European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 18 April 2008
Doc. Ref. EMEA/CHMP/CPWP/182901/2008

OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON CELL-BASED MEDICINAL PRODUCTS

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	Eucomed	Belgium
2	BioIndustry Association (BIA)	UK
3	Biotechnology Industry Organization (BIO)	USA
4	German Pharmaceutical Industry Association (BPI)	Germany
5	Cellartis	Sweden
6	Cyathus Exquirere Pharmforschung (J Rogan)	Germany
7	DC-THERA / CIMT	UK
8	Danish Medicines Agency (DKMA)	Denmark
9	Stem cell transplantation and cellular therapy unit, Regina Margherita children's hospital, Turin, Italy (Dr Franca Fagioli)	Italy
10	University of Turin, faculty of medicine, Italy (Dr Lina Matera)	Italy
11	University of Rome Tor Vergata, Italy (Dr Giuseppe Novelli)	Italy
12	European Biopharmaceutical Enterprises (EBE)	Belgium
13	EuropaBio	Belgium
14	Genzyme	Belgium
15	Dr. Barbara Kubešová, Tissue Bank Brno, Czech Republic	Czech Republic
16	RISET consortium (Anne Cambon-Thomsen)	France
17	Pharmaceutical Research and Manufacturers of America (PhRMA)	USA
18	Tigenix	Belgium
19	Zimmer Ltd and Zimmer Orthobiologics Inc	UK and USA

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Table 2:Discussion of comments

GENERAL COMMENTS – OVERVIEW
1. It would be helpful to include line numbers in draft documents to facilitate the submission of specific comments on specific items (Eucomed).
2. This document will need to be revised to take into account the final version of the ATMP Regulation. Furthermore, this document should be prepared and finalized by the new Committee for Advanced Therapies (CAT) to ensure that the most appropriate guidance for these specialized products is available consistent with ATMP art 23 d (Eucomed).
3. The final version of this guideline is likely to be used by Competent Authorities to assess "pharmaceuticals" components that may be permitted in a revision of the medical devices legislation. It could be appropriate at this stage to include suitable amendments to reflect such use, however, it may be preferable to exclude non-viable human derived materials from the scope of this guideline and allow the development of more appropriate documents CEN/ISO (Eucomed).
4. Assuming that medical devices will be permitted to contain non-viable human tissues, a more appropriate mechanism for guidance generation would be the reference of the topic to the Medical Devices Expert Group, chaired by the Commission. (Eucomed)
5. Scaffolds and matrices are referred to in the document. These may be encompassed in their own right by the Medical Devices legislation. It would be appropriate to acknowledge the role of the Medical Devices Directives and, in particular the essential requirements therein. (Eucomed)
6. The primary legislation covering these products (ATMP) covers both cells and tissues. Clarification is required on the applicability of this guidance document on human tissues based products. If this guidance does not apply to human tissue derived products, then a separate guideline will be required to cover these products and should be developed by the appropriate expert group. (Eucomed)
7. Whilst it is appreciated that the products falling under the scope of this guidelines are medicinal products,, some text should be added to the scope to recognize that the conventional pharmaceutical approach is not always appropriate. Alternative approaches should be permitted when justified. (Eucomed)
8. The numbering and structure of the document is more than somewhat confusing. (Eucomed)
9. The BIA welcomes the guideline on human cell-based medicinal products. In general the draft guidance is comprehensive and useful to companies involved in the development of cell-based medicinal products, providing them with the regulators expectations of the data requirements. However, the numbering and structure of the document is confusing. The guideline should clarify its application to tissue engineered products. We believe the basic principles as proposed in this guideline ought to apply to tissue engineered products. We would suggest revising the title "Cell-Based Medicinal Products", which is inconsistent with the term used in Community law. Annex I to Directive 2001/83/EC refers to "cell therapy medicinal products" and the proposed Regulation on advanced therapy medicinal products similarly describes such products as cell therapy medicinal products. There should be reference to tissue-based products, if they are so classified as medicinal products. We welcome the opportunity to submit these observations and comments and hope they are helpful in improving this guideline with greater clarity. (BIA)

10. 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. (BIO) (EuropaBio) (Genzyme)
11. A clearer correlation to the components of the CTD (Quality, Safety and Efficacy) would be helpful. (BIO)
12. 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). (BIO)
13. 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? (BIO)
14. The guideline should require discussion of hypothesised mechanism of action for the cells in question. (BIO)
15. The guideline is intended for cell-based medicinal products entering the MA procedure. Since there are already several cell-based medicinal products (e.g. cell-based autologous cartilage transplants) legally on the market in European countries (e.g. Germany, Italy) and the products have shown safety and efficacy in daily use, these products should not be classified as new cell-based medicinal product entering the MA procedure. In all different chapters of this guideline special attention should be laid on the question whether the intended requirements are applicable for those already legally marketed products. (BPI)
16. In addition to that, concerning all aspects of the guideline including quality control and manufacturing, the guideline does not adequately distinguish between autologous and allogenic cell based products. Obviously, for autologous products a distinct risk analysis is necessary taking into account that these products are derived from one patient and are used in the same patient for implantation. We suggest that the issue of autologous products should be considered and that risk analysis may define criteria and tests to be done in quality control, manufacturing, and development. (BPI)
17. In the proposal, there is no definition or clear position about the status and requirements for the products that are release from the cells but which might have the role in tissue regeneration, such as platelet derived growth factors. These cell releaseates are of complex nature, so one wonders if such products should be considered as well under the above mentioned guideline or regulated otherwise (Cyanthus Exquirere Pharmaforschung).

18. This is a valuable and generally well-considered document that goes a considerable way towards clarifying and enhancing the guidelines for human cell-based medicinal products (CBMP). The draft guidelines acknowledge the complex and dynamic nature of CBMP but clearly state that some of the current listed requirements may be inadequate for the product in question. In this respect we have two very serious concerns over the guidelines as they stand.

- First, we believe that the proposed requirements are more directly relevant to the development of pharmaceutical drugs, i.e. medicinal drugs for delivery to populations as a whole. Hence they are much less relevant to dendritic cell-based immunotherapy and other cellular therapies that need to be tailored to individual patients. We are concerned that, without specific and unequivocal guidance in relation to the relevant release criteria (standardisation, end points etc), the efficacy and standardisation of future CBMP may be compromised, particularly as a consensus on relevant associated parameters (immunological assays, patient immunomonitoring etc), though close, has yet to be achieved.

- Second, we consider that the guidelines do satisfactorily address the requirements needed to obtain market approval but, at this stage, most CBMP are at the investigational stage and are not yet ready for commercial development. More investigational clinical trials urgently need to be conducted to understand their modes of action and effects on individual patients, but if the current guidelines were adopted they would make the performance of such trials extremely difficult, and would seriously impede clinical research in Europe.

We therefore urge the CHMP to include an additional, clear and unequivocal guideline relating specifically to the development of CBMP for clinical trials, prior to their commercial exploitation. We believe this to be absolutely crucial for the safe conduct of effectively-standardised clinical trials across different European States for the future. Representatives of DC-THERA and CIMT are willing to liaise closely and quickly with those from other Networks and related bodies such that we will be in a position, should the CHMP agree, to assist with the drafting of this specific guideline before the end of the current year (2007). We thank the members of the Committee for their very considerable effort in drafting these guidelines, but hope they will appreciate our serious concerns over the document as it stands. (DC-THERA / CIMT)

19. In the light of the more recent developments in further Regulations the preparation of this guidance document is welcomed. The information should be a useful tool to guide manufacturer's on the expected data for applications of an advanced therapy medicinal product consisting of viable human cells. Attention is also drawn to the earlier comments submitted to this Working Group by the Gene Therapy Working Party (GTWP). (DKMA)

20. To speed up the long and uncertain path to CBMP delivery new guidance should allow small exploratory studies (proof-of principle trials) be performed as academic studies. The following restrictions are proposed for these pre-clinical studies:

- Autologous CBMP will be primary cells cultured for a few passages before being used for the CBMP as treatment on request.
- CBMP must be produced and administered in the same structure.
- The laboratories must meet the minimal requirements stated in Point 4.2.2 ("…The manufacturing area should be physically separated from the area where biological fluids, tissues or organs are collected/procured…". CBMP characterization must conform to point 4.2.3 and CBMP release criteria to point 4.2.4.

(Dr Lina Matera)

21. The draft guideline is well written, comprehensive and gives solid and useful guidance for procurement, manufacturing as well as clinical and non-clincal testing of cell based medicinal products. It addresses very well the broad variety of products to be covered and identifies specific challenges of different types of CBMP in the context of manufacturing, quality assessment and testing. Unfortunately, the guideline appears to be written without taking note of the new Advanced Therapies Regulation (AT) regulation and the specific requirements of the European Clinical Trial Directive 2001/20. The section on Investigational Medicinal Products instead refers to Notes for Guidance that was issued before the Directive 2001/20 coming into force. It would be helpful if guidance was provided to the developers and manufacturers of CBMPs on how to handle the partially conflicting requirements of these documents.

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, i.e. the intended transport vial including lids and at various conditions and the intended and additional storage conditions.
2) With regard to transport there seems to be little coverage of issues like maintenance of cell integrity, potency and viability if the cells did not reach the intended patient in time due to transport problems. Guidance is required on setting criteria for ensuring the cells are still viable in such cases.

General comments on delivery of cells:

1) Delivery of cells to patient can be by a variety of methods. The delivery method should be evaluated to check that the cells have not become inadvertently damaged. For example, shear stress forces on modified cultured cells may render them more fragile and prone to rupture.
2) Also with the individual delivery procedure in mind what is the potential for mis-injection or misplacement of cells.

A hypothesised mechanism of action for the cells in question should be indicated.

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The guideline acknowledges the fact that the CBMP may consist of cells associated/combined with other cells, non-cellular components, structural components or medical devices. These four different options should be addressed separately throughout the complete guideline.
In several sections of the guideline risk analysis and management activities are addressed. The guideline should specify whether for cell-based medicinal products additional activities are required that go beyond those described in the EMEA guideline on risk management systems for medicinal products for human use. If yes the guideline should describe what additional risk analysis and management activities should be performed by the applicants.
(EBE)

22. In general, the draft guidance document is comprehensive, thoughtful, and well-organised – albeit that the numbering and indexation could be improved – providing the developers of CBMP with a useful set of regulatory expectations. It was constructed by individuals that appear to have a good understanding of the challenges to be faced in developing a CBMP bio-processing paradigm. Particularly useful was the initial discussion on analysing risk in the contemplation of the design of CBMP. With regard to quality and manufacturing aspects, it is clear that there was a good understanding of the realities involved. For example, the need for animal-derived materials is not forbidden and directs the reader to outside Guidances, albeit the use of irradiated sera or alternative synthetic media is encouraged. Moreover, the requirements encourage an early development of full characterisation of the product and development of assays. However, while release specifications for identity, purity, impurities, sterility, potency, cell viability and total cell number are recommended, it should be acknowledged that, depending on the product, certain release tests may not 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 when changes in the manufacturing process are contemplated.
(EuropaBio) (Genzyme)

23. We believe that, while the quality aspects have been well-detailed in the guideline, the non-clinical and clinical aspects are still lacking concrete provisions. We would be in favour of additional Guidelines on these aspects that should also consider the type of the CBMP product (e.g., clinical endpoints may be different for tissue-engineered products and somatic cell therapy or gene-therapy products) to complement this first general guideline for CBMP. For example, tissue engineered products require specific guidelines that will clearly be different from other cell-based medicinal products (somatic cell therapies or gene therapies). For example, clarification on the criteria for accepting structural endpoints for clinical investigations on tissue-engineered products will be important.
In its scope (chapter 2), the guideline mentions that "although this document does not cover non-viable cells and cellular fragments originating from human cells, the underlying scientific principles may be applicable". Considering that the products containing non-viable cells may be classified as medicinal products or as medical devices, depending on their primary mode of action; and that medicinal products containing cellular fragments face special challenges (in terms of final product characterisation, e.g., purity / impurities, active substance characterisation, potency assay…), we believe that it would be very helpful to publish guidelines specific for medicinal products based on cellular fragments originating from human cells, such as cell lysates. (EuropaBio) (Genzyme)

24. Context: One WP in RISET (WP3), under the leadership of Lucienne Chatenoud is dedicated to clinical trials related to 1) tolerance induction. 2) Minimisation of immunosuppression. 3) Refining the use of tolerogenic drugs. Four pilot studies are presently being performed, in the context of transplantation:

1. IL-10 anergised T cells.
2. Donor-derived mobilized immature CD34+ bone marrow stem cells.
3. Monocyte-derived transplant-acceptance inducing cells
4. Anti-CD3 and anti-CD7 ricin A-immunotoxins in severe GVHD.

People involved in this WP were asked to comment on the guidelines; in addition Anne Cambon-Thomsen and Virginie Commin are preparing a set of recommendations on ethical, legal and regulatory aspects of such assays at EU level and were also involved in the consultation.

The document was very positively received as a useful, reasonable and well documented set of guidelines. It was considered excellent and nicely polished.
Some comments of general relevance are as follows:
Much relevance should be given to ensure reproducibility among different samples and fully test the final sample cell preparation product, while limiting the tests done for each single patient preparation. This is important in order to avoid that the amount of product dedicated to pharmacological testing and quality controls becomes bigger than that needed for treatment. There was a concern that if primary cells are used as raw material for the manufacturing process, material for several in-process controls may often not be available. Therefore, to obtain the minimal effective dose for the treatment, in-process controls may be reduced to a minimum.

Tumourigenicity is an important aspect of cellular therapy that is not overly emphasized in this document and could be more clearly underlined.
The risk analysis chapter was found to be most useful as this step is an essential one in establishing the risk/analysis balance that is necessary for decision also for clinical trials. This part should be used as a reference by research ethics committees when reviewing protocols submitted for approval.
The "non-clinical" studies paragraph was felt to be very restrictive since not all human cellular-based products might have a suitable animal model to be tested. Therefore, the possibility to complete safety and efficacy testing of the cell product by non-clinical (pre-clinical) in vitro biological and molecular assays should be included. Similarly, the possibility to perform proof-of-principle studies in human specific disease models or pathological settings should be maintained open.

25. The draft guideline does not provide specific guidance on FIH studies with CBMP (with relation to the extent of non-clinical studies to support FIH testing, designs for FIH including calculation of the initial dose and quality requirements to start FIH). In addition to this, note that Gene therapy and Cell therapy medicinal products are excluded from the scope of the draft March 2007 CHMP guideline on requirements for FIH clinical trials for potential high-risk medicinal products. (PhRMA)
26. In general the draft guidance document is a good start to a comprehensive, thoughtful, and well organized document providing the developers of CBMP with a useful set of regulatory expectations. Small suggestion on structure : would adapt numbering; is somewhat inadequate and provide an index. For commenting purposes a column on the left side with line numbering would be easier for referencing purposes. In general would recommend adding glossary of terms with definitions bringing consistency in terminology within this document and bringing in line with already available definitions and glossary terms from existing Directives and more importantly of the now voted ATMP Regulation. The ATMP Regulation mentions that good clinical and good manufacturing practices should be adapted to the particularities of advanced therapy medicinal products. Reference to forthcoming guidelines on adapted GCP and GMP to ATMP should then also be mentioned in this present guideline. The quality/manufacturing section has been developed in depth, both non-clinical and clinical sections could benefit from some more consolidation of requirements (specifics) and structure. We would be in favour of additional publication of concrete guidelines on both these aspects to complement this first general guideline. For example, Tissue engineering products require specific guidelines that will clearly be different from other cell-based medicinal product (somatic cell therapies or gene therapies). Clarification on the criteria for accepting structural endpoints for clinical investigations on tissue engineered products will be important. In general we would welcome an better upfront distinction between the requirements of CBMPs for systemic application and for local implantation. (we acknowledge the risk analysis could take this into account possibly). The risk analysis section is welcomed but should be clarified further as to what exactly is expected since the interpretation between different parties of what risk analysis is, could be different (e.g. medical device vs pharmaceutical framework; quality/manufacturing vs pharmacovigilance only). The non-cellular component requirements seem to be too spread out over the different chapters and go into deep reflections on “mode of actions”; which seems to be out of balance with the cellular component. This should be more concise, focus on real documentation requirements, and refer/take advantage of existing regulations and approvals of medical devices, when the case. (Tigenix)
27. 1. The guideline should clarify its application to tissue engineering products. The title “Cell-Based Medicinal Products” does not tie in readily with the terminology of the Advanced Therapy Medicinal Products Regulation: it would be clearer if it referred to “Somatic Cell Therapy and Tissue Engineering Products”. 2. There should be reference to tissue-based products as opposed to cell-based products where appropriate: the text focuses almost entirely on cells. 3. Whilst it is appreciated that the products falling under the scope of this guidelines are medicinal products, some text should be added to the Executive Summary to acknowledge that whilst the *terminology* of the pharmaceutical concepts is that of medicinal product guidelines, the evaluation of the fundamental issues may be very different from conventional studies. This is crucial as the terms inevitably raise pre-conceived expectations in the mind of the pharmaceutical assessor, and in the evaluation of these non-conventional products a flexible and pragmatic approach will be of critical importance. 4. The numbering and structure of the document is confusing. (Zimmer)

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Line no. + paragraph no.	Comment and Rationale	Outcome
1. Executive summary + Introduction		
Line 4 Paragraph No: 1	Because guidance refers primarily to requirements for registration, point out correlation to CTD components Proposed change: 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.	The amendment proposed here is already part of Chapter 2 "Scope" and repeating the same sentence in the executive summary is not considered necessary.
Paragraph No. 2	Clarification of meaning requested. Proposed change: 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.	The second paragraph is dedicated to introduction of the quality requirements; nonclinical and clinical introductions are provided in paragraphs three and four, respectively.
Line 5 Paragraph No: 2	Types of cells can be classified into 4 broad categories Proposed change: 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). (BIO)	The purpose of the paragraph was to give examples of the variety of cells in the CBMPs and not to provide any definitive categories of cells, which may be too restrictive approach for this purpose.

Introduction	We suggest that this issue should be introduced in the scope of the guideline by stating that "The guideline acknowledges that cell-based medicinal products that are already on the market in the EC may not meet all principles of the guideline. For the MA procedure of these products special consideration should be given to the risk management plan that may demonstrate that the product meets the criteria of pre-clinical and clinical development. Proposal: Addition of the two following paragraphs at the end of this chapter: Since there are already several cell-based medicinal products legally on the market in European countries before the coming into force of the Regulation on ATMP, which have proven clinical safety and efficacy, these products should not be classified as new cell-based medicinal product entering the MA procedure. The guideline acknowledges that cell-based medicinal products that are already legally on the market in the Community need not meet all principles of this guideline in detail. For the MA procedure of 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. (BPI)	The specific requirements proposed for CBMPs currently on the markets based on national manufacturing licences, are not within the remit of this guidance. When ATP regulation is in use, also these products need to seek for centralised MA.
First paragraph, page 3.	Identify more clearly the newer legislation. Proposal: Amend to, for example, ….(including Directive 2004/23/EC on the quality and safety of human tissues and cells, and its two technical Directives) (DKMA)	The first part of the proposal taken into account, but specifying the technical directives as "two" may need revision later. References to the technical directives are made.
First paragraph, line 4, page 3.	In light of the newer regulations it is more correct to refer to a "combined advanced therapy medicinal product" than a "combination product". Proposal: Amend as indicated, and as appropriate later in the document. (DKMA)	Not taken. The broad sense is required. Combined advanced are specifically those with medical devices while other combinations are possible.
Last line, second paragraph, Introduction.	Clarification of information. Proposal: Amend to ….. with structural materials or individual components that may be categorised as a medical device. (DKMA)	Text amended as proposed.
Second paragraph, Introduction, page 3.	Here is first reference to genetically modified cells, so this document appears relevant for somatic cell therapy, gene therapy and tissue engineering of human cells. (see other comments below). Perhaps this could also be expressed in the Executive Summary. Proposal: Amend as required. (DKMA)	Executive summary is only a high-level summary of different sections of the guideline. The issue becomes clear from the introduction onwards.
Paragraph No: 1 Exec	This paragraph does not contain a reference to the new Advanced Therapy legislation which is relevant for al aspects of market authorization for such products Proposal: …(including the Directive 2004/213/EC on Tissues and Cells and the technical	The reference has been included.

