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Comments on Commission's Consultation Paper on Tissue Engineered Products Legislation

The European Commission, DG Enterprise, published a public consultation proposal for a harmonised Regulation on human tissue engineered products (hTEP) in Europe on 6th April 2004.

EBE and EFPIA welcome and appreciate the Commission's initiative to consult all stakeholders at an early stage in this effort to create a harmonised Regulation for hTEPs in Europe. EBE and EFPIA have been working closely with other industry stakeholder groups, and would like to submit the following comments.

EBE and EFPIA **welcome** the Commission's proposals with regard to:

- The efforts of the Commission to develop a hTEP Regulation instead of a Directive;
- The proposed timeframe for publication of the Commission's proposal for the hTEP Regulation being scheduled for June 2004. This means that this Regulation may be effective at the same time that the DG SanCo Directive (2004/23/EC) is implemented into the national law (April 2006);
- The exclusion of xenogeneic TEPs from the scope of Regulation with the proviso that the scope of the Regulation be re-assessed at a later date to consider the inclusion of xenogeneic tissues; and
- The dual role of the EMEA as clearing house function and the assessment body for hTEPs, provided that this is proven workable (e.g., including a specialised Committee comparable to CPMP, CVMP, etc.).

EBE and EFPIA, however, **are concerned** about the following:

- The need for a precise and clear borderline with somatic cell therapy medicinal products;
- The proposed differentiation of regulatory procedure based solely on the origin of the hTEP (central via EMEA for allogeneic and national for autologous cells);
- The two-tier approach for approval of hTEPs, allowing for dispersion of already scarce expertise and less transparency; and
- The lack of specifically adapted clinical trial guidelines for hTEPs.

In the following EBE and EFPIA[2] comments to each section are provided.

SCOPE

- For all trials in human beings, GCP should apply, but the Clinical Trials Directive (2001/20/EC) cannot be fully applied to hTEP products. Only the appropriate part(s) should be incorporated in the hTEP Regulation.

DEFINITION

- Need for clarity in the definition of human Tissue Engineered Products (hTEPs) to ensure an agreed differentiation between hTEPs, Medicinal Products (which include Gene Transfer Medicinal Products and Human Somatic Cell Therapy Medicinal Products) as defined in 2001/83EC (as amended in 2003/63/EC) and Medical Devices.
- Additional parameters besides metabolic, pharmacological and immunological action should be defined in order to better differentiate between somatic cell therapy medicinal products and hTEPs.
- It is difficult to provide a precise and clear borderline between "substantially" and "not substantially" manipulated. This should be sought, however. Solutions used in other legislatures (e.g., the US) could be used as a potential source. This would have the added benefit of increasing harmonisation.
- A precise and clear borderline would mean that if a medical device or a medicinal product is an integral part of a hTEP, the *lex specialis* principle would then result in the product only requiring to be regulated under the hTEP Regulation.

AUTHORISATION PROCEDURE

- Confidence of all stakeholders in a regulatory system which ensures highest level of safety, quality and effectiveness standards for patients
- A fast and simple approval process for hTEPs
- Differentiation for authorisation procedures should not be based solely on the origin of cells / tissues
- Expertise evaluating hTEP dossiers at central level
- Ensuring availability of expertise at central level such as "centre of excellence" to evaluate all hTEPs
- Ensure highest quality and safety standards for hTEPs whatever the origin of the product
- Possibility of conditional and "fast-track" approvals for hTEPs
- Reduction of licensing fees particularly for SMEs
- Transparent authorisation procedures and decisions
- Data protection system analogous to medicines approach
- Optimisation of the reimbursement potential by the credibility of the approval process for all hTEPs
- Balance regulatory requirements for products ensuring continuation of development of experimental new and innovative procedures
- The placing on the market definition should also cover hospital products, which should be subject to the same principles
- Level playing field for all organisations in this field
- Similar incentives as for rare diseases in Orphan Drug Regulation
- Same procedure as for imported products. hTEPs manufactured in non-EU countries should be placed on the market only if authorised. The applicant / sponsor shall prove that the hTEP meets standards of quality safety and effectiveness equivalent to those laid down in the Regulation.
- The site where hTEPs are applied to patients should not be limited only to hospitals

