INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

CLINICAL SAFETY DATA MANAGEMENT: PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS E2C(R1)

Current *Step 4* version

Parent Guideline dated 6 November 1996
(Addendum dated 6 February 2003 incorporated in November 2005)

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

E2C(R1)
Document History

First Codification	History	Date	New Codification **November 2005**

Parent Guideline: Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs

E2C	Approval by the Steering Committee under *Step 2* and release for public consultation.	30 November 1995	E2C
E2C	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	6 November 1996	E2C

Addendum to the Parent Guideline

V1	Approval of the Addendum by the Steering Committee under *Step 2* and release for public consultation.	11 September 2002	in E2C(R1)
E2C Addendum	Approval of the Addendum by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies. The Steering Committee agreed that this document (provisionally called V1) would be an addendum to E2C.	6 February 2003	in E2C(R1)

Current *Step 4* version

E2C(R1)	The parent guideline is now renamed E2C(R1) as the Addendum has been incorporated to the parent guideline.	November 2005	E2C(R1)

CLINICAL SAFETY DATA MANAGEMENT:
PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS

TABLE OF CONTENTS

PART II:

PART I:
CLINICAL SAFETY DATA MANAGEMENT:
PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 6 November 1996, this guideline is recommended for adoption to the three regulatory parties to ICH

1. INTRODUCTION

1.1 Objectives of the Guideline

The main objective of ICH is to harmonize technical requirements for registration or marketing approval. However, because new products are introduced at different times in different markets and the same product may be marketed in one or more countries and still be under development in others, reporting and use of clinical safety information should be regarded as part of a continuum.

The regulatory requirements, particularly regarding frequency of submission and content of periodic safety updates, are not the same in the three regions (EU, Japan, USA). In order to avoid duplication of effort and to ensure that important data are submitted with consistency to regulatory authorities, this guideline on the format and content for comprehensive periodic safety updates of marketed medicinal products has been developed.*

1.2 Background

When a new medicinal product is submitted for marketing approval, except in special situations, the demonstration of its efficacy and the evaluation of its safety are based at most on several thousand patients. The limited number of patients included in clinical trials, the exclusion at least initially of certain patients at-risk, the lack of significant long-term treatment experience, and the limitation of concomitant therapies do not allow a thorough evaluation of the safety profile. Under such circumstances, the detection or confirmation of rare adverse reactions is particularly difficult, if not impossible.

In order to develop a comprehensive picture of clinical safety, medicinal products should be closely monitored, especially during the first years of commercialization. Surveillance of marketed drugs is a shared responsibility between Regulatory Authorities and Marketing Authorization Holders (MAH). They record information on drug safety from different sources and procedures have been developed to ensure timely detection and mutual exchange of safety data. Because all information cannot be evaluated with the same degree of priority, regulatory authorities have defined the information to be submitted on an expedited basis; in most countries this rapid transmission is usually focused on the expedited reporting of adverse reactions that are both serious and unexpected.

---

* Guidelines are not legally binding. Some portions of this guideline may not be reflected in existing regulations. To that extent, until the regulations are amended, MAHs must comply with existing regulations.

Reevaluation of the benefit/risk ratio of a drug is usually not possible for each individual ADR case, even if serious. Therefore, Periodic Safety Update Reports (PSUR) present the world-wide safety experience of a medicinal product at defined times post-authorization, in order to:

- report all the relevant new safety information from appropriate sources;
- relate these data to patient exposure;
- summarize the market authorization status in different countries and any significant variations related to safety;
- create periodically the opportunity for an overall safety reevaluation;
- indicate whether changes should be made to product information in order to optimize the use of the product.

However, if the PSURs required in the different countries where the product is on the market require a different format, content, period covered and filing date, MAH would be required to prepare on an excessively frequent basis different reports for the same product. In addition, under such conditions, different regulators could receive different kinds and amounts of information at different times. Thus, efforts are needed to harmonize the requirements for PSURs, which will also improve the efficiency with which they are produced.

The current situation for periodic safety reports on marketed drugs is different among the three ICH regions. For example:

- The US regulations require quarterly reports during the first 3 years, then annual reports. The FDA has recently published proposed rules[1] which take into account the CIOMS Working Group II proposals[2].
- In the EU, Council Directive 93/39/EEC and Council Regulation 2309/93 require reports with a periodicity of 6 months for two years, annually for the three following years and then every five years, at time of renewal of registration.
- In Japan, the authorities require a survey on a cohort of a few thousand patients established by a certain number of identified institutions during the 6 years following authorization. Systematic information on this cohort, taking into account a precise denominator, must be reported annually. Regarding other marketing experience, adverse reactions which are non-serious, but both mild in severity and unlabeled must be reported every 6 months for 3 years and annually thereafter.

Following a discussion of the objectives and general principles for preparing and submitting PSURs, a model for their format and content is presented. Appended is a glossary of important relevant terms.

1.3 Scope of the Guideline

This guideline on the format and content of periodic safety update reports (PSURs) is considered particularly suitable for comprehensive reports covering short periods (e.g., six months, one year) often prepared during the initial years following approval/authorization.

This guideline might also be applicable for longer term reporting intervals; however,

---

[1] Adverse Experience Reporting Requirements for Human Drug and Licensed Biological Products; Proposed Rule, Federal Register, 27 October 1994, pp. 54046-54064.

[2] International Reporting of Periodic Drug-Safety Update Summaries.
Final Report of CIOMS Working Group II.
CIOMS - Geneva 1992

other options may be appropriate.

1.4 General Principles

1.4.1 One report for one active substance

Ordinarily, all dosage forms and formulations as well as indications for a given pharmacologically active substance should be covered in one PSUR. Within the single PSUR, separate presentations of data for different dosage forms, indications or populations (e.g. children vs. adults) may be appropriate.

