

**Final Concept Paper**  
**Addendum to E2C Guideline : Periodic Safety Update Reports for Marketed Drugs**  
**and**

**E2D: Post-Approval Safety Data Management:**  
**Definitions and Standards for Expedited Reporting**  
**dated 5 February 2002**

*Endorsed by the Steering Committee on 7 February 2002*

**Type of harmonisation proposed**

The PMS group proposes three areas for consideration:

- Periodic Safety Update Reports (PSURs): Further Guidance (addendum to E2C)
- Good case management practices (follow-up of E2A/CIOMS V)
- Early phase post-marketing vigilance (new topic)

The PMS group considers that each of these proposed guidelines will lead to improved public health and better regulation as outlined below.

**Statement of the issues**

*Periodic Safety Update Reports (PSURs)*

PSURs were the subject of ICH E2C. Since implementation, it has become clear that the work for companies and regulators in preparing and assessing these documents has increased significantly. They have become a legal requirement in some regions. Because these reports are of mutual value and importance to both parties in protecting public health, there is an urgent need to reach an understanding on “best practices” for both preparation and review of PSURs. Procedural difficulties to be addressed, include:

- Only having one PSUR for the active ingredient
- consistent use of the international birth date
- establishing and interpreting reporting guidelines to ensure globally consistent periodicity of reporting
- When to restart the PSUR clock?
- flexibility in preparation time
- safeguarding proprietary information
- need for guidance on content and review
- handling solicited reports, consumer reports and line listings
- selection criteria for studies to be included
- estimation of patient exposure, including off-label use.
- Handling of literature reports / frequency and intensity of screening

*Good Case Management Practices*

ICH E2A deals with pre-authorisation safety data management. The key focus is on definitions. Many stakeholders have applied E2A to the post-marketing phase. However, there is a need to formalise this and in addition, to further develop some of the definitions specifically for the post-authorisation phase. Examples include seriousness, expectedness, and identifiability.

*Early phase post-marketing vigilance*

Safety issues may arise early in the life of a marketed product. Globalisation of the industry and harmonisation of regulation is leading to more synchronised introduction of products across the world. This leads to very rapid exposure of large populations to new drugs. Therefore significant drug safety issues have the potential for serious public health impact. An early phase post-marketing vigilance plan at the time of licensing is proposed.

**Proposed solution***PSURs*

For PSURs it is proposed to set up an expert working group. This group will develop an addendum to ICH E2C to provide further guidance on the production of PSURs. The addendum will use the excellent work already carried out by CIOMS V as a basis for its recommendations.

*Good Case Management Practices*

A new guideline will be developed by an expert working group. The document will be based on the content of ICH E2A and will consider how the terms and the definitions are used in the post authorisation phase. CIOMS V was published in 2001, and has addressed some key issues encountered by both industry and regulators. These issues include detailed guidance on expectedness, seriousness and identifiability. The recommendations of CIOMS V on these issues will be considered for incorporation into the guideline.

*Early Phase Post-marketing Vigilance*

It is proposed to hold further informal discussions on early phase post marketing vigilance at the Washington meeting. MHLW and EU will produce a further scoping document prior to the meeting. Early phase post marketing vigilance proposes a plan at the time of licensing. This plan would:

- identify potential risks (safety concerns from pre-authorisation data, and absent data i.e. treatment in at-risk groups likely, when no pre-authorisation data are available)
- document the needs for post authorisation data collection (e.g. need for a post *PSURs* safety study?)
- If significant potential risks are identified, outline risk management strategies (e.g. education of doctors on how to use the product safely)

The proposed guideline would explain how to predict risks in the post marketing period, and would propose a format (including a check-list) for the plan. The guideline would also outline when additional data collection mechanisms (e.g. a study) might be warranted. Furthermore, the guideline would outline principles of best practice for post authorisation safety studies. The PMS group recommended that the guideline would address risk management strategies. However, due to differences in clinical practice in the different regions, this section of the guideline would need to be high-level rather than detailed.

Participants agreed that there is a need for further preparatory work in order to identify the content and scope more specifically and to compile existing practices in the different regions before giving a recommendation on whether to initiate a formal ICH procedure.

*Target dates of actions of the EWG*

<b>Topic</b>	<b>Leader</b>	<b>Washington</b>	<b>Osaka</b>	<b>Priority</b>
Preparatory work on EPPV	MHLW and EU	Informal discussions	-	
New guideline: good case management practice	JPMA	Step 2		2
New guideline: PSURs (addendum to E2C)	EFPIA, PhRMA?	Step 2	Step 3	1

**Types of Expert Working Group**

The PMS group advises setting up two expert working groups, one dealing with EPPV, the other with both Good Case Management Practice and PSURs. The reason for this proposal is that the expertise required for EPPV will be mainly risk assessment, study design, and epidemiology, while the expertise for Good Case Management Practice and PSURs is more about reporting requirement and compliance.

Each working group would be comprised of two experts from each party (and three observers).