ICH Steering Committee
October 27 – November 1, 2007, 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 undertaken to improve communications with ICH stakeholders. The summarized ICH SC Report for Brussels, Belgium 2007 was posted on the ICH website in early October 2007. The ICH Secretariat was also continuing to update the web pages for ICH Concept Papers and Business Plans on the ICH public website.

The SC noted that the ICH Secretariat was also working to develop a library of training materials and presentations on ICH topics for publication on the ICH website.

MedDRA: The Chair of the MedDRA Management Board reported on the decisions taken by the Board on behalf of the ICH SC. The Chair informed the SC that to facilitate further the use of MedDRA the Board had approved for the third consecutive year a significant reduction in subscription rates for lower revenue subscribers. Moreover, no increases to other subscription levels were made. The SC also noted that as of January 2007 access to MedDRA was free for academic organizations, hospitals, healthcare providers, and other users involved in non-commercial activities.

The SC noted that the substantial decrease in the subscription fees in 2006 and 2007 for low revenue companies was likely to have contributed to the 20% increase in MSSO subscribers seen in the first nine months of 2007.

The Chair also reported that to increase the utilisation of MedDRA by non-English speakers, the Board had agreed to abolish the $850 charge for additional European language translations for MSSO subscribers. This would be effective from January 2008. Previously, only one free European language translation was included with each subscription to MedDRA. In addition, the Board directed MSSO to offer free MedDRA training for all new subscribers, and to expand significantly, the training of regulators in 2008 in both US/Canada and Europe.

The SC noted that currently MedDRA was available in nine languages: English, Japanese, French, German, Portuguese, Spanish, Dutch, Italian and Czech. The Chair informed the SC that in view of the increasingly global nature of drug development, the Board had given its approval for the development of a Mandarin Chinese translation of MedDRA. The SC noted that this translation should be made available in late 2009.
The Chair updated the Board on the project with WHO UMC (Uppsala Monitoring Centre) to integrate MedDRA in the WHO global ICSR - Individual Case Safety Report - database (Vigibase). MedDRA’s integration into Vigibase will enable data to be entered directly into Vigibase in either MedDRA or WHO-ART, and allow all Vigibase outputs to display data in either MedDRA or WHO-ART, or in both terminologies. In addition, SMQs (Standardised MedDRA Queries) will also be included. The SC noted that the launch date for MedDRA’s implementation in Vigibase was set for mid-March 2008.

The SC was informed that with the latest release of MedDRA in September 2007, 55 SMQs were available to support more uniform and effective safety surveillance. The SC noted the excellent work of the members of the CIOMS (Council for International Organizations of Medical Sciences) working group on SMQs.

The Chair informed the SC that the Board had endorsed the addition of new terms to MedDRA to support safety surveillance of medical devices and combination products. The SC noted that the first batch of new terms was anticipated to be added to MedDRA in March 2008. The Board agreed that the terms should follow lists from the Center for Device and Radiological Health (CDRH) of FDA and the Global Harmonisation Task Force (GHTF) for medical devices.

The SC noted that the Board had also endorsed a proposal from European regulators to create a gender-specific list of terms and a list of paediatric adverse event terms. The provisional lists would be placed on the MSSO website early in 2008 for Subscriber comment. It is intended that the lists will assist data quality control (for example, a male patient cannot develop uterine cancer) and assist pharmacovigilance for these sub-populations. Both lists are considered recommendations only, and organizations may wish to modify the lists for their own requirements.

Global Cooperation Group: The GCG Co-Chair reported to the SC on the outcome of the GCG meeting. Participants in attendance from the Regional Harmonisation Initiatives (RHIs) included representatives from: APEC, ASEAN, GCC, PANDRH and SADC.

