IMPLEMENTATION OF THE 'ADVANCED THERAPIES' REGULATION No 1394/2007

SUBMISSION OF COMMENTS ON Public Consultation Paper
"Proposals to amend Annex I to Directive 2001/83/EC as regards Advanced Therapy Medicinal Products, version 8 april 2008"

COMMENTS FROM: TIGENIX NV, contact person: Wilfried Dalemans, VP Regulatory Affairs and Corporate Quality

GENERAL COMMENTS
TiGenix welcomes the public consultation and the opportunity for commenting on this important proposal to incorporate more specific technical recommendations for advanced therapy medicinal products (ATMP) into Part IV of Annex I to Directive 2001/83/EC. The company is convinced that the input from developers and manufacturers of ATMPs will provide relevant and essential input, based on real life experience with these innovative medicinal products, that will benefit the finalisation of this annex, and thus be instrumental in providing a clear framework for future ATMP development. It is noted that there already exist several guidance documents providing specific technical requirements for innovative cell-based products. The company would therefore like to emphasize that it is important that this current amendment also takes into account all existing and draft guidance documents relevant to the subject, in order to ensure a harmonized, adequate and clear set of technical requirements. We noted that in the current text, requirements dealing with the same topics (e.g. starting materials or combination products) are addressed within several paragraphs. This makes the text sometimes difficult to interpret. We think that the final technical annex would benefit from a structure aligned with the structure and sections of CTD Module 3. With respect to combination products, it needs to be acknowledged that this term can cover several possible compositions. Whereas Regulation 1394/2007/EC provides a clear definition of combination products where cells are combined to medical devices, combinations of the cell-based substance with other, additional substances do also exist and this is referenced as such in the present document. For sake of clarity, we would recommend that there is a clear distinction between the major types of potential combinations of the cells with other substances (being devices or other). These different types of combinations should be addressed individually as different requirements would apply. Indeed, depending on the specific role the additional substance(s) plays in the combination with the cells, e.g. carrier (non-interactive, pure physical combination), active physical or biological combination, or fully integrated active functional combination (i.e. the combination yields a new active principle), the relevant requirements for testing and characterization would differ (for more specific information, reference is made to the comments section below). The possibility to apply a multifactorial risk-based approach to determine the extent of characterisation in terms of Quality, Nonclinical and Clinical data, taking into account the specific nature of advanced therapy medicinal products, is welcomed. Also, the upfront inclusion of this rationale in the CTD introduction section is supported. It is to be noted however, that given the highly diverse nature of ATMPs, the extent of this analysis and the methodology to be used will likely be different for each specific product. Therefore, it should be up to the applicant to justify and determine the need for, as well as the most appropriate way to document the risk assessment in function of the specificities of the product concerned.

SPECIFIC COMMENTS ON THE TEXT		
GUIDELINE SECTION TITLE		
Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
2.1 Introduction	Although it is acknowledged that the provided list with potential risk factors is not exhaustive, it is proposed to add some additional factors that are expected to have a potential important impact on the risk analysis as well. In addition some adjustments are suggested to make the wording more aligned to the guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006).	"The risk analysis may cover the entire development. Risk factors include but are not limited to: the origin of the cells (autologous-allogeneic-xenogeneic), the ability to proliferate~~, to~~ and/or differentiate, the ability ~~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 or culture or life span of cell, the mode of action, availability of clinical data on or experience with similar products, specific restrictions to the supply of the product, 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."
2.2 Definitions	Although the specifics of combined advanced medicinal products are covered in the respective technical sections, the definition of combination products is not included. It would be welcomed if the definition as written 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.	
2.3.2, bullet 1	It is not entirely clear what is exactly meant with "ready-prepared" nucleic acid sequences(s). In addition, it is suggested to change the wording on the possibility for combination products from "in special cases" to "in certain cases".	"The finished medicinal product consists of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es) formulated in their final immediate container for the intended medical use. In ~~special~~ certain cases, the finished medicinal product may be combined with a medical device."