For combinations of substances also marketed individually, safety information for the fixed combination may be reported either in a separate PSUR or included as separate presentations in the report for one of the separate components, depending on the circumstances. Cross-referencing all relevant PSURs is considered important.

1.4.2 General scope of information

All relevant clinical and non-clinical safety data should cover only the period of the report (interval data) with the exception of regulatory status information on authorization applications and renewals, as well as data on serious, unlisted ADRs (see 1.4.5), which should be cumulative.

The main focus of the report should be adverse drug reactions (ADRs). For spontaneous reports, unless indicated otherwise by the reporting health-care professional, all adverse experiences should be assumed to be adverse drug reactions; for clinical study and literature cases, only those judged not related to the drug by both the reporter and the manufacturer/sponsor should be excluded.

Reports of lack of efficacy specifically for drugs used in the treatment of life-threatening conditions, may represent a significant hazard, and in that sense be a "safety issue". Although these types of cases should not be included with the usual ADR presentations (i.e., line-listings and summary tabulations), such findings should be discussed within the PSUR (see section 2.8), if deemed medically relevant.

Increase in the frequency of reports for known ADRs has traditionally been considered as relevant new information. Although attention should be given in the PSUR to such increased reporting, no specific quantitative criteria or other rules are recommended. Judgement should be used in such situations to determine whether the data reflect a meaningful change in ADR occurrence or safety profile and whether an explanation can be proposed for such a change (e.g., population exposed, duration of exposure).

1.4.3 Products manufactured and/or marketed by more than one company

Each MAH is responsible for submitting PSURs, even if different companies market the same product in the same country. When companies are involved in contractual relationships (e.g., licensor-licensee), arrangements for sharing safety information should be clearly specified. In order to ensure that all relevant data will be duly reported to appropriate regulatory authorities, respective responsibilities for safety reporting should also be clearly specified.

When data received from a partner company(ies) might contribute meaningfully to the safety analysis and influence any proposed or effected changes in the reporting company's product information, these data should be included and discussed in the PSUR, even if it is known that they are included in another company's PSUR.

1.4.4 International birthdate and frequency of review and reporting

Each medicinal product should have as an International Birth Date (IBD), the date of the first marketing authorization for the product granted to any company in any country in the world. For administrative convenience, if desired by the MAH, the IBD can be designated as the last day of the same month. When a report contains information on different dosage forms, formulations, or uses (indications, routes, populations), the date of the first marketing authorization for any of the various authorizations should be regarded as the IBD and, therefore, determine the data lock point for purposes of the unified PSUR. The data lock point is the date designated as the cut-off for data to be included in a PSUR.

The need for a report and the frequency of report submission to authorities are subject to local regulatory requirements. The age of a drug on the market may influence this process. In addition, during the initial years of marketing, a drug will ordinarily receive authorizations at different times in different countries; it is during this early period that harmonization of reporting is particularly important.

However, independent of the required reporting frequency, regulatory authorities should accept six-monthly PSURs or PSURs based on multiples of six months. Therefore, preparation of PSURs for all regulatory authorities should be based on data sets of six months or multiples thereof.

Once a drug has been marketed for several years, the need for a comprehensive PSUR and the frequency of reporting may be reviewed, depending on local regulations or requests, while maintaining one IBD for all regulatory authorities.

In addition, approvals beyond the initial one for the active substance may be granted for new indications, dosage forms, populations, or prescription status (e.g., children vs. adults; prescription to non-prescription status). The potential consequences on the safety profile raised by such new types and extent of population exposures should be discussed between regulatory authorities and MAH since they may influence the requirements for periodic reporting.

The MAH should submit a PSUR within 60 days of the data lock point.

1.4.5 Reference safety information

An objective of a PSUR is to establish whether information recorded during the reporting period is in accord with previous knowledge on the drug's safety, and to indicate whether changes should be made to product information. Reference information is needed to perform this comparison. Having one reference source of information in common for the three ICH regions would facilitate a practical, efficient and consistent approach to the safety evaluation and make the PSUR a unique report accepted in all areas.

It is a common practice for MAHs to prepare their own "Company Core Data Sheet" (CCDS) which covers material relating to safety, indications, dosing, pharmacology, and other information concerning the product. A practical option for the purpose of periodic reporting is for each MAH to use, as a reference, the safety information contained within its central document (CCDS), which will be referred to as "Company Core Safety Information" (CCSI).

For purposes of periodic safety reporting, CCSI forms the basis for determining whether an adverse drug reaction is already Listed or is still Unlisted, terms which are introduced to distinguish them from the usual terminology of "expectedness" or "labeledness" which is used in association with official labeling. Thus, the local approved product information continues to be the reference document upon which

labeledness/expectedness is based for the purpose of local expedited post-marketing safety reporting.

1.4.6 Presentation of data on individual case histories

Sources of information

Generally, data from the four following sources of ADR case information are potentially available to a MAH and should be included in the PSUR:

a) Direct reports to MAH (or under MAH control):

Spontaneous notifications from health care professionals

Spontaneous notifications from non-health care professionals or from consumers (non-medically substantiated)

MAH-sponsored clinical studies* or named-patient ("compassionate") use

b) Literature

c) ADR reporting systems of regulatory authorities

d) Other sources of data:

reports on ADRs exchanged between contractual partners (e.g., licensors-licensees)

- data in special registries, such as maintained in organ toxicity monitoring centers reports created by poison control centers;
- epidemiologic data bases.

Description of the reaction

Until an internationally agreed ICH coding terminology becomes available and its use broadly implemented, the event terms used in the PSUR will generally be derived from whatever standard terminology ("controlled vocabulary" or "coding dictionary") is used by the reporting company.

