

ICH STEERING COMMITTEE

June 6-11, 2009

Yokohama, Japan

SUMMARY

1. Opening Discussions

The ICH Steering Committee (SC) meeting was chaired by the MHLW. The meeting commenced with the provision of updates on the work of the ICH Secretariat, MedDRA and the Global Cooperation Group (GCG).

ICH Secretariat: The ICH Secretariat informed the SC of several recent updates to the ICH website. In March 2009, the Secretariat published on the ICH website a library of training materials and presentations on ICH topics. In addition to general *Step 2 / Step 4* presentations, the library includes training materials from GCG-endorsed training events and presentations from ICH5 and ICH6. The SC also noted the publication on the website of profiles for the Regional Harmonisation Initiatives (RHIs) of ASEAN (Association of Southeast Asian Nations), GCC (Gulf Cooperation Countries) and PANDRH (Pan American Network on Drug Regulatory Harmonization). Profiles for APEC (Asia-Pacific Economic Cooperation) and SADC (Southern African Development Community) were also being developed.

MedDRA: The Chair of the ICH MedDRA Management Board reported on the decisions taken by the Board on behalf of the ICH Steering Committee. The SC noted that the number of MedDRA Subscribers was continuing to grow, which was considered to be due in part to a substantial decrease in subscription fees for four years in a row, as well as the elimination since January 2007 of a subscription fee for direct healthcare providers and not-for-profit organisations.

Also helping the use of MedDRA is the offering of free training. Free training courses are offered on *Coding with MedDRA* and *MedDRA Safety Data Analysis & SMQs*. In 2008, the MSSO (Maintenance and Support Services Organization) conducted 50 classes training almost 1000 MedDRA users, including 350 staff from regulatory agencies. In 2009, an even greater number of free classes will be held in the EU, US and Canada with classes offered in English, French, German and Spanish by native language instructors. As of April 2009, over 500 people had already been trained. With companies and regulators being increasingly under budgetary constraints, and therefore travel constraints, the MSSO has also developed free webinars on *MedDRA Coding Basics* and *MedDRA Data Analysis & SMQs for Physicians*. The SC noted that members of the Board were working with the Drug Regulatory Authority of Malaysia to develop the programme for the MedDRA workshop requested by ASEAN through the ICH GCG which is expected to take place in Kuala Lumpur in March 2010.

Regarding the development of tools to help make MedDRA easier to use, the Chair of the Board informed the SC on an upgrade to the current MedDRA desktop browser and the release of a new web-based browser. The SC noted that the upgraded desktop browser was released to Subscribers in March 2009 along with a downloadable

tutorial. A web-based browser was also being developed and would be made available to Subscribers in early 2010. The SC noted that these tools are provided to Subscribers as part of the MedDRA subscription at no additional cost.

The SC was also informed of the decision of the Board to endorse the recommendations of the Blue Ribbon Panel (BRP) on MedDRA Versioning, as well as the decision to renew the Memorandum of Understanding with CIOMS (Council for International Organizations of Medical Sciences) for the development of Standardised MedDRA Queries (SMQs) for a further year.

Global Cooperation Group: The GCG Co-Chairs reported to the SC on the GCG meeting, which saw the participation of representatives from the Regional Harmonisation Initiatives (RHIs) of APEC, ASEAN, GCC, PANDRH and SADC, and the Drug Regulatory Authorities (DRAs) of Australia, Singapore, India and South Korea.

The report included an update on the establishment of the [APEC Harmonisation Centre \(AHC\)](#) in Seoul, Korea, the inauguration of which would take place on June 15, 2009 following the ICH meeting in Yokohama. As part of the inauguration events, the APEC LSIF (Life Sciences Innovation Forum) Regulatory Harmonisation Steering Committee (RHSC) would be meeting for the first time on June 17-18, and a workshop on Multi-Regional Clinical Trials would also be held on June 17-18, 2009.

Feedback was received at the GCG meeting on the [China Quality workshop](#) which was held in Beijing, China on December 3-5, 2008, and was attended by over 200 participants from across China, including both regulators and industry. The workshop focused on the implementation of the [Q1-Q7 ICH Guidelines](#) in addition to the [Q8](#), [Q9](#) and [Q10](#) Guidelines.

The GCG was also updated on the organisation of the GCG-endorsed APEC LSIF advanced workshops for regulators on the “Review of Drug Development in Clinical Trials” and “GCP Inspections” which were held in Bangkok, Thailand on February 2-6 and March 2-6, 2009, respectively.

