

Final Concept Paper
**Periodic Safety Update Reports for Marketed Drugs E2C(R2) and gap and potential
improvement analysis of ICH E2C, E2E and E2F**
15 December 2010
Endorsed by the ICH SC on 16 December 2010

Type of Harmonisation Action Proposed

An ICH Expert Working Group (EWG) is proposed to evaluate the ICH pharmacovigilance documentation, conduct a gap and potential improvement analysis of ICH E2C, E2E and E2F and to draft a new ICH Guideline E2C(R2) covering periodic benefit risk evaluation reporting. 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.

The proposal is in the context of the vision developed at the November 2010 ICH Pharmacovigilance Brainstorming and presented to the ICH Steering Committee:
'Optimise the lifecycle benefit risk of medicines for the promotion and protection of public health by establishing a modular and improved approach to the documentation of safety information, risk evaluation, risk minimisation and benefit risk evaluation, including how these are evaluated and planned.'

Statement of the Perceived Problem

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. As more than ten years of experience has been gained, it is clear that the existing Guideline was developed for a different era.

New laws and regulations in the different ICH regions mean that if no new ICH Guideline E2C(R2) covering periodic benefit risk evaluation reporting is developed at ICH 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.

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.

Issues to be Resolved

New Guideline E2C(R2)

The new ICH Guideline on Periodic Safety Update Reports for Marketed Drugs E2C(R2) will ensure that reports have the role of being periodic benefit risk evaluation reports. Reports should cover: Safety evaluation, evaluation of all relevant available information which is accessible for MAH with reasonable and appropriate effort (all use), and benefit risk evaluation (focussed within the approved indication(s) but not formal quantitative (mathematical) benefit risk evaluation).

- A key question will be the level of information on benefit and benefit risk and how it is structured (rather than formal quantitative benefit risk evaluation).
- The EWG should consider utilisation of the same benefit risk evaluation in other documents and situations.
- The EWG should review the interface with E2E Safety Specification (need to consider the elements of the periodic report that are common, for example, with the Safety Specification), however, review of the E2E Pharmacovigilance Plan and methods is not considered a priority.
- The Guideline should have a modular approach (i.e., sections that can be separated and submitted independently or combined with other documents) to maximise the utility of the content and minimise duplication to support use of different modules for different regions and potentially across different documents. The EWG should consider whether benefit risk evaluation should be an individual module. Such a modular approach would have impact on the organisation of the Guideline and the reports and will allow the new reports to be used flexibly across regions and at different times in the lifecycle of a product.
- The EWG should consider the format and content of reports in view of the fact that they may be submitted electronically and in modules in some regions (while avoiding placing any constraints regarding continued submission of paper reports). The format and content should not be expanded, however, for the sake of accommodating non-ICH (electronic) standards. The EWG will not develop an electronic standard. ICH may consider to develop an electronic standard once ICH consensus is reached on the non-electronic portion of this topic.
- The Guideline should:
 - encourage critical analysis of new or emerging safety / benefit risk issues;
 - present data in summaries and tables (consider whether tables are cumulative or interval or both).
- The EWG should consider the necessity or lack thereof of line listings and individual case histories (reference ICH E2C(R1) Section 2.6).
- Timing / periodicity:
 - Periodic Reports should contain cumulative knowledge of a product while retaining focus on new information.
 - The EWG should consider the impact of moving to cumulative reports on periodicity of report production, submission and use of International Birth Date.

Products to be the subject of the new periodic report:

- While the Guideline might consider risk as a driver for which products are the subject of periodic reporting, it should not be prescriptive on product types and timing.

Background

In 2009, EU Regulators circulated a concept paper proposing a revision of ICH Guideline E2C(R1) based on technical and regulatory progress. Comments from the other ICH parties suggested that there was a need to have a broader stock-take on ICH pharmacovigilance (E2) Guidelines and in November 2010 at the Fukuoka ICH meeting a pharmacovigilance brainstorming took place.

The brainstorming participants proposed the following vision:

‘Optimise the lifecycle benefit risk of medicines for the promotion and protection of public health by establishing a modular and improved approach to the documentation of safety information, risk evaluation, risk minimisation and benefit risk evaluation, including how these are evaluated and planned.’

In addition, the participants recommended:

- There is no need to amend E2A and E2D.
- There is some over-lap of content between the current E2C, E2E and E2F although it was acknowledged that these Guidelines have different regulatory purposes (safety evaluation, pharmacovigilance planning and clinical trial safety respectively).
- There was consensus acknowledgement that there was a need to have a document that brought together a product’s benefits and risks and there was discussion on the best tool to achieve this.
- That it is not warranted to reopen Guideline E2F so soon after finalisation and before experience had been gained.
- E2C(R1) should be replaced by a new Guideline where the content covered periodic benefit risk evaluation reporting’. However, and importantly, it was agreed that any EWG on a new Guideline to replace E2C(R1) should carefully consider the interface with Guideline E2E (notably the Safety Specification) and that Guideline E2E may well need to be reviewed in the near future.

Regulatory Considerations

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.

Type of Expert EWG and Resources

The ICH EWG should comprise the ICH Parties and Observers plus the Interested Parties (generics industry, over-the-counter and biologics). Because of the multidisciplinary (risk and benefit) nature of the Guideline, each ICH party should be allowed to appoint three experts. The work is likely to be of interest outside the ICH regions.

Timing

The following timing is proposed for the EWG:

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