

**Final Concept Paper**  
**M4E(R2): Enhancing the Format and Structure of Benefit-Risk Information in ICH**  
**M4E(R1) Guideline**  
**Revised on 23 March 2015**  
*Endorsed by the ICH Steering Committee on 27 March 2015*

**Background to the Proposal**

Regulatory agencies approve drugs that are demonstrated to be safe and effective for human use. The meaning of “safe” has historically been interpreted to mean that the benefits of the drug outweigh its risks. The benefit-risk assessment is the fundamental basis of regulatory decision-making. Providing greater structure for the benefit-risk assessment has been an important topic in drug regulation over the last few years; however, the associated guidance and documentation for benefit-risk assessment within the ICH Common Technical Document, revised in September 2002, has not kept pace with this progress. Both regulators and industry have developed approaches for structured benefit-risk assessment that are currently being implemented within their respective organisations. While these approaches may take different forms, there is a common thread evident among them that could inform harmonisation of the format and structure of benefit-risk assessments provided by applicants in their regulatory submissions.

**Type of Harmonisation Action Proposed**

An ICH Expert Working Group (EWG) is proposed to evaluate the current ICH Guideline M4E(R1) (Section 2.5.6), revising it to include greater specificity on the format and structure of benefit-risk information with the goal of harmonising the presentation of this information in regulatory submissions.

**Statement of the Perceived Problem**

The benefit-risk assessment is the core concept of regulatory decision-making. Under current ICH Guideline, M4E(R1), applicants are expected to include their conclusions on benefits and risks in the Clinical Overview of Module 2 of the Common Technical Document (CTD) (Section 2.5.6). There is general guidance provided in M4E(R1) regarding the expected content of this Section, but no further structure is suggested that could aid industry in structuring their benefit-risk assessment. Regulators and industry, therefore, observe a high degree of variability in the approaches taken by applicants in presenting this information, ranging from unstructured to structured descriptive frameworks or quantitative frameworks. This variability may not facilitate efficient communication of industry views to regulators. This will fulfill and promote the original concept of the CTD, resulting in reduced regulatory and industry burden and enhanced communication between regulators and industry sponsors.

**Issues to be Resolved**

Revisions to ICH Guideline M4E(R1) would standardise the presentation of benefit-risk assessment information in regulatory submissions. Such standardisation would include the information inputs as well as the industry views on those inputs that make up the benefit-risk assessment. It would also include guidelines regarding the format and reporting of benefit-risk assessment information. These elements would be addressed by the EWG through the following

key issues:

- A review of the existing content guideline for Section 2.5.6 and either affirming that the existing guideline is still appropriate with respect to content or whether further clarification on content could be beneficial.
- The level of detail expected of the guideline regarding benefit-risk assessment and how benefit-risk information should be structured by the revision.

During the review of Section 2.5.6, the EWG may review the descriptions in other parts of the Clinical Overview to ensure that the revised guidance is both harmonised and appropriate in its entirety. Specifically, the EWG would want to ensure that any new guidance in Section 2.5.6 does not create confusion or unnecessary duplication with the current guidance in other parts of Section 2.5. If an issue is identified between new guidance in Section 2.5.6 and other sections of 2.5, the EWG will first determine whether the problem can be addressed by further revision of Section 2.5.6. If the EWG determines that the specific problem requires clarification in Sections 2.5.1-2.5.5, then this specific issue and the rationale for the change will be thoroughly described by the EWG.

It is important to acknowledge that each regulator is required to follow its own approach in conducting a benefit-risk assessment. These approaches are generally based on the unique laws and regulations relevant to each regulatory authority. Therefore, it is important to also stipulate what is not in the scope of this new proposal. Issues that will not be addressed in the proposed guideline include:

- The approach or process to be applied by regulators in conducting the benefit-risk assessment, such as specifying quantitative and qualitative methodologies and/or;
- Issues that are related to how a regulator reaches a specific conclusion on benefit-risk information.

### **Type of Expert Working Group and Resources**

The EWG will consist of two experts nominated by EU, EFPIA, FDA, PhRMA, MHLW, JPMA, Health Canada and Swissmedic. One member can also be nominated by WHO Observer, and RHIs and DRAs/DoH (if requested).

### **Timing**

The following timing is proposed for the EWG (*~1 year timeline*):

- |  |              |
|--|--------------|
| • First teleconference to initiate preparatory work  | Q3 2014      |
| • Regular email, teleconferences, and web conferences to prepare a consensus draft of the technical document | Q3 - Q4 2014 |
| • Face to face meetings at the semi-annual Steering Committee meetings in                                    | 2014 - 2015  |
| • Draft guideline developed and approved by regulatory parties   | Q2 2015      |
| • Regulatory review and consultation   | Q3 2015      |
| • Present plan to the ICH Steering Committee for review and adoption   | Q4 2015      |
| • Regulatory implementation  | Q4 2015      |