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

Women in Clinical Trials: The SC approved the updates to the ICH Considerations document *Gender Considerations in the Conduct of Clinical Trials* to take account of new and revised ICH Guidelines and current usage of the terms “sex” and “gender”. The SC charged the ICH Secretariat with exploring how to increase the visibility of the document on the ICH website.

Clinical Safety Data Management: Periodic Safety Update Reports (PSURs) for Marketed Drugs (Topic E2C(R1)): The SC had an initial discussion on the potential need for a revision of the E2C(R1) Guideline, but agreed to put the discussion on hold until the finalisation of the E2F *Development Safety Update Report (DSUR)* Guideline. This would be with the aim of seeing how the DSUR and the PSUR fit together.

Impurities: Guideline for Residual Solvents (Topic Q3C(R4)): The SC approved a Concept Paper for a revision of the Q3C(R4) guideline to take account of new toxicity data related to cumene. The group will work by e-mail and teleconference.

3. Reports on Current Topics

Electronic Standards for the Transfer of Regulatory Information and the Electronic CTD (Topic M2/eCTD): The M2 Rapporteur reported to the SC on the outcome of the meeting of the M2 Expert Working Group (EWG) in Yokohama. The report included feedback from the meetings of the eCTD sub-group and the M2 SDO Relationship Management sub-group.

The SC was updated on discussions of the M2 EWG regarding the process for initiating the next major version of the eCTD through the SDO (Standard Development Organisation) process. The Rapporteur informed the SC that further discussion was required on the two options which had been identified for the progression of this work. The SC also noted that the HL7 (Health Level Seven) RPS2 (Regulated Product Submission 2) project was positioned to take on the ICH requirements in the short term. In Yokohama the group finalised a first set of requirements for the next major version of the eCTD for submission to HL7. These were approved by the SC. The SC noted that based on lessons learned the requirements would likely need to be further revised based on feedback received from HL7.

The Rapporteur also reported to the SC on the discussions of the SDO Relationship Management sub-group. In Yokohama the sub-group discussed the newly expanded membership of the Joint Initiative Council, and the development of a working practice document to describe how the sub-group should operate.

The future roles and responsibilities of the M2 EWG were also discussed, with a proposal to be submitted to the SC at its next meeting in St. Louis, Missouri in October 2009.

E2B(R3): Revision of Electronic Submission in Individual Case Safety Reports: The Rapporteur reported to the SC on the outcome of the E2B(R3) EWG meeting in Yokohama, including joint meetings held with the M2 EWG. The SC noted that the ISO (International Organization for Standardization) ballot for the ICSR (Individual Case Study Report) DIS (Draft International Standard) was underway¹. The Rapporteur reported that in parallel with this ballot ICH would be conducting testing of the standard and a period of public awareness (*Feasibility Testing*) would also be carried out. For a one-month period the testing package would be posted on the ESTRi website for comment. The SC noted that comments from the testing would be submitted both directly to ISO and through National Member Bodies.

The Rapporteur also informed the SC that the E2B(R3) Guideline version 3.96, dated November 13, 2008 would no longer be updated by the group. Any additional decisions made by the E2B(R3) EWG would be added into the ICH ICSR Implementation Guide. The SC noted that the guideline would exist for a while as a core set of business requirements and would be added into the Implementation Guide at the end of the project process (before *Step 4*).

¹ In October 2006, the SC agreed that the ICH E2B(R) and M5 messages enter the Standard Development Organisation (SDO) process as a pilot for development by [the Joint Initiative on SDO Global Health Informatics Standardization](#).

The SC noted that until the M5 controlled terminologies are implemented, the E2B(R3) ICSR would use free text or existing code lists in E2B(R2) for data elements supported by M5. Once the M5 terminologies are implemented, the E2B(R3) ICSR will use all available terms and identifiers described in the M5 guideline. The SC noted that where there are no IDMP terms or identifiers available the information would be provided in corresponding free text fields.

M5: Data Elements and Standards for Drug Dictionaries: The Rapporteur reported to the SC on the outcome of the M5 EWG meeting in Yokohama, including the joint meeting held with the M2 EWG. The SC noted that the IDMP (Identification of Medicinal Products) CD (Committee Draft) had been submitted to ISO for ballot. It was also noted that the scope of the five IDMP work items would be revised and resubmitted to ISO for ballot as New Work Item Proposals (NWIPs). Both the CD and NWIP ballots would close on August 12, 2009.

