EuropaBio Feedback on Commission's Consultation Paper on Tissue Engineered Products Legislation*

INTRODUCTION

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

EuropaBio welcomes and appreciates the Commission's initiative to consult the stakeholders, including industry, at an early stage in this effort to issue a harmonized Regulation for hTEP in Europe.

Industry welcomes the Commission's proposals with regards to:

- The efforts of the Commission to develop a hTEP Regulation instead of a Directive
- The proposed timeframe of publication of the Commission's proposal for the hTEP Regulation in June 2004. This means that this Regulation could 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 TEP 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

Industry, however, is 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 solely on the origin of hTEP (central via EMEA for allogeneic and national for autologous cells)
- Two-tier approach for approval of hTEP, allowing for dispersion of already scarce expertise and less transparancy.
- Lack of specifically adapted clinical trial guidelines for hTEP

In the following EuropaBio's comments to each section are provided.

SCOPE

- Ø R&D trials not in human beings should be excluded from the Regulation, although GLP should apply. For all trials in human beings, GCP should apply, but the Clinical Trials Directive (2001/20/EC) can not be fully applied to hTEP products. Only the appropriate part(s) should be incorporated in the hTEP Regulation (*see enclosed Annex "Proposal for Clinical Evaluation for TEPs"*)
- Ø Xenogeneic TEPs are excluded from the scope of Regulation however hTEPs composed of animal cells and tissues which are used in the manufacturing process should be covered by the Regulation

DEFINITION

- Ø Need for clarity in the definition of human Tissue Engineered Products (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
- Ø We propose the addition of cells/tissues derived materials in order to cover all cells/tissues which 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"
- Ø 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
- Ø 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
- Ø 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
- Ø 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:

…..
Human tissue engineered products 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~~….

AUTHORIZATION PROCEDURE

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

AUTHORISATION REQUIREMENTS

- Ø Pool all available expertise – include industry
- Ø Include development of content requirements as early as possible and include in Clinical Trial Approval procedures! (not only in Marketing Authorization procedure). Early communication between Agency and industry on development plan is necessary
- Ø Technical Annexes to be included in the hTEP Regulation
- Ø Include available expertise – also from industry at an early stage for consultation
- Ø Clearing house function as early as possible in development stage NOT when filing for marketing authorization
- Ø Drafting of scientific assessment criteria/extra guidelines: centralize expertise also from industry bodies
- Ø Products to be developed in line with "claim" that is sought

- Ø Data protection during clinical trials to avoid copying confidential information by experts
- Ø 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
- Ø 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 EU

  Conditional approval should also lead to reimbursement, because in many hTEPs additional surgical procedures are needed, which may lead to costly treatments. 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
- Ø 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 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.

- Ø Tissue engineered products (both allogeneic and autologous) should use only one database (e.g. EuroPHARM)
- Ø Reporting by health professionals and market authorization 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
- Ø 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
- Ø Safety reporting should be done through the existing electronic reporting tools which are also used for medicinal products (EudraVigilance)
- Ø 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 authorization 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
- Ø Safety reporting for autologuous and allogeneic TEPs will follow the same processes

CONCLUSION

EuropaBio very much welcomes the new paper from the European Commission allowing stakeholders, including industry, to communicate their position at an early drafting stage.

EuropaBio strongly favors the creation of a new and appropriate Regulation harmonizing the requirements for clinical trials and marketing authorization procedures of innovative tissue engineered products in the entire Community market.

EuropaBio, however, has also some concerns if the current draft proposals were to be enacted.

EuropaBio requires a clear definition of hTEP differentiating with somatic cell therapy medicinal products (for borderline cases).

EuropaBio 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 of the 25 Member States due to lack of sufficient expertise and knowledge to evaluate the autologous hTEPs manufactured in their territory.
EuropaBio, therefore favors the risk management approach to be taken into consideration grouping Member State expertise centrally to evaluate hTEPs instead of the two-tiered approach proposed and based only on the origin of the product.

EuropaBio asks for a fast and simple approval system for hTEPs.

