7 December 2012
EMA/CAT/658287/2012
Committee for Advanced Therapies (CAT)

Overview of comments received on ' Reflection paper on classification of advanced therapy medicinal products' (EMA/600280/2010)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1.	Gilbert VERBEKEN, Biologist (QA/QC/RA Manager – Senior Scientist)
2.	Eucomed
3.	Jean-Paul Pirnay
4.	Superior Health Council - BELGIUM
5.	Alliance for Regenerative Medicine and Alliance for Advanced Therapies
6.	EATRIS (IdiPAZ Centre)
7.	BPI – Bundesverband der Pharmazeutischen Industry – German Pharmaceutical Industry Association
8.	EuropaBio
9.	European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)
10.	Pfizer Inc.
11.	Voisin Consulting Life Sciences

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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1.	In relation to Community Code relating to Medicinal Products for Human use: Directive 2001/83/EC Scope of Directive 2001/83/EC: Title II SCOPE Article 2 1. This Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially of manufactured by a method involving an industrial process. In relation to Regulation on Advanced Therapy Medicinal Products, amending Directive 2001/83/EC Regulation (EC) N° 1394/2007 Scope of Regulation (EC) N° 1394/2007: (6) … The scope of this Regulation should be to regulate ATPMs which are intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process, in accordance with the general scope of the Community pharmaceutical legislation laid down in Title II of Directive 2001/83/EC. Comment: Hospitals who are preparing (even expanded) human cellular therapy products and / or human tissue engineered products on a non-profit	

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	basis for the exclusive use in their own hospital on their own patients are not covered by the SCOPE of referred Directive and Regulation. Since these hospitals (and/or MDs involved) do not perform market placement of these products. They are not interested in applying for European (or other) marketing authorization procedures either. They do not distribute their products (not even at the national level) and they never lose final product-control. They produce on a non-routine basis under their own responsibility, according to specific quality standards. They deliver their products on a named patient bases. In order to comply with an individual medical prescription. These types of products are not covered by Directive 2001/83/EC because of the definition of its SCOPE. These products cannot be considered ATMPs, for the same reason. The issue of ATMP classification for this type of products is, for these reasons, not relevant.	
2.	It is a well-written guidance document, includes lots of helpful background information, and contains many helpful examples as well as decision tree diagrams. Eucomed is a little concerned that the classification determination is legally non-binding.	
3.	The ATMP classification of some human cells, tissues, and cellular and tissue-based products (HCT/Ps) by CAT will hamper the (equal) access to HCT/Ps and will impact Member States' social health security systems. ATMP classification implies an additional layer of expensive	

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	requirements, even when the hospital exemption applies. This will put public (not-for-profit) tissue banks and laboratories, and possibly some small and medium enterprises (SMEs), the key players in the actual HCT/P transplantation field, in jeopardy. They are the only operators that target niche markets (e.g. burns), which are less attractive for large players. Some (established) life-saving, but less lucrative, HCT/Ps will no longer be accessible to patients in need. Because companies will seek to recoup their increased compliance (to national and European standards) costs, the ATMPs that will make it to the '"market" will be many times more expensive than their non-ATMP counterparts. Member States' social security systems (health insurance funds and government fixed reimbursement rates) will struggle to reimburse these products. For example in Belgium, the reimbursement price of autologous chondrocyte cultures that were classified as ATMP and obtained centralised marketing authorisation is ten times higher than that of non-ATMP autologous chondrocyte cultures. The ATMP chondrocytes are only reimbursed to patients younger than 50 y. Some HCT/Ps will only be available to self-paying patients. ATMP classification of some HCT/Ps will thus compromise the equal access to health care, a fundamental principle that is part of the human right to health care and a central objective of health care systems in most Member States, and will lead to the disappearance of some established and safe HCT/Ps. According to the Lisbon Treaty, public services such as healthcare must not subordinate to the internal EU market.	

