Draft Eucomed comments to the document

IMPLEMENTATION OF THE 'ADVANCED THERAPIES' REGULATION

Regulation (EC) No 1394/2007

PUBLIC CONSULTATION PAPER

PROPOSALS TO AMEND ANNEX I TO DIRECTIVE 2001/83/EC AS REGARDS ADVANCED THERAPY MEDICINAL PRODUCTS

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Foreword

This proposal does not apply to those Human Tissue Engineered Products (HTP) which fall outside the scope of the Advanced Therapy Medicinal Products Regulation 1394/2007 (ATMP).

The guidance fails to clarify the borderline between Tissue Engineered Products and Combined advanced therapy medicinal product.
Whenever a scaffold or other products, being an integral part of the final product, fit with the definition of Medical Device as referred to at art 1.2.a of Directives 90/385/EEC and 93/42/EEC, the final product shall be considered as a combined advanced therapy medicinal product. Clause 2.3.2 and 2.3.3(d)(ii) need therefore to be rewritten.

The following comments are applicable to Tissue Engineered Products only. We are not commenting on parts specific to gene therapy.

Original text	Proposed amendment	Comment/Rationale
2.1. Introduction		Comment: While we do not oppose in principle to the use of CTD we warn on the inappropriateness of some of the headings contained in Modules 1, 2, 3, 4 and 5 in respect to the products at stake.

2.1. Introduction The risk analysis may cover the entire development. Risk factors include but are not limited to: the origin of the cells, the ability to proliferate, to differentiate and to initiate an immune response, the level of cell manipulation, the combination of cells with bioactive molecules or structural materials, the nature of the gene therapy medicinal products, the integration of nucleic acids sequences or genes into the genome, their long time functionality or oncogenicity and the mode of use.	*We suggest to replace the term "may" with "shall" in the following paragraph:* "The risk analysis ***shall*** cover the entire development ..."	Risk should be evaluated from development upwards, and so should be made more definitive. The concept of risk management introduced in the medical device sector should be taken into account for these kinds of products. In the document the term "risk management plan" under 2.5.1.8. has to be intended as generally recognized in the medicinal products legislation.
2.3. Technical Requirements regarding Module 3 (Quality data) 2.3.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products **2.** The active substance is composed of the manipulated or engineered cells and/or tissues. Additional substances (*e.g.* scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) 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.	We suggest deleting the second part of the paragraph. New wording: "The active substance is composed of the manipulated or engineered cells and/or tissues. It might include biomolecules or other components which do not fit the definition of medical device as referred to at art.1.2.a of directive 93/42/EEC and Directive 90/385/EEC"	Scaffolds, matrices and devices cannot be considered as part of the active substance: this would require that inappropriate testing is applied to these components, with implications in terms of safety of the final product.
2.3. Technical Requirements regarding		The general requirements should be clearly

Module 3 (Quality data) 2.3.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products **5.** For somatic cell therapy medicinal products and tissue engineered medicinal products, the general requirements for biological medicinal products apply.		specified or referred to with specific references.
2.3.3.6.(a).(i). (i) Information on donation, procurement and testing shall be provided. Where animal cells or tissues are used, specific acceptance criteria shall be provided. If non-healthy cells or tissues are used as starting materials, their use shall be justified.	We suggest to replace with the following wording: (i) For human tissues, assumption of conformity to national transpositions of Directive 2004/23/EC or its equivalence outside the European Union shall be provided.	General comment: Several of the documents required are in the case of human tissues part of the application at national level for an approval on the basis of Directive 2004/23/EC. A certificate issued by Competent Authority of conformity to Directive 2004/23/EC should be a valid alternative to the submission of the documentation. Reference to animal tissues should be removed from this point since covered by 6.(a)(iv).
2.3.3.6.(a).(ii).		We would welcome a definition of what is intended with "complete traceability".
2.3.3.6.(b).(i)	We suggest : "All steps of the manufacturing process starting from the receipt of the organs/tissues/cells up to the formulation and filling of the finished product shall be described"	Several human tissue engineered products are presented in forms other than filled vials (e.g. autologous skin).

	We suggest to replace the word "filling" with "packaging" and "formulation" with "completion of manufacturing".	
2.3.3.6.(b)(iii)	We suggest to replace "should" with "shall": "The manufacturing process ***shall*** be validated to ensure batch …"	
2.3.3.6.(b)(iii)	We suggest the following addition: "The manufacturing processes, including those considered unique to tissue engineered products (i.e. aseptic processing, sterilisation etc.) ***shall*** be identified and validated to ensure batch …"	This will include manufacturing steps different to those currently expected for pharmaceutical products.
2.3.3.6.(c)(i) 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, tumorigenicity and suitability for the intended medicinal use should be provided, unless justified. Genetic stability of the cells shall be described.	We suggest the following re-wording: Relevant information ***should be provided*** 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, tumorigenicity and suitability for the intended medicinal use ~~should be provided~~, ~~unless~~ ***when*** justified. Genetic stability of the cells shall be described.	
2.3.3.6.(c)(ii) Qualitative and quantitative information on product- and process-related impurities as well as on any material capable of introducing	We suggest the following re-wording: Qualitative and***/or*** quantitative information on product- and process-related impurities as well as on any material capable of introducing	In some instances, depending on the risk assessment, qualitative information may be sufficient.

