European Society of Gene and Cell Therapy

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Dear European Commission

ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC

PUBLIC CONSULTATION PAPER

Gene and Stem Cell Therapy

We are responding to the above Public Consultation to comment on the functioning of the Clinical Trials Directive in the context of gene and cell therapies, most particularly from the aspect of academic-led early phase clinical studies.

Gene and Cell-based therapies represent a new medical paradigm that promises many important new treatments across a wide range of diseases. However, as with all fundamentally new treatment approaches, we anticipate there will be a significant lead time before gene and cell –based therapies are ready for product licensure. This long development time is not attractive for commercial investment, particularly for small companies, and the onus for performing early developmental work falls squarely on the academic sector.

It is therefore essential for efficient assessment of these potential new treatments that academic centres are able to undertake high quality early phase interventional clinical studies. This critical first step will pave the way for more focussed and informed commercially-led studies, that will then lead towards specific applications for product licensure.

The Clinical Trials Directive, incorporated into the law of most EU states in 2003-05, has introduced high standards of clinical trials performance to maximise patient safety and simultaneously ensure rapid progress towards product licensure. The CTD was designed to address several important issues on a pan-European basis, including: (i) the need for high quality data in applying for marketing authorisations, (ii) protection of Human Rights, (iii) protection of children and others unable to give informed consent, (iv) avoidance of obsolete and repetitive tests, and harmonisation of procedures across Europe, (v) involvement of European Agency for the Evaluation of Medicinal Products in assessing marketing authorizations, (vi) avoidance of delays in initiation of trials, (vii) establishing a European database of trials, (viii) Good manufacturing practice in investigational medicinal products, (ix) consideration of labelling, (x) special dispensation for academic-led trials being carried out with medicinal products with a marketing authorisation, (xi) transparent trial documentation, and (xii) surveillance of adverse reactions.

For these central purposes the CTD has been generally a great success, and Europe now leads the world in high quality clinical evaluation. However these good practices come at a high cost financially and administratively, more easily met by large pharmaceutical companies (who benefit greatly from the high quality and efficiency of the process) than by academics trying to conduct translational research essential to sustaining the therapeutic pipeline.

It is our contention that meeting the current full terms of the CTD sometimes inhibits the performance of academic-led early phase investigational studies of gene and cell therapies that could establish new approaches to treatment.

We believe there is a strong need to revise the specific requirements pertaining to gene- and cell-therapy clinical trials sponsored by academic/non-profit organizations and therefore propose that it would be important to design a specific track for the evaluation/approval of these studies, especially when they are not aiming towards market authorisation. For clarity, to ensure benefits such as high scientific/clinical quality and harmonisation from the pan-European dimension, it is important that this track should still be developed within a EU framework (and not delegated solely to National Competent Authorities). In this way the trials would benefit from the significant efforts towards more community-wide and streamlined procedures as enshrined in the CTD.

The EU has a number of ongoing projects to improve the resources and infrastructure for academia-initiated clinical trials. We also see a considerable effort of the EU to advance the development of drugs for orphan diseases. Furthermore, we are aware of the initiatives of the EU to support advanced therapy medicinal product (ATMP) development, including the emerging field of regenerative medicine and induced pluripotent cells. This underlines the need to adopt regulations that assure a high degree of product quality and patient safety, as intended in the CTD, but also avoid cost escalation and administrative delays that would effectively preclude future investigator-initiated clinical trials. It is of great importance and should actually be in the interest of the EU to adopt realistic guidelines that support academic centres to continue their efforts in drug/ATMP development and clinical translation.

The CTD needs to be relevant to the variety of treatments in development for the investment in research to be fully realised in terms of patient benefit. This requires some aspects of the CTD to be tailored to the treatment type while still maintaining the core principles that ensure safety across the board. In this way patients can still be protected from avoidable harm but will have access to cutting edge treatments.