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4.	The Superior Health Council would like the following point to be added the document: By definition, any product that contains cells or tissues, and that cannot be classified as ATMP, falls under the regulations on Tissues and Cells (transposition of directive 2004/23/EC).	
5.	1. The ARM and AAT appreciate the opportunity to comment on this paper. The Reflection Paper is helpful to provide clarity to the CAT recommendation process for the classification of ATMPs. This will help manufacturers better understand the applicable regulatory framework for their products which, in turn, will streamline drug development. 2. It would be useful to also assist manufacturers/sponsors to understand/identify the relevant legal basis for ATMPs and their regulation. To achieve this goal, the paper should also include appropriate legal references and citations to the regulation and directive. In the same spirit, we recommend adding applicable definitions from the directive where appropriate. 3. Adding a flow chart to clarify the classification process/timeline and where in the overall development timeline ATMP classification should occur would also be helpful. 4. We recommend adding text that explains the purview of the CAT versus the CHMP and how they work together regarding product review. 5. We recommend adding a decision tree for combined ATMPs. 6. There is no discussion regarding "organs" such as	

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	decellularized/recellularized organs, synthetic or engineered. 7. Where possible and appropriate, we urge consistency of classification with US regulators. 8. We recommend adding text that provides detail about the benefits of ATMP classification in the review process.	
6.	EATRIS centres praise the reflection paper as useful in the clarification of criteria followed for the classification procedure.	
7.	The Executive Summary says that the ATMP Regulation enables the European Medicines Agency (EMA) in close collaboration with the European Commission to determine whether or not a given product meets the scientific criteria, which define ATMPs. Below it is said that the ATMP classification is a non-mandatory, free of charge, legally non-binding procedure that helps developers to clarify the applicable regulatory framework. This construct seems to be too vague. What shall an applicant do in the case the result of the EMA classification is that a given product is a non-ATMP and therefore outside the scope of the Regulation with the effect that it is even not a medicinal product but falls under the Tissue and Cells Directive 2004/23/EC and the competent authority in a member state does not share this view saying that it is an ATMP and the Regulation does apply? Due to the fact that Article 17 of the Regulation says that the Agency shall deliver its opinion after consultation with the Commission our point of view is that the decision becomes binding by the fact that the	

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	Commission is involved. If a member state decides not to take the view of the EMA it even acts against the view of the Commission. This would even be problematic taking into regard the principle of the European single market and the free movement of goods and would contradict the competence of the CAT.	
8.	EuropaBio, the European Association of Biotechnology Industries, thanks the European Medicines Agency (EMA) for the opportunity to submit comments on reflection paper on classification of advanced-therapy medicinal products. EuropaBio's mission is to promote an innovative and dynamic biotechnology based industry in Europe. EuropaBio, has 56 corporate and 11 associate members operating worldwide, 3 Bioregions and 19 national biotechnology associations representing some 1800 small and medium-sized enterprises. In general, we welcome the publication of this guideline which clearly helps to understand how the CAT is proceeding to classify a product as an ATMP or not and what the decision-making criteria are. We found figures 1 and 2 very useful, as well as examples and explanation provided in section 2.3. A paragraph dealing with the impact of an ATMP classification with regard to the MAA dossier and the assessment by the CAT and the CHMP at the time of the MAA would be welcomed. The delineation of responsibilities between CAT and National Medicines Agencies to determine whether an ATMP falls under the "hospital exemption" should be clarified in the introduction of this document. In addition, criteria for classification as "hospital	

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	exemptions" or ATMP should be better defined and elaborated within this document. In addition to the explanations provided in this guideline, we would also suggest providing 2 additional sections to clarify: the right / recommended timing to request an ATMP classification (consider stressing that, when a doubt exists on the classification of the product, it is highly recommended to come early in the development to make sure appropriate development is made) – specific examples may be provided (Orphan Drug Designation, Scientific Advice, for example) In reference to the sentence in lines 33-34, the incentives and services offered by EMA. Moreover, whilst it is reminded that the recommendation for classification of ATMP is non-binding, it should be acknowledged that there might be "grounds for divergent position" expressed amongst the CAT before reaching a recommendation. Likewise, currently such "Annex C: Grounds for divergent position" should still be appended and made available to the applicant since it allows flexibility at national level in the interactions with local stakeholders involved in regulatory processes. (22-23 / 35-39 / 135-143). <u>General remarks</u> Developing cellular therapies for clinical application has become even more complex due to the overhaul of regulations and any clarifications can help to guide the field. It must be kept in mind though that historically most ATMP developments have been started or were conducted in an academic environment. Especially the	

