ICH STEERING COMMITTEE
June 5-8, 2006, Yokohama, Japan
SUMMARY

1. Opening Discussions

The ICH Steering Committee (SC) meeting was chaired by 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 reported on the work being done to address proposals from the ICH Coordinators that identified ways the ICH Secretariat could improve communications with ICH stakeholders. The Secretariat developed a summarised version of the ICH SC Report from Chicago. This report, along with a report of the Yokohama meeting, will be reviewed by Coordinators and once approved the documents will be published on the ICH public web site.

In addition, the ICH Secretariat has been working to improve the user-friendliness of the ICH web site through the development of both a Glossary and a Frequently Asked Questions (FAQs) section. Information on the web site is also being updated. Once approved by the Coordinators the pages will be published on the ICH web site.

MedDRA: The Chair of the MedDRA Management Board reported on the decisions taken by the Board on behalf of the SC. Arising from contract renewal discussions with MSSO (Maintenance and Support Services Organisation for MedDRA), was the decision to provide a further significant reduction in subscription rates compared to the 2006 rates. The new fee structure would be effective from January 1, 2007, with all subscription levels to receive some reduction, but with a greater reduction for low revenue subscribers. In addition, the Board agreed to abolish the subscription fee for basic level subscribers deemed to be non-profit / non-commercial.

The Chair informed the SC of the MedDRA Management Board’s discussion on FDA’s recent announcement that the “Problem List” subset of SNOMED will 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. The Board discussed the difficulties this requirement might have for the MedDRA subscribing community, and the ways to minimise the burden for MedDRA users.

The Chair reported that following FDA’s announcement, an e-mail was sent by the Management Board to all MedDRA subscribers to encourage them to consider several points including FDA’s continuing commitment to using MedDRA for adverse event reporting, and MSSO’s efforts to investigate the feasibility of performing a standard mapping from MedDRA to the “Problem List” of SNOMED. The Management Board and MSSO will continue to keep MedDRA users updated as more information becomes available.
The Chair informed the SC that the Board had endorsed the renewal of the Memorandum of Understanding between ICH (IFPMA) and CIOMS (Council for International Organizations of Medical Sciences) for the development by the CIOMS Working Group of Standardised MedDRA Queries (SMQs). The Board re-expressed the view that this retrieval tool for safety signal detection has an added value to the utility of the MedDRA terminology.

The SC was also asked to note 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.

WHO UMC also presented a proposal on the integration of MedDRA into the WHO Pharmacovigilance database to the Board. This integration would ensure that MedDRA coded data are entered and retrieved in their original format. WHO UMC will provide the MedDRA Management Board with a more detailed proposal in order to advance this project.

**Global Cooperation Group (GCG):** 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 and PANDRH. The SC endorsed the document entitled *Strategy on Training and Capacity-Building*. This document, which relates to the use of ICH guidelines, will be published on the ICH web site.

The GCG Co-Chairs also informed the SC that the findings of a survey of the RHIs activities would be used to develop separate documents on the RHI profiles and their related good harmonisation practices.

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

**Safety Brainstorming Session:** The Chairs reported on the outcome of the brainstorming session, at which the need for revision of ICH non-clinical safety guidelines was discussed. The SC approved the group’s recommendations to revisit the guidelines on *Carcinogenicity [S1C(R1)], Genotoxicity [S2] and Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals [M3(R1)].*

The SC approved the draft Concept Paper for the revision of S1C(R1) and the establishment of an Expert Working Group (EWG). The SC endorsed the establishment of Informal Working Groups to further develop Concept Papers on the revision of S2 and M3(R1) for consideration at the next SC teleconference. The SC supported the participation in each working group of representatives from WSMI and IGPA (ICH Interested Parties), as well as a representative from the biotechnology industry.

**Biotechnology: Manufacturing Process Development and Validation:** The Informal Working Group met in Yokohama to work on their Concept Paper entitled “Manufacture of Biotechnological / Biological Drug Substances”. The SC discussed
the need for consistency in philosophical approaches to quality issues across the different product classes (biotechnology and New Chemical Entities) whenever possible. The SC decided that a framework should be developed on how the work on manufacturing process development and validation for biotechnological/biological substances should now proceed in this context.

**Quality Overall Summary (QOS):** The Informal Working Group discussed the benefit of using the QOS as a primary assessment tool similar to current practice in Japan and the possible consequences that such initiative would have on the CTD. Implications for CTD-Q, e-CTD and regional consequences relating to legislation need to be assessed. The group will finalise their proposal for SC consideration at the next SC meeting in Chicago.

**3. Reports on Current Topics**

**Electronic Standards for the Transfer of Regulatory Information and the Electronic CTD (Topic M2 and eCTD):** With the ever-increasing number of activities for the M2 Expert Working Group (EWG), the SC charged the M2 group with investigating the possibility of interfacing with SDOs (Standards Development Organisations).

In Yokohama, the SC heard presentations from three invited Standards Development Organisation (SDO) representatives; International Organisation for Standardisation (ISO), European Committee for Standardisation (CEN) and Health Level Seven (HL7).

