

ICH STEERING COMMITTEE

15-16 June 2011

Cincinnati, OH, USA

SUMMARY

1. Opening Discussions

The [ICH Steering Committee \(SC\)](#) meeting in Cincinnati was chaired by FDA. The meeting commenced with the provision of updates on the work of the ICH Secretariat, [ICH MedDRA Management Board](#) and the [ICH Global Cooperation Group \(GCG\)](#).

ICH Secretariat: The [ICH Secretariat](#) reported to the SC on some of its recent activities, including the updating of the [ICH website](#) with new training materials for Q8/Q9/Q10 and E16. The SC noted that the [Q8/Q9/Q10 materials](#) included a training package developed by the Quality Implementation Working Group (IWG) to consolidate the training materials from the ICH workshops on Q8/Q9/Q10 which were held in the three ICH regions in 2010. Also included were recordings from the US Quality IWG training workshop that was held in Washington D.C. in October 2010.

For E16, the SC noted that a [recording of a webinar](#) held in October 2010 for Regional Harmonisation Initiative (RHI) and Drug Regulatory Authority (DRA)/Department of Health (DoH) representatives from the ICH GCG had been added to the ICH website.

The ICH Secretariat reported to the SC on the outcome of its first orientation session which was organised to brief all new ICH Rapporteurs / experts on ICH procedures.

ICH MedDRA Management Board: The Chair of the ICH MedDRA Management Board reported on the decisions taken by the Board on behalf of the SC. The SC was updated on training activities undertaken by the [MSSO](#) (MedDRA Maintenance and Support Services Organization). The Chair informed the SC that as of the end of May, 23 classes for subscribers, including regulators, had been conducted in 2011 and a further 30 classes were planned before the end of the year. The SC noted that in 2011 training had also been conducted in a number of locations beyond the ICH regions including China (Beijing & Shanghai), Panama and Singapore.

The SC was also updated on a meeting of the Board with RHI and DRA/DoH representatives from the ICH GCG. The Chair informed the SC that RHIs in attendance included APEC, ASEAN, GCC and SADC, while DRAs/DoH in attendance included Australia, China, Chinese Taipei, Republic of Korea and Singapore. The agenda for the meeting was developed based on interest expressed in certain topics by the representatives at a previous meeting with the Board in Fukuoka in November 2010. The SC noted that the agenda included presentations from Health Canada and EFPIA on the use of [MedDRA](#) in clinical trials, a presentation from MHLW on Japan's experience with MedDRA, and a presentation to explain the respective roles of the MSSO and JMO (Japanese Maintenance Organization). The DRAs of China and Singapore also provided feedback on the MedDRA training which had occurred in their respective countries.

The SC was pleased to hear of the completion of the current phase of development work on Standardized MedDRA Queries (SMQs) by the [CIOMS \(Council for International Organizations of Medical Sciences\)](#) Working Group on this topic. The Board noted that by the time MedDRA 15.0 will be released in March 2012, a total of 90 SMQs will be available to MedDRA users. The SC acknowledged this significant achievement and recognized the benefit of these important signal detection tools for the protection of public health.

The SC was also updated on the outcome of a survey conducted in the first quarter of 2011 on the use of the MedDRA Web-based Browser which had been launched in January 2010. The SC noted that overall there was a high level of satisfaction amongst users. Other items discussed by the Board in Cincinnati included the planned release in late 2011 of a MedDRA Version Analysis Tool (MVAT) which will help users to up-version to a new version of MedDRA.

ICH Global Cooperation Group: The GCG Co-Chairs reported to the SC on the GCG meeting, which saw the participation of representatives from the RHIs of APEC, ASEAN, GCC, and SADC, and the DRAs of Australia, China, the Republic of Korea and Singapore, in addition to the DoH of Chinese Taipei.

Further to the Fukuoka meeting, where the SC agreed to open-up ICH technical working groups to participation from technical experts from the RHIs and DRAs/DoH, the SC noted that in Cincinnati the ICH technical working groups [E2C\(R2\)](#), [M7](#) and [Q3D](#) welcomed for the first time the participation of technical experts from the DRAs of Korea and Singapore in addition to experts from the DoH of Chinese Taipei.

The SC noted that the RHIs and DRA/DoH received two presentations, the first on the revision of the ICH E2C(R1) Guideline on *Periodic Safety Update Report for Marketed Drugs* (PSUR) which is expected to reach *Step 2* in November 2011, and the second on the ICH M7 Guideline on *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* which is expected to reach *Step 2* in autumn 2012. A presentation was also given by the [M8](#) Rapporteur on the electronic Common Technical Document (eCTD) describing how the eCTD is used in the three ICH regions.

