

## GLOBAL HARMONISATION TASK FORCE

### STUDY GROUP 5 – CLINICAL EVIDENCE

Minutes of Meeting Monday 17 January and Tuesday 18 January 2005

TGA, Symonston, CANBERRA, AUSTRALIA

The inaugural meeting of the Global Harmonisation Task Force (GHTF) Study Group 5 was held at the Therapeutic Goods Administration in Canberra, Australia on 17 and 18 January 2005.

#### Present

**SG5 members** 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  
Peter Rattke, COCIR, AUSTRIA  
Klaus-Dieter Willamowski, EDMA, GERMANY  
Christophe Bailleul, EUCOMED, BELGIUM/FRANCE  
Celia Witten, Food and Drug Administration, USA  
Kimber Richter, Food and Drug Administration, USA  
Mitchell Krucoff, Duke University Medical Centre, USA  
Patricia Garvey, AdvaMed, USA  
Mary Anne Hinkson, NEMA, USA  
Keith Butler, Health Canada, CANADA  
Greg LeBlanc, MEDEC, CANADA

**GHTF Steering Committee members** Rita Maclachlan, Therapeutic Goods Administration, AUSTRALIA  
Michael Gropp, Guidant Corporation, EUROPE

#### Item 1 Welcome and introductions

The chair welcomed members and the GHTF Steering Committee invitees to the first meeting of Study Group 5. Members were invited to introduce themselves and describe their areas of expertise relating to SG5's activities.

The chair noted that for many members this meeting would be their first involvement in a GHTF activity. He outlined how the first meeting was principally aimed at members gaining an understanding of the framework within which they would be providing expertise, the reasons for the existence of the group, its terms of reference and planning the way forward.

The Chair pointed to the role the presentations from Rita Maclachlan and Michael Gropp would play in achieving these goals and invited the Steering Committee members to participate freely in the discussions and provide guidance to the group as it worked to establish its *modus operandi* during the meeting.

## **Item2 Adoption of agenda**

Members were thanked for their comments on the draft agenda, circulated late last year. The Chair noted the only change to the draft agenda was a re-ordering of items.

The Chair explained he had prepared a statement for use in response to any inquiries from the print media, such as Clinica, following completion of the meeting. It was his view that members should approve the statement. Members agreed to this approach and the item was included under 'other business'. Members were also advised that approaches by the press or other organisations for comments on matters relating to SG5 activities should be referred to the Chair for a response.

The following agenda was adopted.

1. Welcome, introductions and housekeeping information
2. Adoption of agenda
3. Overview of the goals, objectives, activities and operation of Global Harmonisation Task Force (GHTF)
4. Report from the GHTF ad-hoc Working Group on Clinical Evidence
5. Consideration of the ToRs
6. Project planning
  - Scoping the required work, work flow and outputs
  - Mapping the way forward
7. Overview of experiences of the group with clinical evidence issues
  - Presentation on the activities of the EU Clinical Evaluation Task Force
  - Open discussion - members from other jurisdictions
8. ToR 1 - Consideration of a draft document of harmonised definitions
9. Other business
10. Next meeting

### **Item 3 Overview of GHTF Operations**

Rita Maclachlan, Director of the Office of Devices, Blood and Tissues at the TGA and a member of the GHTF Steering Committee presented an overview of the goals, objectives, activities and operations of the GHTF.

There was general discussion around the operation of GHTF and the implementation of the work products of study groups in jurisdictions. In this regard it was noted that while the overall goal is to have convergence or harmonisation, it is important to recognise there are differing political, legislative and social environments that ultimately determine the degree of implementation within each region.

### **Item 4 Report from the GHTF ad-hoc Working Group on Clinical Evidence**

The group received the report of the ad hoc working group on clinical evidence prepared for the GHTF Steering Committee.

Michael Gropp gave a comprehensive presentation on the global regulatory model developed by GHTF and on the work of the GHTF ad-hoc Working Group. Particular emphasis was placed on where SG5 sits within the model and its relationship with the activities of other GHTF study groups.

