EMA Consultation on ATMP

Comments from the Board of the European Society of Gene and Cell Therapy (ESGCT)

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2.1 MAA requirements

As more ATMP may reach MAA it may be helpful to consider the following options:

- "Vector Master Files" could be created to avoid unnecessary duplication of non-clinical studies when using the same vector platform with different transgenes or designs. Bridging studies may be sufficient to meet the requirements easing up the burden to commercial development, especially in the case of rare diseases.
- In the case of rare diseases, MA could be given as "provisional" when only a limited amount of clinical (and even non-clinical) data is available. Further data collection may be implemented post-MA. Such a provision would help encourage private investment into a field where individual need is great but the market is small.
- There should be continued reassessment of the value of/need for extensive or conventional animal studies for MAA of several types of ATMP. This is particularly true for agents that are species-specific, and for which animal models may not be predictive of the clinical situation.
- many ATMPs rely on patient or donor-derived tissues for which the great variability of human cells should lead to more flexibility in product definition than currently accepted for conventional medicines obtaining MA.

2.3 Hospital Exemption

There is the concern that legislation on hospital exemption may be used to bypass expert assessment of the scientific rationale/safety of a proposed ATMP, at least when such ATMP represents the first-in-human administration of a novel type of product or for a novel disease. In such specific cases, it may be wiser to require prior authorization from an expert Committee at the National level, rather than simply relying on approval by an Institutional bioethical committee. The harmonization of the national regulation rules would be helpful in that respect.

Such authorization conditions would potentially help the use of data arising from these first-in-man cases as part of the investigational medicinal product dossier for subsequent clinical trial applications (« phase 0 »), to reinforce or even replace pre-clinical animal studies.

In an ethical perspective, a registry for these HE data would be important, to ensure the quality of these first-in-man ATMP use and the further availability of obtained data for subsequent clinical trials

HE is a need and should remain available for applications of ATMPs which will not lead to a MA , but there is also a need to harmonize the rules between member states.

2.4. Incentives for the development of advanced therapy medicinal products.

Clear regulatory principles for the conduct of phase zero (microdosing) studies of ATMPs would be very helpful. By 'phase zero' we mean clinical studies with ATMP agents provided at subtherapeutic doses intended to study pharmacodynamics and not efficacy.

The table below (taken from http://ec.europa.eu/health/files/eudralex/vol-10/ctqa_v10.pdf) gives the impression (specifically column D) that such studies may be outside the scope of the Clinical Trials Directive and therefore subject only to local regulation. Clarification would be appreciated, as the study of drug mechanism in humans would significantly accelerate scientific progress with many ATMPs.

ANNEX: DECISION TREE TO ESTABLISH A WHETHER A TRIAL IS A "CLINICAL TRIAL"

This algorithm and its endnotes will help you answer that question. Please start in column A and follow the instructions. Additional information is provided in the notes at the end of the table. If you have doubts about the answer to any of the questions contact the clinical trials unit of your competent authority.

A	B	C	D	E
A CLINICAL TRIAL OF A MEDICINAL PRODUCT?				**A NON-INTERVENTIONAL CLINICAL TRIAL?**
Is it a medicinal product (MP)?[i]	Is it not a medicinal product?	What effects of the medicine are you looking for?	Why are you looking for those effects?	How are you looking for those effects?
If you answer no to <u>all</u> the questions in column A, the activity is not a clinical trial on a MP.	If you answer yes to the question below in column B the activity is not a clinical trial on a MP.	If you answer no to <u>all</u> the questions in column C the activity is not a clinical trial under the scope of Directive 2001/20/EC.	If you answer no to <u>all</u> the questions in column D the activity is not a clinical trial under the scope of Directive 2001/20/EC.	If you answer yes to <u>all</u> these questions the activity is a non-interventional trial which is outside the scope of Directive 2001/20/EC.
If you answer yes to <u>any</u> of the questions below go to column B.	If you answer no to this question below go to column C.	If you answer yes to <u>any</u> of the questions below go to column D.	If you answer yes to <u>any</u> of the questions below go to column E.	If your answers in columns A,B,C & D brought you to column E and you answer no to <u>any</u> of these questions the activity is a clinical trial within the scope of the Directive.
A.1. Is it a substance[ii] or combination of substances presented as having properties for treating or preventing disease in human beings ? A.2. Does the substance function as a medicine? i.e. can it be administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis or is otherwise administered for a medicinal purpose? A.3.Is it an active substance in a pharmaceutical form?	B.1. Are you <u>only</u> administering any of the following substances? • Human whole blood[iii]; • Human blood cells; • Human plasma; • A food product[iv] (including dietary supplements) not presented as a medicine; • A cosmetic product[v] • A medical device	C.1. To discover or verify/compare its clinical effects? C.2. To discover or verify/compare its pharmacological effects, e.g. pharmacodynamics? C.3. To identify or verify/compare its adverse reactions? C.4. To study or verify/compare its pharmacokinetics, e.g., absorption, distribution, metabolism or excretion?	D.1. To ascertain or verify/compare the efficacy[vi] of the medicine? D.2. To ascertain or verify/compare the safety of the medicine?	E.1. Is this a study of one or more medicinal products, which have a marketing authorisation in the Member State concerned? E.2. Are the products prescribed in the usual manner in accordance with the terms of that authorisation? E.3. Does the assignment of any patient involved in the study to a particular therapeutic strategy fall within current practice and is not decided in advance by a clinical trial protocol[vii]? E.4. Is the decision to prescribe a particular medicinal product clearly separated from the decision to include the patient in the study? E.5. Will no diagnostic or monitoring procedures be applied to the patients included in the study, other than those which are applied in the course of current practice? E.6. Will epidemiological methods be used for the analysis of the data arising from the study?

[vi] Efficacy is the concept of demonstrating scientifically whether and to what extent a medicine is capable of diagnosing, preventing or treating a disease and derives from EU pharmaceutical legislation.