

Guidelines for Preparing Core Clinical-Safety Information on Drugs

Report of CIOMS Working Group III



Geneva 1995

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VISION

The Working Group envisions that all manufacturers of pharmaceutical products will harmonize their practices regarding Core Safety Information (CSI) that their internal, central Core Data Sheets must contain. As introduced by CIOMS Working Group II, on periodic safety update reporting, CSI 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 the Working Group for the inclusion of CSI in core data-sheets and its modification will lead to application of consistent decision-rules on its content, to the use in common of standard terms and definitions, and 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.

The absence of internationally agreed standards for the format and content of information on pharmaceutical products for prescribers and other health-care professionals is giving rise to discrepancies and inconsistencies from country to country and manufacturer to manufacturer. Therefore, the Working Group also envisions that national regulatory authorities will harmonize their basic requirements for safety information about medical products to be contained in their data-sheets, 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 will 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 prescribers and other health-care 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,
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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 health care professionals of the most relevant and helpful information on the drug's benefits and risks, a statutory requirement linked to a marketing licence 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 periodic drug-safety update summaries for marketed products¹⁾. The concept of a Core Data Sheet (CDS) [see diagram] had been introduced to ensure the availability of a central reference document for manufacturers, and the 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]...

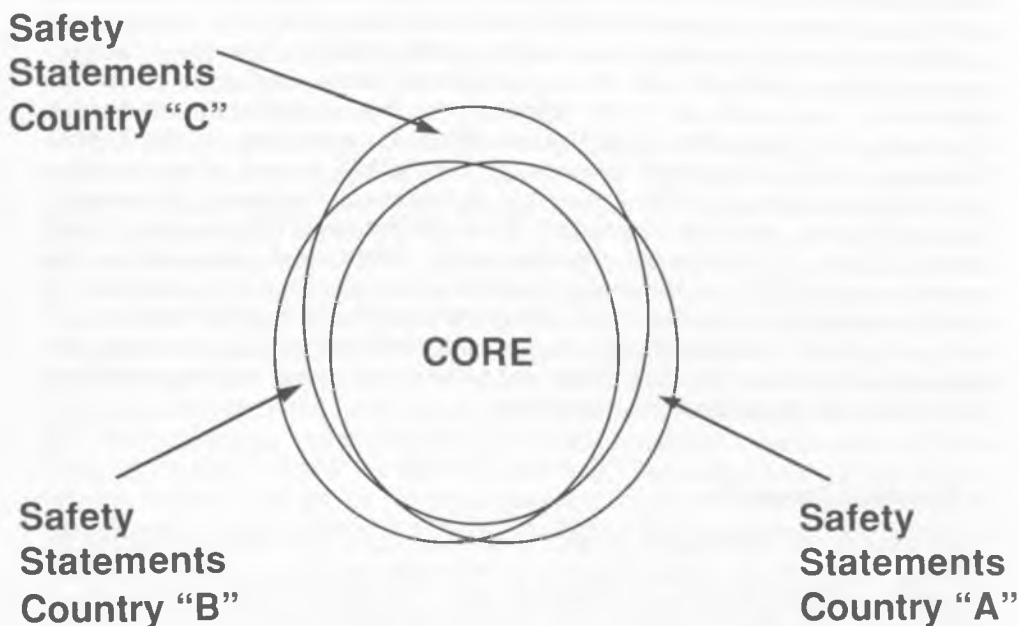
As shown in the diagram, additional safety information of national or local interest or need may be required beyond the CORE. "Safety information" in this report is used as a collective term covering adverse drug reactions (undesirable effects), warnings, precautions, and contraindications, but also 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 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?

¹ *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 Medical Sciences, Geneva.

CORE DATA SHEET



- 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 (CDS) now referred to as Core Safety Information (CSI). It is important to make clear the distinction between a Core Data Sheet (and the 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 CDS contain essential or core information (CSI) about the clinical safety of the medicinal product, including relevant pharmacological properties and information from non-clinical investigation; 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 CSI 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), *Farmaceutiska 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 CDS (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.

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,⁽²⁾ a hospital-based psychiatrist, in proposing a radical revision of data sheets referred to the categorization of adverse reactions with regard to importance and frequency as a "hodgepodge that offers no guidance to physicians." LittleJohn,⁽³⁾ 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 premarketing clinical trial experience or may include postmarketing 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⁽⁴⁾ 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⁽⁵⁾ argued

² Klein, D. F. What Should the Package Insert Be? *Arch. Gen. Psychiatry*, 31:735-41, 1974.

