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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Ref: Docket No. 96D-0041. International Conference on Harmonisation, Draft Guidance on Addendum to E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs.

Abbott Laboratories commends the Agency on their efforts to provide guidance to industry on E2C-Addendum on Clinical Safety Data Management, Periodic Safety Update Reports for Marketed Drugs, published in the Federal Register on December 31, 2002.

We are very pleased to have the opportunity to comment on this draft guidance and thank the Agency for their consideration of our attached comments. Should you have any questions, please contact Ivone Takenaka, Ph.D. at (847)-935-9011 or by FAX at (847) 938-3106.

Sincerely,

D. L. Sporn

Douglas L. Sporn
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96D-0041

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Abbott

January 21, 2003

COMMENTS ON
ICH Draft Guidance on Addendum to
E2C Clinical Safety Data Management
Periodic Safety Update reports for Marketed Products

Docket No. 96D-0041

GENERAL COMMENTS

This document is a significant step forward to handling the practical aspects of PSUR preparation. Several areas are outlined and commented on below. It should be reinforced in section *1. Introduction* that many of solutions in this document are interim steps until regulatory authorities accept the PSUR schedule based upon the international birthdate (IBD) as noted in sections *1.4.4 International Birthdate and Frequency of Review and Reporting and 1.4.4.3 Addendum Reports.*

SPECIFIC COMMENTS

1.4 General Principles

1.4.4 International Birthdate and Frequency of Review and Reporting
In the bullet point referring to the length of time following the preparation of a PSUR where line-listings would be appropriate for local submissions, the timing is reasonable for 6 month and 1 year PSURs where 3 months and 6 months, respectively, are used as a cut off period. However, the period should not be 6 months for longer duration (i.e. 5-year) PSURs. These reports are on a 5-year schedule because they have been marketed for longer periods of time and are deemed to have a more stable safety profile. Provision of line-listings to cover an additional period of up to one year would be reasonable for 5-year PSURs.

A similar comment applies to the second bullet point that addresses when Addendum Reports would be required. An Addendum Report should only be required for 5-year PSURs when the additional period is greater than one year.

1.4.4.1 Synchronization of National Birthdates with the IBD
We agree that for older products where the IBD is not known, the company should designate an IBD which should then be followed. This will provide a rationale to enable company affiliates to take one schedule to all authorities for approval.

We agree with the optional provision to request the synchronization of the IBD of a product for multiple countries.

Related to the third paragraph topic of aligning month and day for reports to be submitted in different regions, it should be further clarified that it is acceptable to use 6-monthly

intervals based upon the IBD to align the PSUR submission schedule (rather than a new date based upon approval in the second region).

1.4.4.2 Summary Bridging Reports

We agree with the provision that provides a mechanism to bridge several PSURs rather than generate new PSURs for the same time period.

We agree with the optional provision to use 6-month and/or 1-year reports indefinitely to help varied submission requirements. Again, this should be emphasized as an interim measure

1.4.4.3 Addendum Reports

We strongly agree that MAHs should set IBDs for all their products and synchronize their local renewals.

For the exceptional circumstances where addendum reports are required, we agree with the provision that provides a mechanism to supplement an existing PSUR rather than generate a new PSUR with different time frames.

Same comment as in *1.4.4 International Birthdate and Frequency of Review and Reporting:* Addendum reports should only be necessary if the time since 5-year PSUR preparation and the locally-required report exceeds one year.

1.4.4.4 Restarting the Clock

We agree with the idea that when re-starting the clock, the data should focus on the newly-indicated population and characterizing any differences from the established safety profile.

We disagree with the concept that the clock may need to re-start when additions or changes are introduced into an ICH region (when already approved in another region). If regular reports based upon the IBD have been prepared since first approval, there is no need to re-start the clock unless one of the other criteria for clock re-start is present. We suggest the following wording be included in the document:

> "Products that are approved for the first time in a new market after being on the market elsewhere and for which PSURs cover longer intervals (e.g., annual reports) should not automatically require restarting the clock for six-monthly PSURs for the new market. For such products, it is recommended that in place of a full, short-term PSUR, regulators in the new market accept a summary tabulation covering the existing IBD-based period (with or without supporting line-listings) of spontaneously reported adverse events over shorter periods in the new market."

We agree with the concept of not needing to provide 6-monthly PSURs to authorities in countries where the product has been recently approved when the product is already approved elsewhere and the schedule is now annual. The alternative of providing summary tabulations and an MAH comment (on whether the experience reflects the established ADR profile) on a six monthly basis is reasonable if the local authorities cannot accept the IBD-based PSUR schedule. This should be emphasized as an exceptional situation.

1.4.4.5 Time Interval Between Data Lock Point and the Submission

Regarding the PSUR assessor comments, we agree with all points in the first paragraph, including the bullets. We would add to the third bullet (that the comments be sent to the MAH before the next data lock point) that comments should be sent 1 month prior to the next data lock point, especially if the preparation time from data lock to submission remains at 60 days.

Additional Time for Submissions

We agree that 60 days after data lock is not always possible for the reasons outlined and agree with the provision allowing a request for additional time when necessary.

1.4.5 Reference Safety Information

We agree that flexibility for use of reference safety information for 5-year PSURs would be beneficial depending upon company processes for determining listedness (at time of PSUR preparation vs ongoing listedness).

We suggest modifying the second paragraph as follows:

> "The MAH should ensure that all relevant content changes to the CCSI...are described in Section 4 of the PSUR..."

There are often formatting, grammatical, and organizational changes to safety sections of the CCSI that should not require explanation in the PSUR.

2.5 Patient Exposure

We agree that there are difficulties associated with estimating patient exposure and that it should still be left to the company to determine which method is appropriate on a product-by-product basis.

We agree that extrapolations may be necessary/used as long as what data were used and the reasons that this represents a valid approach are given.

2.7 Studies

We agree that these sections should only be for identifying studies that provide relevant or new safety information and not to catalog or describe all studies.

2.9 Overall Safety Evaluation

We suggest adding a statement that the decision on providing an update review or a cumulative review on a particular selected event or SOC should be left to the discretion of the company.