19 September 2014
EMA/CAT/20938/2014
Committee for Advanced Therapies (CAT)

Overview of comments on 'Reflection paper on clinical aspects related to tissue engineered products' (EMA/CAT/CPWP/573420/2009)

Adopted

Comments from:

Name of organisation or individual
BPI – Bundesverband der Pharmazeutischen Industrie – German Pharmaceutical Industry Association
Eucomed
EuropaBio
Institute for Quality and Efficiency in Health Care (IQWiG)
Alliance for Advanced Therapies
TiGenix nv
European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

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1. General comments

Stakeholder	General comment (if any)	Outcome (if applicable)
BPI	BPI welcomes this reflection paper dedicated to tissue engineered products (TEP) as it is important to acknowledge their specificities as compared to somatic cell based medicinal products. Giving consideration to their structural aspects and mechanical properties is of utmost importance. We would also welcome in the future another reflection paper/guideline dedicated to their characterisation and release.	EMA/CAT acknowledges the stakeholders' (BPI and Europabio) proposal of a new RP focusing to characterisation and release of TEPs.
Eucomed	1. Eucomed appreciates the acknowledgement that TEPs cannot be studied in the same manner as traditional medicinal (e.g., how PK and PD studies can be run). 2. Eucomed appreciates the use of risk-based approach to determining the post-approval duration of the trials (lines 131-138). 3. Eucomed appreciates the acknowledgement that a representative comparator may not be available, or may be unethical, and agree with the recommendations in the Comparator section (lines 124-130).	EMA/CAT takes note of the comments.
Europabio	EuropaBio, the European Association of Biotechnology Industries, thanks the European Medicines Agency (EMA) for the opportunity to submit comments on reflection paper dedicated to tissue engineered products (TEP). EuropaBio's mission is to promote an innovative and dynamic biotechnology based industry in Europe. EuropaBio, has 56 corporate and 11 associate members	EMA/CAT/CPWP has developed a framework for the risk-based approach and published in February 2013 a guideline on risk-based approach for advanced therapy products (EMA/CAT/CPWP/686637/2011). This concept applies on a case-by-case basis and is intended to support the developer in risk analysis, in planning the development program and can also be used as one starting point for defining risk minimization and risk management plans. Deviations from the central requirements are to be justified by

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	operating worldwide, 3 Bioregions and 19 national biotechnology associations representing some 1800 small and medium-sized enterprises. We welcome this reflection paper dedicated to tissue engineered products (TEP) as it is important to acknowledge their specificities as compared to somatic cell based medicinal products. Giving consideration to their structural aspects and mechanical properties is of utmost importance. EuropaBio wishes to highlight that when developing an ATMP (and more specifically a TEP) definitive clear-cut cannot be reached for a wide array of reasons such as • Unethical to collect such info prospectively, • Advances of scientific knowledge, • Rare occurrence (i.e.; it cannot be seen in clinical program). Therefore, while taking into account the clinical indication being sought, it would be worthwhile applying Risk-Based Approaches (RBA) on a case by case basis, to determine such parameters. One could envision a joint effort partnership between the developer and the regulatory bodies (such as the EMA) within the context of the new pharmaceutical legislation framework. Such interaction might lead to a TEP-specific pattern within the Risk management plan so that specific quality, safety and efficacy data are generated in order to first reach registration and then in view of fulfilling post approval requirements.[1] It is fully acknowledged that the latter point (post approval requirements) should not be seen as a “scapegoat” to	the developer for further evaluation by the EMA/CHMP/CAT. EMA/CAT offers scientific advice (SA) for developers of TEPs as well as certification procedure of early development steps. Furthermore, public consultations such as the present one are to improve tools to reach consensus prior to publication of central regulatory documents. EMA/CAT acknowledges the stakeholders’ (BPI and Europabio) proposal of a new RP focusing to characterisation and release of TEPs.

[1] Directive 2001/83 - Part II: Specific marketing authorisation dossiers and requirements 6. Documentation for applications in exceptional circumstances (p. 101) http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_cons2009/2001_83_cons2009_en.pdf

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	avoid fulfilling all quality, safety and efficacy requirements at time of marketing authorisation application. The following aspects should be placed under this "RBA-Regulatory Action-Timing" envelope to address • PK (line 49 and 71) • PD (line 59) • PK in special cases (line 73-74) • Efficacy endpoints (line 106-107) • Duration of trials (lines 131-138). We would also welcome in the future another reflection paper/guideline dedicated to their characterisation and release.	
Alliance for Advanced Therapies	The Alliance for Advanced Therapies (AAT) welcomes this reflection paper on clinical aspects related to tissue engineered products as a valuable addition that is consistent with the existing guidelines and directions for clinical development of these types of products. AAT recommends addressing relevant aspects of the nonclinical development phase, especially where product characteristics can de demonstrated in pre-clinical models.	EMA/CAT acknowledges the stakeholders' (AAT and TiGenix nv) proposal on expanding the present RP with aspects in non-clinical development phase studies (such as preclinical models to be used in defining TEP characteristics and matters related to pharmacokinetic data), which impact on the clinical development. The present RP does mention the usefulness of non-clinical studies in determining the dose. We have also added a possibility to use preclinical animal studies to describe how to develop and validate imaging methodology. Defining TEP characteristics in preclinical models may have the limitation that human cell characteristics may not be the same under influence of an environment of an animal as compared to the human milieu.
TiGenix nv	The Reflection paper is considered a valuable addition to the available Guidelines and directions for clinical	Please see comment above.

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	development of TEPs. Tigenix also welcomes the consistency that is applied between the available Guidelines and Reflection papers with respect to structural outcome measures. Although the current paper targets clinical aspects, it would be worthwhile to briefly frame the context of the nonclinical development phase. Especially for matters related to pharmacokinetics certain aspects might be adequately addressed in non-clinical models.	
EUCOPE	EUCOPE would like to highlight the importance to acknowledge the specificities of tissue engineered products (TEP) as compared to somatic cell based medicinal products and therefore very much welcomes this reflection paper. It is important to address structural aspects and mechanical properties of TEPs	Thank you for this comment.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
30-32	BPI	**Comment:** A combined ATMP fulfilling the definition of Art 2(b) of 1394/2007, at least to our understanding, is also tissue engineered product. Therefore the sentence: "This also applies … 1394/2007" is dispensable. Moreover the reference to combined ATMPs should be better Art. 2(d), not Art. 7 of 1394/2007. **Proposed change (if any):** Delete the sentence.	Thank you for the comment, the text has been changed accordingly
39-46	BPI	**Comment:** It must be considered that according to the heterogeneous character of TEPs, e.g. their therapeutical indication and origin and nature of tissue they are derived from, the risk profiles and therapeutical effects are differing tremendously within these medicinal products. This must be adequately represented in requirements regarding issues on clinical efficacy and safety. **Proposed change (if any):** Add a passage with the meaning of this comment behind line 46.	The proposed comment is appreciated and the subject addressed in the end of the chapter "3. Discussion, General comments."
Line 47	BPI	**Comment:** This section speaks about referencing TEP therapeutic claims relative to the target organ. The paper does not adequately consider that some TEPs can be used to deliver therapeutic factors remotely. For example, it may be possible to deliver TEPs to the bone marrow compartment with the therapeutic objective of facilitating protein expression in the CNS,	The proposed comment is appreciated and the subject addressed in the end of the chapter "3. Discussion, Therapeutic claims."

