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2.1 **Introduction** 3rd paragraph	« In principle, all relevant guidelines developed by the European Medicines Agency (EMEA) or the International Conference on Harmonisation (ICH) should be followed. Any exception and/or deviation shall be appropriately justified in Module 2.” **Comment** As general quality requirements/characteristics of these products are included in the Ph. Eur. the reference to the Eurepoean Pharmacopoeia seems appropriate.	
5th paragraph	“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. **Comment:** Several relevant “risk aspects” for cell-based products according to the draft guideline on human cell-based products might be included.	“The risk analysis may cover the entire development. Risk factors include but are not limited to: the origin of the cells (e.g., autologous or allogeneic), 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 mode of administration , the duration of exposure, 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.

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2.2 Definitions 2.2.1 Gene therapy medicinal product	*" 2.2.1. Gene therapy medicinal product* means a medicinal product: - that contains or consists of a nucleic acid sequence used in or administered to human beings, *in vivo* or *ex vivo*, with a view to regulating, repairing or replacing a targeted genetic sequence; and - whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid sequence it contains, or to the product of genetic expression of this sequence."	*Gene therapy medicinal product* means a medicinal product: the active substance of which contains or consists of a recombinant nucleic acid, where the recombinant nucleic acid is used in or administered to human beings with a view to regulating, repairing, replacing, adding, mutating or deleting a genetic sequence and/or where the recombinant nucleic acid is an added, mutated or deleted genetic sequence; and whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid it contains, or to the product of genetic expression of this nucleic acid or to cells harbouring a nucleic acid which has these properties.
2.2.2. Somatic cell therapy medicinal product	*"2.2.2. Somatic cell therapy medicinal product* means a medicinal product that: - contains or consists of engineered cells or tissues within the meaning of Article 2(1)(c) of Regulation 1394/2007/EC, and - is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues." **Comment**: See above	*Somatic cell therapy medicinal product* means a medicinal product that: - contains or consists of cells or tissues that have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties have been altered, and - is presented as having properties for, or is used in or administered to human beings with the view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues. The manipulations listed in Annex I to Regulation (EC) No. 1394/2007, in particular, shall not be considered as substantial manipulations."

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2.3 Modul 3 (Quality) 2.3.2 Specific requirements for gene therapy medicinal products 5 (a) iii)	" (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. The principles of Good Manufacturing Practice shall apply from the bank system used to produce the vector onwards."	(iii) In the case of genetically modified cells, the starting materials are the components used to obtain the genetically modified cells, *i.e.* the starting materials to produce the vector and the human or animal cells. The principles of Good Manufacturing Practice shall apply from the bank system used to produce the vector onwards."
2.3.2 Specific requirements for gene <u>therapy medicinal products</u> 5 (e)	"(e) For plasmids quantification of the different plasmid forms shall be undertaken throughout the shelf life of the product." **Comment:** Issue of 5(e) has more character of a guideline and may not have to be outlined in detail in the annex.	Delete.
5 (f)	*"(f) For genetically modified cells the phenotypic characteristics of the cells pre- and post-transduction shall be tested, before and after any subsequent freezing/storage procedures*". **Comment:** "Phenotype characteristics" is not appropriately defined (eg cell surface markers and/or transgene expression). Therefore, we propose to delete "phenotypic".	"(f) For genetically modified cells the relevant ~~phenotypic~~ characteristics of the cells pre- and post-transduction shall be tested, before and after any subsequent freezing/storage procedures".

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2.3.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products	**4.** For certain somatic cell therapy medicinal products and tissue engineered products, ( ) the active substance and the finished product can be closely related or nearly identical. In those cases, only relevant sections and items need to be completed, if justified **Comment:** ( ) "Starting material" has been deleted compared to a similar sentence in the draft guideline on human cell-based products.	**4.** For certain somatic cell therapy medicinal products and tissue engineered products, the starting material, the active substance and the finished product can be closely related or nearly identical. In those cases, only relevant sections and items need to be completed, if justified
6 (a) Starting material (i)	**"**(i) Information on donation, procurement and testing shall be provided…." **Comment:** The subject of the testing should be named.	"(i) Information on donation, procurement and testing of cells/ tissues used as starting material shall be provided…."
(ii)	(iii) The potential variability introduced through the starting material (*e.g.*, variability of donor population such as age, characteristics of cells) shall be addressed insofar as manufacturing process, validation, characterisation, control, stability are concerned, both for the active substance and the finished product. **Comment:** The wording should be clearified. **.** Procedures for selection of appropriate donor material are not mentioned.	(iii) The influence of the potential variability of cells/tissues used as starting material (*e.g.*variability of donor population such as age, characteristics of cells) on the manufacturing process, validation, characterisation, control, stability should be addressed both for the active substance and the finished product.

