## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

**[Docket No. 96D–0041]**

### International Conference on Harmonisation; Draft Guideline on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs; Availability

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is publishing a draft guideline entitled ''Clinical Safety Data Management: Periodic Safety Update Reports For Marketed Drugs.'' The draft guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft guideline provides a unified standard for the format, content, and reporting frequency for postmarketing periodic safety update reports. The draft guideline also provides definitions and terms for key aspects of postmarketing periodic safety reporting. The guideline is intended to help harmonize collection and submission of postmarketing clinical safety data.

**DATES:** Written comments by July 5, 1996.

**ADDRESSES:** Submit written comments on the draft guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm.1–23, Rockville, MD 20857. Copies of the draft guideline are available from the Division of Communications Management (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–1012. An electronic version of this guideline is also available via Internet by connecting to the CDER file transfer protocol (FTP) server (CDVS2.CDER.FDA.GOV).

**FOR FURTHER INFORMATION CONTACT:**

Regarding the guideline: Murray M. Lumpkin, Center for Drug Evaluation and Research (HFD–2), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–6740.

Regarding the ICH: Janet J. Showalter, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–0864.

**SUPPLEMENTARY INFORMATION:** In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

At a meeting held on November 29, 1995, the ICH Steering Committee agreed that a draft guideline entitled ''Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs'' should be made available for public comment. The draft guideline is the product of the Efficacy Expert Working Group of the ICH. Comments about this draft will be considered by FDA and the Efficacy Expert Working Group. Ultimately, FDA intends to adopt the ICH Steering Committee's guideline and to amend its regulations to fully implement the guideline. Until such time as the agency's regulations are amended, sponsors must continue to comply with the existing regulations.

The draft guideline provides guidance on the content, format, and reporting frequency for postmarketing periodic safety update reports. The draft guideline also defines basic terms for postmarketing periodic reporting, such as ''company core data sheet,'' ''company core safety information,'' ''data lock-point (data cut-off date),'' ''international birth date,'' ''listed adverse drug reaction,'' ''spontaneous adverse drug reaction report (spontaneous notification),'' and ''unlisted adverse drug reaction.'' The draft guideline is designed primarily for medicinal products authorized recently or in the future. It is most relevant for products marketed in more than one ICH country.

In the past, guidelines have generally been issued under § 10.90(b) (21 CFR 10.90(b)), which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but are acceptable to FDA. The agency is now in the process of revising § 10.90(b). Although this guideline does not create or confer any rights for or on any person and does not operate to bind FDA, it does represent the agency's current thinking on periodic safety update reports for marketed drugs.

Interested persons may, on or before July 5, 1996, submit written comments on the draft guideline to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the draft guideline follows:

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

1. Introduction

*1.1 Objectives of the guideline*

The main objective of ICH is to harmonize technical requirements before 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 ICH Steering Committee has decided that the harmonization of format, content, and time span covered in periodic safety update reports for marketed drugs should be addressed by ICH, as an extension of the ICH topic on Clinical Safety Data

Management: Definitions and Standards for Expedited Reporting.

The regulatory requirements, particularly regarding frequency of submission and content of periodic safety updates, are not the same in the three regions. To avoid duplication of effort and to ensure that important data are submitted with consistency to competent authorities, it is proposed to establish an international consensus on the format and content for periodic safety updates of marketed medicinal products.

*1.2 Background*

When a new medicinal product is submitted for marketing approval, the demonstration of its efficacy and the evaluation of its safety are based at most on several thousand patients, except in special situations. The limited number of patients included in clinical trials, the exclusion at least initially of 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.

Medicinal products must be closely monitored, especially during the first years of commercialization to develop a comprehensive picture of clinical safety. 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 drug reactions (ADR's) that are both serious and unexpected.

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's) present the worldwide safety experience of a medicinal product at defined times postauthorization to:

- Report all the relevant new 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;
- Decide whether changes should be made to product information to optimize the use of the product.

