

# ICH STEERING COMMITTEE

## October 21-26, 2006, Chicago, USA

### SUMMARY

#### 1. Opening Discussions

The ICH Steering Committee (SC) meeting was chaired by 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 reported on work undertaken to improve communications with ICH stakeholders. Final Concept Papers for topics currently going through the ICH process of harmonisation (Q8, Q10, E15, E2B(R3), and M5) were published on the ICH public website. The Secretariat will gradually add all final Concept Papers and Business Plans.

The first summarized ICH SC Reports of the Chicago 2005 and the Yokohama 2006 meetings were published on the ICH public website. The Secretariat also updated the website, adding user-friendly features like a Frequently Asked Questions (FAQs) section and a Glossary. In addition, the SC was informed that the Q9 Briefing Pack had been made available on the ICH website.

The SC also approved the recommendation of the ICH Coordinators not to apply the new codification system, which was applied to all ICH guidelines, to the M2 Specifications, and to support the proposal to apply a different codification system to the Q4B annexes. It is now intended, that when both the Q4B core guideline and Annex 1 reach *Step 4*, the annex will be a companion document to the Q4B core guideline, and will be renamed Q4B Annex 1.

**MedDRA:** The Chair of the MedDRA Management Board reported on the decisions taken by the Board on behalf of the ICH SC. The Board renewed its contract with MSSO (Maintenance and Support Services Organisation for MedDRA), and agreement was reached on a further significant overall reduction in subscription rates compared to the 2006 rates. The new fee structure will be effective from January 1, 2007, with some reduction for all subscription levels, but with a greater reduction for the low revenue subscribers. In addition, MedDRA will be free for health care providers and organizations involved in non-commercial activities.

The Chair informed the SC of the MedDRA Management Board's continued discussion on FDA's April 2006 announcement that the "Problem List" subset of SNOMED would be used to electronically code important terms in the Highlights section of Structured Product Labeling (SPL) such as adverse reactions, and indications for use for prescription drug products.

In Chicago, the MedDRA Management Board requested further clarification from FDA regarding the intended use of the Problem List in order to evaluate the potential need for the development of a MedDRA to SNOMED-CT Problem List mapping. The Board had the opportunity to discuss the topic directly with a FDA expert who attended the meeting. Based on clarifications provided by the FDA, the Board did not

see a need to support a mapping of MedDRA to the “Problem List” of SNOMED. The Board requested FDA to develop a statement that would provide clarity to MedDRA subscribers for distribution to the MedDRA community.

The Chair also provided the SC with an update on the joint CIOMS (Council for International Organizations of Medical Sciences) / ICH development of SMQs (Standardised MedDRA Queries). In Chicago, the Board authorized the production release of 7 new SMQs, bringing the total number of available SMQs to 35. The Board also supported the CIOMS Working Group recommendation to make the process more efficient by posting the SMQs after their validation by the CIOMS Working Group and evaluating them after 18 to 24 months of release to subscribers.

In addition, the Board approved the conduct of a survey to characterize how SMQs are currently used and elicit suggestions for further enhancements. The survey would be translated into Japanese and distributed through MSSO/JMO users and regulatory/industry associations.

The Chair reported that the WHO-ART (WHO Adverse Reaction Terminology) to MedDRA mapping would be available shortly, and would be made available free of charge to WHO-ART users through WHO UMC (Uppsala Monitoring Centre), and to MedDRA users through the MSSO.

The SC also noted that IFPMA (on behalf of the MedDRA Management Board) would be working with both MSSO and WHO UMC to develop a business plan for the integration of MedDRA into the WHO Pharmacovigilance database. The integration will ensure that MedDRA coded data are entered and retrieved in their original format.

**Global Cooperation Group:** The GCG Co-Chairs reported to the SC on the activities of the GCG meeting. Participants in attendance from the regional harmonisation initiatives (RHIs) included representatives from APEC, ASEAN, GCC, PANDRH and SADC.