³ LittleJohn, J. K. Package Insert: View of a Rural Town Practitioner, *Drug Information Journal*, 21, 63-5, 1987.

⁴ Hollister, L. E. New Ideas About Drug Labels, *Clin. Pharmacol. Therap.*, (3): 309-13, 1973.

⁵ Graham, G. K. Labeling: What Should It Say And How Should It Say It? *Drug Information Journal*, 25: 211-16, 1991.

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 health 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⁽⁶⁾ 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 multinational 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,⁽⁷⁾ an independent audit group, reports similar findings for European-based companies in four countries, and also supports the establishment of national and international labelling standards.

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.⁽⁸⁾ 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 CIOMS III proposals:

- Core Safety Information should be prepared and used to guide the preparation of national data-sheets, designed to provide doctors and other

⁶ *Drug Labeling in Developing Countries*, Office of Technology Assessment Report OTA464, 102nd Congress of the United States, February 1993.

⁷ HAI to Use OTA Labeling Report, *SCRIP*, No.1830, June 18, 1993, p.17.

⁸ Standard on Material Safety Data Sheets Upheld, *Chemical and Engineering News*, November 15, 1993, p. 51.

health-care 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 CSI should apply to all manufacturers of prescription and non-prescription medicines.
- While data sheets may have legal implications,^(9,10) especially in countries with a culture of litigation, such implications are of secondary importance in providing information to health-care professionals.
- Marketing considerations should not play a major role in the preparation of the CSI.
- 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 CSI 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,⁽¹¹⁾ this topic was considered outside the scope of CIOMS III.
- 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 labelling practices” require flexibility. It is in the spirit of balancing idealism and pragmatism that the Working Group presents these proposals.

The CSI 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

⁹ Young, A. L. and Rave, N. L. Jr., Product Liability Considerations in Prescription Drug Labeling, *Drug Information Journal*, 27 915-20, 1993.

¹⁰ Weber, R.C. Product Liability: Trends Heard Round the World, *Pharmaceutical Executive*, September 1992, pp. 82-86.

¹¹ *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.

general aspects, which influence the What, When, How, and Where of 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 Core Safety Information (CSI)?
- 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 prescriber), 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 CSI 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]. The U.S. requires a similar classification of safety-related product-information (“labelling”); a summary of the provisions contained in 21 CFR § 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 addresses 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
<i>Clinical Particulars</i>			
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	—
<i>Pharmacological Properties</i>	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 were representatives of three United States and five European multinational pharmaceutical companies; of regulatory authorities in Canada, Denmark, France, Germany, Italy, Sweden, the United Kingdom, and the United States of America; of the WHO Collaborative 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. 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 CSI document is presented to exemplify the general proposals (Appendix 4).

2. General Guidelines

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

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

The Working Group agreed at its first meeting that all manufacturers need to provide Core Safety Information (CSI) for each of their marketed products; that the CSI 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 practising physician or other health-care provider anywhere in the world.

The contents of the CSI depend partly on the stage of development of a drug. The answer to the question of what to include in the CSI or add to it depends on whether the drug is new (the first CSI) or already on the market. It also depends on the information. For example (Figure 1, p. 44), a substantial amount of information on relatively frequent pharmacologically predictable adverse drug reactions (Type A) will usually be known when the initial CSI is prepared, but the focus of subsequent monitoring efforts shifts towards rarer, unpredictable, patient-idiosyncratic (Type B) reactions. From a theoretical perspective, the approach 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 CSI in the life-cycle of a prescription drug:

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

When there is extensive information from broad marketing experience, the CSI may become stable and consistent (“mature” CSI), 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 CSI, with considerable revision, is needed, but this is beyond the scope of the present work.

* 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 section 8.

The remainder of this section focuses on the Working Group's general recommendations regarding the initial core-safety-information and subsequent updates from marketing experience and additional development of the product.

b. The First CSI

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

The CSI for use in the initial 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, and¹ 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 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 detected through spontaneous case-reports from marketing experience, which are not available when the first CSI 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 CSI should contain. Generally, the inclusion of an adverse effect in the initial CSI 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. Unless subsequently shown to be misleading or incorrect, the data in the initial CSI should remain unchanged and be supplemented from additional experience.

c. Updating the CSI

- *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 CSI 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 CSI should include conclusions of all studies.