Summary	directives drawn from it as well as the Regulation …. on Advanced Therapy Medicinal Products) (EBE) (EuropaBio) (Genzyme) (Zimmer) (BIA) (DKMA)	
Paragraph No: 4 Line: 2 Exec Summ	Typo: pharmacodynamic Proposal: Pharmacodynamic (EBE)	The typo is corrected.
Paragraph No: 2 Line: 5 Introduction	The possibilities of the association of cells with other components may be divided in four major categories Proposal: The cells may be used alone or associated with other excipients such as - other cells (e.g. stem cells) - non-cellular components: bioactive molecules, biomaterials, proteins, cell signalling biomolecules (e.g. growth factors, serum) chemical substances - structural components: scaffolds, beads, matrices, fibres - medical devices, with mechanical functions or active implantable or a combination of all four excipients Furthermore CBMP may be administered with dedicated medical devices which have to be assessed by a Notified Body (EBE)	The purpose of the paragraph was to give examples of the variety of cells in the CBMPs and not to provide any definitive categories of cells and/or other components, which may be too restrictive approach for this purpose.
Page 3, executive summary, line	"...the Directive 2004/23/EC on Tissues and Cells and the technical directives drawn from it" : the N° of these directives could be given here (ACT) Proposal: Add after "from it": 2006/17/EC and 2006/86/EC (RISET)	References to the technical directives are made in the Executive summary.
P3 Exec Summ	Transport and logistics : we would like to emphasize to include the whole chain (including logistics) for validation of conditions (from procurement of material (and all transport, logistics, storage conditions) up and until implantation in the patient. This validation of ALL conditions that might impact the quality of the product should be part of the development through clinical trials (IMP). It would be good additionally to receive clarity on to where a Sponsor's responsibility/liability stops under GMP (in view of these CBMP with their pecularities. (is this when the product leaves the plant or when the product is implanted in the patient ?) . (Tigenix)	Importance of validation of the hold steps (storage) and transportations has been brought up in section 4.2.5. Validation of the manufacturing process. GMP requirements are set in the GMP guideline and in the Annexes drawn from it. Specific GMP requirements for ATPs will be set in the revised Annex 2. The MAH is responsible of the product up to release + everything that is defined in the SPC and should validate the administration protocol to be

		transmitted to the practitioners and should be part of the RMP.
Executive Summary	Whilst it is appreciated that the products falling under the scope of this guidelines are medicinal products, some text should be added to the Executive Summary to acknowledge that whilst the *terminology* of the pharmaceutical concepts is that of medicinal product guidelines, the evaluation of the fundamental issues may be very different from conventional studies. Proposal: Add after paragraph 1: "Whilst the *terminology* of the pharmaceutical concepts used in this guideline is that of standard medicinal product development, the way in which the fundamental issues may be evaluated may be very different from conventional products. Therefore the applicant is encouraged to explain the purpose of the chosen studies and justify how the approach taken addresses the key issues in the context of the specific product.	This issue is discussed already in chapter 4.2. second paragraph. Also the risk-based approach as described in chapter 4.1. may provide some flexibility for products with lower risks.

Line no. + paragraph no.	Comment and Rationale	Outcome
2. Scope & 3. legal basis		
Scope, third paragraph	The scope should specifically exclude non viable products Delete “Although” and from ”the underlying” to “applicable”. (Eucomed)	The scope excludes non-viable cells, but acknowledges that this guidance may be of some help when developing / assessing products containing non-viable cells.
Legal Basis	This section needs to be revised to reference the ATMP Regulation. (Eucomed) (Tigenix) (Zimmer)	The reference is made.
Page 3, para 7	It should be indicated that the guideline covers tissue engineered medicinal products. In our view, the underlying principles on assessment for quality, safety and efficacy apply to both classes of products. We suggest that this is revised as follows: This multidisciplinary guideline will address development, manufacturing and quality control as well as non-clinical and clinical development of **somatic cell therapy** medicinal products **and tissue engineered medicinal products.** (BIA)	The paragraph has been amended.
Page 3	This section should make reference to the characteristics of tissue engineered products, as per article 2 of the Regulation on advanced therapy medicinal products. (BIA)	The paragraph has been amended.
Page 4, para 2	This section needs to be revised referring to the Regulation on advanced therapy medicinal products. (BIA)	The reference is made.
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 … (BIO)	Paragraphs 2 to 4 of the executive summary separately addresses the three modules (quality, nonclinical and clinical).
Third line, Scope, page 3.	These products are only assessed by the centralised procedure. Proposal: Amend to …. entering the centralised MA procedure. (DKMA)	The change is made.
Second paragraph,	Clarify scope of this document.	Genetically modified cells are included, the

scope, page 3.	Proposal: Amend to … These new cell based medicinal products, which excludes cells genetically modified with preventive, diagnostic or therapeutic genes, have the following characteristics: …(DKMA)	change is incorrect.
Last line, page 3.	Clarify text. Proposal: Amend to … This guideline does not cover cell based medicinal therapy products containing xenogeneic cells or cells containing gene therapy medicinal products.(DKMA)	Genetically modified cells are included, the change is incorrect.
Second paragraph, legal basis, page 4.	The present information is incomplete. Proposal: Amend to …. The requirements for donation, procurement and testing in Directive 2004/23/EC, on the quality and safety of human tissues and cells, and its two technical Directives, are applicable. In addition, add ……..This guideline should be read in conjunction with the Regulations on advanced therapy medicinal products dated November 2007. (DKMA)	The paragraph is modified.
Paragraph No: 2 Scope	The scope makes no specific reference to tissue-engineered products. A reference to Art 2 of the AT regulation should be included Proposal: Following par 2, suggest to include the following as par 3: (EBE) The definitions of art.2 AT regulation apply accordingly as it refers to the definition of tissue engineered medicinal products. (EBE)	The scope has been amended.
Paragraph No: 2 Bullet point: 2 Scope	For clarity, all possible combinations should be mentioned Proposal: They may be combined with other cells, non-cellular components, structural components or medical devices (EBE)	Unnecessary, the current version covers all possibilities.
Paragraph No: 3 Line: 1 Scope	Proposal: There should be a superscript “1” before “Although …” to designate it as a footnote.	This paragraph is part of the text, not a footnote.
Paragraph No: 3 Line: 3 Scope	Proposal: Change “product” to “products”.	The correction is made.

Page 3, scope, line 3	MA abbreviation should be made explicit (ACT); in general this should be checked throughout the document also for other abbreviations such as RCT,(P. 21), ADME (P.21) Proposal: Marketing or manufacturing (?) authorization (RISET)	The abbreviation is opened.
Page 3, scope, line 4	"the guideline should be taken into consideration of applicants entering into the clinical trials" (ACT) Proposal: "the guideline should be taken into consideration BY applicants entering into the clinical trials"(RISET)	The correction is made.
Line 42, Paragraph 2, Scope Line 44, Paragraph 2, Scope	There should be a superscript "1" before "Although …" to designate it as a footnote. Change "product" to "products". (PhRMA)	This paragraph is part of the text, not a footnote. The correction is made.
P3 Scope.	Clarification is sought on "undergoing a manufacturing process". Will this now be adapted to the definitions given for hTEPs/CBMPs in the ATP Regulation ? or is this distinction made to clarify vs minimally processed (Dir 2004/23/EC)? (Tigenix)	The manufacturing process is referring to the definition of a medicinal product (industrially produced, Directive 2001/83/EC, article 2.) and to Directive 2004/23/EC, point 1 ("manufactured products derived from human tissues and cells") in order to discriminate the cell-based medicinal products from transplants, which are not in the scope of this guideline.

Line no. + paragraph no.	Comment and Rationale	Outcome
4.1. Risk analysis		
Section 4.1	If non viable materials are to be retained in the scope of this document, reference should be included to the appropriate CEN/ISO standard for Risk assessment/management. Since it is possible for medical devices to be included in these products, this reference is essential. In any case, the relevance of the existing referenced documents would need to be reviewed by the appropriate expert group (CAT). Add reference to EN ISO 14971. (Eucomed)	Non-viable cells are excluded. Reference is made to relevant CEN/ISO standards in chapters, where devices as part of the cell-based products are discussed.
Section 4.1 general risk criteria	This list appears to be incomplete (for example there is no reference to the site to which the product is applied). (Eucomed)	The list is not meant to be definitive, but to provide the main issues relevant for all products.
Page 4	We support using a risk analysis approach to justify the product development and evaluation plans and as a basis for the preparation of a risk management plan. We suggest that this section is expanded to cover the choice of cells and other materials, control of materials, manufacture and the extent of safety and efficacy studies. (BIA)	The risk analysis is meant to cover all issues related to the quality, non-clinical and clinical development of the product as described in bullet points 1 and 2.
Page 4, para 5	The risk criteria listed in this paragraph should not be seen as definitive, rather a series of points to consider when estimating the overall risk of the product. (BIA)	The list is not meant to be definitive, as the issues are very much product-specific.
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.” (BIO)	The point is taken.
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	The point is taken.

	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).” (BIO)	
	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.” (BIO)	The proposed change is not considered necessary.
Chapter 4.1 Risk analysis Fourth para	Second bullet point: It is not necessary that cells proliferate and differentiate in any case, so it should made clear that also one or the other alone is possible Third bullet point: Cryoconservation is added because it is another possibility of manipulation Last bullet point: The guideline is not only made for new products, so it is necessary to say that not only experiences with similar products but also (pre)clinical experiences during the marketing period before the coming into force of the regulation should be taken into regard. Proposal: The following general risk criteria can be used in the estimation of the overall risk of the product: • origin (autologous-allogeneic); • ability to proliferate and/**or** differentiate; • ability to initiate an immune response (as target or effector); • level of cell manipulation (in vitro/ex vivo expansion/activation/genetic	and/or included Cryoconservation added to the list. The exact wording is “clinical data on <u>or</u> experience with similar products”; experience can be either preclinical or clinical, if relevant. and/or included

	manipulation/**cryo-conservation**); • 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, **taking into regard preclinical data and clinical experiences collected with products which were already legally on the market before the coming into force of this guideline,** (BPI) (EuropaBio) (Genzyme) (Tigenix)	Cryo-conservation added Amendment not considered necessary. Products legally on the markets before coming into force of this guideline are not within the remit of this guidance.
4.1, 8th bullet point, page 4	Amend text for clarity Proposal: Replace genetic manipulation by …. extent of manipulation and change of biological characteristics. (DKMA)	Genetic manipulation is only one example, the main text says "level of manipulation". The change is not considered necessary.
Paragraph No: 1 Line: 1- 6	The European Risk Management Plan (EU-RMP) addresses patient's risk. The respective reference is given in paragraph 2. It would be very useful to either provide similar reference for what is meant to address the risk of medical personnel and the general population or clearly describe what precisely is expected from the applicant.	Risk for medical personnel can be foreseen, if e.g. infected/contaminated material is used for production and for general population the risk may be increased if e.g. infective, recombinant virus is used to transduce cells intended for administration. These risks are dependent on the product and should be considered by the applicant as described in this section.
Paragraph No: 2 Line: 5,6,8	The European Risk Management Plan addresses neither the quality nor manufacturing aspects. Clarification is needed on whether EU-RMPs of cell-based medicinal products will require additional documentation on quality aspects that go beyond the non-clinical and clinical development field, i.e. what is covered in section 4.3 and 4.4 of this guideline.	Risk analysis introduced in chapter 4.1. is a separate entity from RMP and will be expected only for ATPs. This risk analysis will provide the basis for the amount and scope of data to be submitted in the MAA (modules 3,4 and 5).
Paragraph No: 2	Reference to article 15 of the AT legislation is missing Proposal: *Ensure consistency of definitions and requirements (EBE)*	Risk analysis introduced in chapter 4.1. is a separate entity from RMP.
Paragraph No: 3 Bullet point: 7	Clarification is needed on the terms *combination product* (which is the combination with a medical device) and *combined product*, which is the combination with a cell, non-cellular component or structural component. Proposal: • *Device combination product*	Combination product and/or combined product is used to describe a product, where cells are combined with non-cellular components. Where a combination of cells with devices is described, the term is combined advance therapy medicinal product, according to the ATP Regulation.

	• *Combined product* (cell, non-cellular component or structural component (EBE)	
Paragraph No: 3 Additional Bullet point (i.e. no 9)	Co-medication might also have influence on the overall risk of the CBMP Proposal: • Co-medication (e.g. immunosuppression) (EBE)	The list is non-exhaustive and gives only few examples. The product- and patient-related risks must be defined by the applicant on case-by case basis.
4.1 Risk Analysis Section 4.1. Risk Analysis par 2	We welcome the introduction of the Risk Analysis approach, and in particular the concept that "*development plans and evaluation requirements need to be adjusted according to multifactorial risk analysis*". We fully agree that the activities in the field of quality, non clinical and clinical have to be planned and conducted based on the result of the individual risk analysis of the product in question. Risk analysis is hence the key and reference basis to all further activities Reference to article 15 of the AT legislation is missing Proposal: Considering that risk analysis / risk management is a concept that may be understood differently depending on the type / the background of the developers, we would appreciate having more indications on how to apply this concept. We think that an additional guideline on the specific subject of risk analysis would be useful. In this guideline, we would encourage further recommendations on what the authorities expect through such a document, and also how to integrate this into the different submissions (scientific advice, clinical trial submissions, marketing authorisation). *Ensure consistency of definitions and requirements.* Risk analyses should also consider the indication and also the high unmet medical need and the current available treatments. (EuropaBio) (Genzyme)	Risk analysis introduced in chapter 4.1. is a separate entity from RMP and should be used as a basis for RMP. There will be additional information concerning this risk analysis in the revision of the Directive 2001/83 The list is non-exhaustive and gives only few examples. The product- and patient-related risks must be defined by the applicant on case-by case basis.
Page 4, Main Guideline, 4.1 risk analysis, last list of bullet points	"The following general risk criteria can be used in the estimation of the overall risk of the product:" Not all the following risk criteria apply to all situations, hence could rather than can is more adapted. Some points should be made more explicit:	Text amended as proposed.

	• level of cell manipulation (in vitro/ex vivo expansion/activation/genetic manipulation) : include DIFFERENCIATION • duration of exposure (short to permanent); include CULTURE (RB) Proposal: The following general risk criteria COULD be used in the estimation of the overall risk of the product: • level of cell manipulation (in vitro/ex vivo expansion/activation/DIFFERENCIATION/genetic manipulation) • duration of exposure OR CULTURE (short to permanent); (RISET)	
P4 Risk analysis	We welcome the introduction of the Risk Analysis approach Considering that risk analysis/risk management is a concept that may be understood differently depending on the type / the background of the developers, we would appreciate having more indications on how to apply this concept. Indeed , eg. the risk analysis and mitigation now required from biotech/pharma – ATP products is based on pharmacovigilance systems mainly and e.g. hazard analysis linked to the product in manufacturing is only briefly touched upon. Therefore this paragraph is important and consolidation and clarification by regulators of how risk analysis is interpreted by them together with very clear documentation requirements is a must. We think that an additional guideline on the specific subject of risk analysis would be useful. In this guideline, we would encourage further recommendations on what the authorities expect through such a document, (Tigenix)	The point is acknowledged.
Section 4.1	Risk analysis should be expanded to cover the development / choice of cells and other materials/ control of materials and manufacture/ choice of safety and efficacy studies, not just the clinical use profile. The ISO standard on risk analysis could usefully be referenced. Proposal: Add reference to EN ISO 14971 (Zimmer)	The proposed reference could be useful, however, the risks associated to each product are specific and relate not only to the product itself, but also to the administration, co-medication etc. as described in other comments. Therefore the risk analysis should cover all development phases (quality, preclinical and clinical.) and to follow the mentioned ISO standard may not be enough.

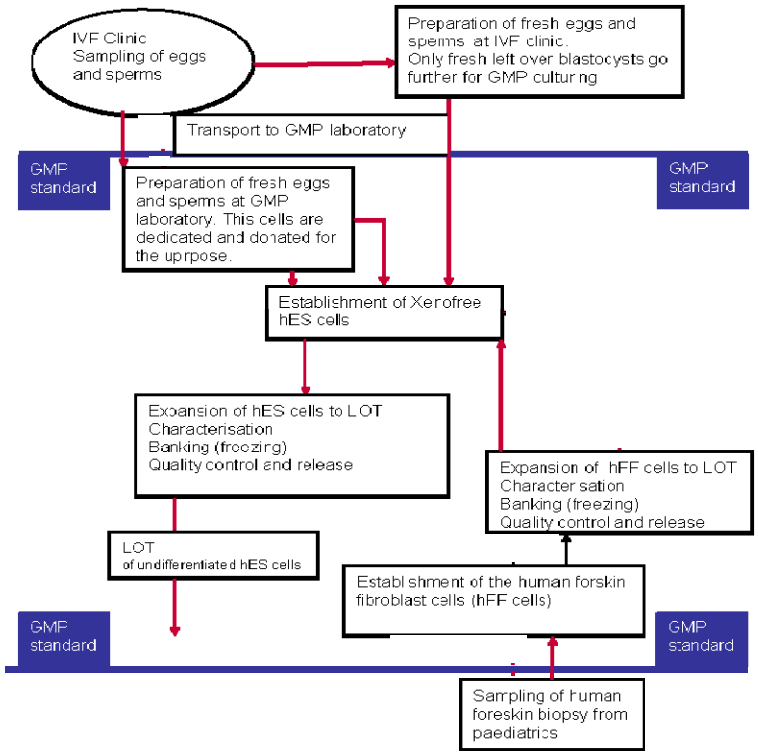
Section 4.1 general risk criteria	This list appears to be incomplete (for example there is no reference to the site to which the product is applied). It should be stated whether this list is intended to be exhaustive or as examples only. (Zimmer)	The list is non-exhaustive and gives only few examples for the readers. The applicants should discover the specific risks associated to their products.

4.2. Quality and manufacturing aspects		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Section 4.2; 4.2.2	This section should include reference to an appropriate and specific version of good manufacturing practices (art 5 of the ATMP Regulation) (Eucomed) (BIA) (Zimmer)	The reference is included.
4.2. Line 2 Paragraph No: 1	Replacement of the expression tissue *establishment* We suggest the alternate wording, "…describes activities by manufacturers after procurement of cells." (BIO)	The text is amended as proposed.
4.2 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." (BIO)	The text is corrected as proposed.
4.2. Page 4, para 6	It should be noted that cells and tissues may be procured. We suggest revising as follows This part of the guideline describes activities by manufacturers **following procurement of cells and tissues.** (BIA)	The text is amended as proposed.
First line, Section 4.2, page 4.	Some clarification is helpful. Proposal: Amend to …. This part of the guideline describes activities by manufacturer's after the receipt of the cells from an authorised tissue establishment or from working cell banks. (DKMA)	The text is amended according to another proposal. See above.
First line, Section 4.2, page 4.	Some clarification is helpful. Proposal: Insert additional text …. The requirements for donation, procurement and testing in Directive 2004/23/EC, on the quality and safety of the cells as a starting material, and its two technical Directives, are applicable. (DKMA)	This issue is already covered in chapter 2. Scope.
Section 4.2 Quality and Manufacturin	Manufacturers may procure cells themselves. Proposal: Change as below, add bold text *This part of the guideline describes activities by manufacturers* following procurement of cells	The text is amended.

g	or tissues ~~*after receipt of cells from the tissue establishments*~~ (EuropaBio) (Genzyme)(EBE)	
Section 4.2.1	Add “sourcing” Line 1 to 2 to be amended: “stringent sourcing requirement, purification steps….”(Eucomed)	The text is amended.
Section 4.2.1 1.1	The national transpositions of directive 2006/17/EC have introduced between Member States inconsistent requirements (Eucomed) (Zimmer) (BIA)	Directive 2006/17 and its implementation on national level are not within the remit of this guidance.
Section 4.2.1 2 first paragraph	Suitability for the intended use should be appropriately defined through the risk management process. Delete from “The sterility” to “for the intended use” (Eucomed)	The second part is deleted and the work “sterility” is replaced by “microbial purity”.
Section 4.2.1 2.2	The CPMP/CVMP TSE guideline still has an outstanding proposed amendment, issued some time ago. Presumably this guidance will be revised and then the correct reference should be included in this guideline. (Eucomed)	Up-to-date reference for the TSE guideline is made. The amendment is still a draft version and not officially accepted.
Section 4.2.1 3.2	The role of the Notified Bodies shall be aligned to the final text of the ATMP regulation. The last sentence is superfluous. Delete last sentence of the clause. (Eucomed)	The sentence is deleted as the same information is given earlier in the text
4.2.1 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. (BIO)	The text is amended as proposed.

4.2.1. 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." (BIO)	The text is amended as proposed.
4.2.1. 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." (BIO)	The text is amended as proposed.
4.2.1. 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." (BIO)	The text is amended according to another proposal.
4.2.1. Section 2.1 Line 4 Paragraph No: 1	Typo We suggest the alternate spelling encephalopathies (BIO)	The word is corrected.