[1] Where available

2.3.3, bullet 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 is too broad and can represent practical problems with respect to the quality requirements for active substances. 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, and hence the active substance. The term "Integral part" in the context of defining the active substance can be interpreted in several ways. Whereas for instance a device would merely act as carrier of the active substance, it should be considered as an excipient rather than a starting material. In cases where a device would alter the properties of the cellular component, both could be considered as starting material given rise to a new entity as drug substance. In cases where a biomolecule would enhance the biological function of the cellular component, the definitions could again differ. A thoughtful reflection on this potential problematic would be welcomed. Moreover, certain of the additional substances mentioned are in fact medical devices and may not have been produced according to GMP standards, though they have been certified by a Notified Body. Classifying them as starting material might raise some problems with respect to the required documentation.	
2.3.3, bullet 4	It is indeed correct that 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. The proposal to allow completion of only the relevant sections and items in those cases, if justified, is therefore welcomed. For clarity reasons, it might even be beneficial to further specify that as a general acceptable approach the drug substance section should contain the core information. Reference to these informations could then be made in the corresponding sections of the drug product. The text proposed here aside summarizes this approach.	"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. As a general acceptable approach i~~I~~n those cases and if justified, only relevant sections and items need to be completed for the drug product section and reference can be made to the relevant information in the corresponding drug substance sections~~, if justified~~."

2.3.3, bullet 6(a)(iii)	Potential variability of the starting material can impact on drug substance, drug product or both. This possibility is clarified in the proposed text.	"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. Depending on the specific impact, either on the active substance (drug substance), the finished product or both, the information should be provided in the appropriate sections."
2.3.3, bullet 6(b)(i)	It is not clear from this paragraph as to why the description of the manufacturing process starting from the receipt of the source material till filling of the finished product would be different for ATMPs as compared to the requirements for classical medicinal products. Therefore, this paragraph can be considered not providing an ATMP specific requirement, and can thus be omitted.	"~~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.~~"
2.3.3, bullet 6(b)(iii)	For autologous applications it can be difficult to ensure typical batch to batch consistency while it would be more appropriate to focus on process consistency instead. For other applications, both batch as well as process consistency can be important. Therefore the following addition is proposed.	"The manufacturing process should be validated to ensure batch and/or process consistency, functional integrity of the cells at …"
2.3.3, bullet 6(c)(i)	The provision to provide relevant information on the characterisation of the cell population or cell mixture should be limited to the characteristics wherefore an impact on the safety or efficacy of the product could be suspected. In addition, karyology and genetic stability are more applicable to cell lines and/or genetically modified products than for products containing cell populations or autologous cell products which can have unique signatures. The genetic stability of the latter is addressed through the assessment of durability of the functional characteristics and by the assessment of tumorigenicity. Consequently, a more discriminative and detailed description of these requirements should be considered. A proposed text is provided.	"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 for those factors having a potential impact on the safety or efficacy of the product. Genetic stability of the cells shall be described for genetically modified products.

2.3.3, bullet 6(c)(v)	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), e.g. carrier (non-interactive, purely physical combination), active physical combination, fully integrated active functional combination (e.g. combined active principle) etc. We propose a case by case approach for the required characterisation, based on the specific nature of the 3-dimensional structure.	
2.3.3, bullet 6(d)(i)	Textual clarification.	"Conventional excipients shall also be characterised with respect to their ~~combination~~ compatibility with cells."
2.3.3, bullet 6(e)	Textual clarification.	"Particularly, the integrity of the cell population regarding its biological characteristics, differentiation state and therapeutic function ~~in the presence of~~ as in the final formulation shall be discussed."
2.3.3, bullet 6(f)(i)	The establishment of reference standards should certainly be encouraged for products manufactured as large batches of identical products. However, it should also be acknowledged that the establishment of a reference standard, relevant and specific for the active substance and/or the finished product can be very difficult in cases where 1 batch actually represents 1 product to treat 1 individual patient. Therefore, a more specific wording of this paragraph is proposed.	"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 number of or single product vials)."
2.4.1, bullet 2	It is noted that the statement in this paragraph implies that the risk analysis becomes a mandatory requirement for all advanced therapy medicinal products. It is concluded that this might not fully be in line with the wording in the introduction section 2.1 emphasises that a risk-based approach can be an appropriate and acceptable methodology to approach these products but not necessarily implies that it is the only acceptable approach.	"The rationale for the non-clinical development ~~should~~ can be based on the above mentioned risk analysis …"

