Plasma Protein Therapeutics Association

13 May 2010 **BY E-MAIL**
Reference: DSanco11003 sanco-pharmaceuticals@ec.europa.eu

European Commission
Directorate General for Health and
Consumers (SANCO)
B-1049 BRUSSELS

Subject: Comments on the Concept Paper on the Revision of the "Clinical Trials Directive" 2001/20/EC

Dear Madame/Sir,

PPTA is the international trade association and standards-setting organization for the world's major producers of plasma derived products and recombinant analogues, collectively referred to as plasma protein therapies. The therapies are used in the treatment of a number of rare diseases. The diseases are often genetic, chronic, life threatening conditions that require patients to receive regular infusions or injections of plasma protein therapies for the duration of their lives. The therapies include clotting factor therapies for individuals with hemophilia A and B and other bleeding disorders; immunoglobulins to treat a complex of diseases in individuals with immune deficiencies; therapies for individuals who have alpha-1 anti-trypsin deficiency, and albumin, which is used in emergency-room settings to treat individuals with shock, trauma, burns, and other conditions.

PPTA welcomes the Commission's initiative to develop a legislative proposal to revise the Clinical Trials Directive 2001/20/EC and to take previous comments into account. We specifically appreciate the intent of the Concept Paper for a coordinated assessment and follow-up of applications for clinical trials.

Consultation item no. 1:

We would welcome a single submission through one EU Portal. Plasma protein therapies are mostly indicated for diseases with limited number of patients or orphan indications and clinical trials in these patient populations must often enrol patients in different countries. A single entry point would significantly simplify submission of the application and subsequent administration. The clinical trials application (CTA) through the EU portal should be appropriate for both National Competent Authority (NCA) and Ethics Committee review. The CTA should remain the reference point for information which characterizes the IMP through the development stages of a medicinal product thus avoiding duplication of submitted information. A fast track for clinical trials following an agreed paediatric plan/scientific advice/protocol assistance should be foreseen.

Consultation item no. 2:

Experiences with other EU procedures for example the MRP have shown that different Member States often have divergent opinions. Therefore, it is of importance to clearly define the roles and responsibilities of EU regulatory bodies and NCAs. Ideally, as for the Decentralised Procedure (DCP) a Reference Member State (RMS) would assess the CTA and provide the other Member States with the assessment report. Only specific national requirements would be directly assessed by the individual Member States, which would mostly relate to the approval by the Ethics Committees. In addition, a system of arbitration under the EMA secretariat between applicant and authorities should be put in place.

Consultation item no. 3 and 4:

PPTA agrees that a central assessment would not be workable and is not necessary, because in most cases only a limited number of Member States are involved. But it could be envisaged to submit the CTA through a central EU portal, then as in the DCP identify a RMS among those countries where the clinical trial is performed (see Annex I potential workflow of CAP). This procedure would not necessarily require an overarching and cumbersome Committee structure. Only the arbitration procedure should involve EMA secretariat, i.e. relevant EMA working groups such as the BPWP for plasma protein therapies. It is important that the national assessment is restricted to ethical requirements avoiding that Member States introduce additional requirements on aspects covered by EU legislation.

Consultation Item No 5:

We agree that only the aspects listed under a) should be in the scope of the CAP. a) should be amended and include definitions of adequate comparators where applicable. For the items listed under b) it must be ensured that the ethical aspects would be addressed by the national ethics committees in compliance with the current Directive and c) that no national requirements are stipulated that are not in line with current EU legislation, There should be provisions defining the scope of the assessment by the CAP and by national Ethical committees. Procedures should be put in place to address the situation when comments by Ethical committees are in contradiction to the assessment of the CAP.

Conditions for shortening review timelines dependent on the relevant information already on file for a medicinal product should be included.

The possibility and conditions of a simplified Investigational Medicinal Product Dossier should be included.

Consultation item no. 6:

We would prefer the simple majority option. In addition, sponsors should have the option to withdraw the application in (a) Member State(s) when is becomes obvious that no agreement can be reached.

