28 May 2015
EMA/CAT/224106/2015
Committee for Advanced Therapies (CAT)

Overview of comments received on 'Reflection Paper on classification of advanced therapy medicinal products' (EMA/CAT/600280/2010 rev. 1)

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

Stakeholder no.	Name of organisation or individual
1.	Cell Surgical Network
2.	Cell Surgical Network
3.	IFAPP (International Federation of Associations of Pharmaceutical Physicians)
4.	Alliance for Regenerative Medicines
5.	Cord:Use Cord blood bank
6.	Paul-Ehrlich-Institut Germany
7.	Finish Red Cross Blood service
8.	Federal Agency for Medicines and Health Products (FAMHP) Belgium
9.	Prof Palamara Italy
10.	International Consortium for Cell Therapy and Immunotherapy ICCTI
11.	STEMSO The International Stem Cell Society
12.	Swedish Health and Social Care Inspectorate
13.	Dr NEMSEFF Spain
14.	LFB
15.	Etablissement Français du Sang (French Blood Service)
16.	IKEM (Inst. Clin. & Experim. Med.) CZ
17.	Novagenit, Italy
18.	R Beretta, Italy
19.	Theravectys
20.	CellThera, CZ
21.	French Orthopaedic Society
22.	Human Med AG
23.	R Beretta - 2nd list

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Stakeholder no.	Name of organisation or individual
24.	David R Harell USA
25.	Immunorheumatology and Tissue Regeneration Laboratory Italy
26.	DENS caninus sro CZ
27.	France Biotech
28.	Hellenic Cord Blood Bank
29.	Platform for Advanced Cellular Therapies
30.	REgenableMED
31.	VFH Vašíček a partneři s.r.o., advokátní kancelář (CZ)
32.	Association of Aesthetic Practitioners (AAP)
33.	National Centre for Tissue and Cell Banking, Poland
34.	European Association of Tissue Banks
35.	GISM (Gruppo Italiano Staminali Mesenchimali)
36.	Italian Society of Vascular and Endovascular Surgery (SICVE)
37.	Xcelia, Advanced Therapies Division. Banc de Sang i Teixits. Barcelona Spain
38.	Lawford Davies Denoon (UK) and Alliance of European Life Sciences Law Firms
39.	Clinic for Plastic, Aesthetic and Reconstructive Surgery, Spine, Orthopedic and Hand Surgery, Preventive Medicine at Heidelberg University Hospital – ETHIANUM – Germany
40.	Stem Center S.L.U., Spain
41.	Alliance for Regenerative Medicine – European Section (formally known as Alliance for Advanced Therapies).
42.	German Pharmaceutical Industry Association – Bundesverband der Pharmazeutischen Industrie (BPI e. V.)
43.	Cook Medical Denmark
44.	European Blood Alliance (EBA)
45.	European Association of BioIndustries (EuropaBio)
46.	Human Tissue Authority, UK
47.	InGeneron
48.	International Society for Cellular Therapy (ISCT)
49.	Italian National Transplant Center
50.	MLB lab DE
51.	National cell and tissue centre, CZ
52.	Pfizer
53.	Regen Lab SA
54.	UK Catapult cell therapy
55.	BIRD-C GmbH&CoKG (DE)
56.	Austrian cluster Tissue regeneration
57.	Dr Mayo Friedlis - Stemso The International Stem Cell Society
58.	Tissue Engineering and Regenerative Medicine International Society (TERMIS-EU) – European Chapter
59.	ARI (AO Research Institute Davos)
60.	EBE (European Biopharmaceutical Enterprises)

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1. General comments – overview

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1.	We understand the need to provide some type of regulation in the area of using biologics for therapeutic goals. Clearly, no one wants to put the public at risk beyond generally acceptable limits that always exist even when employing the therapeutic use of approved drugs or devices. We also realize that much of the regulations developed by a multitude of medical organizations have used the framework developed by the US FDA. The US FDA was mandated to provide regulations about the production of Human Cells, Tissues, and Tissue-Based Products (HCT/Ps) for the expressed purpose to assure the prevention of the transmission of communicable disease. This request by the US Congress (2005 – 21 CFR part 1271) serves as the sole purpose of the regulation. Somehow, competing scientists and doctors that would like to take advantage for self-interested reasons have managed to obscure this important issue. In order to have jurisdiction over HCT/Ps the FDA needed to define under what conditions your body parts could be considered drugs. To that end, of course, much like the mandate in the current "Reflection Paper," they established a set of guidelines that would exempt one from such oversight. When there is a risk of disease transmission, particularly when manufactured under laboratory constraints, then the FDA has particular jurisdiction and it's rather clear how they can implement their authority over such organizations. Indeed, in the USA, the FDA has closed down a number of organizations that claimed production of autologous stem cells from bone marrow and fat. In all cases, the FDA cited lack of GMP facility or overall lack of cleanliness in violation of 21 CFR part 1271. In order to assert their jurisdiction, they needed to show that the process involved in producing the particular HCT/Ps fell under their jurisdiction (i.e. qualified as a drug). Contrary to this the FDA has evaluated a number of organizations that provided same day cells (adipose or bone marrow derived) at the point of care even with collagenase (GMP grade) enzyme and took no action to stop these organizations. While the FDA clearly has jurisdiction over laboratory procedures, other than	Thank you for the comment. This guidance is released by CAT/EMA for classification of ATMPs in Europe. The guidance is written in compliance with the European legislation and concerns all products based on genes and/or cells intended for treatment/diagnosis/prevention of disease or for regeneration/repair/replacement of a tissue defect. As such, cell preparations manufactured using devices (e.g. from Cytori) and given to patients, may be classified as ATMPs, if fulfilling one of the ATMP definition, irrespective whether or not produced and given within one surgical procedure (see Regulation 1394/2007).

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	assessing possible risk of disease transmission with HCT/Ps, they have never had any jurisdiction over surgical procedures. There is not a single surgical procedure approved by the FDA. In this context, there are several situations where physicians (e.g. Cytori, Tissue Genesis, Cell Surgical Network and similar organizations) perform a closed sterile surgical procedure without any laboratory requirements using all GMP products thus eliminating any risk of communicative disease.	
2.	See 1.	See above.
3.	We agree on the proposed contents of the reflection paper.	Thank you.
4.	The Alliance for Regenerative Medicine (ARM) welcomes publication of this Reflection Paper which includes very useful examples and explains further the thinking behind classification decisions by the European Medicines Agency (EMA) Committee of Advanced Therapy (CAT). In the past ARM Members have found this process helpful and look forward to requesting classification for future innovative products. We appreciate the commitment to transparency and communication demonstrated by the revision of this reflection paper. Recognizing that at times EMA and FDA offer coordinated advice (such as coordinated orphan designation and scientific advice), where possible (given differences in the regulatory frameworks for devices), we encourage joint efforts or participation in forums seeking regulatory harmonization of the classification of cell, gene and tissue therapies. Further, in addition to providing ATMP Classification by determining whether the applicant product is an advanced therapy medicinal product (ATMP), we feel the procedure should go further and provide ATMP Definition Recommendations to the applicant and provide preliminary recommendations on the definition of the active substance, the strength (units to be used) and the pharmaceutical form. In addition, it may be helpful to agree on wording for the finished product (formulated active substance). We understand this procedure would not be binding and we understand that the ATMP Classification and the proposed ATMP Definition Recommendations would be	Thank you for the comment and proposals. Classification of gene- and cell-based products is one of the tasks of the CAT, defined in the Regulation 1394/2007. Further considerations on active substance, strength and finished product cannot be separately included into any CAT procedure, but they are part of the marketing authorisation, for which the companies can always ask scientific advice at any stage of product development. Currently, the CAT recommendations for ATMP classifications are not binding and as such, there are no possibilities for appealing about the CAT classifications. Reclassification of a product, on the other hand, is possible, especially if more information is gained about possible MoA of the product. The main difference in development of somatic cell therapy and tissue engineered products may be in the clinical part and especially the

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	reviewed and confirmed or modified by EMA CHMP and CAT during the development of the product (via Scientific Advice or Protocol Assistance) or during the marketing authorisation application (MAA) review. It is also understood that at some point in the product development, the applicant will apply for an International Non-proprietary Name (INN) and a trade name which should help streamline these issues during the MAA process; however, this is usually conducted late in the development and is not necessarily required for MAA review. Therefore, feedback on the anticipated definitions of active substance and potentially finished product early in the development would be helpful to ensure consistent product nomenclature throughout multiple regulatory procedures (i.e. ATMP classification, orphan designation, Paediatric Investigation Plan (PIP), Scientific Advice, clinical trial applications, Eudravigilance, etc.). For example, currently, the list of potential pharmaceutical forms available to applicants in the forms provided by EMA for a PIP is not necessarily the same list of options provided on a clinical trial application EudraCT form, or the list of Standard Terms available from the European Directorate for the Quality of Medicines (EDQM). Further, as is the case for several ex vivo gene therapy products currently, the description of the active substance for the product can differ between the CAT ATMP classification, the orphan designation, and the PIP for the same product. Without clarity on the preferred nomenclature for the active substance and finished product early in development, these differences could have an impact on the definition of product specifications for release, and create significant administrative burden for both the agency and industry, particularly for SME applicants. We suggest that the concept paper also consider information for applicants who wish to appeal CAT decisions on ATMP classifications. Additionally, it may be helpful think about how future innovative technologies which may not fit in the current three ATMP categories (cell therapy, gene therapy or tissue engineering product) could still be classified as ATMPs. It would also be useful for the EMA to explain the implications of being classified as	selection of end points, which may be different for these two product categories. The CAT classifications are always triggered by a request from an Applicant and based on the information provided by the Applicant, including available (published) scientific data/information about the cells and their possible functions. According to Reg.1394/2007, if a product fulfils both somatic cell therapy medicinal product and tissue engineered product (TEP) definitions, the TEP classification prevails.

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	either a somatic cell ATMP or a tissue engineered ATMP with regards to what differences in information the EMA will require at MAA for these two classifications. It seems that a product with a little known MOA is more likely to be classified as a tissue engineered ATMP as the language regenerate, repair or replace is a “catch-all” but as the development of the product progresses then it might be determined that its MOA does indeed involve some pharmacological, immunological or metabolic action. Is reclassification possible or necessary and might this then require the sponsor to develop additional supporting information? If a product regenerated, repaired or replaced human tissue by a pharmacologic, immunologic or metabolic mechanism then which classification would dominate or does it depend on whether the product treats a diseased or non-diseased (eg aging) tissue or organ?	
5.	I have carefully considered the STEMSO response to the EMA Reflection Paper on Classification of Advanced Therapy Medicinal Products. I support, in the strongest of terms, all the recommendations of the STEMSO response letter.	Thank you, the responses are addressed below.
6.	The Paul-Ehrlich-Institut acknowledges/wellcomes the revision of the Reflection Paper.	Thank you.
7.	This paper considers enzymatic digestion of tissue to release cells as substantial manipulation. This classification would have a major impact on the field and would therefore need a deeper scientific reasoning and clarification. Some questions and examples rising: • Is enzymatic digestion always categorically considered as substantial manipulation or is it possible on scientific basis to show that the probability of risk on the biological characteristics is unsubstantial? • For example, in the case of autologous human keratinocytes used for the treatment of e.g. acute skin burns (homologous, autologous): what is the assumed risk to the biological characteristics of the keratinocytes when trypsin is used for separation of keratinocytes from skin tissue? •	Thank you. The substantial manipulation, when based on enzymatic treatment, is further clarified in the reflection paper. In principal, if considered substantial manipulation, the enzymatic release of cells from a tissue is expected to clearly impact the cell characteristics. Devices used in hospitals to manufacture cell-based products are not within the legislation of medicinal products and do not need marketing authorisation. However, the cell preparations manufactured using