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		(http://clinicaltrials.gov/ct2/show/NCT01560182?term=metachromatic+leucodystrophy&rank=2). The paper then discusses the importance of referencing TEP "pharmacodynamics" to healthy volunteer reference ranges. For an example such as that cited, it may not be possible to determine what therapeutically relevant protein levels may be. **Proposed change (if any):** We would suggest to modify the text so as to say "where appropriate" and "where not appropriate exemption should be fully justified".	
Line 49	BPI	**Comment:** Pharmakokinetics does not include longevity, but resorption, distribution and excretion of a drug. Including longevity might lead to extensive durations of clinical studies that would be an undue burden to pharmaceutical entrepreneurs. Also Article 12 of Regulation (EC) 726/2004 does not include longevity as a requirement to obtain a marketing authorisation: "Article 12 1. The marketing authorisation shall be refused if, after verification of the particulars and documents submitted in accordance with Article 6, it appears that the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product." The same applies to Art. 26 of Directive 2001/83/EC: 1. The marketing authorisation shall be refused if, after verification of the particulars and documents listed in Articles	Thank you for the question on including longevity to pharmacokinetic (PK) study objectives. However, the opinion of the CAT is that the character of TEPs composed of biological living cells and/or tissues requires that the applicant demonstrates with PK studies *the longevity* of the product. Longevity is now defined as ''cell and/or tissue persistence'. The longevity is understood to be directly associated with the TEPS's safety and efficacy. The developer is expected to study the patient outcome if cells/tissues die. This RP gives place to apply post marketing follow-up studies (Chapter 'Pharmacokinetics', 3rd section) but at the time of MAA, sufficient data is to be presented on TEP longevity based

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		8, 10, 10a, 10b and 10c, it is clear that: (a) the risk-benefit balance is not considered to be favourable; or (b) its therapeutic efficacy is insufficiently substantiated by the applicant; or (c) its qualitative and quantitative composition is not as declared. Only quality, safety and efficacy are required to obtain a marketing authorisation! European law does not require persistence or long term efficacy or longevity at this point of time. Proposed change: Delete “longevity” in line 49.	either on long-term cell/tissue survival or long-term functionality gained by TEP implantation catalysing to eventually replacement alternatively substance production needed for claimed efficacy by native cells/tissue.
Line 53	BPI	**Comment:** Please consider why the reference physiological values in the therapeutic claims should be from tissues/organs of healthy individuals. Many TEPs are used to treat patients with a defined underlying pathology in which environment the functionality of the tissues/organs may not reach that of healthy organs. Results in the therapeutic claims would then suggest that the tissue/organ does not perform well, when in fact it functions as well as possible under the conditions. **Proposed change (if any):** For the purpose of this document, the physiological values of the reference tissue/organ are the ones measured in tissue/organs from healthy individuals. or representative of the defined therapeutic area.	We thank for the comment. The subject is clarified concerning both a full as well as a partial function being the therapeutic claim for which appropriate value /range of values for physiological parameters are to be chosen.
Line 54	BPI	**Comment:** Could you please clarify what is meant by “For the purpose of	We thank for the comment: The sentence is

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		this document"… **Proposed change (if any):** For the purpose of this document, the physiological values of the reference tissue/organ are should be understood as the ones measured in tissue/organs from healthy individuals.	revised as "For the purpose of this documentation..." , thus, referring to documentation required to support the therapeutic claim.
Lines 54-55	BPI	**Comment:** The paper suggests setting target physiological ranges based on reference to healthy tissue, yet there are multiple know examples where therapeutic effects can be attained with levels of proteins well below that of healthy individuals (e.g. haemophilia where 5% Factor expression can be therapeutic). This "physiological target" concept is reiterated in the subsequent section on pharmacodynamics. **Proposed change (if any):** We would suggest that the paper should encourage the identification of a suitable therapeutic target range through clinical and preclinical investigations and where possible clinical trials should be designed to measure the pharmacokinetics of the active therapeutic agents in an appropriate target tissue.	We thank for the comment. Please, see the response to the previous two comments.
Line 57	BPI	**Comment:** While PK and PD studies are frequently interlinked with ATMP, it is not always the case. Apart from that from our point of view not only PK and PD studies, but also efficacy studies may be interlinked in TEPs. The PD (functionality) of a cultivated skin graft in terms of predefined physiological parameters is reconstituted skin, as is the typical primary efficacy end point of a clinical trial in wound healing.	We agree that in the development of ATMPs, PK and PD, as well as efficacy studies, may be interlinked. The sentence is revised accordingly and moved to the general section.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): PK and pharmacodynamic (PD) studies may be interlinked.	
Lines 58-66	BPI	**Comment:** In the presented Draft Reflection Paper, regarding the pharmacodynamic studies, it is requested to use predefined quantitative physiological parameters as endpoints which correlate with the physiological values. It is very difficult to fulfill this criteria. In the CAT Reflection Paper for Chondrocyte products (EMA/CAT/CPWP/568181/2009) subjective scores for patients are proposed as useful surrogate parameters. **Proposed change (if any):** Thus, it should be clarified that in case the analysis of predefined quantitative physiological values was not feasible, parameters like Patient Reported Outcomes (PROs) and structural parameters would be accepted in pharmacodynamic studies.	We appreciate the comment that reflects the variety of TEPs. The developer is encouraged to develop/improve and validate analytical methods suitable for quantitative physiological parameters to be used in PD studies. Special situations may exist and deviations are possible as long as they are justified by the developer.
Line 59	BPI	**Comment:** While it is always helpful to have as many data points as possible (i.e. when a physiologic effect is reached, how long it is maintained etc.), exhaustive PD studies with TEP are often not practical. Especially TEP will often require large animal models for testing of i.e. physical properties of the TEP, the application procedure and/or biological behavior. Large animal models need an experimental environment that makes large subject numbers impossible. Especially for PD studies, group numbers thereby should and will be limited, also based on the ethical committee review. It is therefore important to stress that sufficient data is needed to make appropriate conclusions on the PD characteristics of a TEP while acknowledging the ethical, practical barriers that exist.	We appreciate the comment. The section 'Pharmacodynamics' has been revised accordingly.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Line 71	BPI	**Comment:** It is not clear, what duration of time is meant by "persistence", same would apply to "longevity". Does persistence mean the lifetime of the patient? It would be an undue burden to the entrepreneur to test the "persistence" for an unknown period of time and again, "persistence" is not part of PK-studies (see comment above line 49). Also Article 12 of Regulation 726/2004 does not include "persistence" as a requirement to obtain a marketing authorisation: "Article 12 1. The marketing authorisation shall be refused if, after verification of the particulars and documents submitted in accordance with Article 6, it appears that the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product." The same applies to Art. 26 of Directive 2001/83: 1. The marketing authorisation shall be refused if, after verification of the particulars and documents listed in Articles 8, 10, 10a, 10b and 10c, it is clear that: (a) the risk-benefit balance is not considered to be favourable; or (b) its therapeutic efficacy is insufficiently substantiated by the applicant; or (c) its qualitative and quantitative composition is not as declared.	Please, see our response to the comment referring to lines 47, 54-55 as well as the CAT opinion to the comment referring to line 49.

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		Only quality, safety and efficacy are required to obtain a marketing authorisation! European law does not require "persistence" at this point of time. **Proposed change:** Delete "persistence"	
Lines 71-95	BPI	**Comment:** The presented Draft Reflection Paper demands that pharmacokinetic studies should include the analysis of persistence and biodistribution of the tissue engineered cells in humans. This is in contradiction to the CAT Reflection Paper for Chondrocyte products (EMA/CAT/CPWP/568181/2009) which states that Pharmacokinetic issues should be part of non-clinical development. **Proposed change (if any):** This contradiction should be resolved.	Thank you for the comment. The issue is addressed in more general terms in this paper and a note is included that PK and PD studies may be interlinked. The wording is thus chosen to be softer to allow for different scenarios.
Line 73	BPI	**Comment:** An additional "evaluation" of the proposed lifespan of the TEP for different groups of patients is an undue burden to the pharmaceutical entrepreneur. Does it mean that additional clinical studies are to be conducted not only for children, but additionally for women and men at different ages? This is not required for "normal" drugs according to GCP and thus not acceptable. **Proposed change:** Delete lines 73-76 or make it clear that the evaluation is retrospective.	The development of a medicinal product with a paediatric indication will follow requirements laid down in the paediatric regulation (Regulation (EC) No 1901/2006) including what will be centrally agreed in the paediatric investigation plan (PIP). In this aspect, TEPs are no exception. We don't support the proposal given. Indeed, in various patient groups depending on age,

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			sex, ethnic group, disease status tissue environment may be different supporting TEP safety, efficacy and survival, and need to be studied in line with the intended patient population.
Line 74	BPI	**Comment:** The severity of the medical condition or underlying pathology should be taken into account when evaluating the proposed lifespan of the TEP. **Proposed change (if any):** .. depending on age, sex, ethnic group and/or the severity of the medical condition,	Please, see the response on the previous comment. The sentence is revised.
Line 78-80	BPI	**Comment:** This sentence could lead to misunderstanding. Further clarification would be welcome. **Proposed change (if any):** At the time of the MAA, the clinical development plan including the post marketing follow up plan, should include investigation of the time to efficacy and the duration of efficacy.	We appreciate the comment. The sentence is revised accordingly adding 'additional investigations' since some study results must already be available for the MAA.
Line 81	BPI	**Comment:** For many Tissue Engineering Products -repeated dosing is not intended. It should be clarified that in these cases studies examining repeated dosing are not necessary. **Proposed change (if any):** The impact of repeated dosing should be addressed as part of the PK studies, if applicable.	We appreciate the comment. The sentence is revised accordingly.

