The European Association for Bioindustries

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B-1049 Brussels

Re: PUBLIC CONSULTATION ON THE PROPOSALS TO AMEND ANNEX I TO DIRECTIVE 2001/83/EC AS REGARDS ADVANCED THERAPY MEDICINAL PRODUCTS

10 June 2008

Dear Mr Rossignol,

Thank you very much for the opportunity to input into the above consultation. EuropaBio is the European Association for Bioindustries, solely and uniquely bringing together bioscience companies from all fields of research and development, testing, manufacturing and distribution of biotechnology products. It has 84 corporate members operating worldwide, 8 associate members, 6 BioRegions and 25 national biotechnology associations representing some 1800 small and medium sized enterprises involved in research. Its mission is to promote an innovative and dynamic biotechnology-based industry in Europe.

The biotech industry has developed more than 200 drugs and vaccines that have helped millions of people worldwide. It currently counts for approximately 20% of all marketed medicines, and represents 50% of all medicines in the pipeline. These figures are significantly higher again in the field of rare diseases - a field affecting some 25-30 million Europeans, where biotech therapies offer the best chance for addressing these diseases (for which 70-80% have a genetic component) and where diagnosis and treatment often come too late.

As such, the relevance of the Advanced Therapies regulation to EuropaBio is very high indeed, and the Association was very supportive both of last year's Regulation, which represented a great leap forward for all those who can benefit from this new generation of truly innovative treatments, as well as the ongoing Proposals to amend Annex I to Directive 2001/83/EC to include Advanced Therapies.

EuropaBio thus welcomes the opportunity to comment on the Public Consultation Paper concerning the proposed amendments to Annex 1 of Dir 2001/83/EC, to include Advanced Therapy Medicinal Products, to replace the existing Part IV of this Annex and facilitate a harmonised approach to the regulation of these products across the EU.

Overall, EuropaBio supports the document which it considers to be well-written, comprehensive and concise in accommodating ATMPs. However, some of the points made regarding starting materials may be unnecessarily duplicated as they are captured in the requirements for biological/biotechnology products. Furthermore, one might consider giving the text a more structured outline, by grouping issues on the same topic together more systematically. Please find attached to this a set of general comments, as well as some more specific suggestions.

Thank you very much again for the opportunity to comment, and we look forward to being involved in the next stages of this process.

Yours sincerely

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1. General comments

EuropaBio would like to underline the necessity of including all advanced therapies within the definitions in Annex I. Only in this way can we ensure that the benefits of the Advanced Therapies Medicinal Products Regulation are available to all innovative therapies, without exception. However, there are clearly distinct differences between the different technologies that fall under that over-arching heading, and to accommodate these, variations in e.g. manufacturing requirements or other matters should be dealt with separately, in other guidelines.

On a separate point, it would be useful to include a list of the relevant guidance documents pertaining to ATMPs, including those in draft or being proposed by EMEA. Finally, it should be acknowledged that these innovative products will require the development of new tools and techniques to establish the safety and efficacy and comply with emerging regulatory requirements. – the spectrum is very broad but that is why a special committee of experts has been set up in order to understand what these requirements are as new products come along, and to make these clear for applicants.

We also support the risk-based approach taken in the draft, but would like to highlight that all the requirements mentioned in this consultation paper for a new part IV of Annex I of Directive 2001/83/EC are addressing products that have yet to be developed. It does not, however, adequately reflect products that have already been administered to patients for several years. Whether experience has already been gained with a product, or whether it is newly developed and being administered to patients for the first time, must be taken into consideration when issuing requirements. EuropaBio therefore strongly advises that this be mentioned explicitly in Annex I, and that the possibility of including an extra chapter within Annex I to deal with this situation is explored.

More concretely, EuropaBio would like to suggest that for ATMPs already legally on the market in the Member States at the time of the coming into force of the ATMP regulation and where experience has been gained in all-day use, it must be possible to use the approach of a mixed marketing-authorisation application where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant as well as documented experience from the use of the already marketed ATMP in the market and of bibliographical references. In addition, relevant available clinical data or experience with other, related advanced therapy medicinal products should also be considered.

As another issue, in this draft tissue engineering products and somatic cell therapy products are formally separated from each other by different definitions. However, regarding the requirements laid down in the new Annex I, it would appear that this distinction is of no practical relevance because, in most cases, the requirements for tissue engineering products and somatic cell therapy products are identical. We believe that this should not be the case, and would ask for differences to be drawn between autologous and allogenic products. Similarly, we would appreciate exact definitions for the terms “active substance”, “drug substance”, “starting material“ and “raw material”, and for these to be used consistently throughout the text.

