Guidance for Industry

Addendum to E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2004
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Contains Nonbinding Recommendations

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INTRODUCTION

This addendum is intended to provide practical guidance for the preparation of periodic safety update reports (PSURs) as recommended in the ICH guidance *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs*, which was endorsed by the ICH in November 1996 and published by the FDA in May 1997. The E2C guidance has been implemented in some but not all ICH countries.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

BACKGROUND

The PSUR is a practical and achievable mechanism for summarizing interval safety data, especially covering short periods (e.g., 6 months or 1 year), and for conducting an overall safety evaluation. It is a tool for marketing authorization holders (MAHs) to conduct systematic analyses of safety data on a regular basis. In addition to covering ongoing safety

[1] This guidance was developed within the Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, February 2003. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the USA.

issues, the PSUR should also include updates on emerging and/or urgent safety issues, and major signal detection and evaluation that are addressed in other documents.

PSURs are of value and importance to all parties in protecting the public health. The ICH E2C guidance was developed to harmonize PSURs submitted to the regulatory authorities in terms of content and format as well to introduce the concept of international birth date (IBD). However, the original E2C guidance has been interpreted in different ways by both MAHs and regulatory authorities. These differing interpretations have resulted in a perception that the guidance was not sufficient to accommodate the broad range of products and diverse circumstances that arise in practice. The Council for International Organizations of Medical Sciences (CIOMS) Working Group V made several recommendations and developed new concepts to harmonize the practice of preparing PSURs that have been taken into account in preparing this addendum.[2]

THE ADDENDUM

This addendum addresses only those E2C provisions considered to need further clarification, guidance, or increased perceived flexibility beyond that provided in the ICH E2C guidance. This document should always be used in conjunction with the E2C guidance. To facilitate the use of this document, the numbering of the sections and paragraphs corresponds to the numbering in the E2C guidance.

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

- Summary bridging report (see section I.D.4.b (1.4.4.2)[3])
- Addendum report (see section I.D.4.c (1.4.4.3))
- Proprietary information (see section II (2))
- Executive summary (see section II (2))
- Risk management program (see section II.H.3 (2.8.3))
- Benefit-risk analysis (see section II.H.4 (2.8.4))

D. General Principles (1.4)

1. One Report for One Active Substance (1.4.1)

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

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

[3] Arabic numbers in parentheses reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, February 2003.

regimen should be presented in a separate section within the body of the PSUR and any safety issues addressed accordingly without preparing a separate PSUR.

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

Examples include:

- Fixed combinations: Options include either a separate PSUR for the combination with cross-reference to the single agent(s) PSUR(s) or inclusion of the fixed combination data within one of the single agent PSURs.

- When an active substance is used in two or more different formulations (e.g., systemic preparations versus topical administration), two or more PSURs, with the same or different IBDs, can be useful.

4. International Birth Date and Frequency of Review and Reporting (1.4.4)

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

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

  or

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

a. Synchronization of national birth dates with the IBD (1.4.4.1)

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

For a drug where the IBD is not known, the MAH can designate an IBD to allow synchronization of reports to all regulatory authorities. Once an IBD is designated, the MAH should notify the regulatory authorities, and the IBD should be adhered to thereafter.

It is recognized that long intervals between approvals could put the drug in a 5-year cycle in one region and a 6-month cycle in another region. For practical purposes, if a single date (month, day, and year) for the IBD is not attainable, the MAH can contact the regulatory authorities to negotiate a mutually acceptable birth month and day. For example,

where there are different approval dates, it can be useful for reports to be submitted on the same month and day (e.g., every January 18 and July 18), whether every 6 months, annually, or every 5th year.

b. Summary bridging reports (1.4.4.2)

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

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

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

c. Addendum reports (1.4.4.3)

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

An *addendum report* is an update to the most recently completed PSUR when a regulatory authority requests or requires a safety update outside the usual IBD reporting cycle. An addendum report should be used when more than 3 months for a 6-month or an annual report, and more than 6 months for a longer-interval report, have elapsed since the data lock point of the most recent PSUR. It might also be appropriate to provide an addendum to the summary bridging report.

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

- Introduction (purpose; cross reference to most recent PSUR)
- Changes to the Company Core Safety Information (CCSI) (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)

d. Restarting the clock (1.4.4.4)

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

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

The decision on whether to restart the clock should be discussed with the regulatory authority no later than the time of granting the relevant marketing authorization.
Even if the clock "restarts," the analyses in the PSUR should focus on the newly indicated population by identifying and characterizing any differences from the established safety profile in the previously indicated populations.

e. Time interval between the data lock point and the submission (1.4.4.5)

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

- as rapidly as possible, if any issues of noncompliance 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

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

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

- A large number of case reports for the reporting period, provided that there is no new significant safety concern

- Issues raised by regulatory authorities in the previous PSUR for which the MAH is preparing additional or further analysis in the next PSUR

- Issues identified by the MAH for additional or further analysis

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

5. Reference Safety Information (1.4.5)

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

PSUR covering a period of 6 months or 1 year

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

PSUR covering a period of over 1 year

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

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

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

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

MAHs should prepare a brief overview, or *executive summary,* of each PSUR to provide the reader with a description of the most important information. This executive summary should be placed at the beginning of the PSUR immediately after the title page. An example of an executive summary can be found in the CIOMS V report, p. 333.

E. Patient Exposure (2.5)

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

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

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

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

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

F. Presentation of Individual Case Histories (2.6)

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

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

1. General Considerations (2.6.1)

Consumer and Other Nonhealthcare Professional Reports

MAHs should prepare standard line listings and tabulations that are considered acceptable by all regulatory authorities, as described in E2C. To achieve this goal, MAHs should follow a consistent practice across all PSURs for all products by presenting consumer and other nonhealthcare professional reports in separate line listings. When included in the analysis of safety issues in section 6 or 9, consumer reports should clearly be identified as such.

3. Presentation of the Line Listing (2.6.3)

"Comments" field

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

G. Studies (2.7)

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

H. Other Information (2.8)

3. Risk Management Programs (2.8.3)

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

4. Benefit-risk Analysis Report (2.8.4)

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

J. Overall Safety Evaluation (2.9)

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