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Lines 87-88	BPI	**Comment :** We do agree with the statement that "structural/histological imaging might be necessary but for a slightly different purpose." **Proposed change (if any):** Structural/histological imaging might be necessary to assess the overall organisation of integration of the implanted artificial tissue/organ within the host environment and its modifications (in particular when part of the product is degradable).	We thank for the comment. The sentence is revised including a modification that not all TEPs will be integrated to the host tissue.
Lines 89-95	BPI	**Comment:** Another problematic issue is the practical implementation of techniques for the analysis of the persistence and biodistribution of the cells. The EMA recognizes that this is not trivial. The EMA suggested to establish new techniques for this purpose. **Proposed change (if any):** The intention is comprehensible but till suitable techniques are widespread available this should not be included as request in the presented Draft Reflection Paper.	We thank for the comment. However, the CAT will encourage the developers of medical products in general including ATMPs to take into account the responsibility in development/improvement and validation of analyse methods to evaluate the safety and efficacy of the products as needed. Special situations may exist and need to be justified by the developer.
Lines 90-92	BPI	**Comment:** The recommendation to use imaging studies for TEP behavior in humans is to be seen with caution. None of the mentioned methods has enough sensitivity or even specificity to result in data that are truly meaningful. Especially any long term evaluation is not feasible with current methods (other than i.e. genetic evaluation of allogeneic approaches; here the sensitivity will most likely be insufficient and probing will be invasive). Radioisotopes available do mostly not remain in any TEP or cellular compartment. Imaging is therefore restricted to short	We thank for the comment, and will in general refer to the previous response. The sentence has been revised taken into account limitations of *in vivo* studies.

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		periods (few days). Leaking radioisotopes in vivo add to the lack of consistent interpretation of the resulting images. Luminescent or fluorescent dyes have similar limitations, with few if any being available for clinical use. While these methods can be used in the preclinical development, no such recommendation should be done for the clinical setting. The Agency should rather recommend distinct methods for a distinct product if its feasibility has been proven and avoid generalization in this case. In vivo imaging methods to visualize TEP in patients should be developed first by appropriate developers, which are not identical to the TEP developer. **Proposed change:** The use of cell markers…. luminescent dyes could be used in ex vivo or in vitro samples.	
Lines 99-102	BPI	**Comment:** We do not agree with the text here. Many TEPs will be researched in rare diseases, for which there may be no fully validated clinical markers. It would be more productive to encourage sponsors to discuss their proposed endpoints with EMA where non validated clinical endpoints are proposed. Also, regarding the use of physiological markers, this may lead to error. For example a cell expressing a growth factor could be placed into the eye, the level of the growth factor could identical to a healthy person, but the factor may not produce a therapeutic benefit because it was the wrong target protein. **Proposed change (if any):** It is suggested emphasising the supporting text in lines 103 onward more strongly and softening the biomarker	We thank for the comment. The EMA/CAT advises the applicant to discuss any proposed deviation from EU guidance during medicine product development through scientific advice. A choice of endpoint representing a normal physiological characteristic or function may also need to be validated in clinical trials.

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		statements in line 102.	
Line 106-107	BPI	**Comment:** Only efficacy is required, not long-term efficacy. Long-term studies would extent clinical studies unduly and are not required for other drugs according to EU-law. Also Article 12 of Regulation 726/2004 does not include longevity as a requirement to obtain a marketing authorisation: “Article 12 1. The marketing authorisation shall be refused if, after verification of the particulars and documents submitted in accordance with Article 6, it appears that the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product.” The same applies to Art. 26 of Directive 2001/83: 1. The marketing authorisation shall be refused if, after verification of the particulars and documents listed in Articles 8, 10, 10a, 10b and 10c, it is clear that: (a) the risk-benefit balance is not considered to be favourable; or (b) its therapeutic efficacy is insufficiently substantiated by the applicant; or (c) its qualitative and quantitative composition is not as declared. Only quality, safety and efficacy are required to obtain a marketing authorisation! European law does not require “long term efficacy” at this point of time.	We thank for the comment. Please, see the response given concerning line 49.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change: Delete the sentence: In cases, where long-term efficacy is expected, the endpoints should also focus on the duration of the response.	
Line 112	BPI	**Comment:** "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." For autologous cell products the dose may be limited by the patient donor. It is possible that there may be no obvious maximum tolerated dose demonstrable in preclinical testing and clinical studies, thus treatment is limited by the initial biopsy from the donor. **Proposed change (if any):** A potential way to address this could be by adding the following wording "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. For autologous cell based products it is accepted that full dose ranging investigations may be constrained by the nature of the initial donor cells".	We appreciate the comment. The last part of the section 'Dose' is revised accordingly.
Lines 113-114	BPI	**Comment:** As acknowledged, dose finding studies may be not always feasible, in particular with TEP where cell density within the tissue might be heterogeneous (e.g. skin). **Proposed change (if any):** The dose selection (i.e. cell density or concentration of main constituents) should be based on findings of quality and non-clinical product development, as far as possible.	We appreciate the comment. The sentence is revised accordingly.

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115	BPI	**Comment:** The word “feasible” seems not to be appropriate. E.g. in the case of skin grafts it would be feasible to administer various transplant sizes and to wait whether also small grafts will do the job over time by cell proliferation. However it would be reasonable to administer grafts with the appropriate size to fill the defect. **Proposed change (if any):** Exchange “feasible” against “reasonable”	We appreciate the comment. The sentence is revised with some modification: “Limitations of amount of available cells/tissue in TEP due to e.g. autologous donation, manufacturing procedure, may lead to use of variable doses on comparable size of defects. In these cases...”
Lines 120-123	BPI	**Comment:** The presented Draft Reflection Paper states that all attempts should be made to have blinded assessments. In cases where the nature of a TEP makes a blinded trial unfeasible hard endpoints are preferred. This is difficult for TEPs, alternatives should be provided. **Proposed change (if any):** It should be added that the use of Patient Reported Outcomes (PROs) is also possible, if the use of hard endpoints is problematic.	We thank for the comment. However, the proposal is not linked to blinding but a possible secondary endpoint.
Lines 121-122	BPI	**Comment:** The tense is not consistent. **Proposed change (if any):** In cases, where the nature of TEP’s will make a blinded trial unfeasible (…)	We appreciate the comment. The sentence is further revised to improve the guidance.
Lines 131 etc.	BPI	**Comment:** The new proposed regulation for clinical trials was set up to shorten the time for clinical trials, as one problem was the	The new proposal for Regulation on clinical trials is still under work. We will refer to our

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		extended duration (doubling) of clinical trials since the Directive 2001/20/EC came into effect and the associated explosion of costs. Long-term trials mean that the marketing authorisation is unduly delayed compared to normal drugs which is not acceptable. Post-marketing studies may be discussed on an individual level with the competent authority, but general requirement for long-term efficacy is not required. Required are safety and efficacy only. **Proposed change:** Delete lines 131-138.	previous response concerning lines 49, 71, 106-107.
131-138	BPI	**Comment:** Not in any therapeutic indication long term effects can be attributed to the efficacy of the TEP. E.g. in chronic leg ulcer therapy the basic pathophysiologic condition, as blood circulation, and compliance of the patient, as the wearing of compression stockings, is of critical relevance on long-term outcome. Recurrence of leg ulcers is a quite common event and an observation period of duration longer than 6 months therefore seems to be of limited value. On the other hand, the effort to follow up on a patient with a healed ulcer will be unreasonably high, since usually he will not reappear within the specialised hospital, where he was treated. **Proposed change (if any):** In line 137 exchange “is” against “may be”	We thank for the comment. We will refer to our previous response concerning lines 49, 71, 106-107, 131.
Line 134	BPI	**Comment:** Non-invasive markers or parameters may not be available for long-term follow-up of efficacy. Invasive markers/parameters may be necessary and the risk for the patient should be taken into account.	We appreciate the comment. The subject has been addressed by adding invasive methods.