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	distinction of a cell therapy that needs a marketing authorisation and normal medical practice is missing and continues to create confusion (for instance as commented in line 208-231 and 261), it should be acknowledged and confirmed that hematopoietic stem cell transplantation (HSCT) using either autologous or allogeneic cells does not fall under the ATMP remit. The different handling of such questions by member states is further complicating the scenario. There must be clear guidance for medical practitioners and there should be legal clarity about what constitutes activities of drug development and utilisation. It would be highly valuable to the field to develop guidance which enables and identifies a clear delineation between medical practice and medicinal products. The medical practice involves many procedures that could otherwise fall under the rules governing medicinal products, thereby, necessitating a marketing approval.	
9.	Developing cellular therapies for clinical application has become even more complex over the last years due to the overhaul of regulations and any clarification can help to guide manufacturers. It must be kept in mind though that historically most ATMP developments have been started or were conducted in an academic environment. Especially, the distinction of a cell therapy that needs a marketing authorization and normal medical practice is missing and continues to create confusion. The different handling of such questions by Member States is further complicating the scenario. There must be clear guidance for medical practitioners. It would be of extreme value if guidance could be developed that allows the clear distinction when the line is crossed from medical	

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	treatment to developing a medicinal product. Furthermore, clarification would be welcomed regarding the binding character of an ATMP classification which involves the EMA and the Commission and the effect on authorities in Member States to ensure a clear distinction to the Tissue and Cells Directive 2004/23/EC.	
10.	The reflection paper is timely and will provide useful clarification to applicants and companies developing ATMPs.	
11.	We would first like to thank you for the draft reflection papers and guidelines recently open for consultation which we commented via an industry association. Despite the clarity of the 2001/83/EC Annex I part IV as last amended and of the draft reflection paper on ATMP classification, there is a piece of information we couldn't find: the definition of what is considered a cell. The reason why we bring this point is that we wonder whether the CAT would regard erythrocytes as cells or not. To our knowledge, erythrocytes are not "true cells" as they don't have the key features of a cell and in particular the ability to perform metabolic and signalling activities. We have noticed that some companies and academics develop some biological medicinal products that are "encapsulated" in erythrocytes. The latter are thus used as a "host" or a "vehicle". We are therefore wondering whether such a biological vehicle should be regarded as a cell.	

2. Specific comments on text

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
9	8.	**Proposed change (if any):** medical devices, transplants~~, and~~ cosmetics, etc.	Accepted.
24	8.	**Comment:** The ATMP classification is also an opportunity for the developer to define what the drug substance and the products are, which is not obvious for some ATMPs. **Proposed change (if any):** (…) and scientific-regulatory guidance to be followed. *In addition, the ATMP classification is an opportunity for the developer to propose a definition for the drug substance and the drug product.*	Not accepted. The definition of drug substance and drug product by the developer will not impact on the outcome of the classification.
22-23 35-39 135-143	8.	**Comment:** Whilst it is reminded that the recommendation for classification of ATMP is non-binding, it should be acknowledged that there might be "grounds for divergent position" expressed amongst the CAT before reaching a recommendation. Likewise it currently the case, such "Annex C: Grounds for divergent position" should still be appended and made available to the applicant since it allows flexibility at national level in the interactions with local stakeholders involved in regulatory processes.	Not accepted. The adopted CAT scientific recommendation represents the position of the Committee with regards to a classification issue. The outcome of the ATMP classification does not change regardless of whether it is adopted by consensus or majority vote.

		Proposed change (if any): … "In borderline cases, reflecting the CAT's transparency and open dialogue with the applicant, the ATMP classification may contain a specific annex capturing the "Grounds for divergent position" expressed during the process.	
35-39	7.	Comment: The language of this paragraph should be changed since the CAT's recommendation should also help to clarify the national marketing authorization requirements for any classified product. It is very problematic if national authorities would decide to overrule the CAT's decision.	Not accepted. The ATMP classification is a legally non-binding procedure.
54 ff.	7.	Comment: In the Chapter "Legal basis of ATMP Classification" the current legal framework is summarised but the legal implication of CAT's decisions for individual member states is not addressed. Proposed change (if any): Reflection paper should not only provide a summary of the legal basis for ATMP classification, but should also clarify the legal consequences, in particular how a legally binding classification for all member states can be obtained.	Not accepted. The ATMP classification is a legally non-binding procedure.
Line 54 et seq.	9.	**Comment:** In the Chapter "Legal basis of ATMP Classification" the current legal framework is summarized but the legal implication of CAT's decisions for individual Member States is not addressed.	Not accepted. The ATMP classification is a legally non-binding procedure.