In addition, as ATMPs fall under the umbrella of the pharmaceutical legislation, the CTD-Format will be applicable for marketing authorisation applications of these products. As this format has not explicitly developed with ATMPs in mind, but rather for medicinal products of chemical origin, EuropaBio would suggest adapting this format to suit ATMPs. It would be useful to produce a guideline on this matter to help applicants.

For the sake of clarity for the user of the new Annex I, we would also ask for the inclusion of a table stating the correlation of the different criteria for the different kinds of products, the starting material, the raw material etc - as they are described in the text. For example:

Product	**Application**	**Starting Material**	**Raw Material**	**Drug Substance**	**Drug Product**
Genetically modified primary cells (e.g. adult stem cells)	*in vivo*	- primary cells - viral vector	- medium - etc.	- viral vector	Finally formulated cell population
Genetically modified cell lines (e.g. tumor vaccines)	*in vivo*				
Viruses and Viral Vectors	*in vivo*	MCB / WCB		- viral vectors	Finally formulated viral vectors
	ex vivo	MCB / WCB		- viral vector	Finally formulated cell population
Nucleic Acid	*in vivo*	MCB/WCB		Formulated plasmid/vector	Filled formulated product?
	ex vivo	"			
Microorganisms	*in vivo*	MCB/WCB			
	ex vivo	"			

2. Specific comments on the text

Page no. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
Page 4; Section 2.1		
First paragraph	If referring only to Annex I of 2001/83/EC, it is not complete, as this annex is not up to date compared to Volume 2B of the Notice to Applicant. For example the requirements for Module 1 end at Module 1.6 in Annex I, whereas in the updated Notice to Applicant section, it is now up to Module 1.9.	Suggest amending wording as follows: "As for any other medicinal product, marketing authorization applications (MAAs) regarding advanced therapy medicinal products must follow the *Common Technical Document (CTD), or e-CTD,* format requirements *as presented in the Notice to Applicants, Volume 2B, incorporating the Common Technical Document (CTD) (June 2006) as published on the website of the European Commission (Enterprise and Industry Pharmaceuticals Sector: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm) and include Module 1 through 5*
Fourth paragraph	Suggest adding clarification on the risk analysis recommended. Module 2.2 is normally required to be very brief, thus we recommend to cross-referencing with Module 1.8.2 if necessary.	Such a risk analysis, when applied, shall be included and described in Section 2.2 of Module 2. *In particular the methodology followed and the resulting risks ranked for criticality should be provided. The impact on the development of the product and potentially on proposed mitigation and post-marketing measures should be described in this section. Cross reference with the Risk Management Plan (Module 1.8.2) for the proposed mitigation and post-marketing measures is acceptable. It is also acceptable to provide the risk analysis and its conclusions as an appendix of Module 1.8.2.*
	Concerning products already legally in the market in Member States; experiences regarding the efficacy and safety have to be taken into regard adequately.	Suggest addition of the following: *"Since there are already several advanced therapy medicinal products legally on the market in the Community before the coming into force of the Regulation on ATMP, which have proven clinical safety and efficacy in daily use, these products should not be classified as new cell-based medicinal product entering the MA procedure.*

		It is therefore acknowledged that advanced therapy medicinal products that are already legally on the market in the Community need not meet all principles of this Annex in detail. For the detailed technical requirements concerning these products, special attention should be laid on the risk analysis that may demonstrate that the product meets the criteria of pre-clinical and clinical development."
Page 5; Section 2.2		
	Although the specifics of combination products are covered in the respective technical sections, the definition of combination products is not included. It would be welcomed if the definition as defined in Article 2(1)(d) of Regulation 1394/2007/EC could be added. In addition, rather than referring to the relevant articles in this Regulation for the exact meaning of the definitions, it might be more appropriate to take over the full description of the definitions instead	
Page 5; Section 2.2.1		
	Definition of a GT product	A clarification of what falls within the scope of the GT definition is sought - as outlined in the above, EuropaBio is of the opinion that *all* advanced therapies, should fall under Annex I. If some aspects do not fit (for example, requirements relating to dedicated production facilities), these should be made clear in accompanying instruments. Furthermore, a process needs to be in place to ensure that requirements can be updated as new processes and techniques come along.
	Possible ambiguity	First bullet point: "targeted" should be placed between brackets as there are examples where one does not target a specific sequence, but adds a specific sequence, such as in case of an Adenovirus expressing the thymidine kinase gene.
Page 6 & 7; Section 2.3.2		
Point 1, first bullet	Ambiguous/un-detailed phrasing	It is not clear what is meant with "ready-prepared". This should be explained or rephrased.