4.2.1. 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') (BIO)	The point is taken.
4.2.1	**Quality and manufacturing aspects: Starting and raw material** In order to ensure a high level of human health protection and to prevent the transmission of diseases by human cells the Commission Directive **2006/17/EC** has been implemented February 2006 (Directive **2004/23/EC** of European Parliament and Council). The directive include quality assurance for the donation procedures, testing, processing, preservation, storage and distribution of human cells intended for human application and of manufactured products derived from human cells. It is also required that starting materials and each step of the procurement process should be fully documented. The Good manufacturing Practice for medical products (GMP) (European Commission for Good Manufacturing practices volume 4) ensures that the establishment, culturing and differentiation of hES cells are consistently performed and controlled according to the quality standards as required by the marketing authorisation or product specification. Referring to a pre-meeting held May 31st 2006 with the Swedish Medical Agency (MPA) it is clarified that it is not required to have Grade A facilities according to the GMP standard if the terms for procurement process are fulfilled i.e. that procurement of cells take place in appropriate facilities and the process is fully documented following standard operating procedures for the procurement, packaging, labelling and transportation minimizing the risk of contamination. The procedures where GMP facilities are not required include the sampling of the human blastocysts and human fore skin cell line (feeder cells). See figure below.	GMP requirements and requirements set for procurement and donation of cells / tissues (Directive 2004/23 and technical directives drawn from it) are not enough to ensure proper quality of a cell-based medicinal product. Where a commercial product is in question, the requirements set in the Regulation 1394/2007 and directive 2001/83 as amended, should be followed GMP issues, not within the remit of this guidance

	 **Conclusion:** GMP standard starts from the establishment of the human embryo stem cell line (Cellartis)	
4.2.1.1.	Proposed new section title: Proposal EBE; Other materials, reagents and <u>excipients</u>	The title is amended.
4.2.1.1 Paragraph No: 1 Line: 5	It is not clear what is meant by “absence of contaminating agents” that is not conveyed by the immediately preceding term, “sterility”. Proposal EBE: It is suggested that “absence of contaminating agents” is redundant and can be eliminated.	The text is amended.

4.2.1.1 Paragraph No: 2 Line: 3	Last sentence refers to “reagents with sensitisation potential”. What does this refer to? (EBE)	Text refers to reagents like antibiotics.
4.2.1.1 Paragraph No: 3 Line: 3	Viral safety only refers to material of animal origin. As feeder cells could also be of human origin it is suggested to include both animal and human cells (EBE)	Previous chapter “Cells of primary origin” does cover also feeder cells and there the viral screening has been addressed.
4.2.1.1 Paragraph No: 5 Line: 1	The word *product* may be misleading in this context. Proposal EBE: When the *other materials, reagents and excipients* have a marketing authorisation or are mentioned in a pharmacopoeia, appropriate references may be given.	“product” replaced by “raw materials and/or reagents”
4.2.1 §2.1 Paragraph No: 1 Line: 7	Replace "alternate" with "use of" (EBE) (phRMA)	The proposal does not properly fit into the sentence and would need further revision of the text. The original form is considered to be better.
4.2.1 .§3.2. Title for section 3.2	It is proposed to treat the topic medical devices in a separate chapter. A new heading for the revised section 3.2 is proposed Proposal EBE: 3.2 Special recommendations for <u>non-cellular components and structural components of combined products</u>	The amendment is not considered necessary.
4.2.1 .§3.2. Paragraph No: 1 Line:1-10	It is proposed to treat the topic medical devices in a separate chapter. A new section should be included and the text should be adapted accordingly. Proposal EBE: Additional specific information on the suitability of the <u>non-cellular components and structural components</u> of the CBMP for the intended use should be provided.	The amendment is not considered necessary. The current structure is accepted by other parties.
4.2.1 .§3.2. Paragraph No: 2 and 3	A heading for the new section 3.3 is proposed. It is proposed to treat the topic medical devices in a separate chapter. The section should be adjusted accordingly. Proposal EBE: <u>3.3 Special recommendations for medical devices of the device combination products</u>	The amendment is not considered necessary.
4.2.1 .§3.2.	Adjustment of the third paragraph to medical devices.	The amendment is not considered necessary.

Paragraph No: 3 Line: 1-2	Proposal EBE: Additional specific information of suitability of the <u>medical device or active implantable medical device</u> of the CBMP for the intended use should be provided.	
4.2.1 Starting and raw materials 1.2 Banking System for established Cell lines First para	"Well" characterised is rather unspecific, the cell banks are either characterised or not, therefore the term "well" should be omitted. Proposal; Where cell lines are used, a ~~**well**~~ characterised Master Cell Bank (MCB) and Working Cell Bank (WCB) should be established. (BPI) (EuropaBio) (Genzyme) (PhRMA) (EBE)	"well" is replaced by "appropriately"
4.2.1 Starting and raw materials Page 5, para 2	This suggests that all raw materials will be required to have purification, viral removal or inactivation to some degree. This testing will not be relevant for some raw materials, e.g. cell banks will undergo extensive testing for viral and other contamination. It should be noted that many raw materials used in cell culture and the manufacture of cell-based medicinal products do not currently undergo purification or viral inactivation or removal. We believe that this requirement may not be necessary in some circumstances and would be restrictive to the development of new cell-based products. Modify as follows **Materials of human or animal origin should be assessed using a risk analysis approach and tested as required** (BIA)	The text acknowledges that the manufacturing process usually <u>does not</u> include stringent purification steps etc. and thus, the acceptance criteria need to be defined according to the intended use. However, TSE and viral safety of preparations containing human and/or animal material must be ensured (Directive 2003/63, part I, 3.2. section 9 and 10).
1.1 Cells from primary origin Page 5 Last para	Clarification is required as to what is meant by the testing regimen of the starting material for autologous donation and the purpose of such testing. The requirements set out in the Directive on Tissues and Cells have been confusingly put together regarding the testing of autologous cells and the subsequent use of such cells even if they are tested positive for certain markers for infectious agents. Greater clarity on the rationale of testing requirements for cells intended for autologous use should be provided. Ordinarily the donor will be screened and tested and the tissue itself will not undergo further screening or testing. Further testing of the tissue is not deemed necessary. (BIA)	This chapter makes a reference to testing related to procurement in the first paragraph. The other guidance described relates to testing that is necessary at receipt of the cell / tissues at the production site, e.g. cell count, viability, purity, identity etc. This testing is necessary as the tissues / cells are mainly procured in non-sterile conditions, transported in a medium to the production site and may undergo degradation at that stage, etc.
1.2 Banking	It is not always appropriate or possible to create both a Master Cell Bank (MCB) and Working	The text is amended.

system for established cell lines Page 6, para 1	Cell Bank (WCB). Cell strains may be used in small quantities and at low passage numbers to manufacture the final product or other starting materials. Creation of a WCB in addition to the MCB under these circumstances is neither appropriate nor possible. It is sometimes necessary to create cell strains within a single tier cell bank system. Additionally, cells for autologous products may also be banked but again more appropriately in a single tier system. We suggest revising this paragraph as follows: **Where cell lines are used, well characterised cell banks should be established within a two tier or single tier cell banking system as appropriate. This should be defined on a case-by-case basis.** (BIA)	
2. Other materials and reagents Page 6, para 2	Materials may be combined and tested prior to use in the manufacturing process and consequently individual testing of each material may not always be necessary. Additionally, cell cultures have a degree of in-built control as contaminated cultures will exhibit signs of contamination by bacteria and other such contaminants. Final product testing may also negate the need for additional testing of starting materials. We suggest revising the third sentence as follows: **The requirement to ensure sterility, absence of contaminating agents and low endotoxin for starting materials should be assessed on a case-by-case basis and appropriate testing regimes should be implemented.** (BIA)	The text is amended according to another proposal.
2.1 Human derived materials Page 6	It may not be appropriate to evaluate all materials of human origin in line with plasma-derived products, which would include validated viral inactivation or removal. This would be extremely onerous and expensive and will be restrictive to the development of many cell-based medicinal products. During product development, the option to assess materials using alternative methods as appropriate should be acceptable, while working towards validated viral inactivation or removal for marketed products. This could include additional raw material testing. All materials are sourced to the highest available quality and testing is done using the most sensitive methods available. These controls minimise the risk of viral contamination. Therefore it is of importance that this requirement is not enforced during product development and that alternative methods of assessment can be used. (BIA)	The guideline described requirements foreseen for products entering the MA procedure and do not interfere with product development. However, TSE and viral safety of preparations containing human and/or animal material must be ensured both for marketed products and products intended for clinical studies (Directive 2003/63, part I, 3.2. section 9 and 10).
2.2 Animal derived material Page 6	The CPMP/CVMP TSE guideline still has an outstanding proposed amendment. It would be helpful to clarify when this guideline will be revised so that the correct reference can be included. (BIA) (Zimmer)	The amendment is still a draft version and cannot be referred to yet.
4.2.1 Starting	The guideline suggests to provide the assessment report, if a medical device is part of the	The text is according to the ATP Regulation

and raw materials 3.2. recommendations for matrix/device /scaffold components Second para	product and has been evaluated by a Notified Body. One should take into account that a medical device that has been evaluated by a Notified Body and that is CE marked definitely meets the criteria laid down in MDD 93/42/EEC as demonstrated by the e.g. CE-Certificate according to MDD 93/42/EEC and/or the CE design-examination certificate according to MDD 93/42/EEC; therefore a re-evaluation is unnecessary; Proposal: ….Furthermore, if the device part has been evaluated by a Notified Body, the assessment report **or relevant EC-certificates according to MDD 93/42/EEC (e.g. EC design-examination certificate)** should be provided …. (BPI)	1394/2007, article 9. CE marking as such is not enough, the application needs to contain the results of the assessment of the NB.
Second line, Section 4.2.1, page 5.	The reference to "materials" is ambigious and could be improved by replacing "materials" by "starting and processing materials". Proposal: Amend as indicated (DKMA)	The sentence goes "materials derived from human or animal origin" and should be clear enough.
4.2.1. Bullet diagram, page 5	Donated cellular material could be a mixed cell suspension i.e. mononuclear cells solution harvested from a bone marrow aspiration, which is currently used in clinical cardiac trials. Proposal: Therefore add a new bullet "A mixture of cells obtained from a single isolation procedure". (DKMA)	Second bullet point describes these products, however, also for mononuclear cells a purification step is used to select the most appropriate cell population from the crude aspirate.
4.2.1. Section 1, Cells, page 5.	Reword the text for clarity. Proposal: The active substance of a CBMP can be interpretated as engineered or manipulated viable cells, which are typically processed with other materials or reagents(e.g. growth factors, serum) and may be combined with other non-cellular components (e.g. matrix, scaffold, medical device). (DKMA)	The text is amended, but in a different way.
4.2.1. First line, Section 1.1, page 5.	Clarify further. Proposal: Amend to …. The specific requirements for donation, procurement and testing in Directive 2006/17/EC shall be met. (DKMA)	The text is amended as proposed.
4.2.1. Third and fourth paragraph, Section 1.1, page 5.	The specific quality related parameters for an organ/tissue and the mandatory requirements for screening tests of biological markers are already specified by the legal requirements of the Tissues Establishments Directives. Quality related parameters <u>additional to</u> the Tissues Establishments Directives should be specified in this document, taking into consideration shipment and storage conditions. Some illustrative examples may be relevant here. Proposal: Amend to reflect the comment. (DKMA)	This is exactly the scope of this chapter.

4.2.1. Third paragraph, Section 1.1, page 5.	Clarify the approach to non-healthy tissues better. Proposal: Amend to …. When cells originate from non-healthy tissues, the product specific criteria should take into account when being defined with regard to the intended use. Quality acceptance criteria should be set for a given organ or tissue , taking into account the shipment and storage conditions. (DKMA)	Non-healthy here means diseased cells/tissues e.g. for autologous production.
4.1.2. Fifth paragraph, Section 1.1, page 5.	Some clarification would be helpful on the "testing regimen" expected for the starting material. If this relates to the screening tests for biological markers then the legal requirements are already specified in the Tissues Establishments Directives. Proposal: Update with relevant information similar to the above. (DKMA)	The "testing regimen" relates to testing that is necessary at receipt of the cell / tissues at the production site, e.g. cell count, viability, purity, identity etc. This testing is necessary as the tissues / cells are mainly procured in non-sterile conditions, transported in a medium to the production site and may undergo degradation at that stage, etc.
4.1.2. Fifth paragraph, Section 1.1, page 5.	For manufacturing and storage reasons the viral/bacterial infection status of any cell sample, including autologous, should be known in order to permit appropriate segregation of infected cells. Proposal: Add additional text as indicated. (DKMA)	This is covered by the existing text.
4.2.1 § 1.2, page 6	The principle of characterisation and testing of established cell banks is also relevant for any cells that are stored by the manufacturer. Proposal: Amend as appropriate. (DKMA)	This is covered by the existing guideline that is referred to in the text.
4.2.1. First paragraph, Section 2, page 6.	In the first line clarify this is for processing materials. Is the term "neo-organ" fully understood by all parties? Proposal: Amend to Various processing materials … Consider alternative term. (DKMA)	The text is deleted.
4.2.1. Fifth paragraph, Section 2, page 6.	Text refers to other products having a marketing authorisation or are CE marked within a section addressing materials and reagents. Is the purpose to highlight other commercially available products may be used as materials in the processing activities or they may be a component of the end product ? Proposal: Amend text as required. (DKMA)	Word "products" changed into "materials"
4.1.2. First line, Section	The context of the animal cells or tissues having a supportive role as a material or reagent is not clear from the existing text.	Meant e.g. mouse cells used as feeder cells for culture of stem cells. The clarification is included.

2.2, page 6.	Proposal: Amend the text to clarify this point. (DKMA)	
4.2.1.Section 3.1. Page 7	A concept paper on the development of a guideline on the quality, pre-clinical and clinical aspects of medicinal products containing genetically modified products was adopted by CHMP for public consultation March 2007. Proposal: This reference would be useful to the readers. (DKMA)	A concept paper as such does not provide any guidance but recognises the need to draft one.
4.2.1. First paragraph, Section 3.2, page 7.	Clarification to first line. Proposal: Amend to ….. Cell-based medicinal products may incorporate structural components which independently are medical devices or active implantable medical devices. (DKMA)	The text is amended as proposed.
4.2.1. Line 5&6, first paragraph, Section 3.2, page 7.	This does not reflect the statements in the Regulations for ATMP's, including tissue engineering. Proposal: Replace by …. Furthermore where the device component has been evaluated by a Notified Body the applicant shall provide evidence of conformity. The Agency may request information on the results of the assessment. (DKMA)	The proposal does not comply with the requirements of Regulation 1394/2007, article 9.
4.2.1. Third paragraph, Section 3.2, page 7.	Editorial. Proposal: Amend to …. product for the stated intended purpose should be provided. (DKMA)	The amendment is not considered necessary, as the intended purpose of a product is usually stated by the company.
4.2.1	Quality criteria of cells from primary origin Proposal: would be possible to specify the different problematicity of the autologous or allogeneic usage? (F Fagioli)	Due to the variety of the products it is impossible to create requirements that fit all CBMPs. For certain autologous products it may be necessary to accept e.g. reduced release testing (one batch = product for one patient). This needs, however, to be justified.
p. 5 / 4.2.1 (3.1)	Proposal: ……..on the level and characteristics of…….(Dr Novelli)	The meaning of the comment is not clear.
Section 4.2.1, 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	The text is amended.

	assay to non-homogeneous populations during assay development, and to set acceptance criteria accordingly. At no point in the guidance is Cell count mentioned as a functional test/assay yet it is implied in many places as a necessary input data for other controls e.g. purity Proposal: Throughout the guideline several references toward 'release' criteria are mentioned. However, it is important to capture the characterisation of the cells at regular intervals prior to release (i.e., 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 *(EuropaBio) (Genzyme)*	Cell number is mentioned as one of the critical release assays, because it relates to the intended dose. Evaluation of cell number from the starting material and during the culture are important for the process, but cannot replace the final testing at release.
4.2.1 2: Other materials Para 3	Viral safety only refers to material of animal origin. As feeder cells could also be of human origin suggest to include both animal and human cells *(EuropaBio)* *Add specific reference to NTA 2B section 3.2.A.2 (Genzyme)*	Text is amended. However, the guideline on plasma-derived products, which is referred to, involves also viral safety aspects.
Section 4.2.1 subsection3. 2 Special considerations	Reference to articles 6, 7 and 10 ATMP Regulation is missing Proposal: Please add reference to articles 6, 7, and 10 of the ATMP Regulation (EuropaBio) (Genzyme)	A reference to the ATP regulation is made.
4.2.1 Starting and raw materials 1. Cells Last para	A population need not be in any case homogeneous, so it is proposed to delete this word. Proposal: 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 (EuropaBio) (Genzyme) (Tigenix)	The work “homogeneous” is replaced by “intended”.
4.2.1 Starting and raw materials 1.1 Cells from primary origin Para 2	We suggest keeping risk factors broad and do not name one specific as proposed in the guideline. Proposal: 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 appropriate testing should be performed. (EuropaBio) (Genzyme)	This risk factor is just an example to be considered.

4.2.1. Starting and raw materials 3.2Special recommendations for matrix/device/scaffold components of combination products	The guideline mentions that "*all structural components should be fully characterised and evaluated for their suitability for the intended use*". We agree with this statement and we would further suggest insisting on the characterisation of product requirements "for the intended use", e.g., combination, interaction with living cells, physical properties, degradation properties. We would like to mention that more information regarding the necessary studies to document the compatibility of the matrix/device/scaffold with the cells, for example degradation properties of the matrix might be different between the nude matrix and the matrix covered by cells would be useful to add to the guideline. Proposal: We believe there is a need for future guidelines on the necessary evaluations of compatibility / interactions between the cellular / tissue components and the matrix / device / scaffold. (EuropaBio) (Genzyme)	The proposal is acknowledged.
line 149 *4.2.1* 1. Cells	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. *If the cells are clearly defined by phenotype (for example microscopically), the genotype identification could not be necessary. The genotype identification is usually expensive and material-consuming, which could be a problem in case of a small-volume product.* *Proposal:* Identity should be verified by relevant genotypic **and/or** phenotypic markers and the proportion of cells bearing these identity markers evaluated as an indicator of a homogeneous population. *(B Kubesova)* (Riset) (BIA)	The text is amended as proposed.
Page 5, 4.2.1, paragraph Cells, 1st line	"The active substance of a CBMP can be defined as viable cells after manipulation"; it is important to mention that simple isolation of cells may be relevant here, which might not be considered not necessary included under "manipulation" (RB) Proposal: "The active substance of a CBMP can be defined as viable cells after ISOLATION AND/OR manipulation" (Riset)	According to Regulation 1394/2007 and Directive 2001/83, the cells in cell therapy and tissue engineering product must be engineered or manipulated. This is to make a clear distinction between medicinal products and cell/tissue transplants.
Page 5, 4.2.1, Cells, 1.1, line 6	"If it is necessary to pool cells from different donors, consideration should be given to the possibility that pooling of allogeneic cell populations may increase the risk of undesired immunological responses in the recipient and compromise its therapeutic activity." It might be worth adding that there is a risk that adding allogeneic cells together in a single product may result in an immunologic reaction of one against the other, which would be unpredictable from one preparation to another. (EG)	The text does cover the issue, amendment not considered necessary.