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	With the new classification for substantial manipulation, is marketing authorization needed for a) a bed-side device intended for the enzymatic processing of tissue to release cells and/or b) for the resulting ATMP cell product in the hospital operating theatre? Or would the user of the device need a manufacturing license?	such devices may be medicinal products, if fulfil one of the ATMP definitions. The one releasing such products for clinical use will need a marketing authorisation, if the product in question fulfils one ATMP definition.
8.	It is stated that “the summary outcome ATMP classifications assessed so far by the CAT is available on the EMA website. This information is updated on a monthly basis.” This is true, of course, but it might be convenient from a practical viewpoint to have the contents made searchablen on the EMA website.	Thank you, the point is noted.
9.	Use of bone marrow derived mononuclear cells to repair injured osseal or chondral tissue. Cells are both harvested and implanted with a single step technique during a single surgery session. The procedure lasts about 15 minutes. The cells are never exposed to the air during the process. In particular, bone marrow is harvested by aspiration from iliac crest and transferred in a sterile sac. It is then transferred, through a big syringe, connected to the sac, to a centrifuge tube where it is filtered to eliminate fibrin clots, cells debris and lipids. After centrifugations, the cells are gently resuspended and harvested with a syringe connected with the tube. In this way, 85% of bone marrow mononuclear cells are collected. The cells are transferred in the lesion zone by proper arthroscopic or other surgical techniques. The protocol might include the use of a collagen membrane to limit cell dispersion and increase their concentration in the target area. The described procedure is safe and has been proved to give good results. To my knowledge, more than 350 patients with osteochondral and post-traumatic lesions have been treated in Italian Institutions with excellent results. In our opinion, this kind of technique should not be included in the “Advanced therapies” defined in the document EMA/CAT/600280/2010 Rev.1 (20 June 2014). We look forward to receiving your opinion on this issue.	Thank you. Bone marrow cells are claimed to have multiple native functions, one of them being bone healing. However, looking into the BM cell composition, clearly the main function is hematopoietic reconstitution. Also the recent information on bone healing indicates that the cells responsible for initiating the healing procedure come from the bone periosteum, not from bone marrow. The CAT reflection paper on ATMP classification is in compliance with the ATMP legislation, which has identified the use cells ´for other than same essential function´ as being one justification for ATMP classification.
10.	The International Consortium for Cell Therapy and Immunotherapy (ICCTI) would like to appreciate the opportunity to submit comments on the Committee for Advanced Therapies (CAT) of the European Medicine Agency’s (EMA) Reflection	Thank you. The recommendation of classification for gene- and cell-based products is one of the

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	Paper on Classification of Advanced Therapy Medicinal Products (ATMPs) (further referred as CAT Reflection Paper). ICCTI is a non-profit organization representing mainly scientists, researchers, physicians, health care providers, attorneys, and patient advocates who have their own particular interests in cell therapies and immunotherapies in Europe and worldwide. ICCTI members have joined together as an organization to respond to the EMA's reflection paper. ICCTI submits the following comments and recommendations concerning the "Reflection Paper on the Classification of Advance Therapy Medicinal Products": **1. Comments from the European Commission and House of Lords** **1.1. Report from the Commission to the European Parliament and the Council** ICCTI believes the proposed classification needs some revision in order to balance the best interests of patients and, at the same time, properly address the EMA's concerns regarding safety and efficacy of cell therapies. ICCTI welcomes the "Report from the Commission to the European Parliament and the Council" issued on March 3, 2014 by the European Commission (further referred as EC Report), especially the following points: a) The realization of randomized controlled clinical trials may not always be feasible, for instance, if the administration of the product requires a surgical procedure (i.e. the majority of tissue engineering products), or where no alternative treatments are available (Section 2, paragraph 4 of EC Report). The ATMP Regulation builds on the procedures, concepts, and requirements designed for	tasks defined for the CAT in the Regulation 1394/2007. The classification procedure or the CAT itself cannot interfere with the legal boundaries established with the Regulation 1394/2007 and Directive 2009/120/EC. Some of the problems described in the Commission report (1.4.2014) are partly shared by the CAT, however, most of them can be solved only by changing the legislation.

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	chemical-based medicinal products. However, ATMPs present very different characteristics (Section 4.4.1., paragraph 2 of EC Report). The possibility to apply a risk-based approach to determine the extent of quality, non-clinical and clinical data is also envisaged. However, the public consultation shows that it is widely felt that additional flexibility should be applied, particularly in the area of quality, with a view to ensure that the marketing authorization application requirements take due consideration of scientific progress and specific characteristics of ATMPs. This view has been shared by respondents representing industry, patients, hospitals, academia and non-for-profit organizations (Section 4.4.1., paragraph 3 of EC Report); b) Since ATMPs Regulations (EC No 1394/2007) are in place, only four have successfully completed the procedure and have been granted a marketing authorization by the Commission (Section 3.2. of EC Report), thus it needs to be considered if there is room to facilitate that more ATMPs can become available to patients (Section 4 of EC Report); c) Approximately 60 derogations from the obligation to obtain a marketing authorization had been granted until April 2012 under “hospital exemption” or “individualized treatment” (Section 4.1.2. of EC Report). Specifically, ATMPs with a marketing authorization face higher developmental and maintenance costs than ATMPs that are made available through the hospital exemption (Section 4.2., paragraph 3 of EC Report). It is therefore necessary to find a balance between the need to ensure that ATMPs are made available to patients only after quality, efficacy and safety thereof has been adequately demonstrated, and the need to facilitate early access for new treatments in case of unmet medical needs. The	

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	lack of harmonization regarding the conditions required by Member States for the application of the exemption has also been identified as a concern in the public consultation (Section 4.2., paragraph 5 and 6 of EC Report); d) In the case of autologous products … the manufacturing process of these products has specific features as compared with other medicinal products. In the public consultation some respondents considered that autologous ATMPs should not be regulated as medicines. While this approach would reduce the developmental costs associated with the use of these products, in the Commission's view, the need to ensure an adequate level of public health protection should prevail over economic considerations (Section 4.4.2. of EC Report); e) However, too burdensome requirements could have detrimental consequences for public health as it could prevent the appearance of valid treatments for unmet medical needs (Section 5., paragraph 3 of EC Report). **1.2. Report by the House of Lords** ICCTI also welcomes The 1st Report of Session 2013-14: Regenerative Medicine Report by the House of Lords published on July 1, 2013 in London, namely the following conclusions formulated at page 107-108 of this Report: a) Phase I and II clinical trials (in the regenerative medicine field using cell therapies) are unlikely to be funded by the private sector – the Government cannot expect this. b) The necessity of incentives (Australian model). c) There is a significant difference between cell therapies and drugs: they are so different that you can´t generalize. d) Conflicting evidence about the efficacy of the UK system but agreement on the	

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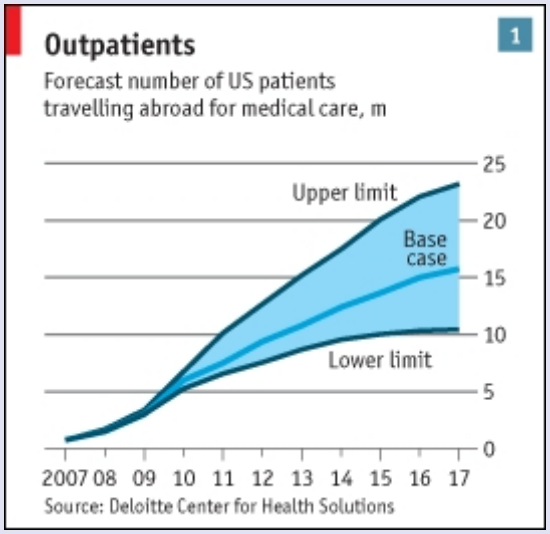
	need for greater engagement between regulators and stakeholders. ICCTI is also aware that medical tourism driven by unproven, poorly regulated treatments have the potential to cause serious harm to patients. Annually, it is estimated that more than 10 million citizens of the US seeks medical care abroad (Figure 1) and about 10% of them are associated with some form of cell therapy outside US. Similar percentage of European citizens is estimated to travel abroad seeking medical tourism for their unmet medical needs. Figure 2 shows numbers of UK medical tourists traveling abroad. Worldwide, OECD project that the number may be as high as 30-50 million people travelling abroad for healthcare in year 2011.  **Figure 1:** US patients traveling abroad for medical care. (in million; based on data from Deloite Center for Health Solutions).	

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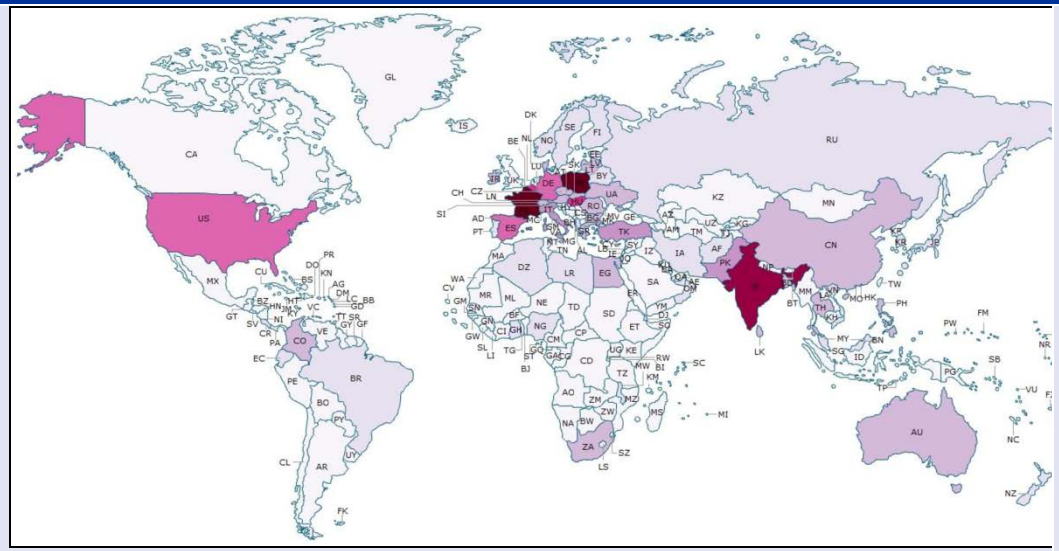

Figure 2: Medical tourism from UK abroad. (Data from: Hanefeld J, Horsfall D, Lunt N, Smith R (2013) Medical Tourism: A Cost or Benefit to the NHS?. PLoS ONE 8(10): e70406).

2. Cell therapy worldwide

In the first decade of the 21st century, more than 17,000 scientific articles involving 2,724 cell therapy clinical trials were published (Culm-Seymour et al., Regen Med, 2012,7:455-462). These results include 323,000 patients treated with more than 675,000 cell therapy units. This number of cell therapy products represent a distinct healthcare sector among other well established medical products; the sector, which is very safe and often very effective in the treatment of various diseases with the potential to significantly improve health worldwide (Mason and Manzotti, Regen Med, 2010,5:307-313). It is also evident that citizens from Australia, Japan, South Korea

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	and many other countries around the globe benefit from simpler regulations of autologous cells. Namely within autologous, minimally manipulated cells, no serious side effects were reported. Based on this information, it is evident that autologous cells are safe, in general, the degree of regulation in cell therapies corresponds directly with the degree of medical tourism: more restrictions leads to more medical tourism from EU and US to other countries. **3. ICCTI comments to EU regulations in cell therapies** Recently, ICCTI also sees some discrepancies within EU regulations in cell therapies, for example: a) In vitro fertilization programs are recently considered as standard treatments in EU, despite the fact they use substantial manipulation (cell culture) in a language of ATMPs and the Regulation (EC) No 1394/2007, but based on administrative, rather than scientific, background, they are excluded from this Regulation. Is the Evidence Based Medicine (EBM) rule different for in vitro fertilization programs from other cell therapies? In CAT Reflection Paper there is no contribution to this issue, Section 2.2. mentions that "…products are classified according to the respective definitions, … , on the basis of scientific information provided by the applicant." What level of scientific information was provided for cells manipulated in in vitro fertilization programs to be excluded from ATMP Regulation? It is just an administrative decision rather than EBM approach. This issue would deserve rather complex evaluation and scientific discussion. b) Homologous use of autologous cells is sometimes unclear. For example, unmanipulated bone marrow cells that are freshly isolated can be used for	ATMPs are medicinal products, which must also fulfil the definitions of a medicinal product (Dir.2001/83/EC). In vitro fertilisation is outside the scope of ATMPs, as the intention is not to treat/prevent/diagnose a disease or to regenerate/repair/replace a tissue defect using the

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	avascular necrosis of femoral head (which is frequently associated with osteoarthritis) according to recent CAT recommendation, but they cannot be used to treat osteoarthritis associated with avascular necrosis. This decision was made despite orthopedic surgeons or traumatologists frequently make incisions through the cartilage to the adjacent bone and bone marrow to get fresh bone marrow blood to improve healing of the damaged cartilage, adjacent connective tissue and synovial tissue of damaged joint. This practice of medicine is considered as standard treatment procedure in certain cases of joint damage among surgeons across the EU. But, based on CAT decision, this should be regulated as ATMP since bone marrow blood cannot be considered homologous tissue to the joint connective tissue or the cartilage. This issue probably needs some more scientific discussion rather than administrative decision. c) The use of enzymatic digestion of the tissue using collagenase that is harmless to cells but rather dissolves collagen fibers is regulated as non-ATMP (pancreatic islets) but is suggested to be regulated as substantial manipulation for other cells, for example stromal vascular fraction cells from adipose tissue. It was clearly demonstrated, that the use of collagenase does not harm and does not influence cell survival, cell functions and does not represent any risk to the patient. ICCTI does not understand what level of evidence was raised against the use of collagenase in cell isolation from different tissues in general. Is there a safety concern? If so, please bring this evidence into the draft of the CAT Reflection Paper. d) The system of clinical trials that was originally developed for chemical-based compounds is hardly acceptable and applicable for cell therapies, which is in	cells, but to reproduce a human being. See comment above. The issue of enzymatic digestion is not related to the use of a particular enzyme, but relates to all enzymes when used to dissociate cells from tissues and use the cells for treatment of patients. The text has been further revised to make the classification based on substantial manipulation more clear.

