



# INFORMATION PAPER

## Step 3 Release E2B(R3)

Revision of Electronic Submission of Individual Case Safety Reports:  
Status & Regional Requirements Update

**28 July 2011**

### ***Introduction***

ICH E2B(R3), “*Electronic Transmission of Individual Case Safety Reports (ICSRs) Implementation Guide Data Elements and Message Specification*,” has been released for public consultation under Step 3 of the ICH Harmonisation Process (Regulatory consultation and Discussion) following achievement of consensus at the June 2011 ICH Steering Committee and Expert Working Group Meetings in Cincinnati, OH, US<sup>1</sup>. This represents the second time this topic has achieved Step 2 of the formal ICH Process (Confirmation of six-party consensus).

The history of the revision of the ICH E2B(R3) Guideline and the reason for this occurrence are explained on the ICH E2B Public Consultation page on the ESTRi website<sup>2</sup>, and in the introduction to the ICH E2B(R3) Implementation Guide itself.

This information paper provides some further detail relating to the relationship between the documents released for Step 3 and the process of standards development that ICH is utilising in collaboration with HL7, ISO and CEN. It also highlights and explains the set of related documents that are being released as part of this consultation package.

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<sup>1</sup> [http://www.ich.org/fileadmin/Public\\_Web\\_Site/News\\_room/B-Press\\_Releases/ICH\\_GCG\\_Press\\_Releases/Press\\_Release\\_Cincinnati\\_2011.pdf](http://www.ich.org/fileadmin/Public_Web_Site/News_room/B-Press_Releases/ICH_GCG_Press_Releases/Press_Release_Cincinnati_2011.pdf)

<sup>2</sup> Via <http://www.ich.org> under the Expert Working Group M2, or directly at <http://estri.ich.org>



## ***Involvement of SDOs***

As discussed in the Implementation Guide and on the website, the ICH standard for electronic submission of Individual Case Safety Reports (ICSRs) has been jointly developed with 3<sup>rd</sup> parties through an external SDO process. ICH representatives have been heavily involved in the development of the international ICSR standard in partnership with other experts from beyond the ICH community. Although this has resulted in a fundamentally different *technical* approach for constructing E2B(R3) messages as compared to earlier versions of the ICH E2B guidelines, the ICH implementation of the standard still reflects the requirements of the ICH community.

Comments received during the initial E2B(R3) Step 3 consultation in 2005 were retained, and were used to revise the ICH requirements which were subsequently fed into the SDO development process. Although there was a timeline and technical development impact in the release of the guideline, the spirit of the original consultation and the ICH Harmonisation process was retained.

Furthermore, during the various SDO ballot stages, the E2B(R3) and M2 Expert Working Groups of ICH undertook extensive testing. Those test results plus other comments received are reflected in the Final Draft International Standards documents from ISO<sup>3</sup>, which in turn are the basis for the ICH implementation of the ICSR message. This testing period was also used to collect comments on the first draft of the ICH E2B(R3) Implementation Guide.

In addition, the Implementation Guide addresses a harmonized approach to ensure backwards and forwards compatibility between the current ICH ICSR message specifications and the new standard – a major aspect during the transition phase until all stakeholders have upgraded their pharmacovigilance systems to handle the new standard.

## ***Document Set for Release***

Unlike the usual ICH Harmonisation Step 3, in this instance a set of documents are being released to the public rather than a single harmonization guidance document or Q&A document. In contrast to past practice the document set for release is substantially more detailed: more specific technical guidance is provided.

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<sup>3</sup> ISO 27953-1: ICSR Framework Reference Model – Health informatics – Pharmacovigilance – Individual case safety report - *Part 1: The framework for adverse event reporting*

ISO 27953-2: ICSR Framework Reference Model – Health informatics – Pharmacovigilance – Individual case safety report – *Part 2: Human pharmaceutical reporting requirements for ICSR*



At this time the following four items are released:

- **ICH Implementation Guide:** A guide for implementing ICH requirements for the electronic transmission of Individual Case Safety Reports. The guide is intended to support the implementation of software tools for creating, editing, sending and receiving electronic ICSR messages. It provides instruction for how the pharmaceutical industry and regulatory authorities will use Part 2 of the ISO standard to construct messages for exchanging pharmacovigilance information between and among themselves in ICH regions and in other countries adopting ICH guidelines.
- **Schema file set:** A set of XML schema files that contain the 'constrained' set of rules, elements and attributes stemming from the HL7 v3 messaging standard that are used in Part 2 of the ISO ICSR standard and are required to construct ICH acceptable ICSR messages. The use of these is explained in the Implementation Guide. These are the technical files required by the IT tools which actually construct, export, read or validate the messages.
- **Reference instance XML files:** An example file that illustrates the coding of an ICSR according to the constraints encoded in the schema files and in compliance with the ICH Implementation Guide. This is provided as an illustrative example and does not contain any real information. It allows for identification of how and where the ICH E2B(R3) elements would appear in an actual transmittable ICSR. A second example file provides a similar illustration of an Acknowledgement message.
- **Backwards and Forwards Compatibility Documents:** An additional document that describes the relationship between elements from E2B(R2) and E2B(R3). This document is intended to assist reporters and recipients (including pharmaceutical companies, authorities and non-commercial sponsors) in implementing systems with special focus on the rules for conversion back and forth between the previous standard. This includes mappings of the elements against one another, with explanation of differences and guidance on how to convert between the message structures and address issues with compatibility.

### ***Relationship to ICH M5 & the ISO IDMP Standard***

A key intention of the revision of the standards for submission of ICSRs is to improve the inherent quality of the data and to enable improved handling and analysis of ICSRs. Early on a critical issue identified was the challenge of the lack of harmonization in medicinal product information and medicinal product terminology.

A first key component needed was clear mapping of international terminologies for routes of administration, dosage forms, and units of administration so that accurate comparison and analysis can be undertaken. A second key component is cross-border identification of medicinal products. In particular, accurate analysis of safety information requires the ability to identify pharmaceutical products in situations where naming conventions and licensing identification varies, and to identify a product's component substances even though they are not necessarily contained within a given safety report.



To this end an ICH M5 harmonisation project for “*Data Elements and Standards for Drug Dictionaries*” was begun. This in turn was also moved into a development process partnered with SDOs, and through the SDO model, with involvement of parties external to the ICH. The resulting project is now developing the ISO Identification of Medicinal Product (IDMP) standards.

The E2B(R3) technical message for ICSRs has been developed in anticipation of these IDMP standards. Specific elements have been incorporated into the message to carry IDMP terminologies and Medicinal Product (MPID) or Pharmaceutical Product (PhPID) identifiers. These are described in detail in the Implementation Guide.

However the timelines of E2B(R3) and M5 differ. Therefore the E2B(R3) Implementation Guide is being prepared to also function without these identification codes and controlled terminologies until they are available. The ICH E2B(R3) Implementation Guide is currently written with the possibility of both approaches. As the ICH M5 guideline reaches Step 4 – adoption of an ICH harmonised tripartite guideline – the E2B(R3) Implementation Guide may either be edited to reflect this outcome or an additional Question & Answer document may be released to provide further detailed guidance.

For the time being the E2B(R3) standard may be implemented without ISO IDMP content.

### ***Regional Requirements***

The ICH strives to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical products, including those related to safety reporting and pharmacovigilance. However, in practice, national legislation and national or regional differences in clinical practice, in health prioritisation, and in attitudes towards privacy and towards characterisation or categorisation of individuals all lead to differing requirements in certain aspects of safety monitoring. National legislation may require information in one region that is inappropriate to share or transmit in another region. Differing attitudes and priorities may require information in one region that is of not of interest in another region, or would not normally be collected.

The ISO standard itself contains a broad set of technical tools (elements and approaches) to capture information that may not be used by ICH as part of the core, harmonised ICSR but may be used only by specific regions. The ICH Implementation Guide is a consensus document that describes a unified approach from the six ICH parties and the related observers. In some cases, the Implementation Guide describes elements that will vary in usage across the ICH regions. In such cases, where appropriate, clarification and explanation will be instead be defined by regional Implementation Guides.



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These regional requirements will be described in sufficient detail in guidance released by individual regulatory authorities according to national and regional requirements, and under the appropriate regional procedures for releasing regulatory guidance. The ICH regulators are committed to maximising the ability for a harmonized ICSR to be acceptable in all regions, and work is ongoing to assess this position. However the assessment of differences and evaluation of where regional variability may be required is partly dependent on the finalisation of the core, harmonised documents. Therefore the regulators aim to publish the regional Implementation Guides shortly after the ICH Implementation Guide reaches Step 4 (which is expected by November 2012). At that time the details of individual ICH regulator's implementation strategies and specific requirements will be publicised. These documents are not contained in the public consultation package associated with releasing E2B(R3) for ICH Step 3 consultation.

### ***Further Information***

Current information on developments and timelines, and access to the aforementioned documents and to further technical details will be made available via the ICH website at [www.ich.org](http://www.ich.org).