With increasing numbers of patients exposed to a drug after 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 signalled 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 CSI 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 CSI and other sections of its data sheets. More than one CSI 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 CSI. Often, it is not clear to which excipient an adverse event may be attributable. However, in that the CSI 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 CSI; particularly they may contain additional information pertinent to a particular country.*

The CSI 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 CSI, or variations in the wording of the CSI.

Thus, in any given country the official safety-information content may be very close to that in the CSI, but may differ from it. The outcomes of possible national decisions, and their consequences for CIOMS I and II proposals for expedited and periodic safety-reporting, are depicted in Figure 2. Variants include:

- full congruence with CSI — i.e., the “label” in the country contains information identical to the CSI
- full inclusion of the CSI 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 CSI.

The last of these variants, in which a national authority is unwilling to accept the manufacturer’s minimum core-safety-information and requires selective removal of certain items, is expected to occur rarely.

3. WHAT?

a. Introduction

- *Core Safety Information should be determined by the needs of health-care 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.*

The decision to include safety information in the CSI 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 CSI 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 is to be used, and thus the relevance and usefulness of the information to the prescriber. The CSI 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, the Working Group agreed that the CSI, directed as it is primarily to supporting communication to the practising physician, should contain "all relevant or essential information" 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 CSI (see description of process in Appendix 2), no fewer than seven related to the concept of relevance and usefulness.

Individual regulators' requirements are addressed in national labelling or prescribing discussions and are beyond the scope of the CSI, yet they must be guided by and built upon the "core" embodied in the CSI (see 2.f. National Data-Sheet Differences). Additionally, inclusion of information for purposes of legal defence should clearly not be the intent of the CSI. The Working Group emphasized the need to limit inclusions in the CSI 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 commonsense 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 CSI is to provide a summary of information necessary and useful to health-care 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, 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 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 CSI 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.

In conclusion, the Working Group proposal was to avoid including in the CSI 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 CSI.*

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 duty when deciding the content of, or changes in, the CSI. Thus, there is a temptation to add to the CSI, 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 CSI and must prevent the potential adverse consequences associated with a "false alarm" based on information included without good reason or unsubstantiated risks.

d. The CSI and General Medical Knowledge

- *The CSI 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 practise 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 CSI where appropriate, and instruction in general medical diagnosis and care, which should not. The following are examples of material which it is often appropriate to include in the CSI :

- 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 with 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 side-effects.
- 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 CSI 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 CSI.*

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 CSI.

The process has already been described (see Appendix 2) by which an inventory of types and sources of evidence was developed and how the relative contribution of each of the components was scored (see “strength of the data” below).

b. The Concept of Threshold

- *The specific time when safety information must be included in the CSI 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 CSI 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 CSI is determined by the concept of "threshold." 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 their inclusion in the CSI.*

The Working Group identified 39 such relevant factors or criteria that may be useful in determining the threshold for adding an adverse event to the CSI and ranked them in order of importance. The range of ranking in Table I highlights the difficulty of the exercise. The most important criteria include positive rechallenges, 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 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.

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.

THRESHOLD CRITERIA GROUPED

I. According to the Source

I a. 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

I b. 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
 overdose
 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 cases
 The data are objective rather
 than subjective

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

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 prescribers' 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 CSI.

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

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 CSI 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).

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 core data sheet especially early if good alternative drugs are available. Also, if the alternative drugs differ significantly in their safety, the CSI 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 CSI.

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 CSI 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 CSI 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. 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 CSI.*

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 may

be sufficient to include 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 CSI.

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 CSI 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 Contraindications, Warnings or Precaution sections of the CSI.

Removal of a warning in the CSI, 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 CSI 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 CSI).

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 CSI is not recommended, the CSI 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 physicians to be alert to such ADRs. However, unless an ADR has been associated with and is included in the CSI for a drug it is still regarded as "unexpected" (unlabelled), 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 CSI, within and among companies. 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 CSI of a new drug if there is already a known and important class-effect.

c. Format of Initial Core Safety Information (CSI)

- *The initial CSI includes information derived from premarketing clinical trials.*

As previously noted, the primary focus of the CSI 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 possibly some value in also 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 CSI must not contain lengthy lists. On balance, it was felt that only the most important information from core pivotal studies should be presented and the presentation should be clear and concise. 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%. It would be important, in any case, to specify the cut-off value.