		Proposed change (if any): The Reflection paper should clarify the legal consequences, especially with regard to the decisions of authorities in the Member States.	
63	8.	**Comment:** A dot is missing at the end of the sentence. **Proposed change (if any):** "(…) the product a medical Device (see below)."	Accepted.
80	8..	**Comment:** Substantial manipulation should be only considered if the physiological function has been altered. Cells and tissues having the same function as their physiological counterpart should be considered as safe.	Not accepted. The text provided in lines 79-82 is part of the legal definition of somatic cell therapy medicinal product. It is not possible to change the definition given in the ATMP Regulation.
Line 80	9.	**Comment:** Substantial manipulation should only be considered if the physiological function has been altered. Cells and tissues having the same function as their physiological counterpart should be considered generally as safe.	Not accepted. The text provided in lines 79-82 is part of the legal definition of somatic cell therapy medicinal product. It is not possible to change the definition given in the ATMP Regulation.
Line 92	9.	**Comment:** Radiolabeling of leukocytes is considered as no substantial manipulation since it has been used in a hospital setting since many years. The restriction to this special cell product (radiolabeling of leukocytes) is not comprehensible. Procedures that have been accomplished safely in the past can be considered as safe in general unless the opposite is proven. **Proposed change (if any):**	Partly accepted. Radiolabeling of leukocytes is provided as an example of non-substantial manipulation. The considerations of the CAT on what constitute a substantial manipulation is not drawn on the basis of the safety of the procedure but on whether the manipulation would alter the biological characteristics, physiological functions or structural properties of the cells and tissues.

		Thus the specification to radiolabeling of leukocytes should be eliminated in line 92.	
92	8.	**Comment:** Radiolabelling of leukocytes is considered as no substantial manipulation since it has been used in a hospital setting for many years. The restriction to this special cell product (radiolabeling of leukocytes) is not understandable. Procedures that have been accomplished safely in the past should be considered as safe in general. Thus, the specification to radiolabeling of leukocytes should be removed in line 92. If radiolabelling of leucocytes is considered as non-ATMP products, it should be generalised. **Proposed Change:** The labelling of primary cells, intended for the application in man, with drugs, radioactive substances or in vivo diagnostics, should be considered as no substantial manipulation.	Partly accepted. Radiolabeling of leukocytes is provided as an example of non-substantial manipulation. The considerations of the CAT on what constitute a substantial manipulation is not drawn on the basis of the safety of the procedure but on whether the manipulation would alter the biological characteristics, physiological functions or structural properties of the cells and tissues.
124-126	5.	Comment: The statement that "any device/cell combination shall consider the cells/tissue as the principal mode of action of the product" does not allow flexibility for combination products where the device may present the actual mode of action of the combination product. Proposed change: A combination product containing viable cells or	Partly accepted. The text has been revised to clarify that the paragraph does not refer to combined ATMPs but to all ATMPs.

		tissues may be considered either a device or Combined Advanced Therapy Medicinal Product; this determination will be made based on the combination product's principal mode of action. Define the criteria for the device/matrix by function.	
190 to 192	8.	**Comment:** This example is according to us very specific and exceptional, as in a general manner such solution for transduction is considered a raw material in the manufacturing process of genetically modified tissue, as opposed to a medicinal product. In this particular case, as this classification is i) very specific i.e. unlikely to be helpful for the majority of stakeholders and ii) likely to be confusing, we suggest removing this example. Alternatively, it could be clarified and emphasised that this would not be systematically applicable to similar products submitted for classification, (as done in section 2.3.1 line 314 to 317 regarding pancreatic beta cell products). As a matter of fact, it pertains to the "borderline cases" which should be addressed on a case by case basis and reference is made to comment on lines 22-23 / 35-39 / 135-143. **Proposed change (if any):** ~~The gene transfer does not necessarily have to take place in the human body, since for example the product encoding <…….> for ex-vivo transduction of corneal tissue has also been classified as a gene therapy medicinal product.~~	Partly accepted. The text has been revised