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		Proposed change: Delete lines 133-134	
149-150	BPI	**Comment:** The draft does not adequately reflect the fact that some TEPs are on the market already for a long period of time, sometimes decades. This is especially seen in these lines. Specific risks are known from the therapeutic use. Scientific publications are as well a source for information on safety aspects. **Proposed change (if any):** Add a new sentence in line 150: "Information on products being already on the market may be a valuable source, as well as results of scientific publications on respective product categories."	We appreciate the comment. The subject is included by adding a new sentence.
Lines 150-152	BPI	**Comment:** The presented Draft Reflection Paper states that rescue strategies should be considered in cases of treatment failures and other severe adverse events. This is not clear in case of Tissue Engineering Products. **Proposed change (if any):** Please add some more examples for feasible rescue strategies or clarify your demands within the given paper.	We appreciate the comment. The subject is addressed with additional guidance.
114-116	Eucomed	**Comment:** We believe it will be impractical to conduct dose finding studies in the clinical settings, despite the fact that the paper modifies the recommendation with the phrase "where feasible." Eucomed suggests considering also the financial implications of running a clinical study in triplicate to try three	We appreciate the comment. The subject is addressed with additional guidance.

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		different doses, for example, when considering whether dose finding studies are feasible. **Proposed change (if any):** This sentence should be removed, because the consideration for dose size is adequately captured in the rest of the "Dose" section and in particular the final sentence (lines 116-118). The dose exploration recommended in lines 114-116 would provide scientifically interesting data, and may refine treatment protocols, but unless it is required based on risk analysis, requiring dose studies for all TEPs will be too high a barrier to entry. Requiring dose studies for all TEPs, even "where feasible," will stifle innovation and inhibit the launch of new therapies.	
Line 47	Europabio	**Comment:** This section speaks about referencing TEP therapeutic claims relative to the target organ. The paper does not adequately consider that some TEPs can be used to deliver therapeutic factors remotely. For example, it may be possible to deliver TEP's to the bone marrow compartment with the therapeutic objective of facilitating protein expression in the CNS, (http://clinicaltrials.gov/ct2/show/NCT01560182?term=metachromatic+leucodystrophy&rank=2). The paper then discusses the importance of referencing TEP "pharmacodynamics" to healthy volunteer reference ranges. For an example such as that cited, it may not be	The proposed comment is appreciated and the subject addressed in the end of the chapter "3. Discussion, Therapeutic claims."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		possible to determine what therapeutically relevant protein levels may be. **Proposed change (if any):** We would suggest modifying the text so as to say "where appropriate" and "where not appropriate exemption should be fully justified".	
Line 49	Europabio	**Comment:** Whilst traditionally PK addresses absorption, distribution, metabolisation and excretion (ADME) of a therapeutic agent, in case of an ATMP (and more specifically of a TEP) the reader is encouraged to refer to the specific comment in section 1. General Comments while taking into account the clinical indication being sought. Such clear-cut cannot be reached for a wide array of reasons. Furthermore, a clear definition of "longevity" is welcomed.	We appreciate the comment. Please, find additional guidance in chapter 3. Discussion, Therapeutic claim, including reference to risk-based approach to support planning safety and efficacy follow-up studies as well as risk management plan. We define 'longevity' as 'cell and/or tissue persistence'. This has been added to the 2nd section of the chapter 'General comments'.
Line 53-55	Europabio	**Comment:** Further assessment as to the reason to refer to physiological values in the therapeutic claims should be from tissues/organs of healthy individuals. Likewise for other medicinal products, many TEPs are used to treat patients with a defined underlying pathology in which environment the functionality of the tissues/organs may either no longer	We thank for the comment. The subject is clarified concerning both a full as well as a partial function being the therapeutic claim for which appropriate value /range of values for physiological parameters are to be chosen.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		be the ones of healthy organs or may never reach that of healthy organs. As proposed in the document, whilst results in the therapeutic claims would suggest that the tissue/organ would not perform well, alas, in fact it might function as well as possible under the "real-life" patient conditions. **Proposed change (if any):** For the purpose of this document, the physiological values of the reference tissue/organ are the ones measured in tissue/organs from healthy individuals or representative of the defined therapeutic area.	
Line 54	Europabio	**Comment:** It would be good to clarify what is meant by "For the purpose of this document"… **Proposed change (if any):** For the purpose of this document, the physiological values of the reference tissue/organ are should be understood as the ones measured in tissue/organs from healthy individuals.	We thank for the comment: The sentence is revised as "For the purpose of this documentation..." , thus, referring to documentation required to support the therapeutic claim.
Lines 54-55	Europabio	**Comment:** The paper suggests setting target physiological ranges based on reference to healthy tissue, yet there are multiple known examples where therapeutic effects can be attained with levels of proteins well below that of healthy individuals (e.g.	We thank for the comment. Please, see the response to previous two comments.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		haemophilia where 5% Factor expression can be therapeutic). This "physiological target" concept is reiterated in the subsequent section on pharmacodynamics. Proposed change (if any): We would suggest that the paper should encourage the identification of a suitable therapeutic target range through clinical and preclinical investigations and where possible clinical trials should be designed to measure the pharmacokinetics of the active therapeutic agents in an appropriate target tissue.	
Line 57	Europabio	**Comment:** While PK and PD studies are frequently interlinked with ATMP, it is not always the case. **Proposed change (if any):** PK and pharmacodynamic (PD) studies may be interlinked.	We agree that in the development of ATMPs, PK and PD as well as efficacy studies may be interlinked. The sentence is revised accordingly.
Line 59	Europabio	**Comment:** It would be worthwhile applying Risk-Based Approaches (RBA) on a case by case basis to determine such parameters. See specific comment in section 1. General Comments while taking into account the clinical indication being sought. While it is always helpful to have as many data points as	We appreciate the comment. The section 'Pharmacodynamics' has been revised accordingly.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		possible (i.e. when a physiologic effect is reached, how long it is maintained etc.), exhaustive PD studies with TEP are often not practical. Especially TEP will often require large animal models for testing of i.e. physical properties of the TEP, the application procedure and/or biological behavior. Large animal models need an experimental environment that makes large subject numbers impossible. Especially for PD studies, group numbers thereby should and will be limited also based on the ethical committee review. It is therefore important to stress that sufficient data is needed to make appropriate conclusions on the PD characteristics of a TEP while acknowledging the ethical, practical barriers that exist.	
Line 71	Europabio	**Comment:** It would be worthwhile applying Risk-Based Approaches (RBA) on a case by case basis to determine such parameters. See specific comment in section 1. General Comments while taking into account the clinical indication being sought. It is unclear, what duration of time is meant by ”persistence”, same would apply to “longevity”. Does persistence mean the lifetime of the patient? It would be an undue burden to the developer to test the “persistence” for an unknown period of time prior to registration.	We thank for the comment. Please, see our response to comment concerning the line 49. ‘Persistence’ is equivalent with ‘longevity’. Please, find the definition given to ‘longevity’ on line 49 (...the longevity (‘cell and/or tissue persistence’).
Line 73	Europabio	**Comment:**	We don’t support the proposal given.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		It would be worthwhile applying Risk-Based Approaches (RBA) on a case by case basis to determine such parameters. See specific comment in section 1. General Comments while taking into account the clinical indication being sought. An additional "evaluation" of the proposed lifespan of the TEP for different groups of patients is an undue burden to the pharmaceutical entrepreneur. A case by case basis using RBA should be envisaged.	Indeed, in various patient groups depending on age, sex, ethnic group, disease status tissue environment may be different supporting TEP safety, efficacy and survival, and need to be studied in line with the intended patient population.
Line 74	Europabio	**Comment:** The severity of the medical condition or underlying pathology should be taken into account when evaluating the proposed lifespan of the TEP. **Proposed change (if any):** .. depending on age, sex, ethnic group and/or the severity of the medical condition,	Please, see the response on the previous comment. The sentence is revised.
Line 78-80	Europabio	**Comment:** This sentence could lead to misunderstanding. Further clarification would be welcome. **Proposed change (if any):** At the time of the MAA, the clinical development plan including the post marketing follow up plan, should include	We appreciate the comment. The sentence is revised accordingly adding 'additional investigations' since some study results must be already available for the MAA.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		investigation of the time to efficacy and the duration of efficacy.	
Line 81	Europabio	**Comment:** The sentence "The impact of repeat dosing should be assessed…" should be rephrased to reflect the fact that not all engineered products will be administered more than once. **Proposed change (if any):** This line should be amended "where appropriate the impact…".	We appreciate the comment. The sentence is revised accordingly.
Lines 87-88	Europabio	**Comment :** We do agree with the statement that "structural/histological imaging might be necessary but for a slightly different purpose." **Proposed change (if any):** Structural/histological imaging might be necessary to assess the overall organisation of integration of the implanted artificial tissue/organ within the host environment and its modifications (in particular when part of the product is degradable).	We thank for the comment. The sentence is revised including a modification meaning that not all TEPs will be integrated to the host tissue.
Lines 90-92	Europabio	**Comment:** The recommendation to use imaging studies for TEP behaviour in humans is to be seen with caution. None of the	We thank for the comment. In general, the CAT will encourage the developers of ATMPs to take into account the responsibility in

