

**Final Business Plan**  
**M4(R2): Enhancing the Format and Structure of Benefit-Risk Information in ICH**  
**M4E(R1) Guideline**  
**dated 20 May 2014**  
*Endorsed by the ICH Steering Committee on 5 June 2014*

**1. The issue and its costs**

- *What problem/issue is the proposal expected to tackle?*

The benefit-risk assessment is the core concept 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.

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.

- *What are the costs (social/health and financial) to our stakeholders associated with the current situation or associated with “non-action”?*

Although there is a general guidance provided in the M4E(R1), there is no further structure suggested that could aid industry in structuring their benefit-risk assessment for efficient communication to a regulator. Regulators and industries, 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 leads to the cost of inefficient communication and poor facilitation of benefit-risk assessment discussions among all Parties.

**2. Planning**

- *What are the main deliverables?*

The ICH EWG would plan to deliver a revision of the ICH Guideline on the Common Technical Document M4E(R1) for submission of marketing applications that incorporates greater specificity on the format and structure of benefit-risk information in Section 2.5.6 of Module 2. This additional content should help standardise the presentation of benefit-risk assessment information in regulatory submissions of marketing applications.

- *What resources (financial and human) would be required?*

The ICH EWG should consist of two members 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).

- *What is the time frame of the project?*

The initial time frame is for one year, i.e. Q4 2015.

- *What will be the key milestones?*

Milestones are:

- |  |              |
|--|--------------|
| • 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 SC 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 SC for review and adoption   | Q4 2015      |
| • Regulatory implementation  | Q4 2015      |

### **3. The impacts of the project**

- *What are the likely benefits (social, health and financial) to our key stakeholders of the fulfilment of the objective?*

Revisions to ICH Guideline M4E(R1) would standardise the presentation of benefit-risk assessment information to include greater specificity on the format and structure benefit-risk information in regulatory submissions. This proposal aims to level-set all key stakeholders in drug regulation with respect to what is important in regulatory decision-making for pharmaceutical products. Greater structure in the presentation of this information should aid regulators in understanding an applicant's perspective on the benefit-risk assessment. Similarly, applicants will have a clear understanding of what is important to a regulator's benefit-risk decision.

- *What are the regulatory implications of the proposed work – is the topic feasible (implementable) from a regulatory standpoint?*

A revision to ICH Guideline M4E(R1) is feasible from a regulatory standpoint. This revision would suggest a new format and structure for the information that applicant provide in Section 2.5.6 of the CTD for marketing applications.

### **4. Post-hoc evaluation**

- *How and when will the results of the work be evaluated?*

Revisions to ICH Guideline M4E(R1) should be evaluated *post-hoc* through a normal feedback process to the ICH Steering Committee. A formal post-hoc evaluation should be conducted after two years following regulatory implementation.