SUBMISSION OF COMMENTS ON Proposals to Amend Annex 1 to Directive 2001/83 as regards Advanced Therapy Medicinal Products

COMMENTS FROM European Biopharmaceutical Enterprises (EBE) / Contact Piers Allin (piers@ebe-biopharma.org)
GENERAL COMMENTS
The proposed definition of "gene therapy product" would have the effect of broadening the scope of the Advanced Therapies Regulation to products that do not have any gene-correcting effect, which we do not believe is appropriate. The existing definition included in Annex I of Directive 2001/83/EC, as amended, should be retained.
Many of the proposed tests would impose an additional development burden for an SME

COMMENTS ON TEXT

Precise Reference and page of consultation document	**Comment and Rationale**	**Proposed change**
Section 2.2.1 Page 5	The definition of "gene therapy product" in section 2.2.1 is a lot broader than the current definition in Annex I of Directive 2001/83/EC. Annex I defines a gene therapy product as one that is "aimed at the transfer" of a gene "(i.e. a piece of nucleic acid)" "to human/animal cells and its subsequent expression in vivo." The consultation paper definition is much broader in that it includes nucleic acid sequences administered with a view to "regulating" a targeted genetic sequence, and whose effect "relates directly to the nucleic acid sequence it contains, or to the product of genetic expression of this sequence." It is not clear whether the definitions in the consultation paper are intended to be included in Annex I, as part of the proposed	Delete definition of gene therapy medicinal product in 2.2.1, and retain current definition in Annex I, i.e.: *Gene therapy medicinal product* shall mean a product obtained through a set of manufacturing processes aimed at the transfer, to be performed either in vivo or ex vivo, of a prophylactic, diagnostic or therapeutic gene (i.e. a piece of nucleic acid), to human/animal cells and its subsequent expression in vivo. The gene transfer involves an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. The vector can also be included in a human or animal cell.

	revisions. However, if they were, the effect would be to include products such as anti-sense oligonucleotides, as well as some existing anti-virals and cancer chemotherapies in the scope of the Advanced Therapies Regulation, which we do not believe was the intent. Such pharmacologically active substances without any gene correcting effect should not be included in the definition of gene therapy medicinal products. The Advanced Therapies Regulation clearly states that "gene therapy medicinal product" is defined in Part IV of Annex I to Directive 2001/83/EC, and we are not aware that there have been any suggestions during the review and approval of the Regulation that this definition should be changed. We do not believe that broadening the definition after adoption of the Regulation is necessary or appropriate. We propose that the definition of gene therapy medicinal product in 2.2.1 should be deleted and replaced with the current definition from Annex I of Directive 2001/83/EC. In addition, it should be made clear if the gene therapy product should interact with the human chromosome sequences, and if e.g. products targeted to pathogens, e.g. bacteria/ parasite/virus derived sequences are excluded from the definition. The proposed definition does not differentiate between DNA and RNA medicinal products. For example, synthetic oligonucleotides are designed to block protein expression by binding to mRNA in the cytoplasm of the cell and preventing its translation into protein. Such drugs are, in reality, specific antagonists of mRNA translation. For the purposes of this paper, we suggest that the generic term, RNA antagonists, can be usefully applied to any antisense oligonucleotide which has been designed to block intracellular mRNA translation to describe and emphasize its mode of action. Such RNA	

	antagonists are typically short (20 or less nucleotides) single stranded, chemically-modified oligonucleotides. Although they can often gain access to the nucleus and may even bind the precursor mRNA in the nucleus, they do not bind to genomic DNA and have never been shown to alter DNA composition. They are not intended to be, nor are they, gene therapy agents. A number of studies have concluded that oligonucleotides designed as RNA antagonists, do not induce genetic aberrations, chromosomal damage, unscheduled DNA repair or any other mutagenic events in mammalian studies. This is consistent with their mode of action, which is to block a post-transcriptional event, the conversion of mRNA to protein, and not to effect genomic DNA or modulate its transcription. The proposed definition would raise regulatory hurdles for the RNA products under development by imposing costly testing which is not scientifically justified. Relevant definitions of other terms (or reference where these definitions are explicitly given) such as replication incompetent (needed in 2.3.2, 5d), microorganism (is virus not a microorganism?), viral vector (what is the difference between a virus and a viral vector, is viral vector a subcategory of viruses?), packaging cells (all production cells?) should be provided to avoid confusion.	
Section 2.2.2 Page 5	The phrase " pharmacological, immunological or metabolic action of its cells" may be too narrow/ need clarification. For example, would cells that release a neurotransmitter or other molecule/peptide be considered " pharmacological, immunological or metabolic action of its cells"? Would muscle tissue or neural cells that might act by contraction or electrical signaling respectively be included.	

