



Assessment of the functioning of the „Clinical Trials Directive“ 2001/20/EC

RE: Public Consultation Paper (ENTR/F/2/SF D (2009) 32674)

CliniGene-NoE comments Jan 25th, 2010

To: European Commission, DG enterprise/Pharma

As the EC-FP6 funded Network of Excellence, '*CliniGene, the EC network for the advancement of clinical gene transfer and therapy*', we are commenting this consultation paper in the context of gene and cell-therapy medicinal products.

In general we would like to mention that gene and cell therapy medicinal products are new and innovative medicinal products. They are biological medicinal products according to Regulation (EC) No 1394/2007 within the meaning of Annex I to Directive 2001/83/EC. Because of the novelty, complexity and technical specificity of advanced therapy medicinal products (ATMPs), specially tailored and harmonised rules are needed to ensure the free movement of those products within the Community and the effective operation of the internal market in the biotechnology sector.

ATMPs are subject to a centralised authorisation procedure, involving a single scientific evaluation of the quality, safety and efficacy of the product at EMEA. As the evaluation of ATMPs requires very specific expertise, which goes beyond the traditional pharmaceutical field and covers areas bordering on other sectors such as biotechnology and medical devices. For this reason the Committee for Advanced Therapies (CAT) was created, which is responsible for preparing a draft opinion on the quality, safety and efficacy of each advanced therapy medicinal product for final approval by the CHMP.

Beside that Part IV, Annex I to Directive 2001/83/EC as regard to the specificity of advanced therapy medicinal products was revised.

Therefore it is consistent to revise the “Clinical Trials Directive” regarding advanced therapy medicinal products.

In addition, a strong statement concerning the funding of ATMPs-based first-in-man trials is formulated at the end of this document, as highlighted in bold.

Comment to key issue No1: Multiple and divergent assessments of clinical trials

Few clinical trials are performed in one single Member State. Rules for clinical trial authorisation should be identical in theory. But as always theory and practice are divergent. The foundation of the “Clinical Trials Facilitation Group” and the “Voluntary Harmonised Procedure – “VHP”” accelerated the progress.

Nevertheless the Commission should take in consideration to centralise the permission of clinical trials for those innovative medicinal products which need a special expertise for evaluation like ATMPs (RE: consultation items 3.3.2, 3.4.1 & 3.4.2). Because centralised procedure are generally expensive for small and medium sized enterprises the Commission should take into account a

- fee reduction and
- administrative support

for SMEs and academic sponsors. This will ensure to maintain high standard clinical trials and foster clinical research which in this field is dominated in contrast to the field of classical biotechnical products and small molecules by academia and SMEs.

Comment to key issue No 2: inconsistent implementation of the Clinical Trial Directive

There is a strong need to revise the legislative procedure in respect to gene- and cell-therapy clinical trials and in particular, those sponsored by academic / non-profit organisations. They are not necessarily performed with the intention to generate data to support an application for a marketing authorisation of a medicinal product. Therefore we propose to design a specific track for the evaluation / approval of these studies, especially when they are not aiming towards marketing authorisation. The model of the clinical trial seems to underpin the current legislation in that of the big pharma driven multi-centre large scale study. Whilst this model may be appropriate when considering the development of small molecules for common diseases, it is increasingly inappropriate when the impact of new knowledge in genetics and biotechnology and the increasing importance of lessons learned from rare disorders, are taken into account.

Comment to key issue No 3: regulatory framework not always adapted to the practical requirements

1. When considering ATMPs again in rare diseases or early development phases of innovative treatment,

there is a demand for patients with serious diseases to participate in relevant, high quality biomedical research, throughout the research process from bright ideas to proven intervention: well designed clinical trials are an essential component of this. The availability of a treatment without a need to travel too far and to prepare a dossier for a single patient in a given member state should be scrutinised with most attention.

Such legislation must therefore be a community legislation, especially to facilitate international cooperation in research in this field. Thus, the legislation should be developed by the Commission rather than individually in the member states as suggested in part 5.4.3.

When considering most rare disorders, the development model from phase I to phase four is not accurate, given the reduced number of patients and the multinational accrual, within an Academic setting in many cases.

2. GMP for ATMPs

Currently there is a discussion if it is useful to meet the cGMP requirements for ATMPs. In our opinion there should be no two class medicine. One for “normal” medicinal products and the other for ATMPs. To work according to the GMP requirements is meaningful when addressing quality towards optimised safety and efficacy of a medicinal product. ATMPs are very new and innovative medicinal products. Raising safety concerns according to quality issues would damage the public perception of these extremely promising products. There are alternative possibilities to reduce the costs than to do without a qualified person. On the other hand there are ways to increase the GMP stringency, as the product enters new phases of development.

In addition, it would be instrumental that EU harmonise its requirements with the US and avoid double standards, if possible.

Other aspects: Using the Common Technical Document (CTD) for ATMPs

The structure of the marketing authorisation application dossiers for all medicinal products has to follow the CTD structure. The CTD was created for new chemical entities (NCE). These products were the first medicinal products which were globally developed and the harmonisation according to the CTD was very useful. At that time, there was no plan for products like advanced therapy medicinal products to use the CTD structure. We think that this is the time to review the CTD according to ATMP requirements. The requirements mentioned in the new part IV, Annex I to Directive 2001/83/EC as regard to the specificities of advanced therapy medicinal products should also be taken into account. In that regard, we have been commenting the CAT-mini quality guideline which is a phenocopy of the currently available CTD-NTA. A more mature format needs to be generated with an intention to be used in all member states. It should be discussed how processes that are customised to each patient individually could be described in a CTD. The idea that all processes can be described as a model is not relevant for individualised products like ATMPs. The structure of the IMPD is similar to the CTD structure. It would be less work and costs for everyone to have the same structure, Europewide. Companies will be enabled to use documents created for the IMPD in the CTD. It could be something like a “rolling submission”. Why not beginning this discussion in Europe?

Finally, even with these proposed modest amendments to the CTD, academic clinical trial costs will still remain high in a non-commercial setting. It is therefore important that such costs are met by dramatically increased funding for academic clinical trials through the European Commission in order to counteract a stagnation of such trials, and promote the expansion of fields with great potential in the future, like gene and cell therapy. In frequent diseases, it is likely that development will be taken up by the Industry sector, fuelled by knowledge acquired in the context of most innovative and cutting-edge academia-driven trials.

We as the CLINIGENE Network of Excellence would be delighted to interact and work together with the European Commission, the EMEA and the other Member States on this subject and to contribute efficiently to medical progress within an ethical framework.

Yours sincerely

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