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		mentioned methods has enough sensitivity or even specificity to result in data that are truly meaningful. Especially any long term evaluation is not feasible with current methods (other than i.e. genetic evaluation of allogeneic approaches; here the sensitivity will most likely be insufficient and probing will be invasive). Radioisotopes available do mostly not remain in any TEP or cellular compartment. Imaging is therefore restricted to short periods (few days). Leaking radioisotopes in vivo add to the lack of consistent interpretation of the resulting images. Luminescent or fluorescent dyes have similar limitations, with few if any being available for clinical use. While these methods can be used in the preclinical development, no such recommendation should be done for the clinical setting. The Agency should rather recommend distinct methods for a distinct product if its feasibility has been proven and avoid generalization in this case. In vivo imaging methods to visualize TEP in patients should be developed first by appropriate developers, which are not identical to the TEP developer. **Proposed change:** The use of cell markers…. luminescent dyes could be used in ex vivo or in vitro samples.	development/improvement and validation of analytical methods to evaluate the safety and efficacy of the products as needed. Special situations may exist and deviations are awaited to be justified by the developer. The sentence has been revised taken into account limitations of *in vivo* studies.
Lines 99-102	Europabio	**Comment:** Many TEPs are and will be researched in rare diseases for	Thank you for the comment. The CAT acknowledges that there may be cases such

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		which there may be no fully validated clinical markers. In order to facilitate further research and product development, we would welcome a more collaborative and flexible approach with the regulators to discuss the sponsor proposed endpoints with the EMA where no validated clinical endpoints are proposed. Then, EuropaBio (EB) would like to stress that the document should clearly delineate between clinical endpoints and biomarkers and their validation thereof. With respect to the use of validated endpoints in confirmatory clinical trials, we agree that it is not always feasible to rely on fully validated endpoints (either because these do not exist or they have limited sensitivity as the initial methodology was validated for other purposes). With regards to biomarkers, currently, to EB members' best knowledge few biomarkers are accepted surrogate endpoints. Further development from the EMA on these aspects is welcomed. With respect to the "validation" we also welcome further clarification from the EMA. For example, mixing the terms of "validation" & of "biomarkers" to make the term "validated marker" requires,	as in rare diseases where the use of a validated endpoint may not be possible. Deviation from guidance is possible and applicants are encouraged to discuss these in scientific advice for example. Clarification on validation terminology is added.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		that the marker(s), which are used in the clinical studies to demonstrate the efficacy of an ATMP are validated. It is acknowledged that to validate a biomarker (e.g. cell surface antigens, secreted cellular products or gene regulatory elements like iRNA) a series of experiments need to be performed in order to meet with those prerequisites: 1. Identification 2. Qualification of the assay methods in concordance with the IVD regulations and 3. Validation that the markers work in clinical settings – robustness and suitability measurements. In other words, the validation of a biomarker is a "stand-alone" project which may take an extended period of time to be accomplished. Per the proposal, a clinical study will only be accepted by the regulatory bodies, if "a validated marker" is used, this requirement does possess a high impact and risk for the sponsor. Nonetheless, use of non-validated methods could get developers and regulators into an interesting position to evaluate the value of the study itself, especially if this relates to the pivotal, confirmatory study(ies) as outlined in the current draft reflection paper. Hence, we acknowledge the importance of validation efforts prior to these confirmatory studies, although we also recognize such validation efforts are not always easy for TEPs and can indeed sometimes benefit from Scientific Advice and/or Protocol Assistance	

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		(SA/PA). Would non validated clinical endpoints be envisaged, we consider that it would be more productive that the EMA's document encourages sponsors to discuss their proposed endpoints with EMA at time of SA/PA. Moreover, we welcome the suggestion by the regulators to use normal (or therapeutic – as suggested further in the comments) physiological characteristics as an acceptable alternative, although it is not completely clear to us how this then should be assessed/interpreted. Further clarification on this respect is welcomed as the use of physiological markers may lead to errors. As a matter of fact, bringing a physiological characteristic of a tissue being replaced to normal values may not be sufficient to bring a therapeutic benefit if the physiological characteristic chosen is not the adequate one or not sufficient to bring a therapeutic benefit. For example, would a cell expressing a growth factor be administered into the patient's eye, the level of the growth factor might be identical to a healthy person. However, the factor may not produce a therapeutic benefit because it might be the wrong target protein. Further caution should be envisaged when referring to "physiological characteristics" as described in the comment of Line 53-55. Once more, the EMA's document should encourage sponsors to discuss their proposed endpoints with EMA at time of SA/PA. **Proposed Change:**	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Line 99-100 Delete: “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”. And changed to “As for any conventional medicinal product, previously validated endpoints should be used. Any use of non-validated endpoint should be justified and discussed on a case-by-case basis in the context of the scientific advice procedure”. **Line 100-102** **Change** **“**However, if the endpoint Reflection paper on clinical aspects related to tissue engineered products 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” Into “However, if the endpoint Reflection paper on clinical aspects related to tissue engineered products represents the normal value for a physiological characteristic of a tissue being replaced, restored and/or regenerated that is key for the therapeutic effect being sought, a formal clinical trial may not be required to validate this endpoint/biomarker”. **Line 102:**	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Delete the word “validated” and just use the word “marker” or “biomarker”. **Add** “Sponsors are highly encouraged to discuss clinical endpoints, biomarkers and their validation thereof during the development of the product preferably before the pivotal confirmatory trials are initiated at time of Scientific Advice, Protocol Assistance with regulators such as EMA-CAT”.EMA”.	
Line 106-107	Europabio	**Comment:** With regards to long-term efficacy determination, it would be worthwhile applying Risk-Based Approaches (RBA) on a case by case basis to determine such parameters. See specific comment in section 1. General Comments within the context of the clinical indication being sought.	Thank you for the comment. As previously mentioned, the EMA/CAT has developed guidance for the risk-based approach for Advanced Therapy Products.
Line 112	Europabio	**Comment:** “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.” For autologous cell products the dose may be limited by the patient donor. It is possible that there may be no obvious maximum tolerated dose demonstrable in preclinical testing and clinical studies, thus treatment is limited by the initial biopsy from the donor.	We appreciate the comment. The last part of the section ‘Dose’ is revised accordingly.

