clear presentation. Tabular summaries of adverse product reactions including those for the studied indications would be useful. Important differences in adverse product reaction patterns/incidences across indications or subgroups should be discussed." We are also told that the IB should provide a description of the possible risks and adverse effects anticipated on the basis of prior experience with the product under

investigation and with related products, along with a summary of any significant information arising during market use. It should also identify all countries where the investigational product did not receive approval/registration for marketing.

Finally, the ICH Guideline suggests that "the Summary of Data and Guidance for the Investigator should provide an overall discussion — and should summarize the information wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data with an assessment of the implications of the information for future clinical trials."

The absence of additional guidance or specificity raises several important questions of interpretation on details for companies, not only in preparing and updating the IB but in meeting regulatory reporting obligations. For example, it is not always clear when a given event should or should not be considered "expected"* in relation to the safety information already included in the IB; this has obvious implications for decisions especially on expedited reporting of adverse reactions to the authorities. This becomes even more complicated when the drug is marketed and for which there exists, therefore, an official, local data sheet ("label") as well as a Company Core Data Sheet with its Company Core Safety Information.

Some guidance would also be welcome on how often safety information in an IB should be updated, and on the process for updating.

The Company Core Safety Information (CCSI) prepared as a result of the first marketing approval contains pre-marketing findings from clinical and non-clinical studies. Controlled clinical studies are the most useful (and initially among the only) data available for identifying and evaluating the absolute and relative rates of the more frequent adverse reactions. Unless subsequently shown to be misleading or incorrect, the clinical trial data in the initial CCSI should remain unchanged and be supplemented from additional experience. (See Chapter 2b.)

In contrast, currently there are no requirements or guidelines on how clinical safety information should be presented or described in an IB, even though in principle, if kept up to date, information in the IB should form the basis for the CCSI.

There is a need to introduce some definition and structure for such data in order to address the issues mentioned. The CIOMS Working Group V proposes that the IB contain a section identical in structure to

---

* Although the terms "labeled" and "unlabeled" are often used by some to indicate events or reactions that are expected or listed in an IB, such terms are inappropriate and their use is discouraged. Rather, the terms "listed" and "unlisted" (possibly "expected" or "unexpected") are recommended; the concept of "listedness" is already accepted as part of the ICH definition of marketed product Company Core Safety Information as described in the guideline on PSURs (periodic safety update reports).

the Company Core Safety Information that is included in the Company Core Data Sheet for a marketed product, and that it be referred to as the Development Core Safety Information (DCSI). This would satisfy the need to help investigators and sponsors more effectively by presenting and updating a focused, dedicated Development Core Safety Information section that can conveniently be placed within the IB, perhaps as an Appendix. Furthermore, it is proposed that the DCSI develop into the CCSI that is included in the first Company Core Data Sheet for the product's entry into the market.

It should be emphasized that the DCSI is not a recognized legal document in and of itself. In keeping with the spirit of CIOMS, however, the concept is offered as a set of guidelines, reached by consensus of Working Group V, that appears compatible with current local laws and existing GCP guidelines.

The goal for the DCSI proposal is to extend to Investigator's Brochures the same philosophy and practices presented in the original CIOMS III guidelines, as discussed here in Chapters 1-7. This should both encourage and support companies in their endeavor to have only one Investigator's Brochure for each drug with one Core clinical safety section (the DCSI) which is kept up to date with the addition of any necessary new information. Additional important goals are to provide guidance on how to determine consistently when a reaction is or is not expected in the regulatory sense and how often to update or amend the Development Core Safety Information and thus the Investigator's Brochures. Finally, guidance is provided on the global distribution to investigators of important new safety information, such as 7-day and 15-day serious, unexpected adverse reaction alerts.

b. Specific Proposals

(1) Each drug in development should have one DCSI which is consistent worldwide.

All investigators participating in a development program, whether local or worldwide, should be given the same information. The content of the DCSI in Investigator's Brochures depends on the stage of development of the drug under investigation. It should contain important conclusions from preclinical and clinical studies aimed primarily at safety evaluation, whether positive or negative. As specified for CCSI, the untoward effects/adverse reactions and other sections of the DCSI should contain only adverse drug *reactions* (see (7) and (9) below for more discussion).

The DCSI should always be dated. An advantage of regarding the DCSI as a discrete document is that it can be maintained without necessarily having to update other sections of the Investigator's Brochure.

There is no need for a DCSI section in an IB that might be used for Phase 4 studies that are conducted under approved labelling; the marketing CCSI and/or the local data sheet should be used. The DCSI applies only to studies or programs covering research outside approved labeling, or when there is no CCSI or approved label. If a Phase 4 study is conducted in more than one country, and those countries do not have the same local data sheets (labeling), it will be more appropriate to use the company's CCSI as a DCSI. See (4) below for additional discussion on this point.

(2) Ideally, there should be one Investigator's Brochure DCSI for all indications, formulations and routes of administration of the active moiety.

However, information specific to different dosage forms, routes or indications should be clearly delineated, but should all be presented in the same DCSI section of the Investigator's Brochure. Whether "expectedness" overall should be determined according to the indication, dosage form, etc. under study will be subject to judgment; for example, certain ADRs will no doubt be of systemic origin, while others may be indication or dosage form specific.

There may be circumstances when an exception is needed for the goal of a single IB for all indications, formulations and routes of administration under study. The IB section of ICH GCP specifies that: "If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared." Thus, an IB may still be in use for new or ongoing studies covering the approved claim(s) for a marketed drug. It may then be more appropriate or convenient to create a new IB. See (4) below for additional discussion.

(3) The Development Core Safety Information should serve as the summary of the identified safety issues described in much more detail in the main body of the Investigator's Brochure.

Investigators of drugs in early development will usually need extensive and detailed information concerning animal toxicology, anticipated class effects, pharmacokinetics, pharmacodynamics, laboratory chemistry data, signs, symptoms, etc., within the main body of the Investigator's Brochure as outlined in the ICH "Guideline for Good Clinical Practice." Until one or more ADR has been observed, it might be useful to mention that no ADRs have been reported (i.e., the initial DCSI template begins with a "clean slate").

(4) When a drug is marketed, it is important that investigators have the same information as prescribers; however, the converse is not necessarily true.

A drug may be marketed in some countries while still under development in others. Another typical situation is the development of

new indications within the same or different countries where the product is on the market. Under all such circumstances, the DCSI should include everything found in the Company Core Safety Information for the marketed product. On the other hand, inclusion of new information in an IB may not be accompanied by a change in the marketing CCSI or official product data sheet (labeling), depending on the nature of the information (e.g., injection site injury for an injectable dosage form under development but not on the market). In addition, changes beyond the IB may also depend on the strength of the evidence deemed appropriate for modifications to the marketed product documentation.

When a drug is marketed in a given country, it is not uncommon for study sponsors to include the local data sheet (labeling) within an IB used for studies of new indications, dosage forms, etc., a reasonable practice. However, because local data sheets often differ from country to country (sometimes considerably depending on approved claims, etc.), it is recommended that the company's marketed product CCSI (a single standard) be used to help define the DCSI as a global "document." Expedited reporting of new, serious ADRs within the development program would then be determined on the basis of the DCSI; as usual, the local data sheet controls expedited reporting of cases arising from marketed use of the product within that country. Thus, it is possible that a particular ADR may be "expected" within the DCSI, but still be unlabeled in the CCSI and local data sheets. In principle, the reverse cannot occur.

(5) Only ADRs included in the DCSI section of the IB should be regarded as "expected" for regulatory reporting purposes.

Under the traditional, non-standard format and content for safety information in IBs, there are currently different company philosophies regarding the designation of adverse reactions as expected or unexpected. Such differences are apparently greater for Investigator's Brochures than for approved labels, as demonstrated with the following examples generated from an informal survey of CIOMS V company representatives. Some companies count as expected events only those which are clearly specified within the IB as due to the drug. Others tend to consider expected any event mentioned anywhere in an Investigator's Brochure even if it were 0% on the drug and 2% on placebo! If a letter describing a single occurrence of a new serious adverse reaction is sent to investigators, some companies regard that event as expected from then on. Others do not consider such an event as expected until the next "formal" update of the entire IB. These and other observations from the survey are summarized in Appendix 6.

Although drug class effects should be mentioned within the IB, in general they are not "expected" and should not be included in the DCSI until and unless they actually occur with the investigational agent.

(6) Although the point at which new safety information should be added to the DCSI cannot be categorically specified, the threshold for inclusion of serious events should ordinarily be higher than for the marketed product CCSI.

Considerations for adding information to the DCSI include all the factors proposed for the marketing CCSI (see Chapter 4). For serious events in particular, however, it is preferred to keep the threshold for their addition to the ADR list in the DCSI relatively high. This seemingly paradoxical recommendation reflects the belief that during the development stage there is a need for heightened vigilance and oversight, by ensuring that accumulating new cases of the same serious event continue to be reported on an expedited basis to regulators, investigators and ethics review committees, until sufficiently convincing evidence exists to warrant the addition of that event to the DCSI.

It might be argued from an ethical perspective that the threshold should be *lower* in order to provide fully informed consent, especially to patients newly enrolling in a study. However, on balance it is the judgment of CIOMS Working Group V that raising the threshold guarantees more careful attention by all responsible parties to the more important risks as new information accumulates. Although it is an important issue, the general topic relating to the timing and methods for communicating and implementing updated informed consent was beyond the scope of Working Groups III and V.

There may be occasions when several cases of a given serious event have been reported but were not attributable to drug by either sponsor or investigators. If an investigator subsequently reports another case which is attributed to the study drug, it must be reported on an expedited basis as usual, but under such circumstances all the relevant cases should be reviewed to ascertain whether the higher threshold criterion has been reached.

