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Comments of

Bundesverband der Pharmazeutischen Industrie e. V. (BPI)

regarding

Public Consultation Paper

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

IMPLEMENTATION OF THE 'ADVANCED THERAPIES' REGULATION

Date: 09 June 2008

Bundesverband der Pharmazeutischen Industrie e.V.

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General comments

BPI would like to thank for the opportunity to comment on the above mentioned consultation. BPI is representing the majority of Germany's industry in the field of tissue engineering, most of these companies being SME. Therefore the comments of BPI represent the voice of SME that are especially invited to comment on this proposal by the Commission.

BPI supports the risk-based approach taken in the draft: "Due to the specific nature of advanced therapy medicinal products, a risk-based approach can be applied to determine the extent of characterisation in terms of Quality, Non-clinical and Clinical data to be included in the marketing authorisation application. …..The risk analysis may cover the entire development. …….Relevant available clinical data or experience with other, related advanced therapy medicinal products may also be considered."

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 to be developed from the beginning not adequately reflecting products that are administered to patients for several years and are legally on the market in the member states before the coming into force of the ATMP Regulation. It is without any doubt not possible to ask for the same requirements independently from the question whether there is already experience gained with a product or whether a product is newly developed and is administered to patients for the first time.

BPI strongly proposes to use the above mentioned risk-based approach for tissue engineering products already legally on the market in the member states for several years and to mention this explicitly in Annex I. The companies represented by BPI are producing in their vast majority tissue engineering products for autologous use that are up to now marketed on the basis of national requirements in Germany for often more than five years. The proposal does not reflect that even in other member states within the EU like Austria, UK, Italy and the non-EU member Switzerland tissue engineering products are marketed for several years. Therefore it is important for these products and the companies producing these kinds of ATMPs to specifically mention this situation and add an extra chapter within Annex I. For ATMPs already legally on the market in the member states and where experience is 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, 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 may also be considered.

Apart from that tissue engineering products and somatic cell therapy products are formally separated from each other by a different definition. Regarding the requirements laid down in the new part IV of Annex I this distinction is practically of no relevance any more. In most cases the requirements for tissue engineering products and somatic cell therapy products are identical. This is not adequate and BPI will focus on this topic within the specific comments. In addition differences between autologous and allogenic products should be more taken into account.

BPI would ask to precisely define the different terms “active substance“, „drug substance“, „starting material“ and „raw material“ and to use them consistently.

As ATMP fall under the umbrella of pharmaceutical legislation the CTD-Format will be applicable for marketing authorisation applications of these products. As this format is not explicitly developed for ATMP but for medicinal products of chemical origin BPI asks to adequately adapt this format to ATMP. Even some of the headlines of the different chapters of the CTD will not adequately reflect the information that has to be included in the relevant part of the dossier for a marketing authorisation application for ATMP (e. g. for tissue engineering products). It would therefore be useful to set up a guideline giving advice which information regarding an ATMP has to be included into which chapter of the CTD. As the CTD format is not self-explaining for ATMPs (for example not for tissue engineering products) this would be helpful for applicants.

For the sake of clarity for the user of the new part IV of Annex I we would ask to include a table stating the correlation of the different criteria regarding the different kinds of products, the starting material, the raw material as they are described in the text:

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*				
	ex vivo				
Microorganisms	*in vivo*				
	ex vivo				

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Specific comments

Page no. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
Page 4; Section 2.1		
4th para	Concerning products already legally in the market in the member states experiences regarding the efficacy and safety have to be taken into regard adequately, therefore it is necessary to mention these products in the introduction	**The following sentences should be added:** **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 7; Section 2.3.2		
Point 5 (a) (iii)	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	Instead of the words “bank system” the words “master cell bank” should be used.

Page 7-10; Section 2.3.3		
	There should be a clearer separation of somatic cell therapy and TEPs within this chapter; these products fall into different categories	
Point 2	This point is not consistent with Point 3 (d) (ii), saying that scaffolds, matrices, devices, biomaterials, biomolecules and/or other components are regarded as excipients. In general the active substance is composed of cells or tissues. Additional substances should generally regarded as excipients. They may be regarded as active substance, too, when they show biological activity. Apart from that it is asked for clarification of the term "integral part" with respect to additional substances needed.	The sentence should read as follows: "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 **when they show biological activity** and are **then** therefore considered as starting materials, even if not of biological origin.
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 legislation.	
Point 6 (a) (i)	Term "non-healthy" cells or tissues should be rephrased or clearly defined	Proposal for a definition: "Cells from patients or cells affected by the disease of the donor."
Point 6 (a) (ii)	In some limited cases complete traceability may not be possible; it would therefore be useful to have	Proposal to add the following sentence: **„In case of incomplete traceability**

