March 27, 2013

European Commission,
DG Health and Consumers,
Unit D5 'Medicinal products – authorisations, EMA'
E-mail: SANCO-ADVANCEDTHERAPY-REPORT@ec.europa.eu

To Whom It May Concern:

On behalf of the Karolinska University Hospital (Karolinska) Innovation Centre, thank you for providing the opportunity to comment on the EMA Regulation 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products ", published at the EMA website on December 12, 2012.

Karolinska is one of Scandinavia's premier health facilities. Together with the world-respected Karolinska Institute, we are in a leading position in medical break-throughs in Sweden. The mission of the Innovation Centre is to promote development of the best possible medical care by providing an environment for innovation offering expertise, services and cutting edge technology for health care, academia and industry. A mission is to advocate for funding, regulatory, and reimbursement policies to facilitate research and product development of regenerative medicine products.

General Comments

Cell therapies could potentially help several patients with severe disease. Many of these illnesses and conditions are not effectively treated by conventional medicine.

EMA appropriately recognizes the differences between traditional small molecule-based drugs, proteins and cell therapies. The requirements for preclinical toxicity testing, which are developed for drug development and device testing, are often not appropriate for evaluating the safety of cell and gene therapy products. The attempt to provide guidance in an area where standard preclinical evaluations for drug development are not applicable maybe alternative methods could be employed, such as cell or tissues based assays, or carefully monitored clinical investigation through Hospital Exemption to establish initial safety and efficacy data.

Karolinska also supports the document's statements supporting improved, early and ongoing communication between the sponsor and the EMA.

It would be appreciated if CAT reflects on the issue when non-clinical studies are requested, on how far the experience from similar products and, if available, **previous clinical experience** can be taken into account.

Many institutions get local classification of their cells i.e. products are classified as ATMPs or non-ATMPS depending on the agency applied to. Even another decision can be made by CAT. Some member states have different agencies that are involved in application and approval of advanced therapies and treatments of patients with an unmet medical need. These agencies classify the advanced therapies differently i.e. classified as ATMP at one agency and non-ATMP/ transplantation in another. The classification can also be different by different competent authorities. It is therefore essential to have a common classification system of advanced

therapies. The reason for this opinion is that it will be difficult to get a routine use/approval for an innovative and effective advanced therapy throughout Europe if different approaches are used.

It is of utmost importance to have clear and consistent classifications system of advanced therapies throughout all member states. Today one can chose to go directly through CAT or through a local authority which may have a more lenient opinion on the ATMP classification. This creates confusion and could also create a barrier to get approval for a product throughout Europe".

Another essential topic that needs to be clearly expressed in the guideline is a clear approach regarding the non-manipulated cells and homologous use (allograft and autograft)

It is stated that cells that are manufactured using an industrial or not sufficiently known process together with substantial manipulation or non-homologous use of the cells they are classified as an ATMP and thus have to be authorized by the centralized procedure. It is not clear if the donation, procurement, and testing of the tissues and cells fall under the scope of Dir. 2004/23/EC. Could be seen as personalized medicines where each cell manufacturing could be regarded as a unique medicinal product. There is no legal definition of an "industrial process" described in the European legislation following could be a definition to describe an industrial process;

- sophisticated (bio-) technical or complex mechanical process (with a clear definition on sophisticated and complicated process)
- use of high-technology or complicated process steps
- wide mechanical, mechanized and automated mass production
- production over X per year, processing in large level (tissue dependent)
- GMP
- production for stocking for unknown customer/patient

If the ATMP fulfills the requirements of the hospital exemption. The hospital exemption can be utilized as a transitional authorization until sufficient data are collected to go through the centralized procedure.

A contradictory point is the processing of the cells where two cases can be identified. In the first case, the cells are processed industrially or with a not sufficiently well-known process. In the second case, they are industrially processed or the manufacturing process is not sufficiently established and well-known. One point is yet clear in both cases: the donation, procurement, and testing of the tissues and cells fall under the scope of Dir. 2004/23/EC. The issue here is that there is no legal definition of an "industrial process".

In case of no substantial manipulation and homologous use, the cell preparation can be authorized nationally.

Cell Therapy Production issues that need to be discussed in the revised 1394/2007/EEC

- Starting material has very high intra-donor variability
- Validation materials ethically difficult to obtain (no paid donors)
- Quantitation and qualification of final product difficult or impossible
- Relevant equipment not available (CE-marked)

- Regulations designed for batch processing rather than single product; single patient
- Sterility testing challenging to perform according to Ph Eur due to very small batch sizes – blood culture systems are the "industry standard"
- The produced product need from a stability reason to be given to the patient before the sterility is QC analyzed.
- Release criteria difficult to define due to large variability among individuals/patients

Hospital Exemption

The Hospital Exemption (HE) is outlined in Article 28 of the ATMP Regulation. Article 28 sets the rules for the implementation of national procedures and control measures to regulate the manufacturing and use of certain non-routinely produced ATMPs outside the scope of the ATMP Regulation.