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 quote statistical significance, it is important to remember that when comparisons of adverse experiences entail multiple comparisons statistical significance may occur by chance alone.

The following example is provided as guidance:

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 “expected” ADRs for regulatory reporting requirements. Unless they also appear in the list of attributable undesired effects they would normally be considered not expected.

	PRODUCT (N = 600) %	Placebo (N = 80) %	Control 1 (N = 90) %	Control 2 (N = 100) %
<i>Gastrointestinal</i>				
constipation	6.9	—	34.1	2.1
diarrhoea	6.5	4.9	8.0	10.3
dyspepsia	5.9	—	13.6	3.1
flatul	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
<i>Musculoskeletal</i>				
myalgia	3.1	1.2	1.1	—
<i>Nervous System</i>				
dizziness	1.3	1.2	—	1.0
headache	—	—	1.5	1.2
<i>Skin</i>				
rash	5.2	—	4.5	—

Whether or not a tabulation of adverse events is included in the CSI, 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 uncertainty inherent in estimating the denominator and degree of under-reporting. However, the Working Group felt that, whenever possible, an estimate of frequency should be provided and in a standard form. The following standard categories of frequency are recommended:

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

* Optional categories.

Precise rates will inevitably be based on studies and limited to the more common reactions. For reactions that are fewer 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 be less precise; therefore, the source of the estimates (spontaneous or clinical) should be indicated. Stating the absolute numbers of cases reported may be misleading since they inevitably will become outdated.

e. Good Safety Information: Ten General Principles

As the Working Group discussed the sample case-histories and formulated its proposals, it developed ten general principles governing the overall content of CSI 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.*

When a side-effect is predictable pharmacologically or has been observed with other drugs in the same class, yet has not occurred despite extensive exposure in a susceptible population, it may be mentioned. 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 CSI*

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 CSI clinical descriptions of specific cases.

- *If the mechanism of the 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 CSI to state general medical knowledge. There are, however, special circumstances in which secondary effects may be included. These include circumstances in which: (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 CSI.*

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 CSI 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 included it should be in the efficacy section. If the drug treatment could worsen the underlying condition this should be included in the CSI.

- *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, it should be included in the CSI. In such circumstances 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 CSI 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. While specific recommendations on medical terminology were beyond the scope of this Working Group, it was agreed that terms should be used consistently and in line with recognized standards of diagnosis¹². 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

¹² Basic requirements for the use of terms for reporting adverse drug reactions. *Pharmacoepidemiology and Drug Safety*, 1 (1992), pp. 39-45, 133-137, and 191-196; 2 (1993), pp. 189-193.

“hallucinations” is more informative and thus more helpful. However, if too many terms are included in the CSI, doctors may not read them. Hence, similar terms (e.g., decreased white-blood-cell 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 CSI may be used for “special populations,” e.g., children or elderly. In the initial CSI, 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 CSI, the manufacturer should amend such a statement to reflect evolving knowledge.

6. WHERE?

a. Introduction

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

Core Safety Information is located in different sections of a 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., 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 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 the Working Group 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).

A useful compromise is the statement included in the European Union’s Summary of Product Characteristics (SPC) [Guideline II/9163/89]: “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.

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 of 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, 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 CSI 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 CSI by the Working Group, 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 CSI; 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, 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 CSI 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 CSI in a consistent manner and as promptly as possible.

f. Pregnancy and Lactation

(i). Use During Pregnancy

- *The 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 systemically 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), but also information on malformations associated retrospectively with drug exposure (retrospective analysis) and therefore less reliable than information obtained from prospective monitoring. The CSI 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 CSI is at the discretion of the manufacturer and subject to national product-information requirements. It should be noted that the Teratology Society⁽¹³⁾ has recently advised "that use of such a categorization ratings 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:

¹³ FDA Classification of Drugs for Teratogenic Risk, *Teratology* 49: 446-7, 1994.

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

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 during lactation.*

During pre-approval clinical testing, a drug is usually not administered to lactating 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 CSI. 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 CSI 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, drug regulating blood pressure, hypoglycaemic drug).*

The following examples provide guidance:

- *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 presentation of ADRs within the CSI has been treated extensively in sections 3, 4, and 5, to which the reader is referred.