As part of the Cincinnati meeting RHIs and DRAs/DoH provided updates on ICH-related matters in their regions including the outcome of several 2011 GCG training events organised in the APEC, ASEAN and GCC regions.

The RHIs and DRAs/DoH also received presentations on *the Pharmaceutical Inspection Co-operation Scheme* and on *Challenges and Activities to promote Multi-regional Clinical Trials*.

The RHIs and DRAs/DoH were updated on the African Medicines Registration Harmonisation (AMHR) Initiative, and noted the endorsement by the SC of the East African Community (EAC) expression of interest to join the GCG.

2. Proposals for New Topics and Revisions/Maintenance of Guidelines

S1A: Proposal for Addendum to S1A: Need for Carcinogenicity Studies of Pharmaceuticals: The SC noted the establishment of an informal Working Group which will work via email and teleconference to finalise a Concept Paper and Business

Plan for an Addendum to the S1A Guideline for SC consideration at its next teleconference.

E3: Proposal for Q&As on E3: Structure and Content of Clinical Study Reports: The SC endorsed a Concept Paper for Q&As (Questions & Answers) on the E3 Guideline and the establishment of an IWG (Implementation Working Group) which will work mainly via email and teleconference to finalise the Q&A document by June 2012. The purpose of the Q&As will be to align E3 with the requirements of the CTD, particularly the requirements for electronic submission of this document (eCTD), and to clarify other issues encountered since the implementation of E3 (1996) that hinder consistent implementation of the Guideline.

3. Reports on Current Topics

EWGs/IWGs/Discussion Groups Meeting in Cincinnati

M2: Electronic Standards for the Transfer of Regulatory Information: The M2 Rapporteur updated the SC on the work undertaken by the M2 EWG in Cincinnati. The SC noted that this was the first M2 EWG face-to-face meeting held under the new Terms of Reference endorsed by the SC in Fukuoka in November 2010. The SC noted that under the new structure the M2 EWG is responsible for SENTRI activities in addition to SDO relationship management, coordination and best practice.

The Rapporteur informed the SC of M2 discussions in relation to OIDs (Object Identifiers). The SC noted that an OID was a globally unique numeric string used to identify an object as an entity or a list of values. The Rapporteur informed the SC that ICH would need to create OIDs for the ICH E2B(R3) Implementation Guide for the ICSR. The SC supported the Rapporteur's proposal to register a Root OID with [HL7 \(Health Level Seven\)](#).

Other M2 discussions in Cincinnati related to work to evaluate the use and applicability of XML content within the eCTD, and the movement of all information from the [ESTRI website](#) (estri.ich.org) to the official, and newly revamped, ICH website. With regards to the latter, the SC noted that a transition period of one year was proposed as well as a comprehensive outreach strategy to stakeholders. The SC supported this move and the other items included in the M2 work plan.

M8: The Electronic Common Technical Document: eCTD: The Rapporteur reported to the SC on the outcome of the M8 EWG meeting in Cincinnati. The SC noted that this was the first meeting of the new M8 EWG following the restructuring of the M2 EWG in November 2010.

The Rapporteur informed the SC of the status of work in relation to the development of the Next Major Version of the eCTD, v4.0. The SC noted that the draft ICH Implementation Guide (IG) for the eCTD was still under development and the plan was to finalise the document at the next meeting in Seville in November 2011 following which the document would be used to support Feasibility Testing (Beta Testing) currently planned to take place between November 2011 and August 2012. The SC noted that Alpha Testing would be carried out from July to August 2011 during the HL7 RPS (Regulated Product Submission) DSTU (Draft Standard for Trial Use) ballot and in collaboration with HL7 RPS technical experts. The Rapporteur

informed the SC that the current timeframe for reaching ICH *Step 2* was June 2013, however this was dependent on HL7 timelines.

The SC supported the work plan of the M8 EWG and endorsed the addition of one further Q&A (Question & Answer) to v1.20 of the eCTD Change Request/Q&A document.

E2B(R3): Revision of Electronic Submission of Individual Case Safety Reports:

The Rapporteur reported to the SC on the outcome of the E2B(R3) EWG meeting held in Cincinnati. The Rapporteur informed the SC that the group had worked in Cincinnati to finalise *Step 2* of the ICH IG for the ICSR (Individual Case Safety Report) based on the draft [ISO \(International Organization for Standardization\) FDIS](#) (Final Draft International Standard) ballot materials.

