

18 July 2013

MEETING REPORT
ICH Steering Committee
5-6 June 2013, La Hulpe, Brussels, Belgium

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

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Opening Discussions

The ICH Steering Committee (SC) meeting in La Hulpe, Brussels on June 5-6, 2013 was chaired by the EU.

Adoption of the Agenda

The agenda was adopted without modification.

1. Membership Update

The SC noted the updated lists of the: ICH Steering Committee Members, Observers and Coordinators; ICH MedDRA Management Board Members and Observer; and RHIs and DRAs/DoH participating in the Global Cooperation session of the SC.

2. Update on MedDRA

The SC received a report on the ICH MedDRA Management Board meeting held on June 1-2, 2013.

The SC noted that the Board approved the 2014 Business Plan and Budget for the MedDRA MSSO (Maintenance and Support Services Organization). They noted that the Board will wait until autumn 2013 before approving the 2014 subscription rates. The past years have seen rates either decreasing or remaining flat.

Training is key to helping facilitate the use of MedDRA. Free training is provided by the MSSO to regulators and other MedDRA subscribers in the form of classroom training, webconferences, and downloadable modules. In 2012, over 42 face-to-face training courses were organised in various countries and regions including the USA, Canada, European Union, China and Turkey. Seven webconferences were also organised in 2012, using VoIP technology to help reduce the costs for users associated with teleconferences. In total, more than 1,400 MedDRA users were trained in 2012. All training materials are available for all on the MedDRA website.

The SC noted that the MSSO has also invested effort in the development of e-learning tools. The following training videos are available on the MedDRA website: *MedDRA Structure and Scope* (available in 5 languages); *What's New with MedDRA Version 16.0*; *MedDRA Version Analysis Tool (MVAT)*; *Primary System Organ Class (SOC) Allocation in MedDRA*; *MedDRA Desktop Browser: Research Bin and Export Functions*; *Introduction to MedDRA Term Selection: PtC*; *Introduction to MedDRA Data Retrieval and Presentation: PtC*; and *Introduction to MedDRA Versioning*; and *Standardised MedDRA Queries (SMQs)* (available shortly). This will include information on practical aspects for new users to MedDRA, including conversion of legacy data, IT considerations and resources available to help facilitate MedDRA's use.

At the invitation of the China Food and Drug Administration (CFDA), an ICH delegation attended a meeting in Beijing in March 2013 to discuss interest expressed in MedDRA and the feasibility of implementing MedDRA in China. The meeting was attended by representatives of the CFDA, Chinese Pharmacopoeia, China ICH Research "M" Group, and Chinese industry. ICH's delegation included several Board regulators, and representatives of the MSSO, JMO and ICH Secretariat. Presentations were given by the ICH regulators regarding the use of MedDRA in their regions.

The SC was also updated on a meeting of the Board with Regional Harmonisation Initiative (RHI), Drug Regulatory Authority (DRA) and Department of Health (DoH) representatives

participating in the ICH meeting in La Hulpe, Brussels. Presentations were made on: *Introduction to MedDRA*; *Communication about MedDRA*; *MedDRA – a multilingual terminology*; *China ICH Research Group activities & MedDRA*; *Facilitating the use of MedDRA*; and *ICH Best Practice approaches for using MedDRA*.

The SC noted that the Board had supported a “revamp” of the MedDRA website, including a more user-friendly navigation, access to all support documentation and training materials, on-line registration for training and subscription and the design of a new logo. The website, along with a general MedDRA brochure, is planned for launch in July 2013. The brochure will be published in paper format and will also be made available in PDF format on the ICH and MedDRA websites and will be followed by factsheets on specific MedDRA topics: *MedDRA access models (e.g., subscriptions, special licenses etc...)*; *MedDRA as a multilingual terminology*; *Use cases of MedDRA*; *Signal detection tools*; *MedDRA and its various tools to facilitate its use*; and *MedDRA as an evolving & robust controlled terminology*.

The SC was updated on activities related to mapping ICD-10 and SNOMED to MedDRA. The MSSO is continuing to investigate the feasibility of an ICD-10 to MedDRA mapping and the UK MHRA is working (with input from the MSSO) to develop a subset of SNOMED to MedDRA mapping. The MHRA experience will inform Board consideration of ICH next steps regarding a SNOMED to MedDRA mapping.