However, if the PSUR's 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 forced 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 PSUR's, 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 United States requires quarterly reports during the first 3 years, then annual reports. FDA has recently published proposed rules [1] that take into account the Council for International Organizations of Medical Sciencesse (CIOMS) Working Group II proposals. [2]
- In the European Union, Council Directive 93/39/EEC and Council Regulation 2309/93 require reports with a periodicity of 6 months for 2 years, annually for the 3 following years, and then every 5 years.
- 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, ADR's that are both nonserious 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 PSUR's, 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 PSUR's is designed primarily for medicinal products approved/authorized recently or in the future.

Although this guideline could be applied to other drugs, modifications in accord with local regulations may be appropriate. (See section 1.4.4 for additional discussion.)

This guideline is most relevant to products marketed in more than one ICH country.

*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. Separate presentations of data for different dosage forms, indications, or populations (e.g., children versus adults) may be appropriate.

For combinations of substances also marketed individually, safety information for the fixed combination might be reported either separately or included in the reports for each of the separate components, depending on the circumstances. Cross-referencing the relevant reports is appropriate.

1.4.2 General scope of information

With the exception of regulatory status information on authorization applications and renewals, which should be cumulative, all relevant clinical and nonclinical safety data should cover only the period of the report (interval data).

The main focus of the report should be ADR's. For spontaneous reports, unless indicated otherwise by the reporting health-care professional, all adverse experiences should be assumed to be ADR's; 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.

Lack of efficacy, especially in the treatment of serious or life-threatening conditions, may be reported as a ''safety issue.'' These types of cases, especially if isolated, are not expected to be included in the PSUR ADR data presentation (e.g., line listings or summary tabulations). However, such findings should be discussed somewhere within a PSUR, particularly if they represent a potential risk to the treated population (see section 2.8.1).

An increase in the frequency of reports for known ADR's 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. Judgment should be used in such situations to determine whether the data reflect a meaningful change in ADR occurrence or safety profile.

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

Each MAH is responsible for submitting PSUR's, even if different companies market the same product in the same country. When companies are involved in contractual relationships (e.g., licensor-licensee), respective responsibilities for sharing safety information and for safety reporting to regulators should be clearly specified between the parties to ensure that all relevant data are duly reported to appropriate regulatory authorities.

When available data received from 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 relevant data should be summarized in a 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 a company's first marketing authorization in any country in the world. 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 cutoff for data to be included in a PSUR. During the initial years of marketing, the MAH should generally freeze its data base (and have a data lock point) every 6 months thereafter.

The need for a report and the frequency of report submission to authorities are subject to

[1] Adverse experience reporting requirements for human drug and licensed biological products; proposed rule, Federal Register, October 27, 1994 (59 FR 54046 to 54064).

[2] International reporting of periodic drug-safety update summaries; final report of CIOMS, Working Group II, CIOMS, Geneva, 1992.

local regulatory requirements. However, independent of the required reporting frequency, preparation of PSUR's for all regulatory authorities should be based on data sets of 6 months or multiples thereof.

The age of a drug on the market may influence this process; 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. Once a drug has been marketed for several years, the need for a comprehensive PSUR 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 versus adults; prescription to nonprescription status). The potential consequences on the safety profile raised by such new types and extent of population exposures 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 product information

The 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 decide whether changes should be made to product information. Reference information is needed to perform this comparison. In addition, having one reference source of information in common for the three ICH regions will facilitate a practical, efficient, and consistent approach to the safety evaluation and make the PSUR a unique report accepted in all areas.

Based on the common practice for MAH's to prepare their own ''Company Core Data Sheet''(CCDS), a practical option for the purpose of periodic reporting is to use, as a reference, the safety information contained within that central document. In addition to this safety information, a full company CCDS covers material relating to indications, dosing, pharmacology, and other areas that are not necessarily safety related. Reference safety information will therefore be referred to as ''Company Core Safety Information'' (CCSI).

For purposes of periodic safety reporting, CCSI forms the basis for determining whether an ADR is already ''Listed'' or is still ''Unlisted,'' terms that are introduced to distinguish them from the usual terminology of ''expectedness'' or ''labeledness'' that 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 ''expedited'' postmarketing safety reporting.