The legal basis of the opt-out option should be further explored. To reduce the risk that the opt-out option could lead to a situation where a Member State decides to block the procedure applicants should have the option for arbitration under the EMA secretariat. The opt-out option should only be applicable in case of different medical practice in different Member States.

Consultation item no. 7:

PPTA would strongly support that CAP is optional. If mandatory for all trials, trials only conducted in one country such as early development clinical trials would unnecessarily fill up the EU portal, for trials conducted in two countries the simple majority option could not be applied. For multinational clinical trials the benefits of CAP would most likely convince sponsors to go via this route making a mandatory CAP superfluous.

Consultation item no. 8:

If a pre-assessment would be introduced to the CAP, timelines and responsibilities need to be clearly defined. Since national ethical provisions have to be taken into account the process could be extremely complex in that each CMS would have to give their preliminary approval, before the RMS could prepare the assessment report. We recommend reconsidering a tacit approval by RMS and CMSs with a time line of no longer than 60 days as a first step (see Annex I). Thereby Member States have the possibility to review the principle compliance with applicable requirements.

The term “insignificant risk” needs to be clearly defined.

Consultation item no. 9:

We would prefer harmonised and proportionate requirements which would apply to all clinical trials falling within the scope of the present Directive.

Widening the scope of the Clinical Trials Directive to include non-interventional trials should be avoided. However the scope should also not be limited and the definition of non-interventional trials should be clarified as Member States keep interpreting them differently. Furthermore members highlighted that the new Directive 2010/84/EU regarding pharmacovigilance lays down provisions for regulatory supervision of all non-interventional post-authorisation safety studies, which will be reviewed by the Pharmacovigilance and Risk Assessment Committee, and therefore such studies would already be conducted under EU regulatory oversight.

Consultation item no. 10:

Clinical trials are intended to evaluate a medicinal product for a certain indication without endangering the health and wellbeing of the study subjects. We do not see any reason to apply different rules depending on the nature of the sponsor or the institution where the trial is performed.

Consultation item no. 11 and 12

The good intention of EU regulation for harmonised approaches within the community is often jeopardised by different interpretation of individual Member States. PPTA has always advocated providing sufficiently explicit guidance to avoid such situations. We would strongly support the establishment of one single, EU wide, risk adapted set of rules for the content of the CTA dossier and for safety reporting. The rules should be legally binding to ensure Member States’ compliance.

Consultation item no. 13:

IMPs are sufficiently well defined. There is a need for EU-wide definition of NIMP and data requirements for IMP/NIMP.

Consultation item no. 14

As stated correctly, the actual risk of a clinical trial for the safety of a participant in that trial depends on a wide range of factors. Furthermore, risk perception remains in the eye of the beholder and may vary between different Member States. The insurance costs in comparison to the overall costs of a clinical trial are in most cases insignificant. Unnecessary hurdles could be avoided if all study participants would be entitled to the same insurance/indemnification regardless of the nature of the intervention or the study site.

Consultation item no. 15:

We agree that it is preferable to maintain the concept of a single sponsor provided that the provisions stipulated in the last two bullet points apply.

Consultation item no. 16:

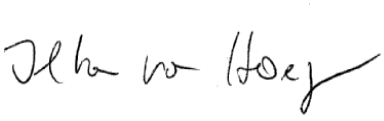
There is a general consensus that the proposal provides both a perfect analysis and a viable solution in line with existing international agreements.

Consultation item no. 17

It should not be mandatory to enter clinical trials conducted outside the EU into the EudraCT data base. Registry of these trials in any publicly available data base should be sufficient.

We hope that you will find our comments constructive and helpful. We remain at your disposal, should you have any questions or need further clarification.

Sincerely Yours,



Dr. Ilka von Hoegen
Senior Director, Quality and Safety

Annex I:
Proposal for a coordinated Assessment Procedure (CAP)