

ICH STEERING COMMITTEE

October 24-29, 2009

St. Louis, MO, USA

SUMMARY

1. Opening Discussions

The ICH Steering Committee (SC) meeting was chaired by the FDA. 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 updated the SC on activities regarding the ICH public website. The SC noted that the Secretariat was continuing to add to the library of training materials and publications which was published on the ICH website in March 2009. Recent additions included general presentations on the *Step 4 M3(R2) Guideline on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* and the E16 *Step 2 Guideline on Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions*.

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 the continued growth in the number of MedDRA Subscribers, with many new subscribers coming from not-for-profit and academic organisations. The SC noted that this increase was likely linked with the fact that starting in January 2007 MedDRA was made free for academics and healthcare providers.

In St. Louis, the Board approved the 2010 subscription rates with no increase over the 2009 rates. The SC noted that this was the fifth year in a row that there was no increase in the rates, with major reductions in rates for small and medium-sized companies having being approved by the Board starting in 2006.

The Chair updated the SC on the training programme offered by the MedDRA MSSO (Maintenance and Support Services Organization). For 2009, the MSSO will have conducted over 65 classes and trained over 1000 people. The SC noted that training was being offered in English, French, German and Spanish. In addition, *What's New* webinars organised twice a year for every version release, and a series of webinars on basic topics were also being offered. The MSSO also started the development of free video casts, the first ones being on *Primary System Organ Class Allocation in MedDRA* and the *MedDRA Desktop Browser*.

The SC was also updated on the organisation of a MedDRA workshop which would take place in Kuala Lumpur in March 2010. The training had been requested by ASEAN through the ICH GCG. The Chair reported that the Board had worked with the Drug Regulatory Authority of Malaysia to finalise the programme for a 3-day training event. Both regulatory and industry speakers had been identified to participate.

The Chair also reported on the release to MedDRA Subscribers in mid-September 2009 of a Mandarin Chinese translation. The SC noted that Chinese speaking volunteers from a number of companies in China had helped with the validation of the translation, as well as the MedDRA Introductory Guide and SMQ Introductory Guide which were also translated. The SC also noted that a one-day MedDRA workshop would be held on November 1, 2009, as part of the first Chinese DIA Annual Meeting in Beijing, China.

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, and PANDRH, and the Drug Regulatory Authorities (DRAs) of Australia, Brazil, China, Russia, Singapore, and South Korea.

The report included an update on the development of a paper describing the *Value and Benefits of ICH to Regulators*. The SC noted that the paper would be finalised and published in mid-2010 to commemorate the 20th anniversary of ICH.

As part of the St. Louis meeting RHI and DRA representatives provided updates on ICH-related matters in their regions. Presentations were also given by ICH experts on the *Use of MedDRA in Pharmacovigilance*, *Global Development Regulatory Hurdles*, and the ICH S9 Guideline on *Non Clinical Evaluation of Anticancer Pharmaceuticals* which reached *Step 4* during the St. Louis meeting.

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

Safety Brainstorming Discussion: In St. Louis ICH Safety experts held a brainstorming discussion to review possible topics that may potentially need ICH guidance. As an outcome of the discussion it was agreed to develop Concept Papers on the following topics: *Genotoxic Impurities*; *Photosafety Testing*; *Non-Clinical Vaccine Testing*; and *M3(R2) Q&As (Questions & Answers)*. It was also proposed that a workshop on *In Vitro Models for Reproduction Toxicity Testing* be held at the time of the next ICH meeting in Tallinn in June 2010 and be attended by ICH Safety experts already present for other meetings. It was agreed that a proposal for the workshop should be developed for SC consideration.

E14 Informal Discussion Group: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs: The Rapporteur reported to the SC on the outcome of the meeting of the Informal Discussion Group to discuss the E14 Guideline in view of experience gained.