(7) There are no accepted rules for determining whether an AE should be included as an ADR in the DCSI. However, it may be useful to consider arbitrary benchmarks to assure that emerging trends are adequately recognized on a timely basis.

Although it is tempting to rely on statistically significant differences in AE rates between study drug and placebo and/or active comparators, the usual caution is advised when making multiple comparisons. On the other hand, such calculations when coupled with medical insights and common sense can provide a reasonable framework for deciding on inclusion or exclusion from the DCSI.

Nevertheless, especially in the absence of statistical confirmation, it is difficult to decide for a given adverse event what "excess" frequency above that observed with placebo should serve as a determinant for the inclusion of that event. A survey of the Working Group found that there

was great variability in the level of frequency increases suggested as a benchmark for adding reactions to the DCSI, particularly during early clinical trials in which small numbers prohibit all but the most crude comparisons. However, as the size of the trial population and duration of treatment (if relevant) increase, it might be useful to consider something like a 5% greater frequency for a non-serious ADR, especially if statistically significant, and the placebo incidence is relatively low. For example, with a placebo incidence of 10%, the threshold would be reached under this arbitrary criterion when a 15% incidence is reached. A similar, arbitrary increase for serious events, keeping in mind the higher threshold advocated in (6) above, can be considered. However, this approach clearly may not be appropriate for large rates of events with the active or placebo comparators.

Another approach, particularly for serious events, is reliance on careful medical evaluation of the study drug cases for their strength of association. Thus, independent of the incidence in a placebo group, two "strong," convincing cases might be sufficient to include the event as an ADR in the DCSI. One serious suspected ADR will generally not be sufficient to warrant inclusion in the DCSI. Comparison to historical (epidemiological) data on the anticipated background incidence of an event in the treatment population might also be useful.

Other findings that must be considered carefully and that should have a key influence in the decision are:

- positive dose response
- a recognized at-risk population
- corroborative evidence from different studies
- consistent trend between studies
- results from a specific safety study, whether the results are positive or negative
- severity (including AE-related dropout rates) or latency of effects compared to comparison group(s).

Also, if there is a clearly anticipated pharmacological effect of the drug leading to an AE, it should be included in the DCSI earlier than otherwise.

The reader is referred particularly to Chapter 4 for discussions of other important factors (e.g., whether the drug is used for diagnostic, prophylactic or treatment purposes) relating to the threshold for including information in the marketing CCSI that apply equally to the DCSI.

Questions that should be kept in mind when deciding on the addition of information, particularly information of potential medical significance, to the DCSI is: Would the inclusion of a suspected ADR influence the physician's decision to enroll a particular patient in a study or use the drug in such a patient? Will inclusion of such information change the way patients are monitored during the trial?

These are suggestions and, as with marketed drug CCSIs, CIOMS Working Group V was not able to define specific quantitative criteria for establishing whether an AE should become an ADR for the DCSI.

(8) Investigators should always be strongly encouraged to express their opinion on what the cause of an adverse event might be.

For individual patients, the investigator/treating physician is usually in the best position to assess the underlying suspected cause(s) of a treatment-emergent adverse event. For serious reactions, especially rare Type B (idiosyncratic) reactions, it is important that the investigator assess not only the possible role of the study medication but also competing aetiological factors as the underlying cause.

It is proposed that the list below be included on case record forms as choices for an investigator to indicate his/her judgement that one or more of the indicated factors represents a reasonable possibility for a causal relationship. It is derived from discussions held on the occasion of various meetings of the Drug Information Association (DIA):

- ❑ medical history
- ❑ lack of efficacy/worsening of treated condition
- ❑ study treatment
- ❑ other treatment (concomitant or previous)
- ❑ withdrawal of study treatment
- ❑ erroneous administration of treatment
- ❑ protocol-related procedure
- ❑ other-specify.

Unless there is convincing evidence to the contrary, an investigator's assignment of positive association with study drug for an individual case should be accepted. However, it is recognized that the study sponsor, in deciding whether an event should be added to the DCSI as an adverse reaction, will consider the totality of data from all studies and possibly information from other sources not available to the investigators. Thus, the final decision may on occasion contradict investigators' assessments of individual cases.

(9) The format for the DCSI should be that same as that intended for the marketing CCSI.

Although there are many similar formats for presenting DCSI and CCSI information, for convenience the CIOMS III proposals arbitrarily used the structure of the European SPC (see Chapters 1d and 6). The headings for clinical safety particulars are:

Posology (dosing) and administration
Contraindications
Special warnings and special precautions for use
Interactions with other medicaments and other forms of interaction

Pregnancy and lactation
Undesirable effects (adverse reactions)
Overdose
Drug abuse and dependence

(10) The DCSI should evolve into the initial CCSI.

In the process of preparing a marketing authorization dossier, all relevant animal and human safety data available will be reviewed and analyzed. This may result in modification of the information contained in the latest DCSI in use prior to the data cut-off point. In practice, as part of the IB this updated DCSI will continue to be the company's reference safety information document between the time of data cut-off and eventual approval for marketing by the authorities, and should be used for any ongoing or newly initiated studies during that period. The first CCSI, that prepared to coincide with the first license/approval for marketing, should be based on the latest DCSI, including any necessary modifications up to the time of approval. In principle, the DCSI will become identical with the proposed "label" submitted with a marketing application, because that label will be based on the company's CCSI.

c. Administrative Considerations for DCSI

(1) Expedited Reporting to Regulators and Investigators

Subsequent to its development and endorsement by ICH, the guideline (E2A) on expedited reporting during new medicines development is being widely adopted by regulatory authorities and study sponsors ("Clinical Safety Data Management: Definitions and Standards for Expedited Reporting," October 1994). General instructions are given there and in the ICH "Consolidated Guideline for Good Clinical Practice" regarding the rapid reporting of serious, unexpected, ADRs to all appropriate regulators and other parties (e.g., investigators, ethics review committees). However, neither guideline addresses some of the practical issues which relate to the DCSI proposals, as in the following examples.

- For an unexpected serious ADR, an expedited report will be sent to appropriate regulators and a letter describing the case should be sent to investigators participating in Phase 1 through 3 studies with the compound. Although the letter may be "attached" to the IB as an informational update, additional cases of the same event(s) should still be regarded as unexpected until the new ADR is added to the DCSI section of the IB. Once it *is* added, the revised, updated DCSI can be sent to all investigators as an "official" modification. See (4) below for additional discussion.
- Although ICH Guideline E2A calls for unblinding isolated serious, unexpected, suspect ADRs, there may be circumstances when the blind is maintained even for expedited reporting (e.g., if the medical event is an efficacy endpoint). Such ADRs should not

be included in the DCSI but should be described elsewhere within the IB, and therefore remain "unexpected."

(2) Expectedness and Medical Terminology

The anticipated widespread adoption of the new medical coding terminology, MedDRA, if used for clinical trial data processing may introduce new complications in assigning expectedness. Given the high specificity (granularity) of preferred terms within MedDRA (several-fold relative to WHO-ART and COSTART), it is important that medical interpretation play a key role in the choice of the term used in the DCSI, rather than strict adherence to a structured terminology.

(3) Periodic Safety Update Reports (PSURs) and the DCSI

For drugs already on the market while still under investigation in the same or different countries, whether for the same or different labeling claims, all relevant information in the DCSI, including differences from the CCSI, should be considered for inclusion in post-marketing PSURs. If an ADR is not included in the CCSI but appears in the DCSI, it should still be regarded as "unexpected" ("unlisted") for PSUR report purposes.

(4) Routine Updates of the DCSI and the IB

There are no specific rules regarding the timing for updates of the DCSI and of the Investigator's Brochure as a whole. The IB section of the ICH guideline on GCP specifies that the "IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information." It is suggested that the DCSI, as a separate, dedicated section of the IB, be updated as often as needed. Depending on the nature of the information, it should be updated as soon as possible and no later than within a month of a decision to add or change information. Circulation of the modified document to investigators and ethics review committees should also take place as promptly as needed, again depending on the nature of the information; it can be sent without replacing the entire IB document or other individual sections, unless considerable explanation and data are needed to accompany the altered DCSI.

9. SUMMARY OF PROPOSALS

General Guidelines

- *All pharmaceutical manufacturers must prepare Company Core Safety Information (CCSI) for each of their marketed products.*
- *The content of the CCSI for marketed products depends partly on the stage of development and the life cycle of a drug.*

- *There are two stages of CCSI reflecting the life cycle of a drug: the initial CCSI and the evolving CCSI.*
- *Unless subsequently shown to be misleading or incorrect, the data in the initial CCSI should remain and be updated from additional experience.*
- *Important conclusions from special studies aimed primarily at safety evaluation should be specified, whether positive or negative.*
- *Information specific to different dosage forms or uses of products should be clearly identified.*
- *Include adverse effects due to excipients.*
- *National data sheets may contain safety information that differs slightly from the CCSI; particularly they may contain additional information pertinent to a particular country or region.*

What?

- *Company Core Safety Information should be determined by the needs of healthcare professionals in the context of a regulatory and legal environment.*
- *Include what is practical and important to enable the prescriber to balance risks against benefits and to act accordingly.*
- *Avoid including events, especially minor events, that have had no well-established relationship to therapy.*
- *There is a legal duty to warn but this must be balanced against the need to include only substantiated conclusions in the CCSI.*
- *The CCSI should include important information which physicians are not generally expected to know.*
- *Lack of efficacy should be considered apart from safety.*

When?