The SC was informed of the success of the GCG-endorsed APEC LSIF (Life Science Innovation Forum) sponsored workshop on ICH Quality Guidelines (Q8, Q9, and Q10), held in September 2007, in Seoul, Korea. The workshop was attended by more than 400 people from 17 countries and included regulators, policy makers, academia and industry. The programme objectives included a practical explanation of ICH guidelines and an interactive discussion of the anticipated challenges and opportunities associated with the implementation of Q8 (Pharmaceutical Development), Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality System) in APEC regions. The SC noted that the training materials from the workshop would be published on the ICH website under a new section on Training Activities.

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

eCTD / Quality Meeting: The Rapporteur for the M2 Expert Working Group (EWG) reported to the SC on the outcome of the meeting held between M2 eCTD experts and
Quality experts to discuss how to address the Quality Change Request issues. The SC endorsed the group’s proposal to (re)establish a CTD-Q Implementation Working Group (IWG) to address the quality issues identified by the M2 EWG. It was agreed that the group would work mainly by e-mail and teleconferences.

**Quality Informal Working Group:** The SC received a report on the outcome of the meeting of the Quality Informal IWG. The group presented the SC with a Concept Paper which included the group’s recommendation for the SC to establish a formal IWG. The formal Quality IWG would be tasked with assuring the globally consistent implementation of the Q8, Q9 and Q10 Guidelines to ensure that the maximum benefit is achieved from the interaction between these guidelines.

The SC noted that implementation issues to be addressed by the formal IWG included various technical issues and related documentation (technical examples and case studies, level of detail to include in the dossier, common understanding of terminology, inter-relationship between Q8, Q9 and Q10), communication, training, scope of implementation and influence on existing ICH guidelines.

The SC endorsed the Quality IWG Concept Paper and the establishment of a formal Quality IWG.

**Quality Roundtable for Small/Large Molecule Scientific Discussion:** The SC was updated on the outcome of the Quality Roundtable discussion for Chemical (Small Molecule) and Biotech (Large Molecule) experts, which was held in Washington DC in September 2007.

The aim of the meeting was to discuss similarities and differences between chemical and biotech drug substances, and to assess key elements of Q8/Q9/Q10 (design space, QbD and quality risk principles) and their applicability to drug substance development and manufacture.

The experts recommended to the SC the development of an ICH guideline on *Development and Manufacture of Drug Substances* (Section S2 of CTD-Q), with biotech and chemical experts working together, and in parallel, if necessary.

The SC endorsed the establishment of an informal EWG to develop a Concept Paper and Business Plan for SC consideration.

**S6 Discussion:** The SC received an update on the outcome of a meeting between ICH Safety experts (S2(R1), M3(R2) and S9) to exchange views on feedback from the S6 regional meetings held to date and discuss if a revision of the S6 Guideline *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* is necessary.

The SC endorsed the group’s request for a further discussion between non-clinical ICH Safety experts at the next SC meeting in Portland in June 2008. The aim of the meeting would be to decide whether a revision is necessary, and if so, how this revision would be best achieved i.e., Revision, Addendum, Q&A (Question & Answer) document.
Proposal for Revision of E7: Studies in Support of Special Populations: Geriatrics: The SC endorsed the establishment of an Informal EWG to consider the issues raised in a draft Concept Paper proposed by the EU on the need to revise the ICH E7 Guideline.

Proposal for Next Genomic Topic: The SC noted that a Concept Paper and Business Plan for a new ICH genomic guideline on Genomic Biomarker Qualification, Format and Content of a Submission was in the process of being finalised and would be submitted for SC consideration at the SC teleconference prior to the Portland meeting in June 2008.

3. Reports on Current Topics

Electronic Standards for the Transfer of Regulatory Information and the Electronic CTD (Topic M2 / eCTD): In February 2007, the E2B(R) and M5 messages were submitted to ISO (the International Organisation for Standardisation) in the form of seven New Work Item Proposals (NWIPs), which were subsequently accepted for ballot by ISO TC 215 (ISO’s Technical Committee on Health Informatics).