	an additional sentence to cope with this situation.	**suitable additional testing should eliminate identified risks“**
Point 6 (b) (iii)	In the second sentence it is asked for information on validation of the cell culture process with respect to cell-growth, function and integrity. This question can not be answered in any case as it belongs often to biomolecular basic research. The answers to the question what kind of matrix would be most useful can only be answered by comparison of different possibilities against each other, the answers are in most cases outstanding.	The last sentence should be amended: “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) (i) first sentence	Not all the different point in this chapter are relevant for each type of cells. E. g. most of the existing tissue engineering products in the market use already differentiated cells in an autologous way having a different risk than for example stem cells. In the case of autologous products the requirement for karyology and tumorigenicity is an additional burden and with questionable effect with respect to product safety.	The first sentence should read as follows: **“In accordance with the initial product specific risk analysis** relevant information on the characterisation….”
Point 6 (c) (i) last sentence	There are manifold differences between the different cell-based or gentherapeutic groups of products (e.g. cell lines or primary cells), therefore this amendment is necessary.	The last sentence should be amended: „**Depending on the characteristic of the product** 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. Concerning this point it has to be kept in mind that for medical products being part of an ATMP these kind 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.	The para should 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" is 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.	The first sentence should be amended: The description of the development program shall **adequately** address the choice of materials and processes **taking into regard that for already legally marketed ATMPs before the coming into force of the Regulation on ATMP this information often cannot be generated retrospectively**.
Point 6 (f) (i)	There are not in each and any case reference standards available. For an ATMP manufactured for an individual patient a reference standard is not possible to provide. What type of reference standard can be imagined for a TEP, e.g. human epidermis? This requirement might be helpful for chemical entities but in the case of autologous TEPs it not possible to provide.	The sentence should be amended: **"If available and up to the specificity of the product in question** a reference standard, relevant...."
Page 11; Section 2.4.1		
Point 4 to be added	As all already marketed products are be administered to patients for often several years 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.	**4. 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. 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 testing can be justified.**

Page 11-12; Section 2.4.2		
Point 1 (a)	Relevant animal species are not always available.	The first sentence should be amended: „In vitro and in vivo pharmacodynamic „proof of concept“ studies should provided using appropriate models and relevant animal species, **if available,** designed**…..”**
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.	
Page 12-13; Section 2.4.3		
Para 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.	There should be a 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)	In a lot of cases an effective dose that is applicable for each patient cannot be given. ATMPs (e.g. autologous tissue engineering products) are often made for an individual patient and the necessary cell count that is needed is differing. The variation between those individual dosages is differing in a way that an effective dose cannot be fixed. For most products already legally in the market a minimum amount of cells is defined giving flexibility to adapt the product to the individual patient it is made for. A clear dose response curve is not to be expected in the case of 3D organized tissues, please specify that. Further the TEP might induce	The sentence should read as follows: The **minimum** amount of product needed to achieve the desired effect/**where appropriate,** the effective dose, and where appropriate, the frequency of dosing should be determined.

	endogenous regeneration e.g. “edge effect” in chronic wounds, where no clear dose response can be delineated.	
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 clinical use?	The first sentence should 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.
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 whether there are relevant data supporting these points.	The second sentence should 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?	
Page 14; Section 2.5.1		
Point 9 should be added	This chapter does not adequately take into regard that there are already ATMP legally on the market in the member states. For these products often non-interventional studies have been conducted. The experience gained with these products in day-to-day use has to be taken into regard.	There should be a 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.**
Page 15; Section 2.5.4		
Point 1	Are these data necessary for autologous products and products that are already legally marketed at the getting into force of the ATMP regulation? Please justify.	
Point 2	Since it is in most cases ethically not acceptable to take biopsies of regenerated, repaired or replaced tissue, non-invasive investigation methods should be used for proof of principle and kinetics of products. There are already scoring system available e.g. for X-Ray and MRI and for patients these methods seems more acceptable from a risk:benefit perspective. Apart from that the requirements are too general. What type of pharmacodynamic marker may be thought of in the case of an	This chapter should 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

	autologous epidermis? Specify and please justify these requirements.	to the intended function(s) and structure should be considered.
Point 3	The question if this 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 too theoretical. Again, ectopic engraftment of a locally applied 3D tissue, how can that happen? Or oncogenic transformation etc.	The first sentence should 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: