Reflection paper on clinical aspects related to tissue engineered products

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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.

Keywords	*Advanced Therapy medicinal products, tissue engineered products, clinical, dossier requirements, safety, efficacy*

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1. Introduction

Tissue engineered products (TEPs) are innovative and complex medicinal products intended to regenerate, repair or replace part of or whole human tissue. As for all medicinal products, it must be demonstrated that a TEP is consistently manufactured to a predefined quality showing a favourable benefit risk balance. In addition to the product characteristics, non-product related factors may be involved (e.g. surgical procedures, area/volume of missing tissue, compatibility of biomaterials (applied in parallel) with cells and tissues) 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. Nevertheless, the principles of ICH/GCP should be adhered to when evaluating TEPs. Principles of GCP and relevant clinical guidelines will apply when developing a TEP.

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. 2(d) 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.

The Guideline on the risk-based approach according to Annex I, part IV of Dir. 2001/83/EC applied to ATMPs (EMA/CAT/CPWP/686637/2011) applies on a case-by-case basis and is intended to support the developer in risk analysis and planning of the development program. It can further be used as one starting point for planning risk minimization and risk management plans. 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).

Existing guidelines on developing medicinal products including specific guidance for the studied indication or disease should be taken into account where/as far as relevant.

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. The heterogenous character of TEPs, concerning the origin and nature of starting material as well as their therapeutic indication influencing the risk profile and intended effects, requires scrutinised and innovative development approaches. This may require the Applicant to develop in parallel or improve and validate

new analytical test methods in order to study identified unique risks and/or effects of the specific TEP. Comparisons between similar TEPs are possible but need to be carefully evaluated.

In this reflection paper pharmacodynamics (PD) addresses structural and/or functional integrity of the TEP, while pharmacokinetics (PK) examines the biodistribution, longevity and possible degradation of the TEP and its components. Longevity studies will describe cell and/or tissue persistence and survival. Since the intention of TEPs is to repair, replace and regenerate tissue, conventional PK studies are not expected. Instead PK and PD studies may be interlinked.

Therapeutic Claim

The therapeutic claim should be full or partial regeneration, repair and/or replacement of the target tissue/organ. Parameters reflecting the therapeutic claim should be predefined. For the purpose of this documentation, the physiological parameters and values of the target tissue/organ are the ones measured in tissue/organs of healthy individuals. If full restoration of these parameters and values is not achieved, this should be fully justified. When the therapeutic claim is a partial recovery of the tissue/organ function, a justification based on clinical relevance is expected on the chosen subset of parameters or value range.

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, where appropriate. The number of tested individuals needs to be sufficient to make appropriate conclusions on PD data. However, this may need to take into account possible ethical and practical considerations.

For combined products the PD studies should refer to the combination of cellular and non-cellular 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/tissues themselves while for others the components of the TEP will be substituted in time with endogenously derived cells and matrix. Based on the intended therapeutic effect of TEPs (regeneration, repair and/or replacement), PK studies should reflect the persistence and biodistribution of the functional cells and/or other components of the TEP, where relevant. The majority of issues regarding biodistribution are expected to be addressed in non-clinical studies. Emerging data and their implications for the safety of the trial subjects need to be addressed in the clinical trial design.

In the case that safe cell tracking methods in humans have been established for the individual TEP, human biodistribution studies should be considered. Information from non-clinical models may be limited due to the fact that the influence of the environment in an animal on human cell characteristics and functionality may not be comparable to the human milieu. An evaluation of the proposed lifespan of the TEP might need to be considered for groups of patients depending on age, sex, ethnic group and/or disease status in line with the intended indication. 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.

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

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. Where matrix, scaffolds or biologically active substances are administered together with cells for the purpose to produce or organize normal tissue/organ architecture, PK studies should be conducted with the combination, unless justified. Structural/histological imaging might be necessary to assess the overall organisation of the implanted artificial tissue/organ within the host environment and its modifications, especially when part of the product is integrated and/or degradable.

It is advisable to implement or develop and validate technologies for the assessment of biodistribution in humans, which do not alter the characteristics and functionality of the TEP, where possible. Cell markers (i.e. genetic profile for non-autologous cells), radioisotopes or luminescent dyes could be used in ex vivo or in vitro samples. It is acknowledged, however, that the sensitivity of such approaches may be limited. For those TEPs characterised by a definite location in the human body, a non-invasive analysis of regeneration, repair and/or replacement within the recipient's "normal" tissue is encouraged, where possible.

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 from quality and non-clinical product development, as far as possible. 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. Limitations of the available amount of cells/tissue in the TEP (e.g. due to. autologous donation, manufacturing procedure) may lead to the use of variable doses on comparable size of defects. 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.

Efficacy endpoints

Clinical efficacy endpoints as defined in specific guidance for the studied indication or disease are the basis for the clinical evaluation of TEPs. Additional cell- and tissue-specific endpoints may be required such as biochemical, morphological, structural and functional parameters, which are relevant for the targeted therapeutic claim. These endpoints can be used as co-primary or secondary variables, and are expected to support the clinical primary efficacy variable.

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. In cases where long-term efficacy is expected, the endpoints should also focus on the duration of the response.

As for any conventional medicinal product, any non-validated endpoint or surrogate endpoint such as novel biomarkers would have to be validated in a prospective study before being used in confirmatory clinical trials. The developer is encouraged to discuss surrogate endpoints and /or non-validated endpoints with regulators, e.g. in a scientific advice.

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.

Additional investigations might be required post-marketing to follow-up on duration of efficacy.

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).

Study design

As for conventional medicinal products, it is advised to apply a double-blind, controlled clinical trial design against an appropriate control.

Blinding

Due to the nature of TEPs and non-product related factors (e.g. surgical procedure) blinding of the physician and/or patient may not be feasible. Furthermore, the use of a placebo or sham procedure may not be possible. In these cases, all attempts should be made to have blinded outcome assessments and objective endpoints should be chosen if available.

Comparator

If an active comparator is not available or inadequate, the comparison to best standard of care or treatment with a placebo or sham procedure could be accepted as concurrent control for the confirmative clinical study. In some instances an intra-individual comparison can be considered when appropriately justified.

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 to follow long term safety and efficacy are to be presented and justified by the developer. If different methods are used for follow-up (e.g. invasive methods such as biopsies) than those used during the confirmatory trials, they should be agreed with regulators prior to marketing authorisation. Of note, post-marketing studies should always be agreed with the regulator even if the methods have not changed. 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, a sufficient amount of data, including some long-term data is needed prior to authorisation taking into account the duration of the clinical effect and considering the risks.

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 (e.g. of surgeons, radiologists) with respect to the surgical or other implantation techniques 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. If improved surgical techniques and rehabilitation protocols are planned to be introduced during the post-marketing phase, this should be discussed with the regulatory authorities.

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 aspects. It is recommended that a thorough risk analysis is conducted early on to guide safety studies of the specific TEP. All risks associated to the starting material, product characteristics, administration procedure and follow-up should be addressed in the dossier. Risks associated with the TEP should be addressed in the MAA. Information on similar

TEPs already on the market or results of scientific publications on respective product categories may be a valuable additional source of supportive data to be included to 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) both when planning clinical trials and for commercialisation. Documentation is expected on available rescue therapies and possible limitations therein, including impact of the TEP treatment itself.

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 (Guideline on Good Pharmacovigilance Practices – Module 5 Risk Management Systems (EMA/838713/2011)).

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).

Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products (EMA/CAT/CPWP/686637/2011).

Guideline on Good Pharmacovigilance Practices – Module 5 Risk Management Systems (EMA/838713/2011)