CLINICAL SAFETY DATA MANAGEMENT: PERIODIC SAFETY UPDATE REPORTS FOR MARKETED MEDICINAL PRODUCTS *)

Guideline Title	**Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Medicinal Products *)**
Legislative basis	**Directive 75/319/EEC as amended, Council Regulation 2309/93**
Date of first adoption	**December 1996**
Date of entry into force	**June 1997**
Status	**Last revised 1996**
Previous titles/other references	**ICH E2C: *Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs*/ CPMP/ICH/288/95**
Additional Notes	**This note for guidance concerns the format and content of comprehensive periodic safety updates of marketed medicinal products which are required to be presented by virtue of Article 29d of Directive 75/319/EEC as amended, and Article 22 of Council Regulation 2309/93.**

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1. INTRODUCTION

1.1 Objectives of the guideline

The main objective of ICH is to harmonise technical requirements for marketing authorisation. 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 is 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 commercialisation. Surveillance of marketed medicinal products is a shared responsibility of the Regulatory Authorities and Marketing Authorisation Holders (MAH). They record information on medicinal product 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.

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

- report all the relevant new safety information from appropriate sources;

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* 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.

- relate these data to patient exposure;
- summarise the market authorisation status in different countries and any significant variations related to safety;
- create periodically the opportunity for an overall safety re-evaluation;
- indicate whether changes should be made to product information in order to optimise 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 harmonise the requirements for PSURs, which will also improve the efficiency with which they are produced.

The current situation for periodic safety reports on marketed medicinal products 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* which take into account the CIOMS Working Group II proposals**.
- 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 authorisation. 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 authorisation.

This guideline might also be applicable for longer term reporting intervals; however, other options may be appropriate.

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

** International Reporting of Periodic Drug-Safety Update Summaries. Final Report of CIOMS Working Group II, CIOMS - Geneva 1992.

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 authorisation applications and renewals, as well as data on serious, unlisted ADRs (see below 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 medicinal product by both the reporter and the manufacturer/sponsor should be excluded.

Reports of lack of efficacy specifically for medicinal products 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., licenser-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, such data should be included and discussed in the PSUR, even if it is known that it is 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 authorisation 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 authorisation for any of the various authorisations 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 medicinal product on the market may influence this process. In addition, during the initial years of marketing, a medicinal product will ordinarily receive authorisations at different times in different countries; it is during this early period that harmonisation 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 medicinal product 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 approval 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 for 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 medicinal product'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 "labelledness" which is used in association with official labelling. Thus, the local approved

product information continues to be the reference document upon which labelledness/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 centres
   - reports created by poison control centres
   - 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

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* 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.

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)
- 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 standardisation 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 set out in section 2.6.4.

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

The following sections are organised 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)*

MAH's 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 Worldwide market authorisation 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 authorisation, and subsequent renewal;
- any qualifications surrounding the authorisation, such as limits on indications if relevant to safety;
- treatment indications and special populations covered by the market authorisation, when relevant;
- lack of approval, including explanation, by regulatory authorities;
- withdrawal by the company of an application for marketing authorisation 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 authorised. 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 authorisations. For multiple authorisations in the same country (e.g., new dosage forms), the IBD for the active substance and for all PSURs should be the first (initial) authorisation date.

Table 1 is an example, with fictitious data for an antibiotic, of how a table might be organised. The medicinal product 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 authorisation withdrawal or suspension;
- failure to obtain a marketing authorisation 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 contra-indications, 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 for the overall safety evaluation and for 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 recognised 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 paediatric 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, recognised 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 medicinal product 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 organised (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 medicinal product (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 medicinal product(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 analysed company-sponsored studies

All relevant studies containing important safety information and newly analysed 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 analysed, 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 summarised 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, an unusual level of 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):

- medicinal product 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 medicinal product, 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 authorisation 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 organisation 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 organised 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.

TABLE 1: EXAMPLE OF PRESENTATION OF WORLDWIDE MARKET AUTHORISATION 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 = authorised; AQ = authorised with qualifications; LA = lack of approval; V = voluntary marketing application withdrawal by company; AR = Authorisation 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 medicinal product (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 studies	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-literaure 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.)