- *As soon as relevant safety information becomes sufficiently well established it should be included in the CCSI.*
- *The specific time when safety information must be included in the CCSI is determined by the concept of "threshold".*
- *Safety information will cross the threshold for inclusion if it is judged that it will influence physicians' decisions on therapy.*
- *It is often not possible to specify exactly when an association becomes well established but all relevant factors should be considered.*
- *Relevant factors can be identified and ranked for weighing the evidence for inclusion of new information in the CCSI.*
- *It is difficult to interpret spontaneous reports of poorly researched and inadequately described cases.*
- *The status of the reporters and their attribution of causality to individual cases are less important than other factors.*
- *The more the applicability and usefulness of the new safety information, the sooner it should be included, i.e., the lower the threshold.*
- *Lower the threshold and add the information earlier if an ADR is medically serious or irreversible.*

- *Add the information especially early if good alternative drugs are available.*
- *The threshold should be lower if the condition being treated is relatively trivial, the drug is being used to prevent rather than treat a disease, or the drug is widely used.*
- *It is important to add hypersensitivity reactions early to avoid re-exposure. If an excipient could be the cause, investigate, but until the excipient is removed add information to the CCSI.*
- *Substantial evidence is required to remove or downgrade safety information.*

How?

- *Keep ADRs identified in the initial CCSI separate from those identified subsequently.*
- *ADRs should be listed by frequency in body system order.*
- *Although a specific "class label" section of CCSI is not recommended, the CCSI may contain statements relative to classes of drugs.*
- *The initial CCSI includes information derived from pre-marketing clinical trials.*
- *Whenever possible, an estimate of frequency should be provided, expressed in a standard category of frequency. The Working Group recommends the following standard categories of frequency:*

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

* Optional categories

Where?

- *Company Core Safety Information is located in different sections of a Company Core Data Sheet but the same information may be repeated in more than one place.*
- *Specific medical interventions to prevent problems with administration of drugs should be mentioned in the section: Posology (dosing) and Method of Administration.*
- *If the drug should not be used under certain circumstances, this should be indicated clearly in the Contraindications section.*
- *"Special Warnings" should help physicians avoid the occurrence of serious adverse reactions, while allowing them to use a drug in patients who could benefit from it.*
- *"Precautions" should alert physicians to exercise special care in appropriate circumstances to ensure safe and effective drug use.*

- *Information on drug-drug and other interactions (e.g., food and cosmetics), including their nature and importance, should be clearly stated.*
- *It is important that manufacturers of interacting drugs communicate promptly with each other to ensure consistency of information and advice.*
- *The Company Core Safety Information section on Pregnancy is intended to help decide whether a (potentially) pregnant woman can be treated safety with a drug.*
- *The same principles as those applied to use during pregnancy apply to the use of a drug during nursing.*
- *If a drug may impair the ability to drive vehicles or operate machinery, appropriate information should be given, depending on the type of drug (e.g., sedative, antihypertensive, hypoglycaemic drug).*
- *The overdose section must include information concerning both observed and theoretical signs and symptoms of overdose.*
- *The overdose section should also include recommendations for clinical management, including the provision of antidotes and proper supportive therapy.*
- *Direct and indirect safety-effects of a drug, as observed in pharmacological and pharmacokinetic studies, should be included in the CCSI.*

Who? — Responsibilities

- *A company should have a diligent and assertive approach towards the CCSI.*
- *When indicated, a company should undertake a scientific study to investigate quickly any possibly serious problem.*
- *It is important that the CCSI reflects the company's interpretation of all available scientific evidence.*
- *The company should attempt to achieve labelling consistency whenever a formulation is marketed for a particular indication. However, there are legitimate exceptions to this general rule, justified, for example, by pharmacogenetics or regional variations in disease patterns.*
- *Where practical, definitions of ADRs should be those agreed internationally.*
- *Apart from the areas already discussed (controlled clinical trial data) a company should not normally make any statements about another company's drug, with the exception of drug-drug interactions(which should be described in the CCSI for all concerned drugs), or of specific antidotes used for treatment of overdose.*
- *Investigators should read the core information conscientiously and help the company keep it up to date by suggesting any new signals.*
- *Healthcare providers need to read data sheets conscientiously and report full and accurate case details on patients with significant adverse reactions.*
- *Patients have a role in helping to provide detailed and accurate medical histories which can lead to better advice for the benefit of subsequent patients.*

- *Editors of medical journals have important responsibilities.*
- *Regulators are responsible for monitoring the information provided by pharmaceutical companies and ensuring that they focus on information that is critical to the proper clinical use of the medicine.*

Development Core Safety Information (DCSI)

- *Each drug in development should have one DCSI which is consistent worldwide.*
- *Ideally, there should be one Investigator's Brochure DCSI for all indications, formulations and routes of administration of the active moiety.*
- *The Development Core Safety Information should serve as the summary of the identified safety issues described in much more detail in the main body of the Investigator's Brochure.*
- *When a drug is marketed, it is important that investigators have the same information as prescribers; however, the converse is not necessarily true.*
- *Only ADRs included in the DCSI section of the IB should be regarded as "expected" for regulatory purposes.*
- *Although the point at which new safety information should be added to the DCSI cannot be categorically specified, the threshold for inclusion of serious events should ordinarily be higher than for the marketed product CCSI.*
- *There are no accepted rules for determining whether an AE should be included as an ADR in the DCSI. However, it may be useful to consider arbitrary benchmarks to assure that emerging trends are adequately recognized on a timely basis.*
- *Investigators should always be strongly encouraged to express their opinion on what the cause of an adverse event might be.*
- *The format for the DCSI should be the same as that intended for the marketing CCSI.*
- *The DCSI should evolve into the initial CCSI.*

10. UNRESOLVED ISSUES

During its deliberations, the Working Groups identified a number of issues that could not be resolved. Many of these issues were considered to be beyond the scope of this initiative and may even become topics for future projects.

Some of the issues that are still unresolved:

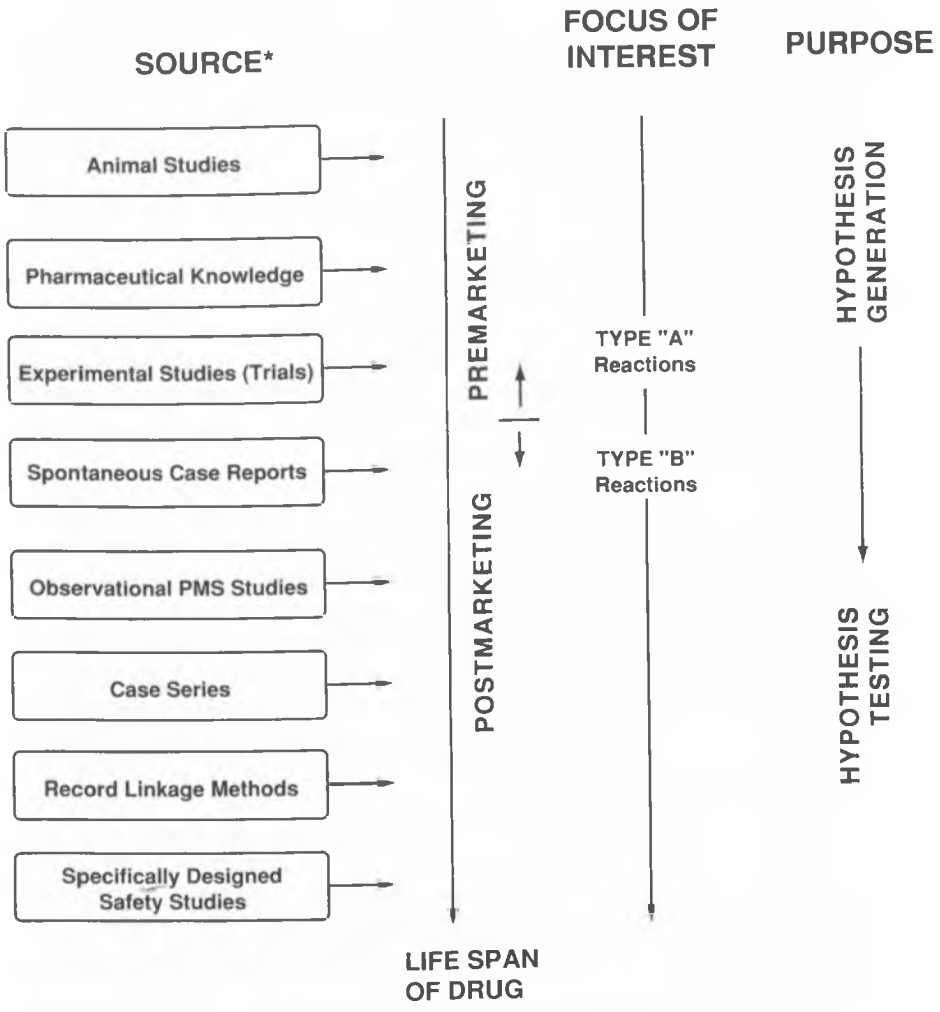
- The Working Group relied on collective judgment to reach consensus on the inclusion or exclusion of information in a CCSI or DCSI. However, would the development of specific threshold criteria or even an algorithm be more consistent and effective than collective judgment? This approach is analogous to the continuing debate about various methods of determining causality in respect of adverse drug

reactions. One obvious difficulty would be that of validating the rules or algorithm.

- Ideally the scope and content of patient-oriented information should be consistent with information for prescribers. However, it was recognized that information for patients has to be modified to ensure understanding by a lay audience. Linguistic and cultural nuances will also influence acceptability of information designed for patients and the Working Groups did not debate the question of guidelines.
- The legislative framework for pharmaceuticals varies considerably throughout the world. Drug regulatory authorities may adopt regulations that require manufacturers to take different courses of action regarding drug safety. Therefore, in practice, the pharmaceutical manufacturer cannot necessarily adhere to a single strategy for dealing with safety issues, although that is the objective. The Working Groups did not feel it was within their remit to discuss ways of trying to limit this source of variability.
- Multiple brands of the same drug substance raise concern about the uniformity of safety aspects of Company Core Safety Information prepared by each manufacturer, including manufacturers of generic products. When one company modifies its data, should all other companies adopt the same change? If so, how would changes be initiated and who would be responsible?
- The Summary of Product Characteristics (SPC) is the approved regulatory document in the European Union (EU). However, whenever the product follows the "multistate" procedure, it is possible that there will be national differences in the local versions of an SPC. Moreover, any differences between the manufacturer's Company Core Data Sheet and the SPC will also be influenced by requirements of regulatory authorities outside the EU, e.g., the FDA in the United States, and the Canadian and Australian authorities. Other areas that would benefit from discussion and consensus relate to whether or how information should be included in the CCSI or DCSI on: effects of withdrawal and drug dependency (including those in newborns); reactions with a possible fatal outcome (e.g., is death due to anaphylaxis "unexpected" if cases with fatal outcome have yet to be reported?); reactions to combination products (are they due to drug interaction or one or more of the component drugs? what effect if any should there be on the CCSI (or DCSI) of the single agent components?).
- The DCSI as proposed by CIOMS Working Group V is a logical and concise but significant addition to Investigator's Brochures. One unresolved issue is how and when to put these DCSI proposals into effect absent current regulatory guidelines. It seems appropriate that they could be used by companies that agree to the suggestions, as soon as they are developed within an organization.

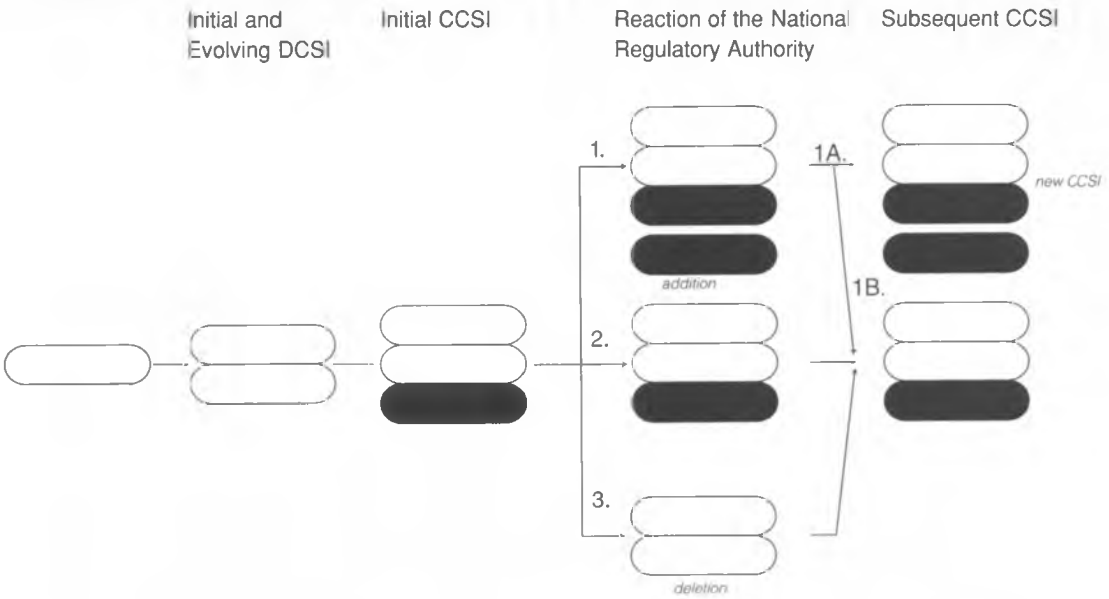
These issues are only examples that serve to demonstrate the complexity of the overall problem.

Figure 1: DRUG SAFETY IN RELATION TO PHASE OF DRUG DEVELOPMENT



* The source is a mixture of study design and information ascertainment.

Figure 2: **INITIAL AND EVOLVING DCSI AND CCSI**



Consequences for CIOMS I and II Proposals for Safety Reporting*

1A. Nil

1B. Over-reporting of labelled reactions (could be filtered by the local affiliate)

2. Nil

3. Either a specific procedure should be set up to prevent under-reporting, or the deleted reaction if non-serious could be reported only in the periodic safety update (if serious, unexpected then expedited reporting still required to that regulator).

* When a Pharmaceutical Manufacturer (PM) proposes a CCSI to different Regulatory Authorities (RA), there are three possibilities:

1. The RA require an additional mention owing to a different evaluation of available data, or to local regulatory/medical requirements, with two possible answers:
   1A. The PM agrees with the RA and includes the new mention in a New CCSI.
   1B. The PM accepts (or rejects) the locally requested version, but considers that confirmation is needed and keeps the initial CCSI
2. The CCSI is approved as proposed.
3. In rare circumstances the RA require a deletion.

12. TABLE

Table: **Ranking of Threshold Criteria***

Criteria	N**	Average Rank	Median	Range
1. Positive rechallenges	18	5.8	5	1-13
2. There is a positive outcome in a study specifically designed to investigate the association between the drug and the adverse drug reaction	18	6.1	6	1-16
3. There are statistically significant differences	17	11.0	8	2-31
4. It is a recognized consequence of overdosage with the drug	17	11.2	9	3-23
5. There is pharmacokinetic evidence (for interactions)	18	12.6	11	3-23
6. Corroborative evidence from different methods of investigation, e.g., clinical trials, animal models	18	12.6	13	3-27
7. There is a relative increase in frequency in treated group over placebo	18	13.1	13	1-33
8. There is a known mechanism	18	13.3	13	1-30
9. Recognized class effect of the drug	18	13.6	12	7-23
10. Definitive cases	15	14.3	6	1-38
11. Consistency between cases in the pattern of presenting symptoms	18	14.7	14	7-27
12. Similar findings in animal models	18	15.5	14	3-26
13. Consistency of time to onset between cases reported	18	15.8	17	4-33
14. Closeness of the drug's characteristics with those of other drugs known to cause the ADR, e.g., being in the same therapeutic class	18	16.1	16	7-25
15. Similar adverse reactions are already recognized for the drug	17	16.6	16	3-27
16. Evidence from clinical trials rather than from spontaneous cases	18	16.7	13	3/38
17. The time to onset is plausible in the cases	18	17.7	16	2-36
18. Positive de-challenges	18	18.0	16	2-36

* Two criteria — viz., Positive dose response, and Positive specific laboratory or in vitro test — were identified after the ranking exercise.

** N = number of Working Group members voting.

Table [Continued]

Criteria	N	Average Rank	Median	Range
19. An identifiable subgroup at particular risk	17	18.6	16	5-36
20. High frequency of reports	16	19.1	19	6-33
21. Biological plausibility		19.5	18	3-35
22. The adverse experience when it occurs in normal clinical practice is usually drug-related	17	20.0	19	12-33
23. There is evidence from observational post-marketing surveillance studies	16	20.3	16	5-38
24. Lack of confounding factors in the reported spontaneous cases	17	21.3	20	5-35
25. The amount and duration of exposure is appropriate in the patients	17	21.8	20	9-32
26. There is a consistent trend in studies, even though not statistically significant	18	22.3	18	5-33
27. The studies identifying the ADR are well designed	17	23.3	22	5-39
28. The drug is known to affect the same body system as the ADE in some other way***	17	23.3	22	5-39
29. Corroboration of the accuracy of the spontaneous case histories	17	24.2	27	3-37
30. Individual cases considered probably due to the drug by the person reporting them	17	24.5	29	6-36
31. A low background incidence	17	24.8	26	8-36
32. Cases are clear-cut, i.e., easily evaluated	17	24.9	30	4-36
33. The data are objective rather than subjective	18	25.1	28	5-36
34. The lack of obvious alternative explanations	17	26.5	29	5-39
35. Co-medication being unlikely to play a role	18	27.2	30	5-36
36. It is reported to occur in children	16	29.1	33	4-39
37. Cases were reported outside any period of turbulence surrounding the drug	18	30.5	31	19-37
38. The reporters are of high status (credibility)	17	33.6	31	16-39
39. Although there is no other corroborative evidence, there is no contrary evidence	18	34.1	35	23-39

***E.g., if a drug is known to cause CNS-related symptoms, a new signal for depression is more likely to be associated.

13. APPENDICES

APPENDIX 1: European Summary of Product Characteristics (SPC) and U.S. FDA Requirements for Labeling

This Appendix contains:

1. The full text of the "Summary of Product Characteristics", the definitive statement, agreed by a manufacturer and the European Communities, of facts and recommendations regarding the prescription and use of a medicinal product approved for marketing; it is referred to as document III/9163/90-EN (approved by the Committee on Proprietary Medicinal Products (CPMP) on 16 October 1991 and effective as of 1 January 1992).
2. A summary of the U.S. FDA requirements found in the 1 April 1993 edition of the US Code of Federal Regulations, under 21 CFR Chapter 1, §201.56 General Requirements on Content and Format of Labeling for Human Prescription Drugs and 21 CFR Chapter 1, §201.57 Specific Requirements on Content and Format of Labeling for Human Prescription Drugs.