	Proposal: Add after this sentence: “ADDING ALLOGENEIC CELLS TOGETHER IN A SINGLE PRODUCT MAY RESULT IN AN IMMUNOLOGIC REACTION OF ONE CELL POPULATION AGAINST THE OTHER THAT WOULD BE HARDLY PREDICTABLE FROM ONE PREPARATION TO ANOTHER” (Riset)	
Page 5, 4.2.1, Cells, 1.1, line 14	(e.g. tumour tissues) , (suppress one space) (EG) Proposal: (e.g. tumour tissues), (Riset)	The error is corrected.
4.2.1. Page 6, section 2. Second paragraph, line 3	It might be helpful to give an example of a reagent that has sensitisation potential or to refer to a list of such reagents (EG, ACT) (Riset)	Included :e.g. β-lactam antibiotics
4.2.1. Page 7, section 3, 3.1, line 3	Consider adding a sentence noting that genetically altered cells from several lots should be tested for oncogenic potential in an experimental model. This is naturally of primary concern with these types of genetically altered cell products, and it seems, must be tested. In general, this was dealt with somewhat in other section of the guidelines (notably clinical safety, P. 22), but seemed a bit underemphasized and remains one major concerns with cell therapy, especially where cells are expanded in vitro. (EG) Proposal: Add: “GENETICALLY ALTERED CELLS FROM SEVERAL LOTS SHOULD BE TESTED FOR ONCOGENIC POTENTIAL IN AN EXPERIMENTAL MODEL” (Riset)	The guidance of GM cells does not go into details, as there will be a specific guideline for them.
Line 101, Section 4.2.1 1, Cells	Change to: "Cells based upon a cell bank system, characterized according to ICH guideline Q5D, and consisting of a master cell bank and a working cell bank, where possible.”	The text is amended.
Line 104, Section 4.2.1 1, Cells	Current wording: “The cells should be stored under controlled and optimal conditions, to ensure cell viability, density…….” Rationale: “Optimal conditions” may be ill defined, and may be different for cell viability than for density, etc. Proposed wording: “The cells should be stored under controlled conditions, to ensure cell viability, density …….”	The text is amended in a different way.
Line 106,	Current wording: “Identity should be verified by relevant genotypic and phenotypic markers	The text is amended according to another

Section 4.2.1 1, Cells	and the proportion of cells bearing these identity markers evaluated as an indicator of a homogeneous population." Rationale: Similar genotypic or phenotypic markers may not necessarily imply a homogenous population of cells. Proposed wording: "Identity should be verified by relevant genotypic and phenotypic markers and the proportion of cells bearing these identity markers."	proposal.
Line 119, Section 4.2.1 1.1, Cells from primary origin	Remove "validated" from assays (PhRMA)	Test that are used to detect adventitious agents in the starting materials need to be validated in order to demonstrate their reliability for this purpose.
Line 137, Section 4.2.1 2, Other materials and reagents	It is not clear what is meant by "absence of contaminating agents" that is not conveyed by the immediately preceding term, "sterility". Proposal: It is suggested that "absence of contaminating agents" is redundant and can be eliminated (PhRMA)	The text is changed.
P5 4.2.1. Para 1.1	We assume the" Virological screening programme" refers to the mentioned Dir2006/17, so that the type of viruses requested are clearly defined Impact of use of antibiotics (in harvest/procurement which cannot be guaranteed to be aseptic process) is not mentioned. For direct culture screening this might be a discussion point. Would appreciate further clarification. (Tigenix)	This virological screening program is for the cells, not for the donor. The text is amended.
P5 4.2.1. Para 1.1	Last sentence: "*in the case of autologous donation, the testing regimen of the starting material should be justified taking into account the autologous use*". Proposal: Would add that " **this justification is only needed in case the testing regimen is less stringent"**. (Tigenix)	The meaning of this point should be clear enough.
P5 Para 4.2.1 - Cells	No mentioning of genetically transformed or ex vivo treated cells (Tigenix)	The guidance of GM cells does not go into details, as there will be a specific guideline for them.
P7 4.2.1. Para 3.2	End of Par 1 and paras 2 and 3 are somewhat confusing and part redundant. It should be clarified what 'additional info' means versus 'suitability' versus 'full characterisation' versus 'chemical ' etc..description. It would be indicated to have one paragraph here clearly stating what is needed, that should be given.	Simple requirements that fit the whole diversity of different products are not possible. The text is, however, amended to correct redundancies.

	Also to bring in line with ATP regulation provisions now on the development and documentation requirements regarding the 'device' part or other in combination products. (as mentioned later in the text).Overall, it might be useful to limit here the data in the context of 'starting' material safety and performance and general suitability and to come with more extensive data in the Characterisation section 4.2.3. (Tigenix)	
Section 4.2.1	Add "sourcing" Proposal: Line 1 to 2 to be amended: "stringent sourcing requirement, purification steps…." (Zimmer)	The text is changed as proposed.
Section 4.2.2 1.3	In the context it would probably be better to refer to justification rather than validation of the number of passages. "Validation" is a concept more applicable to physical processes. Line 5 should read: "number of cell passages should be clearly specified <u>and justified</u>" (Eucomed)	A manufacturing process of a commercial medicinal product needs to be specified and validated.
Section 4.2.2 3 batch definition	The definition of "batch" for these products may need to be different from that applied by the current GMP and this is one aspect that would need to be considered for specific GMP for these products (Eucomed)	The point will be forwarded to the GMP drafting group for discussion. However, the batch for a CBMP has to be specified by the manufacturer.
Section 4.2.2 4 Container and closure system	Reference to Directive 93/42/EEC (as amended) is incorrect (The text suggests that the primary container for ATMP products may carry a CE marking. This would be confused with the whole product being controlled under the Medical devices Directives and therefore having the right for free distribution without further intervention) Third line change "Medicinal" into "Medical" (Eucomed), (BIA) (Zimmer)	The point is taken.
4.2.2. 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	Good suggestion to reorganize the paragraphs in order to have i) the process, ii) premises/equipment The point is taken.

	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." (BIO)	
4.2.2. 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."(BIO)	Same comments as above
4.2.2. 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."(BIO)	First line not understood Not taken : this paragraphs is a general introduction and type of method should not be addressed here (this is better addressed in section 4.2.3 characterization).
4.2.2. 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>." (BIO)	'Where feasible' is suggested in many places. Validation is a very large concept and is up to the manufacturer to determine the extend of the validation
4.2.2. Section 1.1	Medical procedure, so validation not possible.	This step comes after the procurement and this constitutes the first step of the process, therefore it

Line 2 Paragraph No: 1	We suggest replacing "validated" with "well controlled". (BIO), (EBE), (PhRMA)	is not a medical procedure. Concept of validation applies
4.2.2. Section 1.5.3 Paragraph No: 1	Batch definition: to provide language on date of manufacture (BIO) (EBE) (PhRMA)	The meaning of the comment is not clear.
4.2.2. Paragraph No: 2 Line: 1-2	The following wording is proposed, because the risk that potential contaminants of the donor (animal or human body) are carried over to the production area of the CBMP should be minimised. Proposal EBE: The manufacturing area should be physically separated from the procurement area where biological fluids, tissues, organs or specific cells are collected from animal or human body.	The point is taken.
4.2.2. Paragraph No: 3 Line: 1	What is critical is that the combination of the equipment and the premise needs to provide for aseptic production. This could be achieved by using equipment that is designed to achieve aseptic production in a premise that is not aseptic, by non-aseptic equipment (open) used in an aseptic environment or in an appropriate combination of both. Change to "Equipment and/or premises" (EBE) (PhRMA)	Not taken. Both equipment and premises need to be qualified. “Validated changed into qualified”
4.2.2. Paragraph No: 5 Line: 2	Add: "A risk analysis will be conducted on the process." (EBE), (PhRMA)	Not taken. Risk analysis already covered elsewhere in the document.
4.2.2 Manufacturing process Page 7/8	It may not always be possible to sanitise entire pieces of equipment. However, cleaning of contact surfaces should be acceptable. We suggest editing para 1, page 8 as follows: If the same equipment is used for production of e.g. multiple autologous products, sanitation and sterilisation procedures **of contact surfaces** should be described and validated. (BIA)	This detail is included in the old concept of GMP and does not need to be amended.
4.2.2. 1. Cell preparation	It is stated that monitoring of in vitro cell culturing should include tests for the absence of adventitious agents. It is worth noting that in vitro cell cultures are adequately monitored through visual inspection	Visual inspection of a cell culture would require advanced contamination to see e.g. bacteria by

procedures Page 8, para 5	of the cultures for adventitious agents such as bacteria or fungi in combination with adequate controls for starting materials and the environment / operators, thus minimising the risk of introducing contamination into the manufacturing process. Moreover, cells will often be cultured for limited periods and used to formulate the final product long before test results are available. Additionally, final products are tested for contamination as appropriate and extensive viral screening is performed on both donors and cell banks. We therefore believe that further testing during culturing is not necessary. Delete this sentence: Monitoring of in vitro cell culturing should include tests for the absence of adventitious agents, at selected stages of the production. (BIA)	eye. Furthermore, for some products conventional sterility testing may not be possible at release and microbial monitoring during culture is the only way to ensure microbial purity of such products.
4.2.2. 1.3 Cell culture Page 8	The term "cell line" should be clearly defined. Cell lines usually refer to continuous / immortal cell lines such as HELA cells. Cells used to manufacture cell-based medicinal products will often be mortal cells derived from a single piece of tissue. These are often described as cell strains. (BIA)	Reference added to ICHQ5D
4.2.2 Manufacturing process Third Para	A distinction between established production processes and processes for the production of investigational medicional products shoud be made in accordance with Annex 13 of the EU GMP Guideline. Therefore the following insertion is suggested: Proposal: … whenever possible. **Production processes for investigational medicinal products are not expected to be validated to the extent necessary for routine production but premises and equipment are expected to be validated** (cited, from EU-GMP Guideline, Annex 13). Therefore manufacturing processes of ATMP as an IMP for clinical trials are not covered by this guideline (also see. 4.2.2. Manufacturing process). (BPI) (EuropaBio) (Tigenix) (Genzyme)	Already in the scope. This guideline is directed to products entering the MA procedure.
4.2.2 Manufacturing process Cell preparation	As a risk analysis is imperative for the production of human cell – based medicinal products which specifies the risks and the appropriate controls, the sentence is considered to be unclear and should therefore be deleted. Proposal: **To be deleted: "Inappropriate handling and improper processing of cells/tissues must be avoided as they can impair or destroy the integrity and/or function of the cells and thus result in therapeutic failure. Microbiological control is a pivotal aspect of**	Deletion not accepted. The message given in the sentence is valid.

procedures First Para	**process control and quality evaluation of all cell preparations. Monitoring of in vitro cell culturing should include tests for the absence of adventitious agents, at selected stages of the production. The culture should be examined for any microbial contamination in accordance with the culturing procedure and growth characteristics of the cells." (BPI)**	
4.2.2 Manufacturing process 2. In-process controls	See above, 4.2.1.; the term "homogeneity of the" should be deleted. Proposal: process and the ~~**homogeneity of the**~~ final product (BPI)	"Homogeneity" to be replaced by "consistency"
4.2.2, first paragraph, page 7.	Amend the text. Proposal: Change to … The consistency requirements should be defined and justified. (DKMA)	Sentence in the text to be reworded : ~~The consistency~~ Requirements should be defined
4.2.2. Second line, Section 4, page 9.	The present text implies the container systems are medical devices, whereas this may not be the case if they do not fulfil a medical purpose and the definition of a medical device. Proposal: Delete the second sentence and replace by ….. the final container for the finished product shall be suited for its intended purpose. (DKMA)	Not taken. The text requires information whether the container closure system has a CE mark, but does not anticipate that all containers / closures are medical devices.
4.2.2 (1.4)	Information of eventual epigenetic modifications should be addressed, if available. (Dr Novelli)	The message of the comment is not understood.
Page 8, 4.2.2, 1.3, line 1	"consideration should be given to ensure optimal growth and manipulation of the isolated cells." Give some details in addition and consider an alternative expression as "optimal" sounds OK for "growth" but a bit stranger for "manipulation"; consider another adjective: adequate, or appropriate (RB, ACT) Proposal: "consideration should be given to ensure optimal growth and VIABILITY AND CARRY OUT ADEQUATE manipulation of the isolated cells" (RISET)	Amended according to another suggestion.
Page 8, 4.2.2, 1.3, line 5-6	"The relevant genotypic and phenotypic traits of the primary cell cultures"; add OR (RB) Proposal: Change "genotypic and phenotypic" INTO "genotypic AND/OR phenotypic". (RISET)	Accepted
Page 9, 4.2.2, 2,	"The manufacturing process needs to be controlled by several in-process controls at the level of critical steps or intermediate products." If primary cells are used as raw material for the manufacturing process, material for several in-process controls may often not be available. Therefore, to obtain the minimal	Not taken. The extent of all quality controls (IPCs, release tests etc.) should be defined and justified by the manufacturer. However, it is difficult to see cell culture procedures without any in-process

	effective dose for the treatment, in-process controls may be reduced to a minimum. So the intermediate products should be tested only if appropriate. (FF, RB). See also general comments. Proposal: "The manufacturing process needs to be controlled by several in-process controls at the level of critical steps or intermediate products, IF APPROPRIATE (OR UNLESS JUSTIFIED)." (RISET)	controls (pH of the medium, viability, cell number etc.) to monitor appropriate quality of the product prior to release.
Line 249, Section 4.2.2.1.3, Cell culture	Current wording: "During in vitro cell culture, consideration should be given to ensure optimal growth and manipulation of the isolated cells." Rationale: Optimal is not defined, so the growth and manipulation should be within the manufacturer's specifications. Proposed wording: "During in vitro cell culture, consideration should be given to ensure acceptable growth and manipulation of the isolated cells." (PhRMA)	To be taken
P7 Para 422	Not clear what consistency specifications are. (later in text : acceptance criteria and also data that will allow to set release specs are mentioned) (Tigenix)	Comment above
P8 4.2.2. Para 1.1	Delete last phrase, redundant with raw/starting material section Proposal: Should be part of 4.2.1 (Tigenix)	The point is taken.
P8 4.2.2. Para 1.2	Purification Proposal: *Modify text :* **If applicable**, any procedure….(Tigenix)	Not taken. Where such procedures are applied, they should be described and validated.
Section 4.2.3 Characterization	Last paragraph: this section could usefully be expanded to include examples as without this is difficult to interpret the statement. (Eucomed) (Zimmer)	(e.g. growth factors, cytokines etc.) included.
Section 4.2.3 1.1, second paragraph	Provision should be made for applicants to justify their approach (Eucomed)	Text is amended.
Section 4.2.3 4 Potency	"Must" is not appropriate for use in a guidance Fourth paragraph: replace "must" with "may" (Eucomed) (Zimmer)	Text amended.
Section 4.2.3 5	We would welcome a clarification on the term Karyology (not defined in the text) (Eucomed)	The term karyology is replace by Chromosal integrity.

Tumorigenicity		
Section 4.2.3	Viability should be included. (BIO)	Included.
4.2.3. 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. (BIO) (EBE)	The point is one of issues that should be taken into account when considering the amount of characterisation studies needed for a given product.
4.2.3. 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>." (BIO) (EBE)	Accepted.
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"(BIO)	Not taken; the issues are not divided according the proposal.
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." (BIO)	Accepted.
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." (BIO)	Not taken. Viable cells hardly can be "sterile".
Section	In vivo potency as a requirement will <u>only</u> be feasible in a select group of cells and thus for the	This is recognised by the text: In vivo assays for

4.2.3.4 Potency	majority of CBMP will not be required. In the case of autologous cells the human microenvironment will behave much differently than the animal. (BIO) (EBE) (EuropaBio)	potency may also be useful…
Section 4.2.3.4 Potency Line 2 Paragraph No. 3	Move up to flow better Proposal: … 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. (BIO)	The point is taken.
Section 4.2.3.5 Tumorigenicity Paragraph No. 1	Clarification, reference risk analysis Proposal: 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. (BIO)	Amended to: 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. If the risk of cellular transformation and subsequent potential for tumourigenicity can be foreseen, the cellular components should be evaluated for their tumourigenic potential by analysing e.g. proliferative capacity, dependence on the exogenous stimuli, response to apoptosis stimuli and genomic modification.
4.2.3.2 Paragraph No: 4 Line: 1	Delete "Irrespective to cell type" and change "the cell population can be" to "the cell population will contain" (EBE) (PhRMA)	Too definitive, not taken.
4.2.3 §3.2 Paragraph No: 1 Line: 7	Due to a short shelf-life of a CBMP the 14 day sterility test described in the Ph. Eur. may not be applicable. Proposal EBE: In cases where the short shelf life of the CBMP is prohibitive for the testing of absence of bacteria under the Eur Ph. requirements, alternative shorter testing methods may be applied if validated. **(BPI)** . (EuropaBio) (Tigenix)	Text amended as follows: In cases where the short shelf life of the CBMP is prohibitive for the testing of absence of bacteria under the Eur Ph. requirements, alternative validated testing methods may be acceptable, if justified.
4.2.3.4	Potency: needs clarification of potency definition. The current language appears to be stricter than current practice for other products. Is an explanation of how potency linked to mechanism	Mode of action is not mentioned. The definition says: "potency is the quantitative measure of

Potency	of action required? (EBE) (PhRMA)	biological activity based on the attribute of the product, which is linked to the relevant biological properties"
4.2.3.4 Potency Paragraph No: 4 Line: 4	…and must be monitored *constantly* using surrogate markers… The word *constantly* should be removed. (EBE)	"constantly" changed into "during production and at release"
4.2.3. §4.1 Paragraph No: 1 Line: 3	It is unclear what attribute of cell number is to be validated. We believe that the desire is to understand the relationship between the cell number in the product and the cell number used in the potency assay (i.e., whether it is the same, or whether technical considerations require it to be different, but in any case, to understand whether it is the same number of cells or it has a constant and specified relationship to the number of cells in the product). Proposal EBE: Replacing "validated" with "specified" (PhRMA)	Accepted.
4.2.3. §4.1 Paragraph No: 1 Line: 3	There is ambiguity in the second clause "…and when possible…" in terms of whether it is intended to relate to "the potency assay " or the "number of cells" Proposal EBE: It is suspected that the former is implied, and suggest rephrasing to say: "…should be performed using a specified number of cells. When possible, the relative potency of the product should be quantified with respect to a qualified product reference preparation (PhRMA)	The sentence is changed into: The potency assay should be performed by using a specified number of cells and, when possible, quantified against a qualified reference preparation.
4.2.3. §4.1 Paragraph No: 1 Line: 6	"An *in vitro* assay" is the most realistic approach. Proposal EBE: It should be listed first in this section (4.2.3.4.1) (PhRMA)	The text acknowledges the in vitro assays already: An *in vitro* assay can be based on the expression of markers that have been demonstrated to be directly or indirectly (surrogate markers) correlated to the intended biological activity, such as cell surface markers, activation markers, expression pattern of specific genes.
4.2.3 §4.2 Paragraph No: 2 Line: 4	...This will be *easily* carried out by…' The word *easily* should be replaced. It is editorial rather than useful or accurate. Proposal EBE: ...This *might be* carried out by…	The point is taken.
4.2.3	It is stated that an extensive characterisation of the cellular component should be established in	Purity is addressed in sections 3. Cell purity and

Characterisation Page 9, para 8	terms of identity, purity, potency and suitability for the intended use, unless justified. Clear definition regarding the term purity is required. (BIA)	4. Impurities.
4.2.3 Characterisation Page 10, para 2	Characterisation of scaffolds by porosity, density, microscopic structure and particular size may not always be applicable or appropriate. Characterisation of other physical / mechanical properties such as tensile strength should be considered. We suggest rewording as follows: **Characterisation of scaffolds should be considered and assessed using suitable methods as defined on a case-by-case basis.** (BIA)	request is " by chemical and physical terms, such as… The list is not definitive.
4.2.3 1. Identity, 1.1Cellular component Page 10, para 8	Histocompatibility markers are not always relevant for cells of allogeneic origin. This should be assessed on a case-by-case basis. We suggest revising as follows: For cellular components of allogeneic origin, identity should include histocompatibility markers **where applicable**. (BIA) (FF, ACT). (RISET) (PhRMA)	Accepted.
4.2.3. 1.2 Non-cellular component Page 10, para 9	It may not be appropriate or necessary to fully characterise non-cellular components. This should be assessed on a case by case basis. We suggest editing as follows: All non-cellular components should be **appropriately** characterised. (BIA)	Accepted.
4.2.3. 4. Potency Page 11, last para	It may not be possible to choose a suitable potency assay at this stage of product development Given the complexity of products to which this guideline is addressed, the possibility of utilising more than one assay to determine potency should be recognised. A combination of methods may be needed to adequately define the potency / clinical effect of these products on a routine basis. (BIA) (Tigenix) (Zimmer)	The text is amended to include the idea of multiple potency assays during the development.
4.2.3. 4. Potency Page 12, para 2	Clarification is required as to what is meant by constant monitoring of cellular functions. It should be noted that constant monitoring may not be appropriate or necessary. Enforcement of such a requirement will be very restrictive to the development and marketing of many cell-based products, resulting in high costs and potentially decreasing the availability of such products.	The text is amended.