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		Proposed change (if any): A potential way to address this could be by adding the following wording "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. For autologous cell based products it is accepted that full dose ranging investigations may be constrained by the nature of the initial donor cells".	
Lines 113-114	Europabio	**Comment:** As acknowledged, dose finding studies may not be always feasible, in particular with TEP where cell density within the tissue might be heterogeneous (e.g. skin). **Proposed change (if any):** The dose selection (i.e. cell density or concentration of main constituents) should be based on findings of quality and non-clinical product development, as far as possible.	We appreciate the comment. The sentence is revised accordingly.
Lines 121-122	Europabio	**Comment:** The tense is not consistent. **Proposed change (if any):** In cases, where the nature of TEP's would make a blinded trial unfeasible (…)	We appreciate the comment. The sentence is further revised to improve the guidance.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Lines 131 etc.	Europabio	**Comment:** It would be worthwhile applying Risk-Based Approaches (RBA) on a case by case basis to determine such parameters. See specific comment in section 1. General Comments.	We thank for the comment. A reference to the risk-based approach has been introduced in chapter 3 (Discussion, Therapeutic claim).
Line 134	Europabio	**Comment:** Non-invasive markers or parameters may not be available for long-term follow-up of efficacy. Invasive markers/parameters may be necessary and the risk to the patient should be taken into account. It would be worthwhile applying Risk-Based Approaches (RBA) on a case by case basis to determine such parameters. See specific comment in section 1. General Comments.	We appreciate the comment. The point has been addressed by revising the text and combining the alternatives (non-invasive and invasive methods).
Line 27	IQWiG	**Comment:** It should be clearly stated here that the need for "novel approaches" should not be taken as an invitation to depart from well-accepted and legally binding standards of research. **Proposed change:** "…may require novel approaches for their clinical development. Nevertheless, the principles of ICH/GCP should also be adhered to when evaluating TEPs."	We appreciate the comment. The proposed sentence is added.
Line 100-101	IQWiG	**Comment:**	We appreciate the comment. The sentence is

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		The history of medical research has proven that “normal values” and “physiologic characteristics” are not more valid than other surrogate endpoints: Drugs restore bone mineral density but fail to prevent fractures. Drugs restore cardiac rhythm but increase the number of cardiac deaths. **Proposed change:** ~~However~~ Also, 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.	revised by removing ‘however’.
Lines 104-106	IQWiG	**Comment:** In this sentence, validation of a surrogate endpoint is equated with the proof of a correlation between surrogate and clinical endpoint. However, validation of a surrogate endpoint requires much more. (see e.g.: Baker SG & Kramer BS. A perfect correlate does not a surrogate make. BMC Med Res Methodol 2003; 3: 16. http://www.biomedcentral.com/1471-2288/3/16) **Proposed change:** The use of ~~validated~~ biomarkers or surrogate endpoints is possible, provided that the validity of these endpoints with regard to clinically meaningful endpoints and efficacy has been established. In general, a sufficiently large correlation has to be shown between effects (i.e. differences between intervention and control groups) on the surrogate and on the clinically meaningful (patient-relevant) endpoint.	We appreciate the comment. The section is revised accordingly.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Line 119	IQWiG	**Comment:** The following paragraph describes not only blinding but also other key elements of study design. **Proposed change:** ~~Blinding~~ Study design	We appreciate the comment. The title of this chapter is revised accordingly.
Line 120-121	IQWiG	**Comment:** Randomisation is essential and therefore should be described as a cornerstone of study design rather than mentioning it only en passent in line 129. Proposed change: As for conventional medicinal products, it is advised to apply a double-blind, randomised controlled clinical trial designed against a representative comparator.	We appreciate the comment. Randomisation is included the description of an optimal study design.
Line 121-122	IQWiG	**Comment:** The sentence fails to account for the difference between single and double blinding. A trial with blinded assessments may be declared as a single-blind trial. Therefore, blinded assessments would be impossible, if a blinded trial would be unfeasible. It appears indicated to use more specific terminology (see: Montori VM, et al. In the dark: the reporting of blinding status in randomized controlled trials. J Clin Epidemiol 2002; 55: 787- 90 http://www.ncbi.nlm.nih.gov/pubmed/12384193). Moreover, it should be acknowledged that the surgical intervention required for TEP implantation prevents blinding	We appreciate the comment. The sentences are revised accordingly.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		more often than TEP itself. **Proposed change:** Due to the nature of the TEP or non-product related factors (e.g. surgical procedure) blinding of therapist and/or patient may be unfeasible. Furthermore, the use of a placebo or sham procedure may be inappropriate. In these cases all attempts should be made to have blinded outcome assessments.	
Line 125	IQWiG	**Comment:** The availability of a comparator should be discussed separately from the feasibility of blinding (e.g. placebo). Furthermore, comparisons between surgical and pharmacological treatments are difficult but still possible. **Proposed change:** If an active comparator ~~(or placebo, sham procedure)~~ is not available or inadequate, the comparison to best standard of care or no treatment (preferentially with additional application of a placebo or sham procedure) could be accepted as concurrent comparator for confirmative clinical study.	We appreciate the comment. The sentence is revised accordingly.
Line 127	IQWiG	**Comment:** - see comments below (regarding lines 129-130) - **Proposed change:** "…the comparison to best standard of care or no treatment could be accepted as concurrent comparator…"	We appreciate the comment and refer to our response above (the sentence is revised accordingly).
Line 128	IQWiG	**Comment:**	The comment is only partly accepted and the