CPMP OPERATIONAL WORKING PARTY
NOTE FOR GUIDANCE

TITLE: Summary of Product Characteristics

Discussion in Working Party	**February 1991**
Transmission to CPMP	**March 1991**
Transmission to Interested Parties	**March 1991**
Comments Requested Before	**September 1, 1991**
Resubmission to Working Party	**September 26, 1991**
Final Approval by CPMP	**October 16, 1991**
Date for coming into operations, i.e., for new applications	**January 1, 1992**

THE FUNCTION AND ROLE OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Introduction

The function and role of the summary of product characteristics is defined in Directive 65/65/EEC. The summary of the product characteristics forms an intrinsic and integral part of the marketing authorization.

The content of the summary is given in Article 4(a) of Directive 65/65/EEC and must be approved by the competent authority.

The purpose of the summary of product characteristics is to set out the agreed position of the product, as distilled during the course of the review process. It is the definitive statement between the competent authority and the company, and indeed, it is also the common basis of communication between the competent authorities of all Member States.

As such, therefore, the content of this document cannot be changed except with the express approval of the originating competent authority.

In some Member States, a data sheet is prepared based on the summary of product characteristics as a means of communication with prescribers/suppliers. In order to avoid this duplication of effort, the value of also using the SPC as a basis of information for the prescriber/supplier has been appreciated. This objective is compatible with the approach envisaged for user leaflets and the promotion of medicinal products.

In the light of harmonization activities and especially the inclusion of the SPC as part of the CPMP opinion, it was further considered useful to have an agreed sequence for the presentation of information within the SPC, to which all Member States would adhere. The sequence is as follows:

1. Name of the Medicinal Product
2. Qualitative and Quantitative Composition
3. Pharmaceutical Form
4. Clinical Particulars
   - 4.1 Therapeutic Indications
   - 4.2 Posology and Method of Administration
   - 4.3 Contra-indications
   - 4.4 Special warnings and special precautions for use
   - 4.5 Interaction with other medicaments and other forms of interaction
   - 4.6 Pregnancy and lactation
   - 4.7 Effects on ability to drive and use machines
   - 4.8 Undesirable effects
   - 4.9 Overdose
5. Pharmacological Properties
   - 5.1 Pharmacodynamic properties
   - 5.2 Pharmacokinetic properties
   - 5.3 Preclinical safety data
6. Pharmaceutical Particulars
   - 6.1 List of excipients
   - 6.2 Incompatibilities
   - 6.3 Shelf life
   - 6.4 Special precautions for storage
   - 6.5 Nature and contents of container
   - 6.6 Instructions for uses/handling
   - 6.7 Name or styles and permanent address or registered place of business of the holder of the marketing authorization.

SUMMARY OF PRODUCT CHARACTERISTICS

1. **NAME OF THE MEDICINAL PRODUCT**
2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
   in terms of the active ingredients (INN name)
3. **PHARMACEUTICAL FORM**
   (with reference to the standardized terminology)
4. **CLINICAL PARTICULARS**

4.1 Therapeutic Indications

- Avoid a global description. The indication(s) should relate as precisely as possible to the results of clinical trials.
- Indicate: treatment and/or prevention and/or diagnosis.

4.2 Posology and Method of Administration, e.g., adults, neonates, children and the elderly and mention of the posology for each age category.

- dosage (dose and interval) and duration
- dosage adjustment in renal or liver insufficiency, dialysis, concomitant disease
- maximum tolerated daily dose and the maximum dose for an entire course of therapy
- monitoring advice.

4.3 Contra-indications: Situations where patients should NEVER or GENERALLY NOT be treated. In rare cases where the medicinal product should NEVER be given, this must be specifically outlined.

4.4 Special warnings and special precautions for use

They are intended to:

- WARN prescribers or suppliers of the possibility of class- or drug-related adverse reactions (ADR) occurring under normal conditions of use or in particular situations such as renal, hepatic or cardiac failure, elderly, young...[with the exception of pregnancy and lactation, ability to drive and use machines, interactions which are respectively dealt with in 4.5, 4.6, and 4.7]

AND

- describe the conditions under which the medicinal product may be recommended for use in sub-groups of patients at risk, provided that the special conditions of use are fulfilled. Inform prescribers of the tentative ways to prevent the occurrence or the worsening of these ADR, by monitoring patients and/or reduction of doses, discontinuation of the treatment.
  Emphasis can be given to a serious risk by underlining the seriousness (i.e., possibility of death) and presenting the labeling at the top of the paragraph, in bold type, within a box.

4.5 Interaction with other medicaments and other forms of interaction

Only interactions which are observed and/or potential on the basis of experience with drugs of the same pharmacotherapeutic group which are or may be clinically meaningful.

- medicinal products used for the same indications
- medicinal products used for other indications
- daily activities, e.g., meals

The following information should be given for each interaction:

a. mechanism of action (if known)
b. consequences on plasma levels of drugs and/or on laboratory and clinical parameters
c. recommendations:

- contra-indication (cross-referral with 4.3)
- not recommended association
- precautions for use (i.e., dose adjustment)
- or to be taken into account

4.6 Pregnancy and lactation

Refer to guideline "Categorization of medicinal products for use during pregnancy".

a. conclusions from the animal reproduction/fertility study and the human experience
b. the risk in humans at different times of pregnancy, as assessed from a.
c. information on the possibility of using the medicinal product in fertile and pregnant women.

Use during lactation

When the active substance or its metabolites are excreted in the milk, a recommendation as to whether to stop or continue breast-feeding and the likelihood and degree of adverse reactions in the infant should be given.

4.7 Effects on ability to drive and use machines

On the basis of:

- the pharmacodynamic profile, reported ADR

and/or

- impairment of driving performance or performance related to driving, the medicine is:
  1. presumed to be safe or unlikely to produce an effect
  2. likely to produce minor or moderate adverse effects
  3. likely to produce severe adverse effects or presumed to be potentially dangerous

For situations 2 and 3, special precautions for use/warnings relevant to the categorization should be mentioned.

4.8 Undesirable effects

Quantitate these effects (frequency in general terms and seriousness). Significant adverse reactions observed or the most predictable on the basis of:

- toxicology, especially finding from repeated dose toxicity studies;
- previous clinical experience with products of the same class.

4.9 Overdose

- acute experience in animals
- human experience
- management of overdose in man

5. PHARMACOLOGICAL PROPERTIES (so far as this information is relevant for therapeutic purposes). Statements should be brief and precise.

5.1 Pharmacodynamic properties

- pharmacotherapeutic group
- mechanism of action (if known)
- pharmacodynamic effects:

relevant for prescription [effects for which there is a demonstration or at least some evidence of a relationship with the therapeutic effect or which may induce ADR]: they should be concisely described.

5.2 Pharmacokinetic properties

Relevant information should be given on:

a. general characteristics of the active substance

- absorption, with the bioavailability of the dosage form and, for the oral route, whether it is due to liver first pass effect, incomplete absorption, the influence of food;
- distribution, with reference to plasma protein binding, volume of distribution, tissue and/or plasma concentrations, pronounced multi-compartment behaviour;
- biotransformation, to active metabolites, inactive metabolites and in the case of pro-drugs, to the active substance.
- elimination with reference to:
  - the elimination half-lives, the total clearance
  - excretion (with partial clearances)
  - the unchanged substance and metabolites (and their activities)
  - linear or non-linear kinetics

b. characteristics in patients

- any known relationship between plasma/blood concentrations and the therapeutic activity or adverse drug reactions
- variations with respect to confounding factors, age, polymorphic metabolism and concomitant pathological situations (renal failure, hepatic insufficiency)

5.3 Preclinical Safety Data

Information should be given on any findings in the preclinical testing which could be of relevance for the prescriber in recognizing the safety and safety profile of the product used for the authorized indication(s), and which is not already included in other relevant sections of the SPC. The information should be presented in a way that enables the prescribing physician to apply the benefit/risk of use of the product for the individual patient.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

A full statement of the excipients expressed qualitatively.

6.2 Incompatibilities

Information on physical and chemical incompatibilities of the product with others with which it is likely to be mixed or co-administered. This will be particularly important for products to be diluted before parenteral administration. Significant problems of sorption of product to syringes, large volume parenteral containers, etc., should be stated.

6.3 Shelf-life

shelf-life in the product as packaged for sale
shelf-life after dilution or reconstitution according to directions
shelf-life after first opening the container

6.4 Special precautions for storage

The maximum (or minimum) storage temperatures should be stated in Celsius to fully reflect conditions found in any EC Member State in which the product is likely to be sold or supplied, unless the stored product is stable at temperatures up to 30°C when the product need bear no special storage instructions.
Special precautions in relation to humidity and light should also be stated.

6.5 Nature and contents of container

Reference to standardized terminology with a description.

6.6 Instructions for use/handling

Instructions for use/handling are needed where:

- the product as such is not intended for immediate use and has for instance to be suspended or diluted before administration. Claims on compatibilities can be given here provided these have been proven in the dossier.
- due to the nature of the product or the packaging/closure the way of using/handling the product is not obvious without instructions.
- a special dosing device to administer the product has to be used.

6.7 Name or style and permanent address or registered place of business of the holder of the marketing authorization.

7. MARKETING AUTHORIZATION NUMBER

8. DATE OF APPROVAL/REVISION OF SPC

SPECIFIC REQUIREMENTS ON CONTENT AND FORMAT OF LABELING FOR HUMAN PRESCRIPTION DRUGS IN THE USA

21 CFR §201.57. Major Sections. Specific requirements on content and format of labeling for human prescription drugs.

A. Description
B. Clinical pharmacology
C. Indications and usage
D. Contraindications
E. Warnings
F. Precautions
G. Adverse reactions
H. Drug abuse and dependence
I. Overdosage
J. Dosage of administration
K. How supplied
L. Animal pharmacology and/or animal toxicology
M. Clinical studies and references

Major Sections with Brief Comments

A. Description

1. Proprietary and established name
2. Type of dosage form and route of administration
3. Qualitative and/or quantitative ingredient information
4. State "sterile" if product is so
5. Pharmacological or therapeutic class
6. Chemical name and structural formula
7. If the medicine is radioactive, statement of important nuclear physical characteristics.
8. If appropriate, other important chemical or physical information.