The M2 Rapporteur updated the SC on the outcome of the joint meeting in Yokohama of the M2/M5/E2B(R3) EWGs which had been organised to update all EWG members on SDO-related activities since the Brussels meeting in May 2007. The SC noted that at the ISO TC 215 meeting in Brisbane, Australia, in August 2007, the ICH NWIPs had passed the ISO ballot. Following the meeting two Task Force (TF) working groups on Pharmacovigilance (ICSR TF) and Identification of Medicinal Products (IDMP TF) were formally established.

The M2 Rapporteur informed the SC that while the ISO TF working groups would develop the International Standards and Schema, ICH would need to develop ICH Implementation Guides. The purpose of the ICH Implementation Guides would be to define how ICH will use the International Standards for ICH purposes in the ICH regions. The SC noted that M2 would work collaboratively with the M5 and E2B(R3) EWGs to develop the Implementation Guides.

With regards to version 3.3.3 of the eCTD, the Rapporteur informed the SC that there was concern that the effort required to finalise and implement this version might be greater than the benefit gained. The SC supported the recommendation of the M2 EWG to cease the progression of version 3.3.3. A new version of the eCTD specification to improve narrative portions would instead be released as eCTD version 3.2.1. A narrative update to the STF (Study Tagging File) Specification would also be developed as version 2.6.1. A new version of the Q&A/Change Request document version 1.15 would also be prepared.

The M2 EWG recommended to the SC to initiate the business requirements phase for the next major version. The main steps in the process would be the evaluation of the current ICH requirements, the collection of new ICH requirements, and the application of knowledge from the current SDO pilot projects. The SC supported the recommendation, noting that it would take approximately one year to gather the business requirements for the next major version.
M5: Data Elements and Standards for Drug Dictionaries: The M5 Rapporteur reported to the SC on the outcome of the informal meeting of the M5 EWG. The purpose of the meeting was to update EWG members on the SDO process and the work of the IDMP TF working group, and discuss the planning and input required by the M5 EWG.

E2B(R3): Revision of the Electronic Submission in Individual Case Safety Reports: The Rapporteur of the E2B(R3) EWG updated the SC on the outcome of the meeting of the E2B(R3) EWG. The SC noted that the E2B(R3) EWG meeting had been preceded by a meeting of the ISO ICSR TF working group which was also held in Yokohama.

The Rapporteur reported that the E2B(R3) EWG would need to review the documents and actions produced at every step of the ISO ICSR TF work, and would need to consider the impact of the timeline of the SDO process on the ICH step process. The SC noted that the next steps in the process would include the conduct of a gap analysis by the ICSR TF between the HL7 ICSR and E2B(R3), and the development of a working draft. The Rapporteur also highlighted for the SC some important issues that would need consideration. These included ensuring the backwards and forwards compatibility of the E2B(R3) and the eventual ISO ICSR.

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 nine of the eleven General Chapters related to the ICH Q6A Guideline. The Stage 4 draft of the General Chapter on Bacterial Endotoxins (revision) is expected to be for sign-off at the next meeting in Portland in June 2008. The General Chapter on Colour (Instrumental Measurement) would come at a later stage. A proposal was made by the PDG for the SC to consider expanding the scope of Q4B to topics beyond Q6A. The SC agreed to defer discussion on the proposed scope expansion until the next meeting.

Q4B: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions: The Q4B Rapporteur reported to the SC on the outcome of the Q4B EWG meeting. The SC acknowledged the considerable progress made by the Q4B EWG. During the EWG meeting Step 4 was reached for both the Q4B Core Guideline and Q4B Annex 1 on Residue on Ignition/Sulphated Ash. The SC agreed to rename the Core Guideline: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions (the draft Core Guideline had been previously named: Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria). In addition Step 2 was reached for Annex 2 on Extractable Volume and Annex 3 on Particulate Matter. Both the Q4B Core Guideline and the Annexes were signed-off by the SC.