Whenever possible, the notifying reporter's event terms should be used to describe the ADR. However, when the notifying reporter's terms are not medically appropriate or meaningful, MAHs should use the best alternative compatible event terms from their ADR dictionaries to ensure the most accurate representation as possible of the original terms. Under such circumstances, the following should be borne in mind:

- in order to make it available on request, the "verbatim" information supplied by the notifying reporter should be kept on file (in the original language and/or as a medically sound English translation, if applicable);
- in the absence of a diagnosis by the reporting health-care professional, a suggested diagnosis for a symptom complex may be made by the MAH and used to describe a case, in addition to presenting the reported individual signs, symptoms and laboratory data;
- if a MAH disagrees with a diagnosis that is provided by the notifying health care professional, it may indicate such disagreement within the line listing of cases (see below);

* What constitutes a clinical study may not always be clear, given the recent use of, for example, stimulated reporting and patient-support programs. In some of these circumstances, the distinction between spontaneous reporting and a clinical study is not well defined. The MAH should specify how relevant data from such sources are included.

– MAH should report and try to understand all information provided within a case report. An example is a laboratory abnormality not addressed/evaluated by the notifying reporter.

Therefore, when necessary and relevant, two descriptions of the signs, symptoms or diagnosis could be presented in the line listing: first, the reaction as originally reported; second, when it differs, the MAH's medical interpretation (identified by asterisk or other means).

Line listings and/or summary tabulations

Depending on their type or source, available ADR cases should be presented as individual case line listings and/or as summary tabulations.

A line listing provides key information but not necessarily all the details customarily collected on individual cases; however, it does serve to help regulatory authorities identify cases which they might wish to examine more completely by requesting full case reports.

MAHs can prepare line listings of consistent structure and content for cases directly reported to them (or under their control) (see 1.4.6a) as well as those received from regulatory authorities. They can usually do the same for published cases (ordinarily well documented; if not, follow-up with the author may be possible). However, inclusion of individual cases from second- or third-hand sources, such as contractual partners and special registries (see 1.4.6d) might not be (1) possible without standardization of data elements, or (2) appropriate due to the paucity of information, and might represent unnecessary re-entry/reprocessing of such information by the MAH. Therefore, summary tabulations or possibly a narrative review of these data are considered acceptable under these circumstances.

In addition to individual case line listings, summary tabulations of ADR terms for signs, symptoms and diagnoses across all patients should usually be presented to provide an overview. Such tabulations should be based on the data in line listings (e.g., all serious ADRs and all non-serious unlisted ADRs), but also on other sources for which line listings are not requested (e.g., non-serious listed ADRs). Details are found in section 2.6.4.

2. MODEL FOR A PERIODIC SAFETY UPDATE REPORT (PSUR)

The following sections are organized as a sample PSUR. In each of the sections, guidance is provided on what should be included.

SAMPLE TITLE PAGE

PERIODIC SAFETY UPDATE REPORT FOR: (PRODUCT)

MAHs NAME AND ADDRESS (Corporate headquarters or other company entity responsible for report preparation)

PERIOD COVERED BY THIS REPORT: (dates)

INTERNATIONAL BIRTH DATE: Date (Country of IBD)

DATE OF REPORT

(Other identifying information at the option of MAH, such as report number)

TABLE OF CONTENTS FOR MODEL PSUR

2.1 Introduction

The MAH should briefly introduce the product so that the report "stands alone" but is also placed in perspective relative to previous reports and circumstances.

Reference should be made not only to product(s) covered by the report but also those excluded. Exclusions should be explained; for example, they may be covered in a separate report (e.g., for a combination product).

If it is known that a PSUR on the same product(s) will be submitted by another MAH, some of whose data are included in the report (see 1.4.6), the possibility of data duplication should be noted.

2.2 World-wide Market Authorization Status

This section of the report provides cumulative information.

Information should be provided, usually as a table, on all countries in which a regulatory decision about marketing has been made related to the following:

- dates of market authorization, and subsequent renewal;
- any qualifications surrounding the authorization, such as limits on indications if relevant to safety;
- treatment indications and special populations covered by the market authorization, when relevant;
- lack of approval, including explanation, by regulatory authorities;
- withdrawal by the company of a license application submission if related to safety or efficacy;
- dates of launch when known;
- trade name(s).

Typically, indications for use, populations treated (e.g., children vs. adults) and dosage forms will be the same in many or even most countries where the product is authorized. However, when there are important differences, which would reflect different types of patient exposure, such information should be noted. This is especially true if there are meaningful differences in the newly reported safety information that are related to such different exposures. If more convenient and useful, separate regulatory status tables for different product uses or forms would be considered appropriate.

Country entries should be listed in chronological order of regulatory authorizations. For multiple authorizations in the same country (e.g., new dosage forms), the IBD for the active substance and for all PSURs should be the first (initial) authorization date.

Table 1 is an example, with fictitious data for an antibiotic, of how a table might be organized. The drug was initially developed as a solid oral dosage form for outpatient treatment of various infections.

2.3 Update of Regulatory Authority or MAH Actions Taken for Safety Reasons

This section should include details on the following types of actions relating to safety that were taken during the period covered by the report and between data lock-point and report submission:

- marketing authorization withdrawal or suspension;
- failure to obtain a marketing authorization renewal;
- restrictions on distribution;

– clinical trial suspension;
– dosage modification;
– changes in target population or indications;
– formulation changes.

The safety related reasons that led to these actions should be described and documentation appended when appropriate; any communication with the health profession (e.g., Dear Doctor letters) as a result of such action should also be described with copies appended.

2.4 Changes to Reference Safety Information

The version of the company core data sheet (CCDS) with its company core safety information (CCSI) in effect at the beginning of the period covered by the report should be used as the reference. It should be numbered, dated and appended to the PSUR and include the date of last revision.

