

ICH STEERING COMMITTEE

November 8 - 13, 2008

Brussels, Belgium

SUMMARY

1. Opening Discussions

The ICH Steering Committee (SC) meeting was chaired by the EU. 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 reported on work undertaken to improve communications with ICH stakeholders. The SC noted the ICH Secretariat's progress toward posting all final Concept Papers and Business Plans on the ICH website.

The SC was informed that following the Brussels meeting, the ICH Secretariat would launch on the ICH website an initial library containing general presentations on ICH topics in addition to training materials/presentations from GCG-endorsed training events.

MedDRA: The Chair of the ICH MedDRA Management Board reported on the decisions taken by the Board on behalf of the ICH Steering Committee.

Major reductions in fee subscriptions for the last four years and even free subscription for health care professionals combined with free training in MedDRA have facilitated greater access to MedDRA and its implementation. Free training on coding and data analysis is now offered to all MSSO (MedDRA Maintenance and Support Services Organisation) subscribers. By the end of 2008, the MSSO will have conducted over 50 classes and trained almost 1000 MedDRA users, including 350 staff from regulatory agencies.

The Board directed MSSO to continue to offer a similar free training programme in 2009 in EU, US and Canada with some classes offered in French, German and Spanish by native language instructors. The MSSO will also develop e-learning tools on basic topics that users would be able to download to facilitate training on their own time.

The Board also continued its work to ensure that MedDRA develops to respond to user needs. MedDRA is currently available through MSSO/JMO (Japanese Maintenance Organisation) in English and Japanese (1999), French (July 2002), German (July 2002), Portuguese (July 2002), Spanish (July 2002), Dutch (September 2003), Italian (February 2005), and Czech (September 2007). In view of the growing importance of China in global development and production, the Board approved the development of a Chinese Mandarin translation of MedDRA. This translation should be available in late 2009, and as for all MedDRA translations, will be free for regulators.

In Brussels, the Board noted the value of expanding the current list of MedDRA terms to be able to report on all adverse events associated with product quality. The Board approved a proposal to add product quality terms to MedDRA for release in early 2009.

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 SADC, and the Drug Regulatory Authorities (DRAs) of Australia, Singapore and South Korea, in addition to representatives from the Department of Health of Chinese Taipei, and the Russian and Chinese Missions to the EU.

The report included an update on the establishment of the APEC Harmonisation Centre (AHC) in Seoul, Korea, the inauguration of which would be held in June 2009. The AHC mission includes the development and dissemination of harmonisation models across the Asia-Pacific region, and the establishment of cooperative networks for harmonisation.

The SC also noted the organisation of a China Quality workshop focusing on the implementation of the Q1-Q7 ICH Guidelines in addition to the Q8, Q9 and Q10 Guidelines, which would be held in Beijing, China on December 3-5, 2008.

The report also provided an update 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” to be 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: In Brussels, the SC discussed updating 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”. Once updated, the SC agreed that the document should be given greater visibility on the ICH website.

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 Brussels. The report included feedback from joint meetings held with the E2B(R3) EWG (see item on E2B(R3) below), in addition to feedback from the M2 eCTD and SDO Relationship Management sub-groups.

The SC was updated on discussions regarding plans to initiate the next major version of the eCTD through the SDO (Standard Development Organisation) process as a Joint Initiative¹ project. The Rapporteur informed the SC that two options had been identified, but further discussion would be required on which would be the better option. The SC also noted that experts from the ICH Parties would continue to participate in the HL7 (Health Level Seven) RPS2 (Regulated Product Submission 2) project.

¹ [The Joint Initiative on SDO Global Health Informatics Standardization](#) includes the International Organisation for Standardisation (ISO), Health Level 7 (HL7) and the European Committee for Standardisation (CEN).

The Rapporteur also updated the SC on work to develop and agree ICH's requirements for the next major version of the eCTD. The SC supported the recommendation of the group to provide an initial set of requirements to the SDOs for feedback.

Regarding the activities of the SDO Relationship Management sub-group, the SC endorsed a document defining the Terms of Reference for the sub-group. The document defines the purpose and function of the sub-group, which is charged with ensuring processes are in place to facilitate the review and testing by ICH of draft standards developed by the SDOs.

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 Brussels, including joint meetings held with the M2 EWG, and provided an update on the progress made by the ISO (International Standardization Organization) TC 215 (ISO's Technical Committee on Health Informatics) Task Force on Pharmacovigilance (Individual Case Study Report – ICSR)².

The Rapporteur informed the SC that the current time frame for initiation of the ISO ballot for the ICSR Draft International Standard (DIS) was February 2009, with parallel balloting to be conducted across all SDOs for a period of 5 months. The SC noted that the plan would be for ICH to initiate *Feasibility Testing* in parallel of the DIS ballot to be able to provide feedback on the draft standard before the close of the ballot period.