SC Decision/Action:

- *The SC noted the decisions taken by the MedDRA Management Board on its behalf.*

3. Global Cooperation

In La Hulpe, Brussels, the Global Cooperation Group adopted a new format and was Interactive discussions on implementation of ICH Guidelines in the ICH regions and beyond, and training were the main focus of this session. This session saw the participation of representatives from the RHIs of ASEAN (Association of Southeast Asian Nations), APEC (Asia-Pacific Economic Cooperation), GCC (Gulf Cooperation Council), EAC (East African Community), and SADC (Southern African Development Community), and the DRAs of Australia, Brazil, China, the Republic of Korea and Singapore, in addition to the DoH of Chinese Taipei.

The RHIs and DRAs/DoH reported on the outcome of their respective discussions during their pre-meetings on ICH-related matters. The GC members noted the status of implementation of ICH Guidelines in regions and countries and also discussed how RHIs and DRAs/DoH were selecting ICH Guidelines for implementation as well as challenges faced.

The SC noted the outcome of the ICH E11 training organised in China in April 2013. They also noted the proposed forthcoming organisation of a joint SADC/EAC training on ICH Q8/Q9/Q10 Guidelines, and of training on the ICH E2 Series of Pharmacovigilance Guidelines to be organised in collaboration with DIA in Muscat, Sultanate of Oman in September 2013. Interest was expressed on further training on the following ICH Guidelines: E2C(R2), Q7 and Q8/Q9/Q10/Q11.

A presentation was given on the activities of the Training Working Group (TWG), the main objective of which is to promote a better understanding and use of ICH Guidelines and ICH as an organisation. An overview was presented on a proposed ICH Training schematic for the ICH website including its hierarchical organisation in four different levels of complexity and the inclusion of a conceptual model to broaden the ICH Stakeholders and include more the general public. The GC members noted additional projects of the TWG such as the



Figure 1: Life cycle of development

development of: a best practice document on how to conduct training for industry and regulators, a module on *How ICH Works*, the preparation of minimum package of ICH Guidelines and the development of training pilots.

The training development life cycle was also presented (Figure 1). The importance to conduct each step to develop and deliver training that addresses the needs and maintains its relevance over time was noted. The value to deliver training in a cost-efficient manner was also highlighted.

All participants were invited to rank in order of highest priority of interest the proposed activities of the TWG. As presented in Figure 2, the development of training pilots (46 points) was considered of highest priority, followed by the development of a minimum training package of ICH Guidelines (30 points) and the assessment of e-learning tools (27 points).

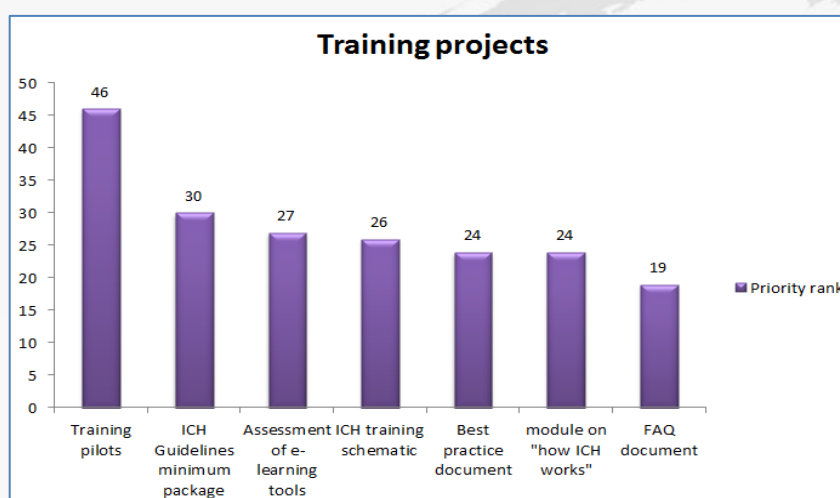


Figure 2: Training Projects ranked by order of priorities by GC members

The development of Frequently Asked Questions (FAQs) was ranked as the topic with the lowest priority (19 points).

SC Decisions/Actions:

- The SC agreed that the TWG should conduct an assessment of required resources and timeframe for the different training projects;
- The SC agreed that the TWG proceed with the training pilots.

4. Status Report on Topics

At the start of the meeting in La Hulpe, Brussels, the SC noted the current status of draft ICH Guidelines and predictions for progress towards *Step 2* and *Step 4*. Updated information was provided during the SC meeting by the ICH Rapporteurs of the EWGs/IWGs meeting in La Hulpe.

