

**Final Concept Paper
E2E: Pharmacovigilance Planning**

Dated and endorsed by the Steering Committee on 11 September 2002

Purpose

This concept paper sets out a proposal for an ICH guideline to aid industry and regulators for prospective planning of pharmacovigilance activities, especially in preparation for the early post-marketing period of a new drug.

For the purpose of this concept paper, the term ‘pharmacovigilance’ refers to the scientific activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem. This includes use of pharmaco-epidemiological studies.

Origin of the concept paper

At the ICH meeting in Tokyo in 2001, MHLW provided the concept of “Early-Phase Post Marketing Vigilance - EPPV” as introduced into Japanese regulation. It was presented as an example of an early post-marketing risk management plan. This topic went through considerable evolution at ICH meetings in Tokyo, Brussels and London to become the current proposal. **It is important to stress that the current proposal is distinct from the EPPV post-marketing risk management plan provided by MHLW in Tokyo.**

Why a guideline is needed

Carefully planned and effective pharmacovigilance activities, particularly for new drugs, can reduce the risk of drug toxicity and increase the benefit to public health. In addition, robust safety data can help avoid withdrawal of effective drugs from the market.

With the increasingly innovative technologies being employed in drug development, the globalisation of the pharmaceutical industry and high profile drug withdrawals due to safety concerns, both industry and regulators have identified the need for better and earlier planning of pharmacovigilance activities, ideally before a licence is granted. To address this need, some ICH participants have been developing pre-approval pharmacovigilance specifications and plans in isolation. There is a need for an ICH guideline on this topic to ensure harmonisation and consistency, to prevent duplication of effort and to minimise risk to public health. In addition, the guideline may be of benefit to public health programs throughout the world when considering new drugs in their country.

Scope and context

The proposed guideline could be used by industry when preparing a pharmacovigilance plan in discussions with regulators during the licensing assessment, when preparing to launch a product and also in case of safety concerns in the post-marketing period.

The proposed guideline will be particularly relevant to new chemical entities and biotechnology derived products, as well as significant changes in established products (e.g.

new dosage form or new route of administration) and those that are to be introduced to new populations or in significant new indications.

This guideline will set out a structured method for documenting the established risks of a drug, the potential for significant unidentified risks and the potentially at-risk populations and situations that have not been studied pre-approval. This guideline will also set out how to plan for pharmacovigilance activities. It will also set out the principles of good practice for the design and conduct of post-approval safety studies. This guideline will not set out other methods to reduce risks from drugs, such as risk communication. The guideline will take into consideration ongoing work in the three regions and beyond on these issues.

The proposed guideline will incorporate the following principles:

- prospective planning of pharmacovigilance activities throughout the product life-cycle
- science-based approach to risk documentation
- effective collaboration between regulators and industry
- applicability of the pharmacovigilance plan across the three ICH regions.

Proposal outline

The guideline will consist of three components:

- pharmacovigilance specification
- pharmacovigilance plan
- post-approval safety studies.

Pharmacovigilance Specification

The guideline will set out a structured method for documenting the established risks of a drug, the potential for significant unidentified risks, and the potentially at-risk populations and situations that have not been studied pre-approval. This will lead to the construction of a pharmacovigilance or safety 'specification' for the drug.

Elements of the specification will be detailed in the guideline and may include but are not limited to:

- identified pre-clinical safety concerns
- missing pre-clinical data
- adverse drug reactions in clinical trials
- size of the human safety database and frequency of ADRs that could have been detected in these trials
- potential adverse reactions that require further evaluation to clarify risk hypothesis
- populations not studied in the pre-approval phase
- documented interactions
- the potential for unidentified interactions that may occur in the post-approval period
- disease epidemiology
- class effects.

This specification will help industry and regulators identify any need for specific data collection in the post-approval period. It will also facilitate the construction of the pharmacovigilance plan.

Pharmacovigilance Plan

A key recommendation of the proposed guideline will be a pharmacovigilance plan that will be driven by the pharmacovigilance specification outlined above. Recognising that effective and proactive safety planning starts early in product development, this plan could be proposed by the company applying for a licence and will be based on the risks (known and potential) identified in the specification. The plan will help to better define the safety profile of the drug. The plan would be scrutinised by the regulators assessing the licence application and would be agreed upon between the company and the regulator following discussion and modification. This will ideally all occur prior to granting a licence. The plan will then be implemented by the company (and regulator, if applicable). The plan could be used as the basis for discussion on pharmacovigilance activities among regulators at the time of review in the different ICH regions.

For a drug with an adequate pre-approval safety database including at-risk groups and a well-documented safety profile, the pharmacovigilance plan may simply propose that spontaneous reporting systems/periodic safety update reports are sufficient for post-approval safety monitoring. For products with risks of concern, or with inadequate pre-approval safety databases, or where at-risk groups have not been studied, the plan might detail additional data collection including protocol outlines for post-approval safety studies. During the course of implementing the various components of the plan, any important emerging risk information will be discussed to revise the plan.

Post-Approval Safety Studies

The guideline will outline the principles of good-practice for the design and conduct of post-approval clinical safety studies based on existing documents.

Conclusions and recommendation

Enhanced pharmacovigilance is essential to better protect public health. The need for prospective planning of pharmacovigilance is clear. Work underway in the three ICH regions on such planning demands harmonisation.

It is recommended that an Expert Working Group is set up on V3 Prospective Planning of Pharmacovigilance (PPP).

Proposed next steps

Membership of EWG – recruited according to the usual ICH six-pack arrangement. It is considered that the contribution of the observers would be particularly valuable with this topic.

Timing – the proposed EWG will meet in February (Tokyo), July (Brussels) and will deliver a step 2 document in Osaka in November 2003.

It is recommended that MHLW continue to lead this project. If an industry partner is required then EFPIA has indicated that it would be interested to help.