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Reflection paper on clinical aspects related to tissue engineered products

Draft

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This reflection paper is intended as a supplement to the Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006) and gives current thinking regarding clinical aspects on TEPs. It is intended to update the Guideline on human cell-based medicinal products with the information in this reflection paper at the next revision.

Comments should be provided using this template. The completed comments form should be sent to Veronika.Jekerle@ema.europa.eu

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1. Introduction

Tissue engineered products (TEPs) are innovative and complex medicinal products intended to regenerate, repair or replace human tissue. As for all medicinal products, it must be demonstrated that a TEP is consistently manufactured to a predefined quality and is safe and efficacious. In addition to the product characteristics there are non-product related factors (i.e. surgical procedures, area/volume of missing tissue, compatibility of biomaterials with cells) that may influence the final outcome. Moreover, some clinical studies (e.g. dose finding and safety) may be challenging for TEPs and may require novel approaches for their clinical development.

2. Scope

This reflection paper is intended to provide specific guidance on clinical testing for tissue engineered products as defined in Regulation (EC) No 1394/2007. This also applies to cells or tissues combined with a medical device and considered a combined Advanced Therapy Medicinal Product (ATMP) according to Art. 7 of Regulation (EC) No 1394/2007.

This reflection paper should be read in conjunction with the clinical part of Annex I, part IV Directive 2001/83/EC and the Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006).

According to 2 (5) of Regulation (EC) No 1394/2007, a TEP can also be classified as a Gene Therapy Medicinal Product (GTMP) as defined in Annex I, Part IV of Directive 2001/83/EC. In this case the principles as outlined in this reflection paper apply equally to such products.

3. Discussion

General comments

The tissue functionality and structural aspects of the regenerated, repaired and/or replaced tissue as well as its persistence in the human body are specific attributes of TEPs that should be taken into account when choosing the clinical endpoints.

A TEP may achieve a total or partial regeneration, repair and/or replacement. An example of the latter may be where only some of the functions required for the target tissue or organ are fully restored (e.g. the mechanical barrier for epidermis). Another example could be the regeneration of a fraction of target tissue or organ resulting in a chimera of normal and dysfunctional tissue.

Therapeutic Claim

In this reflection paper the pharmacodynamic (PD) addresses functionality of the TEP, while the pharmacokinetic (PK) examines the longevity, biodistribution and degradation of the TEP and its components. Reference should also be made to the guideline on safety and efficacy follow-up and risk management of Advanced Therapy medicinal products (EMEA/149995/2008).

The therapeutic claim should be based on the predefined parameters, reflecting full or partial regeneration, repair and/or replacement of the reference tissue/organ. For the purpose of this document, the physiological values of the reference tissue/organ are the ones measured in tissue/organs from healthy individuals.

Since the target of TEPs is to repair, replace and regenerate tissue, conventional pharmacokinetic (PK) studies are not expected. Instead PK and pharmacodynamic (PD) studies are interlinked.

Pharmacodynamics

The time required to reach and to maintain predefined physiological parameters by the administered product should be defined in PD studies.

A set of physiological structural and functional parameters with respect to the specific target tissue/organ should be defined prior to and confirmed during PD studies. Such intended function based on quantitative parameters should be defined by normal physiological values from the individual or a population matched to the recipient.

For combined products the PD studies should refer to the combination of cellular and noncellular components (e.g. collagen, ceramic, synthetic polymers, acellular tissue matrices).

Pharmacokinetics

For some TEPs long term efficacy is based on the persistence of the cells themselves, while for others the components of the TEP will be substituted in time with endogenous derived cells and matrix. Based on the intended therapeutic effect of TEPs (regeneration, repair and/or replacement), the PK studies should reflect the persistence and biodistribution of the cells or other components of the TEP, where relevant.

An evaluation of the proposed lifespan of the TEP might need to be considered for groups of patients depending on age, sex and/or ethnic group. For example, the intended therapeutic effect of a TEP in elderly recipients could be less efficient due to age-related degeneration, imbalance of tissue homeostasis and deficient tissue repair properties.

It is recognized that the replacement, regeneration and/or repair of a damaged tissue might require a fast and/or prolonged response, and might persist for the recipient's life-time. At the time of the MAA, the proposed time to and duration of efficacy needs to be supported by the clinical development plan including the post marketing follow up.

The impact of repeated dosing should be addressed as part of the PK studies.

The cells of a TEP might be reactive to their new environment, for example they may change their phenotype or migration pattern or other characteristics. On the other hand, the PK of TEPs might be dependent on factor(s) released by the implanted cells, thereby influencing cell maturation and/or functionality. When matrix, scaffolds or biologically active substances are administered together with cells, in order to produce or organize a “normal tissue/organ scaffold”, PK studies for the single non-cellular component only are not sufficient, unless justified. Structural/histological imaging might be necessary to assess the overall organisation of the implanted artificial tissue/organ.