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(iv)	(iv) For xenogeneic cell-based products, information on the source of animals (such as geographical origin, animal husbandry, age), measures to prevent and monitor infections in the source/donor animals, testing of the animals for infectious agents and suitability of the animal facilities shall be provided.	(iv) For xenogeneic cell-based products, information on the source of animals (such as geographical origin, animal husbandry, age), measures to prevent and monitor infections in the source/donor animals, testing of the animals for infectious agents <u>including vertically transmitted micro-organisms</u> and viruses and evidence for the suitability of the animal facilities shall be provided.
(v)	(v) For cell-based products derived from genetically modified animals, the specific characteristics of the cells related to the genetic modification shall be described. A detailed description of the method of creation and the characterisation of transgenic animal shall be provided.	(v) For cell-based products derived from genetically modified animals, the specific characteristics of the cells related to the genetic modification shall be described. A detailed description of the method of creation and the characterisation of transgenic <u>and/or knock-out</u> animal shall be provided.
(b) Manufacturing process: (i)	(i) All steps of the manufacturing process starting from the receipt of the organs/tissue/cells up to the formulation and filling of the finished product shall be described. **Comment:** Although donation and transport of cells/tissues are covered by Dir. 2004/23/EC, this shall be described since procurement is a critical step (eg microbiologic safety)	(i) All steps of the manufacturing process starting from the receipt of the organs/tissue/cells up to the formulation and filling of the finished product shall be described. Donation, procurement and transport of cells/tissues as starting material shall be described since procurement is considered to be a critical step (e.g. for microbiological control of the product).
(iii)	(iii) The manufacturing process should be validated to ensure batch consistency, functional integrity of the cells at the moment of application/ administration, the proper differentiation state and the cell function with additional substances throughout the manufacture. If cells are grown	(iii) The manufacturing process should be validated to ensure batch consistency, proper differentiation state, cell function and functional integrity of cells at the moment of application/administration,. ~~the proper differentiation state and the cell function with additional substances throughout the manufacture.~~

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	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. **Comment:** The wording is unclear	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 product shall be provided.
2.3.3 (f) Reference materials	"(f) Reference materials (i) A reference standard, relevant and specific for the active substance and/or the finished product, shall be documented and characterised, unless justified." **Comment:** The term "Reference standard" in this context should be clarified as this term is usually used for authorised Pharmacopoe-standards. This might be hard to achieve for the respective products as mostly in house standards will be used.	
2.4 Module 4 (Non-clinical data) 2.4.1. General requirements for <u>advanced therapy medicinal products</u> 3.	**3.** The safety, suitability and biocompatibility of any additional substances such as … **biomaterials…** **Comment:** This requirement may produce some practical problems as the safety documentation of the mentioned products produced by other companies may not be available for the applicant for reasons of confidentiality.	Delete.

SPECIFIC COMMENTS ON TEXT		
Proposal to amend Annex I to Directive 2001/83/EC		
Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
2.4.2. Specific requirements for gene therapy medicinal products	**Comment:** There is no consistency between Modules 4 and 5 concerning structure and wording.	Adapt according to comment.
1. Pharmacokinetics (b)	"(a) Biodistribution studies, shall include investigations on persistence, clearance and mobilisation. Biodistribution studies should especially address the risk of germ line transmission. (b) Investigations of shedding of transmissible vector, micro-organism or virus and risk of transmission to third parties shall be provided with the environmental risk assessment where appropriate." **Comment**: 1) These two parts should be harmonised with the corresponding parts in Modul 5. 2) The wording "transmissible vector" is misleading. Shedding studies and assessment of the riks of horizontal transmission and its consequences are to be performed for any type of viral vector/virus which can transduce cells or infect humans or animals.	(b) Investigations of shedding of ~~transmissible~~ transducing vector, infectious micro-organism or virus and risk of transmission to third parties shall be provided with the environmental risk assessment where appropriate."

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(c)	(c) Repeated dose toxicity studies …..The duration of the studies may be longer than in standard toxicity studies depending on the persistence of the gene therapy medicinal product and the anticipated potential risks. **Comment:** 1) Justification for the duration of the studies should be provided.	(c) Repeated dose toxicity studies…. The duration of the studies may be longer than in standard toxicity studies depending on the persistence of the gene therapy medicinal product and the anticipated potential risks. A justification for the duration should be provided.
(f)	(f) Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies shall be provided, where appropriate according to relevant guidelines. **Comment:** The requirement for generally studying effects on fertility and general reproductive function is stringent but may not be necessary for, e.g., genetically modified cells administered to the brain.	(f) Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies shall be provided, where appropriate and according to relevant guidelines, unless otherwise justified.