### **Item 5 Consideration of the Terms of Reference**

Members discussed the terms of reference (ToRs) issued by the GHTF Steering Committee, viz:

- “- Harmonised definitions of terms;
- Review of existing GHTF documents on classification, conformity assessment procedures and risk management, and applicable ISO/ICH documents, for relevant principles/considerations and to ensure that terminology is consistent and interfaces are clear;
- Harmonised guidance on how to conduct and document the clinical evaluation;
- Harmonised content and format for clinical investigation reports (summary presentation of clinical evidence should be done in coordination with GHTF SG1, e.g., STED).

Following consideration by the SC of substantial progress of the work in the first phase, in a second phase, the Study Group will work on:

- Harmonised principles to determine when a clinical investigation, as opposed to other forms of clinical evidence, is necessary.”

Members noted that, although the ad-hoc working group had identified ‘clinical investigation’, ‘clinical data’, ‘clinical evaluation’ and ‘clinical evidence’ as terms that should be harmonised, there would almost certainly be other terms identified as requiring harmonisation during the course of the group’s work.

The group also noted:

- ToRs 1 and 2 were interdependent and needed to proceed in parallel – consideration would need to be given to how the work products (especially harmonised definitions) of SG5 could impact on the guidances issued by other study groups;
- ToR 5 is closely linked with and, in many respects, an extension of the work required for ToR 3. It was agreed that guidance about when a clinical investigation is required as opposed to other forms of clinical evidence could be incorporated within clinical evaluation guidelines;
- guidance issued in relation to ToR 3 will need to cover the relationship with quality management systems and risk management procedures (intersection with activities of SG1 and SG3); and
- harmonised guidance on how to conduct and document a clinical investigation is covered within ISO Standard 14155 and therefore probably does not need further guidance (see further discussion under item 6).

Members also asked the Chair to seek clarification of ToR 4 with regard to whether it is about individual clinical investigations or a summary of all clinical investigations, or both.

## **Item 6 Project planning**

Following on from discussion of the ToRs, the members identified three broad work areas that should be addressed in the first phase:

- Harmonisation of definitions;
- How to conduct and compile a clinical evaluation; and
- Review of standards relating to clinical investigation.

### *Harmonisation of definitions*

It was agreed that, in addition to starting to review the draft document provided by the Chair at this meeting, the group should conduct a more detailed review of existing documents with a view to identifying definitions relevant to the work of SG5.

The Chair noted that, although some definitions had been identified during the process of drafting the guidance document for consideration at this meeting, there had not been a comprehensive review of all sites. In particular, national legislation and internal regulatory agency guidance documents relevant to the review were not easily accessed externally. The members agreed to form subgroups, along country/region lines, to each review jurisdictional documents as well as the guidance documents produced by other GHTF study groups as follows:

Australian delegation – Australian documents and SG1

Japanese delegation – Japanese documents and SG3

European delegation – European documents and SG2 (Klaus Willamowski to look at IVD Performance Evaluation Standards)

Canadian delegation – Canadian documents and SG4

USA delegation – USA documents, ISO and ICH

Members were tasked with:

- Identifying any documents and definitions relevant to the activities of SG5; and

- Considering the impact of new or amended definitions in the interpretation and utilisation of those existing documents.

### ***Clinical evaluation***

Susanne Ludgate volunteered to draft a document on how to conduct a clinical evaluation and compile an evaluation report. The group identified EU and Australian documents that could assist in this process. In addition, the subgroups were asked to consider any definitions found in their review of jurisdictional documents in the context of clinical evaluation and to identify any other documents or information of relevance to, or that could assist in, the development of clinical evaluation guidelines.

### ***Standards relating to clinical investigation***

It was noted that the Chair and several members of the group would be attending the Berlin meeting of ISO TC 194 WG4 at which the possible revision of ISO 14155-1 and 14155-2 will be discussed. The Chair indicated he had been invited to discuss the possibility of an MoU between the SG5 and ISO TC 194 WG4.

The group was informed that an MoU exists between GHTF SG3 and ISO TC 210 - it was agreed the Chair would obtain a copy of the MoU and contact Kim Troutman (Chair of SG3) to obtain more information with a view to establishing key principles/issues that would need to be covered by any MoU between SG5 and ISO TC 194 WG4.