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	agreement with European Commission (see Section 1.1.a above). The main reason for such statement belongs to randomization in phase II-III that may be considered unethical. Typically, for autologous therapies, mainly tissue engineered product (TEP), some tissue needs to be taken from the body of a tested human being, typically by a surgical procedure. In case of obtaining cells for producing a cell therapy product, in some case leukapheresis is employed that may bring significant health risk to the donor. Then, in a randomized clinical trial, there is a chance (typically 1:1 for the reasons of statistical analysis to keep the tested groups as small as possible) that the tested patient does not get the cell therapy product but only the placebo. Many ethical commissions feel that such way of randomization is unethical. On the other hand, the investigator is asked to bring the highest level of evidence from randomized (if possible also double-blinded) clinical trial to be considered as the highest degree of EBM approach. But there are other models with a less evidence. We believe that as the level of harm is very low, such as in autologous and minimally manipulated cells, the evidence based on case-control study with proper long-term follow up for safety and efficacy would bring enough EBM to justify such therapy as accepted standard. As ICCTI members, we feel that all above mentioned points 3.a-d would require proper scientific discussion before final implementation to the EU Regulation or EU Directive would be possible. **4. ICCTI suggestions to the draft of CAT Reflection Paper** Based on the above mentioned information, ICCTI believes that the recent draft of CAT Reflection Paper is rather favorable to logistic groups representing Langerhans´ islets transplanters, in vitro fertilization clinics and medical tourism agencies that	Clinical trials and the EU Regulation on ATMPs are outside of the scope of this revision.

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	benefit from organizing medical touristic trips to destinations outside EU because of unmet medical need within EU regarding cell therapies regulations. ICCTI suggests the following additions/changes to the CAT Reflection Paper: a) Initiate discussion among Scientific Societies dealing with cell therapies with respect on novel clinical testing system for cell therapies. b) Reflect recommendations from European Commission (described in Section 1.1.) and from House of Lords (described in Section 1.2. of this Letter) regarding different model for testing safety and efficacy of cell therapies that would be different from recent and broadly unacceptable system of randomized controlled clinical trials previously developed for chemical-based compounds. ICCTI suggests the following scenarios: - Autologous cells minimally manipulated, homologous use – practice of medicine, case reports, case control studies (model adopted from Australia, Japan or South Korea); - Autologous cells substantially manipulated or heterologous use – case control studies (model adopted from Australia, Japan or South Korea) with defined long-term follow-up or simplified clinical trials without the need for randomization based on Ethical Commission consultation for ethically acceptable trial design; - Allogeneic cells – regulation as recently suggested by EMA in clinical trials including Ethical Commission consultation for ethically acceptable trial design. c) Exempt situations when individualized (non-industrial mass-production), autologous cell therapy may be performed with signed informed consent of the patient or delegated informed consent in agreement with the Directive	Clinical trials and the EU Regulation on ATMPs are outside of the scope of this revision.

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	2001/83/EC and Regulation (EC) No 1394/2007 of the European Parliament and of the Council. d) Better definition of homologous use for autologous cell therapies, i.e. based on histology, physiology and cell biology and Scientific Societies definitions and recommendations (such as already published position papers of IFATS, ISCT, etc.). For example, mesenchymal stromal cells should be used for the treatment of damaged tissues of mesenchymal origin and this would be considered as homologous use. e) Enzymatic digestion of tissue (without any exceptions for Langerhans´ islets) should stay within the definition of minimal manipulation, if the scientific data proofs that such technique does not harm cells that are further used in an autologous setting. As previously mentioned in Section 2, there are several hundred thousands or maybe millions of patients being treated with autologous cells worldwide and in general, such treatments are performed safely and in many cases also effectively. While the regulations, especially in autologous cell therapies, in EU are going to be more restrictive, this situation may lead to more harm to the EU citizens since more and more will seek the cell therapy outside EU, mainly in countries with lower than EU standards of medical care. Such situation may lead to suboptimal medical care of those patients despite the autologous cell therapy provided is in general safe. But also other circumstances, for example long-distance air travel, epidemiological and infection risk, cultural differences, language barrier etc., may contribute to suboptimal control of the primary disease the patient asked the treatment for, and increase the risk of disease complications or other side effects.	Clinical trials and the EU Regulation on ATMPs are outside of the scope of this revision. The EU legislation does not mention homologous use, but ´use for same essential function´. This legal definition has been further clarified in the revised reflection paper on ATMP classification. Substantial manipulation, based on enzymatic dissociation of cells from tissues, has been further refined.

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	In addition, there has been no stem cell based treatment that has obtained the marketing authorization in EU, since the ATMP Regulation (EC) No 1394/2007 took place. During that period of 2008-2014 probably several million European citizens underwent stem cell and other cell therapies outside EU quite successfully and we should keep this in mind. Thus ICCTI believes that too many restrictions are rather harmful than protective for the EU citizens and their health. Members of ICCTI are open to provide more materials to CAT and EMA based on their long-lasting experience regarding cell therapies in EU and worldwide.	The decisions on whether certain cell-based products should be in or out of ATMP framework cannot be solved by the CAT. This reflection paper is merely clarifying the definitions set in the current legislation.
11.	The International Stem Cell Society (STEMSO) welcomes and appreciates the opportunity to submit comments on the European Medicine Agency's (EMA's) Reflection Paper on Classification of Advanced Therapy Medicinal Products (ATMPs). http://bit.ly/1rn84cA STEMSO applauds the Committee for Advanced Therapies (CAT) for its efforts in regulating this area of medicine. STEMSO believes that regenerative medicine will be the future of medical practice and the pharmaceutical supply industry and fully understands the need for stringent regulations for the classification of cellular therapies as well as medical guidance by central governments for the purposes of maintaining safety and efficacy of medications and devices. The International Stem Cell Society, STEMSO, is a non-profit organization representing a diverse membership from the regenerative medicine industry such as device manufacturers, physicians, health care facilities, researchers, attorneys, veterinarians, and patient advocates who have their own particular interests in cellular therapies and have joined together as an organization to respond to the	

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	EMA's reflection paper. Non-member organizations and medical doctors have also contributed their input for this letter. STEMSO submits the following comments and recommendations concerning the "Reflection Paper on the Classification of Advance Therapy Medicinal Products". General comments STEMSO believes the proposed classification needs some revision in order to balance the best interests of patients and, at the same time, properly address the EMA's concerns. Therefore, STEMSO believes that allogeneic cells or tissues for the purpose of mass production and distribution should be regulated as a drug. To strike a balance, some allowance for patients to use either their own cells or donated cells for an individual therapy for one time use should be allowed under the classification without classification as a drug. This balance is needed, as it is highly unlikely that any one individual patient or clinic could economically afford or wait for the full Investigational New Drug (IND) process to take place to treat one patient each time, regardless of safety or efficacy concerns. There are many clinics and physicians around the world using autologous and allogeneic cellular therapies to treat several disease conditions and have produced overwhelming documentation showing safety and efficacy. Since these were individualized therapies for individual patients, the cell tissues were never intended to be mass-produced, distributed, or regulated as a drug. Select, individualized cellular therapies have been employed safely and effectively for many years in clinical translation. Authors such as Hernigou describes his use of Bone Marrow Concentrate (BMC) to help bone and rotator cuff tear repair since the late 90s. These procedures have had an excellent safety record. As of 2013, the publicly posted clinical trial database at www.clinicaltrials.gov has shown 359 clinical trials using Mesenchymal Stem Cells (MSCs) with a very wide range of therapeutic applications worldwide. Bone marrow transplants have been utilized to treat blood borne cancers for over 50 years. It must be noted that since 1986, in-vitro fertilization has become commonplace throughout the world as a regenerative procedure that has been completed safely and effectively and involves, in some cases, substantial manipulation of cellular tissues and risk to expectant mothers. The scope of 2001/83/EC (Article 2) http://bit.ly/1uGJ2nN limits the regulation of cells and tissues in Europe as it defines the authority of regulated products when it states," the provisions of this directive shall apply to industrially produced medicinal	Thank you. The ATMP definition in Reg.1394/2007 and Dir.2009/120/EC are legally binding and there, the basis for regulating certain products is not based on autologous or allogeneic nature, but rather on the manipulation level and intended use of the cells. The legal decisions in this respect are outside the remit of the CAT.

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	products for human use intended to be placed on the market in member states." Since Regulation 1394/2007 http://bit.ly/1vbtWrR is an amendment to Directive 2001/83/EC, the provisions of 1394/2007 are guided by the scope of 2001/83/EC, by definition. Therefore, it is clear that cells and tissues that are 'placed on the market' are regulated and, the inverse applies if such cells or tissues are not placed on the market. The term 'placed on the market' is not defined in 2001/83/EC, however, the medical device directive 93/42/EC http://bit.ly/1vbvm5L provides a definition of 'placed on the market' that provides guidance on the intent of such a term/condition. Specifically, article 1(2)h of 93/42/EC defines placed on the market as: " the first making available in the return for payment or free of charge…with a view to distribution and or use in the community market." The 2014 EU 'Blue Guide' also adds clarity to the meaning of 'placed on the market' when it states, "placing on the market is considered *not* to take place were a product is….manufactured for one's own use". Furthermore, the European Commission report of 28 March 2014 on Regulation 1394/2007 has acknowledged the absence of regulatory authority over point-of-care autologous cells and tissues when it stated, "new innovative products, which are *not* clearly captured by existing provisions, are emerging…….its reinjection into the donor with the same procedure raises question as to how these treatments *should* be regulated". The same report illustrates that Regulation 1394/2007 was not intended to apply to autologous point-of-care cells and tissues due to the practical realities of not being able to comply with the quality and GMP requirements of 1394/2007 when it stated, "requiring autologous products that are manufactured at the hospital prior to the administration to the patient to comply with the quality controls and manufacturing requirements of standardized chemical-based medicinal products would prevent the development of these treatments in practice as batch release certification would be required per treatment and a manufacturing license would be required per hospital". Therefore, it is abundantly clear that autologous cells and tissues produced in the same surgical procedure and at the point of care are not regulated in Europe due to the fact that they do not meet the minimal jurisdictional burden of being 'placed on the market', regardless of how the cells are used. We encourage the European Union to clarify the exemption of autologous same surgical procedure cells and tissues in much the same way as Directive 2004/23/EC (Article 2) and in a similar manner as the FDA's exclusion of autologous same surgical procedure cells and tissues (HCT/P) in 21 CFR 1271.15(b). http://1.usa.gov/1Dxo1Cb	Within same surgical procedure is taken from Directive 2004/23/EC, where the requirements for donation, procurement and testing are not directed to those cells/tissues that are taken from the patient and given back within the same procedure. This does not at all mean that cells/tissues, which

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	3. STEMSO brings to the Committee for Advanced Therapies (CAT's) attention that historical data from clinical studies have not shown serious adverse reactions associated with autologous and allogeneic MSC therapy. 1 For this reason, STEMSO believes that single, individualized therapies to treat one patient with autologous or allogeneic cells for homologous or non-homologous use should be allowed under the practice of medicine.	are not used ´for the same essential function´, as defined in Reg.1394/2007, would not be considered as ATMPs, if isolated and given back within the same surgical procedure. The definition of ´putting on the market´ does not necessarily mean transfer of money and as such is not an issue considered during ATMP classification.
12.	1. In view of the scope of the regulation No 1394/2007 that is to… " regulate advanced therapy medicinal products 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…" it is unfortunate that CAT do not reflect on cellular therapies / transfusions of autologous cells. The rapid advances in medical research have opened several possibilities for example to induce immunological responses against malignancies using the patient's own cells after "manipulation". These autologous therapies / transfusions will never enter the market, since they are produced from the patient and intended for autologous use only and therefore should be excluded from the regulation no 1394/2007. In addition, the scientific evidence and their mechanisms of action is usually not fully clarified, especially in the beginning of such autologous treatments. Thus, the classification by CAT will be based on the degree of manipulation rather than scientific evidence which is supposed to be the basis for classification by CAT. Like other "non-manipulated" therapies / transfusions (e.g. hematopoietic reconstitution by hematopoietic progenitor cells and Donor Lymphocyte Infusions) regulated by the Tissues and Cells directive (Directive 2004/23/EC) the quality and safety for the patient receiving "manipulated" autologous therapies would be equally well regulated by the T&C Directive where quality of the transplant and safety for the patient´s is the main scope. A reflection by CAT on autologous vs allogeneic therapies / transfusions would be helpful.	Thank you. Regulation 1394/2007 or other legal documents are not within the remit of the CAT, thus the changes requested cannot be addressed in a revision of a guideline. There are already many autologous products with a marketing authorisation in EU. The ATMP legislation does not segregate autologous products from allogeneic, but the classification is based on level of manipulation and clinical use, which is not for the ´same essential function´. Thus, it is merely the level of risks to the patients