		Suggest to insert the word "packaging" after "the master cell bank of the *packaging* cell line"
Point 3		Suggest inclusion of the following: "the general requirements for medicinal *and biological /biotechnological* product *shall* apply"
Between Points 3 and 4	The section on specific requirements for gene therapy medicinal products is missing a statement about genetically modified organism. A section referring to specific GMO requirements should be added.	Propose to add the sentence *"for certain gene therapy medicinal products, the general requirements for genetically modified organisms (GMOs) shall apply".*
Point 5	Possible ambiguity	Suggest inclusion of a sentence to the effect that "The principles of GMP shall, were relevant, apply to the generation of the host cell bank system onwards"
Point 5, a, iii	Last sentence: "The principles of Good Manufacturing Practice shall apply from the bank system used to produce the vector onwards". Why is this sentence only added to (iii). To our understanding it also applies to (i) and (ii). If yes, this should be clarified. If not, under (i) and (ii) it should be clarified when the principles of GMP do apply. Furthermore, there is no reference to other GXP in the Guidance. Recommend inclusion of requirements to conduct studies to GLP or GCP as applicable As a last point, for the sake of clarity, it should be stated that the master cell bank is the initial point for starting to work under GMP - the current wording is lacking clarity	Suggest inclusion of the following : (iii) In the case of genetically modified cells, the starting materials are the components used to obtain the genetically modified cells, i.e. the vector and the human or animal cells. *Information on cell source, donation, procurement and testing of the cells should be provided in accordance with Directive 2004/23/EC as amended.*
Point 5, b	Suggest inclusion of requirement for sequence analysis as mentioned in EP monograph	Suggest amending as follows: *"(b) For products containing a microorganism or a virus, data on the genetic modification, sequence analysis, attenuation of virulence, tropism for specific tissues and cell types, cell cycle dependence of the microorganism or virus, pathogenicity and characteristics of the parental strain shall be provided."*

Point 5, d	Suggest adding a paragraph pertaining to process impurities	Potential process-related impurities should be discussed in the relevant sections of the dossier. Test procedure to detect residual impurity and assessment of their removal should be described Note that this section should probably be in a new paragraph entitled "Characterization and Control Strategy" to keep consistency with the section related to somatic cell therapy
Point 5, f		Suggest inclusion of the following: "For genetically modified cells the *required or intended* phenotypic…"
Point 5 (general)	Missing from the section on requirements for gene therapy medicinal products are: Section (b) Manufacturing process Section (c) Characterization and Control Strategy Section (d) Excipients Section (e) Developmental studies Section (f) Reference Material <u>Rationale:</u> Keep consistency between section organization of requirements for gene therapy medicinal products and somatic cell therapy medicinal products	Propose to add these sections to discuss process validation requirements, product testing, etc
Point 5 (general)	This section on requirements for gene therapy medicinal products as well as the one on cell-based therapy medicinal product do not provide information related to stability studies. <u>Rationale:</u> The nature of the products is likely to drive diverse approach for stability strategy and therefore indication of the minimal requirement for stability studies would be important	Suggest adding a section on stability requirements.
Point 6 (a) (ii)	In some limited cases complete traceability may not be possible, it would therefore be useful to have an additional sentence to cope with this situation.	Proposal to add the following sentence: *„In case of incomplete traceability suitable additional testing should eliminate identified risks"*
Page 7 & 8; Section 2.3.3		
General	Suggest separating requirements for sCTPs and hTEPs for certain	

	aspects, for example: batch release testing, to take into account the structural key properties of a hTEPs	
Point 1	Clarification is required as to why this point specifically applies to sCTP and TEPs	
Point 2	The requirement that additional substances when combined as an integral part with the manipulated cells are considered part of the active substance and are therefore considered as starting materials, even if not of biological origin goes too far and will represent practical problems with respect to the quality requirements for active substances. Indeed, many of these additional substances are in fact medical devices and may not be produced according to GMP standards. As stated in Article 2(2) of Regulation 1394/2007/EC, where a product contains viable cells or tissues, the pharmacological, immunological or metabolic action of those cells or tissues shall be considered as the principal mode of action of the product. In combination products, both the manipulated cells and the additional substance(s) are to be considered as starting materials for which the final drug substance consists of the integral combination of both. Therefore, as far as EuropaBio is concerned, the nature of the combination should be considered in the characterisation of the drug substance with respect to the exact function of the additional substance(s) instead, e.g. carrier, active role, combined active principle, etc., and the text amended accordingly. For the text as it currently stands, please clarify for this type of product if pre-clinical testing is required for the active substance (cells), excipients and additional substance e.g. scaffolds and matrices separately and/or in combination (final product) only	
Point 4	This may also be the case for gene therapy products, and	

