

ICH STEERING COMMITTEE

November 9-10, 2011

Seville, Spain

SUMMARY

1. Opening Discussions

The [ICH Steering Committee \(SC\)](#) meeting in Seville was chaired by the EU. 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 pilot use of a new webconferencing system which uses VoIP (Voice over Internet Protocol) technology. The SC noted that the system was being used successfully by several of the Working Groups to hold virtual meetings in a cost effective manner.

ICH MedDRA Management Board: The SC received a report on the decisions taken on its behalf by the ICH MedDRA Management Board at its meeting in Seville. The SC noted that the Board had approved the 2012 Subscription Rates for [MSSO](#) (MedDRA Maintenance and Support Services Organization) MedDRA Subscribers which would see no increase over the 2011 rates. 2012 would be the seventh consecutive year without an increase, with past years having seen rates either decrease or remain flat.

The SC noted the growing interest from beyond the ICH regions in the use of MedDRA, and that the Board was working actively to respond to requests for training. So far in 2011, MedDRA training outside the ICH regions was carried out in: Panama (DIA Latin American Regulatory Conference, April 2011); China (May and October 2011); and Singapore (May 2011).

The SC was also updated on a Special Session of the Board which was attended by Regional Harmonisation Initiative (RHI) and Drug Regulatory Authority (DRA)/Department of Health (DoH) representatives from the ICH GCG. This was the fourth Special Session held to-date. The agenda for the meeting was developed based on feedback from previous Special Sessions. Presentations were made on: Australian experience with MedDRA; electronic systems which facilitate adverse event reporting by companies, doctors and consumers (UK MHRA – Medicines and Healthcare products Regulatory Agency [YellowCard Scheme](#) & [EudraVigilance](#)); and analysis of adverse event data. Input was also solicited for the organisation of future sessions.

The SC was also informed on the valuable work of the [CIOMS](#) (Council for International Organizations of Medical Sciences) Working Group on SMQs (Standardised MedDRA Queries), which in addition to continuing to add to the 90 SMQs already developed, was planning to update the CIOMS “Red Book” publication on *Development and Rational Use of Standardised MedDRA Queries (SMQs)*. The SC

acknowledged that this would provide helpful guidance on the use and implementation of SMQs.

Other topics which the SC was updated on included the planned release in Q1 2012 of “MVAT”, the new MedDRA Versioning Analysis Tool, and the planned removal of legacy codes from MedDRA starting with MedDRA Version 15.0 in March 2012. Regarding the latter, the SC noted that the codes to be removed included those from COSTART, WHO-ART, ICD-9, ICD-9-CM, HARTS, and JART, which were originally intended to assist the migration of data to MedDRA when the terminology was first launched. However, since the codes were not maintained or updated over the years, the Board was concerned that there could be the potential for confusion amongst new MedDRA users.

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 (Asia-Pacific Economic Cooperation), EAC (East African Community), PANDRH (Pan American Network on Drug Regulatory Harmonization), and SADC (Southern African Development Community), and the DRAs of Australia, the Republic of Korea, Russia and Singapore, in addition to the DoH of Chinese Taipei. The SC noted that this was the first meeting for the EAC which joined the GCG in August 2011.

The RHIs and DRAs/DoH received a presentation on the EAC Medicine Regulation Harmonisation (EAC MRH) initiative, the official launch of which is planned in February 2012. The RHIs and DRAs/DoH were also updated on the African Medicines Registration Harmonisation (AMRH) initiative, including the recent progress made within several Regional Economic Communities.

The RHIs and DRA/DoH also received presentations on the new [ICH S10](#) Guideline on *Photosafety Evaluation* which is expected to reach *Step 2* in June 2012, and on the new ICH Quality paradigm which consists of developing a harmonised pharmaceutical quality system applicable across the life cycle of the product.

As part of the Seville meeting RHIs and DRAs/DoH provided updates on ICH-related matters in their countries/regions. This included reports on the outcome of [2011 GCG training events organised](#) in the APEC and SADC regions.

The SC noted that the GCG welcomed Health Canada’s training strategy proposal to develop an internal training programme on all [Quality \(Q\)](#), [Safety \(S\)](#), [Efficacy \(E\)](#) and [Multidisciplinary \(M\)](#) ICH Guidelines to ensure an authoritative and consistent presentation of the ICH Guidelines. The SC noted that this project would benefit not only Health Canada’s own purpose but all parties interested in understanding ICH, and that the GCG could also play a strategic role in this regard.

The RHIs and DRAs/DoH also received presentations on *The Importance of Regulatory Harmonisation from the [IFPMA](#) (International Federation of Pharmaceutical Manufacturers & Associations) Perspective* and on *Good Review Practices*.