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, 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 CSI.*

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 CSI (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 CSI.*
- *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

CSI. 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 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 CSI reflects 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 CSI is determined by the company; local regulatory demands should supervene only with appropriate evidence and arguments. Listing an adverse experience in any one country should require re-evaluation of the CSI 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 the Council for International Organizations of Medical Sciences⁽¹²⁾, 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 CSI about another company's drug, with the exception of drug-drug interactions, which should be described in the CSI for all concerned drugs or for antidotes used for treatment of overdose.*

b. Shared Responsibility

- *Health-care providers need to read data-sheets conscientiously and report full and accurate case-details of 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.*

Health-care providers are important partners of regulatory authorities and industry in maintaining quality CSI. 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.*

¹² Basic requirements for the use of terms for reporting adverse drug reactions. *Pharmacoepidemiology and Drug Safety*. 1 (1992), pp. 39-45, 133-137, and 191-196; 2 (1993), pp. 189-193.

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, an editor can 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.*

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 CSI. In that sense the CSI is truly a shared responsibility.

8. SUMMARY OF PROPOSALS

General Guidelines

- *All pharmaceutical manufacturers must prepare Core Safety Information (CSI) for each of their marketed products.*
- *The content of the CSI depends partly on the stage of development and the life cycle of a drug.*
- *There are two stages of CSI, reflecting the life cycle of a drug: the initial CSI and the evolving CSI.*
- *Unless subsequently shown to be misleading or incorrect, the data in the initial CSI 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 CSI; particularly they may contain additional information pertinent to a particular country or region.*

What?

- *Core Safety Information should be determined by the needs of health-care 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 CSI.*
- *The CSI 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 CSI.*
- *The specific time when safety information must be included in the CSI 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 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 their inclusion in the CSI.*
- *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 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 CSI.*
- *Substantial evidence is required to remove or downgrade safety information.*

How?

- *Keep ADRs identified in the initial CSI separate from those identified subsequently.*
- *ADRs should be listed by frequency in body system order.*
- *Although a specific "class label" section of CSI is not recommended, the CSI may contain statements relative to classes of drugs.*
- *The initial CSI includes information derived from premarketing 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:*

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

* Optional categories

- *In general, statements that an adverse reaction does not occur or has not yet been reported should not be made.*
- *As a general rule, clinical descriptions of specific cases should not be part of the CSI.*
- *If the mechanism of the reaction is known it should be stated, but speculation about the mechanism should be avoided.*
- *As a general rule, secondary effects or sequelae should not be listed.*
- *In general, a description of events expected as a result of the progression of the underlying treated disease should not be included in the CSI.*
- *Unlicensed or "off-label" use should be mentioned only in the context of a medically important safety problem.*
- *The wording used in the CSI 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.*
- *The terms used should be specific and medically informative.*
- *The use of modifiers or adjectives should be avoided unless they add useful important information.*
- *A special attribute (e.g., sex, race) known to be associated with an increased risk should be specified.*

Where?

- *Core Safety Information is located in different sections of a 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 any 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, 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 Core Safety Information section on Pregnancy is intended to help decide whether a (potentially) pregnant woman can be treated safely with a drug.*
- *The same principles as those applied to use during pregnancy apply to the use of a drug during lactation.*
- *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, drug regulating blood pressure, 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 CSI.*

Who? — Responsibilities

- *A company should have a diligent and assertive approach towards the CSI.*
- *When indicated, a company should undertake a scientific study to investigate quickly any possibly serious problem.*
- *It is important that the CSI 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 CSI for all concerned drugs or for antidotes used for treatment of overdose.