1.4.6 Presentation of data on individual case histories sources of information

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

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

- Spontaneous notifications from health care professionals;
- Spontaneous notifications from nonhealth care professionals or from consumers (nonmedically substantiated);
- MAH-sponsored clinical studies or named-patient (''compassionate'') use.

(b) Literature.

(c) Other sources: Regulatory authorities; data from exchange between contractual partners (e.g., licensors-licensees) holding their own marketing authorizations; special registries such as organ toxicity monitoring centers, poison control centers, and epidemiological data bases.

*Description of the reaction*

Until an internationally agreed coding terminology (dictionary) is 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 (e.g., WHO–ART, COSTART).

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, MAH's 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:

- 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).
- It is incumbent on the MAH to report and try to understand all information provided within a case report, such as laboratory abnormalities possibly drug related but not identified as such 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 that they might wish to examine more completely by requesting full case reports.

There are other issues regarding the content of line listings:

- MAH's can prepare line listings of consistent structure and content for cases directly reported to them (or under their control) (see 1.4.6(a)); they can usually do the same for published cases (ordinarily well documented; if not, followup with the author is possible). However, inclusion of individual cases from second- or third-hand sources, such as contractual partners and special registries (see section 1.4.6(c)) 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 in these circumstances is acceptable.
- An exception to the above consideration is the case reports received directly by regulatory authorities (but not by MAH) that might be transmitted to the MAH.

In addition to individual case line listings, summary tabulations of the various 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 ADR's and all nonserious unlisted ADR's), but also on other sources for which line listings are not requested (e.g., nonserious listed ADR's). Details are found in Section 2.6.4.

It is worth noting that work in progress may in the future enable routine electronic transmission of detailed ADR case report information on a regular basis between MAH and regulatory authorities. When implemented, this may obviate the need for line listings within a PSUR, which for some products might be very extensive.

2. Model for a 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);
- 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*

- Introduction;
- Worldwide market authorization status;
- Update of regulatory authority or MAH actions taken for safety reasons;
- Changes to reference product information;
- Patient exposure;
- Presentation of individual case histories;
- Studies;
- Other information;
- Overall safety evaluation;
- Conclusion;
- Appendix: Company Core Data Sheet.

*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 section 1.4.6), the possibility of data duplication should be noted.

For multiple dosage forms, indications, populations, etc., one report is preferred in most cases. When appropriate, data presentations within the report may be separated accordingly.

*2.2 Worldwide Market Authorization Status*

This section of the report is ordinarily the only one that 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 or 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 by regulatory authorities;
- Withdrawal by the applicant of a submission;
- Dates of launch when known;
- Trade name(s).

Typically, indications for use, populations treated (e.g., children versus 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 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 PSUR's 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 adults with 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 activity during the reporting period:

- Application withdrawal or marketing authorization 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.

*2.4 Changes to Reference Product Information*

The CCDS with its CCSI should be numbered and dated and include the date of last revision. The version in effect at the beginning of the period covered by the report should be used as a reference; a copy should be included as an appendix with the PSUR.

Changes to the CCSI, such as new contraindications, precautions, warnings, ADR's, or interactions, already made during the period covered by the report, should be clearly described, with presentation of the modified sections. The new document 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, the estimation of patient exposure should cover the same period as the interim safety data. Ideally it should give the number of patients or prescriptions, and duration of exposure, data that are admittedly difficult to obtain and to validate. However, a reasonable method should be used with proper explanation and justification, particularly if it is not the same as used in the previous report(s). Attempts should be made to obtain the most useful and relevant quantification. Examples include patient-months or patient-days of exposure, number of dosage units by form and strength, or if other more precise measures are not available, bulk sales (tonnage). The concept of a defined daily dose may be used in arriving at exposure estimates.

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

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

- Followup 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, MAH's should monitor standard, recognized journals for safety information on their products and/or make use of one or more literature search/summary service(s) 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 nonhealth 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 on specific request by regulatory authorities.