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	2. As indicated in the reflection paper, the classification of cellular therapies in often not clear since many of the therapies fall within the borderline between ATMP and transplants/ transfusions. This is further reflected by the seemingly inconsistency in the classification during the 5 years that CAT has operated. As mentioned in the reflection paper, the Langerhans islet´s prepared with minimal manipulation was considered as not an ATMP. We agree on this recommendation, but it is not in accordance with the definition that "…enzymatic digestion of tissue .." is considered as substantial manipulation (sect 2.2.3) . Also the classification of Fresh and freeze-dried thrombocytes isolated from blood with intention to treat wound healing in orthopedic and dental surgery (13/11/2009), as non ATMP seems inconsistent with the "non-homologous " use in other recommendations. This reflection paper focus on classification between the different ATMP´s (GTMP vs. sCTMP vs. TEP) but a reflection and renewal of the definition of ATMP vs cellular transplants/transfusion would be welcomed.	laying down the legal borders; manipulated autologous products can have higher risks than non-manipulated allogeneic cells. The substantial manipulation with enzymatic treatment is further clarified in the document. The classification of thrombocytes is based on the fact, that platelets are not considered as cells from classification perspective. The main objective of the paper is to clarify the criteria for classification. Some boundaries with transplantation are mentioned in the paper (Section 2.3.1) but it is not the main objective of the paper..
13.	(Translated from Spanish) With reference to the enzymatic digestion, after the digestion and centrifugation in the case of the pancreatic islets, a gradient centrifugation is conducted and only the layer that contains the islets is left (not all the cells obtained from the tissue) In the case of isolation of SVF starting from lipoaspirates, following centrifugation, all the supernatant and all that goes into the pellet is re-suspended, stromal cells, also together with small fragment of the extracellular matrix that also contain cells: SVF (stromal vascular fraction). The SVF of the adipose matrix are one functional unit, and it is not tissue with 'cell to cell contact' since they are united via a collagen matrix, in the cells of the stromal fraction of the adipose tissue, there doesn't exist a 'cell to cell contact', therefore, it cannot be considered a substantial manipulation. If the first case (pancreatic islets) is not an ATMP, then neither can be the second one. In my view both situations are similar.	Thank you. Pancreatic islets are functional units with intact basal membrane and able to secrete insulin. It remains unclear what are the functional units of lipoaspirate. If enzymatic dissociation of SVF is required, it is clear that the intention is to separate e.g. MSCs from the adipose cells.
14.	LFB welcomes the EMA Reflection paper on classification of advanced therapy medicinal products which specifies the scientific criteria that must be fulfilled for	Thank you.

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	ATMP classification as well as the criteria for combined ATMPs.	
15.	There is a general difficulty in drawing a line between somatic cell therapies and tissue-engineered products. This has created uncertainty, and in some cases similar products or activities, carried out by different actors, have been classified under different categories by the same competent authority (the same activity has been authorised as somatic cell therapy for Establishment A, while it has been authorised as Tissue-engineered product for Establishment B).	National classification of cell-based products is outside the remit of the CAT.
16.	The Institute for Clinical and Experimental Medicine (IKEM) would like to appreciate the opportunity to submit comments on the Committee for Advanced Therapies (CAT) of the European Medicine Agency's (EMA) Reflection Paper on Classification of Advanced Therapy Medicinal Products (ATMPs) (further referred to as CAT Reflection Paper). For over 35 years, the Institute for Clinical and Experimental Medicine has provided healthcare services at the highest level. The Institute is committed to continuously improving healthcare for patients, refining medical procedures, and applying latest scientific knowledge in our work. Over the time of its existence, IKEM has become one of the largest specialized clinical and scientific research centres in the Czech Republic, focusing on organ transplantation, treatment of cardiovascular disease, diabetology, and treatment of metabolic disorders. Based on our 7 years of experience with autologous stem cell therapy of critical limb ischemia, we would like to comment on the CAT Reflection Paper: **1. Current state of stem cell therapy of critical limb ischemia** Autologous bone marrow-derived mononuclear cells (BMMNC) have been used to treat critical limb ischemia (CLI) since 2002 with more than 1000 patients worldwide [1, 2]. Several meta-analyses published recently have summarised that BMMNC therapy of ischemic limbs significantly decreases the rate of major amputation and	Thank you. It is the understanding of the CAT that bone marrow cells are mainly for hematopoietic reconstitution and other uses, e.g. for treatment of

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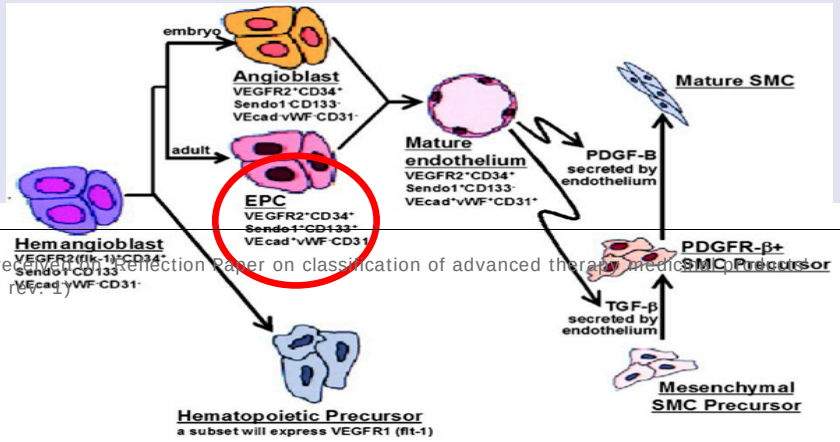
	improves limb ischemia as assessed by transcutaneous oxygen pressure (TcPO2) or ankle-brachial index (ABI), enhances wound healing, decreases pain and decreases mortality [3-5]. For example the follow-up [6] of the original TACT study [7] showed a high 3-year survival rate for patients with CLI after BMMNC treatment (80 %) in comparison with the usually presented data about cardiovascular mortality of patients with CLI - up to 25 % of patients per year. The randomised clinical trial RESTORE-CLI [8] showed a significantly longer interval until treatment failure (major amputation, death, new gangrene or worsening of the ulcer) in a group treated by stem cells compared to placebo. Another randomised study PROVASA [9] proved significant improvement of TcPO2 and faster wound healing in patients treated by intra-arterially injected BMMNC compared to placebo. **2. Homologous use of autologous stem cells** Based on current scientific evidence, autologous non-manipulated BMMNC treatment of intramuscular calf muscles in CLI can be considered homologous because these cells are used in the same essential function (vasculogenesis). Human hematopoietic stem cells precursors are capable of reconstituting all blood cell lineages and have the ability to transdifferentiate not only into hematopoietic precursor cells but, in parallel, also into endothelial cells in vivo. Due to the same original precursor of hematopoietic and vascular lineage (hemangioblast), the bone marrow mononuclear cells (BMMNC) fulfil the same essential function as used for hematopoiteic reconstitution, as during vasculogenesis when removed from bone marrow and injected into ischemic muscle. The hemangioblast is capable of differentiatinge either into VEGFR1 positive hematopoietic precursor or into adult endothelial precursor cell (EPC, which is positive for VEGFR2, CD34, CD31, and CD133) [10] The EPC then differentiate into mature endothelium as shown in Figure 1.  	critical limb ischemia is outside ´use for same essential function´. Majority of the BM cells are hematopoietic with very low number of other cells. The CAT is not aware that hematopoietic cells could contribute for vasculogenesis. Therefore, these products are classified as ATMPs and should follow the EU legislation accordingly. There is wide evidence of all kinds of cells used in various purposes, however the evidence from normal human tissues is not available (e.g. transdifferentiation of cells in vivo). Classification of products, based on in vitro experiments or animal studies is difficult and the CAT has decided to rely on evidence available from human studies.

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	Figure 1. Development of mature endothelium from hemangioblast **3. Ethical issues** As patients after major amputation are at high risk of increased mortality comparable with mortality of cancer (pancreas or lung tumor), every effort should be made to prevent any major amputation. Concerning the evidence of autologous stem cell therapy of critical limb ischemia worlwide, we assume that double-blinded placebo control trials in no-option CLI are unethical, because these patients are at higher risk of mortality due to major amputation. Our results confirmed that stem cell therapy of no-option CLI led to significantly more frequent limb salvage compared to conservative treatment (11.1 vs 50 %, p = 0.009) and long-term increase of TcPO2 (p = 0.02) [11]. The effect of stem cell therapy of CLI was comparable to the effect of standard therapy (percutaneous transluminal angioplasty - PTA) as even patients treated by BMMNC had more severe angiological findings (16.1 vs 16.7 % of amputated patients) [12]. **3. Our previous experience with stem cell therapy at IKEM** Our previous experience with suspension of autologous non-manipulated BMMNC therapy of CLI in patients with diabetic foot disease has been published in three articles [11-13]. CLI is an important predictor of outcome of ulcer healing in patients with diabetic foot ulcers and often leads to major amputations [14]. The therapeutic effect of standard methods of CLI is only partial - almost one third of patients are not eligible for standard revascularization due to widespread or distal location of arterial occlusion or presence of high-risk comorbidities [15]. These patients have poor	Design of clinical trial and ethical considerations do not fall under the scope of the classification. The described use of bone marrow cells is outside their essential function and as per legislation are considered ATMP.

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	chance of improvement of CLI when they are treated conservatively [16], therefore new therapeutic techniques, such as stem cell therapy for these “no-option“ patients are necessary to implement into praxis. We proved comparable benefits of BMMNC and peripheral blood progenitor cell (PBPC) treatment of CLI after unsuccessful standard revascularization in patients with diabetic foot ulcers and significant improvement of ischemia and limb salvage in those treated by stem cells compared to conservative therapy (11.1 vs 50 % of amputated patients, p = 0.009) [11]. In our next paper, we searched for possible adverse events of intramuscular injections of BMMNC by means of systemic vasculogenesis. Our study did not show any increase in the serum levels of pro-angiogenic cytokines during 6 months follow-up and no changes in the retina after autologous stem cell treatment in terms of induction of systemic angiogenesis [13]. We proved a significant increase in the serum levels of the angiogenic inhibitor endostatin after BMMNC therapy in diabetic patients with no-option CLI and its correlation with the number of injected CD34+ cells; this finding can possibly reflect a feedback regulation of angiogenesis. In our last paper, we compared the therapeutic effect of BMMNC treatment with standard revascularization by PTA [12]. Our study showed a comparable decrease in the rate of major amputation after stem cell therapy in no-option CLI patients and after repeated PTA in patients with a possibility of this revascularization. Both these treatment methods showed a comparable effect on improvement of CLI during a one-year follow-up period, and were superior to conservative therapy. BMMNC therapy was more effective in healing of foot ulcers in comparison with repeated PTA and non-intervention (control) groups. **4. IKEM suggestions to the draft of the CAT Reflection Paper** We suggest to add a new paragraph on autologous BMMNC therapy of CLI which is performed at the hospital’s tissue centre under conditions controlled by the national regulatory agency and following approval by an ethics committee in accordance with the rules published by EMA in 2010 (EMA/763463/2009): 1. Clinical trials can only take place after agreement with the national regulatory agency and following approval by an ethics committee. The ethics committee’s	The purpose of the current revision is to further clarify the interpretation of the legal definition. As such, it is not possible to include the proposed paragraph. All of the points 1-3 are outside of the remit of the CAT.

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	role is to look at the way the trial will be run to ensure that patients' rights are fully respected, in particular the right to know about the potential benefits and risks of the treatment. Clinical trials should never involve payment from the patient or their families. 2. Compassionate-use programmes allow a doctor to obtain treatment for a given patient while the medicine is still under development. Doctors obtaining treatment under a compassionate-use programme must ensure that their patients are fully aware of the treatment they are receiving. 3. Hospital exemption allows for a medicinal product containing stem cells to be made available to an individual patient in a European hospital under the exclusive professional responsibility of a doctor. This is a custom-made product that is prepared on a non-routine basis according to specific quality standards. It is authorised for use by the regulatory authority of the Member State where the product is made.	
17.	None	
18.	None	
19.	THERAVECTYS welcomes the initiative of the European Medicines Agency to revise its guideline on the "Classification of advanced therapy medicinal products". In particular, THERAVECTYS welcomes the quotation of numerous examples within the document. However, some areas are not fully addressed in the document such as the classification of therapeutic vaccines for infectious diseases.	Thank you. Vaccines against infectious diseases are excluded from the ATMPs and are outside the scope of this guideline.
20.	Biotech company Cellthera, s.r.o., Czech Republic would like to support the Letter from the International Consortium for Cell Therapy and Immunotherapy (see contribution 10.)	See comments above.
21.	None	
22.	Human Med welcomes and appreciates the opportunity to submit comments on the European Medicine Agency's (EMA's) Reflection Paper on Classification of Advanced Therapy Medicinal Products (ATMPs).	Thank you.