5. M2: Electronic Standards for the Transfer of Regulatory Information

The Rapporteur reported to the SC on the outcome of the M2 EWG meeting held in La Hulpe, Brussels. The report included an update on:

- M2 Management activity in relation to ICH's electronic standards including the development of an information repository which would include M2 developed documents such as Best Practices for Maintenance and Testing;

- Considerations regarding ICH requirements for Regional Object Identifiers (OIDs);
- Work to set-up a Standards Development Organisation (SDO) monitoring process with a pilot monitoring activity to be conducted;
- Conduct of a SDO survey with the E2B(R3) EWG;
- Identification of file format requirements and discussion of where .docx is used in the regions, and plan to test PDF (ISO 32000-1) and .docx against requirements;
- Exploration of use cases for structures data with ISO IDMP being used as an example and a mapping between IDMP and CTD being performed and results reviewed from the perspective of what could be done if this structured information could be referenced in dossiers.

The M2 EWG also presented the SC with its work plan for activity to be undertaken between the La Hulpe meeting and the next ICH meeting in Osaka in November 2013. This included: format of M2 documents for publication, finalisation of the SDO survey summary report on E2B(R3) for presentation to the SC, SDO monitoring activities; testing of file format user requirements against “.docx”; preparation of presentation to the SC on use of structured information; and investigation on .docx capability for tagging commercial and/or personal information from dossier files.

A work plan was also proposed for activities to be undertaken at the Osaka meeting.

SC Decisions/Actions:

- *The SC agreed that the M2 EWG should continue work to investigate use cases and business cases in relation to an ISO IDMP-CTD mapping, with a report on findings to be provided to the SC;*
- *The SC agreed the work plan for the M2 EWG for work to be undertaken between the Brussels meeting and the Osaka meeting in November 2013;*
- *The SC endorsed the work plan of the M2 EWG for activity to be undertaken at the Osaka meeting in November 2013.*

6. M8 EWG/IWG: The Electronic Common Technical Document: eCTD

The Rapporteur reported to the SC on the outcome of the M8 EWG/IWG meeting held in La Hulpe, Brussels.

The report included an update on the work of the M8 IWG with respect to current eCTD specification, for which one new Change Request was processed. The M8 IWG subsequently signed-off *Step 4* of Version 1.24 of the Change Request/Q&A document.

The M8 EWG provided a report to the SC on its work concerning the development of the next major version of the eCTD, Version 4.0. The report included an update on the conduct of *Step* ESTRi website and will be updated as further experience is gained from the testing. Activity undertaken in La Hulpe included: a review of open issues and confirmed next steps, agreement on the content of the Implementation Guide package; agreement on further revision of the draft Implementation Guide; and agreement to have additional testing.

The M8 EWG also presented the SC with its work plan for activity to be undertaken between the La Hulpe meeting and the next ICH meeting in Osaka in November 2013. This included: further *Step 2 for Testing* activities, preparation for *Step 2*; investigation of the timing for communication with ISO; and regular and *ad hoc* teleconferences. A work plan was also proposed for activities to be undertaken at the Osaka meeting which included work related to

the current eCTD (review of Change Requests and processing of Q&As) and work related to eCTD Version 4.0.

SC Decisions/Actions:

- *The SC signed off Step 4 of Version 1.24 of the Change Request/Q&A document;*
- *The SC agreed that the M8 EWG continue to update the Lessons Learnt Document posted on the ESTRi website as further experience is gained during the Step 2 for Testing period;*
- *The SC acknowledged the update to the milestones for eCTD Version 4.0, noting that Step 2 of the ICH eCTD Implementation Guide is currently expected in June 2014 and Step 4 in June 2015;*
- *The SC supported the proposal of the M8 EWG that representatives of the IMDRF be invited to observe M8 EWG teleconferences and emails to ensure communication and avoid duplication of effort;*
- *The SC endorsed the work plan of the M8 EWG for work to be undertaken between the La Hulpe meeting and the Osaka meeting in November 2013;*
- *The SC endorsed the work plan of the M8 EWG for activity to be undertaken at the Osaka meeting in November 2013.*

7. Q3D EWG: Guideline for Elemental Impurities

The Rapporteur reported to the SC on the outcome of the Q3D EWG meeting held in La Hulpe, Brussels.