198 & 199	8.	**Comment:** The last sentence is confusing and not helpful. One may understand that the reason why gene-based medicinal product for the treatment of cancer can be classified as GTMP is because they are intended for (therapeutic) immunotherapy. Some gene-based viral vaccines are also intended for immunotherapy i.e. treatment of infected patients. We therefore suggest deleting this sentence. **Proposed change (if any):** ~~This is, on a scientific level, also stressed by the fact that the term "cancer vaccine" is considered obsolete and should be replaced by "cancer immunotherapy product".~~	Partly accepted. The text has been revised
204	8.	**Comment:** There is a typo in this sentence: "r" is missing. **Proposed change (if any):** "The recombinant nucleic acid is used in or administered to human being with a view to regulating, repairing, replacing, adding o**r** deleting a genetic sequence"	Accepted.
208-231	8.	**Comment:** It should be acknowledged/confirmed that Hematopoietic stem cell transplantation (HSCT) using either autologous or allogeneic cells does not fall under the ATMP remit.	Not accepted. The following clarification has been included in the reflection paper: It is acknowledged that some products containing Hematopoietic stem cell (HSC) using either autologous or allogeneic cells do not fall under the ATMP remit, unless they are substantially manipulated and/or used for non-homologous use. However, when these products are not used for the same

		Proposed change: "For instance, it is confirmed that Hematopoietic stem cell transplantation (HSCT) using either autologous or allogeneic cells does not fall under the ATMP remit."	function in the recipient and the donor they are considered ATMPs. A typical example is minimally manipulated bone-marrow derived stem cells injected in the myocardium intended for post-myocardial infarction cardiac repair.
211	8.	**Comment:** Substantial manipulation should be only considered if the physiological function has been altered. Cells and tissues having the same function as their physiological counterpart should be considered as safe.	Not accepted. The safety of the product does not impact on its ATMP classification.
Line 211	9.	**Comment:** Substantial manipulation should only be considered if the physiological function has been altered. Cells and tissues having the same function as their physiological counterpart should be considered generally as safe.	Not accepted. The safety of the product does not impact on its ATMP classification.
214	8.	**Comment:** The phrase 'cell expansion (culture)' is not precise enough. A culture of cells does automatically mean: expansion or differentiation of cells, both resulting into the ATMP status. Therefore a definition of "incubation" of cells should be given additionally. Cell culture especially needs to be defined and distinguished from storage. The next paragraph talks about structural and biological changes through culture but how does this apply to storage? Storage process (including the freeze/thaw steps) is not intended to result in a cell expansion; it rather aims at preserving a certain state of being. Although it	Not accepted.

		is acknowledged that storage at -20°C and even in dry ice does not stop biological activity and only storage in (gas phase of) liquid nitrogen <130°C can be considered as real 'storage' (hold of time) during which no biological activity occurs, an agreement should be reached between EMA and developers upon further discussion on the expectations of the stakeholders. If no distinction is made, storage of cells for i.e. shipment could be considered cell culture if a cell doubling has occurred. Therefore storage needs to be defined in comparison to culture especially as it relates to time and occurrence of cell doublings or complications such as senescence and chromosomal aberrations. **Proposed changes:** Definition of *Cell Cultivation*: Cell cultivation means the expansion and/or differentiation of the cell(s) in vitro to alter the cell function. Cell cultivation is considered as substantial manipulation. Definition of *incubation* of cells: Cell incubation means the in vitro incubation of cells under appropriate conditions without expansion or differentiation of the cell. Incubation may become necessary to label the cells with e.g. radioactive labels or in vivo diagnostics. Incubation is considered as non-substantial manipulation.	
Line 214	9.	**Comment:** The phrase 'cell expansion (culture)' is not precise enough. Cell culture especially needs to be defined and distinguished from storage. The next paragraph	Not accepted.

