

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

DRAFT CONSENSUS GUIDELINE

ADDENDUM TO ICH E2C
CLINICAL SAFETY DATA MANAGEMENT
PERIODIC SAFETY UPDATE REPORTS FOR MARKETED
DRUGS

Released for Consultation
at *Step 2* of the ICH Process
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At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the three ICH regions (the European Union, Japan and the USA) for internal and external consultation, according to national or regional procedures.

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

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Draft ICH Consensus Guideline

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INTRODUCTION

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

The PSUR should represent a practical and achievable mechanism to summarize interval safety data, especially covering short periods (e.g., 6 months or one year) in order to conduct an *overall* safety evaluation. It serves as a stimulus for Marketing Authorization Holders (MAHs) to conduct systematic analyses of safety data on a regular basis. In addition to covering usual safety issues the PSUR also includes updates on urgent safety issues, major signal detection/evaluation, and changes in efficacy which have been or will be addressed in other documents.

The ICH Guideline E2C was formulated to achieve harmonization of PSURs and to permit acceptance by Regulatory Authorities of the same report covering the same data for the same time intervals. However, the original Guideline has been interpreted in different ways by both MAHs and Regulatory Authorities. This has resulted in a perception that the guideline was not sufficient to accommodate the broad range of products and diverse circumstances which arise in practice.

Because PSURs are of value and importance to all parties in protecting the public health, there was a need to reach agreement on the components forming the PSUR. The Council for International Organizations of Medical Sciences (CIOMS) Working Group¹ made recommendations and developed new concepts that harmonise the practice of summarizing data covering long periods of time as well as the concept of a “summary bridging report” that ties together information from shorter-period PSURs.

A wide range of issues pertaining to PSURs was considered in developing this addendum. However, only those E2C provisions felt to be in need of further clarification guidance or increased flexibility beyond that provided in the ICH E2C guideline have been addressed in this document. This document should always be used in conjunction with the E2C Guideline.

In order to facilitate the use of this document, the numbering of the sections and paragraphs are identical to those of the E2C guideline.

1.1 Objectives of the Guideline

PSURs contain proprietary information. With the exception of the line listing or similar case information, which is comparable to data provided by Regulatory Authorities to the public in some countries, the Regulatory Authorities do not intend to release the remainder of the contents of the PSUR unless there is a local legal

¹ Report of CIOMS Working Group V: Current Challenges in Pharmacovigilance: Pragmatic Approaches. CIOMS, 2001, Geneva.

requirement to do so. The title page of a PSUR should contain a clear statement on the confidentiality of the data and conclusions included in the report.

If, in addition to the usual safety analysis done in the PSUR, a more comprehensive safety or risk-benefit analysis (e.g., all indications reviewed) is considered appropriate this more comprehensive analysis should be prepared and submitted as a “stand alone” document. The results of this analysis should be included in the next PSUR.

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 separate sections within the body of the PSUR and any safety issues addressed accordingly without preparing a separate PSUR.

There are areas where separate PSURs might be considered appropriate.

Examples include:

- Fixed combinations: Options include 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 International Birthdates (IBD), 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 (i.e., when the additional period is less than 3 months for a 6 month PSUR or 6 months for a longer duration PSUR) without further comment unless, of course, 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 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 might wish to synchronize local or national birthdates with the IBD. Although such a process can be difficult (e.g., it might require multiple applications for a variation), such a step might be feasible and can be discussed with the Regulatory Authorities.

For a drug where the IBD is not known, the MAH can designate the IBD in order to allow synchronization of reports to all Regulatory Authorities and to optimize PSUR

workload scheduling. Once the IBD is designated, the MAH should notify the Regulatory Authorities, and the IBD should be adhered to thereafter.

It is recognized that the long interval between approvals could put the drug in a 5 year cycle in one region and a 6 month cycle in the other region(s). 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, yearly or every 5th year.

1.4.4.2 Summary Bridging Reports

A summary bridging report should be a concise document that integrates two or more PSURs to cover a specified period over which a single report is required by those Regulatory Authorities not requiring or desiring PSURs on a more frequent basis. It should not contain any new data but should provide a brief, bridging summary of two or more PSURs (e.g. 2 consecutive 6-month reports for a 1 year report or 10 consecutive 6-month reports to make a 5-year report). It is intended to assist Regulatory Authorities with a helpful overview of the appended PSURs. The data should not be repeated but should be cross-referenced to individual PSURs. The format/outline, which should be identical to the format of the usual PSUR, should follow that of a 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 pages 154-6).

Summary bridging reports can be used in the situation where the MAH prepares short duration reports (e.g. 6-month or 1-year reports) *indefinitely*, especially if new indications or formulations are likely to be introduced over the years. For those reports considered out of date relative to a particular Regulatory Authority's requirement, an addendum report could also be submitted (see 1.4.4.3).

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 such tables will be generated from live databases, which change over time as cases are updated (i.e. these tables will then have the most up to date data available at the time they are generated). The case counts in these summary tables can thus differ somewhat from the contents of the individual tables in the appended PSURs.

1.4.4.3 Addendum Reports

MAHs should set IBDs for all their products and synchronise their local renewals. However, there can be circumstances when a required or requested report covers data that fall outside the defined period. An Addendum Report is recommended for those situations.

An Addendum Report is an update to the most recently completed PSUR when a Regulatory Authority requires a routine safety update outside the usual IBD reporting cycle. It should be used when more than 3 months for a 6-month report, and more than 6 months for an annual or 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 should 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, which should contain 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) (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 yearly 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, and/or
- A previously unapproved use in a special patient population, such as children or pregnant women or elderly, and/or
- A new formulation and/or new route of administration.

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.