	should be added in the appropriate section.	
Point 6	The section on specific requirements for somatic cell therapy medicinal product does not address the topic of cell banking Suggest adding information on cell based therapy products specific requirements for container-closure systems,(in particular injection device) transport and traceability	Suggest to add sentence*: " When applicable provide information related to the cell banking system and apply Good Manufacturing Practice"*
Point 6, a	It has to be stated that the requirements regarding the starting material are laid down in Directive 2004/23/EC and two Commission Directives. It should be carefully considered how far the different requirements concerning donation could be part of Annex I insofar as they are explicitly outside the scope of pharmaceutical law.	
Point 6, a, i	Term "non-healthy" cells or tissues should be rephrased or clearly defined. For transatlantic harmonization, this section should also specify whether donor eligibility and screening of cells for autologous use is required (in the FDA new IND guidance for CMC information for somatic cell therapy it is clearly stated that this is not required)	Proposal for a definition: *"Cells from patients or cells affected by the disease of the donor."*
Point 6,a, iii	Consider inclusion of adventitious agents here also.	
Point 6, b, iii	Validation may be difficult to define for some SCT and TEPs. The development of appropriate guidance for this type of product would be helpful. Furthermore, as both batch as well as process consistency can be important, suggest amending wording	Suggest amending wording as following: "The manufacturing process should be validated to ensure batch *and/or process* consistency, functional integrity of the cells at " Suggest amending of the last sentence to the following: "If cells are grown directly inside or on a matrix, scaffold or device, information on the validation of the cell culture process with respect to cell-growth, function and integrity of the combination shall be provided *if available."*

Point 6, c - overall	Much of this is applicable to other types of GT and biological/biotechnological products; is this duplication required here? Suggest adding more information on the key characterization of the 3-dimensional structure of hTEPs. To achieve this goal, characterization methods like histology, imaging may be required even if not conventionally used in the evaluation of medicinal products because not "pure quantitative" methods. A specific guideline on potency assay for hTEPs would be very welcome to detail this requirement	
Point 6, c, i	The provision to provide relevant information on the characterisation of the cell population or cell mixture should be limited to those cases where there can be an impact on the safety or efficacy of the product. In addition, karyology and genetic stability are more applicable to cell lines and/or genetically modified products than for cell populations. Therefore, it is proposed to take these conditions out of this paragraph and change the wording.	Propose to amend the wording as follows: "Relevant information on the characterisation of the cell population or cell mixture in terms of identity, purity (i.e. adventitious microbial agents and cellular contaminants), viability, potency, ~~karyology,~~ tumourigenicity and suitability for the intended medicinal use should be provided *in those cases where there is an expected impact on the safety or efficacy of the product,* unless justified. ~~Genetic stability of the cells shall be described.~~"
Point 6, c, ii	In this point information about any product capable for degradation is asked for. As concerns this point, it has to be kept in mind that for medical products that are part of an ATMP, these kinds of tests are already part of standards like for example DIN 10993. The already existing tests should be taken into regard. Apart from that, impurities or degradation products may be part of the physiological tissue, too.	Suggest amending the paragraph to read as follows: "Qualitative and quantitative information on product- and process-related impurities as well as on any material capable of introducing degradation products during production shall be provided *taking into regard that impurities or degradation products may be part of the physiological tissue, too."*
Point 6, c, iv	Biological active molecules as part of the ATMPs; since intact cells and tissues produce a variety of cytokines and enzymes this requirement is overloading the GMP controls, the desired effect with respect to Product safety is questionable.	