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 work of the informal WG to discuss the available

data and draft a Concept Paper and Business Plan for an Addendum to the S1A Guideline. The SC will consider progress made by the group at the next SC teleconference in spring 2012.

Q7: Proposal for Q&As on Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients: The SC considered a proposal for the development of Q&As on the ICH Q7 Guideline. The SC agreed to defer its discussion of this proposal until the ICH Q11 Guideline on *Development and Manufacture of Drug Substances* reaches *Step 4* (currently expected in mid-2012) when it would be considered whether Q&As would be the most appropriate way to address the issues noted.

3. Reports on Current Topics

EWGs/IWGs Meeting in Seville

M2: Electronic Standards for the Transfer of Regulatory Information: The M2 Rapporteur updated the SC on the work undertaken by the M2 EWG in Seville. The SC noted that this was only the second meeting of the M2 EWG under the new Terms of Reference endorsed by the SC in Fukuoka in November 2010 and that the group was still working on its model of operations, which included the development of several working practice documents and templates.

The Rapporteur informed the SC that an ICH Root OID (Object Identifier) had been registered officially, and that OIDs had been assigned to the ICH E2B(R3) ICSR (Individual Case Safety Report) code lists and an approach for regional OIDs agreed. The SC noted that the next step would be to define the internal ICH OID maintenance process and publish the ICSR OID and code list on the [ESTRI website](#).

Regarding the ESTRI website, the SC noted the aim to move all information from the ESTRI website (estri.ich.org) to the official ICH website (www.ich.org) in a collaborative effort with the ICH Secretariat. The Rapporteur commented on the importance for the M2 EWG to work with the ICH Secretariat to ensure fixed and stable URLs.

The SC noted that the M2 EWG had also met in Seville with the E2B(R3), M5 and M8 EWGs to discuss a general approach to maintenance for their respective Implementation Guides. The Rapporteur commented that maintenance was becoming more complicated than it had been in the past with the eCTD maintenance, due to the involvement of SDOs (Standards Development Organisations) and the fact that the standards contain more technical components (schema, code lists and OIDs).

The SC supported the work plan of the M2 EWG.

M8: The Electronic Common Technical Document: eCTD: The Rapporteur reported to the SC on the outcome of the M8 EWG meeting in Seville. The Rapporteur informed the SC of the status of work in relation to the development of the Next Major Version of the eCTD, Version 4.0. The SC noted that good progress had been made with the development of the ICH Implementation Guide for eCTD Version 4.0 and that the final version for testing was expected at the next meeting in Fukuoka in June 2012. The Rapporteur informed the SC that the Implementation Guide would then be used to support the *Feasibility Testing/Beta Testing* which would be carried out following the Fukuoka meeting. The SC noted that a first round of *Alpha Testing* had already been

carried out on the draft standard and ICH comments provided back to [HL7](#) (Health Level Seven). The Rapporteur informed the SC that a second round of *Alpha Testing* would be carried out following the Seville meeting and further ICH comments would be provided to HL7 in January 2012. The SC noted that based on the current timelines, *Step 2* was expected by November 2013.

The SC supported the work plan of the M8 EWG and endorsed v1.21 of the eCTD Change Request/Q&A document, which saw the incorporation of five new Q&As, and the removal of a previously added Q&A.

[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 Seville. The SC noted that the *Step 2* package for public consultation was posted on the ESTRi website in mid-September 2011 and included: the ICH E2B(R3) ICSR Implementation Guide; Backwards and Forwards Compatibility (BFC) document; Schema file set; and Reference instances v1. Two informative documents had also been posted – an Information Paper and a BFC conversion stylesheet. The Rapporteur informed the SC that in order to provide supportive information to the technical audience during the public consultation, the E2B(R3) EWG had finalised at the Seville meeting additional documents which would also be added on the ESTRi website. These included: Reference Instance v2, updated with OIDs; a set of lists of ICH OIDs and codes; and use of OIDs and UUIDs (Universally Unique Identifiers) in E2B(R3).

The Rapporteur also updated the SC on EWG discussions in relation to regional requirements, including discussions around having a single set of schema files in all ICH regions and harmonising data validation rules. The SC noted that the EWG recognised that regional legal requirements can change, and therefore it was unlikely that it would be possible to have one full global set of requirements. The Rapporteur commented that regulators remained committed to releasing regional requirements which would enable the acceptance of harmonised files from all regions, and that regulators would make an effort to publish Regional Implementation Guides shortly after the E2B(R3) Implementation Guide reaches *Step 4*.