2.6.2 Cases presented as line listings

The following types of cases should be included in the line listings (Table 2):

- All serious reactions, and nonserious unlisted reactions, from spontaneous notifications;
- All serious reactions (attributable by either investigator or sponsor), available from studies or named-patient (''compassionate'') use;
- All serious reactions, and nonserious unlisted reactions, from the literature;
- All serious reactions from regulatory authorities

Collection and reporting of nonserious, listed ADR's may not be required in all ICH countries. However, a line listing of spontaneously reported nonserious 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 more than one adverse event/reaction term, they should all be mentioned but the case should be listed under the most serious presenting sign, symptom, or diagnosis, as judged by the MAH. The 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);
• Comments, if relevant (e.g., 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 nonserious reactions, for listed and unlisted reactions; other breakdowns might also be appropriate (e.g., by source of report). (See Table 3 for an example of a data presentation.)

A summary tabulation should be provided for the nonserious, listed, spontaneously reported reactions. (See also section 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 section 1.4.6(c)) generally should 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 suitable.

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 (e.g., their nature, medical significance, mechanism, reporting frequency). 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 (nonclinical, clinical, epidemiological) yielding safety information with potential impact on product information, and studies specifically planned or in progress 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 results should be clearly presented with attention to the usual standards of data analysis and description that are applied to nonclinical 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, interim results of ongoing studies may be presented. When completed and analyzed, the 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 containing important safety findings (positive or negative) should be summarized. Published abstracts from relevant meetings should also be discussed.

*2.8 Other Information*

2.8.1 Efficacy-related information

Any information relating to a product's efficacy that has implications or consequences for safety should be described, such as unexpected significant lack of efficacy in the population under treatment for a life-threatening disease.

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 followup 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, followed by the MAH assessment of the significance of the data collected during the period, should highlight any new information on:
• Serious unlisted reactions;
• Nonserious 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 or new information on the following (lack of significant new information should be mentioned for each):
• Drug interactions;
• Experience with overdose and its treatment;
• Drug abuse;
• 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 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 all relevant safety information, material relating to indications, dosing, pharmacology, and other areas that are not necessarily safety related.

*Company Core Safety Information (CCSI)*–All relevant safety information contained in the CCDS 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 6 monthly increments.

*International Birth Date (IBD)*–The date of first marketing authorization for a company's new medicinal product in any country in the world.

*Listed Adverse Drug Reaction (ADR)*–An ADR whose nature and severity are consistent with the information in the CCSI.

*Spontaneous Adverse Drug Reaction Report or Spontaneous Notification*–An unsolicited communication to a company, regulatory authority, or other organization that describes an adverse medical 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, the nature or severity of which is not consistent with the information included in the CCSI.

Table 1.—Example of Presentation of Worldwide Market Authorization Status

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

[1]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 sections 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[1] | S | - | + |
| | NS U | - | + |
| | NS L[2] | + | - |
| • MAH sponsored studies | SA | - | + |
| 2. Literature | S | - | + |
| | NS U | - | + |
| 3. Other sources | | | |
| • Regulatory Authorities | S | - | + |
| • Contractual partners | S | + | - |
| • Registries | S | + | - |

[1]Medically unconfirmed reports should be provided as a PSUR addendum only on request, as a line listing and/or summary tabulation.
[2]Line listing provided as PSUR addendum only on request by regulatory authority. S = serious; L = listed; A = attributable to drug (by investigator or sponsor); NS = nonserious; U = unlisted.

Table 3.—Number of Reports by Term (Signs, Symptoms and Diagnoses) from Spontaneous (Medically Confirmed), Clinical Trial and Literature Cases: All Serious Reactions

| Body system ADR term | Spontaneous/regulatory bodies | Clinical trials | Literature |
|---|---|---|---|
| CNS | | | |
| hallucinations[1] | 2 | 0 | 0 |
| etc. | | | |
| etc. | | | |
| ——— | ---- | ---- | ---- |
| Sub-total | | | |
| CV | | | |
| etc. | | | |
| etc. | | | |
| ---- | ---- | ---- | ---- |
| Sub-total | | | |
| Etc. | | | |
| TOTAL | | | |

[1] Indicates an unlisted term

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 trial, and z-literature cases).

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