EuropaBio would like to point out that hTEPs differ from medicinal products. Therefore the requirements for clinical trials from the clinical trial directive cannot be fully applied to hTEPs. We would like to see specific requirements for clinical trials incorporated in the new proposed hTEP Regulation.

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

April 2004

For any queries or questions please contact Johan Vanhemelrijck
(j.vanhemelrijck@europabio.org); Tel +32 (0)27350373.

*This paper has been prepared by the **EuropaBio Cell and Tissue Working Group**. Its members are: Baxter, BioIndustry Association (UK), Fidia Advanced Biopolymers, Fresenius, Genzyme, GlaxoSmithKline, Hoffmann-La Roche, Novartis, Tissue Engineering Technologies, Tigenix, Xcellentis.* EuropaBio, the European Association for Bioindustries, has 35 corporate members operating worldwide and 21 national biotechnology associations representing some 1200 small and medium sized enterprises involved in research and development, testing, manufacturing and distribution of biotechnology products. www.europabio.org

Proposal for Clinical Evaluation program for TEPs

Question: What should the Clinical Trial Program for TEPs look like, in case the Clinical Trials Directive is not applicable or how should the Clinical Trials Directive be adapted to fit TEPs?

It has been acknowledged that TEPs are different from medicinal products and medical devices and therefore the decision has been made to issue a Regulation instead of a Directive as only a Regulation can guarantee harmonized standards within the entire Community for TEPs. The Clinical Trial Directive (CTD), 2001/20/EC, which will get effective in May 2004 sets standards which some of them do also apply for TEPs. However since CTD is a Directive it means that each Member States (MS) can pose additional requirements. Therefore, the best appropriate way to guarantee European wide harmonization would be to incorporate appropriate parts of CTD directly into the TEP Regulation.

Overall goal: provide timely access to cell and tissue engineered products to the patients in the EU, obtain appropriate routine reimbursement, and guarantee quality, safety and efficacy of TEPs.

Caveat:

- the information in the tables should be seen as trying to illustrate the issues/challenges. By no means they are intended to give a comprehensive overview or solution. The scope of the document has to be seen as a work document for further elaboration

- the distinction made between TEPs, medical devices and medicines is sometimes artificial, since there are/will be a lot of atypical products in each of these categories. We would recommend as discussed that the decision on which regulatory framework to apply would be that, according to the Lex Specialis principle, the majority of these products would fall under the TEP regulation and that for border cases the expert committee at the central Agency will decide.

	TEP(1)(2)	**Medicinal product**	**Medical Device**	**Tissue banking/**
Examples	Range of products in category of 'implantables' /(help in) replacement of (most products at this stage) to complex products with cardiological, neurological etc applications. Very wide spectrum of products, also simpler product e.g. DBM	Could be the 'comparator' in the clinical evaluation depending on the claim that is sought.	Often seen as 'inert'; for our purpose often best compared with implantable devices (class IIb or III)[1] or tool/intervening in surgical procedure	Allografts. 90% of products, time and effort is spent on 'allografts'. Banking of post mortem grafts, banked for later use.
Requirements to be fulfilled regulatory **Legal framework**	Not clear at the moment. Proposed: proof of Quality, Safety and Efficacy/ Effectiveness. 15-25 (?) different national legislations. Not harmonized.	Proof of Quality, Safety, Efficacy Well defined	Proof of Quality, Safety, Effectiveness. Well defined	In the past no proof of Q or S or E required. New proposed Dir. requires proof of Quality and Safety.
Reimbursement	Often not. Since products had no specific framework under which to be approved reimbursement was difficult. Evidence presented was often judged as being insufficient but type of evidence needed was not clarified and judged arbitrarily and different from Member state to Member state.	Routinely if approved	Routinely as part of procedure (often surgical)	Routinely as part of transplantation procedure
Administration	Implanted /grafted/topical Potentially injected.	Oral, i.v., i.m. implanted, (inhaled), topical.	Implanted or tool used in surgical procedure	Surgical/topicali mplantation

Background materials used:

(1) Part of presentation by EuropaBio to Commissioner Liikanen re-used.