The SC noted that the E2B(R3) EWG would be working with the M2 EWG in preparation for the *Feasibility Testing* to develop the ICH Implementation Guide and Test Plan for the ICSR. The Rapporteur informed the SC that in Brussels the E2B(R3) EWG had updated and finalised the E2B(R3) Guideline which they intended to include in the ICH Implementation Guide.

M5: Data Elements and Standards for Drug Dictionaries: The M5 EWG did not meet in Brussels, but the SC was updated on progress made by the ISO TC 215 Task Force on Identification of Medicinal Products (IDMP)² in which several ICH experts were participating. The SC noted that the Task Force was working to finalise the Committee Draft (CD) standards for submission to ISO by December 1, 2008, with initiation of the ISO CD ballot anticipated in mid-January 2009 for a period of 3-months.

The SC noted that the M5 EWG would be working with the M2 EWG to develop the ICH Implementation Guide and Test Plan for the IDMP in preparation for the conduct by ICH of *Feasibility Testing* at the time of the IDMP DIS ballot.

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

It was noted that harmonisation had been achieved on nine of the eleven General Chapters related to the ICH Q6A Guideline. Regarding the two remaining General

² 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.

Chapters, good advances were made on *Colour*, while *Bacterial Endotoxins* was signed-off by PDG and would be submitted shortly to the Q4B EWG.

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 Brussels.

Step 4 was reached for Q4B Annex 4A on *Microbial Enumeration Tests*, Annex 4B on *Tests for Specified Micro-organisms*, and Annex 4C on *Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use*. The SC noted that *Step 4* on Annex 5 on *Disintegration Test* was pending final publication of required pharmacopoeial texts. *Step 2* was reached for the Q4B Annex 6 on *Uniformity of Dosage Units*, Annex 7 on *Dissolution Test* and Annex 8 on *Sterility Test*.

The SC agreed to expand the scope of the Q4B work programme to include: *Tablet Friability; Bulk Density & Tapped Density; Analytical Sieving; Capillary Electrophoresis*, and *Polyacrylamide Gel Electrophoresis*.

Q8: Pharmaceutical System:

In Brussels, the Rapporteur for the Annex to Q8 reported on the Q8 Annex that had initially been intended to address pharmaceutical development for specific dosage forms but had been modified to clarify new concepts (minimal versus enhanced approach (QbD), design space and real time release testing). The Q8 EWG worked to address the comments received from public regulatory consultation and to finalize the Annex to Q8. The final Annex to Q8 was endorsed by the SC under *Step 4* of the ICH process and will be incorporated into the Q8 Guideline. The SC noted that upon incorporation of the Annex into the Q8 Guideline, the Guideline will be re-coded Q8(R1). It was also noted the group would develop a set of slides on the Q8 Guideline and Annex for posting on the ICH public web site.

Q11: Development and Manufacture of Drug Substances: In Brussels, the Q11 Rapporteur provided an update on the activities of the Q11 EWG.

The SC endorsed the work plan developed by the EWG. Due to the complex and challenging nature of the topic, the SC agreed that some flexibility should be given regarding the time frame for reaching *Step 2* and agreed that the Q11 EWG would be meeting in Yokohama, in June 2009.

Quality IWG: The Rapporteur informed the SC of the outcome of the Quality Implementation Working Group (IWG) meeting in Brussels, including progress made in the development of a Q&A (Question & Answer) document. Following the Portland meeting, three regional working groups were established to consider both regulatory and technical aspects related to Quality by Design, Knowledge Management and Pharmaceutical Quality Systems. The SC noted that the group was aiming to reach agreement on the Q&As for endorsement by the SC and publication before the Yokohama meeting in June 2009.

Regarding training, the IWG will develop a common training package and will be prepared to organize regional workshops in and outside ICH regions. The SC noted that all workshops would provide background on the Q1-Q7 Guidelines to facilitate

greater understanding of the new paradigm created by the Q8, Q9, Q10 and Q11 Guidelines.

M3(R2): Revision of Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals: The Rapporteur reported on the progress made by the EWG in Brussels towards reaching *Step 4* of the ICH process.

Following the Portland meeting in June 2008, the EWG received extensive comments on the *Step 2* document. The SC noted that the EWG would complete the review of all comments and continue working on harmonisation of all aspects of the guidance, to prevent implementation difficulties due to regional differences.

The SC endorsed the organization of web conferences in January 2009 and of an interim meeting in mid-March 2009 to ensure *Step 4* is reached in Yokohama in June 2009.