AUTHORISATION REQUIREMENTS

- Pool all available expertise – at an early stage for consultation – including drafting of scientific assessment criteria / extra guidelines: consultation with all stakeholders, including industry bodies
- Include development of content requirements as early as possible and include in Clinical Trial Approval procedures (not only in the Marketing Authorisation procedure).
- Early communication between Agency and industry on development plan is necessary
- "Clearing house" function possible at any stage during the development, not only when filing for Marketing Authorisation
- Mechanism of 'Conditional Approval' to be considered, to balance pre- and post-commitment requirements, in view of many patients often already treated with hTEPs in the EU

  Note: *although not part of the Regulation, it is desirable that conditional approval should also lead to reimbursement, because in many hTEPs additional surgical procedures are needed, which may lead to costly treatments. There is a risk that reimbursement authorities, even with a conditional approval, will delay a reimbursement decision until the conditions for conditional approvals are fulfilled.*
- Since many products are at this moment in development and have not reached market approval stage yet, sufficient attention should be given to Clinical Trial Approval (CTA) mechanisms:
  - A *single standardized format for data requirements* for CTA for hTEPs
  - Review timelines of clinical trial approval for hTEPs – once Ethics Committee approval (one per country) is obtained, approval should be implicit by National Authority. Maximum 60 days
  - One standard for obtaining Import License for investigational hTEPs (and, although not part of the Regulation, ideally customs clearance, too), in line with often very short shelf lives of hTEPs
  - Full Good Manufacturing Practices (GMPs) from Phase I onwards as in the Clinical Trials Directive could be very difficult to achieve
  - Non-clinical testing is limited by availability and relevance of animal models.

POST-AUTHORISATION ISSUES

- Tissue engineered products (both allogeneic and autologous) should use one database (similar to the one used for medicinal products, EuroPHARM)
- Reporting by health professionals and Market Authorisation holder of adverse reactions, product defects and other safety relevant information to national and European health authorities should follow the same standard processes across all Member States.
- The Regulation should include standard pharmacovigilance processes specific for tissue-engineered products. These processes need to be cost-efficient and practical and should be based on the existing processes for medicinal products and devices.
- Safety reporting should be done through the existing electronic reporting tools that are also used for medicinal products (EudraVigilance).
- Safety issues that are specific for certain products or groups / classes of products that may require more substantial post-approval safety monitoring should become part of the Marketing Authorisation of the given product rather than of the standard pharmacovigilance process for hTEPs. Such specific requirements may include long-term traceability of patients treated with a specific product or specific safety reporting requirements. Details should be provided by Guidances or Guidelines to be developed with input from all relevant stakeholders.
- Safety reporting for autologous and allogeneic hTEPs will follow the same processes.

CONCLUSIONS

EBE and EFPIA very much welcome the new paper from the European Commission allowing all stakeholders to communicate their position at an early drafting stage.

EBE and EFPIA strongly favour the creation of a new and appropriate Regulation laying down the requirements for Marketing Authorisation procedures for innovative tissue-engineered products in the entire Community market.

EBE and EFPIA, however, have some concerns if the current draft proposals were to be enacted.

EBE and EFPIA would like to point out that hTEPs differ from medicinal products. Therefore, the requirements for clinical trials from the Clinical Trials Directive cannot be fully applied to hTEPs. We would like to see specific requirements for clinical trials incorporated in the new proposed hTEP Regulation.

EBE and EFPIA require a clearer definition of hTEPs, differentiating them from somatic cell therapy medicinal products (for borderline cases).

EBE and EFPIA suggest that the body responsible for clearing house function should have well-defined terms of reference. It is our opinion that the goal should be to provide hTEPs with the highest quality and safety profile for patients. We are concerned whether this can be ensured in each and all of the 25 Member States, due to the scarcity and spread of sufficient expertise and knowledge to evaluate the autologous hTEPs manufactured in their territory.

Member State expertise should be grouped centrally to evaluate hTEPs instead of the two-tiered approach proposed and the split between the two approaches based solely on the origin of the product.

EBE and EFPIA ask for a fast and simple approval system for hTEPs.

EBE and EFPIA therefore favour the risk management approach.

We look forward to working further with the Commission and other stakeholders on the new Regulation.

30 April 2004