- *Health-care providers need to read data-sheets conscientiously and report full and accurate case-details of 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.*

9. UNRESOLVED ISSUES

During its deliberations the Working Group identified a number of issues that could not be resolved. Many of these issues were considered to be beyond the scope of the CIOMS III 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 the CSI. 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 Group 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 Group did not feel it was within its 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 core safety information prepared by each manufacturer. 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 SPC. Moreover, any differences between the manufacturer's core data sheet and the SPC will also be influenced by requirements of

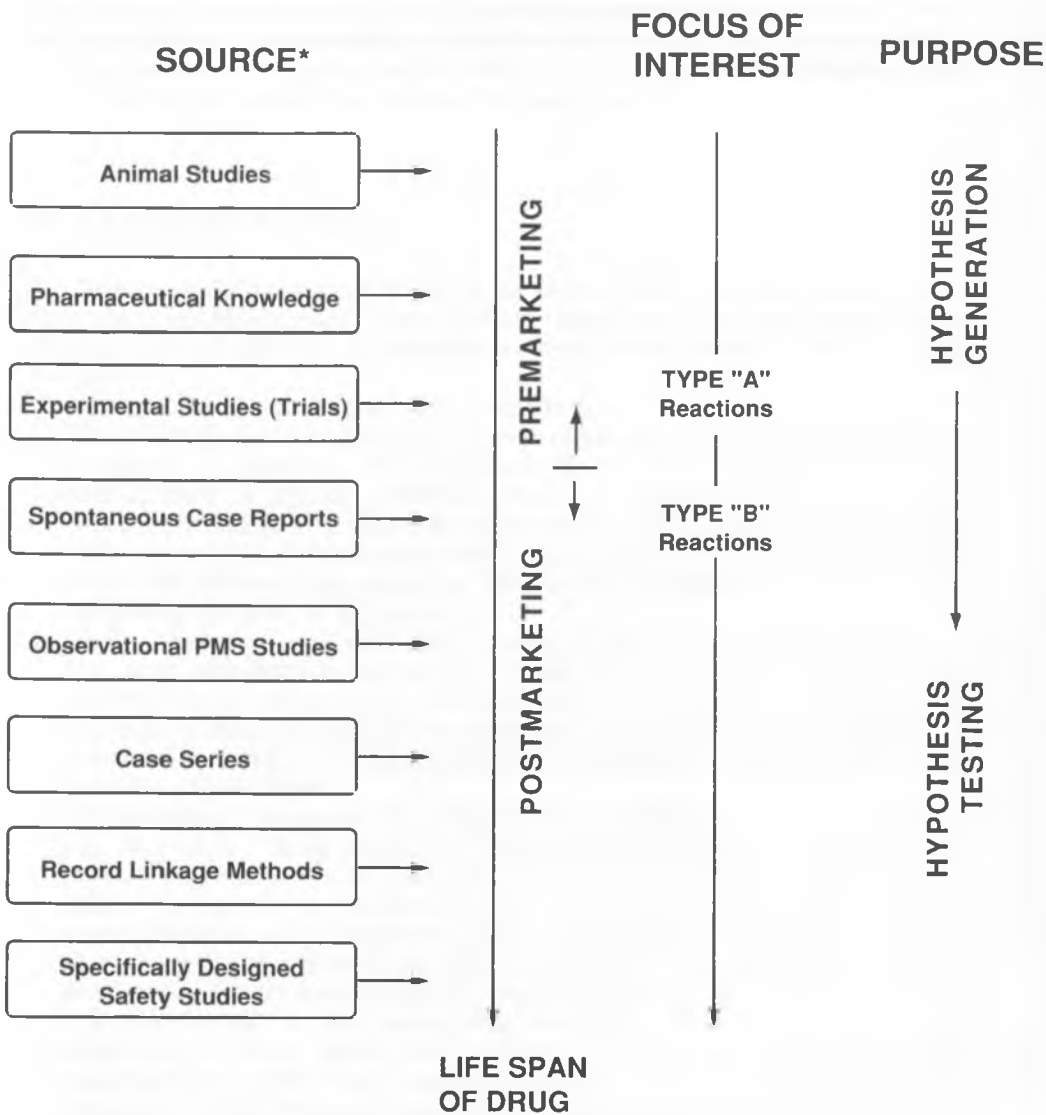
regulatory authorities outside the EU, e.g., the FDA in the United States, and the Canadian and Australian authorities.

- The Working Group also noted that investigator brochures must often be modified because of local regulatory requirements. These modifications complicate the conduct of international studies and the ability to analyse data. It is hoped that an internationally recognized standard for investigator's brochures will become available.