B. Clinical Pharmacology

1. Concise factual summary of the clinical pharmacology and actions of the drug in humans.
2. Selected *in vitro* or animal tests that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use.

C. Indications and Usage

1. The drug is indicated for treatment/prevention/diagnosis of a disease, manifestation of a disease, symptomatic relief, or as adjunctive therapy.

2. If relevant, comment on safety and effectiveness in selected population subgroups, timing of administration (e.g., only for cases refractory to other drugs), etc.

D. Contraindications

Section should describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit.

E. Warnings

Section should describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur.

F. Precautions

1. Information regarding any special care to be exercised by the practitioner for safe and effective use of the drug.
2. Information for patients, e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects.
3. Laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions.
4. Drug-drug interactions/drug-laboratory test interactions.
5. Carcinogenesis, mutagenesis, impairment of fertility.
6. Pregnancy, including teratogenicity (Classification A, B, C, D, X) and non-teratogenic effects.
7. Impact on labor and delivery.
8. Nursing mothers.
9. Pediatric use — if inadequate data to support use in the pediatric population, one of the following statements should be made:
   "Safety and effectiveness in children have not been established."
   or
   "Safety and effectiveness in children below the age of ( ) have not been established".

G. Adverse Reactions

An undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.

H. Drug Abuse and Dependence

1. If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled should be stated.
2. If appropriate for the drug involved, types of abuse and relevant reactions should be stated here.

3. Characteristic effects of dependence, and quantity of drug leading to tolerance or dependence.

I. Overdosage

This section should describe the signs, symptoms, and laboratory findings of acute overdosage and the general principles of treatment.

J. Dosage and Administration

This section should state the recommended usual dose, the usual dose range, and, if appropriate, an upper limit beyond which safety and effectiveness have been established.

K. How Supplied

Information on the available dosage forms to which the labeling applies.

L. Animal Pharmacology and/or Animal Toxicology

In general, this section is not necessary, and relevant information can be placed in other sections of the labeling.

M. Clinical Studies and References

APPENDIX 2: Membership and Process of CIOMS Working Group III and Contributors to this Edition from CIOMS Working Group V

The original CIOMS III Working Group, which met from April 1992 through March 1994, is listed below, followed by a chronology of its work. Those with an asterisk next to their name were also part of the CIOMS V group, which contributed to the current revision of the CIOMS III report.

Additional contributors to the 2nd edition, who were also full-time members of the CIOMS V Working Group, were: Anne Castot (Agence du Medicament, France), Gaby Danan (Hoechst Marion Roussel, France), Peter Folb (University of Cape Town, South Africa), Edith La Mache (EMEA, London), John Milander (Novartis, Basel) and Norbert Paeschke (Federal Institute for Drugs and Medical Devices, Berlin).

Name	Organization	Full time/Part time
*Zbigniew Bankowski	CIOMS	Full time
*Christian Benichou	Roussel Uclaf	Full time
Rudolph Bruppacher	Ciba-Geigy	Full time
*Win Castle	SmithKline Beecham	Full time — Co-Chair
*Diane Chen	CKW Consultants	Full time
Margaret Cone	IFPMA	Part time — Observer
Willard Dere	Lilly	Full time
*Ralph Edwards	WHO Collaborating Centre	Full time
*Arnold Gordon	Pfizer	Full time
Joyce Johnson	FDA	Full time
*Gottfried Kreutz	German Authority	Full time — Co-Chair
*Murray Lumpkin	FDA	Full time
John Nazario	FDA	Part time — Observer
Marisa Papaluca	Italian Authority	Part time
Suresh Rastogi	FDA	Part time — Observer
*Sue Roden	Glaxo	Full time — Secretary
Rene Jean Royer	French Authority	Full time
*Bruce Rowsell	Canadian Authority HPB	Full time
*Jens Schou	University of Copenhagen and CPMP	Full time
*Barbara Sickmuller	BPI (Germany)	Part time — Observer
*Wendy Stephenson	Wyeth-Ayerst	Full time
*Hugh Tilson	Burroughs Wellcome	Full time
*Martin ten Ham	World Health Organization	Full time
*Ernst Weidmann	Hoechst	Part time
Jean-Michel Weiss	Hoffman-LaRoche	Full time
*Bengt-Erik Wiholm	Swedish Authority	Full time
*Susan Wood	British Authority	Full time

At the first meeting of the CIOMS III Group (London, April 1992), the members agreed on the definition of Company Core Data Sheet (CCDS) with special reference to safety components and determined that their primary focus would be information on prescription drugs for prescribers and, particularly, on undesirable effects, and there was a brief brain-storming session. The purpose was to identify factors relevant in deciding whether or not to include an undesirable effect in the CCSI, and it was decided that each member would write, as a basis of discussion, one or two pages of a borderline scenario based on real drugs.

At the second meeting (Ottawa, September 1992), four of the 40 drug scenarios created were reviewed together, and each Working Group member agreed to evaluate the 36 remaining scenarios to decide whether the CCSI should be amended and to list the reasons behind the decision.

At the third meeting (Washington, March 1993), the 174 reasons introduced were reviewed independently and members indicated individually their agreement or disagreement. After the meeting, 39 of the 174 reasons were identified as factors related to "strength of the evidence" that a drug actually caused an ADR as opposed to usefulness or what could loosely be defined as good labelling practices. As homework, these 39 reasons were ranked in order of importance. Although those Working Party members attending the DIA Annual Meeting in Chicago (July 1993) met to review a very early draft report based on discussions and agreements to date, it was at the fourth meeting (Paris, September 1993) that the format of the final report was agreed and work allocated for drafting its different sections. Subsequent discussions and meetings by members of an editorial committee of the Working Group through November 1994 led to the final report. At the final meeting (North Carolina, March 1994), further recommendations were agreed and work was allocated for updating the early draft final report for further circulation and agreement among Working Group members.

At its first meeting in April 1997, the CIOMS V Working Group was aware that supplies of the CIOMS III report were no longer available (out of print) and it recognized that a revision of the CIOMS III report was needed to provide guidance on Company Core Safety Information for Investigator's Brochures (IB). Win Castle prepared a proposal on IBs that went through several drafts for review and discussion by the rest of the CIOMS V group through its October 1998 meeting. Comments were also solicited from selected parties outside the CIOMS V Working Group, not only on the IB proposal but on the original CIOMS III report. These comments were taken into consideration and incorporated when judged relevant and appropriate. Subsequently, an editorial committee, consisting of Win Castle, Arnold J. Gordon (chief editor), Murray Lumpkin, and Hugh Tilson prepared the final manuscript for the second edition. It was finalized in November 1998.

APPENDIX 3: Some illustrative drug scenarios used by the Working Group

HOW SHOULD DIFFERENT DOSAGE FORMS AND RESULTS FROM SPECIAL STUDIES BE HANDLED? INFORMATION SHOULD BE USEFUL TO THE PRESCRIBER AND HELP BALANCE RISKS AGAINST BENEFITS.

Case 1 — Benzodiazepine and Antibiotic Interaction

Background:

Drug A is a benzodiazepine indicated for sedation, available in both tablet and injectable liquid forms. The intravenous formulation of Drug A is often given orally to children, although this is not a use approved by the company or the regulatory authorities. Drug B is an antibiotic available in oral liquid and tablet form.

On the basis of reports in the literature of oversedation after the use of Drug A orally in combination with Drub B, the company decided to conduct an interaction study of Drug A and Drug B.

Data Available:

- *Published Literature*: Individual case reports in the medical literature suggested increased oversedation in patients taking both Drug A and Drug B orally.
- *Clinical Trial Data*: No cases of interaction-related sedation reported. An interaction study showed that, after oral administration of Drug A, the first pass effect of Drug A was altered when Drug B was present resulting in a prolonged sedative effect of Drug A. After intravenous administration of Drug A in the presence of Drug B no clinical-effect changes were observed.
- *Spontaneous Reports*: Only the published literature reports mentioned above were known.

Action Taken: The company decided to amend the core safety data sheets for Drug A Oral and Injectable: "The plasma concentration of Drug A, following oral administration, has been shown to increase when Drug A is used in combination with Drug B and this results in potentiation of Drug A's sedative effect. A much smaller change in plasma concentration, with no observed potentiation of the sedative effects, was observed following intravenous administration of Drug A; however, caution is advised".

Discussion: As a result of the Drug A-Drug B interaction study, the company would be obliged to amend only the Drug A Oral core safety data sheet. Commonsense would dictate, however, that a statement about the interaction be placed in the Core safety data sheet for Drug A Injectable as well, taking into account its use in a way not covered by the approved data sheet without "promoting" its unapproved use.

UPDATING THE CORE SAFETY DATA SHEET: WHAT TERMS WITHIN AN ADVERSE REACTION CATEGORY SHOULD BE ADDED? (Section 3b.)

Case 2 — Antibiotic and Behavioural Disturbance

Background:

Drug A is a cephalosporin indicated for treatment of a variety of bacterial infections in adults and children. In 1990, the Drug A core safety data sheet contained the terms: *reversible hyperactivity, nervousness, insomnia, confusion , hypertonia, dizziness and somnolence.* The actual causal relationship between Drug A and these central nervous system (CNS) adverse events was unclear since the vast majority of events occurred in children given Drug A for infection and the observations were made in the setting of fever, pain, concurrent medications such as anticholinergics and sympathomimetics and disruptions in the home or child-care arrangements associated with illness.