	We suggest revising as follows: Major cellular functions as …**should be monitored** … (BIA)	
4.2.3 4.1. Tissue repair and regeneration Page 12, para 4	We do not believe that *in vivo* tests would provide a suitable system for testing the final product. While animal models may be useful during the development of products, short product expiry periods compared to lengthy tests means that *in vivo* tests are not a suitable way forward. Suitable surrogate markers or demonstration of cells viability provide suitable means of testing product potency. Additionally, testing potency *in vivo* does not necessarily provide a representative assessment of potency, even if the mechanism of action is well established and specific markers identified, because the same product may behave differently in human vs. animal recipients. (BIA)	The point is taken.
4.2.3. 5. Tumourigenicity Page 12/13	It is stated that the tumourigenic potential of the cellular components should be evaluated by analysing proliferative capacity, dependence on the exogenous stimuli, response to apoptosis and genomic modification. We believe that the tumourigenic potential of the cellular components is adequately assessed by tumourigenicity and karyology testing as per cell banks (ICH Q5D) if performed at the level of EOP. EOP cells are defined as cells expanded using the relevant manufacturing process and 1-2 passages beyond that used in the final product. When cells are grown in culture, it is not uncommon to observe changes in the levels of chromosomal abnormalities. However, these changes are not symptomatic of transformation or tumourigenic potential as demonstrated by the tumourigenicity test. Delete: e.g. proliferative capacity, dependence on exogenous stimuli, response to apoptosis stimuli and genomic modification. (BIA)	Not accepted. This issue involves also short term culture of primary cells, e.g. autologous stem cells modified and cultured for longer periods. ICHQ5D is relevant, but is written for cell culture for production of recombinant proteins and these cells are not to be administered into the patient.
4.2.3 Characterisation Last para	It is not necessary to give all possible information but to give all necessary information. Proposal: If biologically active molecules are present as components of the cell-based products, these have to be described ~~**fully**~~ **adequately** and their interaction with the other components of the product and the surrounding tissues after administration should be characterised (BPI) (EuropaBio) (Genzyme)	The word is changed.
4.2.3 Characterisation	The original sentence makes no sense for example in case of mixed cell-type populations this request is not possible. Proposal: The first sentence should read as follows:	Text amended “and/or”

1 Identity 1.1. Cellular component First sentence	The identity of the cellular components, depending on the cell population and origin, should be characterised **by appropriate methods, i.e.** phenotypic **or** genotypic **profiles. (BPI)** (RISET) (ACT)	
4.2.3 Characterisation 1 Identitiy 1.2 Non cellular components	It should be made clear in the headline that this chapter is about non-cellular components in the part of the product acting as "active substance". It is for example not always possible to give a full characterisation of the medium in which the ready-to-use product is transported. Without this clarification in the headline it could be interpreted that also full information are necessary e. g. about the transport media. Proposal: The Headline should read as follows: Non-Cellular components **of the active substance. (BPI)**	Text amended.
4.2.3 Characterisation 5 Tumorgenicity	In this chapter there is made reference to ICH Q5D that clearly shows that the intention is to cover cell lines that are stored in cell banks and multiplied very often. This means that for those cells having a high number of passages the requirements may be useful. In case of autologous cells which are not stored an had only few passages because the cells are only used for the production of one product the requirement to test karyology and tumorgenicity is not necessary and should hence be limited to exceptional cases on justified reasons. Proposal: At the end of this chapter the following sentence should be added: **In case of autologous cell transplants no general testing of karyology and tumorigenicity is required except on justified reasons. (BPI)** (Tigenix)	Not accepted. This issue is important also for primary cells e.g. stem cells that are modified and cultured for longer periods.
4.2.3. First line, second paragraph, 1.2, page 10.	An illustrative example of a distinct active substance would be helpful here. Proposal: Amend as required. (DKMA)	This is clarified in revised Annex I of Dir.2001/83 and should be clear for tissue engineered products
4.2.3. 3.1, page 11	Some additional text on the potential impurities that might result from the interaction between cells and a medical device would be useful here. Proposal: Amend as required. (DKMA)	Not taken. The text includes all materials capable to introduce impurities to the final product.
4.2.3 §5 tumourigenicity, page 12 and	Reposition this text to after "other toxicity studies" on page 20. Proposal: Amend as suggested. (DKMA)	Not taken. These requirements are related to the quality of the product (module 3), whereas toxicity studies are part of non-clinical studies

13		(module 4).
14 + 4.2.3 (4)	Proposal: ……. Q-PCR; RT-PCR and many others (Dr Novelli)	Not taken. Not clear what the comment is referring to.
4.2.3, 2, page 11, line 2	"The cellular population of interest could contain other cells that are of different lineages or differentiation stage from the required population or with cells unrelated to the intended population." (ACT) Proposal: "The cellular population of interest could contain other cells that are of different lineages or differentiation stage from the required population or ~~with~~ cells unrelated to the intended population." (RISET)	The text is changed, see above.
4.2.3, 2, page 11, line 2	In the above sentence and the following one (lines 3-5), it is unclear whether the meaning is that where multiple cell types are present, the relative number of specific cell types need always to be kept within certain limits or just need to be documented. In other words, details should be given on the circumstances where it just needed to document what the proportions are, and those where they should it be held within certain determined limits (EG) (RISET)	Where several cell types are needed for the intended purpose, their proportion in the mixture needs to be specified and evaluated batchwise in order to demonstrate batch consistency.
4.2.3, 3.2, page 11	The stability of the CBMP may be limited and the storing of the finished product until the absence of adventitious agents at the level of the finished product has been tested, could reduce the quality and functionality of the CBMP. Instead, parametric release may be required as an operational alternative. (FF). Consider adding a sentence at the end of this section. The guideline might consider the situation where the product is autologous and the patient is infected with the particular agent (EG). Consider adding a sentence at the end of this section; The last line of 3.2 seems weak: "Although CBMP are excluded from the scope of the ICH Q5A Guideline on Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Product Derived From Cell Lines in of human or animal origin[20], applicants may consult this guideline." Consider recommending it strongly when appropriate. (ACT) Proposal: Although CBMP are excluded from the scope of the ICH Q5A Guideline on Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Product Derived From Cell Lines in of human or animal origin[20], IT IS STRONGLY RECOMMENDED TO APPLICANTS TO CONSULT THIS GUIDELINE, WHEN APPROPRIATE." (RISET)	Not taken. The requested information and reference are already included.
4.2.3, 4., page 12, line 1	"Lot release and shelf life specifications for potency should be determined and amended during product development, as appropriate." Shelf life specifications may not be appropriate in a number of cases. (RB) Proposal: "Lot release and shelf life specifications for potency should be determined and amended during product development, ~~as~~ IF appropriate." (RISET)	Not taken. The proposed change does not provide any improvement to the text.
4.2.3, 5.,	Tumourigenicity.	Highlighted more in preclinical section, but

page 12 - 13	This is an important aspect of cellular therapy that is not overly emphasized in this document, although it is mentioned page 20, under "Other toxicity studies". Perhaps mention here that testing should be performed, or is recommended, to demonstrate lack of tumourigenicity, in experimental animal models. (EG) (RISET)	reference is made to ICHQ5D.
Line 295, Section 4.2.3, Characterisation	Current wording: "An extensive characterisation of the cellular component should be established in terms of identity, purity, potency and suitability for the intended use, unless justified." Rationale: It is unclear upon which marker purity would be determined. Rather, the composition should be specified by the manufacturer. Proposed wording: "An extensive characterisation of the cellular component should be established in terms of identity, composition, potency and suitability for the intended use, unless justified." (PhRMA)	Composition does not fully reflect what is meant by purity. Not taken.
Line 302, Section 4.2.3, Characterisation	Current wording: "Therefore, when considering the extent of characterisation, the following issues should be taken into account: i) autologous cells vs. allogeneic cells, ii) extensively or minimally manipulated in vitro, iii) immunologically active or neutral, iv) proliferative capacity of the cells, v) celllike or tissue-like organisation and dynamic interactions amongst cells and with the structural component, vi) intended use." Rationale: The definition of immunologically "active" or "neutral" is not clear. This should be substituted with "immunogenicity" which can be proposed by the manufacturer. Proposed wording: "Therefore, when considering the extent of characterisation, the following issues should be taken into account: i) autologous cells vs. allogeneic cells, ii) extensively or minimally manipulated in vitro, iii) immunogenicity, iv) proliferative capacity of the cells, v) cell-like or tissue-like organisation and dynamic interactions amongst cells and with the structural component, vi) intended use." (PhRMA)	Not taken. Immunologically active / neutral implies to the status of the cells at release.
Line 348, Section 4.2.3.2 Cell purity	Current wording: "Where a specific cell type is required for the indication, the unwanted cells should be defined and their amount in the final product should be controlled by appropriate specifications, i.e. acceptance criteria for the amounts of contaminating cells should be set." Rationale: It may be impossible to define all "unwanted" cells. It appears more prudent to identify the cells present that are alternative to the specific cell required. Proposed wording: "Where a specific cell type is required for the indication, the alternative cells present and their amount in the final product should be controlled by appropriate specifications, i.e. acceptance criteria for the amounts of contaminating cells should be set." (PhRMA)	Text amended, see comment above.
Line 402, Section 4.2.3.4.1,	Given the problems with animal models in general, even if it works, what does an *in-vivo* test prove? (PhRMA)	See comment above.

Tissue repair and regeneration		
P9 Para 4.2.3	The different paragraphs of this section need to be reshuffled, as they do not convey a clear and logical message. 1 Convey message to what these characterization studies aim for (process / product understanding and allowing to set release specs). 2. Acknowledge specifics and difficulties for these type of products 3. Clarify what is needed for the individual components and what for the combined, final product. (Tigenix)	Definitive answers for all product types cannot be foreseen, the knowledge comes case-by-case from the product and its characteristics.
P10 4.2.3. Para 1.1	The original sentence makes no sense for example in case of mixed cell-type populations this request is not possible. Proposal *Modify first sentence :* The identity of the cellular components, depending on the cell population and origin, should be characterised **by appropriate methods, i.e.** phenotypic **or** genotypic **profiles.** (Tigenix)	The text is changed.
P10 4.2.3. Para 1.1	"Where applicable "…section : this can be very complex . Proposal: Propose to add terminology as : 'feasibility and relevance'. (Tigenix)	The sentence starts "Where applicable", which is feasibility.
P11 Para 3.1	Thorough characterisation of (bio)degradation products might be very difficult as products might be extremely diverse and degradation profiles dependent on stage and timing of administration. Proposal: Prefer to introduce language : '**in case of biological products such characterisation may be more restricted'.** (Tigenix)	Not taken. Degradation properties of biological products (e.g.collagen) should be possible to study.
P11 Para 3.2	Cryptic agents is extremely difficult to assess (e.g. the retrovirus reactivation). Proposal: Propose to loosen the requirement in case of autologous products. (Tigenix)	Autologous products are already recognised in chapters 4.1.and 4.2.1.1.

P11 Para 3.2	last sentence: '*although excluded from the scope … applicants may consult this guideline*' leaves a lot of interpretation on necessity to the evaluator. Proposal: Recommendation to leave this statement out. (Tigenix)	Not taken. The text says: ..may be consulted by the applicant. This guideline may provide useful information for the applicants, but is not the basis for evaluation of a cell-based product.
P12 4.2.3. Para 4.1Tissue repair and regeneration	Because of species specificity or immunological incompatibility of the cells functional animal models may not provide any relevant information To be relevant manufacturers need to assure that the method of manufacture and characterisation of cells used in animal studies is relevant to the human cells. Qualified references might be difficult for autologous products as they are all in a kind unique (also the case for animal models) End of paragraph: physiological response under defined conditions can be used as a potency measure : research already demonstrates that e.g. differentiation of cells in vitro , does not mean these same cells do the same job in-vivo and as such the physiological response under defined conditions does not mean a potency outcome in vivo. This is very loose unless some quantitative parameter is associated with the response. Proposal: Propose to add : Manufacturers should also ensure that the method of characterisation is relevant for the intended biological effect **in vivo**. (Tigenix)	The issue is acknowledged in the text. Therefore the text includes "when possible" The point is taken.
Section 4.2.4 1 Release criteria	Second paragraph, first sentence: possible deviations from the list of test types should be permitted where justified (Eucomed)	Included "unless otherwise justified".
4.2.4. 2. Stability testing Page 13	Clarification is required as to what is meant by intermediate, components of the combined CBMP, active substance and finished product. (BIA)	In the introduction of 4.2. and in the 4.2.2. manufacturing process there is clarification on the difficulties to establish clear cut definitions in such a diverse field. Further clarification deemed unnecessary.
4.2.4. 2. Stability testing Page 14	It may not be appropriate to test the stability of both the cellular and non-cellular components of a CBMP independently. Requirements for stability should be defined on a case-by-case basis and appropriate assessment should be conducted accordingly. (BIA) (Tigenix) (EBE)	*"Due to the complex nature of the active substance of a CBMP, stability must be assessed for both the cellular as well as the non-cellular component separately and together as a finished product in the final packaging, whenever*

		possible." Replaced by: "Due to the complex nature of CBMPs, requirements for stability should be defined on a case-by-case basis. Whenever possible, stability should be assessed for both the cellular as well as the non-cellular component prior to combination and together as a finished product in the final packaging."
4.2.4. Paragraph No: 2 Line: 1	Add to "methods validated" "when possible" (EBE) (PhRMA)	Not accepted. The suitability of the tests for the intended purpose should always be demonstrated.
4.2.4.4. Paragraph No: Line:	Reference to AT regulation and Medical Devices Directive are missing.(EBE)	Reference to the AT regulation is now included in 3. Legal basis. The regulation establishes the cross reference to the medical devices directive in the proper context. No need to repeat here.
4.2.4 Quality control 1. Release criteria Second para	The wording of "purity" and "impurities" does not very well fit in this context as it is not possible to have cell preparations that are "pure" as they always consist of very complex compounds, the wording "composition" would fit much better. In case of autologous chondrocytes for example, it is impossible to determine the "purity" as there are no scientifically recognized surface markers available which are specific for this cell-type. Specifications for release testing should include identity, ~~**purity, impurities,**~~ **composition,** sterility, potency, cell viability and total cell number. (BPI)	Not accepted. Purity is defined in the text 2.4.2. Characterisation. In the Pharmacopoeia, as for other substances for pharmaceutical use, the purity and product related impurities should always be defined and quantified. For genetically modified cells there is no requirement for purity recommended in the general text regarding gene therapy products (only identity, counting and viability) while for haematopoietic stem cells there is a requirement for purity without further definition. Purity does not mean strictly that the product is pure as in well characterised substances. In heterogeneous preparations it is even more relevant to define,

		within feasibility, the parts present in the mixture. The purity shall represent a given distribution of those parts in the mixture. The same applies to impurities.
4.2.4 Quality control 2. Stability testing First para	Only in cases where the intermediates are existing for a longer time due to interruptions in the production process such a testing would be justified, it should not be necessary in any case, so the wording "if applicable" should be added. Proposal: A shelf life for the cells under specified storage conditions shall be determined for the following materials: i) all intermediates **if applicable**, ii) components of the combined CBMP, iii) the active substance, iv) the finished product. Furthermore, a valid in-use shelf life (after opening from the transport container) should be assigned to the CBMP. (BPI) (Tigenix)	"if applicable"already in the text. Clarification: A shelf life for the cells under specified storage conditions shall be determined in the following materials: Replaced: "i) all intermediates, **if applicable"** with**:** **"**all intermediates subject to storage, **if applicable"**
4.2.4 Quality control 3. Special quality requirements for cell therapy products containing cells modified by gene therapy	There has to be made a distinction between clonal and non-clonal products in terms of testing, expression, genetic stability and copy number. In the case of non-clonal products often consisting of some million cells with different individual genetic modification "copy number" should be understood as "average copy number" and "expression" as "average expression". Information about genetic stability and integrity of non-clonal products has to be established in preclinical testings. Proposal: This should include characterisation of the vector used to modify the cells, a description of the modification, and quality control tests on the modified cells that address issues pertaining to the transfected gene(s) of interest, such as integrity, expression, genetic stability and copy number. **In case of non-clonal products the average copy number and the average expression has to be established.** A suitable assay that addresses the newly acquired biological function following transfection should be established and carried out. (BPI) (EuropaBio) (Genzyme)	The requirements related with genetic modification should follow guidance for gene therapy. Therefore, the following amendements are performed: In the SCOPE it is included the following sentence: Genetically modified cells regardless of their intended use are considered gene therapy medicinal products. The present document applies only to the cellular counterpart of those cell based gene therapy medicinal products. In 4.2.4. : **3. Special quality requirements for** cell based gene therapy medicinal products If cells have been genetically modified, quality control must be performed in compliance with guidance available on gene transfer medicinal products[15]. This information is in addition to

		control of the cells according to the guidance presented elsewhere
4.2.4Quality Control 1. Release criteria	Batch release Further guidance should be provided, in our view, regarding batch release arrangements, in particular for companies located outside the European Economic Area. Indeed, while it is feasible to repeat batch release tests for conventional medicinal products imported in the EEA, this is often not feasible due to the short shelf life of many ATMPs, and also not financially viable due to the size of batches. Consideration and guidance should be sought on alternatives in the case of small size ATMP batches (e.g., adaptation of parametric release, paper release through Qualified Person while products are sent directly to the patient). Proposal: We request EMEA to publish guidance documents for batch release of CBMP (EuropaBio) (Genzyme)	Directive 2001/83/EC art. 51 requires full qualitative analysis and at least quantitative analysis of the active substance when from importation from 3rd countries. Further guidance should be provided by the Commission.
4.2.4, 2., page 13-14	Stability study: this paragraph is not completely clear. For cell preparation, preservation of the same phenotypic or biological characteristic should be proved IN FRESH versus THAWED cells, but not real stability may be necessary. Proposal: Please add IF APPROPRIATE, after "period of validity" in line 7 of the last paragraph p. 13. (RISET)	Sentence revised for clarification: Furthermore, a valid in-use shelf life (after opening from the transport container) should be assigned to the CBMP. Also, all storage conditions including temperature range should be defined. Transportation and storage conditions should be supported by experimental data with regard to the maintenance of cell integrity and product stability during the defined period of validity.
P13 Para 424	Broaden Proposal: …performed at the other or by process validation and control (Tigenix)	Exceptions are already considered further down under release criteria : "In these cases an adequate quality control has to rise from the manufacturing process, supported by the results of the clinical studies.
P13 4.2.4. Para 1	The wording "impurities" does not very well fit in this context as it is not possible to have cell preparations that are "pure" as they always consist of very complex compounds, the wording "composition" would fit much better. Mention also that certain tests could be combined like potency, cell viability, cell nrs, especially if sampling is an issue. Proposal: Specifications for release testing should include identity, purity, ~~**impurities,**~~ **composition,** sterility, potency, cell viability and total cell number. Add that : **certain tests may be combined like in view of cases where sampling is an issue.**	Conditions for release of products that are produced in limited amount are already defined in 3rd bullet under Release Criteria.

	(Tigenix)	
P14 4.2.4. Para 4	"Relevant impurities" should be specified as those having an impact on safety or efficacy of the product (Tigenix)	Impurities are defined in 4.2.3.
Section 4.2.5 2. Non-cellular components Line 2 Paragraph No. 2	"affect" should read "effect" (BIO)	Corrected in the present text
4.2.5.	Change title of section Proposal EBE: Control of the manufacturing process	Process validation is the terminology acknowledeged by the pharmaceutical community and is used in quality and GMP guidance and should be kept.
4.2.5. Paragraph No: 1 Line: 3	Proposal EBE: "should be controlled, and validated as possible."	Process validation is the terminology acknowledeged by the pharmaceutical community and is used in quality and GMP guidance and should be kept.
4.2.5. Paragraph No: 2 Line: 2	Proposal EBE: "is well controlled, and validated as possible."	Comment above
4.2.5. Paragraph No: 2 Line: 4	Delete …"in the validation" (EBE) (PhRMA)	Deletion not accepted. See comment above.
4.2.5. Paragraph No: 2	Replace "critical points" with "process parameters" (EBE) (PhRMA)	Not taken. The applicants should define and validate the critical points of the process, not only process parameters.

