**GLOBAL HARMONISATION TASK FORCE**

**STUDY GROUP 5 – CLINICAL EVIDENCE**

**Minutes of Meeting Monday 9 May and Tuesday 10 May 2005**

**Department of Health Offices, Whitehall, LONDON, UNITED KINGDOM**

The second meeting of the Global Harmonisation Task Force (GHTF) Study Group 5 was held at the Department of Health headquarters in Whitehall, London on 9 and 10 May 2005.

Apologies were received from Patricia Garvey who was unable to attend due to company business. She was replaced as the AdvaMed representative for this meeting by Barbara Westrum. Other attendees at the meeting were:

Graeme Harris, Therapeutic Goods Administration, AUSTRALIA (Chair)
Johan Brinch, MIAA, AUSTRALIA
Masaaki Tsukano, Ministry of Health, Labour and Welfare, JAPAN
Kazuhiro Sase, National Cardiovascular Centre, JAPAN
Yoshihiro Noda, JFMDA, JAPAN
Susanne Ludgate, Medicines and Healthcare products Regulatory Agency, UK
Wolfgang Ecker, Federal Ministry of Health and Women, AUSTRIA
Maria Teresa de Martin,
AEMPS Ministry of Health and Consumer Affairs, SPAIN (Monday 9 May)
Peter Rattke, COCIR, AUSTRIA
Klaus-Dieter Willamowski, EDMA, GERMANY
Christophe Bailleul, EUCOMED, BELGIUM/FRANCE (Monday 9 May)
Eric Mann, Food and Drug Administration, USA
Kimber Richter, Food and Drug Administration, USA
Mitchell Krucoff, Duke University Medical Centre, USA
Mary Anne Hinkson, NEMA, USA
Keith Butler, Health Canada, CANADA
Greg LeBlanc, MEDEC, CANADA

## Item 1 Welcome and introductions

The Chair welcomed members to the second meeting of Study Group 5.

The Chair noted that Celia Witten had transferred to FDA's Center for Biologics Evaluation and Research to take up the position of Director of the Office of Cell, Gene and Tissue Therapy and will no longer be participating on SG5. The Chair thanked Dr Witten for her contribution to the group and welcomed her replacement Dr Eric Mann, who works in CDRH's Division of Ophthalmic and ENT Devices.

The Chair also welcomed Barbara Westrum as the AdvaMed representative for this meeting.

Members of the group were invited to introduce themselves for the benefit of new attendees.

**Item 2 Adoption of agenda**

There were no changes to the draft agenda circulated by the Chair on 5 April 2005. The following agenda was adopted.

1. Welcome, introductions and housekeeping information

2. Adoption of agenda

3. Minutes from previous meeting

4. Review of outcomes from Meeting 1

5. Harmonisation of definitions
   - report from subgroup review of jurisdictional and existing GHTF documents
   - revision of SG5/N1R1

6. Guidance for clinical evaluation
   - consideration of SG5/N2R0

7. Standards relating to clinical investigation
   - report from Chair on meeting with ISO TC 194 WG4
   - consideration of draft MoU between GHTF and ISO TC 194

8. Other business

9. Next meeting

**Item 3 Minutes of previous meeting**

Minutes from the January 2005 meeting were included in the agenda papers and incorporated all comments received on the draft Minutes that were circulated on 21 January 2005.

Minutes were sent to the GHTF Secretariat for posting on the GHTF website on 9 February 2005.

**Item 4 Review of outcomes from previous meeting**

For the benefit of new attendees, the Chair provided a brief summary of the main outcomes from the January 2005 meeting through reference to the action list developed by the group. It was noted that each action item would be covered by agenda items 5 through 7.

**Item 5 Harmonisation of definitions**

Members from each of the sub-groups formed at the January 2005 meeting were asked to provide a brief presentation on the findings of their review of definitions in GHTF, jurisdictional and ISO/ICH documents. Members were asked to focus on 4 key areas:

- whether any existing definitions for clinical data, clinical investigation, clinical evaluation and clinical evidence were identified either in documents of other GHTF study groups or jurisdictional legislation/guidelines and ISO/ICH documents;
- where definitions existed, whether there were any conflicts in the definition or context in which the definitions would be applied that could impact adversely on the utility of those documents or the SG5 draft document;
- what action would be required to resolve any conflicts; and
- whether additional terms needed to be included in the SG5 harmonised definitions document.

Members noted that SG1 had two different definitions for clinical evaluation, as well as a reference to the concept of clinical evidence (but no formal definition) in their guidance documents. Members agreed it will be necessary to liaise with SG1 to resolve the differences between the SG1 and SG5 definitions. The conjoint meeting of study groups planned for September 2005 was seen to be the most appropriate avenue for liaison. The Chair indicated that he would raise this issue at the upcoming GHTF Steering Committee meeting. There were no other existing definitions or documents notified where there would be potential conflict over the definitions developed at the first meeting and it was agreed that the four definitions developed at the first meeting should be adopted for use in the harmonised guidance document.