The development and validation of new technologies for the assessment of biodistribution in humans, without altering the characteristics and functionality of the TEP, where possible is advisable. The use of cell markers, for example the cell’s genetic profile (for non-autologous cells), radio isotopes or luminescent dyes could be used. It is acknowledged, however, that the sensitivity of such an approach is limited. For those TEPs characterized by a definite location in the human body, a non-invasive analysis of regeneration, repair and/or replacement within the recipient “normal” tissue is encouraged, where possible.

Efficacy endpoints

Clinical efficacy endpoints defined in specific guidance for the studied indication or disease are the basis for clinical evaluation of TEPs.

As for any conventional medicinal product, any novel, previously non-validated endpoint would have to be validated in a prospective study before being used in confirmatory trials. However, if the endpoint

represents the normal value for a physiological characteristic of a tissue being replaced, restored and/or regenerated, a formal clinical trial may not be required to validate this endpoint/biomarker.

Additional cell- and tissue-specific endpoints may be required such as biochemical, morphological, structural and functional parameters, which are relevant for the targeted function. The use of validated biomarkers or generally accepted surrogate endpoints is possible, provided that a correlation between clinically meaningful endpoints and efficacy can be established. In cases, where long-term efficacy is expected, the endpoints should also focus on the duration of the response.

For issues relevant to stem cell-based products, the clinical part of the reflection paper on stem cell-based medicinal products should be consulted (EMA/CAT/571134/2009).

Dose

It is expected that the dose of the medicinal product to be administered will be defined by the characteristics of the tissue defect to be regenerated, repaired and/or replaced. The dose selection (i.e. cell density or concentration of main constituents) should be based on findings of quality and non-clinical product development. Dose finding studies in the clinical setting should be conducted where feasible. However, the risks related to high or suboptimal cell numbers should be considered and addressed. It may be necessary to treat patients with variable doses on comparable size of defect; in these cases, the variable dosing should be justified and the correlation of the dose with the clinical efficacy should be carefully recorded and reported.

Blinding

As for conventional medicinal products, it is advised to apply a double-blind, controlled clinical trial designed against a representative comparator. In cases, where the nature of TEPs was to make a blinded trial unfeasible, all attempts should be made to have blinded assessments. In this case, hard endpoints are preferred.

Comparator

If a comparator (or placebo, sham procedure) is not available or unethical or inadequate (see for example the comparison between surgical interventions with a pharmacological treatment), the comparison to best standard of care could be accepted as concurrent comparator for confirmative clinical study. Alternatively, an intra-individual comparison can be considered.

Where no comparator is available, a randomisation based on other grounds (e.g. no treatment, best supportive care) should be performed, where possible.

Duration of the trials

Long term efficacy and safety follow-up, which cannot be achieved during pre-authorisation clinical development should be conducted and reported post-marketing, where needed. Non-invasive markers or parameters should be available for the clinician in order to follow long term safety and efficacy. It is expected that there will be long term follow-up of both efficacy and safety, even if there is some long term data at the time of authorisation. However for benefit-risk evaluation, sufficient amount of data, including some long-term data is needed prior authorisation taking into account the duration of the clinical effect and considering the risks on the basis of a risk-based approach.

Concomitant treatments/procedures

The surgical and rehabilitation procedures required for the functionality of the administered product are relevant for the evaluation of efficacy and safety and should be standardised during clinical development. A requirement for specific training in the clinical use of such products should be considered in the Summary of Product Characteristics (SmPC). This should be complemented with

mandatory training of surgeons with respect to the surgical technique and rehabilitation procedures with the help of educational material. The adherence to the standard defined during the clinical development should be maintained during post-marketing follow-up.

Clinical safety

The sponsor is expected to present and justify the choice of endpoints representing clinical safety including both short-term and long-term safety concerns. Specific risks associated with TEPs should be studied during clinical development and addressed in the MAA. The developers should consider rescue strategies in cases of treatment failure and other severe adverse events (e.g. tumourigenicity, graft failure, acute degeneration of the regenerated, replaced and/or repaired tissue or organ).

The specific risks including potential loss of efficacy should be part of pharmacovigilance and traceability monitoring and described in the EU Risk Management Plan according to the relevant guideline (Eudralex Volume 9A).

4. References

Regulation on Advanced Therapy Medicinal Products (Regulation (EC) No 1394/2007)

Directive 2009/120/EC amending Annex I, Part IV of Directive 2001/83/EC

Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006)

Guideline on safety and efficacy follow-up and risk management of Advanced Therapy medicinal products (EMEA/149995/2008)

Reflection paper on stem cell-based medicinal products (EMA/CAT/571134/2009).

Eudralex Volume 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use