afssaps
Agence française de sécurité sanitaire des produits de santé

Comments on the Commission's review of the clinical trials directive

Afssaps, as the French National Competent Authority (NCA) for clinical trials (CT), would like to thank the Commission for having performed the impact analysis of the Clinical trial directive (CTD), and welcomes the opportunity to comment it.

We believe that this document is important since not only it assesses the way the CTD has been implemented in the Member states (MS), highlighting some weaknesses of the system, but also it proposes options to improve it.

The comments presented hereunder are focused on aspects of CTD which fall in the remit of national competent authorities (NCA)

As a general comment, although we fully recognise that simplification is a necessity, it should be better emphasised how much the CTD has improved CT's subjects' protection and safety and the CTs' quality as well, by introducing appropriate ethics assessment, mandatory scientific evaluation of quality and safety of IMPs before and during the trials, information sharing by NCAs (assessors and inspectors) and application of Good Clinical Practices (GCP) all around the Community.

The reference to GCPs in line with ICH E6 GCP should be more explicit, with a reference to principles and guidelines to be adopted in the form of a directive, and detailed guidelines in line with those principles. Wording of Art. 47 of the Directive 2001/83/EC amended, for reference to GMPs, should be used.

Key issue n°1: multiple and divergent assessment of CTs:

The description of weaknesses of CTD by the Commission does not appear accurate, mainly due to the assumptions of absence of added value of the CTD, "detriment of safety of CT participants", longer time-lines for 1st-patient-in and unefficient use of staff by NCAs.

As a matter of fact it is important to refer to the situation of CTs in EU prior the implementation of the CTD where several different systems were co-existing, with few or not at all scientific assessments of IMPs, poor monitoring of adverse reactions and no obligation for compensation and GCP.

We take note of the figures provided by the Commission highlighting that 75% of CTs performed in EU are single-states CTs, and that full harmonisation in the implementation of the CTD is strongly needed for the 25% multi-states CTs.

Among them, it is important to remind that extremely rare are those with divergent decisions from NCAs (<0.1%) . This situation has been recognised by HMAs as a potential issue in the field of EU research and has been then taken on board by the Clinical Trials Facilitation Group (CTFG) in its last mandate and action plan, through several actions aiming at better harmonisation; among them, the Voluntary Harmonisation Procedure (VHP) being offered to sponsors since February 2009.

3 options to introduce a better harmonisation of CTs assessment by NCAs are proposed by the Commission:

1. the VHP, which is poorly described in the Commission's document, although it gives concrete answers to the stakeholders' requirements for a one-stop-shot for applications to NCAs, single electronic repository, same dossier in English, simultaneous and coordinated assessment and a unified position by NCAs concerned and appropriate time lines. Moreover, this process has been set up within the current legal framework and is welcomed and appreciated by all sponsors who have tested it.
2. a mutual recognition or a decentralised procedure
3. a centralised procedure at EMA.

Afssaps strongly supports the VHP process, since it does not require the change of the EU legislation, it needs only cooperation of NCAs, it is an easy way to avoid rare divergent decisions and it gives response to practical issues raised by sponsors. Furthermore, a sound implementation of the VHP may lead to a decentralised system coordinated by CTFG on a basis similar to CMDh's process. Finally, consideration has to be given to the complexity of a centralised procedure which is not useful and may even be counter-productive for the great majority of CTs.

Eventually, a 4th option which should be proposed, is the national procedure, which fits 75% of CTs in EU.

Key issue n°2: inconsistent implementation of the CTD:

We agree with the Commission, that the CTD was inconsistently transposed across the European Union, for instance regarding interpretation of definitions of substantial amendments and rules for reporting Susars.

This can be corrected by clarifying guidances and making their application mandatory, since they are referenced in the CTD itself.

Regarding Susars reporting, we need to emphasise the NCAs' legal responsibility in ensuring participants'safety. In order to do it, NCAs need to get as soon as possible all the information currently available on the IMPs'safety. This is why the directive has set up a common database on Susars (Eudravigilance clinical trials module, EVCTM). Unless EVCTM is able to provide automatically each NCA with the corresponding information (all Susars on IMPs used in the trials they have authorised and occurring not only in its territory but also in the world), NCA will still need to receive them by the sponsors.

This double reporting to EVCTM and to NCAs, which is heavy for sponsors, could be deleted in the guidances as soon as EVCTM answers correctly to NCAs' legal demand.