Q8: Pharmaceutical Development: The SC signed-off Step 2 of the Addendum to the Q8 Guideline Pharmaceutical Development on specific dosage forms (solid oral, liquid oral and
ICH Steering Committee Meeting, Yokohama, Oct 27-Nov 1, 2007

Summary

parenterals). Focus was given in the Addendum to exemplifying Quality by Design concepts to enhance product and process understanding and to encourage industry’s sharing with regulators. The Addendum would be released for regulatory public consultation in the three ICH regions.

**Q10: Pharmaceutical Quality System**: The Q10 EWG did not meet in Yokohama. The SC endorsed the Q10 work plan and agreed that the next meeting of the Q10 EWG would take place in Portland in June 2008.

**S2(R1): Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use**: The Rapporteur of the S2(R1) EWG updated the SC on the activities of the EWG and the progress made towards reaching Step 2. The SC was informed of the major points of the revision which included: the S2A and S2B Guidelines being merged into one; options provided for the test battery (with and without *in vitro* assays); the integration of genotoxicity endpoints into routine toxicology studies; advice on choice of second *in vivo* genotoxicity endpoint; provision of advice on weight of evidence and data evaluation to determine relevance of positive findings; and the timing of genotoxicity studies for Phase 1.

The SC noted that the revision would have some positive benefits for the 3Rs agenda which aims to “Reduce”, “Refine”, and “Replace” animal testing. These benefits would include: concurrent positive controls in every *in vivo* assays no longer being required; the integration of genotoxicity into toxicology assays; and the reduction in “non-relevant” *in vitro* results which will reduce the number of follow-up *in vivo* assays.

The Rapporteur informed the SC that the EWG would work to finalise the Step 2 document prior to the next ICH meeting in Portland in June 2008.

**M3(R2): Revision of Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals**: The Rapporteur reported on the outcome of the M3(R2) EWG meeting in Yokohama, as well as that of the interim meeting held in Washington D.C. in September 2007. The SC was updated on the main outcomes of the review of the draft M3(R2) Guideline which included consensus being reached by the EWG in support of 9 month non-rodent studies in almost all cases in all regions. Twelve month studies would only be used to support replacement of chronic non-rodent and juvenile toxicology study where the primary population is paediatric.

The SC approved the group’s proposal to include new sections in the Guideline to address timing on new ICH and regional guidances (immunotoxicology studies, phototoxicity studies and non-clinical abuse liability studies), as well as the inclusion of general language for initial starting doses in First-in-Man (FIM). The SC endorsed the work plan of the M3(R2) EWG and agreed that the EWG would meet in Portland in June 2008 to work towards finalising the Step 2 document.
**S9: Oncology Therapeutics:** The Rapporteur updated the SC on the outcome of the meeting of the S9 EWG in Yokohama. The SC noted that radiopharmaceuticals, botanicals and supportive care would be specifically excluded from the scope. The SC approved the work plan of the S9 EWG and agreed that the S9 EWG would meet in Portland in June 2008. The Rapporteur informed the SC that the EWG would also pay attention to the 3Rs agenda (Reduce/Refine/Replace animal testing) in the preparation of the draft S9 Guideline. The SC noted that the target would be to reach Step 2 in autumn 2008.

**E2F: Development Safety Update Report:** The Rapporteur reported to the SC on the outcome of the meeting of the E2F EWG in Brussels and progress made by the EWG towards reaching Step 2. The SC noted that one of the benefits of the Development Safety Update Report (DSUR) would be to provide harmonisation with previous E2E and E2C Guidelines. The E2F Guideline would provide harmonisation of format, content and scheduling of annual reports. The Rapporteur informed the SC that some examples of DSURs were being developed. The SC supported the EWG’s recommendation that the examples be published as separate documents rather than as an appendix to the Guideline. It was agreed that the EWG would develop a proposal on how the examples should be published.

The SC noted that the EWG planned to reach Step 2 in Portland in June 2008.