(2) NIST study (2003)

[1] In the tables the comparative parameters in both the medicinal and device section of the table withheld for illustrative purposes are the examples that are possibly close enough to TEPs (for e.g. implantable devices is a comparison because they could be close to the musculoskeletal area or the cardio-area e.g.. TEPs will often restore function to 'defects' that would otherwise lead to 'chronic'deterioration.

Conclusion:

- **Regardless of the type/background of the product (i.e., medicinal products, medical devices, tissue banking), marketing authorization holders of the product can apply for reimbursement of the approved products. 'In the future, reimbursement will have to cover TEPs. Most products (i.e., traditional tissue transplants) have a mechanism in place through which Quality, Safety and Efficacy/Effectiveness is proven.**

- **It should not be possible that 'safe' products come to market that are potentially inefficacious (because they have never been tested).** (re. Level 'regulation' field including pre-clinical and clinical testing for all actors in the field e.g.products developed by individual doctors, tissue banks).[2]

- **A mechanism will have to be put in place for products already in use (grantfathering clause)**

It will be important to distinguish combination products that contain, as an integral element, a medical device, biomaterial or medicine, and therefore are regulated as a TEP (Lex specialis) and combination of products, in other words, TEPs that are used together with other products which are not an integral part of the product, and therefore separately regulated under their own regulatory framework.

Question: Will these combination products follow the same clinical development path or will certain aspects require that they might be tried versus other legislation? In the end, these products represent innovative changes for the same 'indication' for the same type of patient. What e.g. will be the required extent of the clinical evaluation of the individual components of a combination product if the components cannot be separated?[3]

Re-visiting the Clinical Evaluation Part of the development of TEPs

- Should look at the entire development plan for such compounds.
- Cannot really succeed without looking into the Quality part of the dossier as well.
- Cannot succeed without looking into the Safety – Non clinical part of the dossier.
- Should look into the timeline of when 'clinical' evaluation of compounds can start vis-à-vis the 'status' of pre-clinical work.
- Should look into the content of the dossier to be submitted for obtaining Clinical Trial Approval.
- Should look into procedure and timelines for obtaining Clinical Trial Approval.
- Should possibly provide guidances (Guidance documents e.g. PCT- ICH) on the overall development plan.

[2] Example can be provided e.g of individual doctors immediately going to human application (without pre-clinical work) in 1 Member state, where at the same time in 2 other Member States, the clinical trials for that application were all ON HOLD because of major toxicity risk encountered within the trial setting.

[3] This applies in particular to the use of non-approved materials for components of the finished product or for parts of the production process.

For the sake of clarity, the scope of this document relates to obtaining clinical evaluation authorization, the content of the dossier to be presented and the procedure related to obtaining authorization, this as opposed to obtaining market authorization. Of course both are interrelated.

Risk Assessment – Risk Mitigation

As a first step in the 'overall assessment of the (clinical) development plan for TEPs', it is thought that a risk/benefit assessment approach is a *key precursor* to the further steps. From the risk/benefit assessment (standard to be finalized) the subsequent risk control measures could be indicative of the type of clinical evidence that would/could be required for a particular type of product so that safety of products can be guaranteed.

Clinical Evaluation Track for TEPs

1. Quality and Safety (Non-clinical) Part of dossier

1.1. Quality

	TEP	**Medicinal Product**	**Device**	**Tissue banking /Hospital product**
Manufacturing process	Highly innovative; cell and tissue 'engineering' evolving requirements	From evolving to established processes	Established processes	No quality standards exist on EU level.
Marginal cost/treatment	Very high	Low to very high	Low/medium	Not known
SPECS[4] =>SPC	Sometimes difficult to define, especially with regards to the "therapeutic dose"	Sometimes complex	Product characteristics defined	Not required. Safety profile mandatory (2002/0128)
Batch definition/batch release	If autologous: 1 patient is 1 batch.[5] If allogeneic: 1batch is many patient treatments.	1 batch: Multiple thousands of treatments. But not at early clinical stages and never for some biological medicinal products.	1 batch: many patients treatments. (custom made devices exist – ruled differently)	1 patient can provide a few 'allografts' to a few patients.
Shelf life	Often only some hours ! – also longer[6]	Variable, but long as compared to living cells.	Long	Often very short
	TEP	**Medicinal Product**	**Device**	**Tissue banking /Hospital product**
Quality System	A clear look will have to be	License of	QS certification	National tissue

[4] SPECS : means 'specifications'; to be developed by each manufacturer and leading to what is called under Medicinal legislation the SPC (summary of product characteristics) , leading in its turn to the 'package insert'.

[5] Autologous products have to be regarded as privileged products (immunologically privileged)'custom made products; the implication on 'development of specifications' and inherent 'limit definition' for eventual batch rejection (1 patient = 1 batch) should be very carefully evaluated. Straightforward transposition of medicinal/biotech lot rejection criteria (and proof of) is NOT indicated.

[6] Shelf life includes transport time (and customs clearance time e.g) and operation time. Often setting extreme requirements on transport and logistics of these TEPs because of the very short shelf life of some.

for manufacturing	taken into the specific issues for TEPs	production plant – GMP certified at the latest by Phase I clinical trial phase.	depending on class of product – based on ISO standard but not necessary for devices for clinical evaluation.	bank legislation if any exists or nothing. In future: 2002/0128
Variations to manufacturing process during clinical evaluation	Needs to be discussed what constitutes a change in manufacturing that would render the 'specs' of the product no longer to be valid for the product under clinical evaluation. Together with the consideration of allowance for changes till quite late in the development path, the critical contributing factors to safety and efficacy/effectiveness should be defined.	Not recommended and difficult once in Phase III..	Design changes only after additional approval.	NA

(1) Additional notes:

- Some guidance documents on the Quality part of the dossier exist already (PTC) , they could be extended. More definition is necessary on what constitutes 'SPECS' (specifications) for TEPs, what evidence should be delivered (based on which type of information) so that specifications set, can be acceptable, and what would constitute the 'out of spec' boundaries that would lead to 'lot/batch rejection'. [7]

- Also, thought should be given on e.g. how many batches (batch information) should be reviewed before approval could be given? (certainly in view of autologous products where 1 patient = 1 batch). How would 'reproducibility of the manufacturing process' be evaluated?

- For TEPs intended for allogeneic use, management of Master Cell Bank and Working Cell Bank can be mutuated from Biological medicinal products

1.2. Safety – Non-clinical

This part of the dossier constitutes at this moment the biggest challenge for TEPs.

Since in the Clinical Trials Directive appropriate Quality and Non- clinical data parts should already be submitted to obtain Clinical Trial Approval, this part constitutes the biggest bottleneck towards OVERALL development of TEPs.

Animal models are often not available, or not entirely or really suitable. Testing as in the 'framework of medicinal products ' on minimum 2 different species will often be

[7] This discussion together with the discussion on how products should be characterized (which parameters for product identification/characterization to be included) should not be led by hematologists who historically have often been involved in cell- and tissue therapy evaluation.

completely irrelevant or not even feasible. It could even be the case that it would be applicable to say that in many cases 'the most appropriate large animal model is the human'.

It is clear that as not to endanger patients, the critical components of the safety evaluation will need to be developed. Which type of evidence will lead to go/no go decisions for human application of TEPs? Flexibility is needed since paradigms from medicinal products cannot just be transferred to TEPs.

- *Would it e.g. make sense to test 'human cells' in a large animal (non-rodent) if later on the treatment is 'autologous human cells or tissue' and the autologous equivalent of the large animal model does not exist or does exist but the cell/tissue finished product is human?*

- *Would testing then in a rodent (1 species only) e.g. nude mice be sufficient? It would often have to be.*

- *A number of questions also need further definition: dose, length of clinical trials in order to assess sustainability of the effect of the product, how to assess cell viability and proof of engraftment, …*

General:

- From the biologics development framework we read: "Non-clinical studies are intended to define the 'pharmacologic and toxicologic effects' predictive of human response, not only prior to initiation of clinical trials, but also throughout compound development."