Article 28 specifies that an ATMP only qualifies for a HE if all of the following criteria are met:

- Preparation on a non-routine basis;
- Preparation according to specific quality standards (equivalent to those for ATMPs with a centralized marketing authorization);
- Use within the same Member State;
- Use in a hospital; (what about two hospitals?)
- Use under the exclusive responsibility of a medical practitioner;
- Comply with an individual medical prescription for a custom-made product for an individual patient, (how many patients can be seen as an individual patient?)

With these criteria, the European legislators intend to provide patients with the possibility of benefiting from a custom-made, innovative, individual treatment in the absence of valid therapeutic alternatives, under the strict condition that community rules related to quality and safety are not undermined (ATMP Regulation, Preamble 6).

The development of advanced therapies for patients requires large investments in time and money that cannot be done without legislation that offers a clear regulatory situation assuring fair and beneficial market conditions for new therapies.

Local therapies under the HE might not be tested for safety and efficacy in the same way as ATMPs through the clinical trial route since for example no study-protocol is submitted to the national competent authority. Furthermore, it is essential to understand if these products can get "approval" and become available for all European patients. It is therefore crucial for the development of new advanced therapies that the European regulation is harmonized implemented in all of the Member States, so that all cell therapy actors can count on a transparent and harmonized use of the HE in the EU without unwanted and unfair competition, with the aim to benefit all eligible patients in Europe.

Karolinska acknowledges that the implementation of Article 28 requires national policy to accommodate the existing national and local healthcare specificities in each Member State. However, these national policies have to fit within the requirements set by Regulation 1394/2007. National policies should also foster innovation according to the intentions formalized

in the ATMP Regulation. In other words, national policies should be a guideline in the development of new and safe ATMPs with approval by EMA, while allowing for non-routine treatments for individual patients.

Karolinska believes that a harmonized European approach is crucial to bring more innovative therapies to all European patients, therapies that are both safe and effective.

Terminology such as 'preparation on a non-routine basis' as a well as individual patient (few patients, what is few 5, 10, 25 or 100?) to be treated used in the ATMP Regulation leaves room for different interpretations, which makes it difficult to establish a uniform interpretation across stakeholders, resulting in national differences. An EU-wide harmonization of the definitions and criteria would be appreciated.

The national implementation for a HE should be similar in all member states and according to the EMA criteria. The manufacturing and use of an ATMP requires attention to safety and quality, especially because of the high level of biological variability, complexity and sensitivity of these types of products. Therefore, national implementations of the HE should ensure that the manufacturing and use of all exempted activities adheres to all applicable safety and quality standards, such as GMP, GCP; ISO and ICH.

When cell therapies are intended to be used in individual patients only and/or the production is produced in limited series, the process to treat patients needs to be clarified. One clarification that needs to be clarified by the EMA is if autologous or allogenic products that are prepared on a regular basis will fall under the ATMP Regulation or not. It seems fairly demanding to require that hospitals and institutions should have to provide documentation similar to common medicinal products to get a centralized marketing approval for treating individual patients and when such cell therapy never will be used to treat many patients. The system and regulations created need to be flexible so patients will be treated with the best possible treatment.

It would be appreciated if it is clarified in 1394/2007 or at the website how to relate to 2001/83/EC article 5.1 "to be able to fulfill special needs of an advanced therapy medicinal product to be supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health-care professional and for use by an individual patient under his direct personal responsibility". Which leaves considerable scope for the national legislation.

A harmonized and transparent implementation based on Article 28 of European Regulation 1394/2007 is crucial to bring more innovative, effective and safe therapies to all European patients. Therefore it needs to be clarified how ATMPs through the HEs and non-routine preparations could get an "approval" and common use throughout the EU. The alternative is to clarify their possibility to perform clinical trials with the information obtained from the earlier HE treatments as supportive information for performing clinical trials and to be a basis for the marketing Authorization Application. Furthermore, it needs to be clarified if it will be allowed to perform treatments under the HE when centrally approved ATMP are available.

Questions that need to be raised before an optimal guideline can be implemented

Could a national or centralized approval be given for products that have been used through the HE for rare diseases using supportive data such as case reports, instead of controlled clinical trials?

In some member states the Annex 13 compliance is required for non-ATMPs and HE, vital indication and for clinical trials. Other states do not have the same high requirement and it would therefore be appreciated that the same standard is used everywhere so that patient safety is the same throughout Europe

Is it possible to do clinical trials with products authorized by the National Competent Authority under the HE? A strict legal interpretation would imply that these products are exempt from MA, not from the requirement specified by the directive 2001/20/EC on clinical trial applications. However, the same equivalence is requested in both cases to the product on the market.

As an alternative to the HE would it be possible to also make the special license (unlimited HE) (such as MHRA (UK) and Fimea (FI), an incentive where an "unlimited use can be possible for ATMPs for which there is no licensed alternative) available so patients can be treated in multiple center and across national borders?

Will there still be a possibility for a National Marketing Authorization as an alternative to the centralized?

Article 5 (Good manufacturing practice) in 1394/2007 need to be expended or cross reference made to a particular annex in the GMP legislation to specify the general and specific principles for good manufacturing for ATMP's.

It is essential to remember that patients need to be treated with the best possible treatments available, therefore all stake holders need to take their responsibility to make this a possibility.

Yours Sincerely

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