Changes to the CCSI, such as new contraindications, precautions, warnings, ADRs, or interactions, already made during the period covered by the report, should be clearly described, with presentation of the modified sections. The revised CCSI should be used as the reference for the next report and the next period.

With the exception of emergency situations, it may take some time before intended modifications are introduced in the product-information materials provided to prescribers, pharmacists and consumers. Therefore, during that period the amended reference document (CCDS) may contain more "listed" information than the existing product information in many countries.

When meaningful differences exist between the CCSI and the safety information in the official data sheets/product information documents approved in a country, a brief comment should be prepared by the company, describing the local differences and their consequences on the overall safety evaluation and on the actions proposed or initiated. This commentary may be provided in the cover letter or other addendum accompanying the local submission of the PSUR.

2.5 Patient Exposure

Where possible, an estimation of accurate patient exposure should cover the same period as the interim safety data. While it is recognized that it is usually difficult to obtain and validate accurate exposure data, an estimate of the number of patients exposed should be provided along with the method used to derive the estimate. An explanation and justification should be presented if the number of patients is impossible to estimate or is a meaningless metric. In its place, other measures of exposure, such as patient-days, number of prescriptions or number of dosage units are considered appropriate; the method used should be explained. If these or other more precise measures are not available, bulk sales (tonnage) may be used. The concept of a defined daily dose may be used in arriving at patient exposure estimates. When possible and relevant, data broken down by sex and age (especially pediatric vs. adult) should be provided.

When a pattern of reports indicates a potential problem, details by country (with locally recommended daily dose) or other segmentation (e.g., indication, dosage form) should be presented if available.

When ADR data from clinical studies are included in the PSUR, the relevant denominator(s) should be provided. For ongoing and/or blinded studies, an estimation of patient exposure may be made.

2.6 Presentation of Individual Case Histories

2.6.1 General considerations

- **Follow-up data** on individual cases may be obtained subsequent to their inclusion in a PSUR. If such information is relevant to the interpretation of the case (significant impact on the case description or analysis, for example), the new information should be presented in the next PSUR, and the correction or clarification noted relative to the earlier case description.
- With regard to the **literature**, MAHs should monitor standard, recognized medical and scientific journals for safety information on their products and/or make use of one or more literature search/summary services for that purpose. Published cases may also have been received as spontaneous cases, be derived from a sponsored clinical study, or arise from other sources. Care should be taken to include such cases only once. Also, no matter what "primary source" is given a case, if there is a publication, it should be noted and the literature citation given.

In some countries, there is no requirement to submit **medically unconfirmed spontaneous reports** that originate with consumers or other non-health care professionals. However, such reports are acceptable or requested in other countries. Therefore, medically unconfirmed reports should be submitted as addenda line listings and/or summary tabulations only when requested by regulatory authorities. However, it is considered that such reports are not expected to be discussed within the PSUR itself.

2.6.2 Cases presented as line listings

The following types of cases should be included in the line listings (Table 2); attempts should be made to avoid duplicate reporting of cases from the literature and regulatory sources.

- all serious reactions, and non-serious unlisted reactions, from spontaneous notifications;
- all serious reactions (attributable to drug by either investigator or sponsor), available from studies or named-patient ("compassionate") use;
- all serious reactions, and non-serious unlisted reactions, from the literature;
- all serious reactions from regulatory authorities

Collection and reporting of non-serious, **listed** ADRs may not be required in all ICH countries. Therefore, a line listing of spontaneously reported non-serious listed reactions that have been collected should be submitted as an addendum to the PSUR only when requested by a regulatory authority.

2.6.3 Presentation of the line listing

The line listing(s) should include each patient only once regardless of how many adverse event/reaction terms are reported for the case. If there is more than one event/reaction, they should all be mentioned but the case should be listed under the most serious ADR (sign, symptom or diagnosis), as judged by the MAH. It is possible that the same patient may experience different ADRs on different occasions (e.g., weeks apart during a clinical trial). Such experiences would probably be treated as separate reports. Under such circumstances, the same patient might then be included in a line-listing more than once, and the line-listings should be cross-referenced when possible. Cases should be organized (tabulated) by body system (standard organ system classification scheme).

The following headings should usually be included in the line listing:

- MAH case reference number
- Country in which case occurred
- Source (e.g., clinical trial, literature, spontaneous, regulatory authority)
- Age and sex
- Daily dose of suspected drug (and, when relevant, dosage form or route)
- Date of onset of the reaction. If not available, best estimate of time to onset from therapy initiation. For an ADR known to occur after cessation of therapy, estimate of time lag if possible (may go in Comments section).
- Dates of treatment. If not available, best estimate of treatment duration.
- Description of reaction as reported, and when necessary as interpreted by the MAH (English translation when necessary). See Section 1.4.6 for guidance.
- Patient outcome (at case level) (e.g., resolved, fatal, improved, sequelae, unknown). This field does not refer to the criteria used to define a "serious" ADR. It should indicate the consequences of the reaction(s) for the patient, using the worst of the different outcomes for multiple reactions.
- Comments, if relevant (e.g., causality assessment if the manufacturer disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s); dechallenge/rechallenge results if available).

Depending on the product or circumstances, it may be useful or practical to have more than one line listing, such as for different dosage forms or indications, if such differentiation facilitates presentation and interpretation of the data.

2.6.4 Summary tabulations

An aggregate summary for each of the line listings should usually be presented. These tabulations ordinarily contain more terms than patients. It would be useful to have separate tabulations (or columns) for serious reactions and for non-serious reactions, for listed and unlisted reactions; other breakdowns might also be appropriate (e.g., by source of report). See Table 3 for a sample data presentation on serious reactions.