Section 2.3.2 Point 1 Page 6		1. We s*uggest the wording of first sentence is changed to match the sentence that follows* "In <u>the</u> case where a gene therapy medicinal product ~~contains~~ <u>consists of</u> ready-prepared nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es)"
Section 2.3.2 Point 5 Page 6	5 (b) Please clarify whether data on these characteristics (e.g. tropism and cell cycle dependence) must be provided for all viruses and viral vectors or whether these characteristics must be addressed only for those viruses which are claimed to have specific or restricted cell tropism and cell cycle dependence. As the section stands now, data pertaining to these points must be provided for ALL microorganisms or viruses irrespective of the claim to be cell type or cell cycle restricted. 5 (c) The use of the term "drug substance" does not seem consistent with other language in the document 5 (e) Will the frequency of plasmid qualification be specified? 5 (f) Regarding phenotypic characteristics, it would be helpful to have this expressed relative to purity and potency measures. Does this apply to detection of proteins expressed by genetic modification, or just the basal cells?	
Section 2.3.3 Point 4 Page 8	*"4. For certain somatic cell therapy…., the active substance and the finished product can be closely related or nearly identical…."* This sentence is confusing. Somatic cells and transplants could be included in this definition.	
Section 2.3.3 Point 6	6 (a) (i) Do cells collected from an individual known to be positive for an infectious disease marker (e.g. HIV) fall into the non-healthy definition?	

Page 8		
Section 2.3.3 Point 6 Page 9	6 (c) (i) Please amend wording to make it clear if genetic stability of gene vector producer cell lines is intended. *". …purity (i.e. adventitious microbial agents….), viability, potency, karyology, tumorigenicity and suitability…. Genetic stability of the cells should be described."* - It would be helpful to have guidance on how the genetic stability of cells should be monitored and how these studies are differentiated from karyology ? Should karyology be performed on each production run or is it acceptable to use a limited number of samples? - Adventitious microbial agents: In view of the time required to obtain the results, what would be the recommendation when the patient has to be injected with fresh cells? - tumorigenicity: is an *in vitro* approach acceptable? These tests are very costly and would impose a severe restraint on an SME company. 6 (c) (ii) *"Qualitative and quantitative information on product- and process-related impurities…of introducing degradation products."* Impurities and degradation products: a clear definition of impurities should be indicated. Guidance on the type of testing would be helpful. 6 (c) (iii) It would be helpful to define if the finished product is the cryopreserved product, or a product prepared for infusion after thaw 6 (c) (iv) *"if biological active molecules are present as*	

Page 10	*components of the cell-based product…."* How are "components" defined? Does it include any factors or receptors expressed by the cells? A clear definition of "biological active molecules" should be provided. Does it mean "the molecule supporting the biological activities of the product" ? 6 (d) (i) Does "used for the first time" mean in the EU/EEA or could they have been used elsewhere? Does investigational versus approved use change the requirements? 6 (e) *"…and therapeutic function in the presence of the final formulation shall be discussed."* What is expected in this step? How could the "therapeutic function" be discussed at the manufacturing step? Clarification indicating the type of testing required would be useful. 6 (f) (i) It is not clear if a primary standard is required or if "product-specific" standards would be acceptable.	
Section 2.4.2 Point 3 Page 12	3 (a) It would be helpful to have the "finished gene therapy product" defined. Is the viral vector or the viral vector modified gene therapy cells the medicinal product? 3 (c) Will there be any guidance on the duration required for integrating vectors such as retroviral and lentiviral vectors 3 (d) Very clear. We agree.	
Section 2.4.3 Point 1 Page 12	1 (b) *"The amount of product needed to achieve…, the frequency of dosing should be determined."* The need for the determination of the frequency of the dosing should be modulated depending on the target organ or species and should be determined on an individual basis.	"The amount of product needed to achieve the desired effect/the effective dose, and where appropriate, the frequency of dosing should be determined <u>on a case by case basis.</u>"
Section 2.4.3	2 (a) *"Conventional studies…are not relevant. However, such parameters such as…migration should be investigated over*	

Point 2 Page 13	*time, as appropriate."* What does "over time" mean? How would this apply in the case of one single administration into patient? This sentence should provide more detail.	
Section 2.4.3 Point 3 Page 13	3 (b) *"The duration of observations may be longer than in standard toxicity studies depending on the lifespan of the medicinal product."* Need to be more specific. For example, in case of very long lifespan of the medicinal product due to very low remodelling of the target organ/tissue, how to proceed with toxicological studies? 3 (c) *Conventional carcinogenicity and genotoxicity studies….However, the tumourigenic potential of the product shall be studied unless otherwise justified."* The difference between carcinogenicity and tumourigenic potential in the context of cell therapy should be defined. 3 (d) *Potential immunogenic and immunotoxic effects should be studied."* Is it relevant for cell-based medicinal product? How to proceed: *ex-vivo, in vivo*? Need to be detailed. What kind of testing is expected? These tests impose a considerable cost burden for an SME.	
Section 2.5.1 Point 4 Page 14	*Dose selection and schedule of use should be defined by dose-finding studies, unless otherwise justified."* The notion of dose-finding need to be linked to Module 4.	
Section 2.5.3	The requirements specified in this section seem to be difficult to achieve without using extremely invasive methods. All these	

Points 1&2 Page 15	tests seem to be inappropriate to humans. Will it be acceptable to an Ethics Committee? How to address the question in case autologous cell-based medicinal product?	
Section 2.5.3 Point 1 Page 15	The wording "shall be addressed" is not specific. We assume that data establishing a pharmacokinetic profile in humans are required where feasible. However, for particular somatic cell therapy medicinal products, such a pharmacokinetic profile may not be feasible or reasonable. The question should then be addressed by discussing in vitro or pre-clinical data.	.. 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 molecule shall be addressed **with clinical and/or non-clinical data, as appropriate.**

Please feel free to add more rows if needed.