Point 6, c, v	A differentiation between self organized tissue and scaffold directed tissues is required.	
Point 6 (d) (ii)	A definition of the term "integral part" required.	
Point 6, e	Especially for products already on the market, this question often cannot be addressed anymore because the development of the product is already done and during the lifetime of the product improvements were done on the basis of experience gained with the product.	Suggest amending wording as follows: "The description of the development program shall *adequately summarise and justify* the choice of materials and processes *taking into regard that for ATMPs already legally marketed before the coming into force of the Regulation on ATMP, this information often cannot be generated retrospectively.*
Point 6, f, i	There are not always reference standards available. For an ATMP manufactured for an individual patient, it is not possible to provide a reference standard. What type of reference standard can be imagined for a TEP, e.g. human epidermis? This requirement might be helpful for chemical entities but not e.g. in the case of autologous TEPs.	Suggest amending text as follows: *"If available and up to the specificity of the product in question,* a reference standard, relevant...."
Point 6, f	This could be problematic for some types of SCT or TEP and the development of EU guidance on appropriate reference standards for this type of product would be helpful. Also suggest amending text to acknowledge the difficulty with individual patient products.	Suggest amending text: "The provision to document and characterise a reference standard, relevant and specific for the active substance and/or the finished product, shall be documented and characterised, unless justified *(e.g. in case of patient specific products with batches consisting of a limited or single number of product vials)."*
Page 11; Section 2.4.1		
Point 2	Risk analysis should not become a mandatory additional requirement, unless really justified for all ATmPs.	Suggest to amend text to reflect this: "The rationale for the non-clinical development ~~should~~ *can* be based on the above mentioned risk analysis …"
Point 4 to be added	As already marketed products have often been administered to patients for several year, the additional experience that would be gained with non-clinical studies at this point of time would be quite limited for these products taking into regard that unnecessary animal studies should be avoided.	Suggest adding point to reflect this: *4. Concerning the question of non-clinical studies in case of already marketed products special attention should be laid on the initial risk analysis answering the question if for those products non-clinical studies are needed and the use of animal experiments can be justified.*
Page 12 & 13; Section 2.4.2		

Point 1, a		Suggest amending wording as follows: *"The duration of the nucleic acid sequence function and the proposed dosing regimen in the clinical studies shall be extrapolated from these studies and provided"*
Point 1 (a)	Relevant animal species are not always available.	Suggest to amend the first sentence as follows: „In vitro and in vivo pharmacodynamic „proof of concept" studies should provided using appropriate models and relevant animal species, *if available***,** designed*….."*
Point 1 Pharma- **cology**	Guidance is required as to the scope of the studies that will be required for SCT & TEPs. Sponsors may wish to test the final product in an animal model before proceeding to patients. Animal models may suffer from a lack of cross-reactivity and therefore relevance of pharmacological data. Larger animal studies may require immunosuppression which may complicate data interpretation.	
Point 2, b	Further clarification is requested on this point. Is the expectation for sponsors to develop autologous models (mouse cell is mice with mice secreted proteins – if homologous to the human protein)? Cross reactivity issues may generate PK but not PD data.	
Point 3, f	Reproductive and developmental tox in the case of gene therapy products can only be justified if affection of the germline might be expected.	Suggest amending wording as follows: *"where appropriate based on the outcome of biodistribution and toxicology studies and to relevant guidelines.*
Point 3, g	Currently there is little evidence of immunogenicity to certain gene therapy medicinal products and therefore such assessment should not be ascribed to all such products	Recommend addition of the following sentence at the end of the paragraph: *"Immunogenicity should be evaluated on a case by case basis based on risk assessment and should not be considered routine for all nucleic acid based therapeutics*
Point 3 Toxicology	Further guidance is requested to clarify the data requirements for toxicology studies on SCT and TEP to include suggestions on	

	study duration, species selection and design.	
Point 3, g, second paragraph		Suggest amending wording as follows: Inclusion of the words *"where relevant"* at the end of this sentence as it may prove problematic to generate relevant pharmacological/immunological data in an animal model.
Page 11; Section 2.4.3		
General	Guidance is required as to the scope of the studies that will be required for SCT & TEPs. Sponsors may wish to test the final product in an animal model before proceeding to patients.	
Point 1, a	This chapter does not take into regard that there are already ATMP legally on the market in the member states. For these products primary pharmacological studies showing the "proof of principle" would often be unnecessary as the products have shown during their use for several years that they are effective.	Suggest addition of sentence: sentence added: *"For tissue engineering products legally on the market in the Community before the coming into force of the Regulation on ATMP the experience gained with these products shall be taken into account."*
Point 1, b	Classical 'dose-response' studies are often not feasible for this type of products. A clear dose response curve is not to be expected in the case of 3D organized tissues – it would be helpful if this was specified	Suggest amending text as follows: "The *minimum* amount of product needed to achieve the desired effect/the effective dose, and where appropriate, the frequency of dosing should be ~~determined~~ *justified."*
Point 1, c	The experience gained with autologous tissue engineering products already administered to patients show low very low risks for side effects. Potential side effects are related to the kind of product and the cells that are used. Therefore the initial risk analysis should define if and what kind of studies are needed here. Please justify this requirement, otherwise it is opening the door for unlimited experiments /studies etc. At this point the RMP might be of help. Finally, what makes a autologous TEP, e.g. epidermis more dangerous than an allogeneic cadaver skin, where no such requirements are given for a	Suggest amending the first sentence to read as follows: *"Based on the results of the initial risk analysis* secondary pharmacological studies should be considered to evaluate potential physiological effects that are not related to the desired therapeutic effect of the somatic cell therapy medicinal product and tissue engineered product or of additional substances."