A summary tabulation should be provided for the non-serious, **listed**, spontaneously reported reactions (see also 2.6.2)

The terms used in these tables should ordinarily be those used by the MAH to describe the case (see Section 1.4.6).

Except for cases obtained from regulatory authorities, the data on serious reactions from Other Sources (see 1.4.6c) should normally be presented only as a summary tabulation. If useful, the tabulations may be sorted by source of information or country, for example.

When the number of cases is very small, or the information inadequate for any of the tabulations, a narrative description rather than a formal table is considered suitable.

As previously described, the data in summary tabulations should be interval data, as should the line-listings from which they are derived. However, for ADRs that are both serious and unlisted, a cumulative figure (i.e., all cases reported to date) should be provided in the table(s) or as a narrative.

2.6.5 MAH's Analysis of Individual Case Histories

This section may be used for brief comments on the data concerning individual cases. For example, discussion can be presented on particular serious or unanticipated findings (their nature, medical significance, mechanism, reporting frequency, etc.). The focus here should be on individual case discussion and should not be confused with the global assessment in the Overall Safety Evaluation (Section 2.9).

2.7 Studies

All completed studies (non-clinical, clinical, epidemiological) yielding safety information with potential impact on product information, studies specifically planned or in progress, and published studies that address safety issues, should be discussed.

2.7.1 Newly analyzed company-sponsored studies

All relevant studies containing important safety information and newly analyzed during the reporting period should be described, including those from epidemiological, toxicological or laboratory investigations. The study design and results should be clearly and concisely presented with attention to the usual standards of data analysis and description that are applied to non-clinical and clinical study reports. Copies of full reports should be appended only if deemed appropriate.

2.7.2 Targeted new safety studies planned, initiated or continuing during the reporting period.

New studies specifically planned or conducted to examine a safety issue (actual or hypothetical) should be described (e.g., objective, starting date, projected completion date, number of subjects, protocol abstract).

When possible and relevant, if an interim analysis was part of the study plan, the interim results of ongoing studies may be presented. When the study is completed and analyzed, the final results should be presented in a subsequent PSUR as described under 2.7.1.

2.7.3 Published safety studies

Reports in the scientific and medical literature, including relevant published abstracts from meetings, containing important safety findings (positive or negative) should be summarized and publication reference(s) given.

2.8 Other Information

2.8.1 Efficacy-Related Information

For a product used to treat serious or life threatening diseases, medically relevant lack of efficacy reporting, which might represent a significant hazard to the treated population, should be described and explained.

2.8.2 Late-Breaking Information

Any important, new information received after the data base was frozen for review and report preparation may be presented in this section. Examples include significant new cases or important follow-up data. These new data should be taken into account in the Overall Safety Evaluation (Section 2.9).

2.9 Overall Safety Evaluation

A concise analysis of the data presented, taking into account any late-breaking information (Section 2.8.2.), and followed by the MAH assessment of the significance of the data collected during the period and from the perspective of cumulative experience should highlight any new information on:

- A change in characteristics of listed reactions, e.g. severity, outcome, target population
- Serious unlisted reactions, placing into perspective the cumulative reports
- Non-Serious unlisted reactions
- An increased reporting frequency of listed reactions, including comments on whether it is believed the data reflect a meaningful change in ADR occurrence.
- The report should also explicitly address any new safety issue on the following (lack of significant new information should be mentioned for each):
- drug interactions
- experience with overdose, deliberate or accidental, and its treatment
- drug abuse or misuse
- positive or negative experiences during pregnancy or lactation
- experience in special patient groups (e.g., children, elderly, organ impaired)
- effects of long-term treatment.

2.10 Conclusion

The conclusion should:

- indicate which safety data do not remain in accord with the previous cumulative experience, and with the reference safety information (CCSI);
- specify and justify any action recommended or initiated.

APPENDIX: COMPANY CORE DATA SHEET

The Company Core Data Sheet in effect at the beginning of the period covered should be appended to the PSUR.

3. GLOSSARY OF SPECIAL TERMS

Company Core Data Sheet (CCDS)

A document prepared by the MAH containing, in addition to safety information, material relating to indications, dosing, pharmacology and other information concerning the product.

Company Core Safety Information (CCSI)

All relevant safety information contained in the Company Core Data Sheet prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.

Data Lock-Point (Data Cut-off Date)

The date designated as the cut-off date for data to be included in a PSUR. It is based on the International Birth Date (IBD) and should usually be in six-monthly increments.

International Birth Date (IBD

The date of the first marketing authorization for a new medicinal product granted to any company in any country in the world.

Listed Adverse Drug Reaction

An ADR whose nature, severity, specificity, and outcome are consistent with the information in the CCSI.

Spontaneous Report or Spontaneous Notification

An unsolicited communication to a company, regulatory authority or other organization that describes an adverse drug reaction in a patient given one or more medicinal products and which does not derive from a study or any organized data collection scheme.

Unlisted Adverse Drug Reaction

An ADR whose nature, severity, specificity or outcome are not consistent with the information included in the CCSI.

TABLES

- Table 1 -

EXAMPLE OF PRESENTATION OF WORLD-WIDE MARKET AUTHORIZATION STATUS

Country	**Action-Date**	**Launch Date**	**Trade Name(s)**	**Comments**
Sweden	A - 7/90 AR - 10/95	12/90 -	Bacteroff -	- -
Brazil	A - 10/91 A - 1/93	2/92 3/93	Bactoff Bactoff-IV	- IV dosage form
United Kingdom	AQ - 3/92 A - 4/94	6/92 7/94	Bacgone Bacgone-C (skin infs)	Elderly (> 65) excluded (PK) Topical cream
Japan	LA - 12/92	-	-	To be refiled
France	V - 9/92	-	-	Unrelated to safety
Nigeria	A - 5/93 A - 9/93	7/93 1/94	Bactoff Bactoff	- New indication
Etc...				

