One of the results of the 2007 EMA Conference on clinical trials was the need to harmonise multinational CTs in Europe in order to ensure the protection of participants and the scientific value of clinical trials, by harmonising NCAs’ processes and practices relating to MN-CTs (about 25% of CTs in EU).

In that context, the EU Heads of Medicines Agencies (HMAs) established the Clinical Trial Facilitation Group composed by clinical trials professionals from National Competent Authorities (NCAs) to agree common principles and processes and to improve harmonisation of the CTs assessment decisions. The HMAs agreed that this should become a priority for the CTFG.

This document presents the CTFG activities during its 2008-2009 mandate.

A - Harmonisation of CTA assessment and the Voluntary Harmonisation Procedure

In order to organise NCAs cooperation on CTA assessment, CTFG has first developed and expanded scientific CT assessors networks and data exchanges by:
- sharing information through the European information systems, (a CTFG mail box, automatic electronic alerts on refusals of CTs, withdrawals, grounds for non acceptance issued by other MS and Eudravigilance data warehouse reports)
- promoting regular exchanges of information via email and teleconferences
- building common assessment criteria in CTFG meetings dedicated to specific issues:
  o meetings on non-clinical issues : Afssaps-France (15 February 2008), Italy (10 June 2008)
  o meeting on pharmaceutical issues : MPA-Sweden (19 September 2008)
  o meeting on exploratory trials : Afmps-Belgium (October 2008 and October 2009)
  o meeting on gene-cell therapies: Afssaps – France (March 2009).

The organisation of the coordinated assessment of multinational CTA applications through the Voluntary Harmonisation Procedure (VHP) was the 2nd step forward harmonisation and one major objective of the CTFG work plan for 2008-2009. Within the current legal framework, the VHP gives concrete answers to the stakeholders’ requirements for a one-stop-shop for applications to NCAs, a solely electronic repository, one single CTA dossier in English, a simultaneous and coordinated assessment, a unified position by NCAs concerned and appropriate timelines.

The guidance document for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications was published on the HMA web site in January 2009 and a pilot has started in March 2009. It defines the clinical trials which are considered suitable for the VHP, the documentation which has to be submitted and the procedural steps/ timelines and responsibilities during a VHP. VHPs are coordinated by a VHP coordinator (VHP-C), who organises the distribution of the Clinical Trial Application documents, ensuring the
adherence to timelines and facilitates the assessment work of the NCAs. During the pilot phase the Paul-Ehrlich Institute serves as the VHP-Coordinator.

Results of the Voluntary Harmonisation Procedure

The VHP and its results have been presented at several international and national meetings. Most of the 27 Member States took part in the VHP. Only Poland and The Netherlands regularly refused to join the VHP process. In Italy only Phase I clinical trials were accepted by the NCA. In December 2009 The Netherlands agreed to join the VHP for future trials.

During the reporting period of 11 months, 25 VHPs were performed. Of these 25 applications, 14 standard VHP and 11 accelerated VHP (Pandemic Influenza Vaccines) were processed. Accelerated VHP were performed at the request of the EMA to harmonise the approval of clinical trials of pandemic Influenza Vaccines. These VHP were processed in a total of 30 days with rolling submissions/assessments of the documentation and only 1-2 Member States per VHP. The experience of the Member States was that the VHP is not suitable for clinical trial with rolling submissions/assessments of the documentation and very few Member States per VHP. As a result the Clinical Trials Facilitation Group introduced a minimal involvement of 3 Member States per VHP.

Of the 25 VHPs 22 finished positively, 1 negative as one applicant did not address the GNA within the 10 day limit), 2 applications were withdrawn before the clinical trial dossier were submitted and without giving reasons.

Of the 25 VHPs 11 could be used for the calculation of timelines for standard VHPs.

The 2009 experience of the VHP indicates that a harmonised assessment with up to 18 Member States is possible within 60 days (mean 52.4 days; [29-68 days] if the VHP is used.

In the last year the VHP has been modified several times to simplify the process for applicants, proving that a new process without new laws and within the existing legal frameworks is possible, to the benefit of both applicants and NCAs.

The VHP process was updated several times during 2009, on request of the applicants as well as the NCAs in order to streamline it. This led to a reduction of almost 4 weeks in the duration of the VHP, the enlargement of the pilot’s scope, the consolidation of the lists of grounds for non-acceptance by a leading NCA as well as the introduction of substantial amendments within the Voluntary Harmonisation Procedure. All these changes were approved at the HMA meeting in November 2009 and will be proposed in the new version of the VHP in 2010.

The pilot phase of the Voluntary Harmonisation Procedure is to continue during 2010.

B – Harmonisation and simplification of CTA and SA substantial amendments

The CTFC set up a subgroup focusing on harmonisation/simplification of the Clinical Trials Authorisation applications (CTA) requirements and the notification/request for authorization of Substantial Amendments (SA).
1. CTA
- A comprehensive table, listing of all specific national requirements for a CTA was produced. This work contributed to the elaboration of a single CTA dossier by the Commission. A single set of information/documentation requirements for CTA submission to NCA’s was agreed by CTFG as NCA-CTA core documents and is being used for the VHP.
- A guideline on the content of the NIMP dossier has been established, put on public consultation on each NCA’s website and forwarded to the Commission in order to include it in the new draft of the CTA guidance. It is now proposed to use it in the next version of the VHP.
- The possibility of harmonization of electronic CTA submissions was considered and a proposal for an electronic CTA submission standard format structure was drafted. A pre-CTA submission standard format structure was implemented for VHP package and is currently in use.