The SC signed-off *Step 2a* of the ICH Q3D Technical Document and the SC regulatory parties signed-off the *Step 2b* Q3D draft Guideline which will be submitted for regulatory public consultation. The SC supported the work plan of the Q3D EWG and noted that the regulatory consultation was expected to be concluded by November 2013 which should allow the group to conduct a preliminary review of the public comments received in Q1 2014. The SC supported the proposed timeframe for reaching *Step 4* in June 2014.

SC Decisions/Actions:

- *The SC regulatory and industry parties signed-off the Step 2a Q3D Technical Document;*
- *The SC regulatory parties signed-off the Step 2b Q3D draft Guideline;*
- *The SC supported the work plan of the Q3D EWG and the proposed timeframe.*

8. Q7 IWG: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

The Rapporteur reported to the SC on the outcome of the Q7 IWG meeting held in La Hulpe, Brussels and progress made in the development of the ICH Q7 Questions and Answers (Q&A) document. Experience gained with the implementation of ICH Q7 since its approval in November 2000 has shown the need for clarification related to the interpretation of several sections such as application in the supply chain control, contractor/supplier management, monitoring of impurity profiles, quality systems, applicability for biological/biotech and relationship with Q5D, and GMP expectations in the development phase.

The SC noted the feedback from a survey which was conducted in late 2012 on ICH Q7 technical issues considered as needing clarification. About 200 questions were collected from twelve Q7 IWG constituencies covering all sections of the ICH Q7 Guideline. The SC noted

the progress made by the group to review the results of the survey and start drafting the Q&As to address the most valuable sections.

SC Decision/Action:

- *The SC supported the work plan of the Q7 IWG.*

9. S1 EWG: Rodent Carcinogenicity Studies for Human Pharmaceuticals

The Rapporteur reported to the SC on the outcome of the S1 EWG meeting held in La Hulpe, Brussels.

The SC noted the review of public comments received from the three ICH regions on the draft S1 Regulatory Notice Document (RND) and that anonymised surveys of ongoing and planned carcinogenicity studies were conducted by the three ICH regulators.

The RND will address the need to have confidentiality arrangements between all regulatory members (including Observer DRAs participating in the EWG) in place in order to receive Carcinogenicity Assessment Documents (CADs) and study results and to maintain the confidentiality of industry proprietary data received (both personal and commercial confidential information).

The SC supported the work plan of the S1 EWG which included the publication of the final RND on the ICH public website in Q3 2013 and the subsequent launch of confidential submissions of CADs by sponsors to DRAs within each region. The SC noted that the EWG will continue to organise bimonthly teleconferences. The SC also supported the proposed timeframe for reaching *Step 2* in November 2017.

The SC noted the publication by Jan Willem van der Laan and Joseph J. DeGeorge (editors) of a book entitled *Global Approach in Safety Testing – ICH Guidelines explained* (AAPS Advances in the Pharmaceutical Sciences, Series 5, aapspress, Springer, 2013).

SC Decisions/Actions:

- *The SC supported the work plan of the S1 EWG and the proposed timeframe for finalising the RND between August and November 2013, and for reaching S1 Step 2 in late 2017;*
- *The SC agreed that the regulatory authorities should reflect on confidentiality arrangements already in place and the need for further arrangements;*
- *The regulatory authorities will inform the SC at the autumn SC webconference on how best to address the request to share confidential submissions of CADs by sponsors with DRAs beyond the ICH regions.*

10. S10 EWG: Photosafety Evaluation

The Rapporteur reported to the SC on the outcome of the S10 EWG meeting held in La Hulpe, Brussels. The SC noted that the group had progressed to review the 156 comments received from the regulatory public consultation conducted in the three ICH regions on the *Step 2* S10 draft Guideline.

The SC supported the work plan of the S10 EWG and the proposed timeframe for reaching *Step 4* in November 2013, subject to availability of additional data with which the new proposed criteria for the international validation of the ROS assay would be evaluated.

SC Decisions/Actions:

- *The SC supported the work plan of the S10 EWG;*

- *The S10 EWG will inform the SC at the autumn SC webconference on whether the ROS data would be available in time to facilitate the group to work to reach Step 4 at the time of the ICH meeting in Osaka in November 2013.*

11. EWGs/IWGs not Meeting in La Hulpe, Brussels

❖ Q4B: Evaluation and Recommendation of Pharmacopoeial Texts for use in the ICH Regions

The Q4B EWG did not meet in La Hulpe, Brussels. The SC noted that the amendment to the Japanese Pharmacopoeia text regarding *Uniformity of Dosage Units* had been completed. This would allow the Q4B EWG to progress Annex 6 on *Uniformity of Dosage Units* to Step 4. The SC noted that once this last Annex would be finished, the Q4B EWG's work would be completed.