The M2 EWG reported to the SC on discussions held with the SDO representatives to investigate how ICH could potentially use SDOs for the development of technical standards relating to the electronic transmission of regulatory information. The group recommended to the SC that ICH should work collaboratively with SDOs through the establishment of a Consortium in which ICH would participate to ensure that standard development meets ICH standards.

The SC agreed to a List of Critical Requirements developed by the M2 EWG that outlines ICH’s requirements in any interaction with SDOs. Based on these critical requirements the M2 EWG will begin discussions with SDOs and will develop a working Concept Paper on the process.

**Pharmacopoeial Discussion Group:** On behalf of the Pharmacopoeial Discussion Group (PDG), the Japanese Pharmacopoeia reported on the current status of the PDG harmonisation efforts. Harmonisation has been achieved on ten of the eleven General Chapters related to the ICH Q6A guideline. The General Chapter on Color (Instrumental Measurement) was circulated to industry for preliminary comments. The PDG agreed to a revision of the harmonised Bacterial Endotoxins Chapter and to a new topic on Uniformity of Delivered Dose of Inhalations.
The Q4B EWG considered interchangeable Residue on Ignition / Sulphated Ash and Extractable Volume, and is currently evaluating the package on Sterility Test, Particulate Matter in Injectables and Dissolution Test.

PDG will shortly submit packages to the Q4B EWG on Disintegration Test, Uniformity of Dosage Units and Microbiological Quality.

The PDG informed the SC of a review of their working procedures, and reported that the precise language to explain the changes of procedures that will be incorporated in the three Pharmacopoeias will be finalised at the next PDG meeting.

**Q4B: Regulatory Acceptance of Pharmacopoeial Interchangeability:** The Rapporteur informed the SC that the EWG had reached consensus on the Q4B Step 2 Core Document. The group proposed that the Q4B title be changed from Regulatory Acceptance of Pharmacopoeial Interchangeability to Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria.

The EWG also reached consensus (ICH Step 2) on the first Annex on Residue on Ignition / Sulphated Ash. The group recommended that the Q4B Annexes should also go through a regulatory consultation process.

The SC signed-off Step 2 of both the Q4B core guideline and the Q4B Annex. The SC also endorsed the change in the Q4B title and the regulatory consultation period for the Q4B Annexes.

**Q8: Pharmaceutical Development:** The Rapporteur reported to the SC on the progress made on the addendum to Q8. The EWG discussions focused on defining and exemplifying how Quality by Design concepts can enhance product and process understanding and encourage industry’s sharing of its knowledge with regulators.

In response to issues raised with the core guideline and early drafts of the addendum, the EWG has established multiple drafting groups to clarify the baseline expectations, enhanced understanding, regulatory flexibility, Design Space and Quality by Design. The group will focus on solid oral dosage forms to develop the further guidance that addresses these needs. Wherever possible, references to the opportunities to use relevant tools from Q9 in the appropriate sections of Q8 will be illustrated by use of case-study examples.

The SC endorsed a Quality plenary session at the next SC meeting in Chicago with New Chemical Entity and Biotechnology representatives to agree on the direction, priorities and fundamental principles, and consequences in terms of the need to update existing guidelines.

It was noted that when the addendum will be added to the core Q8 guideline, the core guideline and the addendum will be renamed Q8(R1).

**Q10: Pharmaceutical Quality Systems:** The Rapporteur reported to the SC on the progress made by the Q10 EWG in Yokohama. The group reached conceptual agreement on all issues, and ensured that all ISO concepts were incorporated in a pharmaceutical context.

The SC supported to the group’s recommendation to change the title from GMP Quality Systems to Pharmaceutical Quality Systems.
The EWG reported that the next key step would be the evaluation of Q10 against Q7A for consistency of common elements. The group will also organise a discussion with the Q8 experts at the next meeting in Chicago to ensure the appropriate linkages. The Step 2 Q10 document is expected in 2007.

**E2B(R3): Revision of the Electronic Submission in Individual Case Safety Reports:** The SC was updated on the progress made by the EWG on the development of the draft E2B(R3) Step 4 guideline. At the last meeting in Chicago in November 2005, the EWG reviewed 361 comments received from Step 3 consultation. 157 comments were Japan oriented issues, 58 were major issues of which 22 were M2 related and the remaining 146 required few or no revisions to the guideline.

In Yokohama, the EWG resolved the 11 remaining issues and the draft E2B(R3) Step 4 document is now available for the development of a draft plan and a draft schema for the Proof of Concept (PoC) testing. The E2B(R3) EWG will interface with M2 for the PoC development and testing.

It was noted that time did not allow in Yokohama to develop the PoC with M2, due to M2’s discussions with SDOs (Standards Development Organisations). The group reported that the time frame for reaching E2B(R3) Step 4 would be subject to completion of the PoC and revision of the draft Step 4 guideline based on the outcome of the PoC testing.