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	Human Med AG applauds the Committee for Advanced Therapies (CAT) for its efforts in regulating this area of medicine. Human Med AG believes that regenerative medicine will be the future of medical practice and the pharmaceutical supply industry and fully understands the need for stringent regulations for the classification of cellular therapies as well as medical guidance by central governments for the purposes of maintaining safety and efficacy of medications and devices. Human Med AG is a company in Germany developing medical devices for sterile, closed-loop aspiration and autologous transplantation of viable human fat tissue. The company has introduced various medical devices for water-jet assisted dissection, gentle liposuction and autologous fat transfer worldwide since more than twenty years. For the safe and effective treatment with these Human Med AG devices, clinical evidence is documented by a large number of peer reviewed international publications. Human Med AG will also develop an innovative device for the safe and effective separation and concentration of adipose stem cells during liposuction. This device will be placed and operated on the sterile operating table. Isolated stem cells are to be applied directly to the patient in the same procedure, and will not leave the operating room. Human Med AG submits the following comments and recommendations concerning the “Reflection Paper on the Classification of Advance Therapy Medicinal Products”. http://bit.ly/1rn84cA <u>General comments</u> Human Med AG believes the proposed classification needs some revision in order to balance the best interests of patients and, at the same time, properly address the European Medicine Agency’s (EMA’s) concerns. Therefore, Human Med AG believes that allogeneic cells or tissues for the purpose of mass production and distribution should be regulated as a drug. To strike a balance, some allowance for patients to use either their own cells or donated cells for an individual therapy for one time use should be allowed under the classification without classification as a drug. This balance is needed, as it is highly unlikely that any one individual patient or clinic could economically afford or wait for the full Investigational New Drug (IND) process to take place to treat one patient each time, regardless of safety or efficacy concerns. There are many clinics and physicians around the world using autologous and allogenic cellular therapies to treat several disease conditions and have produced	Please see answer to the same comment above.

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	overwhelming documentation showing safety and efficacy. Since these were individualized therapies for individual patients, the cell tissues were never intended to be mass-produced, distributed, or regulated as a drug. Select, individualized cellular therapies have been employed safely and effectively for many years in clinical translation. Authors such as Hernigou describes his use of Bone Marrow Concentrate (BMC) to help bone and rotator cuff tear repair since the late 90s. These procedures have had an excellent safety record. As of 2013, the publicly posted clinical trial database at www.clinicaltrials.gov has shown 359 clinical trials using Mesenchymal Stem Cells (MSCs) with a very wide range of therapeutic applications worldwide. Bone marrow transplants have been utilized to treat blood borne cancers for over 50 years.It must be noted that since 1986, in-vitro fertilization has become commonplace throughout the world as a regenerative procedure that has been completed safely and effectively and involves, in some cases, substantial manipulation of cellular tissues and risk to expectant mothers.	
23.	Second submission of comments by R Beretta	
24.	None	
25.	None	
26.	See general comments ICCTI	
27.	France Biotech member companies welcome the opportunity to contribute to the public consultation on the “reflection paper on classification of advanced therapy medicinal products”. This document brings clarifications about the classification determination made by the CAT and use practical examples to share the experience.	Thank you.
28.	Although it is clear that it refers to “cells and tissues” I would like to bring to your attention another borderline element. Platelets fall under Blood and Blood components directives, however, in the last years there is an increasing use of platelet-based products (such as platelet rich plasma, platelet lysates etc.) for non-transfusion purposes ranging from aesthetics plastic surgery to orthopedics and other applications, their action resembling more to advanced therapy products. It might be of interest for CAT to clarify the issue of characterization of such borderline products.	Platelets are not considered cells from classification perspective.

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29.	The Platform for Advanced Cellular Therapies hereinafter referred to as PACT (www.pact.ac.at) is a Platform established in December 2012 in an agreement signed between the Universities of Medicine, the Veterinary Medicine and Natural Resources and Life Science together with the Ludwig Boltzmann Institute for Trauma and the Austrian Red Cross. The objective of PACT is to establish a communication centre, a forum for the exchange and propagation of knowledge and the critical discussion of ideas or research leading to potential collaboration between interested parties in order to accelerate and facilitate the use of cell based therapies in the treatment of disease or conditions with the aim to relieve human and animal suffering. PACT is grateful for the opportunity to express an opinion on the European Medicine Agency's (EMA's) Reflection Paper on Classification of Advanced Therapy Medicinal Products (ATMPs). Furthermore, PACT appreciates the efforts of the Committee for Advanced Therapies (CAT) in the endeavour to provide fundamental guidelines by the regulation of this extremely important area as part of present or future potential medicinal practices. It is expected that so called "cell based" or closely related therapies like gene therapy, tissue engineering or regeneration will have huge implications in the beneficial treatment of patients with disease and/or ailments many of which have inadequate therapies or indeed are totally untreatable. We are very much in favour of the provision of standards dictated by sensible and meaningful regulation in compliance with and according to "the state of the known art" for the purposes of maintaining ethically the safety and efficacy of all medications and devices with the aim to provide the patient with the optimal form of healthcare care suited to their particular needs. PACT fully intends to increase its membership and extend its principles in a trans-European network of similar interests between the fundamental sciences, the disciplines in advanced engineering or technologies, in medicine, veterinary medicine, regulatory or compliance agencies and patient organisations for the synergistic acceleration of innovative approaches to the treatment and care of patients and for the relief or eradication of animal and human suffering. PACT also welcomes the comments and supports the documentation provided by the British Government's House of Lords, Science and Technology Committee in their Report "Regenerative Medicine" Published by HMSO July 2013, the comments provided by the International Stem Cell Society, STEMSO and the International Consortium for Cell Therapy and Immunotherapy (ICCTI).	Thank you. See comments above.

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	Regarding the comments of the ICCTI we would also like to support a broad discussion on a scientific basis on sensitive definitions such as of the terms “minimally manipulated cells” and “substantially manipulated cells” as well as of “homologous use of autologous cell therapies”. Regarding the reflection papers mentioned above, we fully agree that treatments with minimally manipulated autologous cells should be considered similar to treatments like in vitro fertilization. During ATMP classification it could be considered to define exemptions or special product categories for treatments such as in vitro fertilization and therapy with autologous minimally manipulated cells. We would highly appreciate to be kept informed about further developments also in the future.	See comments above.
30.	All the partners of the REGenableMED project are aware of the existence of this reflection paper. We welcome the opportunity to review this Reflection paper on classification of advanced therapy medicinal products. The scientific criteria applied for the classification of ATMPs by the CAT on the basis of its experience gained through recommendations issued so far are often very subtle. They are complicated to understand especially for non-specialists, which is mainly due to the complexity of the field itself. Thus giving concrete examples for each criterion highlighted is a good initiative that reflects the case by case basis approach undertaken. To enhance clarity and to limit potential lacks of understanding, it will be relevant to refer to the specific summaries of recommendations that are the basis of the CAT examples. This could be done in footnotes to avoid text heaviness. The direct consequences of the ATMP classification (i. e. which guidelines should be followed after a recommendation on classification) should be underlined to facilitate the guidelines navigation, an issue for ATMP that has been relevantly identified by the CAT and its interested parties focus groups (EMA/CAT/463795/2011). (See specific comment below line 188). The classification of a product as a combined ATMP or not may evolve in accordance with the future adoption of the medical devices regulations (ongoing revision of the medical devices directives). Indeed, cells and tissues that are not viable and that do	Thank you. Further examples are included. The summaries of past classifications can be found on EMA/CAT website. The work on guideline navigation is ongoing.

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	not exert the primary action of the combined product compare to the device should be covered by these future regulations. Regarding the medical devices regulatory framework, the European Commission groups (the classification and borderline group as well as the potentially future Medical Device Coordination group) may provide information regarding the classification of such medical devices which are borderlines with combined ATMP. Although medical devices do not fall under the remit of the EMA, coordination between these groups and the EMA will have to be established or strengthened to avoid contradictory recommendations. Thus, the classification as not combined ATMP may evolve according to the works of these groups. It will be relevant to consider this reflection paper or future guidelines on the classification of ATMP as subject to evolution regarding not only science but also the regulatory landscape.	The revision of the device legislation has to take into consideration of current ATMP legislation and possible overlaps/borderline cases therein. The CAT is, through its´members, taking part also to these activities ensuring that the borderlines are properly considered.
31.	Referring to the issued "*Reflection Paper on Classification of Advanced Therapy Medicinal Products"* (further referred to as "Reflection Paper") we would like to present you with our comments and remarks on the content within a given deadline. Firstly, a few words about our activities and profile: our Czech law firm has been specialising in the medicine law in the long run. Following our specialisation we have had many opportunities to deal with various professional issues and questions, including those stretching over national borders of individual member states. After all, medical law field in particular has been greatly affected and influenced by the European Union harmonisation and unification effort. Supposing that this effort is intended to increase the protection of public health and to improve the access to better health care quality, such effort can only be welcomed. On the other hand, we consider vital and essential to point out possible dangers and risks of such situations where the legislation activities of the European Union or of its bodies and authorities can endanger the above-mentioned goals. In these cases we actively call for a discussion which should possibly lead to abandoning such practices. Regretfully, we need to inform you that we see such danger in your views issued in the Reflection Paper. We have already discussed their subsequent impact with cell technology professionals and other medical fields specialists. Following (not only) their comments **we must completely agree with and accept in full text the International Consortium for Cell Therapy and Immunotherapy** (further referred to as "ICCTI") **comments on Reflection Paper from 14 October 2014,**	Thank you. See responses to ISSTI comments above.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	which in our opinion indicate and state clearly some of the fundamental risks of the content. Furthermore, the legitimacy of these reservations against the text can also be demonstrated by the same European Commission opinions, expressed in *"Report from the Commission to the European Parliament and the Council"* (further referred to as *"Report"*) from 28 March 2014. It is impossible to ignore the fact that according to Article 25 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, this institution in particular was authorized to give reports and reviews on applicability of such regulation. We find it more than surprising that even though in its recent "Report" the European Commission itself *de facto* acknowledges the necessity for moderation of demanding requirements on placing advanced therapy medicinal products on the market, as well as it admits the need for adaptation of requirements on these products, especially the autologous ones, to suit their special characteristics, the **Committee for Advanced Therapy** (further referred to as "**CAT**") suggests further regulation tightening. Such suggestion we find completely unreasonable. As ICCTI aptly remarks, such tendencies will bring about the potentially dangerous development of EU citizens' medical tourism, unfortunately directing also to countries where the level of health care services cannot match either the European quality or safety. On the other hand, it is essential to consider justified the EU citizens' interest in using the most advanced medical knowledge when caring for their health. The above mentioned gets even more true in light of the fact that citizens of other developed countries, (such as Australia, Japan or South Korea), can take advantage of using for example autologous products much more freely, because their usage in these countries is not obstacled by CAT's complicated registration procedure. It is equally necessary to note that the above-mentioned CAT's procedure has not only political or medical dimension, but also a legal one. **In our opinion**, **there is no legal basis in any European law system for the way CAT approaches and practices the medicinal products classification, not to mention the intention to tighten the regulation even further in the future.** Even within the Reflection	With the revision of the RP on classification, the CAT is not tightening any requirements, but rather clarifying the interpretations of the legal ATMP definitions. It should be noted, that the CAT recommendations on the classifications are not legally binding. CAT classification is based on the legal remit given in the Reg.1394/2007. The classifications are based on the legal definitions of ATMPs.

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	Paper **CAT**, as a display of its habitual shortcoming, **ignores the conditions under which advanced therapy medicinal products classification can be approached. Unlike CAT, we are thus convinced that a mere definition of advanced therapy medicinal products or a definition of their individual types is simply insufficient.** On the contrary, the crucial classification criterion of any medicinal product according to Regulation (EC) No 1394/2007 should be the consideration of its applicability, i.e. determining whether it is possible to use the Regulation at all. **What we miss in the Reflection Paper most is aiming at questioning the applicability of Regulation (EC) No 1394/2007 as such.** As will be shown later, this question can be crucial for putting things in practice. As Regulation (EC) No 1394/2007 represents a *lex specialis* to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (further referred to as the **Directive 2001/83/EC**), it is thus necessary to use the same directive when determining its applicability. The specific relation between the Directive 2001/83/EC and the Regulation (EC) No 1394/2007 is explicitly described in paragraph 6 of the Preamble, as following: "...This Regulation is a ***lex specialis*, which introduces additional provisions to those laid down in Directive 2001/83/EC. The scope of this Regulation should be to regulate advanced therapy medicinal products 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…." It is thus necessary to supplement the classification criteria of all advanced therapy medicinal products specified in the Reflection Paper with the following conditions: • the product must be produced industrially or produced by a method involving an industrial process, **and at the same time** • such product must be intended for being placed on the community market	Please see the response to this same comment above.