The SC supported 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 Seville. The SC noted that the five [ISO](#) (International Standardisation Organisation) IDMP (Identification of Medicinal Product) Final Draft International Standards were awaiting ISO ballot initiation. The Rapporteur informed the SC that the final ISO IDMP standards were expected in mid-2012.

The Rapporteur updated the SC on progress made to develop the ICH M5 IDMP Implementation Guide which was expected to reach *Step 2* in November 2012. The Rapporteur presented the overall structure of the Implementation Guide, which would include a general overview (Module 0) and five modules: Module 1 – *Medicinal Product Identifiers (MPIDs)*; Module 2 – *Pharmaceutical Product Identifiers (PhPIDs)*; Module 3 – *Substances*; Module 4 – *Routes of Administration, Dose Forms, Units of Presentation and Packaging*; and Module 5 – *Units of Measurement*.

The Rapporteur also informed the SC on the plan and timelines for both *Alpha* and *Beta Testing*. The SC noted that the *Beta Testing* would be carried out during the *Step 3* public consultation period.

The Rapporteur also reported to the SC on the M5 EWG's discussions in Seville in relation to the maintenance of the five IDMP standards. The SC noted that the group had considered various maintenance options, including a subscriber funded license model and government-funded organisations, with various possibilities being considered such as having maintenance by the regulators and the contracting out of maintenance to third parties. The Rapporteur stressed the importance of having a mechanism which would ensure the use of unique IDs across all ICH regions in line with IDMP requirements.

The SC supported the work plan provided by the M5 EWG, which included plans to conduct a *Maintenance Impact Analysis* to better estimate the resources and costs which would be associated with the maintenance of the M5 IDMP standards, and plans to finalise maintenance options for SC consideration at the next meeting in Fukuoka in June 2012.

Quality IWG: The Rapporteur reported to the SC on the work undertaken by the Quality IWG in Seville. The SC noted that in Seville the IWG had finalised the last three PtC (Points to Consider) topics on: *Process Validation / Continuous Process Verification*; *Role of Models in Quality by Design*; and *Design Space*. These would be added to the existing PtC document which contained the first three PtC topics finalised in Cincinnati in June 2011 on: *Level of Documentation in Enhanced (QbD) Regulatory Submissions*; *Criticality of Quality Attributes and Process Parameters*; and *Control Strategy*.

The SC noted that this completed the current work programme for the Quality IWG. The SC congratulated the group for its work in assisting the implementation of the ICH Q8(R2), Q9 and Q10 Guidelines. The SC noted that training had been a major achievement of the Quality IWG with: three training workshops organised in the three ICH regions in 2010; one ASEAN GCG-endorsed training held in Kuala Lumpur, Malaysia in 2010; an enhanced training workshop conducted in Ottawa, Canada in September 2011; and a GCG-endorsed training workshop held in Seoul, Korea in October 2011.

Q3D: Guideline for Metal Impurities: The Rapporteur reported to the SC on the outcome of the Q3D EWG meeting held in Seville and progress made towards reaching *Step 2*. The SC noted that the group was working to finalise a "pre" *Step 2* document, which would be for broader distribution within the Parties on the EWG, and that the aim was to reach *Step 2* at the Fukuoka meeting in June 2012.

The Rapporteur informed the SC that all safety assessment drafts had been completed and that the PDE (Permitted Daily Exposure) recommendations for all identified metals of concern had been established (oral, parenteral and inhalation). The SC noted that the control strategy section draft had also been completed and included an example of risk assessment, example calculations and a flow chart.

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

Q11: Development and Manufacture of Drug Substances: The Rapporteur reported to the SC on the outcome of the Q11 EWG meeting held in Seville. The SC noted that a total of 1,300 comments had been received from the public regional consultation conducted in the three ICH regions on the *Step 2* Q11 Guideline. The Rapporteur informed the SC that the group had worked in Seville to review the comments.

The SC noted that the only remaining issue related to the need for further elaboration of control strategy and its application to drug substances. The Rapporteur informed the SC that the group would continue to work towards reaching agreement on the control strategy text.

The SC supported the work plan of the Q11 EWG and the proposed timeframe for reaching *Step 4* in Q1 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 Seville. The SC noted the group's progress to revise the E2C(R1) Guideline with the aim of reaching *Step 2* in December 2011 and *Step 4* subsequently in December 2012. The SC agreed on the group's proposal to rename the E2C(R2) Guideline as follows: *Periodic Benefit Risk Evaluation Report (PBRER)*.

The SC supported the work plan of the E2C(R2) EWG and noted that the regulatory consultation period would be initiated as soon as possible after *Step 2* is reached in order for comments to be available before the Fukuoka meeting in June 2012.

E14: Q&As on 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 Seville. The SC noted that the group had progressed the work on the following two Q&As: *Gender (sex)* and *QTc Evaluation in Late Stage Clinical Development*, and that the Q&As on *Technology* and *Heart Rate Correction* would be finalised shortly.

It was also noted that more time and discussion would be needed for the development of the further two Q&As: *Concentration Response Relationship* and *Late Stage ECG Collection*.

The Rapporteur informed the SC that the group did not have sufficient time to discuss when to begin Phase 2 of their work which would require the re-opening of an E14 ICH EWG that would 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 an enhancement of the current Guideline.

S10: Photosafety Evaluation: The Rapporteur reported to the SC on the outcome of the S10 EWG meeting held in Seville. The SC noted that the group had discussed the use of 3-D skin model, ROS assay and a tiered testing strategy which consists of assessing Active Pharmaceutical Ingredients (APIs) for photochemical properties and photosafety.

The SC supported the work plan of the S10 EWG and noted that the group was close to completing a *Step 1* document and was expecting to reach *Step 2* in June 2012 and *Step 4* subsequently in June 2013.

M3(R2): Q&As on 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 Seville. The SC noted that the first set of three Q&As on *Limit Dose, Reversibility of Toxicity* and *Metabolites* was posted on the ICH website in June 2011 and that the group progressed its work on the remaining five Q&As on *Exploratory Clinical Trials, Juvenile Studies, Reprotoxicity, Safety Pharmacology* and *Combination Products*.

The SC supported the work plan of the M3(R2) IWG and the proposed timeframe to finalise the current set of Q&As by June 2012.

M7: Genotoxic Impurities: The Rapporteur reported to the SC on the outcome of the EWG meeting in Seville. The SC noted the progress made by the EWG to finalise a full *Step 1* document by the end of the Seville meeting. The SC also noted that the group reached agreement on the following subtopics: *Staged Less-Than-Lifetime Acceptable Risk Limits; Structured-Based Assessments - QSAR; Excipients* (novel excipients in scope, existing out of scope); *Degradation; Control Strategy and Documentation*.

The SC supported the work plan of the M7 EWG and the proposed timeframe for reaching *Step 2* in November 2012.

M1 PtC: MedDRA Points to Consider (PtC) Working Group: The Co-Rapporteurs reported to the SC on the outcome of the M1 PtC WG meeting in Seville. The SC noted that the role of the PtC WG was to update the MedDRA PtC documents on *Term Selection* and *Data Retrieval and Presentation* with each MedDRA version release (twice a year) to facilitate consistent use of MedDRA.

The Co-Rapporteurs informed the SC that the group had not met face-to-face since June 2010, but had worked via email and teleconference. In Seville, the WG worked to finalise the revision of both PtC documents for the next scheduled release in April 2012 (MedDRA v15.0). The WG also considered whether several new concepts in MedDRA needed to be addressed in the PtC documents. These included: pharmacogenomic terms; new pregnancy related terms; and Hy's law case.

The SC supported the work plan of the MedDRA PtC WG.

EWGs/IWGs Not Meeting in Seville

Q4B: Evaluation and Recommendation of Pharmacopoeial Texts for use in the ICH Regions: The Q4B EWG did not meet in Seville. The SC noted that Annex 13 on *Bulk and Tapped Density* and Annex 14 on *Bacterial Endotoxins* would be ready shortly for *Step 4* sign-off. *Step 4* for Annex 6 on *Uniformity of Dosage Units* was still pending. In addition, the SC noted that a set of Frequently Asked Questions (FAQs) was in the process of being finalised for publication on the ICH website.

The SC noted that once this work was finished, the Q4B EWG's work programme would be complete.

CTD-Quality: Q&As: The CTD-Quality IWG did not meet in Seville. The SC noted the ongoing work of the group to address the Quality Change Request issues identified by the M2 EWG (now under M8) and work by the CTD-Q to propose revisions to the CTD Granularity Document.

E3: Q&As on Structure and Content of Clinical Study Reports: The E3 IWG did not meet in Seville. The SC noted the progress made by the group to develop a series of six Q&As to align E3 with the requirements of the CTD and to clarify other issues encountered since the implementation of E3 in 1996.

The SC noted that the group would continue to work by email and webconference towards reaching *Step 4* for its Q&A document in June 2012.

S2(R1): Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use: In Seville, the SC signed-off *Step 4* of the ICH S2(R1) Guideline which will now be for implementation in the three ICH regions.

4. Dates of Next Meetings for 2012:

June 2-7, 2012

Japan, Fukuoka

November 10-15, 2012

San Diego, CA, USA