European Medicines Agency

SUBMISSION OF COMMENTS ON THE

GUIDELINE FOR HUMAN CELL-BASED MEDICINAL PRODUCTS

EMEA/CHMP/410869/2006

COMMENTS FROM: The Biotechnology Industry Organization/Sara Radcliffe, Vice President, Science and Regulatory Affairs
GENERAL COMMENTS
The Biotechnology Industry Organization (BIO) submits these comments on the European Medicines Agency's (EMEA's) draft guideline *The Guideline on Human Cell-Based Medicinal Products.* BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and 31 other nations. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. Our members invest heavily in the research and development of biotechnology and pharmaceutical products in the European Union (EU) and elsewhere, and employ thousands of highly skilled persons in the EU. We appreciate the opportunity to submit comments on the draft guideline.
In general the draft guidance document is comprehensive, thoughtful, and well organized, providing the developers of Cell-Based Medicinal Products (CBMP) with a useful set of regulatory expectations. The document is grounded in a good understanding of the challenges to be faced in developing a CBMP bioprocessing paradigm. Particularly useful was the initial discussion on analyzing risk in the design of CBMP. The document also reveals a good understanding of quality and manufacturing aspects of CBMPs. For example, the document permits the use of animal derived materials and directs the reader to outside guidances for further information, as well as encouraging the use of irradiated sera or alternative synthetic media. The requirements encourage an early development of full characterization of the product and development of assays, and recommend release specifications for identity, purity, impurities, sterility, potency, cell viability and total cell number, but also acknowledge that there may be good reasons why certain release tests cannot be performed. A number of good examples are cited where flexibility will be considered. Finally, there is a good section encouraging the use of published ICH documents on Comparability that instructs the reader on how to proceed when changes in the manufacturing process are contemplated.
A clearer correlation to the components of the CTD (Quality, Safety and Efficacy) would be helpful.
General comments on transport of cells: 1) The guidance mentions screening starting materials, however it is important to specifically capture interaction and compatibility with the transport material more thoroughly (e.g. the intended transport vial including lids in the intended and additional storage conditions). 2) With regard to transport there does not seem to be any coverage for possible interventions. For example, maintenance of cell integrity, potency and viability if the cells did not reach the intended patient in time due to transport problems, incremental weather, large fluctuations in temp, etc. We request more discussion of setting criteria for ensuring the cells are still usable for a patient if such incidents happen (e.g. identify worst case scenario).

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 95
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

General comments on delivery of cells: 1) Delivery of cells to patient could be by IV or insertion. The actual delivery method should be evaluated in the event that the cells become inadvertently damaged during instillation. For example, shear stress forces on modified cultured cells may render them more fragile and prone for rupture. Investigators should have prior knowledge of how the cells function following injection through the intended needle bore. 2) Also with the individual delivery procedure in mind, what is the potential for mis-injection or misplacement of cells outside intended locale?
The guideline should require discussion of hypothesised mechanism of action for the cells in question.

SPECIFIC COMMENTS ON TEXT

EXECUTIVE SUMMARY

Line no. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
Line 4 Paragraph No: 1	Because guidance refers primarily to requirements for registration, point out correlation to CTD components	This guideline is replacing the existing CPMP Points to Consider on somatic cell therapy products. It takes into account the current legislation (including the Directive 2004/23/EC on Tissues and Cells and the technical directives drawn from it) and the heterogeneity of human cell-based products, including combination products. This multidisciplinary guideline will address quality, safety and efficacy aspects of cell-based medicinal products, including manufacturing, quality control and non-clinical and clinical development. A risk analysis approach can be used to justify the development and evaluation plans and can be a basis for the preparation of a risk management plan.
Paragraph No. 2	Clarification of meaning requested.	In the quality section, guidance is provided on the selection criteria and testing of all starting materials, on the design and validation of the manufacturing process, on characterisation of human cell-based medicinal products, and on quality control aspects including traceability, biovigilance and comparability. Guidance specific to the matrix/device/scaffold component in combination products is provided. In the safety and efficacy sections, guidance is provided on the components of the nonclinical and clinical development plan.

1. INTRODUCTION (background)		
Line 5 Paragraph No: 2	Types of cells can be classified into 4 broad categories	Cells may be: ▪ autologous or allogeneic ▪ stem, progenitor or terminally differentiated ▪ unmodified or genetically modified ▪ administered alone or in association with biomolecules or chemical substances and/or combined with structural materials that alone might be classified as medical devices (combination products).
2. SCOPE		
Line 1 Paragraph No: 1	Correlate to CTD	We suggest the alternate wording, "This multidisciplinary guideline will address quality, safety and efficacy aspects of cell-based medicinal products, including manufacturing, quality control and non-clinical and clinical development. This guideline is intended …"
4.1 RISK ANALYSIS		
Line 6 Paragraph No: 1	Emphasize case by case nature of risk analysis	We suggest the alternate wording, "This heterogeneity means that the development plans and evaluation requirements need to be adjusted on a case by case basis according to a multifactorial risk analysis."
Line 6 Paragraph No: 2	Clarification of the evolving nature of the risk analysis	We suggest the alternate wording, "In particular, the results of the initial risk analysis should be used: • to identify risk factors associated with the quality and safety of the product • to determine the extent and focus of data required during non-clinical and clinical development; • to establish the need for risk minimisation activities, • to determine the post market risk management activities to be specified in the pharmacovigilance plan. As data are collected during development, the applicant should update the risk analysis and make appropriate adjustments to the non-clinical and clinical development plans. The updated risk analysis can be used as a basis for the preparation of a risk management plan in accordance with the