Overall, the Group recognised that there had been significant advances in knowledge, experience and technology since the E14 Guideline was issued in 2005. The Group informed the SC that it did not recommend opening the E14 but proposed that an Implementation Working Group (IWG) be established to develop Q&As to clarify the existing E14 Guideline. The group proposed to the SC several topics for which Q&As could be developed within a short time frame. It was agreed that the Group should develop a Concept Paper for SC consideration and approval.

Q3D: Guideline for Metal Impurities: The SC discussed a Concept Paper proposing the development of a new ICH Guideline on Metal Impurities. The SC approved the Concept Paper, with a small modification, and endorsed the establishment of a Q3D Expert Working Group (EWG).

3. Reports on Current Topics

Electronic Standards for the Transfer of Regulatory Information and the Electronic CTD (Topic M2/eCTD): The SC was updated on the outcome of the meeting of the M2 EWG in St. Louis. The report included feedback from meetings of the eCTD sub-group, the M2 SENTRI sub-group, and the M2 SDO Relationship Management sub-group.

Concerning the next major version of the eCTD, the Rapporteur informed the SC that feedback had been received from HL7 (Health Level Seven) on the initial set of ICH requirements which ICH had provided. Based on the feedback the requirements were revised and approved by the SC for provision to HL7. The SC noted that in consideration of the options to progress the next major version of the eCTD the SDO Relationship Management sub-group had concluded that ICH should continue working with the HL7 RPS R3 project. The SC noted the participation of several ICH M2 experts in the HL7 RPS R3 project.

The SC was also updated on the activities of the SENTRI sub-group, which planned to investigate the feasibility and extent of a potential move from PDF to XML for content.

The Rapporteur also informed the SC that a paper on the future roles and responsibilities of the M2 EWG would be prepared for discussion by the ICH Parties with the aim of having the paper endorsed by the SC at its next meeting in Tallinn in June 2010.

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 St. Louis, including joint meetings held with the M2 EWG. The Rapporteur informed the SC that based on the comments which had been submitted to the ISO (International Organization for Standardization) DIS (Draft International Standard) ballot for the ICSR (Individual Case Study Report) it had been agreed at the recent ISO meeting in Durham to carry out a second DIS ballot. The SC noted that HL7 was updating the ICSR model to address the comments received ahead of the second ballot.

The Rapporteur also updated the SC on the outcome of ICH's *Feasibility Testing* for the ICSR. The SC noted that the documents related to the ICSR had been posted on the ICH ESTRIM website for one month in order to collect comments from the public. Testing was also carried out in the three ICH regions. The Rapporteur informed the SC that most of the comments which were received on the ICH Implementation Guide for the ICSR had been addressed during the St. Louis meeting. The SC also noted that in parallel with the second ISO DIS ballot a second round of *Feasibility Testing* would be carried out.

The SC was informed of the current timelines for the ICSR standard which foresaw the ISO ICSR International Standard to be available in January 2011, and the ICH ICSR Implementation Guide to reach *Step 4* at the ICH meeting in spring 2011.

M5: Data Elements and Standards for Drug Dictionaries: The SC was updated on the outcome of the joint meetings the M5 EWG held with the M2 and E2B(R3) EWGs in St. Louis. The SC noted that the IDMP (Identification of Medicinal Products) CD (Committee Draft) documents and the IDMP New Work Item Proposals had passed the ISO ballot. The Rapporteur informed the SC that no party had identified any substantive issues to indicate that ICH requirements will not be met. The SC also noted the Maintenance Technical Report ballot which was currently underway for a 3-month period.

The SC was also informed on the activities of the M5/M2 experts in relation to the development of the ICH IDMP Implementation Guide and Test Plan. The Implementation Guide will be modular in structure with five modules to explain the data elements and structures from each of the five ISO work item: *Regulated Medicinal Product Information (MPID)*; *Pharmaceutical Products (PhPIDs)*; *Substances*; *Pharmaceutical Dose Forms, Units of Presentation and Routes of Administration*; and *Units of Measurement*.