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Proposal to amend Annex I to Directive 2001/83/EC		
Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
2.4.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products	**Comment:** There is no consistency between Modules 4 and 5 concerning structure and wording.	
1. Pharmacology	(a) The primary pharmacological studies should be adequate to demonstrate the proof of principle. The desired interaction of the applied cells with the non-cellular structural component(s) of the product and the interaction of the cell-based products with the surrounding tissue should be studied. **Comment:** The interaction of cells and surrounding tissue may be difficult to study in some cases.	(a) The primary pharmacological studies should be adequate to demonstrate the proof of principle. The desired interaction of the applied cells with the non-cellular structural component(s) of the product and the interaction of the cell-based products with the surrounding tissue should be studied unless otherwise justified.
3. Toxicology		
(b)	(b) The duration of observations may be longer than in standard toxicity studies, depending on the lifespan of the medicinal product. **Comment:** See comment (b) under 2.4.2 .Justification for the duration of the studies should be provided.	(b) The duration of observations may be longer than in standard toxicity studies, depending on the lifespan of the medicinal product. A justification of the duration should be provided.

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(c)	(c) Conventional carcinogenicity and genotoxicity studies are normally not required. However, the tumourigenic potential of the product shall be studied unless otherwise justified.	(c) Conventional carcinogenicity and genotoxicity studies are normally not required. However, the tumourigenic potential of the product shall be studied unless otherwise justified.
(e)	(e) In case of cell-based products containing animal cells, the associated specific safety concerns such as virus reactivation shall be addressed. **Comment:** Instead of the virus reactivation the main safety concern should be pointed out. This is transmission of xenogeneic pathogens humans	(e) In case of cell-based products containing animal cells, the associated specific safety concerns such <u>as ~~virus reactivation~~ xenogeneic pathogens which may be transmitted to humans</u> shall be addressed.
2.5 Module 5 (Clinical data)	**General comments:** See comments 1), 3) 4) under general comments. There is no consistency between Modul 4 and 5 concerning structure and wording,. There should be consistency between sections egarding pharmacology-pharmacodynamics, pharmacokinetics. The assessment of “efficacy”.is not addressed. In the “general requirements” there is only a statement in relation to combined products and in relation to long term efficacy follow-up, and a weak statement that “proposed indications …supported by clinical studies….	Adapt.

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Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
2.5.1. General requirements for advanced therapy medicinal products	**"1.** In general, the requirements for Module 5, as described in Part I of the Annex shall apply. Deviations from Module 5 and from applicable existing guidelines shall be justified in Module 2." **Comment:** For clinical data deviations from the applicable existing guidelines should only be acceptable if appropriately scientifically justified.	**1.** In general, the requirements for Module 5, as described in Part I of the Annex shall apply. Any deviations from Module 5 and from applicable existing guidelines shall be scientifically justified in Module 2.
4./5.	**4.** Dose selection and schedule … **Comment:** The sequence of bullet points should be changed. Bullet point 5 should be point 4, and 4 should be 5 and followed by point 6.	
6.	**6.** Proposed indications should be supported by relevant results from clinical studies using clinically meaningful endpoints for the intended use. In certain clinical conditions evidence of long term efficacy may be required. The strategy to evaluate long term efficacy should be provided. **Comment:** It should be clarified that long term efficacy data are not suitable to replace efficacy data at the time of marketing authorisation.	**6.** ~~Proposed indications~~ The efficacy in proposed indications should be supported by relevant results from clinical studies using clinically meaningful endpoints for the intended use. In certain clinical conditions evidence of long term efficacy may be required. The strategy to evaluate long term efficacy should be provided.

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Proposal to amend Annex I to Directive 2001/83/EC		
Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
2.5.2. Specific requirements for gene therapy medicinal products 2.5.3. Specific requirements for somatic cell therapy medicinal product 2.5.4. Specific requirements for tissue engineered products	There is no consistency in structure and requirements between the sections and with the corresponding sections of Module 4 (non-clinical data) .	
2.5.2. Specific requirements for gene therapy medicinal products 3.	**3.** Safety studies shall address aspects such as: - emergence of replication competent vector; - emergence of new strains; - reassortment of existing genomic sequences; - neoplastic proliferation due to insertional mutagenicity **Comment:** Safety studies for gene therapy MPs. Immune system monitoring is considered important	**3.** Safety studies shall address aspects such as: - emergence of replication competent vector; - emergence of new strains; - reassortment of existing genomic sequences; - neoplastic proliferation due to insertional mutagenicity - immune system monitoring and immune response against all components of the gene therapy medicinal product.

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Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
2.5.3. Specific requirements for somatic cell therapy medicinal product	**1.** For somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s), the pharmacokinetic profile (in particular distribution, duration and amount of expression) of these molecules shall be addressed. **Comment**: These requirements are relevant for both somatic cell therapy and tissue engineered products and should be addressed in both sections. However the requirement itself to address the PK profile of biomolecules is too stringent and can often only be addressed in preclinical studies.	**1.** For somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s), the pharmacokinetic profile (in particular distribution, duration and amount of expression) of these molecules should be addressed, if feasible.
	Comment: Requirements specific for xenogeneic somatic cell therapy medicinal products and xenotransplants should be summarized in a separate chapter.	