**E14: The Clinical Evaluation of QT/QTc Interval Prolongation and ProArrhythmic Potential for Non-Antiarrhythmic Drugs Q&A document:** The E14 IWG did not meet in Yokohama. The SC agreed that the IWG should develop a concrete work plan and continue work by e-mail and teleconferences to finalise the E14 Q&As document. Depending on the progress made it was agreed that the group may need to meet in Portland in June 2008.

**Gene Therapy Discussion Group (GTDG):** The GTDG did not meet in Yokohama, but in Rotterdam at the time of the workshop organized by the GTDG on viral/vector shedding, which was held on October 30, 2007. A report was presented to the SC on the outcome of the workshop and the GTDG meeting.

The SC noted that the workshop on viral/vector shedding which was held in Rotterdam was held in conjunction with the annual conference of the European Society for Gene and Cell Therapy. The workshop received financial support from the Clinigene European Network of Excellence in Gene Therapy.

The objectives of the workshop were to: discuss data available on shedding of diverse vector systems; discuss assays to detect vectors shed into excreta; discuss the current requirements in the different regions; discuss third party exposure and public health concerns; and contribute information to the drafting of an ICH considerations paper on viral/ vector shedding. Topics discussed at the workshop included the current regulatory requirements of each region, non clinical and clinical investigations (relevant animal models, types of assays, clinical monitoring), and review of experience of shedding data for in vivo gene therapy (Adenoviruses, Adeno-associated viruses, Seneca Valley Virus).

The SC was informed that the workshop was well attended, with approximately 70 participants, with active participation from the audience including the open sharing of
ICH Steering Committee Meeting, Yokohama, Oct 27-Nov 1, 2007

Summary

A number of issues were raised during the workshop, with information gained by health authorities in the regions and a general awareness created on ICH GTDG activities.

The SC approved the plan for the next ICH Considerations document on Viral/Vector Shedding. It was noted that data and reflections gained from the workshop would be incorporated into the ICH Considerations document.

The SC was also updated on the progress made by the GTDG in the development of the ICH Considerations document on Oncolytic Viruses. The first draft of the document had been completed and the second draft was in progress.

**M1 PtC WG: MedDRA Points to Consider Working Group:** The Co-Rapporteurs of the MedDRA PtC WG updated the SC on the outcome of the group’s meeting in Yokohama. The SC noted that the main role of the PtC WG is to update the two MedDRA PtC documents for consistent use of MedDRA (Term Selection PtC document and Data Retrieval & Presentation PtC document) with each release of MedDRA (twice a year) and in response to MSSO users comments. In Yokohama, the group worked to address complex issues raised by users (e.g., guidance about the definition of and appropriate use of combination terms, guidance on coding difficult topics including medication errors, age versus event specificity, off label use and pregnancy (mother/baby cases)).

The SC endorsed the proposal for the PtC WG to extend the discussion of SMQs within the PtC Data Retrieval and Presentation document with the aim of providing further user guidance on SMQs. It was agreed that the group should work closely with the CIOMS WG on SMQs for this activity. It was noted that there was an overlap of experts between the CIOMS WG on SMQs and the PtC WG. The Co-Rapporteurs informed the SC that the timeframe for the development of the extended guidance was 12 to 18 months.

**4. Communication about ICH:** In Chicago, in October 2006, the SC considered the organisation of smaller, more frequent and more focused ICH public meetings. 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.

In Yokohama, MHLW and JPMA updated the SC on the organisation of the first ICH regional public meeting which would take place in Tokyo on November 2, 2007 following the SC meeting in Yokohama. The SC noted that the ICH Tokyo Symposium “Hot Topics and Influence on Asia” would be attended by more 460 participants.

**5. Dates of Next Meeting for 2008:**

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<tr>
<td>June 2-5, 2008</td>
<td>Portland, Oregon, USA</td>
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<tr>
<td>November 8-13, 2008</td>
<td>Brussels, Belgium</td>
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