	clinical use?	
Point 2, a	The question of migration is connected to the kind of product in question. For example: when the cells administered to the patient are fixed (for example in a matrix) the assessment of migration would not be necessary. Is there any scientific based evidence for a risk induced by cells migrated e.g. from a 3D organized tissue? Before requiring such data, transplant surgeons should be consulted as to whether there is relevant data supporting these points.	Suggest amending the second sentence to read as follows: "However, parameters such as viability, longevity, distribution, growth, differentiation and**,** *depending on the product in question,* migration should be investigated over time, as appropriate.
Point 2, b	In the case of autologous TEPs it makes no sense to require distribution kinetics of biomolecules secreted by the cells within the TEP, unless a non-homologous use of the cells is intended.	
Point 3	Please differentiate between autologous and allogenic products, esp. when requiring immunotox studies. Further, please define "lifespan". What is a lifespan, if a TEP is transplanted, not rejected and will be there during the whole patient´s life?	
Point 3, a	It is not clear what type of toxicity study would be appropriate for these ATMP's. The type of studies will depend on the actual components of the product. Different components can be tested in different designs, fitted to the type and nature of the component (chemical vs. biological).	Suggest amending wording as follows: "It is essential that the toxicity of the finished product shall be assessed. Individual testing of active substance(s), excipients, additional substances and any process-related impurities shall be taken into consideration, where appropriate. *For excipients, impurities, etc, conventional toxicology studies would generally be applicable. However, for the cellular/biological component(s) of the product such conventional toxicology assays might not apply and more relevant safety assessments should be considered."*
Page 14, Section 2.5.1		
Point 2	Suggest adding requirements that information of the administration tools (example : injection device) is provided, and in particular the	

	compatibility studies to check that this injector will not intervene badly on the quality and potency of ATMPs	
Point 9 should be added	This chapter does not adequately take into regard that there are already ATMP legally on the market in Member States. For these products, often non-interventional studies have been conducted. The experience gained with these products in day-to-day use have to be taken into regard.	Suggest adding the following sentence: *For tissue engineering products legally on the market in the Community before the coming into force of the Regulation on ATMP the experience gained with these products shall be taken into account.*
Page 14; Section 2.5.2		
Point 1, 2nd bullet	Suggest clarification that the authorities acknowledge that only a limited set of tissue/body fluid specimen can be studied in clinical studies (in contrast to biodistribution studies in animals).	
Page 15; Section 2.5.4		
Point 1	Suggest adding that dose finding studies might not be relevant for tissue engineered products considering that the objectives are often to fill the gap of missing native tissue	
Point 2	Suggest adding other methods than pharmacodynamic markers to characterise the intended functions and structure of hTEPs. As mentioned above, techniques like imaging or histopathology could also be useful means.	Suggest for chapter to read as follows: "Pharmacodynamic studies should be designed and tailored to the specificities of tissue engineered products. The evidence for the proof of principle and the kinetic of the product to obtain the intended regeneration, repairing or replacement should be provided, unless justified. *Non invasive methods (e.g. X-ray, MRI,..) should be used preferably for these investigations. If non invasive methods are not available,* suitable pharmacodynamic markers, related to the intended function(s) and structure should be considered.
Point 3	The question if these safety studies are needed should be related to the initial risk analysis. For tissue engineered products for autologous use. this seems not to be necessary. Please reconsider these requirements; they seem to be	Suggest amending the first sentence to read as follows: *If for the specific cell-type risk can be expected as a result of the initial risk analysis* **s**afety studies shall address aspects, such as:"

	too theoretical.	