SC Decision/Action:

- *Once Annex 6 has been finalised by the Q4B EWG, the SC will be invited to sign-off the Step 4 document after which the Q4B EWG's work will be completed.*

❖ M1 PtC: MedDRA Points to Consider (PtC) Working Group

The MedDRA PtC Working Group (WG) did not meet in La Hulpe, Brussels. The SC noted the ongoing activities of the group with respect to the updating with each MedDRA release of the two PtC documents on *Term Selection* and *Data Retrieval and Presentation* to facilitate consistent use of MedDRA. The documents for MedDRA Version 16.0 were released on April 1, 2013.

SC Decision/Action:

- *The SC supported the work plan of the MedDRA PtC WG and noted that the group will continue to work by email and teleconference.*

❖ M7: Genotoxic Impurities

The M7 EWG did not meet in La Hulpe, Brussels. The SC noted that the comments from the regulatory public consultations would be reviewed by the group following the closure of the consultation period.

The SC noted that the group would also continue its work on the following activities:

- Development of a table of acceptable intakes for more commonly encountered mutagenic/carcinogenic impurities;
- Conduct of an assessment on the time needed to develop the list and to consider whether the table would need to be submitted for regulatory consultation;
- Review of the current maintenance process for solvents (Q3C) to see whether it could apply for the maintenance process for M7.

SC Decision/Action:

- *The SC supported the work plan of the M7 EWG.*

❖ E14: Q&As on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

The E14 IWG did not meet in La Hulpe, Brussels. The SC noted the challenge for the group to progress their work by teleconference due to the complexity encountered with the two remaining Q&As: *Guidance for Collecting ECG Data in Drugs that are not Amenable to TQT studies*, and *Combination Products*.

SC Decision/Action:

- *The SC agreed to consider at its autumn webconference whether it would be necessary for the group to meet face-to-face to complete its work.*

❖ E2C(R2): Clinical Safety Data Management: Periodic Benefit-Risk Evaluation Report (PBRER)

The E2C(R2) IWG did not meet in La Hulpe, Brussels. The SC noted the recent establishment of the IWG which will work to ensure that the E2C(R2) Guideline is properly implemented. The IWG has the objective of developing several documents such as a Q&A document, a training slide set, a sample PBRER and guidance on handling different periodicities/modular approach. The Rapporteur presented the work plan of the group to the SC via teleconference including the group's accomplishments and anticipated milestones.

SC Decision/Action:

- *The SC supported the work plan of the E2C(R2) IWG and the proposed timeframe for reaching Step 4 of the first set of Q&As by the end of September 2013, for publication on the ICH website.*

12. Communication about ICH

ICH Regional Public Meetings

The SC received a proposal from MHLW/PMDA and JPMA for the organisation of a workshop with DIA Japan at the 10th Japan Annual Meeting to be held on November 6-8, 2013 in Tokyo, Japan. The SC noted that this would immediately precede the next ICH meeting to be held in Osaka, on November 9-14, 2013, and should facilitate participation of ICH representatives in the meeting. The SC noted that the workshop proposed to take place on November 7, 2013 included sessions aimed at enhancing transparency in ICH activities and communicating the value of ICH. It was noted that the workshop would include the following themes: *Global Approach for ICH Activities and Guidelines, The Future of ICH, Collaboration with Members of the Regulatory Forum, and Collaboration with EWG members in the USA, EU and other regions.*

The SC also noted that two regional ICH public meetings will be organised by JPMA with collaboration with MHLW/PMDA in Japan just after the 2013 ICH biannual meetings to enhance transparency in ICH activities and communicate ICH achievements. The first one will be held as Workshop on July 26, 2013 in Tokyo, Japan and the second one as "ICH Japan Symposium 2013" on December 10, 2013, also in Tokyo.

Any Other Business

No other business was raised.

Dates of Next Meetings for 2013-2014

November 9-14, 2013 in Osaka, Japan

June 2014 in the USA (location and date to be confirmed)

EWG/IWG's Meeting in Osaka, Japan

A list of EWG/IWG's which will meet face-to-face at the next ICH meeting in Osaka, Japan on November 9-14, 2013 will be made available on the ICH public website following the autumn SC webconference.