PROPOSAL FOR A HARMONISED REGULATORY FRAMEWORK ON HUMAN TISSUE ENGINEERED PRODUCTS: DG ENTERPRISE CONSULTATION PAPER

RESPONSE BY BIOINDUSTRY ASSOCIATION

INTRODUCTION

The BioIndustry Association (BIA) welcomes and appreciates the Commission's initiative to consult the stakeholders, including industry, at an early stage in this effort to issue a harmonised Regulation for human tissue engineered products (hTEP) in Europe.

The BIA is the trade association for innovative enterprises in the UK's bioscience sector. Its mission is to promote a thriving, financially sound sector of the UK economy, built upon developments across the biosciences, to create economic growth and an expanding skills base. The BIA has over 350 members, the majority of which are involved in realising the human health benefits that bioscience promises.

The BIA supports the comments made by EuropaBio, the European Association for Bioindustries, in their submission to this consultation.

In particular, we welcome the following proposals by the Commission:

- The introduction of a hTEP Regulation rather than a Directive.
- The proposed timeframe of publication of the hTEP Regulation in June 2004 means it could be effective at the same time as Directive 2004/23/EC is implemented into national law (April 2006).
- The exclusion of xenogeneic TEP from the scope of the Regulation, with the proviso that the scope of the Regulation be re-assessed at a later date to consider the inclusion of xenogeneic tissues.

However, we are concerned about the following:

- Dual role of the EMEA as clearing house function and the assessment body for hTEP, unless proven workable.
- The provision of a precise and clear borderline to somatic cell therapy medicinal products
- Differentiation of regulatory procedure based only on the origin of hTEP (central via EMEA for allogeneic and national for autologous cells).
- Two-tier approach for approval of hTEP, which would mean the dispersion of already scarce expertise and less transparency.
- Lack of specifically adapted clinical trial guidelines for hTEP.

The BIA's comments on each section are outlined below.

SCOPE

- R&D trials not in humans should be excluded from the Regulation, although GLP should apply. For all trials in humans, 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.
- § Xenogeneic TEPs are excluded from the scope of the Regulation – however, hTEPs composed of animal cells and tissues which are used in the manufacturing process should be covered by the Regulation.

DEFINITION

- § There is a need for clarity in the definition of hTEPs such that there is 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.
- § We propose the addition of cells/tissues derived materials in order to cover all cells/tissues that have tissue regenerative properties. Thus hTEPs are "derived from living cells or tissues with the final product containing viable or non-viable cells or their derivatives".
- § Additional parameters besides metabolic, pharmacological and immunological action should be defined in order to better differentiate between somatic cell therapy medicinal products and hTEPs. This is important as some hTEPs may also act in the same way. Indeed, nearly all products will have some metabolic, immunological or pharmacological mode of action, but will not have this as primary mode of action, but rather secondary or even tertiary. There is a need to clarify that tissue based substances are not medicines, even though their effectiveness may be driven or aided by metabolic, immunological or pharmacological means.
- For future HTEP developments there will be a need for clarity between Gene Transfer Medicinal Products with delivery systems, Somatic Cell Therapy and Cell and cell-derived regenerative therapies, including those that may have been modified genetically. It is suggested that the new Regulation should cover all products that are made up of or contain human cell and cell derived materials and that qualify by virtue of the intended therapy definition.
- It is difficult to provide a precise and clear borderline between "substantially" and "not substantially" manipulated. We would therefore prefer to see the word "substantially" deleted and the phrase amended as suggested below.
- 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.

We propose the following changes in the definition:

HTEPs are derived from living cells or tissues, with the final product containing viable or non-viable cells or their derivatives. ……

- *Engineering* means any process whereby cells and tissues removed from a human donor (source materials) are ~~substantially~~ manipulated, to achieve the desired ~~so that their normal~~ physiological functions as described above ~~are affected~~….