Examples of requirements that might be revised for academic-led trials:

Gene & Cell therapy trials in patients with good life expectancy: For these individuals it is essential that the experimental treatment reaches the highest possible quality of medical definition and safety. However there are some aspects of the CTD that impose burdens that are not directly related to safety, and we would suggest that such requirements could be waived for academic-led early phase trials of gene and cell therapy. Although this is a complex area, that requires detailed consideration, illustrative examples include these:

- Academic-based early phase gene therapy trials in these patients could be relieved of the regulatory requirement for trials-specific use and labelling. Following cGMP manufacture and QP release within the EU, such agents could be available for use in academic-led clinical trials throughout the EU with labelling and local release to trial being undertaken by trained teams within academia, and not necessarily by QPs. This would not impact on the quality of materials, but would significantly simplify local release requirements and could decrease costs and delays.
- For academic cell therapy trials it should be possible to obviate the necessity to perform these trials under strict pharmaceutical GMP guidelines without jeopardizing the patient's safety, meaning that all procedures would be performed in clean room facilities recognized by National Competent Authorities that maintain high quality standards but not identical to full cGMP. The latter is economically not viable for academic laboratories given the high costs of ingredients and consumables (let alone infrastructure requirements and human resources) and given the patient-specific nature of cell-based (gene) therapy.

Given the complex interpretations of CTD-related legislation, one approach to this could be to specify aspects of regulatory activity that are NOT required for academic-led early phase trials. This could be of great benefit to National Competent Authorities, QPs and sponsors to ensure they do not over-interpret the requirements.

Trials in patients with limited life expectancy: We would also raise the issue of gene therapy trials that are conducted in patients with no standard treatment available and who have limited life expectancy. While we do not underestimate the importance of maximising quality of life for these vulnerable individuals, there is an argument that more experimental research is needed for these diseases than in less life threatening situations. If academic research is being limited by costs of working under the CTD, the regulation may be having a counter-productive effect. Many European Healthcare systems prioritise patient choice, and it may be appropriate to give these individuals the choice to participate in academic led trials, subject to full informed consent, without necessarily full CTD compliance. One particular example could be in the requirement for cGMP manufacture:

- In the United States the FDA do not insist on full cGMP for early phase agents, although this is assessed on a case by case basis. In the case of experimental cancer treatments there is greater justification for lower cGMP compliance than in some other situations. We would argue that academic-led early phase clinical trials in cancer should be subject to similar regulation as the equivalent trials in the USA, and that a case could be made for not operating to full cGMP where costs of manufacture are prohibitive – provided that key safeguards (eg sterility) are observed. This would represent an ethically-justified example of ‘optimum patient safety’, as opposed to ‘maximum patient safety’.

- Indeed the EU already operates a relatively relaxed approach to preclinical toxicology assessments prior to phase I clinical trials in patients with advanced cancer http://www.emea.europa.eu/pdfs/human/ich/64610708en.pdf, although gene and cell therapies are specifically excluded from this guideline (for no obvious reason). Including gene and cell therapies within this guideline and extending the principle to other regulatory aspects of early phase trials in patients with life threatening disease would be welcomed.

Overall we would be in favour of a modus operandi whereby full cGMP for early phase agents would not a priori be required but whereby this would be assessed on a case-by-case basis. Consequently, this could contribute to an improved harmonization of EU and US regulatory requirements, thereby avoiding double standards. Moreover, within the EU the same criteria should apply across all member states for such ad hoc assessment of full cGMP requirements for a given ATMP.

Microdosing studies: We would also mention the problems of performing predictive toxicology for biologicals, including gene and cell therapies, in animals. Many of these agents are species-specific, and results from preclinical animal screening may be not informative – which can give false negative as well as false positive results. In that situation there is a clear need for more characterisation of agents using human tissues, either in living biopsies or by mechanistic studies following administration of subtherapeutic doses in humans (microdosing, or 'phase zero' studies). However, although this concept has been widely discussed (particularly in the USA, in the context of requiring less regulatory oversight than full phase I trial) it does not seem to be an established principle within the CTD. Enabling it would improve both the quality and safety of clinical trials of gene and cell therapies.

Academic-based studies have previously led to very important advances in healthcare - cisplatin, monoclonal antibodies, penicillin etc – and we are keen to ensure that the academic sector in Europe can make its due contribution to this important and emerging new medical field. This will make a measurable contribution to improving healthcare in Europe, and also to ensuring that European science and technology remains at the international fore.

We urge you to consider seriously the possibility that academic-led early phase trials of gene and cell therapy are not helped by the CTD as it stands, and to make provisions to allow the European academic sector to contribute efficiently to medical progress within an ethical regulatory framework.

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