degradation products during production shall be provided.	degradation products during production shall be provided ***and documented in the risk assessment***.	
2.3.3.6.(c)(v) (v) Where a 3-dimensional structure is part of the intended function, the differentiation state, structural and functional organisation of the cells and, where applicable, the extracellular matrix generated shall be part of the characterisation for these cell-based products.	For clarity, we suggest to move this point to make it a subsection of point (i).	
2.3.3.6.(d)(ii)	(ii) ~~Matrices, scaffolds, devices, biomaterials or~~ biomolecules which are not an integral part of the active substance, shall be considered excipients of the finished product.	Scaffolds, matrices, biomaterials and devices cannot be considered as excipients: this would require that inappropriate testing is applied to these components, with implications in terms of safety of the final product.
2.3.3.6.(e) (e) Developmental studies The description of the development program shall address the choice of materials and processes. Particularly, the integrity of the cell population regarding its biological characteristics, differentiation state and therapeutic function in the presence of the final formulation shall be discussed.	We suggested the following modification: (e) Developmental studies The description of the development program shall address the choice of materials and processes. Particularly, the integrity of the cell population regarding its biological characteristics, differentiation state and therapeutic function in the presence of the final formulation ***or the intended purpose***	

	shall be discussed.	
2.3. Technical Requirements regarding Module 3 (Quality data) 2.3.4. Specific requirements for advanced therapy medicinal products containing devices 1. For advanced therapy medicinal product containing medical devices, bio-materials, scaffolds or matrices, a description of the physical characteristics and performance of the product and a description of the product design methods shall be provided. The interaction and compatibility between genes, cells and/or tissues and the structural components shall be described.	We suggest to change this point to read: "For advanced therapy medicinal product containing medical devices, bio-materials, scaffolds or matrices, a description of the physical characteristics and performance of the product and a description of the ***design of the*** product ~~design methods~~ shall be provided." ~~The interaction and compatibility between genes, cells and/or tissues and the structural components shall be described.~~	Wording provided in order to be consistent with medical devices terminology (see MDD). The second part of the sentence is redundant with point 2.3.4.2(b) since it is an Essential Requirement of the MDD.
2.3.4.2(a) Information on the choice and intended function of the medical device / implantable medical device shall be provided. Compatibility of the device with other components of the product shall be demonstrated.	We suggest the deletion of this point (a).	This point is redundant with point 2.3.4.2(b) since it is an Essential Requirement of the MDD.
2.3.4.2(c) (c) Where available, the results of the assessment by a notified body in accordance with		General comment: We would nevertheless draw the attention that when such an assessment is not delivered by the applicant, Article 9 of the ATMP reads:

Directive 93/42/EEC or Directive 90/385/EEC of the medical device part or active implantable medical device part shall be provided.		"If the application does not include the results of the assessment, the Agency shall seek an opinion on the conformity of the device part with Annex I to Directive 93/42/EEC or Annex 1 to Directive 90/385/EEC from a notified body identified in conjunction with the applicant, unless the Committee for Advanced Therapies advised by its experts for medical devices decides that involvement of a notified body is not required."
2.4. Technical requirements regarding Module 4 (Non-clinical data) 2.4.3.1.(b)	We suggest to add the following sentence at the end of this point: Consequences of such dosing studies should be carefully considered and described for autologous tissue engineered products, based on risk assessment.	The success in producing the autologous tissue engineered products depends on the ability to collect and manufacture cells from specific patient biopsies which are inherently variable. Although the effective dose will have been established for a particular therapy, dosing studies are difficult to design and carry out. The consequences of this variability should be considered within the product risk management process.
2.4.3.3.(a)	We suggest to modify the text accordingly: (a) It is essential that the toxicity of the finished product shall be assessed. Individual testing of active substance(s), excipients, additional substances and any processrelated	Clarification: The most appropriate methodology to evaluate toxicity depends on the nature of the components of the final product.

	impurities shall be taken into consideration, where appropriate ***according to the relevant methods***.	
2.4.3.3.(b) The duration of observations may be longer than in standard toxicity studies, depending on the lifespan of the medicinal product.	We suggest the following modification: "The duration of the observations of the toxicity studies shall be appropriate, depending on the anticipated lifespan of the medicinal product".	
2.5. Technical requirements regarding Module 5 (Clinical data) 2.5.1.7. General requirements for advanced therapy medicinal products For combined advanced therapy medicinal products, the safety and efficacy studies shall be designed and performed with the combined product as a whole.		General comment: In applying the relevant guidelines, including GMP, the specificities of these products should be taken into account. Reference for example could be made to applicable guidance and/or standards relevant to medical devices.
2.5. Technical requirements regarding Module 5 (Clinical data) 2.5.4.3. Specific requirements for tissue engineered products Safety studies shall address aspects, such as: - distribution and engrafting following administration; - ectopic engraftment; - oncogenic transformation and cell/tissue lineage fidelity.	We suggest the following modification: "Safety studies shall address aspects, such as: - distribution and engrafting following administration; - ectopic engraftment; - oncogenic transformation and cell/tissue lineage ~~fidelity~~ ***stability***."	