		EMEA guideline on risk management systems for medicinal products for human use (EMEA/CHMP/96268/2005)."
Line 7 Paragraph No: 2	Emphasize initial risk analysis vs. updated risk analysis; reorder to flow better	We suggest the alternate wording, "An initial risk analysis may be performed based on existing knowledge of the type of product and its intended use. The following general risk criteria can be used in the estimation of the overall risk of the product: • origin (autologous-allogeneic, single donor or pooled donors); • ability to proliferate and differentiate; • ability to initiate an immune response (as target or effector); • level of cell manipulation (in vitro/ex vivo expansion/activation/genetic manipulation); • mode of administration (ex vivo perfusion, local, systemic); • duration of exposure (short to permanent); • combination product (cells + bioactive molecules or structural materials) • availability of clinical data on or experience with similar products."
4.2 QUALITY AND MANUFACTURING ASPECTS		
Line 2 Paragraph No: 1	Replacement of the expression tissue *establishment*	We suggest the alternate wording, "…describes activities by manufacturers after procurement of cells."
Line 4-8 Paragraph No. 2	Meaning is unclear.	We suggest the alternate wording, "For certain cell-based medicinal products, the starting material, the active substance and the finished product can be closely related or nearly identical. For such products, some requirements listed below could be inappropriate and in that case only relevant sections and items should be addressed."
4.2.1 STARTING AND RAW MATERIALS		
Subsection "1. Cells"	The Draft Guideline states that "Identity should be verified by relevant genotypic and phenotypic markers and the proportion of cells bearing these identity markers evaluated as an indicator of a homogeneous population." For some cells the identity assay may be based on measurement of a marker (RNA or protein) in a population of cells using a technique such as PCR or immunoblotting. It may not be	

	possible to determine the percentage of cells expressing a given identity marker using these approaches. In such a situation, one alternative would be to characterize the sensitivity of the assay to non-homogeneous populations during assay development, and to set acceptance criteria accordingly. Throughout the guideline several references to 'release' criteria are mentioned. However, it is important to capture the characterization of the cells at regular intervals prior to release (ie beginning & middle of culture in addition to release) in order to track changes resulting in unanticipated modification in the culture process. Extensive characterisation of normal cellular culture with multiple cell 'lots' allows better QC and will allow easier and more visible tracking of variation due to necessary serum lot substitutions for example.	
Paragraph No: 3	Clarification requested.	We suggest the alternate wording, "An adequately controlled cell storage system should be established to allow maintenance and retrieval of cells without any alteration of their intended final characteristics. Storage conditions should be optimized to ensure cell viability, density, purity, sterility and function."
Section 1.1 Lines 2-8 Paragraph No: 2	Reference to risk analysis requested.	We suggest the alternate wording, "If it is necessary to pool cells from different donors, the risk analysis should address the possibility that pooling of allogeneic cell populations may increase the potential for undesired immunological responses in the recipient and compromise the therapeutic activity of the product. In addition, pooling of cells from different donors may increase the risk of disease transmission. Depending on the nature of the source of the cells and tissues, other risk factors, e.g. previous radiation exposure, should be also considered and addressed."
Section 2.1 Paragraphs 1 & 2	Reduce redundancy; clarify quality elements to be documented	We suggest the alternate wording, "**2. Other materials and reagents** Various materials are needed for collection, selection, culture or even genetic or phenotypic modification of cells, such as other cells, enzymes, antibodies, cytokines, sera and antibiotics. Exposure to such materials can also compromise the quality, safety and efficacy of the final product. As a consequence, each substance used in the procedure, including cells that function as supports for growth and/or adhesion of effector cells, should be clearly specified and evaluated as to its suitability for the intended use.

