

**Final Business Plan  
Periodic Safety Update Reports for Marketed Drugs E2C(R2) and gap and potential  
improvement analysis of ICH E2C, E2E and E2F**

**10 December 2010**

*Endorsed by the ICH SC on 16 December 2010*

**1. The issue and its costs**

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

The technology and science of pharmacovigilance has progressed significantly and the associated documentation has not kept pace. Of note, is the widespread electronic reporting of individual case safety reports to regulators and the recognition that balanced evaluation of risk should include information on a product's benefits. The various ICH Guidelines driving pharmacovigilance documentation have evolving interdependencies.

ICH Guideline E2C was originally drafted in the 1990s and despite revisions it has not taken account of recent regulatory and technical progress. More than ten years of experience has been gained and it is clear that the existing Guideline was developed for a different era. There is some over-lap of content between the current E2C(R1), E2E and E2F.

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

There is overlap of content of ICH Guidelines E2C(R1), E2E and E2F. This overlap, combined with the lack of a modular approach to allow individual modules to be used at different times for different authorities and for different purposes means that resources are diverted to duplicative document production and reporting, and away from pharmacovigilance and risk management activities that could be more productively linked to public health promotion.

New laws and regulations in the different ICH regions mean that if no new Guideline is developed at ICH to replace the existing E2C(R1) then regional development of Guidelines will occur, resulting in divergences and increased regulatory burden on the industry. This will also interfere with the ability of regulators to share and discuss information, including their assessments of products in the post-licensure phase.

**2. Planning**

- *What are the main deliverables?*

The EWG will deliver an ICH Guideline on Periodic Safety Update Reports for Marketed Drugs E2C(R2). The content of the Guideline will ensure that such reports have the role of being periodic benefit risk evaluation reports. Furthermore, based on an evaluation of the ICH pharmacovigilance documentation, and a gap and potential improvement analysis of ICH E2C, E2E and E2F, the EWG will deliver a plan to the ICH Steering Committee for review of other ICH Guidelines.

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

The ICH EWG will comprise the ICH Parties and Observers plus the Interested Parties (generics industry, over-the-counter and biologics). The topic is likely to be of interest outside

the ICH regions. Because of the multidisciplinary (risk and benefit) nature of the Guideline, each ICH party may appoint up to three experts. The initial mandate should be delivered within two-years and will necessitate five face to face meetings (four at the time of the ICH Steering Committee and one interim meeting). To meet the challenging timeframe for delivery, the EWG will need to additionally work through monthly three-hour teleconferences/webconferences.

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

The initial time frame is for two-years i.e., Q4 2012. *Step 2* of the new Guideline will be in Q4 2011 and the plan to the ICH Steering Committee for review of other ICH Guidelines by the end of 2011. The *Step 4* Guideline should be delivered by Q4 2012.

- *What will be the key milestones?*

Milestones are:

- First teleconference January 2011 to initiate preparatory work e.g., gap analysis and mapping
- 3 day interim EWG meeting, hosted by EMA (February 2011)
- Regular teleconferences/webconferences
- Two face to face meetings at the time of the Steering Committee meeting in 2011
- *Step 2* (Q4 2011)
- Present plan to the ICH Steering Committee for review of other ICH Guidelines by the end of 2011
- *Step 4* (late 2012)

### **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?*

Optimising the evaluation of benefits and risks will consequently enable the optimisation of risk minimisation and of benefit maximisation through product labeling and other risk minimisation and health promotion activities.

Reduced duplication of effort will free up resources that can be directed to public health promotion and protection.

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

The following regulatory considerations are of note:

- EU – new ICH Guideline E2C(R2), if revised in a timely manner, would be reflected in the implementing measures for the new legislation.
- MHLW – in principle, a new Guideline should be drafted under the current legislation.
- FDA – guidance can be amended. While regulation may be amended, this is difficult and FDA would consider that this should be avoided. Law cannot be changed by FDA.
- Health Canada – there is an opportunity for new regulation over the coming years.

Taken together it can be concluded that, if an ICH Guideline E2C(R2) covering periodic benefit risk evaluation reporting is delivered within the proposed timeframe then the topic is

feasible from a regulatory standpoint. The regulatory feasibility of any additional Guideline modification, supplementation or replacement will be assessed as part of the evaluation of the ICH pharmacovigilance documentation, and a gap and potential improvement analysis of ICH E2C, E2E and E2F.

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

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

The evaluation of the ICH pharmacovigilance documentation, and a gap and potential improvement analysis of ICH E2C, E2E and E2F are, de facto, post-hoc evaluations of previous ICH Guideline development. The post-hoc evaluation may lead to modification, supplementation or replacement of ICH E2E or E2F. Given its very recent introduction, it is proposed that feedback on the implementation of ICH E2F is actively sought during 2011/2012 to inform the review.

The new ICH Guideline E2C(R2) covering periodic benefit risk evaluation reporting should be evaluated post-hoc through the normal feedback process to the ICH Steering Committee ('Implementation Issues'). A more formal post-hoc evaluation should be conducted but not for at least three-years following adoption by the ICH Steering Committee of the *Step 4* Guideline.