  ð In the case of TEPs: classical pharmacologic and pharmacodynamic studies need to be replaced with more suitable designs and terminology. e.g. early pharmacology studies – could be proof of principle studies – and should often be sufficient.

  Pharmacodynamics/kinetics: could be replaced with cell trafficking studies, so that an idea of compound ADME could be gained through e.g. the use of labeled cells in an animal model.

  Nevertheless all of these studies will be limited by the availability and/or relevance of the animal model.

- Due to the unique and diverse nature of the products employed in cell and tissue therapy, conventional pharmacology as well as toxicity testing will usually not be appropriate to determine the safety and biologic activity of these compounds. ICH Guideline S6 discusses the flexible application of GLP in testing of biotech products. Although one could argue that pivotal safety studies in support of marketing (e.g. carcinogenicity, reproductive toxicology) are expected to be conducted in compliance with the regulations, it is recognized by the FDA that studies in support of entry into clinical trials may not always strictly adhere to GLP. In these cases, the FDA writes, the principles of the regulation should be followed as closely as possible, and where deviations occur, they should be evaluated for impact on the expected clinical application.

  ð In the case of TEPs: the classical approach to toxicologic studies is usually not relevant and the use of e.g. carcinogenicity testing for the cells and tissues (e.g.

autologous) according to GLP, would create an enormous obstacle. GLP qualified service labs that can both handle the relevant animal model, the GLP environment AND the cell culture (fully characterized cell or tissue engineered product for human application, with its underlying process represents highly protected knowledge with on top often very restricted shelf lives) do not exist. Also, TEP developers (often SMEs at the moment) do not have the possibility to develop GLP qualified labs in the early stages of development.

The scope of the document does not allow to go further in detail on this topic but clearly much more effort should be spent on defining what is relevant in this part of the dossier and what is not.

This part does however deserve sufficient reflection since it would normally give us the necessary 'safety' information before going into human clinical trials.

We refer here to the above-mentioned Risk Management approach and advise to additionally review existing Guidance documentation (e.g. ISO 10993 and ICH S6 a.o.), in order to develop an acceptable set of Safety Evaluation standards that is specific for TEPs.

Clinical evaluation of TEPs

The generally accepted – certainly towards the future – way of providing sufficient evidence to authorities, and the approach used more and more by governments and academia alike is Evidence Based Medicine (EBM)[8]. The detailed development plans for different types of products may vary broadly. Nevertheless, the principle two-step approach in clinical development of therapeutics with an exploratory and a confirmatory / pivotal phase can also be applied to TEPs.

Challenges related to clinical trials with TEPs

	TEP	**Medicinal**	**Device**	**Tissue Bank or Hospital**
CLINICAL TRIALS	Challenging both from methodology as from product side	Extensive but well defined for most pharmaceuticals, challenging for many biologics	Not a requirement per se, it is nevertheless expected that , in particular for implants clinical data are available.	None but diverse. Terra incognita (often surgeons are at present still unaware of prospective clinical trials methodology
Administration of compound	Implantation or injected or topical	Iv, im, oral, sc., implanted etc.	Used according to instructions for use.	implantation
Reversibility of treatment.	Long term to Life time contact	Stop possible+ withdrawal. Kinetics well established also ADME known.	Varies depending on the nature and the action proposed in the case of implants. Limited duration of benefit – often 1 to 2 decades.	Long term contact.
Possible benefit of 1 treatment	1 treatment, possible very long time benefit (life long)	If treatment stops, for many products benefit stops		Limited duration of benefit – often 1 to 2 decades
DOSING	1 administration only (re-administration possible)	Multiple administrations (often decades) if chronic condition.	For implants: 1 surgery but might have to be renewed after 'wearing out'	1 surgery but often leads to further degeneration.
Prospectiveness	possible	required	Manufacturer will indicate.	Clinical trials data in relation to tissue bank products hardly exist. Prospective data: hardly any reliable.