Line: 5		
4.2.5. Paragraph No: 3 Line: 2	Replace “validated” with “justified” (EBE)(PhRMA)	Not taken. See comment above.
4.2.5. Paragraph No: 4 Line: 4	The question is if the manufacturing process is even a validation as the relationship to the process is, at best, a model. This paragraph should be rewritten without the word validation used. (EBE) (PhRMA)	See comment above.
4.2.5 Validation of the manufacturing process Fourth para	The example within the brackets should be deleted; there are other examples possible where sample sizes are limited. To explicitly name autologous products for single administration may exclude others that are not explicitly named here. Apart from that also the limited availability of patient-derived materials would additionally be a reason to use cell preparations of comparable characteristics. Often the procurement of an adequate amount of cell material for validation purposes is not possible due to ethical reasons. In this case validation should be possible with material having comparable characteristics. The necessity of a “validation on a regular basis” should not apply in these cases, as the release testings would provide sufficient data of the validity of the manufacturing process. Hence the last sentence in bold should be added. Proposal: In case of limited sample sizes **or limited availability of patient-derived materials** ~~**(e.g. autologous preparations for one single administration)**~~, it is recommended that a more extensive validation is performed with cell preparations of comparable characteristics but available in sufficient amounts for validation purposes. It is recommended that validation of such manufacturing process is performed on a regular basis, depending on the product characteristics, for adventitious agents, identity, potency, viability, purity/impurities and other product specific parameters. **In case of patient derived materials validation on a regular basis is unnecessary if release testing provides sufficient data to prove the validity of the manufacturing process.** (BPI) (Tigenix)	Not taken. The sentence is general and the example represents the most probable situation. Release data is not enough to fully cover the need for validation.
4.2.5	validation of the manufacturing process Proposal: it would be useful to specify how to collect validation data and how perform the	Not taken. Specific guidance can be found from GMP guideline and its annexes and from CHMP

	validation plan (F Fagioli)	guidelines CPMP/QWP/848/96 and CPMP/QWP/2054/03
4.2.5, first paragraph, line 3, page 14	The following sentences are unclear and/or badly constructed: "Combined CBMP can either correspond to a combination of active substances forming a final product, or in some cases, the supportive structures can be considered as excipients or devices, or a mixed situation. In any case, the combination should be consistently produced." (ACT) Proposal: "Combined CBMP can ~~either~~ correspond to a combination of active substances forming a final product, or in some cases, the supportive structures can be considered THEMSELVES as excipients or devices, or a mixed situation CAN BE ENCOUNTERED. In any case, the combination LEADING TO THE FINAL PRODUCT should be ~~consistently~~ produced ACCORDING TO CONSISTENT AND WELL DEFINED SPECIFICATIONS." (RISET)	The text is changed into: Validation of the production process of a combined product should encompass all steps from separate components up to the final combination to ensure consistent production.
4.2.5, second paragraph page14, last line,	Typographic errors: at the end of this second paragraph that there are two periods. There should be a comma between materials and their Proposal: "critical points of the manufacturing process should be defined." (RISET)	The point is taken.
Line 503, Section 4.2.5, Validation of the manufacturing process	Control of the manufacturing process –(PhRMA)	Comment above.
Line 506, Section 4.2.5, Validation of the manuf	"should be controlled, and validated as possible." (PhRMA)	Comment above

process		
Line 511, Section 4.2.5, Validation of the manuf process	"is well controlled, and validated as possible." (PhRMA)	Comment above
P14 Para 4.2.5	1.Validation is a very broad term. 2.The entire manufacturing process should be validated…including transport conditions ie. Both upstream and downstream the final product. Until the product is implanted in the patient. Proposal: 1.Please refer to existing references to explain what this precisely means. 2.Please add to text : ….filling, packaging, **transport, storage**…should be validated (Tigenix)	See comment above. The proposal is accepted.
Section 4.2.6 2	Absence of toxic response to be reworded as "confirmation that the substrate does not interfere with cell growth" (Eucomed)	Suggestion not accepted. The interference might be also in the performance in terms of the intended use. This is already reflected in the initial part of this paragraph. Reworded : - absence of components or leachables that might be toxic to cell growth and/or intended performance. See below.
4.2.6.2. Complete section Page 15	The guideline should provide clearer guidance on non-cellular and structural components. As outlined in the introductory section additional to cellular components the CBMP may contain three types of other components such as non-cellular components, structural components and medical devices. It is proposed to describe in section 2. "Non-Cellular Components" all aspects referring to non-cellular components and structural components. For medical devices, which have to be assessed by a Notified Body, it is proposed to describe	In this rapidly evolving field it is necessary to avoid being prescriptive. The text as it stands gives sufficient guidance for development. As stated in the ATP Regulation, products containing medical devices shall include a description of the physical characteristics and

	all aspects to be considered in a separate section or subsection. (EBE)	performance of the product and a description of the product design methods, in accordance with Annex I to Directive 2001/83/EC. Therefore, the information on the device itself as assessed by the notified body is only part of the information required to be described in relation to development and assessed.
4.2.6.2. Paragraph No: 6 Line: 2	A discussion of the structural and functional characteristics of the non-cellular components is not feasible for every component. It is proposed to consider this possibility in the guideline. Proposal EBE: ….of the non-cellular components of a combination product should be provided <u>wherever feasible.</u>	In previous paragraph it is stated that "The evaluation of individual non-cellular components is required although aspects of this evaluation may be incorporated into studies designed to assess the product as a whole." Nevertheless, the text is revised as: A discussion of the structural and functional characteristics of the non-cellular components in a combination product should be provided
4.2.6.2. Paragraph No: 9 Line: 4-5	In this section, the guideline should provide clearer guidance on in-vitro and in-vivo testing of non-cellular and structural components. Taking into consideration that these paragraphs are under the main header **4.2 *Quality and manufacturing aspects*** it is not clear which tissues e.g. 'compatibility of the biomaterial with the tissue with which it is in contact' or 'surrounding tissue' are referred to. During the manufacturing of the CBMP it might be necessary to use other tissue components. The impact on the quality of the CBMP by this specific manufacturing tissue can be assessed by in-vitro studies from a CMC point of view, whereas biocompatibility and effect of degradation of the structural components at the target sites may be assessed by in-vivo studies (section 4.3 Non-clinical development). (EBE)	The present paragraph deals with development pharmaceutics not with quality control. The studies required should be targeted to optimisation of formulation. It is not the purpose of this section to be prescriptive in terms of strategies adopted. Revision of the paragraph and indents (also from previous comment): - absence of components or leachables that might be toxic to cell growth and/or intended performance.; - characterisation of features (e.g. topography, surface chemistry, strength) critical to structural support, optimisation of viability and cellular growth or other functional characteristics; - biocompatibility of the structural material with the cells or tissues to confirm that the system maintains the desired cell differentiation, functionality and genotype during production and

		until use; - release kinetics of any bioactive molecules, to verify that they are appropriate for the achievement of the intended effect; - the influence of the nature and rate of degradation on critical mechanical and structural properties of the product.
4.2.6.2. Paragraph No: 9 Line: 4-5	Proposal EBE: The effect of the cellular component on the degradation (rate and, if appropriate, products) or stability of the structural component should be assessed, <u>wherever possible.</u>	The present paragraph deals with development pharmaceutics not with quality control. The studies required should be targeted to optimisation of formulation considering the intended use throughout the lifespan of the product. These considerations are not necessarily translated into quality control.
4.2.6.3	Reference to art 12 and 13 of AT regulation is missing (EBE)	Reference to ATMP regulation is now given in 3. legal basis. This chapter does not deal with information and traceability.
4.2.6 Development pharmaceuticals 1. Cellualr Components Second para	In regard to ICH Q5D this part should be changed. In chapter 2.3.1.0 it is clearly stated that "either genotypic or genotypic characteristics may be used in identity testing". In case of autologous products genotypic tests are not useful. Therefore autologous products should be exempted from this requirement except duly justified. Proposal: Stability of cellular component is the most critical for the CBMP and must be assessed by the ability of cells to survive, and maintain the genotype ~~**and**~~ **or** phenotype needed for the intended functions (regeneration, repair or replacement). Cell viability can be easily assessed in culture by employing widely applied assays. However, detection of possible changes in cellular nature that may influence the intended function, can be feasible by analysis of cellular surface antigens, proteomics and functional genomics analysis (e.g. microassay for gene expression profile, flow cytometry etc.). The ability of cells to continue to produce or express products should be evaluated as part of the stability programme. Such stability studies should be carried out as long as the defined period of validity requires. **Genotypic characterization is not required for autologous cell preparations except duly justified. (BPI)** (EuropaBio) (Genzyme)	ICH Q5D is not applicable for tissue engineered products for which a regeneration, repair or replacement indication is to be granted. Furthermore, considering the dynamic nature of some cell based products namely those based on stem cells, the condition of autologous origin cannot warrant per se the required genetic stability.
4.2.6 Development	The referenced "Notes for Guidance" were issued before the release of the Clinical Trials Directive 2001/20. This guideline contains no reference to this Directive and does not explain	Quality of clinical trial materials are outside the remit of this document. Only marginally

Pharmaceutics	how the quality of IMPs should be tested and documented. Proposal: Section 4.2.6 needs to be adapted to cover the Clinical Trial Directive. The processes and suggested documentation is not compatible with the requirements of the Directive 2001/20 and does not refer to appropriate articles of the ATMP Regulation e.g. with regard to the assessment of the medical device part by a Notified Body. (EuropaBio) (Genzyme)	recommendations are applicable and it is competence of each member state to establish how it should be followed. Reference to ATMP regulation is now given in 3. legal basis.
4.2.6 page 15, 2., 3rd paragraph and 4.2.6 page 15, 2., 5th paragraph 4.2.6, 2. Page 16, line 24 4.2.6, 2. Page 16, line 29	Typographic errors: at the end of this second paragraph that there are two periods. There should be a comma between materials and their "The choice of structural materials, their properties,..." ------ Please correct the tense in one of the sentences: "For example when a cellular components is combined with a structural component reference to an assessment of a medical device by a Notified Body may be relevant." (note that it should not be "components" and a comma is needed). For example when a cellular component is combined with a structural component, reference to an assessment of a medical device by a Notified Body may be relevant. ------ "To establish biocompatibility, it is necessary to specify the nature of biological response..." "the non-cellular component undergoes degradation, physico-chemical alterations" (EG) "To establish biocompatibility, it is necessary to specify the nature of biological responseS" "the non-cellular component undergoes degradation OR physico-chemical alterations" (RISET)	Typogrphical errors corrected.
4.2.6, 1. page 15, line 2 of second paragraph	"the genotype and phenotype needed" Again it may be genotype AND/OR phenotype (ACT) Proposal: "the genotype and/OR phenotype needed" (RISET)	Considering the dynamic nature of some cell based products namely those based on stem cells with an indication for replacement, regeneration, or repair require the maintenance of a given genotype and phenotype to ensure stability.
P 15 Para 4.2.6	Would have expected this topic closer to the Characterisation chapter. The referenced Notes for Guidance were issued before the release of the Directive 2001/20	Quality of clinical trial materials are outside the remit of this document. Only marginally recommendations are applicable and it is

	which is the document which now describes the quality procedures for Investigational Medicinal Products. This guideline contains no reference to this directive and does not explain how the quality of IMPs should be tested and documented. Would recommend to refer to existing guidance that is in effect at the top of the chapter (e.g. the ISO norms only come at the end of the chapter. (Tigenix) The entire chapter goes into quite some detail on the non-cellular component and could generate quite some burden to development therefore recommendation to add language like 'where relevant'. Chapter goes into quite some detail on the non-cellular component. The logic and flow of the text is not always clear. There is also redundancy with parts in the Characterisation section. In general the chapter is not balanced enough between cellular and non-cellular component, where the non-cellular component is only relevant as part of the combination product and the primary mode of action is determined by the cellular component. Would recommend to review entire section on non-cellular component in detail and adapt in view of development timelines of these products focus on the critical path and least burdensome way to obtain the required data. The required documentation requirements should be clearly stated. Proposal: Section 4.2.6 needs to be adapted to the new legislation. The processes and suggested documentation is not compatible with the requirements of the Directive 2001/20 and does not refer to appropriate articles of the AT regulation e.g. with regard to the assessment of the device part by a Notified Body. (Tigenix)	competence of each member state to establish how it should be followed. The unbalanced guidance of the cellular vs noncellular component, can be explained by the fact, acknowledged in the introductory section, where it is clearly stated that previous experience exist with the cell component and guidance on the Development Pharmaceutics of other biological products can be applied. Intrinsic variability of the cellular component is more thoroughly addressed in manufacturing process and characterisation. The issues resulting from the combination with structural materials were considered equivalent to formulation.
P15 4.2.6. Para 1	Biological/therapeutic function Proposal: Prefer to modify slightly and adapt to ATP Regulation : …regeneration, repair, replacement, or therapeutic action. (Tigenix)	The guidance is for all cell based products and should not be restricted to Tissue engineered as in the Regulation.
P16 4.2.6. Para 5 and 6	Needs adaptation. Would delete 'The continuing ability of the non cellular …..up to can be verified through clinical study.' This is not really correct in view of biodegradable products. Would rephrase. The paragraph thereafter is correct. There seems to be some redundancy. 'The effect of degradation ….until for the intended functioning of the product.' is preferred. Proposal: Delete : 'The continuing ability of the non cellular …….. can be verified	The sentences are all required although their assemblage should be revised. "The continuing ability …" refers to all types of desired tissue responses while the other starting "The effect of degradation…" refers specifically to mechanical properties. Paragraphs rearranged:

	through clinical study.' (Tigenix)	The stability of the non-cellular components should be assessed in the presence and absence of cellular components in order to determine whether the non-cellular component undergoes degradation, or physico-chemical alterations (e.g. aggregation, oxidation) that may impact on the quality of the product by affecting cellular behaviour and survival. The effect of the cellular component or of the surrounding tissues on the degradation (rate and, if appropriate, products) or stability of the structural component should be assessed considering also the effect of the non-cellular components throughout the expected efficacy of the product. The continuing ability of the non-cellular components to promote the desired tissue response and support the function of the CBMP over its intended lifespan, or until a steady state has been established, should be assessed, taking into account factors identified as relevant in the non-clinical evaluation of biological activity and which can be verified through clinical study. As an example, the effect of degradation of any structural biomaterial should be assessed to verify that the required and specified mechanical properties are maintained for as long as is necessary for the intended functioning of the product.
4.2.7	**Quality and manufacturing aspects: Traceability** In the Swedish law , Swedish Ministry of Health and Social Affairs, **Genetic Integrity Act 2006:351 297, 6 §,** from July 1st 2006**,** the integrity of the patients/donors should be protected and anonymity ensured. The Swedish law clearly specifies the right to perform research on fertilized eggs and derivatives thereof, but forbids the commercial use of human biologic	Reference to Art. 15 of the REGULATION (EC) No 1394/2007 added. text added: The Regulation on ATMP (art. 15) defines a two tiered system connecting the required traceability from cell donation and procurement (Dir

	material if the material could be identified and linked to the donor. In other words, unlinked anonymized human biologic material can be commercialised and thus suitable for human clinical use. The directive **2004/23/EC** on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells regulates what to do with the donation of the cells and requires complete traceability of the patient as well as the product and its starting material. According to the national legislation in Sweden, the tissue and cell donation should respect the anonymity of the donors. Therefore the rule in the new guidelines requesting a system allowing complete traceability of the donor would not be applicable. After the pre-meeting held May 31st 2006 with the Swedish Medicinal Product Agency (MPA) it was confirmed that it is acceptable to have traceability beginning with the stem cell line i.e. traceability ensured from the first moment the human embryo stem cell line is established. However, the rule of transparency does not request that the anonymity is broken but each donation and thereby stem cell line should have a traceable code. The code should however not disclose the identity of the donor. The traceability systems are therefore divided into one for the procurement of the cells and one for the identification of the cell product. Defined medical information could be attached to the donation and the information accompanies the cells produced from the fertilised egg. In that medical base, information about the race or ethnic group will not be given. A genetic investigation may not be forbidden but has to be asked for in the donation letter. The genetic information has also to be balanced in relation to the traceability and genetic integrity. As full traceability is not requested, the coded anonymity will be the standard procedure for the donation. **Conclusion:** Acceptance of unlinked anonymized human cell lines under clinical trials and marketing of human cell based medicinal products (Cellartis)	2004/23/EC) to the manufacturer and user (hospital or practice). This means that anonymity can be guaranteed. At the tissue establishment there has to be a link between the donor and the donation. At the manufacturing side, there has to be a link between donation and product and at the hospital/practice side there has to be a link between the product and the recipient. The systems should allow full traceability from donor to recipient although through anonymous coding systems. Manufacturers should establish their coding systems in a rational way, building from the coding system of the tissue establishment, and designing it to facilitate the tracing of the donation to the product and to the patient. Bar coding and peeling labelling systems could be advantageous for patient management. Clinical trial materials should follow the same traceability system.
4.2.7 First paragraph, page 17.	The single identifying code is applicable to the material at tissue establishments, and by the healthcare establishment to the clinical site where it is applied to the patient. Where such material is used in further processing (e.g. for attachment to matrix scaffolds) then the CBMP manufacturer is required to ensure similar traceability systems are in place. Proposal: Amend the text to reflect this principle. (DKMA)	Specific reference to Art. 15 of the ATMP Regulation is inserted in the text. See above for new text.
4.2.7	A detailed description of the requirements is in article 16 of the AT regulation and should be referenced here. The specific needs to include the required process for ensuring traceability	Specific reference to Art. 15 of the ATMP Regulation is inserted in the text.

	need to be included in the informed consent process for clinical trials. (EBE)	See above for new text.
4.2.7.Traceability and Biovigilance	We would welcome further clarifications regarding the borderline and the complementarities between the provisions of the ATMP Regulation regarding traceability and biovigilance with those specified in Directive 2004/23/EC. Indeed, two systems of vigilance will apply for the full development of an ATMP: biovigilance and traceability as required by the Directive 2004/23/EC for the cells/tissue donation, procurement and testing and the pharmacovigilance and traceability as required by the pharmaceutical framework for the rest of the product development and the marketing of the final product. The fact that the Directive 2004/23/EC and its associated technical Directives must be implemented into national laws, the National Agencies could set additional national specific requirements. This is not facilitating standardised homogeneous development and commercialisation of Advanced Therapy Medicinal Products all over Europe: for example, the biopsy (cell or tissue starting materials) import/export requirements are widely differing from one member state to another. Therefore, we would welcome further advice pointing this regard. The specific needs to include the required process for ensuring traceability need to be included in the informed consent for clinical trials. Proposal: We request the EMEA and Commission to provide guidance on facilitating a harmonised traceability and vigilance requirements for CBMP in Europe. Further, we recommend to add information about traceability in informed consent in clinical trials. (EuropaBio) (Genzyme)	Specific reference to Art. 15 of the ATMP Regulation is inserted in the text. See above for new text.
4.2.7, page 17	"The establishment and maintenance of that system should be done in such a way as to ensure coherence and compatibility with traceability requirements laid down in Directive 2004/23/EC and in Directives 2006/17/EC and 2006/86/EC[27]" One would expect more detailed specifications here than a simple reference to the Directives. (ACT) (RISET)	Specific reference to Art. 15 of the ATMP Regulation is inserted in the text. See above for new text.
4.2.8. Comparability Second Para	There are a considerable number of products legally on the market for long periods which are not known to cause any harmful effects but for which no clinical studies are available. For these products the same demands should be applied for the comparability of case report studies. Proposal: During the pivotal clinical **or observational case report** studies, changes should not… (BPI)	Observational case reports can be used as proof of principle and indicative of the clinical safety of the product although controlled clinical trials may be required for demonstration of efficacy in a MA. As stated in the guideline on Comparability ICH Q5E "Due to the limitations of the analytical tools

		in early clinical development, physicochemical and biological tests alone might be considered inadequate to determine comparability, and therefore, bridging nonclinical and/or clinical studies, as appropriate, might be needed."
4.2.8	This sentence, and its placement under "Comparability" heading raises the question whether the guidance is literally proposing that it is necessary to establish the comparability of each batch of product used in clinical studies to every other batch of product, which is a very high standard to which no other product category is held. Comparability is usually understood in both EMEA and ICH guidelines to relate to the comparison of the properties of the product before and after process changes or manufacturing facility changes. But this sentence does not address such changes, only routine manufacturing within one process and facility. It is undeniably essential that the manufacturer must establish that each batch possesses characteristics that are representative of the process, and meet specifications in order to be able to compare the results of clinical trials. But this sentence implies that each batch must be subjected to a comparability study, consisting of QC tests and characterization studies and stability profiling to establish the comparability of each lot to every other lot. We do not believe that this is the intent of EMEA and suggest that this sentence be deleted or moved to the introduction of section 4.2.4 (Quality Control) Proposal EBE: Delete "well"	The sentence was revised to avoid misinterpretation. "well" was removed. It now reads: Data on the behaviour and characteristics of developmental prototypes should be retained as it could provide background information relevant to the evaluation of the final product. During the pivotal clinical studies. Changes should not be introduced to the manufacturing process and the final product. Materials used in the clinical studies should be sufficiently characterised in order to allow the demonstration of consistency of production. The manufacturers should consider the critical parameters drawn from the characterisation of their product to establish the analytical tools necessary for the required comparability studies throughout development.
4.2.8 Paragraph No: 2 Line: 3	The *companies* are expected…. Proposal EBE: The *applicants* are expected…	Changed to "manufacturers"
4.2.8. Comparability	Said bio-comparability protocol should, where possible, be based on assay of surrogate markers of phenotype/genotype; and EMEA might seek to establish validated markers together with acceptance limits for licence variations. Proposal: As a suggestion, we would propose that a biocomparability protocol with well-identified classes of process modifications, based on experience gathered during the development, should be submitted for evaluation to regulatory agencies, either as part of the	The intrinsic heterogeneity of the cell based product does not allow predefining a biocomparability protocol as proposed. The comparability exercise as stated in the Guideline Q5E, has to be drawn from information gathered at different levels, from characterisation to manufacturing, stability and to variable extent to

	MAA submission, or within the framework of a specific procedure with the CAT (to be defined). Once the EMEA has validated this comparability protocol, when manufacturing changes remain within the categories identified in the protocol, then only a simple type IA notification would be required, rather than a type II variation, with limited documentation. This suggestion shall go hand-in-hand with the review of the Variation Regulations concerning biologics including cell based-medicinal products. (EuropaBio) (Genzyme)	bridging non-clinical and clinical studies. In the future when more experience can be gathered with this type of products, a more generalised approach might be considered.
Line 642, Section 4.2.8, Comparability	Current wording: "During the pivotal clinical studies changes should not be introduced to the manufacturing process and the final product." Rationale: It may be in the best interest of the product and patients to introduce changes in the manufacturing process, especially valuable technological advances. The responsibility should rest on the manufacturer to ascertain whether those changes impact the interpretation of clinical results. Proposed wording: "During the pivotal clinical studies changes introduced to the manufacturing process and the final product could effect the interpretation of results (PhRMA)	As stated in ICH Q5E "Improvement of product quality is always desirable and encouraged. If the results of the comparability exercise indicate an improved quality suggesting a significant benefit in efficacy and/or safety, the pre- and post-change product may not be comparable." Therefore, a comparability exercise is required to demonstrate the improved quality.
P17 Para 4.2.8	Experience shows that Marketing Authorisation Holders are facing more and more difficulties to comply with their regulatory obligations in terms of variations submissions as they are time and resource consuming. This is particularly true for biological products which manufacturing sometimes involve a large number of steps and starting materials, subject to regular changes. This administrative workflow raises many problems in terms of the logistics of the manufacturing changes (urgent manufacturing changes due to update in the state-of-the-art would need urgent modification approval by the agency). We believe the administrative burden should not discourage ATMP companies from modifying their manufacturing process in order to take into account the rapid scientific advances in the field. For advanced therapy medicinal products, there are quite a number of changes that can be foreseen, such as changes in suppliers of raw materials, changes in culture media, new cell lines... We would appreciate that the EMEA considers an alternative notification process, based on the existing one, to account for well defined changes with a less administrative burden. Proposal: As a suggestion, we would propose that a biocomparability protocol with well identified classes of process modifications, based on experience gathered during the development, should be submitted for evaluation to regulatory agencies either as part of the MAA submission, or within the framework of a specific procedure with the CAT (to be defined). Once the EMEA has validated this comparability protocol, when manufacturing changes remain within the categories identified in the protocol, then only a simple type IA	Same as above: The comparability exercise as stated in the Guideline Q5E, has to be drawn from information gathered at different levels, from characterisation to manufacturing, stability and to variable extent to bridging non-clinical and clinical studies. In the future when more experience can be gathered with this type of products, a more generalised approach might be considered.

	notification would be required, rather than a type II variation, with limited documentation. (Tigenix)	
P17 4.2.8	We know there are voices to defend comparability on the basis of observational case report studies. We would like to request clarification that the regulators clarify their position on this. Without adequately controlled trial material and in-vivo potency assay for comparison we are not sure any comparability can be drawn from any 'observational 'data. (Tigenix)	As above: Observational case reports can be used as proof of principle and indicative of the clinical safety of the product although controlled clinical trials may be required for demonstration of efficacy in a MA. As stated in the guideline on Comparability ICH Q5E "Due to the limitations of the analytical tools in early clinical development, physicochemical and biological tests alone might be considered inadequate to determine comparability, and therefore, bridging nonclinical and/or clinical studies, as appropriate, might be needed."