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	However, the question of a product fulfilling these conditions is commonly omitted by medicines agencies which directly move on to assessing specific definition markers of individual product types. **Such procedure is, of course, incorrect and is not supported by any European legislation**. **We still think that if the respective medicines agencies took seriously into consideration the above-mentioned conditions, the application of the Regulation (EC) No 1394/2007 on many products would be completely out of question, and, as a consequence, no practical problems how to meet the inappropriate requirements would arise.** The requirement for clinical tests in autologous cell products in order to prove them ethical can serve as an example. **In our opinion, the respective norm-setting authorities have little or no interest in "European" regulation of most medicinal products and thus they do not even expect that the manufacturers of these products would have to undergo a lengthy registration procedure required by the Regulation (EC) No 1394/2007.** **Therefore, it is essential to refuse resolutely EMA's approach to classification activities which ignores the above-mentioned aspects and applies the Regulation (EC) No 1394/2007 without further consideration. Such approach must be understood as incorrect,** as it makes things even worse by setting a bad example for other national medicines agencies which like to follow it. Not only that CAT does not dissociate from such approach at least in the Reflection Paper, but it also ignores the classification criteria and it directly proceeds to assessing subsequent individual qualifications, thus making the situation even more complicated. When focusing in detail on single applicability conditions of Regulation (EC) No 1394/2007, we will find out that the very essence of many products makes them a priori **excluded from being placed on the European market or from being put to any distribution chain at all.** Even though the Regulation (EC) No 1394/2007 or the Directive 2001/83/EC do not formulate their own definition of "**placing on the Community market**", we find	There are already many autologous products with EU marketing authorisation. It is not within the remit of the CAT to get the autologous products out from ATMPs, as they have been described in Regulation 1394/2007. See comments above. See comments above.

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	perfectly acceptable the definition from Medical Device Directive 93/42/EEC which states that "*placing on the market"* means "*the first making available in return for payment or free of charge ... with a view to distribution and/or use in the community market."* As for other inspirational sources we can use the definition from Article 2 of Regulation 765/2008 of the European Parliament and of the Council of 9 July 2008 which sets out the requirements for accreditation and market surveillance relating to the marketing of products, repealing Regulation (EEC) No 339/93. According to this "*placing on the market"* means "*first making available of a product on the Community market*", while "*making available on the market*" is defined as " *any supply of a product for distribution, consumption, or use on the Community market in the course of a commercial activity, whether in return for payment or free of charge*." Last but not least, we can mention a recently published *The 'Blue Guide' on the implementation of EU product rules*, which uses almost the same definitions as the above-mentioned ones. What are especially worth noting are the following statements: - *„The making available of a product supposes an offer or an agreement (written or verbal) between two or more legal or natural persons for the transfer of ownership, possession or any other right concerning the product in question after the stage of manufacture has taken place. The transfer does not necessarily require the physical handover of the product…"* - *"Placing on the market is considered not to take place where a product is manufactured for one's own use…"* We are of the view that by applying these conditions correctly on some products (which might be otherwise subject to Regulation (EC) No 1394/2007), we can abandon using the Regulation without further consideration. By way of example, we can use a cell product – stromal vascular fraction cells – made of fat tissue (further referred to as "***cell product***") that is administered within a single surgical procedure	This Blue guide is not part of EU legislation.

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	for an autologous application into a patient's joint. The possibility that it could fall into the category of products intended to be placed on the community market can already be denied from the following reasons: - all stages of cell product processing occur within a single surgical procedure when a fat tissue is harvested from the patient's body and immediately processed into a cell product which is promptly administered back to the body of the fat tissue's donor. Therefore, there is no intention to sell the cell products or to transfer title in the cells to a third party or to put the cells into circulation on the EU market, - there is no real or legal transfer of property rights, possession rights or any other rights between two or more parties, - we can see clearly from the fact that the cells are harvested from and administered to the same patient that the cell product is processed for personal need only. In such a way public health protection is also secured to full extent. As can be understood from above, the Regulation (EC) No 1394/2007 condition of placing the product on the community market cannot be applied to cell products. At the same time, however, **the industrial production condition cannot be fulfilled in cell products either,** for reasons which include the following: - the treatment using cell products is always tailored to suit individual patients, - the producer is not the owner of the material, as the material comes from the patient's body into which it is immediately administered back, - a ready cell product can only serve for a particular purpose to a particular patient whose body was used for harvesting the production material,	Please see earlier response on the same comment.

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	- cell product processing does not involve either substantial manipulation or combination of the cells or tissues with other substances (e.g. chemical ones) As we have shown on the example of cell products, we can see **how important it is to attract EMA's attention to applicability conditions of the Regulation (EC) No 1394/2007 when considering the classification criteria. <u>We are strongly convinced that it would be of high importance to state these conditions explicitly in the reviewed Reflection Paper as well.</u>** This would also discourage national medicines agencies from classifying products' character according to individual regulation categories without questioning its applicability, as it has already been mentioned earlier in the text. The above-stated suggestion could represent the first remedial step in current situation, where ignoring these conditions results in excessive abuse of application of Regulation (EC) No 1394/2007. Consequently, the situation turns against EU citizens who, contrary to the European legislators' will, are denied using advanced therapy methods for no reason. In light of the foregoing we appeal to CAT to take our comments, as well as ICCTI's remarks, into account seriously and to include them properly in the Reflection Paper.	Use of cells for purpose, which is not the ´same essential function´ is considered cell engineering in the legislation and is a criterion for cell-based products to be classified as ATMPs. This is part of the legal definition both for tissue engineered products and somatic cell therapy medicinal products.
32.	The Association of Aesthetic Practitioners (AAP) is a medical and scientific association of board-certified general practitioners/doctors of general medicine who are working in the field of aesthetic and regenerative medicine (aesthetic practitioners) within the scope of their legal authorization. Aesthetic and regenerative medicine are driven by the scientific progress made in all fields of medicine and cell biology. Therefore a multidisciplinary approach is essential for optimal care and maximum benefit and safety for patients in aesthetic and regenerative medicine. The Regulation (EC) No. 1394/2007 on advanced therapy medicinal products (ATMP	

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	Regulation) came into effect in 2008. However, this regulation failed to increase availability of cell therapies to patients in the EU until 2014. There has been no stem cell based treatment that has obtained the marketing authorization in the EU since the establishment of the ATMP Regulation. During that period probably several million European citizens underwent stem cell and other cell therapies outside the EU successfully. However, medical travelling poses risks to patients, such as language barriers, high travel expenses, and complicated follow-up care due to the large distance. This shows that too many restrictions are rather harmful than protective for the EU citizens and their health. As human cells have a high therapeutic potential that can be utilized in the treatment of many kinds of diseases and ailments of the body, lacking availability of cell therapies is fatal from a therapeutic point of view. Moreover, non-availability of cell therapies to patients in the EU due to overly strict regulations raises serious concerns from a fundamental rights and human rights perspective. **Prohibiting cell therapies violates the patient's fundamental rights** Regulations that prevent patients from utilizing their own stem cells to cure diseases they suffer from violate fundamental rights of the patients, namely the Right to live (article 2, par. 1 of the Charter of Fundamental Rights of the European Union (2010/C 83/02), see also article 3 of the Universal Declaration of Human Rights). This is particularly evident in case of no-option patients suffering from life-threatening conditions for whom an experimental, novel therapy often is the only option to potentially extend their lifespan and improve their heath condition and quality of life. The patient's cells are the sole property of the patient. Thus when used for autologous cell therapy they are obviously not "placed on the market". This would	CAT recommendation for ATMP classification is not preventing patient from access to therapies with proven efficacy and safety. Furthermore, EU legislation allows preparation of medicinal products for single patients in urgent need for therapy (art.5 of Dir.2001/83). Price and reimbursement do not fall under the remit of the CAT

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	not even be the case in allogeneic cell/tissue therapies where money must not be taken by the donor of the cells/tissue (see according regulations in national laws and article 3, par. 2 c of the Charter of Fundamental Rights of the European Union). Also in case another therapy for the patient's condition exists that does not fall under the ATMP Regulation, cell therapy needs to be available as it must always be the patient's choice (based on thorough information provided by the practitioner) which therapy he/she believes to best suit his/her personal requirements regarding potential success and risks. **Prohibitive regulations violate the patient's freedom to agree into a cell therapy of his/her choice and the medical therapy freedom** The free choice of therapy by patients (informed consent, or delegated consent in certain cases) based on an explanation of treatment methods, chances for success, potential outcome of the therapy, risks, etc. by the practitioner has been a proven tradition in medicine for long time. Ultimately it is the *patient only* who decides which treatment option he/she believes to be most suitable for him/her based on comprehensive information provided by the practitioner. However, the practitioner must be legally allowed to perform therapies he believes to be applicable based on his/her professional medical evaluation of the therapy and the individual patient's condition. This also applies to experimental therapies involving novel/individualized surgical techniques, custom-made compounds (magistral formula), and other novel treatment methods. Taking this decision out of the patient's hands by factually preventing doctors from offering certain cell therapies from which the patient could benefit is an unacceptable breach with the established ethical and proven tradition of informed consent.	There are two issues, why ATMP legislation was originally established: access/availability of novel therapies and protection of EU patients from unsound treatments. This classification will not change the legislation currently in force.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Prohibitive regulations of cell therapies harm public health in the EU Broad availability of stem cell therapies is crucial for public health in the EU. Several hundred thousand or maybe millions of patients are being treated with autologous cells worldwide and in general such treatments are performed safely and in many cases also effectively. If these therapies were unavailable to patients because of overly restrictive regulations, patients will seek the cell therapy outside the EU. The degree of regulation in cell therapies corresponds directly with the degree of medical tourism: More restrictions lead to more medical tourism from the EU to other countries. This situation may lead to suboptimal medical care of those patients despite the autologous cell therapy provided is generally safe. Circumstances like long-distance flights, epidemiological and infection risk, cultural differences, language barriers, patients missing check-ups with the practitioner who treated them because of high travel costs, etc. may contribute to suboptimal control of the patient's primary disease and increase the risk of complications or other unwanted side effects. Patients who are totally immobile or cannot afford travelling to medical centers outside the EU could not benefit from cell therapy at all if it was unavailable in the EU. This discrimination for reasons of a severe medical condition or lack of funds is clearly unethical. Treatment in the EU is more convenient and less costly for patients. **Cell therapies are safe and have the potential to increase public health worldwide** In the first decade of the 21st century more than 17,000 scientific articles involving 2,724 cell therapy clinical trials were published (Culm-Seymour et al. 2012). These results include 323,000 patients treated with more than 675,000 cell therapy units.	Please see earlier responses to this same comment.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Cell therapies represent a distinct healthcare sector which is very safe and often very effective in the treatment of various diseases and has the potential to significantly improve health worldwide (Mason and Manzotti 2010). It is also evident that citizens from Australia, Japan, South Korea and many other countries around the world benefit from simpler and less prohibitive regulations of autologous cells. Namely for autologous, minimally-manipulated cells, no serious side effects were reported. Based on this information it is evident that autologous cells are generally safe. A number of individualized cell therapies have been employed safely and effectively for many years in clinical translation. As of 2013, the publicly posted clinical trial database at www.clinicaltrials.gov has shown 359 clinical trials using Mesenchymal Stem Cells (MSCs) with a very wide range of therapeutic applications worldwide. Examples of cell therapies which are already performed for many years and which are considered as standard treatments among surgeons worldwide: • Hernigou describes his use of Bone Marrow Concentrate (BMC) to help bone and rotator cuff tear repair since the late 90s, as do other authors. These procedures have had an excellent safety record. Bone marrow cells are used in the treatment of avascular necrosis of femoral head and osteoarthritis by orthopedic surgeons, traumatologists, and other doctors who frequently make incisions through the cartilage to the adjacent bone and bone marrow to get fresh bone marrow blood to improve healing of the damaged cartilage, adjacent connective tissue and synovial tissue of damaged joint. • Bone marrow transplants have been utilized to treat blood borne cancers for over 50 years. • Since 1986, in-vitro fertilization has become commonplace throughout the world as a regenerative procedure that has been completed safely and effectively and involves, in some cases, substantial manipulation of cellular tissues (cell culture)	International Pharmaceutical Regulators Forum with 9 different jurisdictions (US, Japan Canada, EU, Korea etc.) made a survey of classification of cell-based products and the results show that the rules are very much in line globally. The results have been submitted for publication.