Abbreviations for Action: A = authorized; AQ = authorized with qualifications; LA: lack of approval; V = voluntary marketing application withdrawal by company; AR = Authorization renewal.

- Table 2 -

PRESENTATION OF INDIVIDUAL CASE HISTORIES

(See 2.6.2 and 2.6.4 for full explanation)

Source	Type of Case	Only Summary Tabulation	Line Listing and Summary Tabulation
1. Direct Reports to MAH			
- Spontaneous ADR reports*	S	-	+
	NS U	-	+
	NS L**	+	-
- MAH sponsored studies	SA	-	+
2. Literature	S	-	+
	NS U	-	+
3. Other sources			
- Regulatory Authorities	S	-	+
- Contractual partners	S	+	-
- Registries	S	+	-

** Medically unconfirmed reports should be provided as a PSUR addendum only on request by regulatory authorities, as a line listing and/or summary tabulation.*

*** Line listing should be provided as PSUR addendum only on request by regulatory authorities.*

S = serious; L = Listed; A = attributable to drug (by investigator or sponsor); NS = non-serious; U = Unlisted.

-Table 3 -

(EXAMPLE OF SUMMARY TABULATION)#

NUMBER OF REPORTS BY TERM (SIGNS, SYMPTOMS AND DIAGNOSES) FROM SPONTANEOUS (MEDICALLY CONFIRMED), CLINICAL STUDY AND LITERATURE CASES: ALL SERIOUS REACTIONS

(An * indicates an unlisted term)

Body system/ ADR term	Spontaneous/ Regulatory bodies	Clinical trials	Literature
CNS			
hallucinations*	2	0	0
etc.			
etc.			
_____ Sub-total	_____	_____	_____
CV			
etc.			
etc.			
_____ Sub-total	_____	_____	_____
Etc...			
TOTAL			

In a footnote (or elsewhere), the number of patient-cases that represent the tabulated terms might be given (e.g., x-spontaneous/regulatory, y-clinical study, and z-literature cases)

#This table is only one example of different possible data presentations which are at the discretion of the MAH (e.g., serious and non-serious in the same table or as separate tables, etc.)

PART II:

ADDENDUM TO ICH E2C

CLINICAL SAFETY DATA MANAGEMENT
PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 6 February 2003 and incorporated into the core guideline in November 2005, this guideline is recommended for adoption to the three regulatory parties to ICH

1. INTRODUCTION

This addendum is intended to provide practical guidance for the preparation of the Periodic Safety Update Report (PSUR) as recommended in the ICH Guideline E2C, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, which achieved Step 4 in November 1996. That guideline has been implemented in some but not all ICH countries.

The PSUR is a practical and achievable mechanism for summarizing interval safety data, especially covering short periods (e.g., 6 months or 1 year), and for conducting an overall safety evaluation. It is a tool for Marketing Authorization Holders (MAHs) to conduct systematic analyses of safety data on a regular basis. In addition to covering ongoing safety issues, the PSUR should also include updates on emerging and/or urgent safety issues, and major signal detection and evaluation that are addressed in other documents.

PSURs are of value and importance to all parties in protecting the public health. The ICH E2C Guideline was developed to harmonize PSURs submitted to the Regulatory Authorities in terms of content and format as well to introduce the concept of International Birthdate (IBD). However, the original E2C Guideline has been interpreted in different ways by both MAHs and Regulatory Authorities. These differing interpretations have resulted in a perception that the guideline was not sufficient to accommodate the broad range of products and diverse circumstances that arise in practice. The Council for International Organizations of Medical Sciences (CIOMS) Working Group V[3] made several recommendations and developed new concepts that harmonize the practice of preparing PSURs that have been taken into account in preparing this Addendum.

This Addendum addresses only those E2C provisions considered to need further clarification, guidance, or increased perceived flexibility beyond that provided in the ICH E2C guideline. This document should always be used in conjunction with the E2C Guideline.

This Addendum addresses the following concepts not previously addressed by E2C:

- Summary Bridging Report (see Section 1.4.4.2)
- Addendum Report (see Section 1.4.4.3)
- Proprietary information (see Section 2)

---

[3] Report of CIOMS Working Group V: Current Challenges in Pharmacovigilance: Pragmatic Approaches. CIOMS, 2001, Geneva.

- Executive Summary (see Section 2)
- Risk management programme (see Section 2.8.3)
- Benefit-risk analysis (see Section 2.8.4)

To facilitate the use of this document, the numbering of the sections and paragraphs is identical to those of the E2C guideline.

1.4. General Principles

1.4.1 One Report for One Active Substance

It is strongly recommended that information on all indications, dosage forms, and regimens for the active substance be included in a single PSUR, with a single data lock point common for all aspects of product use. There is a great advantage to having a consistent, broad-based examination of the safety information for the active substance(s) in a single document. When relevant, data relating to a particular indication, dosage form, or dosing regimen should be presented in a separate section within the body of the PSUR and any safety issues addressed accordingly without preparing a separate PSUR.

There are instances when separate PSURs might be considered appropriate. In these cases, the Regulatory Authorities should be notified and their agreement obtained at the time of authorization.

Examples include:

- Fixed combinations: Options include either a separate PSUR for the combination with cross-reference to the single agent(s) PSUR(s) or inclusion of the fixed combination data within one of the single agent PSURs.
- When an active substance is used in two or more different formulations (e.g., systemic preparations vs topical administration), two or more PSURs, with the same or different IBDs, can be useful.

1.4.4 International Birthdate and Frequency of Review and Reporting

Whenever possible, PSURs should be based on the IBD. If, in the transition period to a harmonized birthdate for that product, the use of a local approval date is appropriate, the MAH can submit its already prepared IBD-based PSUR plus:

- Line-listings and/or summary tabulations covering the additional period (when the additional period is less than 3 months for a 6 month or annual PSUR, or 6 months for a longer duration PSUR) with comment on whether the data reveal a new and important risk;

or

- an Addendum Report when the additional period is greater than 3 months for a 6 month or an annual PSUR, or 6 months for a longer duration PSUR (see section 1.4.4.3).

1.4.4.1 Synchronization of National Birthdates with the IBD

For drugs that are on the market in many countries, the MAH can synchronize local or national birthdates with the IBD.

For a drug where the IBD is not known, the MAH can designate an IBD to allow synchronization of reports to all Regulatory Authorities. Once an IBD is designated,

the MAH should notify the Regulatory Authorities, and the IBD should be adhered to thereafter.

It is recognized that long intervals between approvals could put the drug in a 5 year cycle in one region and a 6 month cycle in another region. For practical purposes, if a single month, day and year for the IBD is not attainable, the MAH can contact the Regulatory Authorities to negotiate a mutually acceptable birth month and day. For example, where there are different approval dates, it can be useful for reports to be submitted on the same month and day (e.g., every January 18 and July 18), whether every 6 months, annually, or every 5th year.

1.4.4.2 Summary Bridging Reports

A Summary Bridging Report is intended to be a concise document integrating the information presented in two or more PSURs to cover a specified period over which a single report is requested or required by Regulatory Authorities. The report should not contain any new data but should provide a brief summary bridging two or more PSURs (e.g., 2 consecutive 6-month reports for an annual report or 10 consecutive 6-month reports to make a 5-year report). The Summary Bridging Report is intended to assist Regulatory Authorities with a helpful overview of the appended PSURs. The PSUR data should not be repeated but should be cross-referenced to individual PSURs. The format of the Summary Bridging Report should be identical to that of the usual PSUR, but the content should consist of summary highlights and an overview of data from the attached PSURs to which it refers (see CIOMS V Report pp. 154-156). Upon request from the Regulatory Authority, a summary tabulation of serious, unlisted reactions should be included in the Summary Bridging Report.

Summary Bridging Reports can be used in situations where the MAH prepares short duration reports (e.g., 6-month or annual reports) indefinitely, especially if new indications or formulations are likely to be introduced over the years. For reports considered out of date relative to a particular Regulatory Authority's requirement, an Addendum Report could also be submitted (see Section 1.4.4.3). For a PSUR that spans longer time intervals, e.g., 5 years, an Addendum Report would only be considered appropriate if the time since preparation of the 5-year PSUR and the locally-required report is greater than 6 months.

The Summary Bridging Report ordinarily should not include line listings. If summary tables covering the period of the appended PSURs are considered appropriate, there should be a clear understanding that the tables will be generated from live databases, which change over time as cases are updated. These tables will then reflect the most up-to-date data available at the time they are generated. It is recognized that the case counts in these summary tables can differ somewhat from the contents of the individual tables in the appended PSURs. A general statement describing the differences should be provided.

1.4.4.3 Addendum Reports

MAHs should set IBDs for all their products and can synchronize their local renewals. However, when a requested or required report covers data that fall outside the defined period, use of an Addendum Report is recommended.

An Addendum Report is an update to the most recently completed PSUR when a Regulatory Authority requests or requires a safety update outside the usual IBD reporting cycle. An Addendum Report should be used when more than 3 months for a 6-month or an annual report, and more than 6 months for a longer-interval report,

have elapsed since the data lock point of the most recent PSUR. It might also be appropriate to provide an addendum to the Summary Bridging Report.

The Addendum Report should summarize the safety data received between the data lock point of the most recent PSUR and the Regulatory Authority's requested cut-off date. It is not intended that the Addendum Report provide an in-depth analysis of the additional cases, as these can be included in the next regularly scheduled PSUR. Depending on circumstances and the volume of additional data since the last scheduled report, an Addendum Report can follow the ICH E2C format or a simplified presentation. The proposed minimal report should include the following sections containing any new information or changes beyond the most recent PSUR to which the Addendum Report refers:

- Introduction (purpose; cross reference to most recent PSUR)
- Changes to the Company Core Safety Information (CCSI)[4] (including a copy of the most recent CCSI document if it differs from the one in the PSUR)
- Significant regulatory actions bearing on safety
- Line listing(s) and/or summary tabulations
- Conclusions (brief overview of new information and any impact on the known safety profile)

1.4.4.4 Restarting the Clock

For products in a long-term PSUR cycle, the return to 6-monthly or annual reporting could apply after important additions or changes in clinical use are first approved in an ICH region, such as:

- A new, clinically dissimilar indication
- A previously unapproved use in a special patient population, such as children, pregnant women or the elderly
- A new formulation or new route of administration

The decision on whether to restart the clock should be discussed with the Regulatory Authority no later than the time of granting the relevant marketing authorization.

Even if the clock "restarts," the analyses in the PSUR should focus on the newly-indicated population by identifying and characterizing any differences from the established safety profile in the previously indicated populations.

1.4.4.5 Time Interval between the Data Lock Point and the Submission

In regions where they are required, PSURs are to be submitted within 60 days of the data lock point. To facilitate the preparation of both current and future PSURs, as well as safety reports outside of the PSUR, the RA will attempt to send comments to the MAH:

- as rapidly as possible, if any issues of non-compliance with the ICH format and content of a PSUR are identified (particularly those that preclude review)
- as rapidly as possible, if additional safety issues are identified that could prompt further evaluation by the MAH that should either be included in the next PSUR or provided as a separate stand-alone report

[4] Report of CIOMS Working Group III and IV, CIOMS, Geneva, 1999

- before the next data lock point, if any additional analyses or issues of content are identified that should be included in the next PSUR.

