I. General considerations

CTFG met 13 times between January 2010 and December 2011 within plenary meetings; meetings were chaired by Chantal Bélorgey (Afssaps) and co-chaired by Hartmut Krafft (PEI) with the support of Kristof Bonnarens (FAGG) as the CTFG secretary and EMA who generally hosts the group. Two meetings were held in Brussels (FAGG) and in Rome (AIFA).

In order to support the CTFG activities, CTFG subgroups have continued or have been created. The use of Vitero has been extended and all plenary meetings are now attended by several NCAs through that system. Furthermore, teleconferences are extensively used between plenary sessions, particularly by the subgroups and also to manage VHP dossiers or urgent safety measures.

The CTFG has also set up collaborations with several working groups at EU Commission and EMA levels. Finally, CTFG has organised or participated in public meetings to inform stakeholders on its activities and proposals.

II. Priorities of the 2010-2011 work plan

CTFG priorities highlighted in the action plan for years 2010-2011 were the following:
- Active participation of all MS in work-sharing assessment procedures:
  o Contribution to a successful enlargement and improvement of the voluntary harmonisation procedure (VHP);
  o Implementation of work-sharing of clinical trials (CTs) safety information;
- Use of a risk based approach, to simplify processes and assessment of CTs.
- Extending work to assist the European Commission in the simplification of the EU legislation and active interaction with other European working groups and active participation in EU working groups.
- Improved transparency and communication to stakeholders to assist them in conducting CTs in EU.
- Agreement on methods to allocate / utilise resources effectively and development of the use of Vitero to improve networking and enhance expert's participation.
- Improvement of information systems to facilitate work-sharing and simplify processes.

Those priorities have been taken into account in the activities of CTFG during the concerned period.

III. CTFG activities 2010-2011

3.1. CTA assessment – the VHP

3.1.1 Process

Early in 2010, the CTFG has implemented a VHP version 2 with enlarged scope and inclusion of substantial amendments and non investigational medicinal product (NIMP) dossier, has developed the concept of the leading Member state (LMS) and has worked on developing an internal flexible consensus process of assessment in order to have all National competent authorities (NCAs) on board and with the objective to apply VHP to all multinational clinical trials (MN CTs).
After HMA endorsement, the internal procedure has been reviewed in September 2011 to introduce reference NCA, with the possibility to introduce a co-reference NCA, depending on the nature of the investigational medicinal product (IMP) or clinical trial design, and updated the assessment report template including list of grounds for non acceptance (GNAs). The other participating NCAs receive the preliminary assessment report and can decide on this basis whether they agree or whether they have additional GNAs. With this, a more stringent list of GNAs and a more efficient use of resources is aimed. The second alteration of the new VHP process is the possibility to have a second round of VHP to add additional MS in an already approved VHP.

3.1.2: VHP metrics
Starting in March 2009, the VHP received increasing acceptance. From March 2009 until 17th November 2011, 97 applications were received in total, comprising 86 standard VHP and 11 accelerated VHP due to the pandemic influenza vaccines.

83% of VHP applicants are commercial and 17% are non-commercial applicants. 55 different sponsors applied for VHP. Sponsors came from the USA (31), Germany (12), France (11), the United Kingdom (11), Belgium (10) and Switzerland (10), but also from Austria, Italy, Sweden, Denmark and the Netherlands.

The nature of the IMPs is nearly equally distributed, 50% of them have been of chemical origin and 50% are biological. 86% of IMP are non authorised products. Also, VHP application concerned every phase of a clinical trial: 4 first-in-human trials, 4 applications related to phase I, 37 to phase II, 48 to phase III and 3 to phase IV trials.

The average number of MS selected for a VHP and participating in the assessment is 6 MS, ranging from 2 to 14 MS per application. 22 MS have been chosen by sponsors to join the VHP. Within this number, Germany, France and Spain have participated in at least every second application. Only few countries have not been selected up to now by sponsors for a VHP, i.e. Malta, Cyprus, Luxemburg, Slovenia and Liechtenstein. Poland so far cannot participate, due to lack of a legal basis.

The implementation of the leading MS, in order to consolidate the list of questions of all the participated MS and to avoid redundancy of questions resulted in an average reduction of initial questions to around 50% before they were sent out to the applicant.

Out of the 86 standard applications, 74 have been completed with a positive outcome, 4 were negative, because GNAs had not been answered, 4 applications have been withdrawn by applicants; for 4 applications single participating MS required additional changes in documents to be able to approve the national application. 10 applications are still in the assessment process.

Mean times for a VHP decision from start VHP until the end was 50.4 days.

Following also the application of VHP version 2, a total of 25 substantial amendments were reviewed within 20.3 days.

3.2. Coordination of CT Safety information assessment

The sponsor is responsible for continuous monitoring of safety in CTs and NCAs’ responsibility is supervision of safety of clinical trial participants. The major sources for safety signal detection in clinical trials are suspected unexpected serious adverse reactions (SUSARs) and Development Safety Update Reports (DSURs).

CTFG’s goal is a functional environment which ensures proper reporting, work sharing processes and harmonized common interpretation, assessment and actions with regard to safety in CT in the EU/EEA, all supported by adequate IT tools.
CTFG has set up a new CT safety subgroup chaired by Elke Stahl (Bfarm), composed by Chantal Bélorgey (AFSSAPS), Karin Hedenmalm (MPA), Mariantonia Serrano (AEMPS) and Martyn Ward (MHRA), and including CT safety assessors. Its objectives are:
- to improve the monitoring of CT safety by NCAs sharing work
- to improve harmonisation of SUSARs reporting by sponsors
- to participate in the improvement of Eudravigilance CT module (EV-CTM).

The CTFG safety subgroup work focussed on SUSAR reporting and database, annual safety Report (ASR)/DSUR assessment work sharing, support to regulatory legislation and guidance and communication with stakeholders.

3.2.1 Network of NCAs safety assessors

In 2010 the safety subgroup started to build a network of safety assessors. Goal is contact points for safety (SUSAR, ASR) related exchange of information and integration of all expertise in CTFG’s safety activities.

3.2.2 Suspected Unexpected Serious Adverse Reactions (SUSARs)

a) Development of an appropriate single EU database

CTFG supports the development of a single European Safety Database for clinical trials (namely Eudravigilance CT module/EV-CTM and data analysis system/ EV-DAS).

In order to ensure adequate functionality for CT’s safety assessors responsibilities, the primary needs regarding EV-CTM improvement were defined by the CTFG safety subgroup, agreed on by CTFG and submitted to the EMA and the Commission in June 2010. The Commission considered them for the CT3 review in June 2011.

The essential needs comprise:
- the subsequent forwarding of SUSARs to NCAs for new “MS relevant SUSARs” like at least in daily messages and alerts for certain specified types of SUSARs,
- the access of all data by NCAs including the post marketing data,
- the retrieve of information by standard set of queries and reports, which can also be customized and stored
- the quality of data in the database and
- the validation of the database functionality.

For proper assessment of information, it is essential to combine search criteria from ICH E2B fields which lead to information from EV-DAS (EV-CTM) and EV-MPD (like common MPD for EV database and EudraCT) and especially from EudraCT (like EudraCT number or member states concerned and so on).

CTFG’s proposal also covers enhanced functionalities, which will be necessary for further signal detection.

The project is now depending on EMA resources and decisions. Status is need of action points and timing (implementation plan) by EMA as well as workshops in cooperation with EMA in order to compile further specification of the EV-CTM in conjunction with EV-DAS, EV-MPD and EudraCT.

b) Actions in favour of EV CTM reporting by sponsors

CTFG and EV-EWG CTSG supported the facilitation of EV database training for small commercial or non commercial sponsors. On CTFG request, training is now offered by EMA/DIA at some NCA’s location, dedicated only to CTs, which reduces resources like costs for sponsors; this will start in autumn 2011. Further suggestions of e.g. web-based e-training and shorter seminar time also were proposed to EMA.
3.2.3. Development of NCAs cooperation and coordination of decisions where safety signals are detected

Several major safety concerns regarding multinational CTs have been worked together by NCAs concerned, and, where appropriate, with links with the CHMP, in different contexts; refusal or suspension of centralised MA due to not acceptable benefit/risk ratio, new safety clinical or non clinical data with potential impact on CT subjects safety. NCAs concerned reached common position in order to issue the same national decisions.

3.2.4. Annual Safety Report / Development Safety Update Report (ASR / DSUR) work sharing by NCAs.

According to the CTFG action plan, CTFG was supposed to:
- finalise the ASR work-sharing procedure;
- prioritise coordinated ASR assessment when the DSUR is released by ICH;
- set up a pilot work-sharing by starting with prioritised ASR;
- ensure a harmonised interpretation of the DSUR.

The concept of work sharing in assessment of annual safety reports was further elaborated by the subgroup towards implementation of a work sharing procedure first on ASR, then on the new DSUR format (ICH E2F) published end of 2010.

The internal procedure of ASR/DSUR worksharing comprises the:
- scope of the assessment
- roles and responsibilities of concerned parties
- time lines
- template for assessment report (AR) including letter to/from the sponsor
- validation of DSUR content
- procedure for selecting investigational medical product / active pharmaceutical ingredients (IMP / API) and NCAs to do the assessment.

CTFG’s agreed scope of the assessment is an update of the safety profile of the IMP, of the benefit risk evaluation to participants of CTs and of actions which were taken or need to be taken to mitigate any potential risk and consequences for follow up. In addition especially important are changes to the reference safety information for the upcoming reporting period, which define the assessment of expectedness for the reporting rules of SUSARs.

The developed procedures and AR template were tested by the safety subgroup in 2 small internal pilots and further optimized by the experiences gained. After the 3rd pilot with focus on DSUR format the procedure is going to be refined again and presented to CTFG and HMA for adoption. In addition this (voluntary) DSUR assessment work sharing is opened up to the whole CTFG group in Autumn 2011.

In parallel, it is agreed to share national assessment reports of ASR/DSUR of IMPs of interest by NCAs.

Regarding the resources, a discrepancy between the number of submitted ASRs and the number of safety assessors in the EU/EEA exists. In addition there are identified IT needs of a DSUR repository with submission gate, a tracking system, a DMS and a database for DIBD (development international birth day) and inclusion into EudraCT. Synergies with the pharmacovigilance package e.g. PSUR should be evaluated and might be used.

It would be also valuable to include in the DSUR repository the IBs and the updating of IBs.
3.3 Adaptation of processes according to a risk-based approach

The reflection paper established by CTFG and GCP-IWG on a risk-based quality management system in clinical trials has been finalised and circulated for public consultation in Summer 2011 on the EMA and HMA websites.

How to develop and implement processes for a risk based approach to CTA and CT safety information process and assessment is being discussed. An analysis of current criteria and processes applied by MS with respect to phase IV CT has been made in order to check possible discrepancies and to look for common criteria.

3.4 Improvement of information systems to facilitate work-sharing and simplify processes

CTFG has interacted with Eudravigilance working group (EV-WG) to improve EV-CTM with the objective to make it the primary safety database for CTs in EU (see 3.2.2.a) and is exploring the development of a single repository of ASR.

CTFG has defined with EMA reports and metrics on CTs from EudraCT data warehouse that could be made public and is working on speeding up the development of links between Eudract and EV-CTM.

3.5 Input in the development of EU legislation and harmonised interpretation.

- CTFG has strongly cooperated with the European Commission in developing future legislation. CTFG has provided significant input to the review of the related guidance (the CTA guidance/CT1 published in March 2010, and the SUSARs and Eudravigilance CT3 guidance published in June 2011).

- CTFG is also involved in the CT subgroup of EV WG to support common interpretation of the safety legislation and to propose Q&A to Volume 10.

- CTFG develops an internal forum for a common interpretation of legislation and guidance in order to support a consistent implementation of the new guidance in all MS, like CT1, IMP/NIMP, the ICH E2F (DSUR) and CT3 (on going) and promotes the harmonization between NCAs.

- CTFG is developing and proposing Questions and Answers (Q and A) for frequent issues raised by sponsors (e.g, DSUR; novel-novel CTs; follow up treatments; integrated protocols; definition of IMP/NIMP; contraception in CTs). They are about to be published on the HMA website.

3.6 Active participation in EU working groups

- CTFG has continued input to and liaison with the European Commission’s ad hoc experts working group for the development of the new CT legislation and revised guidance. CTFG has also provided answers to all the EU public consultations on CTs particularly the EC concept paper.

- An action plan regarding interaction between CTFG and EMA and its committees has been drafted and procedures are being finalised regarding CHMP and ITF.

- CTFG has appointed link members in EMA working groups (EudraCT working group, Eudravigilance working group). There are also interactions with other working groups or parties of the EMA such as GCP inspectors working group, CHMP, CAT, ENCepp.
3.7 Communication to stakeholders to assist them in conducting CTs in EU

3.7.1 Improvement and development of external and public communication
CTFG has organised 3 dedicated public meetings with stakeholders (in Bonn on the VHP, in Paris on streamlining CT assessment, in Brussels on specific issues raised by industry) and has strongly participated in several European public meetings or fora on CTs, organised by the Commission, National Agencies, EMA, ECRIN, EFGCP, DIA, TOPRA.

3.7.2 Development of circulation of information on the CTFG/HMA website
We published CTFG deliverables on the CTFG/HMA website including public presentations, Q and A and metrics.

Conclusions/overview of the last 2 year CTFG activities

CTFG is progressively achieving:
- regulatory consistency in EU by developing
  o a harmonised view on the interpretation of the legislation
  o a harmonised project for the future legislation on CTs in EU
- scientific consistency in EU through the
  o development and enlargement of VHP
  o development of safety data worksharing

CTFG developed links with other EU working groups
CTFG is functioning well:
  o the group is composed by dedicated and hard working members
  o the cooperation between CTFG members is excellent
  o the common objectives to keep CTs in EU and to ensure health protection are well endorsed
  o the approach is pragmatic with the strong idea to find solutions
  o CTFG have great support from some MS involved in CTFG secretariat or chairing

CTFG needs improvement in resources and IT (urgent need for a TF on resources and IT)