4.3 Non-clinical development		
Line no. + para no.	**Comment and Rationale**	**Outcome**
4.3	non-clinical development Proposal: would be possible to report same example of pharmacology, tossicology studies? (F Fagioli)	No modification. Due to the varied nature of these products, it is not possible to give more specific examples than already done.
4.3 Non-clinical development Third para	In many cases relevant animal models are not available. If those animal models are not available in-vitro studies should be possible, too, replacing them. Proposal: The non-clinical studies should be performed in relevant animal models**, if available. If relevant animal models are not available, in-vitro studies may replace animal studies.** The rationale underpinning the non-clinical development, and the criteria used to choose a specific animal model must be justified. The inherent variability of some cell-based medicinal products should be reflected in the non-clinical studies. (BPI)	**Addition:** If relevant animal models cannot be developed, *in-vitro* studies may replace animal studies.
4.3 Non-clinical development	There are a lot of products already on the market for several years. A lot of patients have been safely treated with these products. For these products additional preclinical testings makes no sense. Apart from that unnecessary animal testing should be avoided. Genotoxicity and carcinogenicity testing may in some cases nevertheless be useful, this should be decided on a case-by-case basis. Proposal: Adding of a paragraph at the end of this chapter: **The guideline acknowledges that there are cell-based medicinal products already legally on the market in the Community before the getting into force of the Regulation on Advanced Therapy Medicinal Products. These products are already safely used in men. Hence non-clinical trials are generally not necessary except duly justified. It is the intention of European law to avoid unnecessary animal testing. In case of genotoxicity and carcinogenicity testings a decision should be made case-by-case. (BPI)**	No modification. Experience with already marketed products may be included in module 4 with adequate documentation.
Paragraph No: 1 Line: 6	Correct reference: should be 15 (not 16) (EBE)	corrected
Paragraph No: 3	The meaning of this sentence is unclear. Is EMEA advocating the performance of non-clinical studies on multiple batches chosen to reflect batch to batch variability? Upon what process or product parameters is this recommendation to be based? The fullest extent of such variation is	The sentence has been rewritten in a more general way.

Line: 3-4	typically not understood until process development and validation is completed just before the marketing dossier is to be filed. Proposal EBE: Perhaps clarification of the meaning of "some cell based medicinal products" would clarify the intentions of EMEA. Clarification on the types of products for which such an evaluation is recommended.	
Paragraph No: 5 Line: 2	Current wording: "The number of animals, the genders and frequency and duration of monitoring should be appropriate to detect possible adverse effects." Rationale: No pre-clinical program could detect all possible adverse events. The program should be reasonably structured to detect potential adverse events that may be important before proceeding into human studies. Proposal EBE:Proposed wording: "The number of animals, the genders and frequency and duration of monitoring should be appropriate to detect potential adverse effects that are compatible with the benefit-risk expectations of the product."	No modification. The requested flexibility is already expressed in the introduction to 4.3.
4.3 Non-clinical development Para 3	In many cases relevant animal models are not available. If those animal models are not available *in-vitro* studies should be possible, too, replacing them. Proposal: The non-clinical studies should be performed in relevant animal models**, if applicable. If relevant animal models are not available, *in-vitro* studies may replace animal studies.** The rationale underpinning the non-clinical development, and the criteria used to choose a specific animal model must be justified. The inherent variability of some cell-based medicinal products should be reflected in the non-clinical studies. (EuropaBio) (Genzyme)	**Addition:** If relevant animal models are not available, *in-vitro* studies may replace animal studies.
4.3, page 18, 3rd paragraph, 1st line	"The non-clinical studies should be performed in relevant animal models." see the general comments on the "non-clinical studies" paragraph; the messages of animal model testing if available, and of proof of principle studies in restricted human disease models/pathological settings should be integrated. (RB) Proposal: "The non-clinical studies should be performed in relevant animal models, IF AVAILABLE. IN CASE SUCH MODELS DO NOT EXIST PROOF OF PRINCIPLE STUDIES IN RESTRICTED HUMAN DISEASE MODELS COULD BE CAREFULLY CONSIDERED AND STRICTLY MONITORED IF AUTHORIZED? AFTER ALL IN VITRO TESTING HAS BEEN CONDUCTED? CAREFUL RISK ANALYSIS	**Addition:** If relevant animal models are not available, *in-vitro* studies may replace animal studies.

	CONDUCTED AND PROVIDED EXTENSIVE INFORMATION OF THE PATIENT IS PERFORMED" (RISET)	
4.3, page 18, 5th paragraph	The construction of the following sentence should be clarified. "The number of animals, the genders and frequency and duration of monitoring should be appropriate to detect possible adverse effects." (ACT) Proposal: "The number of animals, THEIR genders, THE ~~and~~ frequency and duration of monitoring should be appropriate to detect possible adverse effects." (RISET)	Accepted
Line 660-664 Section 4.3 non-clinical development	Current wording: "The goals of these studies include the following: to provide information to select safe doses for clinical trials, to provide information to support the route of administration and the application schedule, to provide information to support the duration of exposure and the duration of the follow-up time to detect adverse reactions, to identify target organs for toxicity and parameters to monitor in patients receiving these therapies." Rationale: Monitoring should include safety parameters. Proposal: "The goals of these studies include the following: to provide information to select safe doses for clinical trials, to provide information to support the route of administration and the application schedule, to provide information to support the duration of exposure and the duration of the follow-up time to detect adverse reactions, to identify target organs for toxicity and parameters to monitor safety in patients receiving these therapies." (PhRMA)	No modification. ..."parameters to monitor" should not be restricted to safety parameters, at the expense of dynamic parameters.
Line 667-668 Secion 4.3 non-clinical development	The meaning of this sentence is unclear. Is EMEA advocating the performance of non-clinical studies on multiple batches chosen to reflect batch to batch variability? Upon what process or product parameters is this recommendation to be based? The fullest extent of such variation is typically not understood until process development and validation is completed just before the marketing dossier is to be filed. Proposal: Perhaps clarification of the meaning of "some cell based products" would clarify the intentions of EMEA. Clarification on the types of products for which such an evaluation is recommended. (PhRMA)	The sentence has been rewritten in a more general way.
Line 667-668 Section 4.3 non-clinical development	Related to the comment given above: Current wording: "The inherent variability of some cellbased medicinal products should be reflected in the non-clinical studies." Rationale: Should be variability, regardless of whether it is inherent. Proposed wording: "Variability of some cell-based medicinal products should be reflected in the non-clinical studies." (PhRMA)	Accepted
Line 669-670 Section 4.3	Current wording: "Expression level of biologically active molecules, the route of administration and the dosages tested should reflect the intended use in humans."	No modification. It is important that the cells used in the non-clinical studies have correct and

non-clinical development	Proposed wording: Add the following sentence at the end of the paragraph, “Cell characterization may be utilized to confirm the nature of the CBMP.” (PhRMA)	intended characteristics, but this issue is covered eleswhere (pharmacodynamics section).
Line 672-673 Section 4.3 non-clinical development	Current wording: “The number of animals, the genders and frequency and duration of monitoring should be appropriate to detect possible adverse effects.” Rationale: No pre-clinical program could detect all possible adverse events. The program should be reasonably structured to detect potential adverse events that may be important before proceeding into human studies. Proposed wording: “The number of animals, the genders and frequency and duration of monitoring should be reasonably appropriate to detect potential adverse effects.” (PhRMA)	No modification. The requested flexibility is already expressed in the introduction to 4.3.
P18 4.3	Clarification is sought from regulators regarding the requirements for products already legally on the market. The assumption that these products are safe because they have been widely used is not correct in the absence of a thorough and reliable safety database based on scrutinised data from clinical trials and thorough safety follow-up. In the past for hTEPs it was standard not to invest in very good safety follow up with active monitoring of adverse event information and soliciting information from physicians. So underreporting has been and is standard and nobody really knows. We do agree that in most cases human information overrules the extra implementation of animal studies but the human data should then provide much more comprehensive and scrutinised safety data in order to know whether the safety profile is indeed reliable. (Tigenix)	No modification. Experience with already marketed products may be included in module 4 with adequate documentation.
Section 4.3.1	The general text relating to pharmacology and pharmacodynamics should be reviewed because the general concept of pharmacology (e.g. dose response curves) is often inapplicable for this kind of products. An alternative form of words for the type of studies expected may avoid confusion. (Eucomed)	No modification. It is already pointed out e.g. in line 704- that conventional pharmacology is not always appropriate
4.3.1 Pharmacology Primary pharmacodynamics Page 18, para 8	As previously discussed, if the exact mechanism of action is complicated or novel, it is not appropriate to use a specific marker of biological activity to assess the action or potency of the product. Alternative methods such as demonstration of general metabolic activity, viability or other tests may be more suitable. A further difficulty is the availability of suitable models for assessment of proof of principle. Some intended indications do not have an appropriate animal model that allows the demonstration of proof of principle for the product in question (e.g. VLU: there is no suitable chronic wound model). (BIA)	No modification. The requested flexibility is already expressed in the (modified) introduction to 4.3.

Kinetics, migration and persistence Page 19	These studies may not always be relevant. Add: **The requirement for such studies should be assessed on a case-by-case basis as these may not be relevant or appropriate.** (BIA)	No modification. The requested flexibility is already expressed in the introduction to 4.3.
Interactions Page 19	Clarification is required as to how long these interactions should be monitored for and to what extent. The requirements for interaction studies should be assessed on a case by case basis. (BIA)	No modification. The requested flexibility is already expressed in the introduction to 4.3.
4.3.1 Pharmacology Primary pharmacodynamics Second para	In some cases justified markers are not known or not available. This should be taken into regard. Proposal: **If available,** reasonably justified markers of biological activity should be used to adequately identify the pharmacodynamic action of the CBMP in the host (BPI)	No modification. The requested flexibility is already expressed in the introduction to 4.3.
4.3.1 Pharmacology Secondary pharmacology	These tests should be limited to products showing a high risk profile during initial risk analysis. It is not necessary to generally require these tests for all products. Apart from that it is scientifically questionable if these tests are feasible. **Proposal: For special products with high risk profiles** potential undesirable physiological effects of human CBMP including their bioactive products should be investigated in an appropriate animal model.(BPI)	No modification. The requested flexibility is already expressed in the introduction to 4.3.
4.3.1 Pharmacology Kinetics, migration and persistence First para	These tests should be limited to products showing a high risk profile during initial risk analysis. It is not necessary to generally require these tests for all products. A decision about the necessity of these tests should be made on a case-by-case basis taking into regard the individual characteristics of the product in question. Proposal: Conventional ADME studies are usually not relevant for human CBMP. However**, for products with high risk profiles** studies should be carried out to demonstrate tissue distribution, viability, trafficking, growth, phenotype and any alteration of phenotype due to factors in the new environment**, which should be considered on a case-by-case basis depending on the characteristics of the CBMP. (BPI)**	No modification. The requested flexibility is already expressed in the introduction to 4.3.

4.3.1. Sec pharmacology Paragraph No: 1 Line: 1	Current wording: “Potential undesirable physiological effects of human CBMP including their bioactive products should be investigated in an appropriate animal model. Cells may migrate from their intended location and, after a systemic administration, may home to other organs beside the intended location. Also, somatic cells may secrete additional biologically active molecules besides the protein of interest. Also, the protein(s) of interest can have additional targets beside the desired one. Proposal EBE: Proposed wording: The following sentence should be added to the end of the paragraph, “In the case of allogeneic CBMP, analogous animal-derived cells may be utilized to model the human allogeneic situation in the animal species concerned.”	No modification. The comment is appreciated; however, the issue is already addressed in the primary pharmacodynamics section.
4.3.1. Kinetics Paragraph No: 4 Line: 3	…..the distribution, duration and amount of expression of these molecules and the survival and the functional stability of the cells at the target sites should be studied, if possible. (EBE)	No modification. The requested flexibility is already expressed in the introduction to 4.3.
Line 693-696 Section 4.3.1 Pharmacology	Current wording: “If possible, studies should be conducted in order to determine the minimal or optimal effective amount of cell-based medicinal product that is needed to achieve the desired effect. In addition to cell numbers or concentrations, emphasis must be laid on the required specific characteristics (e.g. differentiation stage and heterogeneity) of the applied cells or tissues. Proposed wording: The following sentence should be added to the end of the paragraph, “These specific characteristics can be based on the assays used for cell characterization.” (PhRMA)	No modification. The sentence "In addition to cell numbers or concentrations, emphasis must be laid on the required specific characteristics (e.g. differentiation stage and heterogeneity) of the applied cells or tissues." is proposed to be deleted, since the issue relates to quality rather than non-clinic.
Line 697-702 Section 4.3.1 Pharmacology	Current wording: “Potential undesirable physiological effects of human CBMP including their bioactive products should be investigated in an appropriate animal model. Cells may migrate from their intended location and, after a systemic administration, may home to other organs beside the intended location. Also, somatic cells may secrete additional biologically active molecules besides the protein of interest. Also, the protein(s) of interest can have additional targets beside the desired one. Proposed wording: The following sentence should be added to the end of the paragraph, “In the case of allogeneic CBMP, analogous animal-derived cells may be utilitzed to model for the human allogeneic situation.”	No modification. The issue is already addressed in the primary pharmacodynamics section.
4.3.2	An immune response against the CBMP will be dependent on the cell type and component	No modification. The requested flexibility is

Toxicology Page 20, para 2	sources and immunogenicity should therefore be assessed on a case-by-case basis. A number of cell types have already been used in products that have been approved. For cell types with a well known safety profile this information should be taken into account. It would be unnecessary and inappropriate to duplicate animal studies to demonstrate information that is well established. (BIA)	already expressed in the introduction to 4.3.
Single and repeated dose toxicity studies Page 20	The requirement for single and repeated toxicity studies should be assessed on a case-by-case basis. (BIA)	No modification. The requested flexibility is already expressed in the introduction to 4.3.2
4.3.2. Toxicology First para	It should be stated at the beginning of this chapter that the basis for requirements the field of toxicology for an individual product should be bases on the initial risk analysis. Proposal: **Toxicology assessments should be conducted in compliance with the results of the initial risk analysis.** The need for toxicological studies depends on the product. However, as conventional study designs may not be appropriate, the scientific justification for the models used, or the omission of studies, shall be provided.(BPI)	No modification. The requested flexibility is already expressed in the Risk analysis section and the introduction to 4.3
4.3.2. Toxicology Single and repeated dose toxicity studiesFirst para, last sentence	What is the rationale for explicitly picking out autologous CBMP? If there is no rationale we would recommend deleting this sentence. (BPI)	Proposal accepted. (For homologous models see Introduction)
4.3.2. Toxicology Other toxicity studies First para	These tests should be limited to products showing a high risk profile during initial risk analysis. It is not necessary to generally require these tests for all products. A decision about the necessity of these tests should be made on a case-by-case basis taking into regard the individual characteristics of the product in question. Proposal: The risk of inducing tumourigenesis due to neoplastic transformation of host cells and cells from the CBMP should be considered, as appropriate, on a case-by-case basis **and if initial risk analysis has shown relevant evidence**. (BPI)	No modification. The requested flexibility is covered in the risk analysis section
4.3.2. Single	Current wording: “Toxicity studies should be performed in relevant animal models. If the	

repeat tox Paragraph No: 1 Line: 1	human cells are not immediately rejected, the studies may be combined with safety pharmacology, local tolerance, or proof of concept and efficacy studies. In the case of autologous CBMP, the use of homologous models may be considered." Rationale: It may be impossible to detect immediate rejection of human cells in animal models. Even relatively rapid rejection of these cells may not obviate a biological effect prior to destruction. Proposed wording: "Toxicity studies should be performed in relevant animal models. If the human cells are not immediately rejected, the studies may be combined with safety pharmacology, local tolerance, or proof of concept and efficacy studies. Sufficiently characterized analogous animal-derived cells may be used for some allogeneic CBMP when not immediately rejected. In the case of autologous CBMP, the use of homologous models may be considered." (EBE)	Accepted
4.3.2. Other tox studies Paragraph No: 1 Line: 3	Current wording: "Tumourigenesis studies should preferably be performed with cells that are at the limit of routine cell culturing or even beyond that limit." Proposed addition: "However, persistence of the cells is also a key factor in a relevant tumourigenesis study, and should be taken into account if cells at the limit of routine cell culturing do not fulfil this criterion."(EBE)	No modification. The proposal may be correct, but does not add significant guidance.
4.3.2. Toxicology Para 1	It should be stated at the beginning of this chapter that the basis for requirements the field of toxicology for an individual product should be bases on the initial risk analysis. Proposal: **Toxicology assessments should be conducted in compliance with the results of the initial risk analysis.** The need for toxicological studies depends on the product. However, as conventional study designs may not be appropriate, the scientific justification for the models used, or the omission of studies, shall be provided. (EuropaBio) (Genzyme)	No modification. The requested flexibility is already expressed in the introduction to 4.3.
Line 748-751 Section 4.3.2. Toxicology	Current wording: "Toxicity studies should be performed in relevant animal models. If the human cells are not immediately rejected, the studies may be combined with safety pharmacology, local tolerance, or proof of concept and efficacy studies. In the case of autologous CBMP, the use of homologous models may be considered." Rationale: It may be impossible to detect immediate rejection of human cells in animal models. Even relatively rapid rejection of these cells may not obviate a biological effect prior to destruction. Proposed wording: "Toxicity studies should be performed in relevant animal models. The studies may be combined with safety pharmacology, local tolerance, or proof of concept and efficacy studies. In the case of autologous CBMP, the use of homologous models may be	Accepted

	considered. In the case of allogeneic CBMP, the use of analogous animal-derived cells may be considered" (PhRMA)	
P19 Para 4.3.2	We have the feeling as well that in the toxicology section (except for tumorgenicity testing) the focus should be on the toxicology possibly induced by the non-cellular components and excipients since the answer on the cellular component and its behaviour (aberrant or not) will already be dealt with in sections secondary pharmacology, safety pharmacology. In general we would like to see a much clearer distinction in the tox section between CBMP for systemic application and those for local implantation. Although we acknowledge that this differentiation can hopefully be brought about by the risk analysis we would nevertheless already welcome a clearer distinction from the outset in the guideline. Also the PMOA will determine if long term tox is needed (e.g. if degradation of combi is reasonably fast etc.). Cells are not always supposed to be there for a long time in a single dose - what if implanted cells recruit cells from surroundings to effect long term repair but die themselves reasonably fast? (Tigenix)	The comment is appreciated. However, current knowledge does not allow us to issue guidance that specifically address the different tox risks more than already done in the Risk analysis section. A modification covering the fact that the cells may die, but induce long-term effects, has been made.
P20 Para 2	Induction of immune response could belong in category of Secondary pharmaco. (Tigenix)	No modification. Antigenicity is assessed as Toxicology: Other toxicity studies, according to the CTD format.
P20 Para 5	Single dose tox: '*observations might be much longer than in standard single dose studies*'. What would be an acceptable design then? Would recommend sticking with the principle that the tox testing for products for long term implantation e.g. would have to test whether the long term safety can support the clinical trial use. At the same time for products with a 'single dosing/single implantation' maximum 12 months follow up initially (in animal/human studies) should be sufficient. (Tigenix)	No modification. The duration of the studies should be decided case-by-case.

