EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Directorate D - Health systems and products

D4 – Substances of Human Origin and Tobacco Control
D5 – Medicinal products – Authorisations, European Medicines Agency

MINUTES OF THE JOINT MEETING OF COMPETENT AUTHORITIES RESPONSIBLE FOR TISSUES AND CELLS, COMPETENT AUTHORITIES RESPONSIBLE FOR HUMAN MEDICINAL PRODUCTS AND CAT MEMBERS OF 23 APRIL 2015

Disclaimer: The positions expressed by the representatives from the competent authorities/CAT members do not represent the views of the European Commission.

Topic 1: Overview of the legislation governing substances of human origin (tissues, cells and blood) and medicines.

The Commission services (SANTE units D4 and D5) explained the respective regulatory frameworks.

An exchange followed, where the following positions were expressed:

Representatives from the competent authorities responsible for medicines/CAT:

It was recalled that the legislator established a (non-binding) classification mechanism for cases where a developer had doubts as to whether a product is an ATMP or not. There is therefore a mechanism to address borderline cases, which is quick and free of charge. Although non-binding, CAT recommendations provide a harmonised position to be considered by Member States in their respective jurisdictions.

Representatives from the competent authorities responsible for EUTCD:

It was noted that the classification recommendations from the CAT are not binding and that requests for a classification can only be made by developers.

The Commission services noted that the classification recommendations by the CAT presupposes that the product is a medicinal product within the scope of the Medicinal Products legislation, meaning it to be either prepared industrially or manufactured by a method involving an industrial process (Art 2 of Directive 2001/83/EC). It was likewise explained that that the ECJ had so far provided a very extensive interpretation of the term "industrially produced" so as to ensure that operators do not circumvent the application of the medicines rules. Reference was made also to a ruling that explained that Member States should have into account the recommendations of EU bodies.

Topic 2: Borderline issues

As introduction to the topic, the following presentations were made: (1) Classifications under ATMP Regulation (by CAT); (2) the UK perspective on borderline products (by Human Tissue Authority, UK); (3) Processing of de-epidermised skin allografts (by National Centre for Tissue and Cell Banking, Poland); (4) Tissues and Cells, Medicinal Products and ATMP in Germany (by Paul-Ehrlich-Institute and the Ministry of Health, Germany) and (5) National classification procedure (by State Institute for Drug Control, CZ)

An exchange followed, where the following positions were expressed:

Representatives from the competent authorities responsible for medicines/CAT:

It was explained that the medicines legislation aims to ensure that the products given to patients are safe and efficacious and reference was made to unsound therapies that have been given to patients in the past (outside medicines rules). It was also said that the ATMP Regulation had been instrumental in dealing with the Stamina case in Italy. Clinical trials (Directive 2001/20 relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use), were deemed the only way to ensure efficacy and safety and it was stressed that safety requirements should not be lowered to increase the number of treatment options available. Reference was made to the large number of projects in the pipeline (as illustrated by the large number of clinical trials and the scientific advice submitted to EMA), which illustrate that serious research is taking place under the medicines rules. Rigorous science and appropriate regulation (addressing benefits and risks) is necessary to bring new products to patients. Legal certainty about the classification (i.e. whether a product is or not ATMP) at early stage of development was deemed important.

Representatives from the competent authorities responsible for EUTCD

It was explained that clinical investigations can also take place outside the framework of clinical trials (as regulated under Directive 2001/20 relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use), e.g. in the context of (novel) transplant monitoring programmes. The need to improve communication between the national competent authorities responsible for pharma and T&C was deemed important, and different existing national coordination models were recognised. When considering borderline products, attention should be paid to the respective benefits as well as respective requirements of the T&C legislation and the pharmaceutical/ATMP legislation.

Topic 3: Differences in national rules on donation, procurement and testing: impact on the ATMP sector

The Commission services (unit D5) made a presentation about differences in the national rules on donation, procurement and testing of tissues and cells and the impact thereof on ATMP developers. Unit D4 made a presentation about the Member State requirements for donation, procurement and testing of tissues and cells for human application.

An exchange followed, where the following positions were expressed:

Representatives from the competent authorities responsible for medicines/CAT:

It was noted that the EUTCD was designed to ensure safety of recipients (avoiding risks from donors) but that these concerns were not present in the case of autologous products (*i.e.*, there is no donor and recipient but a single patient). It was considered that some of the requirements stemming from the EUTCD could be too burdensome for the development of ATMPs and hinder the distribution thereof to patients, in particular for autologous products. Finally, it was recalled that strict requirements apply under the medicines rules to avoid cross-contamination and to protect those engaged in the processing of tissues/cells.

Representatives from the competent authorities responsible for EUTCD:

It was noted that the T&C requirements for donation, procurement and testing are equally important to ensure safety and quality of autologous processes, e.g., to avoid mix-ups or cross-contamination and to ensure traceability. The proof that these requirements are met could e.g., be integrated in a cell-therapy history file for ATMP manufacturers.

The Commission services announced a mapping exercise with national competent authorities T&C to create transparency in different national requirements for donation, procurement and testing. Pharmaceutical authorities/CAT members will be informed and invited for comments, once the mapping data are collected

Topic 4: Availability of human tissues and cells based therapies.