[8] For background information we refer to the Cochrane Library.
What constitutes evidence under EBM ?The highest level of certainty – the best evidence comes from Meta –analysis of different prospective large randomized clinical trials. This is in the field of TEPs not available.The second best evidence comes from 'prospective randomized multicenter trials'.In third place come 'open non-randomised prospective clinical trials' In fourth place comes 'assessment of patient series /cohorts ' prospectively.In last place : patient series assessed retrospectively or description of case studies or expert opinions and reports in the medical literature.

	TEP	**Medicinal**	**Device**	**Tissue Bank or Hospital**
Multicenter	possible	Customarily done	Customarily done	Not done
Blinding	Often very difficult because of surgical component. However blinding is NOT an absolute requirement also not in pharmaceutical trials, and some measures to avoid bias are able to be implemented.	Often done; not an absolute requirement. In general measures to avoid bias should be included in overall design.	Not done	Not done in relation to tissue or cells.
Standardisation	Very difficult because of often surgical technique; but possible to some extent. Different medical culture throughout EU.	Possible. Dose effects known.	Toxicological safety evaluated beforehand by using ISO 10993 series.Clinical investigation performed acc. To ISO 14155	Standardization amongst centers does not exist.
Assessment/ containment of variability	Wide – to extreme variability at present in many of the indications for which TEPs are developed. Hardly any validated endpoints, outcome measures, information on comparators exist because often the comparator is a surgical treatment and the compound is too new. Not only surgery introduces variability but also anesthesiology, rehabilitation protocols.	Less variability. Better contained. Lots of information on outcomes, comparators, chemical groups and structures exists for NCEs less for biologicals.	Variability controlled upfront. Application of risk management according to EN ISO 14971.	For allografts : 'Surgical ' skill – no comparisons are made or required. Not known as such. On the other hand intensive literature and exchange and controlled trials exist when 'organ transplantation'. This concerns 'indirect' evidence on the organ since the trials are undertaken to evaluate immuno-suppressive compounds. Direct evaluation if e.g. the organ would have to be re-grown does not exist.
Randomisation	Possible	Routinely done	Sometimes	Possible, but not done, because clinical trials do not exist.

	TEP	Medicinal	Device	Tissue Bank or Hospital
Patient recruitment	Often very difficult – slow to very slow recruitment	variable	variable	Not done. See above
Endpoint assessment	Often have to wait long time before outcome /endpoint can be measured (over 12 months !!)	Variable; But use of surrogate markers or endpoints accepted. Usually endpoints are measured between 3 to 6 months of treatment. Some later.	Variable. Endpoints can be measured usually on a 6 to 12 month timeline.	Not done. See above.
Evolution of medical techniques	Change in 'surgical' or other aspect of procedure by end of trial possible	Often relatively stable over study period	Stable – controlled-monitored	Possible surgery changes have no effect since only 'cases' are done. No trials.
Choice of comparator	When compared with traditional tissues, the comparator often not completely assessed	Lots of information available.	Lots of information available.	Not available.

Step 1: Early Exploratory Clinical Studies

Open prospective studies looking into dose – response (outcome)[9], safety (monitoring of target organs, general safety parameters in relation to indication and intended patient population).

These study(ies) should absolutely look into the 'variability' present in the design, so that the study can provide answers as to how to minimize the variability in the confirmatory trials and that a suitable sample size can be calculated.

Historically many clinical studies in the TEP area, have been inexistent, underpowered , lacking correct sample size estimations, lacking validated endpoint measurements, lacking randomization and prospectiveness of design etc. (see comments at the beginning of this section)

Often multiple goals can be combined in 1 study, although from a statistical point of view not too many objectives should be combined in one study.
(we refer to the ICH Guideline E9 on statistical principles for clinical trials)

The ICH Guideline E9 does e.g. not exclude that exploratory trials looking into safety, do not at the same time also look into confirmation of proof of principle (as probably tested earlier on in non-clinical testing). As such Early Exploratory Clinical Studies with TEPs will at the same time look at some outcome measurement and indication of activity/efficacy.