2. SA
- The subgroup developed a substantial amendments Q&A agreed on examples of SA. It was considered that the publication of those clarification documents would be endorsed by the Commission. Most of those examples should be included in the updated Commission's CTA guidance (publication pending).
- Substantial amendments have been added to the VHP features.
- It is important to note that the lack of harmonization regarding scope of assessments between NCAs and ECs rendered difficulties to the establishment of lists of SA. Survey tables were produced and circulated for identification of areas of divergence and improvement, which were discussed by the CTFG. A table “who assesses what in the member states?” has been published on HMA website.
- Algorithm on “is it a substantial amendment” has been proposed to be included in the EC CTA guidance.

C - Clinical Trial Safety Monitoring

The CTFG-CT safety subgroup continued, within the CT subgroup of EV-EWG (set up in 2009) to implement completely operational EV-CTM, worked on procedure for ASR work sharing and participated to the DSUR.

1. Electronic population of Eudravigilance Clinical Trial Module (EV-CTM)

The key areas of progress relating to population of the EV-CTM database and quality of the data are:

(a) CTFG has agreed a standardised approach to allow sponsors to enter SUSARs into EV-CTM and where required EMEA to forward copies to the MS database. Implementation will be taken forward when the required technical upgrades to EV are available.

(b) CTFG & EV-EWG have agreed a set of business rules that will send error messages to the reporter (i) when specific fields are not completed and (ii) when the format and content of specific fields are completed incorrectly. These business rules will be implemented June 2010.
CTFG & EV-EWG have agreed a number of detailed Q&As for scenarios related to reporting SUSARs not covered in the CT Directive or current guidance. The Commission published the first set in Q&As in Volume 10 of the Rules… in July 09. It is planned to regularly agree further Q&As on transmission of SUSAR reports to be published by the Commission.

2. Investigational Medicinal Products Dictionary

EMEA considered a number of options for the telematic approach to linking active substances of IMPs in the EudraCT and Eudravigilance databases. In consultation with CTFG and the EU Technical Controlled Terms implementation group, it decided to introduce into both databases a Controlled Term List (CTL) with all the known active substances in medicinal products. A procedure will be in place to obtain a ‘provisional new active substance’ term rapidly for new substances and to validate the new term. The provisional new active substances will be validated by the EV Medicinal Product Dictionary (EV-MPD) team and if valid added to the EV-MPD for use in the two databases. This will be taken forward in 2010.

3. Appropriate reports from Eudravigilance-Data Analysis System

CTFG members (a) agreed the content and format of standard database queries for SUSAR data; and (b) participated in User Testing of EV-DAS. They identified a number of important problems and omissions that were corrected before the system release. Standardised and custom queries can now be run by staff in the NCAs who have been trained.

4. ASR move to DSUR

CTFG has provided input to the draft ICH DSUR guideline during 2009 via a CTFG member of the ICH E2F Group. It is anticipated that the DSUR will be finalised and published in Q1 2010. CTFG proposals (a) for a 1-year implementation period and (b) to allow sponsors to submit the DSUR in place of the ASR during the transitional period have been accepted by the Commission.

5. ASR work sharing plan

CTFG agreed not to implement an ASR work sharing plan until the DSUR is finalised and published in the EU. The anticipated date for publication of the DSUR is Jan 2010 with an implementation date of Jan 2011. CTFG will establish a work sharing procedure starting during 2010.

C – Improvement of EudraCT

The CTFG contributed to the development of EudraCT and achieved:
- Technical improvements
- New functionalities for sponsors
- New functionalities for NCAs:
o Electronic alerts on CTAs (refusals by NCAs or ECs, withdrawals by sponsors...)

o Design of standard reports by the EudraCT data warehouse, allowing basic statistics and pre-defined queries

o Ability to attach documents

o Development of the EU-CT public registry (2010)

D - External communication and cooperation with other working group

Communication with stakeholders has been also taken on board. Stakeholders have been invited to CTFG meetings to discuss the ICREL report and the VHP experience. Several public lectures were given about CTFG’s activities (DIA, TOPRA, EFGCP, ACRO, EMEA meetings and European workshops...) and also documents and deliverables of the CTFG have been communicated through the HMA website.

CTFG has provided input to the development and implementation of future CT legislation and guidelines by the European Commission’s ad hoc experts group. CTFG made several surveys and recommendations to this group when appropriate; one CTFG representative was specifically dedicated to link with this group and several MS representatives are members of the 2 groups.

CTFG representatives have also been nominated to other European working groups (ie.: EudraCT TIG, JOG subgroup, EudraVigilance Expert Working Group; furthermore CTFG and CHMP work together whenever needed.