4.4. Clinical development		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Section 4.4 Clinical development	Insert the following text before 4.4.1 Special consideration will need to be given to the situation applying when only non viable materials are used which are therefore more appropriately controlled as medical devices. The wording related to clinical development should reflect the requirements of the medical devices directives. It is pointed out that, for medical devices, it is necessary for demonstrate usefulness rather than efficacy. This can affect the acceptable design of clinical studies that would be accepted by medical devices competent authorities – e.g. power of design and number of patients permitted. The need for clinical studies depends on the product. However as conventional study design may not be appropriate, scientific justification for the studies conducted or the omission of studies shall be provided (Eucomed)	This guideline is restricted to product containing viable cells as stated in the scope
Line 816-818 Section 4.4 Clinical Development	Current wording: "If possible, it should be individuated also the Safe Maximal Dose, defined as the maximal dose which could be administered on the basis of clinical safety studies without adverse effects." Rationale: It is likely that all doses are associated with adverse events, but not causally. This may be especially true when adverse events occur with the intended indication. Acceptable adverse events should be driven by the estimated risk/benefit of the product. Proposed wording: "If possible, it should be individuated also the Safe Maximal Dose, defined as the maximal dose which could be administered on the basis of clinical safety studies with acceptable adverse effects." (PhRMA)	The paragraph has been modified and the comment has been integrated.
Line 856-857 Section 4.4 Clinical Development	Current wording: "CBMP may need special long-term studies to monitor specific safety issues, including lack of efficacy." Rationale: Lack of efficacy may be addressed early in development. Immunogenicity or tachyphylaxis may not occur until later in dosing, and may require long-term follow-up for assessment. Proposed wording: "CBMP may need special long-term studies to monitor specific safety issues, including loss of efficacy." (PhRMA)	The suggestion has been accepted
Section 4.4 Clinical	Proposal: Add after paragraph 1: "The extent of clinical studies depends on the product. However as conventional study design may not be appropriate, scientific justification for the	It is implicit in the text already that absence of clinical studies can be justified

development	studies conducted and their design, or the omission of studies, shall be provided" (Zimmer)	
4.4.1 General aspects Page 21	Add after paragraph 1: **The extent of clinical studies depends on the product. However as conventional study design may not be appropriate, scientific justification for the studies conducted (or not) and their design shall be provided.** (BIA)	Same as the comment before
4.4.1 clinical development general aspects First para, first sentence	The Regulation on Advanced Therapy Medicinal products clearly says that the **general** requirements of the Clinical Trials Directive will apply to ATMP. Because of the specificities of these products making them different from conventional medicinal products these requirements have to become adapted. This means that not all details of this Directive are fitting in the context of ATMP. This should be reflected here. Proposal: In general when a CBMP enters the clinical development phase the same **general** principles as for other medicinal products apply. (BPI)	The sentence has been modified to be clarified.
4.4.1 clinical development general aspects second para	The guideline acknowledges that clinical development of cell-based medicinal products might be associated with special problems (e.g. no blinding possible, state-of-the-art surgical procedures not defined etc.). Therefore, in accordance with the risk management plan, clinical developmental issues may only be addressed in serial case report studies or prospective observational studies. Apart from that other clinical experience especially for already marketed products should be considered. Proposal: While a deviation from Phase I to Phase III clinical trials progression is acceptable, it needs to be justified by the specificity of CBMP, the non-clinical studies, previous clinical experience, **especially in case of products already on the market before the getting into force of the Regulation on ATMP,** and the treated pathology. In such cases, the initial clinical studies **as well as observational clinical studies** may be adequate to demonstrate the "proof of principle" for CBMP and pharmacodynamic parameters (related to efficacy) should be obtained in these studies. (BPI)	The paragraph has been rewritten and the concerns taken in account.
Second line, Section 4.4.1, Page 21	Please see the comments below. Proposal: Amend to …. The clinical development plan should if possible include ….(DKMA)	The suggestion was considered and it was deemed not relevant for the meaning of the sentence
4.4.1 clinical	The Regulation on Advanced Therapy Medicinal products clearly says that the **general**	The first comment has been already been taken

development general aspects Para 1, first sentence	requirements of the Clinical Trials Directive will apply to ATMP. Because of the specificities of these products making them different from conventional medicinal products these requirements have to become adapted. This means that not all details of this Directive are fitting in the context of ATMP. This should be reflected here. Proposal: In general when a CBMP enters the clinical development phase the same **general** principles as for other medicinal products apply. **Reference to the Directive 2001/20 as well as to the new First in Man Guidance are missing and would be welcomed. (EuropaBio) (Genzyme)**	into account, see above The reference to the directive 2001/20 has been inserted.
4.4.1 clinical development general aspects Para 2	The guideline acknowledges that clinical development of cell-based medicinal products might be associated with special problems (e.g. no blinding possible, state-of-the-art surgical procedures not defined etc.). Therefore, in accordance with the risk management plan, clinical developmental issues may only be addressed in serial case report studies or prospective observational studies. Apart from that other clinical experience especially for already marketed products should be considered. Proposal: While a deviation from Phase I to Phase III clinical trials progression is acceptable, it needs to be justified by the specificity of CBMP, the non-clinical studies, previous clinical experience, **especially in case of products already on the market before entry into force of the ATMP Regulation,** and the treated pathology. In such cases, the initial clinical studies **as well as observational clinical studies** may be adequate to demonstrate the "proof of principle" for CBMP and pharmacodynamic parameters (related to efficacy) should be obtained in these studies.(EuropaBio) (Genzyme)	The paragraph has been rewritten and the comments taken in account.
4.4, 4.4.1, second paragraph, page 21, line 3 of the paragraph	"While a deviation from Phase I to Phase III clinical trials progression is acceptable, it needs to be justified by the specificity of CBMP, the non-clinical studies, previous clinical experience and the treated pathology. In such cases, the initial clinical studies may be adequate to demonstrate the "proof of principle" for CBMP and pharmacodynamic parameters (related to efficacy) should be obtained in these studies." In the case of tolerance induction in the transplantation context, it is not an existing pathology that is treated in itself, but the possibility of immunosuppressive treatment complications. Replace pathology by condition in order that this sentence apply to these situations. (ACT) Proposal: "While a deviation from Phase I to Phase III clinical trials progression is acceptable, it needs to be justified by the specificity of CBMP, the non-clinical studies, previous clinical experience and the treated ~~pathology~~ CONDITION. In such cases, the initial clinical studies may be adequate to demonstrate the "proof of principle" for CBMP and pharmacodynamic	The paragraph has been rewritten and the comments taken in account.

	parameters (related to efficacy) should be obtained in these studies." (RISET)	
P21 Para 4.4.1	While a deviation is allowed for phase 1 through 3 clinical trials we believe a deviation in the clinical development plan should also be allowed for pharmacodynamic and pharmacokinetic studies in humans. It can often be envisaged that we are not going to implant or deliver a CBMB product to a 'human volunteer' just for the sake of studying pharmacodynamics or kinetics. For ethical reasons we would often prefer to go directly to 'patients with the target indication'. Proposal: The clinical development plan should include …..recommend to change this text to include that : **a deviation is allowed for pharmacodynamic and pharmacokinetic studies in humans depending on the risk analysis and that a justification should be provided.** (Tigenix)	The sentence is not restrictive and the deviations might be justified, the modification was rejected.
4.4.2 Pharmacodynamics First para, starting with third sentence	It is not necessary to name specific forms of assays in this more general guideline like structural/histological assays. It is better to generally talk about suitable markers keeping more flexibility. Hence sentence three and four can be contracted. It is proposed to add a sentence saying that non-invasive methods are preferred. Proposal: The part starting with sentence three should read as follows: **If the intended use of the CBMP is to restore/replace deficient or destroyed cell/tissues, with an expected lifelong functionality, suitable pharmacodynamic markers, such as defined by microscopic, histological, imaging techniques or enzymatic activities, could be considered. Non-invasive methods are to be preferred.** (BPI)	The sentence has been considered but it was deemed not adding a relevant guidance.
4.4.2. Paragraph No: 2 Line: 2	It is proposed to consider both, the non cellular component or structural component of a CBMP. Proposal EBE: When CBMP includes a non cellular component or structural component this component should be assessed clinically for compatibility, degradation rate and functionality where administration of the non cellular component or structural component alone is	The sentence has been modified to clarify the meaning.

	appropriate. (EBE)	
4.4.2 Pharmacodynamics Para 1, starting with third sentence	We suggest not to name specific forms of assays in this more general guideline like structural / histological assays. It is better to generally talk about suitable markers keeping more flexibility. Hence sentences three and four can be contracted. Many non-invasive methods e.g., MRI, are not currently accepted as fully validated for the purposes of licensing. It is proposed to add a sentence saying that non-invasive methods are preferred. Proposal: The part starting with sentence three should read as follows: **If the intended use of the CBMP is to restore/replace deficient or destroyed cell/tissues, with an expected lifelong functionality, suitable pharmacodynamic markers, such as defined by microscopic, histological, imaging techniques or enzymatic activities, could be considered. The use of properly validated non-invasive methods are to be preferred. (EuropaBio) (Genzyme)**	See the reply for the same comment above
P21 Para 4.4.2	Propose that non-cellular component is not tested as stand-alone but as part of the final product. Might not be ethical to put "negative or neutral" control in a diseased patient if the PMOA is considered to be the biological/hTEP/Advanced Therapy product.. (Tigenix)	The sentence has been modified to clarify its meaning
4.4.4 Dose finding studies Page 22	Dose finding is an extremely difficult concept to apply to a tissue construct, the effect of which may be related to its structure as well as to its cellular composition. Further, the presence of extracellular matrix or other materials that are biologically active confounds the idea that clinical effect is related simply to the number of cells applied. Add new paragraph: **Although feasible for somatic cell therapy products, dose finding studies may be impractical to conduct for tissue-based products. The suitability of the applied dose may be justified by demonstrating the histological and structural appropriateness of the tissue for its intended function.** (BIA)	The answer is based on the definition of the drug substance. If the drug substance is the cell solution, then a dose might be defined as the cells/volume or another unit. If the drug substance is the construct, the dose is defined in the characterisation of the product itself

First line, Section4.4.4 paragraph, page 22	When using bone marrow derived stem cells/mononuclear cells/progenitor cells it is impossible to determine the amount of cells which will be harvested from the bone marrow aspirate in an individual patient, and when using autologous culture expanded cells without unlimited proliferation capacity, it is also impossible to pre-estimate the amount of cells available for clinical treatment. Therefore, it can be hard to impossible to perform regular dose titration studies. When using stem cells in regenerative medicine the amount of cells needed may vary very much depending on the amount of tissue needing regeneration. It is not clinical feasible to divide the patients into sub-group depending of the amount of tissue needing treatment, which is a demand for performing meaningful dose titration studies. In addition the regenerative capacity of the obtained autologous cells may vary considerably from patient to patient depending on patients age, diabetes etc. It is likely, that the patients will need more than one treatment depending on the regenerative capacity of the cells, the extent of the tissue i.e. myocardial scar, complexity of the bone fracture etc. Since most patients only will be treated one or two times with cells, then to individuate the safe maximal dose is not possible. Does the term of “biovigilance” have a different meaning to that of “pharmacovigilance” on page 22 ? Proposal: Amend to Phase I/II studies should if possible and feasible be designed to identify…… Amend to text as line 6. However, dose titration studies are not always applicable in clinical cell treatment studies because of the varying amount of autologous cells obtainable from the individual patient, the variation in functional capacity of the cells between different patients, the amount of tissue for regeneration, the variations in complexity of the lesion for treatment and concurrent diseases as i.e. diabetes. Amend text as required. Delete the sentence line 3: If possible, it should……. Clarify the use of these terms. (DKMA)	As above The term biovigilance is not longer used.
4.4.4. Dose finding	Current wording: “If possible, it should be individuated also the Safe Maximal Dose, defined as the maximal dose which could be administered on the basis of clinical safety studies without	The text has been reworded.

Paragraph No: 2 Line: 4	adverse effects." Rationale: It is likely that all doses are associated with adverse events, but not causally. This may be especially true when adverse events occur with the intended indication. Acceptable adverse events should be driven by the estimated risk/benefit of the product. Proposed wording: "If possible, the sponsor should identify the Safe Maximal Dose, defined as the maximal dose which could be administered on the basis of clinical safety studies with adverse effects that are compatible with the benefit-risk expectations of the product." (EBE)	
4.4.4. Dose finding studies Paragraph 2	Autologous products are prepared for an individual known patient and not in advance for a group of unknown patients (like it is in case of allogeneic products). Because of the individuality of the specific preparation in case of an autologous product a dose finding studies fitting for different patients is often not possible, therefore the relevance of such a study should be discussed in advance. Proposal: The current system for the definition of dose for pharmaceuticals is not easily applicable to medicinal products containing cells. **The relevance of dose finding studies should be discussed, especially in regard to autologous products.** These products are often used as a single administration with the dosage defined by individual characteristics of the intended patient, such as body weight (i.e. cells/kg. of body weight), volume of missing tissue (i.e. bone defect reconstruction/ regeneration), or surface (i.e. skin replacement). (EuropaBio) (BPI) (Genzyme)	It seems that for autologous products there is a misconception that all the cells available should be administered. It is not impossible to define a dose, even for an autologous product. The dose should be explored during product development.
Section 4.4.4	Dose finding is an extremely difficult concept to apply to a solid tissue construct, the effect of which may be as much related to its structure as to its cellular composition. Further, the presence of extracellular matrix or other materials confounds the idea that clinical effect is related simply to the number of cells applied. Proposal: Add after paragraph 2: Although feasible for somatic cell therapy products, dose finding studies may be impractical to conduct for tissue-based products. The suitability of the applied "dose" may be justified by demonstrating the histological and structural appropriateness of the tissue for its intended function (Zimmer)	See comment above
P21 Para 4.4.4	Both for ethical reasons in depth dose ranging studies could present problems. Also for autologous products the design of such studies and relevance should be discussed. Propose to add : The current system for the definition of dose for pharmaceuticals is not easily applicable to medicinal products containing cells. **The relevance of dose finding studies should be**	For autologous product, see comment above

	discussed, especially with regard to autologous products. (Tigenix)	
P22 4.4.4.Para 1	As above, limitations for ethical reasons (especially for the lower amounts) (Tigenix)	The limitation due to ethical reasons is not well understood. See above for comment on autologous products
Second line, Section 4.4.5 page 22	Please see comments above Proposal: Amend the sentence: to demonstrate an appropriate dose-schedule if possible that results…….Consider further. (DKMA)	All the comments are for a large degree of variability, but this is for the dossier evaluator, not for the guideline.
Line 17, Section4.4.5 page 22	…CBMP were…. Change to …CBMP <u>where</u>….(DKMA)	Editorial change accepted.
4.4.5, page 22, 5th line under Clinical efficacy	"alternatives for the target population"; add patient (as previously in the document, the notion of target cell population was used. Idem under 4.4.6, 4th paragraph, same page. (ACT) Proposal: ""alternatives for the target PATIENT population"; (RISET)	Accepted
4.4.5, 3rd paragraph of the section, page 22	"For new therapeutic applications of CBMP were limited guidance exists, consultation of regulatory authorities on the clinical development plan, including the confirmatory studies, is recommended." Recommendation sounds weak. A stronger incentive would be more adequate. (ACT) Proposal: "For new therapeutic applications of CBMP were limited guidance exists, consultation of regulatory authorities on the clinical development plan, including the confirmatory studies~~, is recommended~~ SHOULD BE CONDUCTED." (RISET)	The sentence has been modified
4.4.6 Clinical safety First para	Not only the clinical experience of similar products should be taken into regard but also the already marketed products have previous clinical experience that should be noticed. Proposal: The safety database should be able to detect common adverse events. The size of the database might be decided also in the light of previous clinical experience with similar **products or experience gained with products which are already on the market at the getting into force of the Regulation on ATMP (BPI)**	The assessment of quality of the clinical data is done at the moment of MAA , The sentence was too broad and was rejected
4.4.6 Clinical safety second para	Especially the different options for autologous or allogeneic use will have impact on the decision. Hence this differentiation should be named here. Proposal: A risk assessment of the therapeutic procedure as a whole **(including autologous / allogeneic use**), e.g. the required surgical procedures inherent to the application of the cell	The sentence has been modified to clarify the meaning

	based product or the use of immunosuppressive therapy, should be performed and used to justify the clinical studies and the choice of the target population. (BPI)	
4.4.6. Paragraph No: 2 Line: 1-3	It should also be considered that beside an assessment of the therapeutic procedure as a whole differentiated assessments of risks due to surgical procedure, the CBMP itself and any concomitant treatment (e.g. immunosuppression) could be of great importance. Differentiated assessments could enable targeting of risk minimization activities to the applicable "sub-procedure" (e.g. a surgical risk may be effectively reduced by modification of the surgical procedure alone) Insert additional phrase: "Differential risk assessment of various components of the therapeutic procedure is recommended (e.g. risks associated with the method of administration, administration devices or non-cellular components, cellular components and medical devices, concomitant medication) in order to provide a basis for targeted risk mitigation should it be required." (EBE)	The sentence has been modified to clarify the meaning
4.4.6. Paragraph No: 4 Line: 1-3	This could also be applicable to non-cell based medicinal products, but we agree that particular attention should be drawn on these three topics during development of cell-based medicinal products. We suggest a re-wording of the paragraph: Proposal EBE: ..to various biological processes. Particular attention should be paid to those biological processes including immune response, infections, malignant transformation and concomitant treatment during development and post-marketing phase of cell-based medicinal products.	The proposed modification has been accepted
4.4.6 Clinical safety Para 1	Not only the clinical experience of similar products should be taken into regard but also the already marketed products have previous clinical experience that should be noticed. Proposal: The safety database should be able to detect common adverse events. The size of the database might be decided also in the light of previous clinical experience with similar **products or experience gained with products which are already on the market before entry into force of the Regulation on ATMP where the post-market surveillance systems applied to such a product has the sensitivity to detect and assess adverse events that is equivalent to that of a licensed product (EuropaBio) (Genzyme)**	The assessement of quality of the clinical data is done at the moment of MAA , The sentence was too broad and was rejected
4.4.6, 3rd paragraph of the section page 22	"All the safety issue arising from the preclinical development should be addressed" Typography to be corrected. (EG) Proposal: "All ~~the~~ safety issueS arising from the preclinical development should be addressed" (RISET)	Accepted (editorial)

4.4.6, page 22, last sentence of the section	"Repeated administration may be associated to new or accumulated adverse effects." This sentence is just a statement and some guideline of relevance to this issue is lacking. (ACT) (RISET)	The sentence has been modified to be clarified. .
P22 Para 4.4.6	With regard to safety reporting especially where the product is applied through surgical implantation we would recommend to insert that an effort should be made to distinguish between adverse events due to the product per se and the intervention/surgery. The impact of such differentiation of side effects on the labelling should also be discussed with EMEA. (Tigenix)	The impact of the surgery is deemed to be inherent to the product use and cannot be separate din the overall evaluation .
Section 4.4.7	For products containing non-viable materials device vigilance would be more appropriate than pharmacovigilance and the CHMP guidelines on risk management plans would not be applicable. (Eucomed)	The guideline does not apply to non viable cells; if it is non cellular material it is regulated by pharmacovigilance and by Regulation
4.4.7. Paragraph No: 1 Line: 3-4	Current wording: "CBMP may need special long-term studies to monitor specific safety issues, including lack of efficacy." Rationale: Lack of efficacy may be addressed early in development. Immunogenicity or tachyphylaxis may not occur until later in dosing, and may require long-term follow-up for assessment. Proposed wording: "CBMP may need special long-term studies to monitor specific safety issues, including loss of efficacy."	The sentence has been modified accordingly.
4.4.7, page 23, last line of paragraph before references	"the (draft) Regulation for Advance Therapy Medicinal Products." (ACT) Proposal Add the reference to this document in the list of references. (RISET)	The reference has been added
References, page 24, ref 20	Typography : "Viral Safety Evaluation of Biotechnology Product Derived From Cell Lines in of human or animal origin" (ACT) Proposal: "Viral Safety Evaluation of Biotechnology Product Derived From Cell Lines ~~in~~ of human or animal origin"(RISET)	Accepted (editorial)