The Rapporteur also updated the SC on the current timelines associated with the IDMP project with regards to anticipated timelines for the DIS and FDIS (Final Draft International Standard). The SC noted that the next steps for the M5 EWG in order to prepare for the DIS would be the development of the ICH IDMP Implementation Guide and Test Plan. The Rapporteur informed the SC that the group had agreed the inclusion of both version 5.1 of the M5 Guideline and the M5 *Step 2* document as annexes in the *Step 2* Implementation Guide. However, these would not be included in the *Step 4* Implementation Guide. The SC noted that this approach was similar to that agreed by the E2B(R3) EWG for the ICSR Implementation Guide.

Pharmacopoeial Discussion Group: On behalf of the Pharmacopoeial Discussion Group (PDG), the Japanese Pharmacopoeia reported on the current status of PDG harmonisation efforts.

It was noted that harmonisation had been achieved on eight of the ten General Chapters related to the ICH Q6A Guideline. Regarding the two remaining General Chapters, *Bacterial Endotoxins* should be submitted to the Q4B EWG in February 2010, while work is still ongoing on *Colour*.

Q4B: Evaluation and Recommendation of Pharmacopoeial Texts for use in the ICH Regions: The Q4B Rapporteur reported to the SC on the progress made by the Q4B EWG in Yokohama.

Step 4 was reached for Q4B Annex 5 on *Disintegration Test* and Annex 8 on *Sterility Test*. *Step 2* was reached for Annex 9 on *Tablet Friability* and Annex 10 on *Polyacrylamide Gel Electrophoresis*.

The SC also noted that the Q4B EWG would develop training materials on the use of the Q4B Annexes.

Q11: Development and Manufacture of Drug Substances: In Yokohama, the Q11 Rapporteur provided an update on the activities of the Q11 EWG which was continuing its work towards reaching *Step 2*. The SC noted that the Chinese SFDA (State Food & Drug Administration) had accepted an invitation to nominate a technical expert to the Q11 EWG and that the Chinese expert had attended the Yokohama meeting.

Quality IWG: The Rapporteur informed the SC of the outcome of the Quality Implementation Working Group (IWG) meeting in Yokohama. The SC noted that *Step 4* had been reached in April 2009 for the first set Q&As on the Q8/Q9/Q10 Guidelines. A second set was finalised (*Step 4*) at the Yokohama meeting.

The Rapporteur also presented a proposal for the organisation of regional workshops. The workshops would cover the integrated use of the ICH Q8, Q9 and Q10 Guidelines and Q&As across the product life cycle, from development to manufacturing and commercialisation. Regulatory assessment and GMP inspection implementation aspects would also be discussed. It was proposed that the workshops be 2-day events which would be organized by the same faculty. The SC noted that the key point would be to ensure consistency in each region. It was also noted that the content of the workshops would be defined by the Quality IWG.

S2(R1): Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use: The Rapporteur informed the SC that good progress had been made by the S2(R1) EWG at the Yokohama meeting. The SC noted that the main motivation for the revision of this guideline was to address the high frequency of positive results (up to 30%) in *in vitro* mammalian cell assays, many considered non-relevant. Another motivation was to address the 3Rs agenda for the reduction, refinement and replacement of animal testing.

The Rapporteur confirmed that a draft *Step 4* document had been developed in Yokohama and was close to finalization. The SC noted that the document would need to be discussed internally at FDA before sign-off to try to address some points pertaining to the revision which were raised by FDA staff.

M3(R2): Revision of Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals: The SC signed-off *Step 4* of the revised Guideline which promotes more rapid discovery and development of innovative medicines, by reducing the reliance on animals required in drug development studies. These efforts continue ICH's commitment to the 3Rs (reduction, refinement and replacement) of animal testing.

S9: Nonclinical Evaluation for Anticancer Pharmaceuticals: The Rapporteur reported to the SC on the meeting of the S9 EWG in Yokohama. Good progress was made towards reaching *Step 4*, with all comments received during regulatory consultation addressed. The SC noted that *Step 4* was expected at the next meeting in St. Louis, Missouri in October 2009.