The company decided to review all spontaneous reports received between 1983 and 1989 for event terms related to CNS/behavioural disturbances (abnormal dreams, agitation, anti-social reaction, confusion, delirium, emotional instability, hallucinations, hostility, nervousness, paranoid reaction, personality disorder, psychosis) to determine what adverse reactions, if any, should be added to the data sheet.

Data Available:

- *Published Literature:* A few articles attributing CNS/behavioural disturbances to the use of beta-lactam antibiotics; included were reports of irritability associated with systemic hypersensitivity reactions and hyperactivity associated with medications used for "colds".
- *Clinical Trial Data:* A few isolated reports of various CNS/behavioural disturbances were reported during clinical trials in both Drug A and placebo groups.
  Spontaneous Reports (1983-1989): a total of 236 events representing 199 cases were reviewed, of which 22 cases met the company categorization of "severe" event, while the remainder were assessed as being "mild" or "moderate". Of the 22 reports, 16 were reports of hallucinations, all occurring in patients with proven or presumed infections. Of the 16 reports of hallucinations, six patients had received concurrent medications such as decongestants with antihistamines which may have provoked CNS disturbances and, in four patients, the temporal sequence of Drug A administration and hallucinations was unclear. In the remaining six patients, there appeared to be a temporal relationship between Drug A administration and event — hallucinations occurred during therapy and stopped after Drug A was discontinued or occurred within five days after discontinuation of Drug A. No rechallenge information was available.

Action Taken: The company added the adverse event term "hallucinations" to the core safety data sheet safety data sheet.

Discussion: This is an example of the difficulty frequently encountered by drug-safety professionals in the reviewing of spontaneous reports when they must decide whether or not to include an event where the association is highly uncertain. A temporal relationship between Drug A and hallucinations appeared to exist in 6/22 patients. The clinical trial data did not corroborate the spontaneous reports and rechallenge data were not available in the spontaneous cases. However, in the presence of a plausible temporal relationship and given the severe nature of the hallucinations, the company decided to make a change to the Drug A core safety data sheet.

WHEN SHOULD THE CORE SAFETY DATA SHEET OF A NEWLY MARKETED DRUG BE MODIFIED IN RELATION TO THE AVAILABILITY OF OTHER TREATMENTS (see Section 4g)

Case 3 — Antibiotic and Hypoglycaemia

Background:

Drug A is a broad-spectrum oral antibacterial agent, approved and newly marketed. The initial approved core safety data sheet for the product did not include "hypoglycaemia". The data sheet did mention "additional laboratory adverse events including elevation of blood glucose". Within three months of marketing, a regulatory authority received multiple spontaneous reports of hypoglycaemia associated with Drug A. A comparison with other antibiotics of the same chemical class yielded only occasional reports of hypoglycaemia reported over many years of marketing.

Data Available:

- *Published Literature:* No published reports of hypoglycaemia associated with Drug A.
- *Clinical Trial Date:* No cases of hypoglycaemia reported, although elevation of blood glucose was reported and an abnormal laboratory value.
- *Spontaneous Reports:* Eleven cases of documented severe hypoglycaemia associated with Drug A use were reported to the regulatory authority. All patients were over 70 years of age (nine were female) and five were taking various glucose-lowering agents. Of the 11 patients, one (with a previous history of stroke) had a stroke at the time of the hypoglycaemia, and another (with no previous history of CNS disorder) had convulsions with the hypoglycaemia. The time to onset of hypoglycaemia was from 1-5 days after initiation of Drug A therapy with half of the cases occurring after 2-3 days treatment with Drug A.

Action Taken: The company was asked to amend the Drug A data sheet to reflect the "severe hypoglycaemia" data from spontaneous reports.

Discussion: These cases of hypoglycaemia were serious with documented low serum-glucose levels in patients with and without histories of glucose instability.

There appeared to be to be a similar temporal relationship to Drug A use in all cases. Further, these 11 cases were of particular concern because they represented a significant percentage of the total number of initial post-marketing reports on Drug A. As the product was only recently marketed, the drug use (denominator) was believed to be relatively low. It was felt that this problem appeared to be unique to Drug A and did not occur with other drugs in its class, and thus only a modification of the Drug A data sheet (and to the company's CCSI) was considered necessary.

APPENDIX 4: Fictitious example of CIOMS III proposals

QWEASYTROL: COMPANY CORE SAFETY INFORMATION

POSOLOGY (DOSING) AND METHOD OF ADMINISTRATION

Adults and Children 12 Years and Over

NB. Reduce dose in severe renal impairment (see relevant section).

- **Oral**
  The starting dose is **10mg three times daily**. The daily dose of 30mg may be increased by increments of 15mg per day every **three** days until symptoms are relieved. More rapid dose escalation may result in severe sedation.

  Maximum daily dose: 75mg daily.

- **Parenteral (For Short-Term Treatment Only)**
  2mg diluted to 50ml in normal saline and administered by slow intravenous infusion over at least 20 minutes. More rapid or more concentrated administration may result in visual disturbance or, rarely, transient blindness. The dose may be repeated every eight hours until oral therapy is possible.

  Maximum dose: 6mg daily for no longer than three days.

Children Under 12 Years

Experience with qweasytrol in children under 12 years is limited and its use has not been fully evaluated in clinical studies. No dose recommendations can be made.

Elderly

Qweasytrol is generally well tolerated by patients over 65 years but it may be necessary to titrate the dose more slowly (e.g., by five-day increments) to prevent sedation.

Renal Failure

Dose reduction is only necessary in patients with severe renal impairment **(creatinine clearance $\leqslant$ 30ml/min)**.

- **Oral**

The starting dose is **5mg twice daily** titrated by increments of **5mg** every **three** days until symptoms are relieved.

Maximum dose: 45mg daily.

- **Parenteral (For Short-Term Treatment Only)**

  1mg diluted to **50ml** in normal saline and administered by slow intravenous infusion over **at least 20 minutes**. More rapid or more concentrated administration may result in visual disturbance or, rarely, blindness. The dose may be repeated **every 12 hours** until oral therapy is possible.

  Maximum dose: 2mg daily for no longer than 3 days.

CONTRAINDICATIONS

- Qweasytrol is contraindicated in patients who have received **monoamine oxidase inhibitors** (excluding MAOI-B) within the previous 14 days, as there have been reports of fatal hypertensive crises.
- Qweasytrol is also contraindicated in patients who have shown hypersensitivity to any component of the product.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

- When qweasytrol has been used in the unlicensed indication of sedation prior to minor investigative procedures there have been isolated reports of acute **hepatic necrosis**. One case, in which a single oral dose of 150mg had been administered, was fatal.
- Use with caution in patients with a history of **epilepsy** or **structural brain lesions**, which may lower seizure threshold.
- Administer reduced doses in patients with **severe renal impairment** (see POSOLOGY).
- Use with caution in patients receiving concurrent **hypnotic** or **anxiolytic** therapy as severe sedation may occur.

INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION

- For interaction with monoamine oxidase inhibitors (excluding MAOI-B), anxiolytic and sedative therapies, see above.
- Consumption of alcohol may also result in severe sedation. Studies in normal volunteers pre-treated for three days with qweasytrol, 30mg daily, and then given 10g of alcohol, showed that the clearance of alcohol was delayed by up to 30% compared with controls.
- **Interference with Laboratory Tests**
  Qweasytrol may be responsible for false-positive results in the direct Coomb's test.

USE IN PREGNANCY

There is limited information on the use of qweasytrol in pregnancy. In those cases where an outcome is known, the majority have resulted in normal, healthy infants but there have been isolated reports of cleft lip

and palate in babies born to mothers who have taken qweasytrol during the first trimester of pregnancy. The incidence is similar to that seen in the general population of non-drug users. There is no evidence from animal studies of teratogenicity or developmental delays with normal doses. At very high doses, in excess of those achieved during therapeutic use, there was some evidence of fetal resorption in rabbits.

Qweasytrol may be continued during labour and delivery but the newborn should be monitored for signs of sedation.

Use During Lactation

Qweasytrol is mildly lipophilic and excreted in breast milk in rats, with a milk-to-serum ratio of 1.5 to 1.0. When administered to nursing mothers in oral doses up to 30mg daily, the dose ingested by the baby is unlikely to exert a pharmacological effect but the mother should be advised to monitor the baby for signs of sedation. No reliable data are available at higher doses and, therefore, safe use of qweasytrol during lactation has not been established.

EFFECTS ON ABILITY TO DRIVE VEHICLES AND OPERATE MACHINERY

When starting therapy, qweasytrol may affect reactivity to the extent that the ability to drive vehicles or to operate machinery is impaired. This may also occur with high-dose prolonged therapy (over 45mg daily) and at all doses after alcohol consumption.

UNDESIRABLE EFFECTS

Clinical Trial Data

The table below shows the adverse experiences reported among patients in controlled clinical trials of oral* qweasytrol, for 12 weeks, in the management of nausea and vertigo associated with Meniere's disease. In includes all adverse experiences reported with an incidence of 1% or greater. A dash represents an incidence of less than 1%.