The Rapporteur informed the SC that work was still ongoing to finalise the Backwards and Forwards Compatibility (BFC) document which would be published in the *Step 2* package with the IG. The Rapporteur also informed the SC that other informative materials would be posted alongside the *Step 2* package on the ESTRi website. These included an Information Paper (to explain E2B(R3) history and position of regional requirements); a list of ICH ICSR OIDs and reference instances v2; and a BFC conversion stylesheet. The Rapporteur confirmed that the timeframe for the publication of the *Step 2* package on the ESTRi website was August 2011. The SC noted that the ISO ICSR FDIS ballot would take place from July to August 2011.

The SC signed-off the *Step 2* ICH IG for the ICSR and confirmed support for the work plan proposed by the E2B(R3) EWG.

M5: Data Elements and Standards for Drug Dictionaries: The Rapporteur reported to the SC on the outcome of the M5 EWG meeting held in Cincinnati. The Rapporteur informed the SC that at the recent ISO TC (Technical Committee) 215 meeting in May 2011 a resolution had been passed to progress to FDIS the five ISO IDMP (Identification of Medicinal Product) standards (ISO/FDIS 11615: Data elements and structures for unique identification and exchange of regulated medicinal product information; ISO/FDIS 11616: Data elements and structures for unique identification and exchange of regulated pharmaceutical product information; ISO/FDIS 11238: Data elements and structures for unique identification and exchange of regulated information on substances; ISO/FDIS 11239: Data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging; and ISO/FDIS 11240: Data elements and structures for unique identification and exchange of units of measurement).

The SC noted that in Cincinnati, the M5 EWG had worked on the ICH IG for the IDMP based on the FDIS documents and planned to finalise *Step 2* of the IG at the next meeting in Seville in November 2011. The maintenance process for the IDMP standards was also discussed.

Quality IWG: The Rapporteur reported to the SC on the work undertaken by the Quality IWG in Cincinnati. The Rapporteur informed the SC that the group had worked to finalise three implementation PtC (Points-to-Consider) documents on *Level*

of Documentation in enhanced (QbD) Regulatory Submissions, Criticality of Quality Attributes and Process Parameters, and Control Strategy. The SC noted that the PtC documents covered topics relevant to the implementation of the ICH Q8(R2), Q9 and Q10 Guidelines and would supplement the Q&As and workshop training materials already produced by the IWG. The Rapporteur informed the SC that the PtC documents were not intended to introduce new regulatory requirements, but were intended to provide clarity for both regulators and industry and to facilitate preparation, assessment and inspection related to applications filed for marketing authorisations. The SC noted that the IWG had also had preliminary discussion of the next three PtC documents on *Process validation/process verification*; *Role of modelling in Quality by Design*; and *Design Space*.

The SC endorsed the Quality IWG work plan, which included work related to the organisation of two Q8/Q9/Q10 training workshops, one in Ottawa, Canada, on September 26-27, 2011 and the other in Seoul, Korea, on October 4-5, 2011. The SC noted that these workshops followed similar workshops organised by the Quality IWG in Europe, Japan and the USA in 2010.

Q3D: Guideline for Metal Impurities: The Rapporteur reported to the SC on the outcome of the Q3D EWG meeting held in Cincinnati. The SC noted that the group had discussed the scope of the Guideline and had reached agreement that biotechnological drug products should remain in the scope of the Guideline. The Rapporteur informed the SC that a section in the control strategy part of the Guideline would be added to reflect the limited risk associated with inclusion of metal impurities in biotechnologically derived drug substances. He also commented that conventional vaccines would be excluded from the Guideline.

The approach to the development of the Guideline was also discussed and the Rapporteur informed the SC that the EWG had agreed that the Guideline needed to include the following three components: an established PDE (Permitted Daily Exposure), safety assessments supporting the assignment of a PDE and a control strategy. The SC also noted the work done in relation to the drafting and review of metal safety assessments and agreed with the recommendation of the EWG to include the safety assessments in the *Step 2* Guideline.

The SC supported the work plan of the Q3D EWG and noted that the proposed timeframe for reaching *Step 2* was June 2012.

E2C(R2): Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs: The Rapporteur reported to the SC on the outcome of the E2C(R2) EWG meeting held in Cincinnati. The SC noted the group's progress to revise the E2C(R1) Guideline and that in Cincinnati the group had discussed the majority of the sections of the Guideline in detail. The SC noted that the proposed timeframe for reaching *Step 2* was November 2011 and *Step 4* by the end of 2012.