		mentions structural and biological changes through culture. It is unclear how this should relate to storage? Storage is not intended to result in a cell expansion; it rather aims to preserve a certain state. If no distinction is made, storage of cells e.g. for shipment could be considered cell culture if a cell doubling has occurred. **Proposed change (if any):** Therefore storage needs to be defined in comparison to culture especially as it relates to time and occurrence of cell doublings or complications such as senescence and chromosomal aberrations.	
216	7.	Comment: It should be clarified that cell enrichment alone is not by default considered substantial manipulation. Nothing should by default be considered substantial manipulation. All decisions should be taken on basis of scientific evidence.	Partly accepted. The text has been revised as follows: Cell enrichment and expansion by culturing is currently considered substantial manipulation. Although it may not necessarily lead to immediate changes in cell functionality or the phenotype of the cells before and after culture, it is possible that the biological characteristics, physiological function(s) or structural properties of the cells are changed by cell culture
216	8.	**Comment:** The CAT admits that cell enrichment and expansion may not necessarily lead to apparent changes in cell behaviour. Therefore cells that do not change in terms of cell behaviour should not be classified as ATMPs. The paragraph about culturing conditions of MSC gives no further information on the estimation of risks associated with the application of MSCs.	Partly accepted. The text has been revised as follows: Cell enrichment and expansion by culturing is currently considered substantial manipulation. Although it may not necessarily lead to immediate changes in cell functionality or the phenotype of the cells before and after culture, it is possible that the biological characteristics, physiological function(s) or structural properties of the cells are changed by cell culture
Line 216	9.	**Comment:**	Partly accepted.

		The CAT states that cell enrichment and expansion may not necessarily lead to apparent changes in cell behaviour. Therefore cells that do not change in terms of cell behaviour should not be classified as ATMPs.	The text has been revised as follows: Cell enrichment and expansion by culturing is currently considered substantial manipulation. Although it may not necessarily lead to immediate changes in cell functionality or the phenotype of the cells before and after culture, it is possible that the biological characteristics, physiological function(s) or structural properties of the cells are changed by cell culture
226	8.	**Comment:** The treatment of a patient always implicates that physiological functions are disturbed. Therefore it is not comprehensible that cells must be used the same way in the patient as in the donor.	Not accepted. *The legal definition cannot be changed.*
Line 226	9.	**Comment:** The treatment of a patient always implicates that physiological functions are disturbed. Therefore it is not clear why cells must be used the same way in the patient as in the donor.	Not accepted. *The legal definition cannot be changed.* .
227	8.	**Comment:** Mentioning the injection of bone marrow derived cells into the heart is given as an example for non-homologous use. Since there is evidence that CD133 positive stem cell can migrate from the bone marrow into the heart while physiological cell regeneration processes take place the evidence of this example is not comprehensible. Furthermore the application of CD133 positive cells has been shown to be safe in clinical trials. Zeile 247 As mentioned in line 247 isolated pancreatic cells are classified as non-ATMP since the restoration	Not accepted. *The number of cells administered in case of administration of these kinds of products is much higher than normal physiological migration from bone marrow. According to the current view of the CAT when bone marrow derived cells are injected into the heart, intended for of the myocardium, which is considered non-homologous use.* Isolated pancreatic islets, when non-substantially manipulated, are not ATMPs.

		of beta cell activity is not considered as tissue regeneration. It should be taken into account that hibernated heart muscle cells are restored by the action of CD133 positive stem cell, too. The difference between restoration and reparation should be clarified. Apparently no risked based approach that has been taken into account differentiating between restoration and reparation.	Pancreatic cells, in alginate matrix have been classified as ATMPs
Line 227	9.	**Comment:** The injection of bone marrow derived cells into the heart is given as an example for non-homologous use. Since there is evidence that Cd133 positive stem cell can migrate from the bone marrow into the heart while physiological cell regeneration processes take place, the evidence of this example is not comprehensible. Furthermore the application of CD133 positive cells has been shown to be safe in clinical trials. As mentioned in line 247, isolated pancreatic cells are classified as non-ATMP since the restoration of beta cell activity is not considered as tissue regeneration. It should be taken into account that hibernated heart muscle cells are restored by the action of CD133 positive stem cell, too. The difference between restoration and reparation should be clarified. Apparently no risked based approach that has been taken into account differentiating between restoration and reparation.	Not accepted. *The number of cells administered in case of administration of these kinds of products is much higher than normal physiological migration from bone marrow. According to the current view of the CAT when bone marrow derived cells are injected into the heart, intended for of the myocardium, that is considered non-homologous use.* Isolated pancreatic islets, when non-substantially manipulated, are not ATMPs. Pancreatic cells, in alginate matrix have been classified as ATMPs
260 (Decision Tree)	5.	Comment: Viability of cells as criteria -- a. It is not clear how nonviable cells can act by	Partly accepted. The flow chart has been updated.