Sufficient attention should be paid to the development of possible surrogate markers and validation of these, in order to win time in the overall timeline afterwards.

[9] Do not expect classical dose-response curves. In cell /tissue therapy more cells do not mean more effect (or response). But a (1) dose should e.g. definitely be tested for its 'potency' to reach/proof the endpoint/outcome. MTD as concept as such is also not transferable.

Combination of the 2 steps into 1 overall design might be possible depending on a multitude of factors (claim, comparator, existing evidence, risk etc.).

Step 2 - Pivotal Confirmatory Clinical Study

Depending on the claim (which indication in what type of patient, does the manufacturer want to treat), a confirmatory clinical study might be performed.

Whether this will be a randomized prospective clinical trial or an open prospective controlled clinical trial will depend on many aspects. (Please see table).

Randomized and blinded designs could represent difficult hurdles in some indications.

On the other hand if the comparator is well known, many patients are available, sufficient information on the comparator is available, randomized designs are probably the most efficient way to demonstrate efficacy/effectiveness.

Note: In conjunction with the foregoing, thought should be given to a development track by which TEPs could gain e.g. 'conditional approval' with post-commitment studies once approved.

In any case, it is clear that in view of many elements, regulators should work towards a system where extensive clinical testing can be avoided (certainly in view of the fact that in some cases – many patients have already been treated without any legislation in place) and dossiers can be approved with 'reasonable' amounts of data (as opposed to extensive data as required for pharmaceuticals).

At the same time this pleads – and industry fully supports this – for an earlier intervention / communication with authorities on the development plan.

Note: Thought should be given to 'Combination Products' development plan in the case e.g. where 1 component of the combination has already been validated, will only the new part require clinical validation or will the 'combination' require validation. Also in this case a Risk assessment approach could be of assistance.

Proposals for an IND-like system have been submitted earlier.

Procedural aspects of obtaining Clinical Trial Approval

In summary: on the procedure to obtain Clinical Trial Approval, some of the desirable characteristics are the following:

1. Once Ethics Committee approval has been obtained, approval should be implicit by National Authorities, with a maximum timeline of 60 days for authorities to respond otherwise the study can start.

2. One approval for the entire EU would be much better, after 1 EC approval per country e.g.
   - ð *The delays at this moment for countries with notification only for TEP are: a few days to 60 days.*
   - ð *The delays for countries with 'approval' system of CTA!! (not market authorization) is between 4 months to 20 months !!!*

3. A single standardized format for data requirements for clinical trial applications for TEPs is an absolute must as shown above.

4. One standard for obtaining an Import License for investigational TEPs is necessary in view of often very short shelf lives.

5. Early communication /interaction on clinical development.
   - ð As a manufacturer having only a single request from the EC in order to respond to if the information is judged insufficient – the vote will be negative, is not feasible.
   - ð As a sponsor (manufacturer) having on one occasion only the chance to amend the content of the request for clinical trial authorization is absolutely insufficient for TEPs. If the sponsor fails to amend the request accordingly the request shall be considered rejected and the clinical trial may not commence.
   - ð In reality, for the type of products (very new, legislation undefined, legislators not very clear on technical content requirements) we are developing, this single chance only for a sponsor to amend clinical trial applications will stall clinical trials in our areas.

6. Clinical Trial Database
   - ð Probably it would be indicated to start with a requirement for ALL actors in the field (sponsor, hospital, tissue bank etc.) with Establishment Registration, in order to obtain an overview of not only the clinical trials that are being undertaken, but on who is doing what, which types of products etc.. This would definitely add to the 'safety' overview involved and the possible risk assessment that needs to be undertaken to rule these products further.

7. Product Designation / Ombudsman/Clearing House
   - ð It is of the utmost importance that the Clearing House function is not only applied at the end of the development line (e.g. when the dossier is submitted for marketing authorization). The sponsor should be able to obtain a clear 'product designation' at the beginning of the (clinical) development.