2.4.2, bullet 3(g)	The use of homologous models mimicking the clinical approach to address immunogenicity and immunotoxicity is a sound proposal, but it should be born in mind that such models represent also important limitations with respect to their relevance for the human situation. Indeed, profound or subtle differences in animal physiology and in particular in the immune mechanisms might exist (e.g. epitope specificity, MHC restriction, CD species-specific populations, etc) which might lead to wrong or irrelevant conclusions. The difficulty to develop highly predictive models should therefore be recognised, and the requirements should reflect this.	
2.4.3, bullet 1(a)	It is not understood why the desired interaction of the applied cells with non-cellular structural components of the product should be studied as part of the non-clinical pharmacological assessments, as this type of investigations are usually covered in Module 3.	"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."
2.4.3, bullet 1(b)	Although it is recognized that it is important to determine "the amount of product needed to achieve the desired effect/the effective dose, and where appropriate, the frequency of dosing", it should be recognized that classical 'dose-response' studies are often not feasible for certain types of ATMP product, in particular tissue-engineered products. Moreover, non-clinical dose range studies have only limited predictability for the human situation, and they should therefore only be considered to demonstrate to which extent dosing could affect the biological activity. Therefore, it would be better to change the wording to 'should be justified' instead of 'determined'.	"The amount of product needed to achieve the desired effect/the effective dose, and where appropriate, the frequency of dosing should be ~~determined~~ justified."
2.4.3, bullet 3(a)	Although it is acknowledged that it is essential that the toxicity of the finished product shall be assessed, it is not clear what type of toxicity study would be appropriate for advanced therapy medicinal products. The following additional clarification is proposed.	"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 conventional toxicology assays might not apply and more relevant non-clinical safety assessments should be considered."

2.4.3, bullet 3(b)	It is not clear what design would be applicable for such longer duration toxicity studies. Therefore, the following wording is proposed.	"The duration of observations may be longer than in standard toxicity studies~~, depending on~~ and the lifespan together with the biology and function of the medicinal product should be considered."
2.4.3, bullet 3(d)	The need to study potential immunogenic and immunotoxic effects is in part depending on the type of product, i.e. autologous products do not face the same issues as allogeneic or xenogeneic products. Therefore, the following wording is proposed.	"Potential immunogenic and immunotoxic effects should be studied where appropriate, unless justified."
2.5.1, bullet 3	It is not understood why the development of advanced therapy medicinal products would in particular differ with respect to manufacturing changes during clinical development versus other medicinal products. As this is a common requirement, it is proposed to remove this statement. On the other hand, it is important to discuss the potential impact of changes to the product on the clinical results of the different clinical stages.	"As for other medicinal products, ~~Due to the nature of advanced therapy medicinal products, their~~ the manufacturing process might change during clinical development. ~~Additional studies to demonstrate comparability might be needed.~~ The potential impact on the clinical results should be discussed."
2.5.2, bullet 3	It is not clear what the design of a safety study could be to address the safety of the product with respect to insertional mutagenicity for non-gene modified ATMPs. The nature of the ATMP should thus be considered, e.g. the presence of extraneous genetic sequences or the nature of similarity between gene sequences are important factors to consider when the defining the need for and extent of such studies.	
2.5.4, bullet 1	It is important that the determination of the need for certain clinical pharmacokinetic studies takes into account the observations from non-clinical investigations as well. The following addition is proposed to emphasis this point.	"Conventional pharmacokinetic studies might not be relevant for tissue engineered products. However, the biodistribution, persistence and degradation of the tissue engineered product components should be addressed during the clinical development, taking into account the observations from non-clinical investigations."