		pharmacological or metabolic action. b. Viability of cells may not always be an appropriate criteria -- should consider whether a product causes a systemic effect in the body. Comment: Propose addressing how to address if a product is both a sCTMP and TEP. How non-viable cells affect viable cells and the device as a whole.	
261	7.	Comment: It is confusing that there are two arrows which lead away from the answer "Yes" to the question "Cells or tissue(s) substantially manipulated?". Moreover, it is confusing, that one possible outcome is "END". Proposed change (if any): The arrow running from the aforementioned answer "YES" to the question "Are the cells genetically modified?" could be removed. Instead, the question "Are the cells genetically modified?" could be integrated in the remaining single arrow leading away from the "YES". The outcome "END" could be removed and the answer "NO" could be re-connected to the single arrow aiming at the two possibilities "Product intended for treatment … / regeneration …".	Partly accepted. The flow chart has been updated.
261	8.	**Comment:** It should be clarified that Hematopoietic stem cell transplantation are an exemption from the classification.	Not accepted. It is acknowledged that traditional transplantation containing Hematopoietic stem cell (HSC), either autologous or allogeneic, do not fall under the ATMP remit, unless they are substantially manipulated and/or used for non-homologous

			use. However when these products are not used for the same function in the recipient and the donor they are considered ATMPs. A typical example is minimally manipulated bone-marrow derived stem cells injected in the myocardium intended for post-myocardial infarction cardiac repair.
263	8.	**Comment:** Further guidance as to whether a component would be considered as a medical device or not would be helpful. **Proposed change (if any):** Add a flow chart for the combined product decision process with an option regarding the designation of a component as a medical device or not. This would also be reflected in additional explanatory text in section 2.2.4.	Not Accepted. *The decision on whether a component is a medical device or not is not under the remit of CAT but of the MD competent authority.* *Included references to MDD and IVD* *OK, consider to add a 3rd decision tree or modify the 2 existing*
266-269	6.	Comment: *Combined ATMPs should also include devices (not physically including cells but) which may steer and interact with cells and tissues in order to modify or to direct them to specific body locations.* *An example of this could be guidance of cells, charged with magnetic material, to specific locations by a device able to produce and modify magnetic forces.* Proposed change: At the end of line 269 add: *"Combined ATMPs also include devices which may*	Not accepted. The examples provided does not fit in the definition of combined ATMPs. The medical device should be integral part of the combination product..

		steer and interact with (engineered) cells and tissues in order to modify or direct them to specific body locations."	
271 & 272	8.	**Comment:** Details about culture expansion are not needed to explain the classification here. **Proposed change (if any):** Autologous chondrocytes are ~~put in culture medium in order to proliferate until the appropriate number of cells is reached. The expanded cells are thereafter~~ seeded onto a collagen membrane (…)	Accepted
277 to 279	8.	**Comment:** The description of this product could be simplified. **Proposed change (if any):** Autologous osteoprogenitor cells~~,~~ ~~isolated from bone marrow~~, *are grown within and around a* ~~cultured together with~~ a bioresorbable scaffold, which is CE marked for surgical use~~. During cell culture, the cells expand and grow within and around the scaffold~~ ~~that~~ and acts as physical support.	Accepted.
277-283 & 371-373	10.	**Comment**: In the examples provided, it is stated that the device is CE marked for surgical use. We are unclear on the CATs distinction between 'medical devices, 'bio-materials', 'scaffolds' or 'matrices' (see Article 7 of Regulation 1394/2007). We consider that medical	Not accepted. It is not part of the CAT ATMP classification to make the distinction between MD, scaffolds or matrices but the distinction is included in the ATMP regulation (include X-ref to specific article).