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	and risk to expectant mothers. • Tissue engineering using cell cultures is an established procedure for the treatment of various skin and tissue defects. Thus situations where individualized (non-industrial mass production), autologous cell therapy may be performed with signed informed consent of the patient or delegated informed consent should be exempted from the CAT Reflection Paper and the ATMP Regulation. **Cell therapies must be available to patients outside clinical trials to guarantee optimal medical care** Limiting experimental, novel cell therapies to clinical trials would practically make them unavailable to numerous patients who would otherwise benefit from these therapies. Clinical trials are unsuitable to ensure availability of optimal medical care to all patients for reasons outlined below. Thus it is essential for public health that cell therapies are also available to patients who do not take part in clinical trials. Randomized controlled clinical trials may not always be feasible, for instance, if the administration of the product requires a surgical procedure (such as in tissue engineering) or where no alternative treatments are available (section 2, par. 4 of the EC Report). Clinical trials can only be established for patients suffering from certain comparable conditions and are thus often unavailable for patients with rare diseases. The system of clinical trials that was originally developed for chemical-based compounds is hardly acceptable and applicable for cell therapies because the randomization in phase II-III is considered unethical. For autologous therapies, mainly tissue engineered products (TEP), some tissue needs to be taken from the body of a tested patient, typically by a surgical procedure. In case of obtaining cells	See earlier comments on autologous products. Not within the remit of the CAT classification.

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	for producing a cell therapy product, in some case leukapheresis is employed that may bring significant health risk to the donor. Clinical trials can be offered in a limited number of medical centers for reasons of missing infrastructure, lack of specialists for certain diseases, etc. Consequently participation in a clinical trial is impossible for patients with limited mobility and those who cannot afford travelling. Travelling also poses an additional health risk to seriously ill patients. Clinical trials are not available for certain patients at all, who are left with no option if experimental, novel therapies unavailable elsewhere because of overly strict regulations. In randomized clinical trials there is a chance (typically 1:1 for the reasons of statistical analysis to keep the tested groups as small as possible) that the tested patient does not get the cell therapy product but only the placebo. Many ethical commissions feel that such way of randomization is unethical, as is the limitation of cell therapies to clinical studies where only a limited number of select patients can participate. **Enzymatic separation of cells from tissue is safe and harmless** Cell separation by enzymatic digestion of tissue is the universally accepted standard method for separating and then evaluating properties of cells, and defining cellular essential function (Tomlinson et al. 2013). Nearly all biological, physiological, and structural properties of cells that histologically populate solid tissues have been described using cells obtained from enzymatically dissociated tissues. Endogenous collagenase metabolism is part of cell function in any tissue containing collagen. Collagenase can be made by the body as part of its normal immune response. This production is induced by cytokines which stimulate cells such as fibroblasts, macrophages, or osteoblasts, causing degradation of extracellular matrix in a variety of physiological situations. Human cells produce their own endogenous	Not agreed. Enzymatic release of cells from tissues and systemic administration have shown high accumulation of the cells into lungs, liver etc. Furthermore, there is growing evidence that cell surface proteins, their signalling etc. are impacted by the enzymatic treatments. However, the CAT retains the possibility for the Applicants to demonstrate, if the characteristics and structural & functional properties are not changed by the enzymatic dissociation, thus suggesting a non-

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	collagenase as a natural part of tissue repair and remodeling (Hibbs et al. 1984). The use of enzymatic digestion of the tissue using collagenase is harmless to cells but rather dissolves collagen fibers. It was clearly demonstrated that the use of collagenase does not harm and does not influence cell survival and the cell's essential function, e.g., insulin secretion of pancreatic islet cells as used in pancreatic islet transplantation (Jamiolkowski 2012). *Ex vivo* enzymatic digestion of tissues to separate cells is in common clinical use for different applications such as wound healing, joint osteoarthritis, fat grafting, etc. Enzymatic digestion using collagenase is currently legally used to safely separate pancreatic islet cells for transplantation and for separation of adipose-derived stromal vascular cells for various kinds of applications. A significant number of preclinical and clinical studies been performed using cells isolated by enzymatic digestion (e.g., Casteilla et al. 2011, Gimble et al. 2010, Ribes-Koninckx et al. 2012, Cervelli et al. 2011, Gentile et al. 2012, Ichim et al. 2010, Koh et al. 2013, Lee et al. 2012, Lendeckel et al. 2004, Riordan et al. 2009, Rodriguez et al. 2012, Dos-Anjos Vilaboa et al. 2014). There are no adverse or mild secondary effects reported in the literature, even when cells were applied intravenously (Pak et al. 2013). Further, use of collagenase *in vivo* is currently accepted as therapy for direct application in several diseases such as debridement of wounds (Shi and Carson 2009, Tallis et al. 2014), treatment of Dupuytren disease and Peyronie's disease (Thomas and Bayat 2010, Jordan 2008). Accordingly, EMA-CAT has previously considered that cell populations derived by collagenase digestion of tissue do not fall within the definition of an sCTMP. Examples include cryopreserved adipose-derived stromal vascular fraction or regenerative cells and suspensions of viable, adult, autologous, unexpanded, and uncultured regenerative cells of stromal vascular fraction from subcutaneous adipose tissue (EMA/500724/2012, EMA/129056/2013).	substantial manipulation. Such a decision will be made on case by case basis and requires data from the Applicant.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Conclusions Patients must be able to benefit from the full therapeutic potential of their own cells. Any restriction of cell therapies by ATMP Regulations or the CAT Reflection Paper preventing or reducing availability to patients would constitute a violation of the patient's basic human rights. The reasons above lead to the following conclusions regarding the ATMP Regulation and the CAT Reflection Paper: (1) Cell therapies have specific features compared to other medicinal products. Thus both individualized autologous and allogeneic point-of-care cell therapies have to be exempted from the list of ATMPs. For example, Bone Marrow Concentrate (BMC) used for purposes other than hematological use and Stromal Vascular Fraction (SVF) derived from adipose tissue by enzymatic digestion. (2) Individualized cell therapies that are not industrially produced and not "placed on the market" have to remain excluded from the ATMP Regulation and the CAT Reflection Paper. Too burdensome requirements could have detrimental consequences for public health in the EU as they could prevent the availability of novel (experimental) cell therapies for unmet medical needs for patients. (3) Enzymatic digestion of tissues is safe, retains the cells' properties and is common clinical practice. It thus has to be exempted in the ATMP Regulation and the CAT Reflection Paper and stay within the definition of minimal manipulation without any exceptions. (4) Homologous vs. non-homologous use is an unsuitable criterion for classification of cell therapies. The potential of stem cells to develop into certain cell types due to cytokines and other mechanisms is an inherent natural biological capability of stem cells.	Please see comments above.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	(5) Individualized, homologous or non-homologous, autologous or allogeneic cell therapies performed with signed, informed consent of the patient or delegated informed consent for compassionate care situations have to be exempted from the ATMP Regulation and the CAT Reflection Paper. In order to accomplish this individualized practice of medicine cell expansion with culture, enzymatic digestion of tissue, and differentiation/activation with growth factors needs to be exempted from the list of substantial manipulations.	
33.	None	
34.	None	
35.	The reflection paper is useful and provides an important guide for the interpretation of the Regulation (EC) No 1394/2007. We agree that the classification of a product is an important first step, however, some terms used are difficult to apply to biological products. They need to be better clarified to avoid significant contradictory conclusions (as that referred to pancreatic islets, bone marrow concentrate or fat). For example the term “same essential function” (page 10, line 293) would suppose that: 1) that cells have a single function, 2) that minimally manipulated tissues are composed of a single cell type, This is not true because 1) a cell can express several functions, due to the microenvironment etc., and 2). minimally manipulated tissues are usually composed of many cell types. More homogeneous material can be obtained only by extensive manipulation. Therefore, it seems difficult to describe the essential function of a tissue composed of different cell types with the current terminology.	Thank you. The definitions have been clarified and more examples are included. The microenvironment is taken into consideration in the definition and the borderline cases are further clarified.

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	Line 294 explains the meaning of the same essential function: “have the same essential function cells that have been removed from a tissue and are used to maintain the original function in the same anatomical and histological environment”. The same anatomical and histological environment must be better defined. In fact, according to the example in line 304, pancreatic islets implanted subcutaneously are considered a “homologous use”. Does this signify that the pancreas and the skin have the same anatomical and histological environment? If this is the case, why does bone marrow implanted in a bone is not considered the same anatomical and histological environment (line 296 and line 424)? It would be important to dedicate a specific consideration to mesenchymal/stromal cells. The current understanding on these cells clearly indicates that they can be found in a niche in almost all mammal tissues. If so, minimally manipulated mesenchymal/ stromal cells should be considered an “homologous use” also when implanted into a number of other tissues.	Please see comments above. Pancreatic islets are functional units with intact basal membrane and able to secrete insulin. Bone marrow is composed of mainly hematopoietic cells and their progenitors, which are needed for hematopoietic reconstitution. The minute amount of MSCs in BM aspirate may be beneficial for healing of bone fractures, but is not according to current knowledge the cell population initiating the healing cascade.
36.	None	
37.	We have found at least two statements, regarding the eventual essential functions and homologous use of bone marrow concentrates, that should be re worded. Both are presented as universal trues that could be discussed according to current knowledge. We intended to show that some exceptions to the general position should be considered.	The paragraph on same essential function has been revised for clarity.

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38.	We are writing on behalf of Lawford Davies Denoon and the Alliance of European Life Sciences Law Firms. The Alliance of European Life Sciences Law Firms is an alliance of independent European life sciences boutique law firms from around Europe, active in all areas of life sciences and medical technology. As with all of the members of the Alliance, we have a keen interest in this developing area and advise a number of clients in relation to this complex regulatory landscape. Please find attached a table addressing a number of points in relation to page 10 of the Draft Reflection Paper regarding "homologous use" and "substantial manipulation". We have not commented on the Draft Reflection Paper more broadly as others, such as the European Legal and Regulatory Committee of the International Society for Cellular Therapy, have conducted a comprehensive review and prepared a comprehensive report regarding the Draft Reflection paper. We would like to take this opportunity to endorse the comments regarding the Reflection paper from the European Legal and Regulatory Committee of the International Society for Cellular Therapy. We would like to make a broader point regarding commentary about the regulatory framework for cell-based therapies. It is important to draw a clear distinction is drawn between the role of the Committee for Advanced Therapies (which is a scientific expert committee) and the role of National Competent Authorities in enforcing and interpreting	Please see comments above.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	national laws implementing the Medicinal Products Directive (2001/83) as amended by the ATMP Regulation (1394/2007). Incorrect summaries can and do have a significant impact on researchers, clinicians and, as a result, patients. This is exacerbated in a relatively young and inexperienced sector such as cell therapies as many participants will not understand the roles of the regulators and non-binding guidance. It is particularly unhelpful is guidance is presented in such a way as to create new regulatory requirements or rules. The Draft Reflection Paper should restrict itself to matters related to scientific classification rather than the broader regulatory framework. By way of example, quite correctly, the Draft Reflection Paper does not comment on matters such as: • the "hospital use exemption" in Article 3(7) of the Medicinal Products Directive 2001/83, let alone the various implementing laws at a Member State level; • the "specials exemption" in Article 5 of the Medicinal Products Directive 2001/83, let alone the various implementing laws at a Member State level; or • the threshold requirement for regulatory involvement that the product must be: o "intended to be placed on the market" and o "either prepared industrially or manufactured by a method involving an industrial process" as required by Article 2 of the Medicinal Products Directive 2001/83, let alone the various implementing laws a Member State level.	
39.	**Arguments against Classification of Enzymatic Tissue Digestion as Substantial Manipulation** Previous use of enzymatic tissue dissociation to isolate cells	Please see comments above. The paragraph on enzymatic digestion has been further clarified.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Cell separation comprises a set of physical and chemical processes widely used in multiple fields of basic biological and biomedical research and in clinical therapy. For research, the ability to sort cells from different tissue sources into distinct populations enables the study of individual cell types isolated from a heterogeneous starting population without (or with greatly reduced) contamination from other cell types. Before studying cell behaviour and function, usually whole tissue is disaggregated into a cell suspension by enzymatic or mechanical means or a combination of both (8). Most discoveries in cell biology, as well as general knowledge of cell specific functions, have been obtained from cells isolated from tissues using enzymatic digestion, that are then processed for biochemical analysis or expanded using cell culture to study their function. Thus, enzymatic separation of cells is the standard method for separating and then evaluating biological, physiological, and structural properties of cells, and defining cellular essential function. There is an increasing use of enzymatic methods to isolate cells with therapeutic potential. A significant number of preclinical and several clinical studies have been successfully performed using freshly isolated cells after enzymatic tissue dissociation (9-20). There were no adverse effects reported in the literature. Endogenous collagenase metabolism is part of cell function in any collagen containing tissue. Collagenases can be made by the body as part of its normal immune response. This production is induced by several cytokines, which stimulate cells such as fibroblasts, macrophages or osteoblasts, causing degradation of extracellular matrix in a variety of physiological situations. Thus, human cells produce their own endogenous collagenase as a natural part of tissue repair and remodeling (21). We performed a study comparing isolation of adipose derived stem cells (ADSCs) using collagenase with ADSCs isolated by a non-enzymatic mechanical method (considered a non-substantial manipulation). A summary of the methods and results can be found in appendix 1. The study carried out has shown that enzymatic dissociation of adipose tissue, for the purposes of extracting ADSCs, has no statistically significant impact on the biological properties of the ADSC tissue units when compared to mechanical	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	dissociation of the adipose. Therefore, in our view, enzymatic dissociation for this purpose should be considered a non-substantial manipulation. Current State of the Art Collagenase is an enzyme that specifically acts on the collagen fibers present in extracellular matrix of tissues. Enzyme digestion of tissue using collagenase is currently and legally used to safely separate pancreatic islet cells for transplantation and for release and separation of adipose-derived stromal vascular cells for homologous applications. These current and legally used processes separate viable and intact cells from the extracellular matrix of the respective tissues. Our position with respect to the use of collagenase for separation of cells from extracellular matrix of tissue is that this procedure should NOT be considered as substantial manipulation. This statement is based on the established separation of high numbers of viable cells from different human tissue sources and the use of these cells clinically for different purposes without adverse effects or significant complications (22-35). The procedures using the separated cells have been shown to be safe, to yield sterile final cellular product, and to be effective in humans in a variety of clinical conditions. Further, use of collagenases in vivo are currently accepted as therapy for direct application in several human diseases such as debridement of wounds (36, 37), treatment of Dupuytren disease (FDA approved use of Xiaflex), and Peyronie´s disease (38, 39). Consequences: Impact of Classification of Enzymatic Digestion of Tissue as Substantial Manipulation Classification of enzymatic tissue digestion methods as substantial manipulation carries significant consequences. Specifically it would: eliminate all autologous cell therapies for solid organ and musculo-skeletal disorders which are based on homologous use of solid tissue parenchymal or mesenchymal cell components within their essential function, as such therapy would be classified as a drug; restrict therapeutic strategies to those stakeholders with sufficient investment	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	capacity to cover the high costs associated with drug development; eliminate most personalized point-of-care therapies and technologies transform clinical use of autologous cells into a drug product, quite contrary to the non-commercialization principles that currently rule use of autologous human derived cells and tissues in the European Community. restricts access to autologous use of patient own cells obtained by ex vivo tissue enzymatic digestion during the same surgical act in the operating room <u>Conclusions</u> Enzymatic digestion of tissues is historically used to separate cells from extracellular matrix for biologic, physiologic, and structural characterization, thus defining their essential function. Ex vivo enzymatic digestion of tissues to separate intact cells from extracellular matrix is in common clinical use for different clinical applications such as: fat grafting, wound healing, knee osteoarthritis, etc The proposed language for substantial manipulation in the Reflection Paper would transform use of autologous cells and tissue to a drug (ATMP). The changes to the language for substantial manipulation as provided herein provide a more permissive regulatory framework for minimally manipulated freshly isolated autologous cells and will enable physicians to provide personalized point-of-care therapies for their patients	
40.	See 39.	
41.	The European Section of the Alliance for Regenerative Medicine (formerly known as Alliance for Advanced Therapies) welcomes the opportunity to comment the reflection paper on classification of advanced therapy medicinal products. The paper provides several examples that are useful to understand the complexity of these products and it positively contributes to lift some uncertainties around the use of genes, cells, and tissues for therapeutic uses. One of the difficulties for ATMP developers is the co-existence and sometimes overlapping requirements of different legislations and requirements, such as those relevant to human tissues and cells, blood products, medical devices, transplants	Thank you. The legal framework for ATMPs is presented on the European Commission website; information on the CAT/EMA guidelines and procedures are available

