

**Comments submitted by: Dr Markus Hartmann, European Consulting and Contracting in Oncology, Trier (Germany), 9 May 2011 (hartmann@ecc-oncology.de)**

By its Consultation paper *Revision of the 'Clinical Trials Directive' 2001/20/EC – Concept Paper submitted for Public Consultation* (SANCO/C/8/PB/SF D(2011)143488), the EU Commission took an appropriate step forward to end shortcomings of the current legislative framework.

As a consultancy focused on clinical development issues and with dedicated experience in legislative and regulatory issues surrounding clinical research<sup>1</sup>, European Consulting & Contracting in Oncology would like to place emphasis on some of the consultation items in order to share its practical work experience with the Commission.

**Consultation items no 1 – no 8 (Cooperation in assessing and following applications for clinical trials):**

EU Commission's proposals (**items no 1 to no 5**) to reduce duplicate assessment of trials by national competent authorities (NCA) and ethics committees (EC) and to define primary responsibilities for (i) NCA (R/B assessment and oversight of IMP, trial design and intended labeling issues) and (ii) EC (IC suitability, investigator/site suitability & compensation, insurance/indemnity and data protection provisions), can prove to be very beneficial in case, these provisions will be transposed rigorously into EU member state law.

**Items no 6 and no 7:** Due to the huge variability in the nature, purpose and risk of clinical trials, a maximum of flexibility is desirable: Opt-out options (for a country/authority) and optional use of the CAP (i.e. as an option for the applicant) are both the preferable options.

**Item no 8:** The EU Commission should not hesitate to enforce forms of 'tacit approval' among EU member for trials with a modest or low risk (the so-called 'Type A trials'). A return to a trial notification system, which is indeed a 'tacit approval', would largely contribute to reduce administrative burdens. Such a pre-assessment, made by the applicant, should pose no problem in practice, as the national competent authority can issue an authorization in case, the content of the application is judged not to comply with a "type A-trial".

**Consultation items no 9 – no 16 (Better adaptation to practical requirements and a more harmonized, risk-adapted approach to procedural aspects of clinical trials):**

**General comment:** Unfortunately, the move towards a risk-based approach is reduced to a few issues/items only (see **item no 8**: some kind of risk-adapted approach might be incorporated into guidance CT1 to CT3; **item no 14**: insurance/indemnity provisions). The EU Commission should use

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<sup>1</sup> (i) Hartmann M et al. *How to Avoid Further Legislative Fragmentation of Clinical Research in the European Union*. RAJ Pharma (2010) 21(3), 163-8; (ii) Hartmann M et al. *Patient Protection and Access to Innovative Medicinal Products in the European Union*. Drug Inf J (2008) 42:281-95; (iii) Hartmann M et al. *The Clinical Trials Directive: How is it Affecting Europe's Non-commercial Research*. PLoS Clin Trials (2006) 1(2):e13 0001-5 [http://clinicaltrials.plosjournals.org/archive/1555-5887/1/2/pdf/10.1371\\_journal.pctr.0010013-L.pdf](http://clinicaltrials.plosjournals.org/archive/1555-5887/1/2/pdf/10.1371_journal.pctr.0010013-L.pdf)

the present opportunity to discuss with stakeholders how risk-based approaches can be introduced more comprehensively into EU's clinical trials legislation. Predominantly, the discussion should focus on the question, whether a risk-based approach should be based (i) rather on characteristics of investigational medicinal products (i.e. categorizing specific classes/groups), (ii) on methodological characteristics of a trial (e.g. trial phase), or (iii) on class-waiver approaches for defined situations in which trials are exempted from single or several provisions of trial authorization and oversight.

**Item no 9:** Harmonized and proportionate (!) requirements should be able to facilitate 'patient-oriented research', in which not the clinical development of a medicinal product, but the optimal use of a product (i.e. a health intervention) or a combination/sequence of interventions with a strong focus on patient outcomes is investigated. Such therapy-optimization trials are relevant, because they allow medical practitioners to define the best place of a new medicine in clinical practice – a question which can often not be answered by results of global phase III trials, which deliver only a snapshot of a given product's tolerability and efficacy in a risk-limited and outcome-optimized trial population. Such patient-oriented research, which often poses no or only insignificant additional risk to the safety of patients compared to normal clinical practice, would much benefit from class waivers similar to those issued in the United States<sup>2</sup>, by which patient-oriented research in life-threatening diseases with limited therapeutic options is facilitated. Such an approach would facilitate many 'academic trials' without necessitating a general exclusion of academic / non-commercial sponsor trials from the scope of the Clinical Trials Directive (**Item no 10**)

**Items no 11-12:** Hereby, the Commission proposes the set-up of a kind of 'Annex I'<sup>3</sup> for clinical trials. Although such guidance must be critically considered to constitute a potential source of further (over)regulation, such an 'Annex' might be inevitable as a pre-requisite to successfully implement a central EU-portal to submit trial application and to initiate a feasible 'coordinated assessment procedure' (CAP).

**Item no 13:** The scope/definition of an IMP itself requires more clarification. Still today questions are repeatedly posed regarding the applicability of the Clinical Trials Directive for several classes of medicinal products. Especially for biologicals (antigens and sera), the scope of the current legislation remains a source of uncertainty. In current legislation, but also in the Commission's consultation, definitions of an IMP refer to the definition of medicinal product in Directive 2001/83. The parallel notion of definitions for 'medicinal products', 'immunological medicinal products', 'homeopathic medicinal products', 'medicinal products derived from human blood or human plasma' and 'radiopharmaceuticals' in Chapter 1 of Directive 2001/83/EC is a source of misinterpretation: one can conclude that the four latter subgroups are excluded from the legislative framework for IMP. Existing differences in the transposition of the definition of an IMP into national legislations – various classes of medicinal products were regulated over time in form of stand-alone legal acts – render the IMP-classification of some 'borderline' products (e.g. antigens, sera, homeopathics) today extremely difficult. Hence the EU Commission should directly and clearly define within the new legislative framework (annexed 'positive list'), which classes of products will be covered by new legislation.

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<sup>2</sup> See e.g. 'FDA Guidance for Industry. IND exemptions for studies of lawfully marketed drug or biological products for the treatment of cancer. January 2004 (Rev. 1)' <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071717.pdf>

<sup>3</sup> See Directive 2003/63/EC of 25 June 2003, by which the EU Commission provided explicit guidance on the detailed content of the 'Common Technical Document', i.e. the structure of the marketing authorization dossier.

**Item no 14:** The Commission raises meaningful policy options for this important issue. Option B (optional indemnisation by MS) bears some promise and could be very helpful to reduce administrative burden especially for academic trialists in case it is assured that the EU member states opt for a true research-friendly interpretation of option B.

**Consultation items no 17 (GCP compliance in trials performed in third countries):**

**Item no 17:** The mandatory publication of trial results of all trials conducted in non-EU-countries via the EudraPharm database would surely help to promote transparency and public trust in clinical drug research.

**Consultation items no 18 (Figures and data):**

**Item no 18:** No further data<sup>4</sup> regarding the impact assessment of current legislation on the number of clinical trials conducted in the EU since 2001 can be provided at this time.

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<sup>4</sup> See contribution to EU Commission's previous consultation (October 2009), submitted on 8 January 2010: [http://ec.europa.eu/health/files/clinicaltrials/docs/responses\\_2001-20/european\\_consulting\\_and\\_contracting\\_in\\_oncology.pdf](http://ec.europa.eu/health/files/clinicaltrials/docs/responses_2001-20/european_consulting_and_contracting_in_oncology.pdf)