For the above circumstances, a decision on whether to restart the clock should be discussed with the Regulatory Authority no later than the time of approval of the relevant application dossier.

1.4.4.5 Time Interval Between the Data Lock Point and the Submission

To facilitate the preparation of both current and future PSURs, as well as safety reports outside of the PSUR, the Regulatory Authority reviewers intend to attempt to send any comments on the PSUR 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
- 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

ICH E2C recommends that PSURs be submitted to Regulatory Authorities within 60 days of the data lock point. However, in rare circumstances, an MAH should make a special request to the Regulatory Authority for a 30 additional calendar days to submit a PSUR. Ideally, this request should be made before the data lock point. The Regulatory Authority intends to respond 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 that might require 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

For 6 month and 1 year reports, the version of the Company Core Safety Information (CCSI)² in effect at the beginning of the period covered by the report should be used as the reference.

When producing a longer duration PSUR, such as a 5 year report, it is often impractical to base the analysis of listedness on the CCSI that was in effect at the beginning of the 5 year period. There can be considerable variation in listedness over 5 years, depending on when the assessment of listedness is made (i.e. 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 5-year 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 it is generally considered acceptable 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 5-year period should include the current version of the CCSI and comment on the reasons for the change in listedness assessment over time. In both cases, changes added since the previous PSUR should be explained in Sections 4 (Changes to Reference Safety Information) and/or 9 (Overall Safety Evaluation).

If a long duration PSUR is prepared using several shorter duration PSURs (e.g. a 5-year report using 10 consecutive 6-month PSURs), the CCSI in force at the beginning of each shorter duration report should be used. A discussion of the changes that occurred in the CCSI and its implications over the long duration should be included in the summary bridging report.

Whether listedness is assessed at case entry or as a batch process at the time of preparing the PSUR, there will be an impact on Section 6 of the PSUR. For example, as non-serious unlisted ADRs are added to the CCSI over the 5 year period, they

² Report of CIOMS Working Group III and V, CIOMS, Geneva, 1999

become listed, and therefore cease to appear in the line listing. Instead, they should be included in the summary tabulation of non-serious listed ADRs.

Please refer to section 2.4 of the E2C document regarding highlighting of the differences between the CCSI and the local product information/local labeling in the cover letter or other document accompanying the local submission of the PSUR.

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

2.1 Executive Summary

MAHs should prepare a brief (e.g., one page), stand-alone overview of each PSUR to provide the reader with a description of the most important information. The 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 CIOMS V page 333.

2.5 Patient Exposure

Estimating patient exposure data for marketed drugs often relies on gross approximations of in-house or purchased sales data or volume to determine patient exposure. This 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 drugs for which there is use of generic versions. For nonprescription drugs, use is often on an as-required basis, and individual packages are frequently used by multiple family members of different ages and weights. Background information, detailed explanations, and examples of patient exposure estimations are given in the CIOMS V report (pages 167 – 181).

When the 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, etc.).

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

In a summary bridging report every effort should be made to avoid patient exposure data and calculations that overlap time periods.

2.5.1 Off-Label Use

Estimating the extent of off-label use of a product is difficult. Without careful, separate studies, such as special prescription surveys or drug-utilization audits, data covering off-label use can be misleading. Although suspect ADR reports involving unapproved uses are received and processed by the MAH as usual, the extent of underreporting is unknown.

Clearly, if an important safety signal arises with regard to off-label use, special attempts should be made to understand the scope of use and the problem; however, such efforts are generally not considered appropriate for routine PSUR purposes and should be made only if there is evidence of off-label use associated with a suspected safety issue.

2.6 Presentation of Individual Case Histories

There is no specific guidance in E2C on the presentation of individual case report narratives. It is sometimes impractical to present all individual case safety reports for the reporting period and/or for specific issues in this section. 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 containing new or relevant safety information and grouped by medically relevant headings/System Organ Classes (SOCs).

2.6.1 General Considerations

Consumer and Other Non-healthcare Professional Reports

MAHs should prepare standard line listings/tabulations that are acceptable to all Regulatory Authorities as described in E2C.

In order 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 consumer reports are included in the analysis of safety issues in section 6 and/or 9, they should clearly be identified as such.

2.6.2 Cases Presented as Line Listings

Solicited Reports

A solicited report is one that does not come to an MAH spontaneously from a consumer or health care professional. It is one in which the MAH or its agent has made an effort to elicit safety information from the patient, his or her health care provider, or his or her representative (e.g. a family member). Such cases should be handled as follows:

- Solicited reports, if not medically confirmed, should be treated as consumer reports, and thus not reported in the PSUR unless specifically requested by the authorities (same as for spontaneous consumer reports)
- Solicited reports should be processed separately and categorized in the data base as solicited reports. The reports should also be identified as solicited cases in any reports or tabulations that are prepared.

All AEs from solicited reports should be handled in the same way as similar reports from clinical trials.

Recognition of medically important information from the aggregate data of solicited reports can on rare occasions be possible. Therefore, the MAH should review the data on an ongoing basis, particularly at the time of periodic report preparation, to ensure that potential signals are captured.

The MAH should follow a consistent practice across all PSURs for all products by presenting solicited reports in separate line listings. When solicited reports are included in the analysis of safety issues in section 6 and/or 9, they 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 special information that helps to clarify individual cases. That field should not be routinely used to convey causality assessment conclusions and other non-essential information.

2.7 Studies

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

2.9 Overall Safety Evaluation

Discussion and analysis for the Overall Safety Evaluation should be organized by SOC rather than by listedness or seriousness; the latter properties should, of course, still be covered under each SOC. Although related terms might be found in different SOCs, they should be reviewed together for clinical relevance.