

ICH STEERING COMMITTEE

May 31 – June 5, 2008

Portland Oregon, 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. The SC noted that presentations and training materials from the recent ICH GCG endorsed workshops had been published on the ICH website under a new section on GCG Training Activities.

These included presentations from the GCG-endorsed Korean APEC LSIF ICH Quality Workshop (i.e., Q8, Q9 and Q10) held in September 2007, as well as those from the GCG-endorsed APEC LSIF preliminary workshop for regulators on the “Review of Drug Development in Clinical Trials” held in March 2008 in Bangkok, Thailand. Presentations from the recent GCG-endorsed APEC LSIF preliminary workshop on “Good Clinical Practice/Clinical Research Inspection”, held on May 27-30, 2008, would be published shortly.

MedDRA: The Chair of the MedDRA Management Board reported on the decisions taken by the Board on behalf of the ICH Steering Committee. In Portland, the Board authorized the MSSO (Maintenance and Support Services Organisation) to provide free training on coding and data analysis to all MSSO Subscribers. Training will be offered at various locations in the US, as well as in Europe, where training will be dispensed in English, French, Spanish and German.

This action further extends the Board's commitment to facilitating MedDRA's use, coming in addition to the recent elimination of the fee for all European MedDRA translations, and the elimination of subscription fees for academic organizations, hospitals, healthcare providers, and other users involved in non-commercial activities.

Mid-March saw the implementation of MedDRA in the WHO global ICSR database (Vigibase), bringing to completion a one-year project between the WHO Collaborating Centre for International Drug Monitoring (UMC, Uppsala Monitoring Centre, Sweden) and the MedDRA Management Board. Vigibase processes are now as compatible with MedDRA as they are with WHO-ART, the WHO Adverse Reaction Terminology. The SC noted the belief of the Board and the UMC that MedDRA's implementation in Vigibase will provide a global repository of MedDRA-coded safety data that can be used as a substantial tool for pharmacovigilance and be of significant benefit to patient safety and public health.

In Portland, the Board endorsed the renewal of a revised Memorandum of Understanding (MoU) between ICH (IFPMA) and CIOMS (Council for International Organizations of Medical Sciences) to complete the development of the initial set of SMQs (Standardised MedDRA Queries) and transition to their maintenance phase. The revised MoU calls for the establishment of a Core group of the original CIOMS SMQ Working Group to finish work on the remaining SMQs. The Board expressed their appreciation to the members of the CIOMS Working Group on SMQs for their efforts in the development of the sixty SMQs already in production.

The SC noted that a Hungarian translation of MedDRA was being developed and was expected to be made available in 2009. This would be added to the Czech, French, German,

Portuguese, Spanish, Dutch and Italian versions already available, in addition to the English and Japanese translations. The Board also recently gave its approval for a Mandarin Chinese version of MedDRA, which is expected for release in early 2009.

Global Cooperation Group: The GCG Co-Chairs reported to the SC on the GCG meeting. The Portland meeting was of significant importance for the GCG, with the participation for the first time of new representatives from a number of individual DRAs (Drug Regulatory Authorities) including Australia, Chinese Taipei, Singapore and South Korea. Their participation comes in addition to that of representatives from RHIs (Regional Harmonisation Initiatives). RHIs in attendance at the Portland meeting included representatives from APEC, ASEAN, GCC, and SADC.

The report included feedback on the development of new procedures on how to address and prioritise requests from the RHIs and DRAs for training and capacity-building related to the use of ICH guidelines. The SC endorsed the ‘Revised Procedure on Training Activities’, in addition to the more general ‘Revised Principles and Procedures’ document which was also developed by the GCG.

The SC noted the successful organisation of the two GCG-endorsed APEC LSIF preliminary workshops for regulators on the “Review of Drug Development in Clinical Trials” and “GCP Inspections” held in March and May 2008 respectively, in Bangkok, Thailand. The preliminary workshops will be followed by advanced workshops in early 2009.

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

S6 Discussion: In Portland, Safety experts from the S2(R1), M3(R2) and S9 Expert Working Groups (EWG) met to exchange views on feedback from regional scientific meetings held in the US, Japan and Europe in 2007 to discuss specific items identified as issues when applying the S6 Guideline *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*.

The experts informed the SC that there were a number of items that should be addressed including species selection, study design, reproductive/developmental toxicity, carcinogenicity, immunogenicity and reference to the 3Rs (Reduce/Refine/Replace animal testing). The experts presented the SC with a draft Concept Paper proposing to develop an *Addendum* to the S6 guideline and the establish a S6(R1) EWG to carry out the work.

The SC endorsed the S6(R1) Concept Paper and the establishment of an EWG. The SC supported the participation in the EWG of representatives of the Interested Parties IGPA, WSMI, and the biotechnology industry association.

The S6(R1) EWG will have their first meeting in Brussels in November 2008.

3. Reports on Current Topics

Electronic Standards for the Transfer of Regulatory Information and the Electronic CTD (Topic M2 / eCTD): The M2 Rapporteur updated the SC on the progress made by the ISO (the International Organisation for Standardisation) TC 215 (ISO’s Technical Committee on Health Informatics) Task Force groups on Pharmacovigilance Individual Case Study Report (ICSR) and Identification of Medicinal Products (IDMP) in which several ICH experts were participating.¹

¹ 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 which includes the International Organisation for Standardisation (ISO), Health Level 7 (HL7) and the European Committee for Standardisation (CEN).

The M2 Rapporteur reported that the M2 and E2B(R3) EWGs would work jointly to develop the ICH Implementation Guide for the ICSR and to create a test plan. The SC endorsed a joint meeting of the M2 and E2B(R3) EWGs in Brussels, in November 2008 to further progress this work. Noting that the process for the IDMP was slightly behind that for the ICSR, the SC agreed that a meeting of the M5 EWG in Brussels would not be necessary.

The SC also supported the M2 EWG proposal on the future role of the group. The whole M2 EWG would continue to focus on technology standards, while a smaller sub-group would be established and charged with SDO relationship management.

The SC was updated on work by the M2 eCTD sub-group to develop a list of the ICH requirements for the next major version of the eCTD. The SC noted that the sub-group had completed the initial collection and collation of requirements from each region and aimed to produce a final list of ICH requirements for SC endorsement in Brussels in November 2008.

In Portland the SC endorsed *Step 4* of v3.2.1 of the eCTD Specification, and v.2.6.1 of the STF (Study Tagging File) Specification. A new version Q&A/Change Request document would be circulated to the SC for endorsement following the meeting.

The SC also supported the M2 proposal that the M2 recommendations for media (floppy disk, DVD-RAM and CD-R) be removed, agreeing that acceptable formats should be defined on a regional basis.

Pharmacopoeial Discussion Group: On behalf of the Pharmacopoeial Discussion Group (PDG), the USP (US 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. Minor revisions for General Chapters were signed-off on *Tests for Specified Micro-Organisms* and *Microbial Enumeration Tests*. The sign-off of one of the two remaining General Chapters, *Bacterial Endotoxins*, is expected at the Brussels meeting in November 2008. The second remaining General Chapter on *Colour* is expected to be signed-off at a later stage.

It was noted that the three Pharmacopoeias had all taken emergency measures to react to the heparin safety crisis, and that the revisions undertaken by the three Pharmacopoeias on the heparin monographs were following the same general direction. At the Strasbourg Heparin Workshop in June 2008, experiences by official control laboratories and industries would be discussed, potentially leading to the identification of alternative and more adequate analytical test methods. The three Pharmacopoeias would work collaboratively to improve the respective heparin monographs.

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 Portland. *Step 4* was reached for both Annex 2 on *Extractable Volume* and Q4B Annex 3 on *Test for Particulate Contamination: Sub-visible Particles*. *Step 2* was reached for Annex 4A on *Microbial Enumeration Tests*, Annex 4B on *Tests for Specified Micro-organisms*, Annex 4C on *Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use*, and Annex 5 on *Disintegration Test*.

Good progress was also made on the draft *Step 2* document for Annex 6 on *Uniformity of Dosage Units*, and Annex 7 on *Dissolution Test* which are expected to be ready for *Step 2* sign-off by November 2008, while Annex 8 on *Sterility* continues to be worked on. The two remaining General Chapters in the Q4B work programmed are still at an early stage in the PDG process.

The SC considered a proposed expansion of the scope of Q4B to topics beyond Q6A. Based on industry survey results, the following General Chapters for PDG harmonization were identified: (1) Chromatography, (2) Heavy Metals, (3) pH, (4) Spectrophotometry, (5) Water Determination, (6) X-ray Powder Diffraction, (7) Analytical Sieving, and (8) Bulk Density and Tapped Density. It was noted that Chapters 2, 6, 7 and 8 were already under development by the PDG. The SC agreed to defer a decision on whether to expand the scope until the Brussels meeting.

Q10: Pharmaceutical Quality System: In Portland, the Q10 EWG worked to address the comments received from public regulatory consultation and to finalize the Q10 Guideline. The final Q10 Guideline was endorsed by the SC as final under *Step 4* of the ICH process.

Q11: Development and Manufacture of Drug Substances: The Q11 Rapporteur provided an update on the activities of the Q11 EWG following their first meeting in Portland. The SC endorsed the work plan developed by the EWG and the time frame for reaching *Step 2*. The SC also supported the recommendation of the Q11 EWG that given the nature of the guidance to be developed an invitation be sent to the drug regulatory authorities of India and China inviting them to nominate a technical expert to participate in the EWG.

Quality IWG: The Rapporteur informed the SC of the outcome of the Quality Implementation Working Group (IWG) meeting in Portland, including work on the establishment of working procedures for the Quality IWG and the drafting of responses to initial questions raised in relation to Q8, Q9 and Q10.