In addition, the SC noted the discussions at the GCG meeting on the Stability Testing Conditions for Climatic Zones IV, and that WHO would revise its Stability Guidelines using the recent EMRO (WHO Regional Office for the Eastern Mediterranean) guideline as a basis. The draft WHO guideline will include a comprehensive list of countries within each climatic zone and corresponding stability storage conditions. The draft WHO document will go through a consultation process.

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

**Maintenance of ICH Controlled Terminology Lists:** In Chicago, the SC agreed that the M5 Controlled Vocabulary (CV) Lists for Routes of Administration, Units and Measurements, Pharmaceutical Dose Forms and Drug Substance Controlled Vocabularies would enter into the SDO process (see below discussion for M2). It was noted that an ISO accredited maintenance process for the maintenance of the M5 CV lists would need to be in place by October 2008.

Options for the maintenance process were discussed by the Maintenance of ICH Controlled Terminology Working Group. The SC charged the Working Group with

keeping all options open and to continue discussions following the Chicago meeting. It was agreed that an interim teleconference of the SC be organised in February 2007, at which a report would be made by the group to the SC on their activities.

**Quality Strategy Discussion:** The SC received a report on the outcome of the Quality Strategy Discussion. The scope of the meeting covered the identification of those areas in pharmaceutical quality that need to be addressed at ICH level in order to further advance towards the goal of achieving the same global submission.

The group agreed that the current topics (Q8, Q10, and Q4B) should be continued. It also identified a series of gaps and opportunities in quality topics, which need further consideration. The SC agreed that the group should continue and finalize the ICH Quality Strategy Discussion in Brussels, in May 2007, in order to develop a harmonised quality strategy and work plan. The SC also agreed that the group should continue the dialogue between chemical experts and biotech experts to address chemical and biotech (similarities & differences), traditional and “best scientific practices” for section 2.S.2 of Module 3 of the CTD.

**S2A(R1) / S2B(R1): Revision of S2 Genotoxicity Guidelines:** The Rapporteur reported to the SC on the progress made at the first meeting of the S2(R1) EWG. The Rapporteur highlighted the multitude of options to address the use of in vitro mammalian assays in the battery. To aid in the decision, a survey will be conducted to gather case studies from drug companies to see whether they support changes in the standard tests battery. The EWG will also consider the suitability of repeat dose toxicity studies for genotoxicity endpoints. The EWG will assess data provided by companies and determine whether scoring genotoxicity endpoints in repeat dose toxicology studies will be generally acceptable.

The SC supported the proposal of the EWG to merge the S2A and S2B guidelines. The ICH Secretariat was tasked with confirming the new title of the guideline.

**M3(R2): Revision of Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals:** The Rapporteur informed the SC of the progress made by the M3(R2) EWG. The EWG reviewed and prioritized the following proposals on the issues to be addressed by the revision: (1) M3 reference to Biotechnology products; (2) Need for single dose toxicity studies; (3) Components of the Genotoxicity testing battery prior to FIH (first entry into human); (4) Reproductive Toxicity to Support inclusion of WoCBP (women of childbearing potential); (5) Timing of chronic in relation to clinical phase; (6) Clarification of non-rodent chronic study duration.

Consensus was reached within the EWG to exclude proposal (1) from the scope. The Group made recommendations on how to revise proposals (2) and (3), deferred discussion on proposal (4), and would discuss data requirements from industry and health authorities for clarification of chronic testing duration (6).

**Safety Discussion:** The SC received a report on the outcome of the joint meeting of M3(R2) and S2(R1) EWGs to discuss how to proceed with the revision of the S6 Guideline “Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals”, and the newly proposed draft Concept Paper “New Proposal for a Preclinical Guideline on Oncology Therapeutic Development”.