AUTHORISATION PROCEDURE

- Confidence of all stakeholders in a regulatory system that ensures the highest level of safety, quality and effectiveness standards for patients.
- A fast and simple approval process for hTEPs is essential.
- We are not in favour of the differentiation of authorisation procedures based solely on the origin of cells/tissues.
- We doubt that the two-tier marketing authorisation system for autologous hTEP will work – if implemented, it will be rather precedent driven, and may end up with complex autologous products automatically being called medicines.
- Expertise evaluating hTEP dossier at central level.
- Ensuring availability of expertise at central level such as “center of excellence” to evaluate all hTEPs.
- Ensure the 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.
- Optimise 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 manufacturer 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 – include industry.
- Include development of content requirements as early as possible and include in Clinical Trial Approval procedures (not only in Marketing Authorisation procedure). Early communication between Agency and industry on development plan is necessary.
- Technical Annexes to be included in the hTEP Regulation.
- Include available expertise – also from industry at an early stage for consultation.
- Clearing house function as early as possible in the development stage, NOT when filing for marketing authorisation.
- Drafting of scientific assessment criteria/extra guidelines: centralise expertise also from industry bodies.
- Products to be developed in line with “claim” that is sought.
- Data protection during clinical trials to avoid copying confidential information by experts.
- Risk /benefit assessment approach is key precursor already in early development and could be indicative of the type of non-clinical and clinical evidence that would/could be required.

- 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.
- Conditional approval should also lead to reimbursement, because in many hTEPs additional surgical procedures are needed, which may lead to costly treatments. The risk exists that reimbursement authorities, even with a conditional approval, will delay a reimbursement decision until the time that conditions for conditional approvals are fulfilled.
- Since many products are currently in development and have not reached the market approval stage yet, sufficient attention should be given to Clinical Trial Approval (CTA) mechanisms.
    - A single standardised format for data requirements for CTA for TEPs.
    - Review timelines of clinical trial approval for TEPs – once EC approval is obtained; approval should be implicit by National Authority. Maximum 60 days.
    - One standard for obtaining Import License for investigational TEPs and customs clearance requirements in line with often very short shelf lives of TEPs.
    - Requirements in line with reality and actual state of knowledge. 100% exhaustive preventive testing is unfeasible and impossible.
    - Full Good Manufacturing Practices (GMPs) from phase I onwards as in CTD could be very difficult to achieve
    - Non-clinical testing is limited by availability and relevance of animal models – especially for autologous treatments.

POST-AUTHORISATION ISSUES

- Tissue engineered products (both allogeneic and autologous) should use only one database (e.g. 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 which are also used for medicinal products (EudraVigilance).
- Safety issues which are specific for certain products or groups/classes of products may require more substantial post-approval safety monitoring, which should become part of the market authorisation of the given product rather than of the standard pharmacovigilance process for TEPs. 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 autologuous and allogeneic TEPs will follow the same processes.

CONCLUSION

The BIA strongly favours the creation of a new and appropriate Regulation harmonising the requirements for clinical trials and marketing authorisation procedures of innovative tissue engineered products in the entire Community market.

However, we would also have some concerns if the proposals were to be enacted as currently drafted.

A clear definition of hTEP is required, differentiating with somatic cell therapy medicinal products (for borderline cases).

We suggest that the body responsible for clearing house function should have well defined terms of reference. 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 of the 25 Member States due to lack of sufficient expertise and knowledge to evaluate the autologous hTEPs manufactured in their territory. We therefore favour the risk management approach to be taken into consideration, grouping Member State expertise centrally to evaluate hTEPs instead of the two-tiered approach proposal and based only on the origin of the product.

A fast and simple approval system for hTEPs is essential.

HTEPs differ from medicinal products, therefore the requirements for clinical trials from the Clinical Trials Directive should not be fully applied to hTEPs. We would like to see specific requirements for clinical trials incorporated in the new proposed hTEP Regulation. The BIA would also like to highlight the need for urgent consultation with the aim of producing early guidance for clinical trials.

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