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

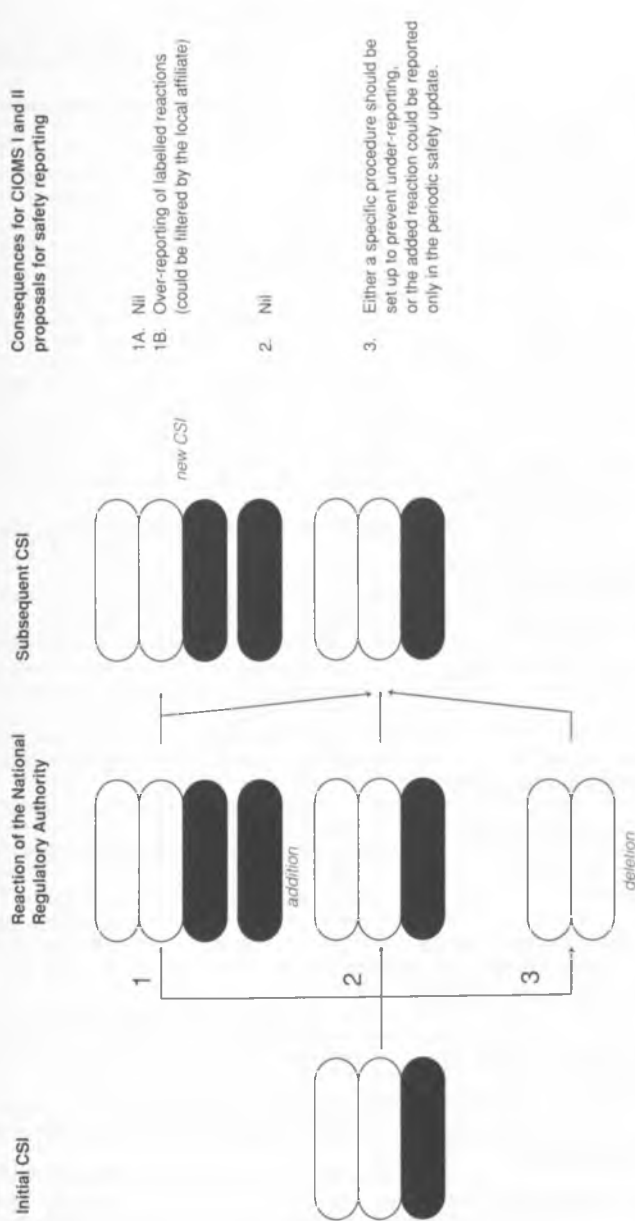
10. FIGURES

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 EMERGING CSI



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

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

11. TABLE

Table 1: 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 1 |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 postmarketing 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	23.1	25	3-39
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.

12. 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 US 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 operation, 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 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 in 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 behavior;
- 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 U.S.A.

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 Section 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.

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

Name	Organization	Full time/Part time
Zbigniew Bankowski	CIOMS	Full time
Christian Bénichou	Roussel Uclaf	Full time
Rudolph Bruppacher	Ciba-Geigy	Full time
Win Castle	Glaxo	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
René 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	Merck Research Laboratories	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 (London, April 1992), the members agreed on the definition of Core Data Sheet (CDS) 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 CSI, 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 CDS 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 "the 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.

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 Drug 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, antisocial 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.

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 MARKETING 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 Data:* 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 core safety 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 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 postmarketing 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 core safety-data sheet was considered necessary.

APPENDIX 4: Fictitious example of CIOMS III proposals

QWEASYTROL: CORE SAFETY INFORMATION

POSODOLOGY (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 30 mg 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.

Maximum dose: 50mg daily.

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 \leq 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. It includes all adverse experiences reported with an incidence of 1% or greater. A dash represents an incidence of less than 1%.

	Qweasytrol 30-45 mg Daily (n = 579) %	Qweasytrol 50-75 mg 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 ($150 \times 10^9/l$) on at least one occasion

** Value ≥ 3 times upper limit of normal on at least one occasion ($\geq 120IU/l$)

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

Post-Marketing Data

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

• 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 in patients 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 common: Sedation — usually occurs only on starting qweasytrol and resolves within a few days on continued therapy. It may occasionally limit dose escalation.

Common: Headache.
Drowsiness.

Rare: Seizures — predominantly in patients with a history of epilepsy or structural brain 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 5HT₁₇ receptor and also has a weak effect on dopamine at the D₈ 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 50 ng/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 50 ml normal saline, the mean serum level 5 minutes saline, the mean serum level was 204 ng/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 (≥ 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 20-30ml/min (see POSOLOGY).

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