As introduction to the topic, presentations were made on national perspectives on the availability of human tissues and cells based therapies (NL/MoH and IT/CNT) and on development of cell-based products from academic developments into authorised products (CAT) and on the experience with the hospital exemption (DE/PEI).

An exchange followed, where the following positions were expressed:

Representatives from the competent authorities responsible for medicines/CAT:

Doubts were expressed about the approach described by IT. It was considered that the use of the cells was non-homologous and therefore this is an ATMP. Additionally, questions were raised regarding the protocol followed and the reported results. Moreover, regrets were expressed that no clinical trial (as regulated under Directive 2001/20) had been performed (despite the 25 mio EUR spent on it) in order to generate

data on efficacy and safety which could allow the product to seek a marketing authorisation and to be available across EU (provided that the treatment works). Another concern expressed was that the patient registry remains under the control of the clinical team without prior approval and mechanisms for unbiased results. The shortcomings of extrapolation from literature were explained and specific reference was made to Holoclar (the observational data were related to a very-well characterized product). Holoclar was presented as an example of how a good product developed in academia can obtain a marketing authorization and be given to patients across the EU.

Representatives from the competent authorities responsible for EUTCD:

Italy presented the experience with autologous bone marrow transplant for no option critical ischemia (CLI). Based on positive results in scientific literature covering 1276 patients (16% reduction of amputation rate over 45 trials, of which 7 randomized), and in a study that had been authorised in 2012, the Italian Society of Endovascular Surgeons considered it unethical to withhold this therapy and has submitted an amendment to this study protocol to involve 300 patients in 30 centra. Processing methods and characterization were described. This treatment is considered to be an experimental transplant, with minimal manipulations only and homologous use of the cells. Follow-up data on all patients are collected in a national professional registry, with access by authorities and continuous monitoring of safety. It is also noted that the clinical protocol followed same standards of GCP as for medicinal products. Public health funds are paying for the therapy which allow for a significant saving (8-10,000 Euro cost for bone marrow transplant, instead of 20,000€ for an amputation and consequent social costs). No industrial nor profit purposes are intended.

Topic 5: Quality and safety requirements for starting materials for ATMPs: examination of possible duplications

The Commission services (unit D5) made a presentation on the examination of possible duplications as regards quality and safety requirements for staring materials. Unit D4 made a presentation about the tissue and cells perspective regarding quality and safety requirements for starting materials. A discussion followed, where the following positions were expressed:

Representatives from the competent authorities responsible for medicines/CAT:

It was noted that the duty of the authorities is to protect society. In this regard, it is their duty to ensure that efficacy of products is demonstrated before they are administered to patients and that there is a positive benefit-risk balance. Reference was made to cases where thousands of patients had been exposed to inefficacious treatments (leading even to death) such as the injection of bone-marrow cells in the heart or the bone marrow transplants for the treatment of breast cancer. . When it comes to efficacy and safety data, it was not considered appropriate to solely rely on the internal evaluation of the entity that has a commercial interest in the selling of its products. It was stressed that clinical trials (as regulated under Directive 2001/20) remain the primary instrument to

evaluate benefit and risks of medicinal products and that "pseudo efficacy demonstration" or "pseudo GCP" are not acceptable. The possibility that the efficacy and safety profile of a product could be established on the basis of data obtained from the clinical advisors of tissue establishments, single patient reports, or published data was heavily contested.

Representatives from the competent authorities responsible for EUTCD:

It was noted that, under EUTCD, new tissue/cell processes are subject to in-house operational validation and they are subject to inspections. National rules can provide for clinical follow-up of patients after transplants, e.g., in DE through specific legislation or in PL through registries for cardio-vascular grafts. A lot of evidence is therefore available on "well-established" transplant therapies. In line with art 4 of Directive 2006/86/EC, it was also noted that some Member States have introduced robust procedures for authorisation and validation of new processes in TE's that include a detailed review of published data and upfront in-house validation and demonstration of reproducibility. Such authorisations take account of safety, foresee in defined end-points and robust follow-up, in line with GCP. A discussion followed on quality of sources of evidence that can be considered and on possible biases in publications from investigators in both sectors. It was noted that EU pharma legislation provide that donation, procurement and testing of tissues and cells used as starting materials for ATMP shall be made in accordance with Directive 2004/23/EC.

Topic 6: Exchange of information on alerts between competent authorities responsible for tissues and cells and competent authorities responsible for medicines.

Due to time constraints, this point could not be addressed.

Topic 7: New devices used for providing cell-based therapies at bedside.

Due to time constraints, there was only a short exchange of views on this point. The AT representative gave an overview of her planned presentation concerning point of care devices. In particular, it was noted with concern that nowadays cell processing, possibly manufacturing of advanced therapy medicinal products, may be accessible to any doctor (not only specialists), which might entail risks for patients. A further risk factor is that some of these devices permit the modulation of the output by the user so that it is not even clear what is being given to each patient. A plea was made to reflect on how to regulate these products, together with the authorities responsible for medical devices.