S6(R1): Revision of Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals: In Yokohama, the Rapporteur reported on the outcome of the S6(R1) EWG meeting and progress made in the development of an addendum to the S6 Guideline. The SC was informed of the progress made on the drafting of the following topics: Species Selection, Study Design, Reproductive/Developmental Toxicity, Carcinogenicity, and Immunogenicity. The Group also discussed the impact on the 3Rs agenda for the reduction, refinement and replacement of animal testing.

The Rapporteur informed the SC that work towards *Step 2* would be further advanced through a series of monthly teleconferences following the Yokohama meeting. The SC noted that the EWG expected to reach *Step 2* in St. Louis, Missouri, in October 2009

and were proposing a 3-month consultation period with the aim of reaching *Step 4* in June 2010.

E2F: Development Safety Update Report: The Rapporteur updated the SC on the outcome of the E2F EWG meeting in Yokohama and progress made towards reaching *Step 4*.

The report included an update on the development of draft model DSURs for sponsor-investigator, relationship to the eCTD, acceptance of a table for combination products and clearer definitions of DIBD and DLP.

The EWG reviewed more than 75% of the Guideline in Yokohama and informed the SC that it hoped to reach *Step 4* prior to the meeting in St. Louis, Missouri in October 2009. The SC noted that the group would work by e-mail, teleconferences and web conferences to try to achieve this.

The EWG recommended that the implementation period for the DSUR should be at least one year after publication of the final guideline.

E7: Studies in Support of Special Populations: Geriatrics: The Rapporteur reported to the SC on the outcome of the first face-to-face meeting of the E7 IWG and progress made in the development of Q&As (Questions & Answers).

The SC noted that work still needed to be done in relation to questions on elderly-relevant safety and efficacy endpoints, and pharmacokinetics. Regarding the representation of geriatric patients in clinical trials, it was specified that elderly, fragile patients may not be included in certain clinical trial programs. This will need to be discussed with the regulatory authority on a case-by-case basis. If this special elderly population is not included in the clinical development program, there should be an assessment of benefit-risk post-approval for this population. The SC agreed that this should be reflected in the Q&A document.

Given the nature of the Q&As, the SC agreed that a period of public consultation would be necessary, and once final the Q&As should go to *Step 2* rather than directly to *Step 4*.

E16: Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions: The SC signed-off *Step 2* of the E16 Guideline which aims to facilitate submission and review of biomarker qualification data among regions. The SC noted that the EWG planned to proactively solicit comments on the document from an extended expert network and key interest groups. The aim would be to consolidate comments received during Q4 2009 with the aim of reaching *Step 4* in spring 2010.

GTDG: Gene Therapy Discussion Group: The Co-Rapporteurs reported on the outcome of the GTDG meeting. The SC noted that the meeting was attended by a representative of the Chinese SFDA, who had been invited due to China's expertise in the field of gene therapy. The SC was informed that there were currently two products on the Chinese market with further post-marketing studies ongoing.

An update on work to finalise the ICH Considerations Document on Viral/Vector Shedding was provided. The Co-Rapporteurs also presented to the SC the rationale for the development of a Guideline on Viral/Vector Shedding. While the Considerations

document focuses on general principles, the Guideline would provide harmonised requirements, avoid unnecessary and/or uninformative studies and provide for more efficient and cost-effective development. The SC agreed that the GTDG should develop a Concept Paper and Business Plan for a new guideline for presentation at the SC teleconference in autumn 2009. The SC noted that if a guideline is developed, the Considerations document would be withdrawn. The SC noted that the expertise of the current GTDG would be appropriate for the Guideline development.

E14: The Clinical Evaluation of QT/QTc Interval Prolongation and ProArrhythmic Potential for Non-Antiarrhythmic Drugs: The E14 Q&As document reached *Step 4* in June 2008. In Yokohama the SC discussed the future of the E14 IWG. The SC agreed that the mailbox on the ICH website to collect questions on E14 should be closed and the IWG disbanded.

Comments from some of the ICH Parties on whether certain aspects of the E14 Guideline were out-of-date were also discussed by the SC. The SC agreed to the organisation of an expert discussion at the next ICH meeting in St. Louis in October 2009 to assess the E14 guideline in view of experience gained.

4. Communication about ICH:

JPMA reported on the organisation of the ICH Public meeting which would take place in Tokyo following the ICH meeting on June 12, 2009. The SC noted the strong interest from the public with approximately 600 registrants from 18 countries.

5. Dates of Next Meetings for 2009 & 2010:

October 24-29, 2009	St. Louis, Missouri, USA
November 6-11, 2010	Yokohama, Japan