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		In an intra-individual comparison, one can compare an anatomical site after TEP treatment with A) the same site before treatment (i.e. before-and-after comparison), B) another site, which is healthy and thus serves as a 'reference standard' or C) another site, which is affected by the disease and receives comparator treatment. Comparisons of category A and B are in general insufficient to establish efficacy, because such designs are unable to detect a difference between the natural course of the disease and the treatment effect, unless 'dramatic' differences are observed (see: Glasziou P et al. When are randomised trials unnecessary? Picking signal from noise. BMJ 2007; 334: 349-51 http://www.ncbi.nlm.nih.gov/pubmed/17303884). Comparisons of category C are suitable to assess efficacy, given that the two anatomical sites are randomly assigned to TEP and comparator treatment. Therefore, this design is already included in the general statement on randomised controlled trials. Thus, the sentence on intra-individual comparisons is misleading and should be deleted. **Proposed change:** ~~Alternatively, an intraindividual comparison can be considered.~~	revised wording reflects that.
Line 129-130	IQWiG	**Comment:** A situation where "no comparator is available" simply does not exist, as patients have been under medical care in some	Thank you for the comment, the text has been revised to take account of this comment.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		way (with or without treatment) already before the TEP was developed. The option of using "no treatment" as comparator should be listed in the paragraph above together with best standard of care (line 127). Randomisation should be described in the initial paragraph (line 120). **Proposed change:** ~~Where no comparator is available, a randomisation based on other grounds (e.g. no treatment, best supportive care) should be performed, where possible)~~	
Lines 33-34	Alliance for Advanced Therapies	**Comment:** AAT recommends including a reference to future, more specific guidelines or reflection papers that may be relevant. **Proposed change:** '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), and any other relevant guideline or reflection paper to be published after this reflection paper.'	We thank for the comment. The proposed revision is, however, not implemented. It is EMA practice to only refer to finalised guidance documents that are adopted by the relevant committee and published on our website.
Line 53-55	Alliance for Advanced Therapies	**Comment:** The current text states that 'the reference physiological values in the therapeutic claims should be from tissues/organs of healthy individuals'. However, many TEPs are used to treat patients with a defined underlying pathology in which environment the functionality of the	We thank for the comment. The sentence is revised and includes additional guidance for therapeutic claim of full or partial physiological function.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		tissues/organs may never reach that of healthy organs. Therefore, using values from healthy individuals might not be the optimal solution. Proposed change: "For the purpose of this document, the physiological values of the reference tissue/organ are the ones measured in tissue/organs from healthy individuals, or tissue/organs representative of the defined therapeutic area."	
Lines 67-95	Alliance for Advanced Therapies	**Comment:** AAT suggests specifying in which instances, what type of clinical kinetic data would be expected if certain issues may have been adequately addressed in the non-clinical phase, as there seems to be a lack of agreement on the need for additional clinical kinetic data in addition to pre-clinical data.	We appreciate the comments. The chapter has been revised with additional guidance.
Lines 112-114	Alliance for Advanced Therapies	**Comment:** The current text states that 'the dose selection (i.e. cell density or concentration of main constituents) should be based on findings of quality and non-clinical product development.' The text states correctly that 'dose finding studies in the clinical setting should be conducted where feasible.' AAT would welcome clarification on the statement: "dose selection (i.e. cell density or concentration of main constituents) should be based on findings of quality", considering that proper dose finding studies with TEPs are not always feasible, in particular when we consider that the cells are the active ingredient and that they might be distributed non-homogenously within the tissue. Therefore, the quantity of finished product (TEP) to be used in order to	We appreciate the comments. The chapter has been revised with additional guidance.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		fill the tissue defect to be regenerated, repaired and/or replaced might not be linked to a strict reproducible dose of active ingredient (i.e. cells). Moreover, in case of autologous products, the availability of starting material (biopsy) might be too low to allow multiple conventional dose finding studies. Therefore, AAT recommends clarifying the meaning of 'findings of quality'.	
Lines 122-123	Alliance for Advanced Therapies	**Comment:** AAT proposes to clarify the meaning of 'hard endpoints'. We recommend including 'objective endpoints', but also certain surrogate endpoints that are properly validated and based on objective data.	We appreciate the comment. The sentence has been revised by using 'objective endpoints'. Also additional guidance has been included.
Lines 145-146	Alliance for Advanced Therapies	**Comment:** AAT agrees that it is important to prevent bias in studies by standardisation of surgical techniques and rehabilitation protocols. Nevertheless, it is in the interest of patients to include improved surgical techniques and rehabilitation protocols as they become available during continued post-marketing follow-up over the years. AAT recommends stating that improved surgical techniques and rehabilitation protocols can be introduced during post-marketing follow-up in a controlled and uniform manner.	We appreciate the comment. The section has been improved by this additional information; a procedure that is to be managed using post-marketing regulatory processes.
Lines 33-34	TiGenix	**Comment:** The current text specifies that the 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). With progressing experience, it can however be expected that additional, more specific	We thank for the comment, however the comment is not endorsed. It is EMA practice to only refer to finalised guidance documents that are adopted by the relevant committee and published on our website.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		product-type or indication-related guidelines can be introduced. A first example being the Reflection paper on in-vitro cultured chondrocyte containing products for cartilage repair of the knee (EMA/CAT/CPWP/568180/2009). Therefore, the current text might be amended in a general manner to include such additional specific guidelines. **Proposed change (if any):** '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), and any other relevant product or indication specific guideline or reflection paper.'	
Lines 67-95	TiGenix	**Comment:** Certain kinetic aspects such as the persistence and biodistribution of the cells or other components can be adequately and thoroughly investigated in non-clinical models. It would be welcomed to specify what extent of clinical kinetic data would be expected if certain issues have been adequately addressed in the non-clinical phase, especially since there is no clear common agreement for conventional clinical kinetic data needed to be analysed in the clinical setting as exemplified in the Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006).	We thank for the comment. The chapter has been revised with additional guidance.
Lines 122-123	TiGenix	**Comment:** It would be worthwhile to further specify what is exactly meant by 'hard endpoints' as this likely refers to	We appreciate the comment. The sentence has been revised to write 'objective endpoints'.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		'objective endpoints', but could also be interpreted as the opposite of 'surrogate endpoints'. In this context it needs to be acknowledged that certain surrogate endpoints, if appropriately validated and based on an objective read-out are in fact qualifying as 'hard endpoints'.	A case-by-case evaluation will be applied if surrogate endpoints will be proposed when a true double-blinded, randomised, placebo controlled clinical trial is not feasible.
Lines 145-146	TiGenix	**Comment:** With respect to standardisation of surgical techniques and rehabilitation procedures, it is indeed important to maintain study adherence to avoid introduction of bias. However, since continued post-marketing follow-up might comprise several years, it also needs to be recognised that rehabilitation protocols might be further improved over the years. The same applies for surgical practices. It would be not ethical to deny patients access to such improved techniques if available. This is also not considered to hamper study validity as long as the changes are introduced in a controlled and uniform manner.	We appreciate the comment. The section has been improved by this additional information; a procedure that is to be managed using post-marketing regulatory processes.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Line 47	EUCOPE	**Comment:** This section speaks about referencing TEP therapeutic claims relative to the target organ. It should be adequately considered that some TEPs can be used to deliver therapeutic factors remotely. For example, it may be possible to deliver TEPs to the bone marrow compartment with the therapeutic objective of facilitating protein expression in the CNS, (http://clinicaltrials.gov/ct2/show/NCT01560182?term=metachromatic+leucodystrophy&rank=2). The paper then discusses the importance of referencing TEP "pharmacodynamics" to healthy volunteer reference ranges. For an example such as that cited, it may not be possible to determine what therapeutically relevant protein levels may be. **Proposed change (if any):** We would suggest modifying the text so as to say "where appropriate" and "where not appropriate exemption should be fully justified".	The proposed comment is appreciated and the subject addressed in the end of the chapter "3. Discussion, Therapeutic claims."
Line 49	EUCOPE	**Comment:** Pharmacokinetics does not include longevity, but resorption, distribution and excretion of a drug. Including longevity	We thank for the addressed question on including longevity to pharmacokinetic (PK) study objectives. However, the opinion of the CAT is that the character of TEPs composed of biological living cells and/or tissues requires

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		might lead to extensive durations of clinical studies that would be an undue burden to pharmaceutical entrepreneurs. Also Article 12 of Regulation 726/2004 does not include longevity as a requirement to obtain a marketing authorisation: “Article 12 1. The marketing authorisation shall be refused if, after verification of the particulars and documents submitted in accordance with Article 6, it appears that the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product.” The same applies to Art. 26 of Directive 2001/83: 1. The marketing authorisation shall be refused if, after verification of the particulars and documents listed in Articles 8, 10, 10a, 10b and 10c, it is clear that: (a) the risk-benefit balance is not considered to be favourable; or (b) its therapeutic efficacy is insufficiently substantiated by the applicant; or	that the applicant demonstrate with PK studies *the longevity* of the product. Longevity is now defined as ‘‘cell and/or tissue persistence’. The longevity is understood to be directly associated with the TEPS’s safety and efficacy.

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		(c) its qualitative and quantitative composition is not as declared. Only quality, safety and efficacy are required to obtain a marketing authorisation. No European law requires persistence or long term efficacy or longevity. **Proposed change:** Delete “longevity” in line 49	
Lines 54-55	EUCOPE	**Comment:** The paper suggests setting target physiological ranges based on reference to healthy tissue, yet there are multiple know examples where therapeutic effects can be achieved with levels of proteins below that of healthy individuals (e.g. haemophilia where 5% Factor expression can be therapeutic). This “physiological target” concept is reiterated in the subsequent section on pharmacodynamics. **Proposed change (if any):** We would suggest that the paper should encourage the identification of a suitable therapeutic target range through clinical and preclinical investigations and where possible	We thank for the comment. The subject is clarified concerning both a full as well as a partial function being the therapeutic claim for which appropriate values /ranges of values for physiological parameters are chosen.

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		clinical trials should be designed to measure the pharmacokinetics of the active therapeutic agents in an appropriate target tissue.	
Line 59	EUCOPE	**Comment:** While it is always helpful to have as many data points as possible (i.e. when a physiologic effect is reached, how long it is maintained etc.), exhaustive PD studies with TEP are often not practical. Especially TEP will often require large animal models for testing of i.e. physical properties of the TEP, the application procedure and/or biological behaviour. Large animal models need an experimental environment that makes large subject numbers impossible. Especially for PD studies, group numbers thereby should and will be limited, also based on the ethical committee review. It is therefore important to stress that sufficient data is needed to make appropriate conclusions on the PD characteristics of a TEP while acknowledging the ethical, practical barriers that exist.	We appreciate the comment. The section 'Pharmacodynamics' has been revised accordingly.
Lines 71-95	EUCOPE	**Comment:** The Draft Reflection Paper requests that pharmacokinetic	Thank you for the comment. The issue is addressed in more general terms in this paper and a note is included that PK and PD studies

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		studies should include the analysis of persistence and biodistribution of the tissue engineered cells in humans. This contradicts the CAT Reflection Paper for Chondrocyte products (EMA/CAT/CPWP/568181/2009) which states that pharmacokinetic issues should be part of non-clinical development. **Proposed change (if any):** This contradiction should be resolved.	may be interlinked. The wording is thus chosen to be softer to allow for different scenarios.
Line 71	EUCOPE	**Comment:** It is not clear, what duration of time is meant by ”persistence”, the same would apply to “longevity”. Does persistence mean the lifetime of the patient? It would be an undue burden to the manufacturer to test the “persistence” for an unknown period of time and again, “persistence” is not part of PK-studies (see comment above line 49). Also Article 12 of Regulation 726/2004 does not include “persistence” as a requirement to obtain a marketing authorisation: “Article 12	We thank for the comment. Please, see our response to comment concerning the line 49. ‘Persistence’ is equivalent with ‘longevity’. Please, find the definition given to ‘longevity’ on line 49 (...the longevity (‘cell and/or tissue persistence’).