Additional Time for Submissions

In rare circumstances, an MAH can make a special request to the Regulatory Authority for 30 additional calendar days to submit a PSUR. Ideally, this request should be made before the data lock point. The RA will attempt to send response to MAH as rapidly as possible.

The basis of such a request should be justified and could include:

- A large number of case reports for the reporting period, provided that there is no new significant safety concern
- Issues raised by Regulatory Authorities in the previous PSUR for which the MAH is preparing additional or further analysis in the next PSUR
- Issues identified by the MAH for additional or further analysis

The MAH should make such a request only for the single PSUR in question and not for subsequent PSURs. The Regulatory Authority will generally expect subsequent PSURs to be submitted on the appropriate date and to retain their original periodicity.

1.4.5 Reference Safety Information

It is important to highlight the differences between the CCSI and the local product information/local labelling in the cover letter accompanying the local submission of the PSUR, as described in E2C section 2.4.

PSUR covering a period of 6 months or 1 year

For 6-month and annual reports, the version of the CCSI in effect at the beginning of the period covered by the report should be used as the reference.

PSUR covering a period of over 1 year

When producing a longer duration PSUR or a Summary Bridging Report, it is often impractical to base the analysis of listedness on the CCSI that was in effect at the beginning of the period. There can be considerable variation in listedness over the reporting period, depending on when the assessment of listedness is made (e.g., on an ongoing basis, such as at AE/ADR case entry, or when a PSUR is compiled). The latest CCSI in effect at the end of the period can be used. The MAH should ensure that all changes to the CCSI made over the period are described in Section 4 of the PSUR ("Changes to the Reference Safety Information").

When listedness is assessed at the time of PSUR preparation after the data lock point, it is generally considered appropriate to use the current version of the CCSI as the reference document, as long as that choice is made clear in the PSUR text. MAHs assessing listedness at case entry or on an ongoing basis throughout the reporting period should include the current version of the CCSI and comment on the reasons for any changes in listedness assessment over time. In both cases, changes made to the CCSI since the previous PSUR should be explained in Sections 4 ("Changes to Reference Safety Information") and/or 9 ("Overall Safety Evaluation").

2. MODEL FOR A PERIODIC SAFETY UPDATE REPORT (PSUR)

PSURs contain proprietary information. Therefore, the Title page of a PSUR should contain a statement on the confidentiality of the data and conclusions included in the report.

MAHs should prepare a brief overview of each PSUR to provide the reader with a description of the most important information. This Executive Summary should be placed at the beginning of the PSUR immediately after the Title page. An example of an Executive Summary can be found in the CIOMS V report (pp. 333).

2.5 Patient Exposure

Estimations of patient exposure for marketed drugs often rely on gross approximations of in-house or purchased sales data or volume. This information is not always reliable or available for all products. For example, hospital-based (inpatient exposure) statistics from the major use-monitoring sources are frequently unavailable. It is also difficult to obtain accurate data for generics, non-prescription drugs, or multiple drug regimens. Background information, detailed explanation, and examples of patient exposure estimations are given in the CIOMS V report (pp. 167–181).

When exposure data are based on information from a period that does not fully cover the period of the PSUR, the MAH can make extrapolations using the available data. When this is done it should be clearly indicated what data were used and why it is valid to extrapolate for the PSUR period in question (e.g., stable sales over a long period of time, seasonality of use of the product).

The MAH should use a consistent method of calculation across PSURs for the same product. If a change in the method is appropriate, both previous and current methods and calculations should be shown in the PSUR introducing the change.

In Summary Bridging Reports, recalculation of patient exposure data to cover the entire reporting period can be appropriate if the exposure periods used in the individual PSURs overlap.

As described in E2C, when the pattern of reports indicate a potential safety problem, detailed presentation by clinical indication, approved or unapproved, should be provided when available.

2.6 Presentation of Individual Case Histories

There is no specific guidance in E2C on the presentation of individual case report narratives. As it is impractical to present all case reports for the reporting period in this section of the PSUR, a brief description of the criteria used to select cases for presentation should be given.

This section should contain a description and analysis of selected cases, including fatalities, presenting new and relevant safety information and grouped by medically relevant headings or System Organ Classes (SOCs).

2.6.1 General Considerations

Consumer and Other Non-healthcare Professional Reports

MAHs should prepare standard line listings and tabulations that are considered acceptable by all Regulatory Authorities, as described in E2C. To achieve this goal, MAHs should follow a consistent practice across all PSURs for all products by presenting consumer and other non-healthcare professional reports in separate line

listings. When included in the analysis of safety issues in section 6 or 9, consumer reports should clearly be identified as such.

2.6.3 Presentation of the Line Listing

"Comments" field

E2C indicates that the "Comments" field should be used only for information that helps to clarify individual cases.

2.7 Studies

Only those company-sponsored studies and published safety studies, including epidemiology studies, that produce findings with potential impact on product safety information, should be included with a discussion of any final or interim results. The MAH should not routinely catalogue or describe all the studies.

2.8 Other Information

2.8.3 Risk Management Programmes

When an MAH has specific risk management programmes in place, they can be discussed in this Section.

2.8.4 Benefit-risk analysis report

When a more comprehensive safety or benefit-risk analysis (e.g., all indications reviewed) has been conducted separately, a summary of the analysis should be included in this Section.

2.9 Overall Safety Evaluation

Discussion and analysis for the Overall Safety Evaluation should be organized by SOC rather than by listedness or seriousness. Although related terms might be found in different SOCs, they should be reviewed together for clinical relevance.