		Documentation should be maintained for each substance used to demonstrate: ▪ identity (including origin) ▪ sterility ▪ purity ▪ activity ▪ low endotoxin level ▪ absence of adventitious agents It is further recommended that reagents with sensitization potential be avoided.”
Section 2.1 Line 4 Paragraph No: 1	Typo	We suggest the alternate spelling encephalopathies.
Section 4.2.1.3 Special Considerations	1) In addition to the level of expression, the length of expression should also be documented (this is also 'potency')	
4.2.2 MANUFACTURING PROCESS		
Paragraphs No: 1& 4	Combine to flow better.	We suggest the alternate wording, “*4.2.2 Manufacturing process* The manufacturing process of cell-based medicinal products should be carefully designed and validated to ensure product consistency. The consistency specifications should be defined and justified. A detailed description of the manufacture of the active substance and of the finished product should be provided. The type of manipulation(s) required for cell processing and the physiological function of the cells shall be described. A flow diagram of the entire process starting from biological fluid/tissue/organ or from cell banks should be prepared indicating critical steps and intermediate products (e.g. intermediate cell batches), as well as operating parameters, in-process controls and acceptance criteria. Manufacture of combined medicinal products consisting of cells and matrices/devices/scaffolds, require additional consideration regarding the cell-matrix/scaffold interactions and consequent quality issues. Attention should be paid to biodegradable materials that may possess the potential to alter the cellular environment

		(e.g. raising pH) during the manufacture or after administration."
Paragraph No: 2, 3, 5	Add heading "Premises/Equipment" to clarify subject Combine to flow better	We suggest the alternate wording, "Premises/Equipment: Premises and equipment used for manufacturing of CBMP should be suitable and validated for aseptic production. The manufacturing area should be physically separated from the area where biological fluids, tissues or organs used for starting materials are collected/procured/stored. If diverse tissues and cellular products are collected, processed and stored in the same manufacturing area there is an increased risk of cross contamination during each step of the procedure, e.g. via processing equipment or in storage containers such a liquid nitrogen tanks, and therefore, adequate control measures should be described and validated to prevent cross-contamination between products of diverse origins. It is recommended that dedicated, product-specific or single-use equipment are used in the production, whenever possible. If the same equipment is used for production of e.g. multiple autologous products, sanitation and sterilisation procedures should be described and validated. Information on procedures used to transport material during the manufacturing process of the product, including transportation and storage conditions and holding times, should be provided."
Section 1. Cell preparation procedures Line 5 Paragraph No. 2	For clarity, microbial culture conditions, not cell culture conditions, must be used	We suggest the alternate wording, "The culture should be examined for microbial contamination using established microbial culture conditions and/or genetic analysis."
Section 1.1 Line 1 Paragraph No: 1		We suggest the alternate wording, "The procedure to obtain the cells from the organ/tissue has to be described (type of enzyme, media, etc.) and validated <u>where feasible</u>."
Section 1.1 Line 2 Paragraph No: 1	Medical procedure, so validation not possible.	We suggest replacing "validated" with "well controlled".

Section 1.2 Line3 Paragraph No: 1		We suggest replacing "validated" with "well controlled".
Section 1.5.3 Paragraph No: 1		Batch definition: to provide language on date of manufacture
4.2.3 CHARACTERISATION		
Section 4.2.3	Viability should be included.	
Line 9-10 Paragraph No: 3	Regarding "…v) cell-like or tissue-like organisation and dynamic interactions amongst cells and with the structural component," - does this refer to in-vitro studies? A specification appears to be missing.	
Section 1.3 Line 4 Paragraph No: 1		We suggest the alternate wording, "Consequently a distinct way to define identity should be established for the combination, <u>if possible</u>."
Section 4.2.3. 2. Cell Purity Headings	Change heading to "Purity" with two subheadings	We suggest the alternate wording, "**2. Purity** 2.1 Cellular Component 2.2 Non-cellular Component"
Section 4.2.3. 2. Cell Purity		We suggest the alternate wording, "The cellular population of interest could contain other cells that are of different lineages and / or differentiation stage or that may be unrelated to the intended population."
Section 4.2.3, 3.2 Adventitious Agents Heading, Line 1 & 2 Paragraph No. 1	Separate from Impurities and retitle "Sterility"	We suggest the alternate wording, "**3. Sterility** A critical aspect is to establish that CBMP are free from adventitious microbial agents (viruses, mycoplasma, bacteria, fungi). Contamination may originate from the starting or raw materials (see above), or be introduced during the manufacturing process."
Section 4.2.3.4	In vivo potency as a requirement will <u>only</u> be feasible in a select	

Potency	group of cells and thus for the majority of CBMP will not be required. In the case of autologous cells the human microenvironment will behave much differently than the animal.	
Section 4.2.3.4 Potency Line 2 Paragraph No. 3	Move up to flow better	… is strongly recommended that the development of a suitable potency assay be started as soon as possible. Preferably, a suitable potency assay should already be in place when material for the first clinical trial is produced and it should be validated prior to pivotal clinical trials unless otherwise justified.
Section 4.2.3.5 Tumorigenicity Paragraph No. 1	Clarification, reference risk analysis	The tumourigenicity of CBMP differs from the classical pharmaceutics as the transformation can also happen in the cellular component of the product (eg insertional mutagenesis) and not only in the treated individual. The risk of cellular transformation and subsequent potential for tumourigenicity should be evaluated in the risk analysis on a case by case basis that reflects both the cell type(s) used in the product as well as the degree of post-collection manipulation. Analyses may include an assessment of proliferative capacity, dependence on exogenous stimuli, response to apoptosis stimuli and genomic modification.
Section 4.2.5 2. Non-cellular components Line 2 Paragraph No. 2	"affect" should read "effect"	