Key issue n°3: regulatory framework not always adapted to the practical requirements:

- Risk based approach for requirements : simplification of the CTD processes is necessary, not only for substantial amendments and Susars reporting but also for the CTA process, labelling, archiving, monitoring, insurance... The risk assessment is an ongoing process that focuses on all stages of design, conduct, analysis and reporting of clinical trial in respect to the well being of trial subjects and the quality of trial data.

We strongly believe that allowing flexibility through a risk based approach would be a major improvement of the EU CT system. Afssaps is involved in the GCP inspectors working group which is already working on this approach in cooperation with the CTFG, under the current directive 2001/20.

As the Good Clinical Practice ICH E6 are already introducing the concept of risk assessment including monitoring or auditing, it is preferred to introduce more explicitly in the Directive the concept of the risk-based approach in clinical trials. Guidelines could provide clarification of risk-based approach with common rules shared in practice by authorities and sponsors. A guidance dedicated to lower risk CTs should be proposed by the Commission.

Excluding CTs of "academic" sponsor from the scope of CTD cannot be accepted within the GCP framework for ethics and quality which does not make a distinction between the sponsors. This approach may generate deviations in the practice of conducting CT because it does not take into account the concept of risk specific to the product being tested, or to the methodology of the investigation, characteristics which are not linked to the sponsor. As mentioned in the description of CTs in the EU (table 3), the risk-profiles of CTs vary considerably whatever the characteristic of the sponsor. The implementation of two standards of protection for the persons and of supervision of the trials according to the status of sponsors is not acceptable. CTs subjects'safety and quality of the CT results should be insured with the same degree of reliability in all CTs in EU, whatever the status of the sponsor. Consequently we believe that GCPs must remain mandatory for all trials and we do not support the Commission's proposal to exclude non commercial CTs from the CTD'scope.

- Non compliance with GCP: It is proposed to introduce in the Clinical Trials Directive, Art. 12.2., provisions related to notification of serious breaches by sponsor/CRO to national competent authorities, based on paragraph 5.20 "Non compliance" of the note for guidance on GCP (CPMP/ICH/135/95). This paragraph states that when an investigator's/institution's participation is terminated because of non-compliance, the sponsor should notify promptly the national competent authorities. It is also proposed to extend the scope of this requirement to "serious breaches" having a significant impact on the integrity of the participants of the trial or on the scientific value of the trial and also to allow the notification by legal representative/CROs and not only by sponsors. Moreover, serious non compliance with GCPs , identified and checked by competent authorities, could be made publicly available.

Key issue n°5: ensuring compliance with GCP in CTs performed in 3rd countries.

This point is crucial as many CTs are conducted in third countries (65% of the trials supporting clinical documentation of Centralized procedures Marketing Applications are from abroad European Union) and Afssaps welcomes this initiative. We appreciate the Commission's proposals aimed at ensuring an appropriate level of subjects'protection and data quality in 3rd countries CTs.

However, as said before, we do not agree with the centralisation of CT assessment at EMA as the main option offered by the Commission, considering that other processes can be proposed mainly the national assessment.

The options described in the paper (Supporting framework and capacity building, self-regulation by EU–based sponsors, strengthening internal cooperation in GCP compliance, strengthening a culture of transparency, strengthening scrutiny of CT results submitted in the EU) are in line with the initiatives within the scope of the strategic paper implemented by EMA, which are actively supported by Afssaps as rapporteur for 2 sub-groups. Afssaps supports optional assessment of 3rd country CT by a 'concerned' National competent Authority ('Art. 58 like' procedure). The concerned authority could be the authority of the member state where the initial sponsor of the trial is located.

Three main kinds of contexts will have to be addressed, with regard to such clinical trials conducted in third countries, which are in line with the 'linkages' presented in point 7.3.6.
1) 3rd country clinical trials to be evaluated by European Union, in the context of a clinical trial authorization, or in a marketing authorization procedure:

- Clinical Trial Authorization dossier: Previous clinical trial experience with an IMP
- Clinical trial conducted in the scope of a development plan dedicated to EU registration (P.I.P., …)
- an obligatory commitment by sponsors to apply GCP in clinical trials performed with the same IMP in third countries.

2) 3rd country clinical trials within the scope of a program granted/financed by a European institution or a Member state.

3) Context not in relation with any EU procedure (assessment or granting)

- an obligatory commitment by European sponsors to apply GCP in clinical trials performed with the same IMP in third countries;
- a regime similar to Article 58 of Regulation 726/2004 for assessment of clinical trials by NCA;
- a regime for assessment by M.S. Ethics committees for assessment of clinical trials.

Complementary point:

AFSSAPS believes that CTD should determine ethic principles for consent in CTs in emergency situations.