	Qweasytrol 30-45mg Daily (n = 579) %	Qweasytrol 50-75mg Daily (n = 104) %	Placebo (n = 98) %	Control (n = 326) %
Gastrointestinal				
diarrhoea	7.3	8.5	3.1	8.6
abdominal pain	5.2	7.6	5.1	9.8
nausea	4.8	3.6	37.8	37.8
metallic taste	2.6	3.4	—	—
constipation	1.0	2.2	4.1	—
Neurological				
sedation	18.0	24.0	2.0	2.8
headache	7.1	9.6	1.0	—
drowsiness	4.0	6.4	1.0	—
dizziness	1.2	1.8	50.0	23.0
tremor	—	1.5	—	1.2
Skin				
rash	1.4	—	3.1	5.5
pruritus	—	1.0	—	4.0

	(n = 286) %	(n = 75) %	(n = 98) %	(n = 241) %
Laboratory Data				
low platelet count*	1.7	**2.7**	1.0	—
increased AST**	2.4	**4.1**	—	—
increased ALT**	2.4	**2.9**	—	—

* Platelet count below lower limit of normal (150 x 10^9/1) on at least one occasion
** Value ⩾ 3 times upper limit of normal on at least one occasion (⩾ 120IU/1)

* A similar table covering intravenous dosing experience would be appropriate.

Post-Marketing Data

very common	$\geq 1/10$
common	$\geq 1/100$ and $< 1/10$
uncommon	$\geq 1/1000$ and $< 1/100$
rare	$\geq 1/10{,}000$ and $< 1/1000$
very rare	$< 1/10{,}000$

- **Blood Disorders**

Uncommon: Thrombocytopenia — rapidly reversible on drug withdrawal.

- **Eye Disorders**

Uncommon: Blurred vision.

- *Rare:* Temporary blindness.

Both are associated with rapid intravenous bolus doses of qweasytrol; they are minimized by slow intravenous infusion, the recommended method of intravenous administration (see POSOLOGY).

There have been very rare spontaneous reports of bilateral subcapsular cataracts inpatients on long-term qweasytrol therapy. A record-linkage study has shown that the incidence is no greater than in similar age groups in the general population.

- **Gastrointestinal**

Common: Diarrhoea
Metallic taste

- **Hepatobiliary**

Common: Asymptomatic rises in aminotransferases

Very rare: Hepatic necrosis, particularly with high doses

- **Neurological**

Very Sedation — usually occurs only on starting qweasytrol and resolves

Common: within a few days on continued therapy. It may occasionally limit dose escalation.

Common: Headaches
Drowsiness

Rare: Seizures — predominantly in patients with a history of epilepsy or structural brain lesions.

- **Hypersensitivity and Skin**

Uncommon: Rash, usually maculopapular
Urticaria

Rare: Bronchospasm, associated with severe hypersensitivity reaction only
Very rare: Anaphylaxis

- **Reactions to Excipient**
  Qweasytrol tablets contain the dye, moonrise peach, which may cause hypersensitivity reactions and hyperactivity in susceptible patients.

OVERDOSE

Overdose may result in central nervous system depression ranging from mild sedation to coma and death from respiratory failure, depending on the dose taken. Treatment depends on the time elapsed since the overdose.

Within 4 hours

- Owing to the mode of action of qweasytrol, it is unlikely that ipecacuanha syrup will be effective in inducing vomiting.
- Gastric lavage with isotonic saline followed by activated charcoal is the treatment of choice.
- Plasma qweasytrol levels should be monitored and haemoperfusion considered, if necessary (see below).
- Give symptomatic and supportive treatment for respiratory distress.

After 4 hours

- The overdose will have been absorbed. Give symptomatic and supportive treatment for respiratory distress.
- Measure plasma qweasytrol levels and, if in excess of 2mg/l, begin haemoperfusion.
- Doses in excess of 200mg have been fatal.
- Monitor liver function tests as acute hepatic necrosis has been reported, particularly with high doses of 150mg and above.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Qweasytrol is a highly selective epsilon-G2 receptor antagonist which modulates the effect of serotonin at the $5HT_{17}$ receptor and also has a weak effect on dopamine at the D_8 receptor. At therapeutic doses, it has little effect on other serotonin or dopaminergic pathways.

Pharmacokinetics

- After **oral** administration, qweasytrol is rapidly absorbed, 70% of the maximum concentration being achieved within one hour. After a 10mg dose, the mean maximum plasma concentration is 50ng/mL. The mean absolute bioavailability is 50%, partly due to pre-systemic metabolism.

- At the end of a 20-minute infusion of a single 2mg dose in 50ml normal saline, the mean serum level was 204ng/ml.
- The **disposition** following oral and intravenous dosing is similar.

The elimination half-life is 3.0-3.5 hours. The principal route of excretion is the urine, with approximately 20% of the orally administered dose collected in the urine as unchanged drug in 24 hours.

Non-renal clearance accounts for about 30% of the total clearance.

Metabolism

The major metabolite is the indole acetic acid analogue, which is excreted in the urine as the free acid and the glucuronide conjugates. This metabolite is inactive. No other metabolites have been identified.

Pharmacokinetics in the Elderly

In studies in healthy elderly volunteers ($\geq$ 65 years), the oral bioavailability is increased slightly from 50% to 56% and the elimination half-life is increased from 3.5 hours to 5 hours.

Pharmacokinetics in Severe Renal Impairment

The elimination half-life is increased to 10 hours in patients with a creatinine clearance between 20 and 30ml/min (see POSOLOGY).

APPENDIX 5: Investigator's Brochure: Section 7 of ICH Harmonized Tripartite Guideline For Good Clinical Practice (IFPMA, Geneva, May 1996)

INVESTIGATOR'S BROCHURE

7.1 Introduction

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigator's and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedure. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are

responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

7.2 General Considerations

The IB should include:

7.2.1 *Title Page*

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

7.2.2 *Confidentiality Statement*

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

7.3 Contents of the Investigator's Brochure

The IB should contain the following sections, each with literature references where appropriate:

7.3.1 *Table of Contents*

An example of the Table of Contents is given in Appendix 2.

7.3.2 *Summary*

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3 *Introduction*

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product(s) pharmacological class and its expected position within this class (e.g., advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4 *Physical, Chemical and Pharmaceutical Properties and Formulation*

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5 *Nonclinical Studies*

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g., milligram/kilogram (mg/kg)
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:

- Nature and frequency of pharmacological or toxic effects
- Severity or intensity of pharmacological or toxic effects
- Time to onset of effects
- Reversibility of effects
- Duration of effects
- Dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

(a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single dose
- Repeated dose
- Special studies (e.g. irritancy and sensitisation)
- Reproductive toxicity
- Genotoxicity (mutagenicity)

7.3.6 *Effects in Humans*

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

(a) Pharmacokinetics and Product Metabolism in Humans

A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available.

- Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
- Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
- Population subgroups (e.g., gender, age, and impaired organ function).
- Interactions (e.g., product-product interactions and effects of food).
- Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

(b) Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

(c) Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7 Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

7.4 APPENDIX I:

TITLE PAGE (Example)
SPONSOR'S NAME
Product:
Research Number:
Name(s): Chemical, Generic (if approved)
Trade Name(s) (if legally permissible and desired by the sponsor)
INVESTIGATOR'S BROCHURE
Edition Number:
Release Date:
Replaces Previous Edition Number:
Date:

7.5 APPENDIX II:

TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE

(Example)

N.B. References on 1. Publications, 2. Reports:

These references should be found at the end of each chapter

Appendices (if any)

APPENDIX 6: Results of an informal survey of Seven Regulatory Authority and Eleven Industry CIOMS V Representatives (and Associates).

"EXPECTEDNESS" IN INVESTIGATOR BROCHURES

Imagine that an event **'X'** is only mentioned in an Investigator's Brochure as follows. In which of the following 15 separate circumstances, if any, would you consider **'X'** to be "expected" (listed)?

'Y' means you would consider 'X' to be "expected"
'N' means you would not

	Considered "Expected"	
	REG. AUTH. N = 7	INDUSTRY N = 11
1. 'X' has only been observed during anima toxicology studies to date.	1	0
2. 'X' is stated to be a predicted class effect but it has not yet been observed after treatment with the new drug under development.	2	0
3. 'X' is observed but is considered to be due to the formulation rather than the drug per se.	3	4
4. 'X' is the primary keyword (i.e., the most serious adverse event) in only one circulated investigator letter and was considered possibly drug related in that subject.	4	0
5. 'X' is the primary keyword in 1 circulated investigator letter. There was a positive rechallenge in this case and 'X' was considered to be definitely drug related.	5	1
6. 'X' is a keyword in 3 investigator letters but in none was 'X' considered drug related.	1	0
7. 'X' was not a keyword in any investigator letter but was mentioned "en passant" in a case narrative.	0	0

[Assume the differences in incidence in the following 5 examples did not achieve statistical significance]

			"Expected" YES	
			REG.	IND
	Incidence on Placebo	**Incidence on Drug**		
8. 'X'	0%	5%	**4/6**	**6/11**
9. 'X'	3%	5%	**2/6**	**4/11**
10. 'X'	0%	2%	**2/6**	**4/11**
11. 'X'	2%	0%	**0/5**	**0/11**
12. 'X'	10%	14%	**3/6**	**4/11**
13. 'X'	10%	15%	**3/6**	**4/11**
14. 'X' is a drug reaction stated to occur in the Investigator Brochure in an established indication but not yet in the new indication **4/11**			**4/7**	
15. 'X' is listed for the drug where marketed in established indications but has not yet been encountered in the development program for a new indication.			**4/7**	**7/11**

CIOMS publications may be obtained directly from CIOMS, c/o World Health Organization, Avenue Appia. 1211 Geneva 27, Switzerland. They are also distributed by the World Health Organization, Distribution and Sales Unit, 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 by writing to the above address.

Price: SF 15.—