		devices requiring CE marking have an independent medical function (e.g. stents). Scaffolds and matrices, however, structurally support the administration of the active material (advanced therapy). These materials would therefore comply with Article 3 of Directive 93/42/EEC and would not require a CE mark. **Proposed change (if any)**: Clarification by CAT of CE marking requirements of medical devices in combination therapies and clarification of definition/distinction of 'medical device' and 'scaffold/matrix'.	
283	6.	Comments: Proposed change: *After line 283 add: "Mother cells charged with magnetic material are modified or directed to specific body locations by a device able to produce and control magnetic forces."*	SEE ABOVE
308-317	10.	**Comment**: In the example provided (a preparation of human pancreatic Langerhans' islets), CAT did not consider this an ATMP, because the described 'process steps do not constitute substantial manipulations'. We presume the processing did not include substantial manipulation as described in §2.2.3(paragraph 1). It would be helpful if this was made explicit. It would also be helpful if CAT could provide comments on the distinction between Tissues and Cells for	Partly accepted. *Clarification has been included in section 2.2.3 of the reflection paper.*

		transplant/transfusion and ATMPs. In our recent experience an EU CA considered an IMP was controlled under national transplant legislation, distinct from ATMP legislation. Does CAT consider there may be examples where products would be both ATMPs and transplant products? **Proposed change (if any)**: Explicit guidance on the assessment distinction between products at the border between the EU Tissue and Cells Directive (2004/23 EC).	
Lines 381 et seq.	9.	**Comment:** It is unclear why all data mentioned should be deemed as minimal and necessary to be submitted. In certain cases the complete data set may be required for a decision about classification. This is, however, not necessary for every case. In such cases less information should be required. **Proposed change (if any):** Add a sentence such as: "Comprehensive scientific information relevant to the decision is essential to be submitted in order for the CAT to classify a product, e.g. on following areas:"	Partly accepted. The text has been changed as follows: "Sufficient scientific information relevant to the decision is essential to be submitted in order for the CAT to classify a product, e.g. on following areas:"
353	5.	Comment: This section assumes no role of the device in the mechanism of action and contains contradictions; more clarity on the definition of "active integral part" is needed.	Not accepted. It is not possible for the CAT to provide a list of approved polymers and matrices today available CE marked for human use.

		Proposed change: list of approved polymers and matrices today available CE marked for human use	
379-380	2.	The CAT is supposed to deliver a recommendation within 60 days of receipt of a valid request. But if there is not enough data to support the claimed mechanism of action, we presume it will be considered an invalid request. This will be a difficult hurdle to pass for those new technologies whose mechanisms of action may not be completely understood, let alone substantiated by data.	Accepted. *Clarification:* *The validation of the request is an administrative step ensuring that the scientific information needed to classify the product is included. This step does not entail a pre-assessment of the information provided.* *In case the CAT needs additional information to conclude on the classification of the product the clock of the procedure is stopped.* *In the case that the mechanism of action is not fully clarified the classification is based on the information provided by the Applicant.*
381 ff.	7.	Comment: It is not clear, why the complete information mentioned is deemed as minimal and necessary to be submitted. It is not questionable, that all this information from case to case may be required and contribute to a decision about classification. However, there are cases, where much less information is	SEE ABOVE

		relevant to this decision. In these cases a lot of information is dispensable. Proposed change (if any): A sentence like the following would contribute to this: "Comprehensive scientific information relevant to the decision is essential to be submitted in order for the CAT to classify a product, e.g. on following areas:"	
388	8.	**Comment:** By "Qualitative and quantitative", one might understand that an extensive characterization of the product is required to request for a scientific recommendation for classification, while a qualitative description is likely to be sufficient. **Proposed change (if any):** Finished Product: ~~qualitative & quantitative~~ composition (at least qualitative, hence semi-quantitative where relevant), (…)	Partly accepted. Finished Product: qualitative and quantitative (where available) composition
406	8.	**Comment:** Same remark as 388. **Proposed change (if any):** In addition to the qualitative and semi-quantitative description of the product to be classified, (…)	*SEE ABOVE*