The Rapporteur informed the SC that work to develop the ICH IDMP Implementation Guide and Test Plan would be resource intensive as the comments received from the ISO IDMP ballot would need to be reconciled in parallel and new drafts of the ISO documents drafted.

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

It was noted that the *Bulk and Tapped Density* and the *Bacterial Endotoxins* General Chapters should be submitted to the Q4B EWG in January and February 2010, respectively.

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 St. Louis.

Step 4 was reached for Q4B Annex 7 on *Dissolution Test*, Annex 9 on *Tablet Friability*, and Annex 10 on *Polyacrylamide Gel Electrophoresis*. *Step 2* was reached for Annex 11 on *Capillary Electrophoresis* and Annex 12 on *Analytical Sieving*.

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

Q11: Development and Manufacture of Drug Substances: The Q11 Rapporteur provided an update on the activities of the Q11 EWG and progress made in St. Louis in the development of the Q11 *Step 2* Guideline.

In St. Louis the EWG made major progress in relation to the designation of starting materials, control strategy, restructured development and manufacturing description. Outstanding matters remained on validation and lifecycle. The SC noted that the

whole document had yet to be reviewed by the whole Group, as the various sections had been developed sub-teams.

The SC encouraged the EWG to make every effort to reach *Step 2* at the ICH meeting in Japan in November 2010.

Quality IWG: The Rapporteur reported to the SC on the outcome of the Quality IWG meeting and progress made in St. Louis towards developing a training program for workshops in the ICH regions that will cover the ICH Q8, Q9, Q10 Guidelines and Q&As across the product life cycle.

The SC noted that the first training on the integrated implementation of Q8, Q9 and Q10 should take place in June 2010 in Europe, to be followed by training in the USA in October 2010 and in Japan in November 2010. The training would cover pharmaceutical development and manufacturing, regulatory assessment, implementation and Quality System considerations, and GMP inspections.

The SC also approved an interim meeting of the Quality IWG to be held in Paris in March 2010 to complete the training programme.

In St. Louis the Quality IWG also reached *Step 4* on its third set of Q&As. The SC noted that the five new Q&As would add to the forty questions already finalised.

Q3C(R5) EWG: Impurities: Guideline for Residual Solvents: The Q3C(R5) EWG did not meet in St. Louis. The SC received an update on the Q3C(R5) EWG's work by e-mail and teleconferences to take account of new toxicity data related to cumene. The SC was informed that *Step 2* was expected shortly.

S2(R1): Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use: The S2(R1) EWG did not meet in St. Louis. The SC was updated on discussions within FDA regarding the draft *Step 4* S2(R1) Guideline. It was noted that an open public workshop would be held by FDA in January 2010 to inform FDA on whether the revisions to the Guideline are justified. It was noted that several ICH experts would participate in the workshop.

S9: Nonclinical Evaluation for Anticancer Pharmaceuticals: The SC signed-off the S9 *Step 4* Guideline following work by the S9 EWG in St. Louis to address all comments received from public consultation. It was noted that the 3Rs agenda related to the reduction, refinement and replacement of animal testing had been kept in focus by the EWG to ensure that the goals outlined in the Concept Paper were realised.

S6(R1): Revision of Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals: Following finalization by the S6(R1) EWG in St. Louis, the SC signed-off *Step 2* of the S6(R1) Guideline.

E2F: Development Safety Update Report: The E2F EWG did not meet in St. Louis. The SC was updated on efforts by the Group to reach *Step 4*. It was noted that the group would continue its work through e-mail, teleconferences, and web conferences.

GTDG: Gene Therapy Discussion Group: The Co-Rapporteurs reported on the outcome of the GTDG meeting. The SC was supportive of the GTDG's proposal to write an ICH Considerations document on *General Principles to Address in Preparation for First-in-Human Gene Therapy Studies*. The document will address manufacturing and quality, non-clinical studies and clinical study issues. The aim would be to complete