The IWG identified the following topics for implementation: general strategic aspects, technical aspects, regulatory aspects and training issues. Areas identified for discussion included: (1) design space, control strategy and real time release, and criticality; (2) PQS (Pharmaceutical Quality System) and Inspections in a Q8, Q9, Q10 environment; and (3) knowledge management. Each topic area was assigned to a sub-group.

Each group will cover both regulatory and technical aspects related to their topic. The sub-groups will consider the options for each item including short-term versus long-term effort, work/efforts already existing or in progress in their regions, and the desired approach (Q&A, workshop, training, white papers etc...).

In Brussels in November 2008 the IWG will work to progress a short-term implementation Q&A document.

S2(R1): Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use: The S2(R1) Rapporteur reported on the meeting of the S2(R1) EWG in Portland, and on the progress made towards reaching *Step 4*. In Portland, the Group addressed comments received from public consultation. The SC noted the need to gain more experience with practical aspects of integrated studies, especially *in vivo* Comet assay.

The *Step 4* guideline will include a paragraph developed by the S2(R1) EWG on the impact of the S2A/S2B revision for the 3Rs (Reduce/Refine/Replace animal testing) agenda. The benefits will include: concurrent positive controls in every *in vivo* assay no longer being required, the integration of genotoxicity into toxicology assays, and a reduction in “non-relevant” *in vitro* results which will reduce the number of follow-up *in vivo* assays.

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 Portland towards reaching *Step 2* of the ICH process. In Portland, the M3(R2) EWG reached consensus on topics related to exploratory clinical studies and the reproductive toxicity section. The SC noted that the M3(R2) EWG would seek the input of the S2(R1) EWG to ensure that the M3(R2) strategy will have a positive impact for the 3Rs (Reduce/Refine/Replace animal testing) in the context of genotoxicity testing. The SC noted

that the new strategy should produce a major reduction in the use of both rodent and non-rodent animals.

The Rapporteur informed the SC that the EWG expected to reach *Step 2* shortly after the Portland meeting.

S9: Oncology Therapeutics: The Rapporteur reported to the SC on the meeting of the S9 EWG in Portland and the timeframe for reaching *Step 2*. The SC noted that the timeframe for reaching *Step 2* depended on the progress made by the EWG.

E2F: Development Safety Update Report: The Rapporteur reported on the meeting of the E2F EWG in Portland and the finalisation of the E2F *Step 2* document. The SC endorsed the E2F *Step 2* document.

Also in Portland, the EWG discussed and agreed a way forward with regard to finalizing the DSUR examples and publishing them as separate documents. In Yokohama, in October 2007, the SC had agreed that the DSUR examples would not be attached as an appendix to the Core E2F Guideline.

E14: The Clinical Evaluation of QT/QTc Interval Prolongation and ProArrhythmic Potential for Non-Antiarrhythmic Drugs Q&A document: In Portland, the E14 Rapporteur reported to the SC on the progress made by the E14 IWG at its meeting. The E14 EWG finalised the E14 Q&A document which includes seven questions and answers covering assay sensitivity, ECG reader, outlier categorization of male versus female, ECG reading methods, metrics in Thorough-QT study, baseline assessment, and blinding positive control.

The SC endorsed the E14 Q&A document under *Step 4* of the ICH process. The SC agreed that given the rapid scientific progress in the field, the E14 IWG should have yearly teleconferences to consider whether there any outstanding questions that need to be addressed.

E16: Pharmac Genomic (PG) Biomarker Qualification: Format and Data Standards: The Rapporteur reported on the outcome of the first E16 EWG meeting held in Portland. The guideline will define the context, structure and format of the submission. The EWG proposed to modify the title of the E16 to: *Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions*.

The SC noted that the aim of the E16 EWG was to reach *Step 2* in 2009 and *Step 4* in 2010.

Gene Therapy Discussion Group (GTDG): The Co-Rapporteurs reported on the outcome of the GTDG meeting held in Portland. It was noted that the group was planning to finalize the draft ICH Considerations for Oncolytic Viruses at the November 2008 meeting in Brussels, for completion in conjunction with the ICH Considerations for Viral/Vector Shedding document by the end of 2009.

M1 PtC WG: MedDRA Points to Consider Working Group: The Co-Rapporteurs reported to the SC on the outcome of the M1 PtC WG meeting in Portland. The SC noted that the two main roles of the M1 PtC WG related to the maintenance of the two PtC documents (Term Selection PtC document and Data Retrieval & Presentation PtC document) with the release of each MedDRA version, and responding to comments/questions from MedDRA Users and the MedDRA MSSO.

The SC noted that a new remit from the Yokohama meeting in October 2007 was the expansion of the guidance on the use of SMQs within the Data Retrieval and Presentation document. The work would be carried out by the M1 PtC WG with input from the CIOMS WG on SMQs.

In Portland, the M1 PtC WG developed the first draft of the guidance on the use of SMQs. Comments would be sought from the user community on the draft, with the aim being to finalize this document at the next meeting in Brussels in November 2008.