S9: Nonclinical Evaluation for Anticancer Pharmaceuticals: The Rapporteur reported to the SC on the meeting of the S9 EWG in Brussels and the substantial progress made with consensus reached on several aspects including: approaches to setting a safe start dose for clinical trials and on study design to support initial clinical development; duration of repeated dose toxicity testing; reproduction toxicology studies; and a flexible approach to safety evaluation of metabolites and impurities. The SC noted that the 3Rs (reduction, refinement, replacement of animal testing) agenda was kept in focus during all discussions.

The Rapporteur informed the SC that the EWG would consult with the S6(R1) EWG to ensure scientific input.

The SC signed-off the *Step 2* document and endorsed the time frame for reaching *Step 4* in late 2009 /early 2010.

S6(R1): Revision of Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals: In Brussels, the Rapporteur reported on the outcome of the first S6(R1) EWG meeting and the progress made in the development of an addendum to the S6 Guideline. The EWG started work by discussing the following five sections: species selection; study design; reproductive/developmental toxicity; carcinogenicity; and immunogenicity. The SC noted that there could be a positive impact on the 3Rs agenda if consensus can be reached on the following aspects: enhanced Peri-Post Natal Development (PPND) study design; inclusion of fertility aspects in chronic toxicity studies; use of only one relevant species for chronic toxicity studies even if two relevant species; recovery groups not required for all treatment groups; only 2 repeat dose studies required for non-oncology products; use of surrogate in order to avoid use of Non-Human Primates (NHP); and lifetime bioassays in rodents not required.

Step 2 of the addendum to the S6 Guideline is expected to be reached in October 2009 and *Step 4* in 2010.

E2F: Development Safety Update Report: The E2F EWG did not meet in Brussels, but the E2F EWG work plan was presented to the SC for endorsement. The SC noted that the E2F Guideline was undergoing regulatory consultation in the three ICH regions, with the deadline for comments in December 2008.

E7: Studies in Support of Special Populations: Geriatrics

The E7 IWG did not meet in Brussels, but the SC endorsed the E7 IWG work plan for the development of a Q&A document. The SC approved the time frame for reaching *Step 2* on the Q&A document at/ahead of the autumn 2009 meeting.

E14: The Clinical Evaluation of QT/QTc Interval Prolongation and ProArrhythmic Potential for Non-Antiarrhythmic Drugs: The E14 IWG did not meet in Brussels, but the SC endorsed the E14 work plan for addressing additional questions received in the E14 mailbox.

E16: Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions:

The Rapporteur reported on the outcome of the second E16 EWG meeting held in Brussels. The E16 Guideline will define the context, structure and format of regulatory submissions for genomic biomarker qualification. The SC noted that the aim was to facilitate submission and review of biomarker qualification data among regions, but not to establish global evidentiary standards or a global regulatory process for biomarker qualification.

The SC agreed to the proposed E16 work plan and the time frame for reaching *Step 2/4* in 2009 and 2010, respectively.

GTDG: Gene Therapy Discussion Group: In Brussels, the Co-Rapporteurs reported on the outcome of the GTDG meeting.

The GTDG finalised the ICH Considerations document on Oncolytic Viruses and the SC approved the document for posting on the ICH GTDG web page to elicit comments.

Concerning the ICH Considerations document on *Viral/Vector Shedding*, the SC noted the GTDG recommendations regarding the development of a Concept Paper and Business Plan for an ICH Guideline on *Viral/Vector Shedding*. The plan would be to commence work on the development of a Concept Paper and Business Plan once the Considerations document on this topic is finalised.

MedDRA PtC: MedDRA Points to Consider Working Group: The Co-Rapporteur reported to the SC on the outcome of the MedDRA Points to Consider (PtC) WG meeting in Brussels.

The SC noted that the main roles of the PtC WG related to the maintenance with each MedDRA version release of the two PtC documents on *Data Retrieval & Presentation* and *Term Selection*.

The report included an update on the progress made towards finalisation of the extended guidance on SMQs within the *Data Retrieval & Presentation* PtC document. The guidance was developed in collaboration with the CIOMS (Council for International Organizations of Medical Sciences) WG on SMQs and MedDRA user community. The release of the enhanced document is anticipated with the next scheduled release of the PtC documents (MedDRA version 12.0, April 2009). The SC noted that the WG also updated the *Term Selection* document in Brussels.

4. Communication about ICH:

EFPIA reported on the organisation of the ICH Public meeting which would take place in Brussels following the ICH meeting on November 14, 2008. The SC noted that over 130 participants had registered including regulators from several EU Member States and industry experts from small and medium-sized enterprises. It was noted that the presentations from the meeting would be posted on the ICH website.

5. Dates of Next Meetings for 2009:

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