The SC supported the group’s recommendation that regional meetings be organised in the three ICH regions during the second half of 2007 with a central meeting in spring 2008 to discuss whether or not a revision of S6 should be recommended.

The group discussed the newly proposed Oncology Therapeutics Concept Paper, and agreed that a guidance to address the development of oncology therapies should be drafted in the future, but the scope of the guidance had yet to be decided. Potential topics could encompass therapeutic vaccines, RNA, immunostimulants, or cancer vaccines. The group also recommended that it should be separate from S6. The SC agreed to the establishment of an informal working group to define the scope of the Concept Paper and to develop a robust Business Plan for consideration at the SC teleconference.

### 3. Reports on Current Topics

**Electronic Standards for the Transfer of Regulatory Information and the Electronic CTD (Topic M2 / eCTD):** In June 2006, the SC agreed that the M2 EWG should begin discussions to work collaboratively with Standards Development Organisations (SDOs) through the establishment of a Consortium in which ICH would participate to ensure that the development of electronic standards meets ICH standards.

In Chicago, the SC approved that E2B(R) and M5 messages enter the SDO process for development by a Consortium that would be composed of ICH, the International Organisation for Standardisation (ISO), Health Level 7 (HL7) and the European Committee for Standardisation (CEN). This would allow ICH to evaluate the process for working with SDOs.

The Rapporteur reported to the SC on the activities undertaken by M2 to initiate the liaison with the SDOs. The SC was informed that IFPMA (International Federation of Pharmaceutical Manufacturers and Associations) had applied, on behalf of ICH, to ISO for Liaison Organisation Status, and that a Memorandum of Understanding with HL7 was in the process of being drafted.

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

Harmonisation has been achieved on ten of the eleven General Chapters related to the ICH Q6A Guideline. The PDG is currently revising the harmonised *Bacterial Endotoxins* Chapter with Stage 4 draft to be published in Spring 2007 for public review. The Stage 4 draft of the General Chapter on *Color (Instrumental Measurement)* is currently in preparation.

The SC was also provided an update on the status of submitted packages. The Q4B EWG considered interchangeable the *Residue on Ignition / Sulphated Ash*. The PDG

expect to sign-off the revised text for *Sterility Test* in May 2007, followed by subsequent resubmission to Q4B. The PDG discussed major points of difference for *Particulate Matter in Injectables*, and presented documents for final Q4B evaluation for *Extractable Volumes of Parenterals*. The PDG will submit packages to Q4B on *Disintegration Test* and *Uniformity of Dosage Units*, in the first quarter of 2007, and *Microbiological Quality* in the second quarter of 2007.

**Q4B: Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria (RAAPAC):** The Rapporteur reported to the SC on the progress made by the Q4B EWG. The EWG worked to revise the Q4B core guideline and the first annex on *Residue on Ignition / Sulphated Ash* based on the comments received from the regulatory consultation process.

The EWG felt that the Q4B core guideline would need to reach *Step 5* prior to completion of the steps for the annex. The Rapporteur informed the SC that the target was to have the *Step 4* Q4B core guideline signed-off by or before May 2007.

The EWG discussed the title of the core guideline and proposed to modify it to encompass the outcome process and the process itself. The SC was informed that a new title was still under discussion by the EWG.

The EWG also received an updated submission from the Pharmacopoeial Discussion Group (PDG) for the second annex on *Extractable Volume*.

The SC noted that when both the Q4B core guideline and Annex 1 reach *Step 4*, the annex will be a companion document to the Q4B core guideline, and will be renamed Q4B Annex 1.

**Q8: Pharmaceutical Development:** The Rapporteur informed the SC of the progress made on the addendum to Q8. The EWG invested significant time in reaching consensus on a description of Quality by Design, which will be supported with illustrative case-study examples.

The EWG will develop a *Step 2 / Step 4* strategy for SC consideration at the Brussels SC meeting in May 2007. The Q8 EWG will liaise with the Q10 EWG at the May SC meeting to ensure consistencies.