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		1. The marketing authorisation shall be refused if, after verification of the particulars and documents submitted in accordance with Article 6, it appears that the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product." The same applies to Art. 26 of Directive 2001/83: 1. The marketing authorisation shall be refused if, after verification of the particulars and documents listed in Articles 8, 10, 10a, 10b and 10c, it is clear that: (a) the risk-benefit balance is not considered to be favourable; or (b) its therapeutic efficacy is insufficiently substantiated by the applicant; or (c) its qualitative and quantitative composition is not as declared. Only quality, safety and efficacy are required to obtain a marketing authorisation. No European law requires "persistence". **Proposed change:** Delete "persistence"	

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Line 73	EUCOPE	**Comment:** An additional “evaluation” of the proposed lifespan of the TEP for different groups of patients is an undue burden for the manufacturer. Does it mean that additional clinical studies are to be conducted not only for children, but additionally for women and men at different ages? This is not required for “normal” medicinal products according to GCP and there is no reason to include this additional condition for TEPs. **Proposed change:** Delete lines 73-76 or clarify that the evaluation is retrospective.	We don’t support the proposal given. Indeed, in various patient groups depending on age, sex, ethnic group, disease status tissue environment may be different supporting TEP safety, efficacy and survival, and need to be studied in line with the intended patient population.
Line 74	EUCOPE	**Comment:** The severity of the medical condition or underlying pathology should be taken into account when evaluating the proposed lifespan of the TEP. **Proposed change (if any):** .. depending on age, sex, ethnic group and/or the severity of	Please, see the response on the previous comment. The sentence is revised.

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		the medical condition,	
Lines 78-80	EUCOPE	**Comment:** This sentence could lead to misunderstanding. Further clarification would be welcome. **Proposed change (if any):** At the time of the MAA, the clinical development plan including the post marketing follow up plan, should include investigation of the time to efficacy and the duration of efficacy.	We appreciate the comment. The sentence is revised accordingly adding 'additional investigations' since some study results must be already available for the MAA.
Lines 90-92	EUCOPE	**Comment:** The recommendation to use imaging studies for TEP behavior in humans is to be seen with caution. None of the mentioned methods has enough sensitivity or even specificity to result in data that is truly meaningful. Especially any long term evaluation is not feasible with current methods (other than e.g. genetic evaluation of allogeneic approaches; here the sensitivity will most likely be insufficient and probing will be	We thank for the comment. In general, the CAT will encourage the developers of ATMPs to take into account the responsibility in development/improvement and validation of analytical methods needed to evaluate the safety and efficacy of the products as needed. Special situations may exist and deviations are awaited to be justified by the developer. The sentence has been revised taken into account limitations of *in vivo* studies.

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		invasive). Radioisotopes available do mostly not remain in any TEP or cellular compartment. Imaging is therefore restricted to short periods (few days). Leaking radioisotopes in vivo add to the lack of consistent interpretation of the resulting images. Luminescent or fluorescent dyes have similar limitations, with few if any being available for clinical use. While these methods can be used in the preclinical development, no such recommendation should be done for the clinical setting. The Agency should rather recommend distinct methods for a distinct product if its feasibility has been proven and avoid generalization in this case. In vivo imaging methods to visualize TEP in patients should be developed first by appropriate developers, which are not identical to the TEP developer. **Proposed change:** The use of cell markers [...] luminescent dyes could be used in ex vivo or in vitro samples.	
Lines 99-102	EUCOPE	**Comment:** It should be recognized that many TEPs will be researched in rare diseases, for which there may be no fully validated	We thank for the comment. The EMA/CAT advises the applicant to discuss any proposed deviation from the EU regulations during medicinal product development through

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		clinical markers. Sponsors should be encouraged to discuss their proposed endpoints with EMA where non validated clinical endpoints are proposed. Also, regarding the use of physiological markers could lead to errors. For example, a cell expressing a growth factor could be placed into the eye, the level of the growth factor could identical to a healthy person, but the factor may not produce a therapeutic benefit because it was the wrong target protein. **Proposed change (if any):** It is suggested emphasising the supporting text in lines 103 onward more strongly and softening the biomarker statements in line 102.	scientific advice. A choose of endpoint representing a normal physiological characteristic or function may also need to be validated in clinical trials.
Line 106-107	EUCOPE	**Comment:** Only efficacy is required, not long-term efficacy. Long-term studies would extend clinical studies unduly and are not required for other medicinal products according to EU law. Also Article 12 of Regulation 726/2004 does not include longevity as a requirement to obtain a marketing authorisation:	We thank for the comment. Please, see the response given concerning line 49.

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		"Article 12 1. The marketing authorisation shall be refused if, after verification of the particulars and documents submitted in accordance with Article 6, it appears that the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product." The same applies to Art. 26 of Directive 2001/83: 1. The marketing authorisation shall be refused if, after verification of the particulars and documents listed in Articles 8, 10, 10a, 10b and 10c, it is clear that: (a) the risk-benefit balance is not considered to be favourable; or (b) its therapeutic efficacy is insufficiently substantiated by the applicant; or (c) its qualitative and quantitative composition is not as declared. Only quality, safety and efficacy are required to obtain a marketing authorisation. No European law requires "long term efficacy".	

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		Proposed change: Delete the sentence: In cases, where long-term efficacy is expected, the endpoints should also focus on the duration of the response.	
Line 112	EUCOPE	**Comment:** For autologous cell products the dose may be limited by the patient donor. It is possible that no obvious maximum tolerated dose can be demonstrated in preclinical testing and clinical studies, thus treatment is limited by the initial biopsy from the donor. **Proposed change (if any):** A potential way to address this could be by adding the following wording “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. For autologous cell based products it is accepted that full dose ranging investigations may be constrained by the nature of the initial donor cells”.	We appreciate the comment. The last part of the section ‘Dose’ is revised accordingly.

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Lines 113-114	EUCOPE	**Comment:** As acknowledged, dose finding studies may be not always feasible, in particular with TEP where cell density within the tissue might be heterogeneous (e.g. skin). **Proposed change (if any):** The dose selection (i.e. cell density or concentration of main constituents) should be based on findings of quality and non-clinical product development, as far as possible.	We appreciate the comment. The sentence is revised accordingly.
Lines 131 et seq.	EUCOPE	**Comment:** The new proposed regulation for clinical trials was set up to shorten the time for clinical trials, as one problem was the extended duration (doubling) of clinical trials since the directive 2001/20 came into effect and the associated explosion of costs. Long-term trials mean that the marketing authorisation is unduly delayed compared to normal medicinal products, which is not acceptable. Post-marketing studies may be discussed on an individual basis with the authority, but general requirement for long-term efficacy is not required. Required are quality, safety and efficacy only.	The new proposal for Regulation on clinical trials is still under work. We will refer to our previous response concerning lines 49, 71, 106-107.

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		Proposed change: Delete lines 131-138.	
Line 134	EUCOPE	**Comment:** Non-invasive markers or parameters may not be available for long-term follow-up of efficacy. Invasive markers/parameters may be necessary and the risk for the patient should be taken into account. **Proposed change:** Delete lines 133-134	We thank for the comment. The subject has been addressed by adding invasive methods.
Lines 149-150	EUCOPE	**Comment:** It should be recognized and reflected in the paper that some TEPs have been on the market already for a long period of time, sometimes decades. Specific risks are known from the therapeutic use. Scientific publications are as well a source for information on safety aspects. **Proposed change (if any):**	We appreciate the comment. The subject is included by adding a new sentence.

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		Add a new sentence in line 150: “Information on products being already on the market may be a valuable source, as well as results of scientific publications on respective product categories.”	