E14: Q&As: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs: The Rapporteur and the Co-Rapporteur reported to the SC on the outcome of the E14 IWG meeting held in Cincinnati. The SC noted that the group had discussed four Q&As which would be

finalised shortly: *Gender (sex), Technology, Heart Rate Correction, and Concentration Response Relationship*. It was also noted that the development of a further two Q&As (*QTc Evaluation in Late Stage Clinical Development and Late Stage ECG Collection*) was still ongoing.

The Rapporteur informed the SC that the group did not have sufficient time to discuss the time to initiate Phase 2 of their work which is to create an ICH working Group that will initiate collaborative data gathering and analyses in all ICH regions in order to address in an ongoing manner additional questions identified that could lead to enhancement of the current Guideline. The SC noted that the group did not yet determine whether there is adequate data to address the most important issues in current E14 guidance.

The SC encouraged the IWG to initiate as soon as possible the data gathering and analyses needed to see whether an enhancement of the current E14 Guideline would be needed.

S10: Photosafety Evaluation: The S10 Acting Rapporteur reported to the SC on the outcome of the S10 EWG meeting held in Cincinnati. The SC noted that the group had reached agreement on the scope of the Guideline and discussed: different testing strategies for systemic drugs; Table of Contents (agreement reached in Fukuoka reconfirmed); endpoints for phototoxicity and photoallergy; tissue distribution (impact of melanin binding, if any); and *in vitro* and *in vivo* non-clinical assays.

The SC endorsed the S10 work plan and noted that the proposed timeframe for reaching *Step 2* was June 2012 and subsequently *Step 4* in June 2013.

M3(R2): Q&As: Guidance on Nonclinical Safety Studies For the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals: The Rapporteur reported to the SC on the outcome of the M3(R2) IWG meeting in Cincinnati. The IWG finalised three Q&As on *Limit Dose, Reversibility of Toxicity and Metabolites*. The SC endorsed the three Q&As and noted the progress made on the remaining Q&As on *Exploratory Clinical Trials, Juvenile Studies, Reprotoxicity and Safety Pharmacology and Combination of Drugs*.

The SC noted that the proposed timeframe to finalise the current set of Q&As was December 2011.

M7: Genotoxic Impurities: The Rapporteur reported to the SC on the outcome of the EWG meeting in Cincinnati. The SC endorsed the M7 work plan which proposed to work by web-conference between meetings, and to communicate with Q3D and Q11 quality members on control strategy to ensure that the scope of M7 is aligned with the scopes of the Q3D and Q11 Guidelines currently under development. The SC noted that the group will come back to the SC with a proposal on ICH Q3A/B alignment with M7.

The SC noted that *Step 2* was expected in November 2012.

EWGs/IWGs/Discussion Groups Not Meeting in Cincinnati

Q4B: Evaluation and Recommendation of Pharmacopoeial Texts for use in the ICH Regions: The Q4B EWG did not meet in Cincinnati. The SC noted that Annex 6

on *Uniformity of Dosage Units*, Annex 13 on *Bulk Density and Tapped Density* and Annex 14 on *Bacterial Endotoxins* were expected to be signed-off at *Step 4* shortly, which would then complete the Q4B EWG's work programme.

Q11: Development and Manufacture of Drug Substances: The Q11 EWG did not meet in Cincinnati. The SC noted that the Q11 had reached *Step 2* of the ICH process in May 2011. The SC noted that regulatory public consultation would shortly be initiated in the three ICH regions and would be complete in time to allow the group to discuss and address the comments received at the next ICH meeting in Seville in November 2011.

CTD-Quality: Q&As: The CTD-Quality IWG did not meet in Cincinnati. The SC noted the ongoing work of the group to address the Quality Change Request issues identified by the M2 EWG (now under M8). The SC noted that a first set of Q&As had already been finalised, and a second and third set of Q&As were being developed.

S2(R1): Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use: The S2(R1) EWG did not meet in Cincinnati. The SC noted that discussion was still ongoing within the FDA regarding the next step for the S2(R1) draft Guideline which had reached *Step 2* in March 2008.

S6(R1): Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals: The SC noted that the postal *Step 4* sign-off was completed on June 12, 2011. The Addendum was then integrated as Part II into the S6 Guideline which was renamed S6(R1).

M1 PtC: MedDRA Points to Consider (PtC): The MedDRA PtC Working Group did not meet in Cincinnati. The SC noted the ongoing work of the group in relation to the development and maintenance of the two MedDRA PtC guidance documents on *Term Selection* and *Data Retrieval and Presentation*.

4. Dates of Next Meetings for 2011 & 2012:

November 5-10, 2011	Europe – Seville, Spain
June 2-7, 2012	Japan – Fukuoka