The general consensus within the group was that ISO TC 194 WG4 was the appropriate avenue through which amendments to the Standard for clinical investigation of medical devices should occur. However, it was felt that SG5 would be an important contributor to this process, for example, in considering issues relating to the interaction of ISO 14155 and regulatory requirements.

At the close of this discussion, an overall action list (below) was compiled.

### **Item 7      Overview of experiences with clinical evidence issues**

Susanne Ludgate gave a presentation on the problems associated with the interpretation and implementation of the Medical Device Directives in Europe and how the EU Clinical Evaluation Task Force was seeking to address these problems through the development of guidance documents. Areas covered by the documents include evaluation of clinical data, post market clinical follow up, adverse incident reporting, a checklist for clinical investigations and notification of investigations for competent authorities. The discussion was supplemented by the presentation of the CETF's three layer model of clinical evaluation by Wolfgang Ecker.

The Chair invited the regulatory and industry members from each jurisdiction in turn to outline concerns and issues of importance with regard to clinical evaluation and the compilation of clinical evidence.

<b>Item no.</b>	<b>Date</b>	<b>Subject/Details</b>	<b>Date Due</b>
<b>Definitions/Concepts</b>			
1	17/1/2005	Review draft document from Chair	Mtg 1 & Ongoing
2	17/1/2005	Review relevant existing documents	
2.1	17/1/2005	Appoint sub-groups and review documents	Done Mtg 1
2.2	17/1/2005	Sub-groups to complete review and submit to chair	Mid March
2.3	17/1/2005	Chair to collate comments and distribute for meeting 2	Mid April
2.4	17/1/2005	Consider review outputs and further amend draft document	Mtg 2, May 12-13
3	17/1/2005	Circulate draft to SG chairs, seek input	
4	17/1/2005	Draft to Steering Committee with SG5 timeline/update for information only	May SC Mtg
6	17/1/2005	Conduct consultation	Complete by end of August
7	17/1/2005	Final document to Steering Committee	November
<b>How to conduct a clinical evaluation and compile a report</b>			
8	17/1/2005	Circulate existing Australian and EU documents to members	End January
9	17/1/2005	Identify additional relevant documents, references for clinical evaluations. Conduct as part of follow up of jurisdictional documents (see item 2.2 above)	Mid March
10	17/1/2005	Draft document to be prepared (SL)	Mid April
10.1	17/1/2005	Chair to forward documents, comments identified in item 9 to SL	Mid March
11	17/1/2005	Draft document for presentation and discussion.	May & Sept Mtgs
<b>Clinical investigation Standards</b>			
13	17/1/2005	Look at MOU between ISO TC210 and SG3 (Chair)	Before ISO Mtg (Feb 21-22)
14	17/1/2005	Chair to attend TC194 WB4 meeting (other SG5 members also)	February 21, 22
15	17/1/2005	Chair, SL, KR, CW and WE to work on key points for possible MOU with ISO TC194 ahead of May mtg	Mid April
16	17/1/2005	Proposal to be developed for Steering Committee	SG5 May Mtg
17	17/1/2005	MOU proposal to Steering Committee	SC May Mtg

#### **Item 8 Consideration of draft document of harmonised definitions**

Members reviewed the draft guidance document titled “*Clinical Evidence – Key Definitions, Concepts and Principles*”, prepared by the Chair. Revisions were made to the text. It was

agreed that the document would not include a section on principles as these would be covered in the individual guidance documents.

#### **Item 9 Other business**

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

Members discussed the Japan-US “Harmonisation By Doing” project for cardiovascular stents. Interest was expressed in extending the collaboration to include a subgroup of CETF. It was agreed that individual jurisdictions would pursue this matter at this stage but a proposal to develop an initiative across all GHTF jurisdictions could be developed for consideration by the GHTF Steering Committee at a later stage when more experience had been gained.

Members also discussed issues around the sharing of clinical investigation information globally, particularly through the use of clinical trial registers. Difficulties were highlighted with respect to jurisdictional differences in privacy and commercial-in-confidence legislation.

#### **Item 10 Next meetings**

- London 12-13 May 2005. Venue TBA
- Gaithersburg 13-16 September 2005