During discussion of the draft clinical evaluation guidance, it was agreed that 3 additional harmonised definitions were required – 'clinical performance', 'investigation site' and 'monitor'. It was agreed that the definitions for 'institution' and 'monitor' from ISO 14155 should be used. The group noted that ISO 14155 also contained a definition of 'clinical performance' but members felt this could be improved. The following definition was proposed:

> "Clinical performance of a medical device is the ability of the device to achieve its intended use as claimed by the manufacturer."

The Chair noted the importance of using terminology consistent with that developed by ISO TC 194 WG4 in ISO Standard 14155, pending the revision of ISO 14155-1 & 2 (see item 7). Particular note was made of the interchangeable use of the terms 'clinical investigation plan' and 'protocol'.

Members discussed the concept model that was developed at the first meeting and refined subsequently by the Chair. During discussion it was agreed that the basic relationship between clinical investigation, clinical data, clinical evaluation and clinical evidence as developed at the first meeting was acceptable. However, it was felt that attempts to give clinical evidence context in relation to other technical documentation had made the model unnecessarily complex. It was agreed that the basic relationship model could be inserted into the global regulatory model developed by SG1 and this would be included in the guidance document.

**Item 6 Guidance on clinical evaluation**

Members reviewed the draft guidance document titled '*Evaluation of Clinical Data'*, prepared by Susanne Ludgate. There were suggested revisions to the content, text and

format. It was also agreed that the title be changed to '*Clinical Evaluation*'. SL agreed to make revisions ahead of the next meeting.

After considerable discussion about the role of literature reviews during both product development and in the preparation of clinical evidence as part of a submission for regulatory purposes, it was decided that the guidance document would focus solely on the use of clinical evaluation for regulatory submissions. Separate guidance would be developed about the use of literature searching and risk management to assess whether clinical investigation as opposed to other forms of clinical data would be required during product development.

**Item 7 Standards relating to clinical evaluation**

The members received copies of correspondence between the Chair and the Convenor of ISO/TC 194 WG4. The Chair reported that his presentation to WG4 was well received and that in-principle agreement had been reached to proceed with an MoU. The Chair also reported that WG4 resolved to have a revised standard for clinical investigation in which both parts (1 & 2) are merged and harmonised as much as possible with ICH GCP principles, while respecting differences in national requirements and policies.

Members considered and agreed to a draft MoU that will be submitted by the Chair to the GHTF SC meeting in Seville on 17-20 May 2005. It was noted that the MoU draws heavily from the existing MoU with ISO/TC 210 and is aimed at a high level to allow other ISO/TC 194 working groups and GHTF study groups to interact in the area of biological evaluation.

The Chair also reported that WG4 had referred several matters to SG5 for advice and asked the members who are also members of WG4 to explain the requests. Kimber Richter reported that members of WG4 had formed 5 taskforces to carry the review and amendment of discrete sections of the standard, with the expectation that the outcomes of that first phase of review would be discussed at the next meeting of WG4 in June 2005. It was anticipated that the revision of ISO 14155 (including any editing, consultation and voting rounds) was expected to take about 2 years in total.

Members noted the issues referred by ISO TC 194 WG4, namely;

- SG5 was asked to clarify requirements for the content of clinical investigation reports, including guidance on how to report details of design, methodology and deviations from the clinical investigation plan, and types of safety data required so that the data should be acceptable to authorities worldwide for pre-market review purposes;
- SG5 was asked to consider and clarify who should review and sign a clinical investigation report;
- SG5 was asked specifically for advice on whether information about the content of clinical investigation reports, which currently appears as an informative item in ISO 14155, should be a normative reference; and
- In noting the scope of activities of SG5, WG4 asked that SG5 notified it of any guidance developed by SG5 in relation to literature searching and, in particular, of any changes in the language used.

Members agreed:

- that the content of the final study report will be driven largely by the clinical investigation plan/protocol for which guidance would come from WG4. SG5 will

focus on regulatory aspects of what should be in the report. Therefore SG5 will review and provide advice on who would agree and sign an investigation report.

- with respect to guidance on literature searching, SG5 will develop advice on how to conduct and report literature reviews. Members were of the view that WG4 and SG5 should work to have a single document that addresses how to conduct and document the literature review process and this would most appropriately come from SG5. However members also noted that a literature review is a critical component in determining whether a clinical investigation is required during product development. Therefore it was essential that the revised ISO Standard 14155 refer to and be consistent with guidance developed by SG5.
- that WG4 should be asked to note that SG5 has developed a definition of clinical performance that differs slightly from that currently in ISO 14155, and that WG4 consider adopting the SG5 definition in the revised standard (see item 5).

The Chair indicated that he will be sending a copy of the Minutes of each SG5 meeting to the Convenor of WG 4 as a matter of routine to assist the interaction of the two groups.

**Item 8 Other business**

Members agreed to a statement that would be used by the Chair if approached by the media.

Members noted correspondence from EUROM VI TC Medical Technology Technical Committee. It was noted that Peter Rattke is a member of that group and he was asked to be a liaison point between the two groups.

**Item 9 Next meetings**

- Gaithersburg 14 - 15 September 2005, including meeting with GHTF SG1 on afternoon of 15 September
- Sydney 16 - 17 January 2006