The SC will review the progress on the PoC at the next SC teleconference.

**E15: Pharmacogenomics:** The Rapporteur reported on the progress made at the first meeting of the E15 EWG. The scope of the EWG discussion is to develop definitions for (1) genomic biomarker, (2) pharmacogenomics / pharmacogenetics and (3) 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 Yokohama, consensus was reached on the three definitions.

The EWG proposed to notify various other interested organisations on the ICH EWG activities, being international (OECD, CIOMS, ISP, PWG) or national (US: ASHG, PMC and others; Europe: EC Directorates, ESHG, European Scientific Networks on Genetics, Working Party of Patient’s Organisations; Japan: JHSF, JSCP).

The group reported that the Step 4 guideline was expected by the end of 2007.

**M5: Data Elements and Standards for Drug Dictionaries:** The Rapporteur reported to the SC on the progress made by the M5 EWG. The SC noted that the EWG was on schedule to finalise the M5 Step 4 core document. The lists of Controlled Vocabulary for Routes of Administration and Units & Measurements were published in May 2005 for information. Comments received were taken into consideration. The SC noted that the work on the Controlled Vocabulary for Pharmaceutical Dose Forms was almost complete. The EWG is currently working on the Drug Substance Controlled Vocabulary with compilation of lists of chemical, biological and herbal drug substances.
The group reported that they had begun to further define drug substance structure for Controlled Vocabularies with the M2 EWG. Business requirements were further clarified and documented with M2. The Proof of Concept (PoC) plan and protocol was further refined with the M2 EWG. The group recommended that the maintenance process for the Controlled Vocabularies needed to be further clarified and implemented.

The SC noted the important interface with both the M2 and E2B(R3) EWGs. The SC recommended that a draft Options Paper for the long-term maintenance of the M5 Annexes be developed for consideration at the next meeting in Chicago. It was agreed that the issue regarding the maintenance process for the annexes should be resolved before finalisation of the M5 Step 4 core document.

**Gene Therapy Discussion Group (GTDG):** The Rapporteur reported to the SC on the progress made by the GTDG in Yokohama. An update on the development gene therapy in the three ICH regions and by EFTA was provided. It was noted that there are a lot of clinical studies being conducted but that the only gene therapy products licensed were in China for cancers.

The SC approved an invitation to the Chinese Regulator to participate in the GTDG discussions.

The GTDG group agreed on the general scientific principles and content of draft 4 of the ICH Considerations document on *General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors*. The SC noted that the Considerations document should be finalised at the next meeting in Chicago in October 2006.

The SC supported the group’s recommendation for the development of an ICH Considerations document on *Oncolytic Viruses* and an ICH Considerations document on *Virus/Vector shedding*.

**4. ICH Reflections Paper**

FDA reported on the *ICH Reflections Paper*, drafted by FDA upon the request of the SC, and revised to incorporate comments arising from the last meeting in Chicago in November 2005.

The paper proposes new operating principles for the ICH to adopt and describes topics such as the Greater Inclusion of Non-ICH Organisations, Increased Transparency and the Leveraging of ICH Efforts.

The SC agreed in Chicago on the basic principals of the document, however a decision on the posting of Concept Papers on the ICH web site had been deferred. In Yokohama, the SC agreed to post final Concept Papers on the ICH public web site.

Other proposals from the Reflections Paper are currently being addressed. Since Chicago, the ICH Secretariat has developed a communication strategy in the context of the Global Cooperation Group (GCG), and the GCG is working to revise its procedures and training strategy. A proposal to evaluate the options of potentially working with accredited SDOs (Standards Development Organisations) to leverage the development of technical standards for ICH e-Initiatives is also being addressed by the M2 EWG.
5. Any Other Business

**Q1F: Stability Data Package for Registration Submissions in Climatic Zones III/IV:** The Rapporteur reported to the SC on the group’s recommendation for the immediate withdrawal of the ICH Q1F guideline due to acceptance problems in relevant hot and humid regions. The group also recommended to keep Q1A(R2) as it is.

The SC agreed to the Q1F EWG’s recommendations and approved the publication on the ICH web site of an explanatory note drafted by the group to inform the public of the withdrawal. The note also contains a paragraph relating to Q1A(R2), stating that although the intermediate testing conditions of 30°C/65%RH would be retained, flexibility would be given to industry to use more stringent testing conditions if they wished.

**Q9: Quality Risk Management:** The Rapporteur of the Q9 EWG reported to the SC on the development of a briefing pack of slides to promote the concept of Risk Management. Additional features include the development of an executive summary and a Questions & Answers document.

The SC agreed that once the slides are finalised they will be published on the ICH web site and offered as a training aid, rather than as an officially endorsed ICH product.

**ICH7:** With the decision to cancel the previously announced 2007 ICH7 Conference, the SC agreed to explore the possible models to facilitate public dissemination of information relating to ICH activities.

**Dates of Next Steering Committee Meetings:**
- October 21-26, 2006    Chicago, USA
- May 7-10, 2007        Brussels, Belgium