**Q10: Pharmaceutical Quality System:** The Rapporteur reported to the SC on the progress made by the Q10 EWG in Chicago. It was noted that the discussion would be aligned with Q8 either prior to or at the Brussels SC meeting. The SC endorsed the work plan of the Q10 EWG and the timetable for reaching *Step 2* in Brussels in May 2007.

**E15: Pharmacogenomics:** The Rapporteur reported to the SC on the progress made at the second meeting of the E15 EWG. The scope of the EWG discussion is to develop definitions for terminology and descriptions of genomic biomarkers, pharmacogenomics, pharmacogenetics and categories of sample & data coding. The current inconsistent definitions make it difficult to achieve agreement on parameters

for implementation of pharmacogenomics in global pharmaceutical development and might lead to inconsistent assessments by regulators.

In Chicago, consensus was reached on the three definitions and on the descriptions of genomic data & sample coding categories, and of summary table. In Chicago, the SC signed-off the *Step 2* document.

The SC was also informed that the EWG had notified various interested organisations on the current efforts of the E15 EWG. The notification included a description of the ICH process and highlighted the fact that it would be possible for them to provide comments on the *Step 2* document.

**M5: Data Elements and Standards for Drug Dictionaries:** The Rapporteur reported to the SC on the progress made by the EWG on the development of M5 Controlled Vocabulary (CV) Lists for Routes of Administration, Units and Measurements, Pharmaceutical Dose Forms and Drug Substance Controlled Vocabularies. The SC agreed that these CV Lists would be handed over to the SDO process (see above discussion for M2).

In addition, the SC supported the M5 proposed work plan for the development of new controlled vocabularies for the remaining drug substance classes.

**E2F: Development Safety Update Report:** The Rapporteur reported to the SC on the progress made by EWG, and informed the SC that the EWG would be inspired by the CIOMS VII Report on Development Safety Update Report.

The Group agreed that the scope of the guideline would include drugs, vaccines and biologicals to apply to both commercial and non-commercial clinical trials.

**Gene Therapy Discussion Group (GTDG):** The Co-Rapporteurs reported to the SC on the progress made by the GTDG at the Chicago meeting. An update was provided on gene therapy clinical trials and the development of related guidelines/guidance (including environmental risk assessment) in the three ICH regions, EFTA, and Health Canada.

A representative from the Chinese SFDA informed the group about two gene therapy products licensed in China for the treatment of cancer. It was noted that a number of clinical studies are being conducted worldwide but apart from a licensing application in the EU, the only licensed gene therapy products were on the Chinese market. The group felt that participation from a Chinese representative was very beneficial.

The SC verbally endorsed the first GTDG Considerations document on *General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors* for publication on the ICH GTDG website, and agreed to the development of a survey to assess the usefulness of the document for SC consideration and approval.

In addition, the SC approved the group's draft proposal for the development of an ICH Considerations on *Oncolytic Viruses*. The GTDG plan to have the first draft by May 2007, with completion of the document planned by 2008.

The SC also approved the development by the GTDG of a plan for a workshop on Viral/Vector Shedding, for consideration by the SC. The GTDG would like to plan the workshop in conjunction with a scientific conference in Europe.

**4. Communication about ICH:** Following the ICH SC meeting in Yokohama in June 2006, the SC agreed to explore possible models to facilitate public dissemination of information relating to ICH activities. In Chicago, the SC considered alternative models, and it was suggested that smaller, more frequent and more focused ICH meetings should be organised. These could either take place as one-day meetings at the end of ICH SC meetings, or as ICH-branded regional meetings in collaboration with other non-profit organisations.

The SC agreed to reflect on the new approach for discussion at the next SC meeting in Brussels in May 2007.

**5. Dates of Next Meetings for 2007:**

May 7 – 10                      Brussels, Belgium

Oct. 27 – Nov. 1              Yokohama, Japan