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	and GMOs. We would therefore welcome any initiative from CAT and/or EMA to further clarify the list of regulations and requirements that are applicable and need to be followed in the different examples provided in the paper. In particular, it would be useful to indicate the status and applicable European legislations for products that are not classified as an ATMP, such as whether or not they are considered as a medicinal product, a cell/tissue or a blood product. This advice could also be published in the summary outcome ATMP classifications available on the EMA website. We propose that not only the outcome of all classifications is published but also a summary of the justification leading to the decision. National Competent Authorities (NAC) can also be called upon to provide an advice on whether products are to be considered as ATMP or not, for instance in situations they have to assess and approve products under the hospital exemption scheme. We believe that national authorities should be encouraged to seek CAT advice particularly in case of borderline products and that CAT scientific recommendation for the classification of ATMPs should prevail over national advice. Indeed, diverging opinions cannot be ruled out and we are of the opinion that CAT offers the right expertise and may be in a better position than some national authorities to take a decision on ATMP classification. Acknowledging the limitations due to the fact that decisions are not legally binding, this would contribute to ensure increased consistency and harmonisation across Member States and predictability for all stakeholders. There may be situations in this complex and rapidly evolving field where a revision of an ATMP classification is required which may either revise a former decision or confirm a NCA/CAT position. We are of the opinion that it may be useful to confirm whether this is possible by for instance indicating this under paragraph 2.4.	on CAT/EMA webpages. Classification of medicinal products and blood/tissues and cells regulation are within the remit of national authorities. Thus, CAT is not able to further clarify regulation of products classified as non-ATMPs. The summaries published on CAT/EMA webpage cannot contain confidential information, which limits the information that can be provided about the decision. Also the hospital exemption and possible classifications related to the HE procedures are outside the CAT remit. A product may be reclassified, based on the additional scientific information that comes available after the initial classification. This has been clarified in the reflection paper.
42.	BPI represents the majority of German companies active in the field of ATMP with a focus on of cell-based products. Most of these companies are SME, so BPI represents especially the voice of SME in this field. BPI welcomes the opportunity to contribute to this public consultation. The draft paper contains the experience gained since the start of the classification procedure. BPI acknowledges the great efforts by the CAT to support ATMP	Thank you.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	developers within the different processes. Although more than 100 classifications are finalised there is no systematic overview about core criteria that are relevant for the evaluation included in the document. To the contrary often isolated cases are mentioned where scientific opinions are different. It would be appreciated if a systematic overview about the finalised classification procedures would be provided. In addition, the main rationale for the CAT decisions should be provided in an aggregated form as well and as far as it does not interfere with the requirement to protect commercially confidential information with regard to the manufacturing and/or manipulation. This systematic overview could be based on the overview provided here: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000301.jsp&mid=WC0b01ac05800862c0 In addition, the systematic overview could be differentiated according to the different types of ATMP. Apart from that there are several concrete cases mentioned in the paper that are given as examples of “demarcation” between combined or non-combined ATMP, homologous or non-homologous use, SCTMP and TEP, substantial or non-substantial manipulation etc. Although the paper provides reasons for the decision this information is not regarded as being sufficient to take these examples to mark a clear border. The reason for that is that CAT has to protect commercially confidential information with regard to the manufacturing and/or manipulation of developing products. It would be appreciated if this would be mentioned within the Scope of the paper. In addition to the ATMP classification at European level national competent authorities conduct their own classification procedures, e. g. when it comes to clinical trial applications. It would be considered beneficial if EMA could provide a centralised database where the different recommendations together with the relevant rationale are collected. This could contribute to a more harmonised view concerning the classifications given by different authorities especially when it comes to borderline cases. This database could have an open part to inform future applicants about results of previous classification procedures. Apart from that it could contain a closed part with detailed information that is relevant for a more harmonised assessment of the applications at the level of the competent authorities and the EMA.	Include in the scope All NCAs are represented in the CAT and as such, it is expected that the information from the CAT classifications does reach the NCAs. It is also understood that the CAT classifications are widely recognized and followed by the member states.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
43.	We consider the publication of these procedures to be of significant importance to industry. In most cases, the summaries are easy to understand and clearly follow the established parameters within the applicable legislation. However, there are some classification procedures that seem to have come to conflicting decisions. We recommend that the CAT clarify the rationale behind these decisions. In the classification for a bone marrow derived product dated 12 February 2013 (EMA/82120/2013) it is stated that the product under evaluation (derived from autologous bone marrow) is “administered with a view to increase new bone formation…” and thus considered not for the same essential function. In the classification dated 30 October 2013 (EMA/661080/2013), a product also derived from autologous bone marrow was described as being used as “natural and effective repair mechanism and for the same function -namely bone repair – in the recipient site as in the donor site.” This product, intended for repair of necrotic femurs, was determined to not be an ATMP as the formation or repair of bone by these cells was, in this case, determined to be the same essential function. Additional information regarding the rationale for why the essential function of a bone marrow derived cellular product may be considered to include bone healing in one case but not another should be included. Two classification procedures published in April 2013 (EMA/129099/2013 and EMA/129056/2013) describe either a suspension of viable, non-substantially manipulated cells or the same suspension in an unnamed matrix, derived from stromal vascular fraction. Stromal vascular fraction is understood to be the cells recovered from enzymatic digestion and centrifugation of adipose tissue. The product was described as not having been subjected to substantial manipulation and are being used for the same essential function, specifically contributing to enhanced tissue renewal and turnover of sub-cutaneous tissue. According to the strict understanding of same essential function described in the reflection paper, these cells should be used only within adipose tissue to achieve a homologous use determination. However, in both classifications, “regeneration, repair, or replacement of weakened or injured subcutaneous tissue” rather than of adipose tissue was described. Based on the classification, the essential function of	Thank you. The classification is based on the information provided by the Applicant and on available scientific literature. Especially important for classification is the mode of action of the product, which may not be fully elucidated at the time of classification. Thus, sometimes the classification basis may look very different when more information and data becomes available. Also the procedures used in manufacture (e.g. cell selection) may differ and have different impact on the characteristics of the cells thus leading to different classification outcomes. There may also be different classifications for similar products, if the classifications have taken place before and after the revision of the guideline. Both ´substantial manipulation´ and ´same essential function´ are further clarified in the revised guideline. For SVF, there are also different manufacturing procedures used, some leading to substantial manipulation, some not.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	regenerative cells derived from adipose tissue is to repair or regenerate sub-cutaneous tissues generally, not just adipose tissue. The reflection paper should provide additional information clarifying why the same essential function criterion is specific in some cases but general in others.	
44.	This is a very complex topic and clearly a lot of thought has been given to try and classify these new and emerging products into a useful classification. It is also very useful that CAT are offering their expertise free of charge in helping applicants/developers to classify their ATMP products. Although this is a voluntary route it is an exceptionally useful one to take. The stated aims of this document, is that it would help provide clarity on the scientific and regulatory framework to be followed. It is this aspect that EBA think merits some further thought. A paragraph or flow chart as to the different regulatory pathways to be followed would be extremely helpful. This reflection paper on classification of ATMPs could also provide a forum to define the status of extracellular vesicles. EBA believe that extracellular vesicles are an emerging field of new treatment modalities. There one usually relies on cells as starting material, thus extracellular vesicles could be regulated as ATMPs. Furthermore EBA want to draw attention on the need to go beyond classification to facilitate and harmonize the regulatory procedures regarding ATMPs in the EU countries.	Thank you. As mentioned above, clarifying different regulatory routes for different products (especially non-ATMPs) is outside the remit of the CAT. Regulation 1394/2007 defines that ATMPs must be composed of genes or cells. If this is not the case (e.g. for extracellular vesicles), such products cannot be classified as ATMPs. Further classification of such products is in the remit of NCAs.
45.	EuropaBio member companies welcome the opportunity to contribute to the public consultation on the “reflection paper on classification of advanced therapy medicinal products”. The paper reflects upon the knowledge gained since the inception of the process and uses illustrative practical examples to share this experience. EuropaBio acknowledges the deployed efforts by the EMA CAT to help ATMP developers. Notwithstanding the outcome of the current 5 year reassessment process of the ATMP Regulation by the EU Commission’s DG SANCO, as much as the classification	Thank you.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	procedure is voluntary and free of charge (line 62) and not binding (line 63), EuropaBio members believe it would be very important to: 1. Consider and depict appropriate mechanisms by which an appeal to EMA CAT can be introduced by the ATMP developer. As a matter of fact, currently ANNEX C 'GROUNDS FOR DIVERGENT POSITION' of the CAT's opinion on the classification outlines both the reasons for divergent views from the final CAT opinion and the names of the Signatory CAT members supporting this divergent view. One option to introduce an appeal procedure might perhaps be to appoint one or more of the diverging Signatory CAT Members as CAT co-ordinator(s) of the re assessment/appeal process; 2. Confirm and clearly explain that re submission(s) to EMA CAT for a scientific recommendation for the classification is allowed and acceptable. In addition, explain that, in any case, the initial recommendation by EMA-CAT does not preclude that the subsequent recommendation diverges from the initial one. The re submission option should be allowed and clearly defined because of the rapid scientific/technology progress and on the further knowledge/data driven evidence of the product that is typical to ATMPs. 3. Acknowledge the freedom for ATMP developers to choose whether or not to undergo this classification procedure. There are instances where the developer, via a National Competent Authority (NCA), might either obtain a similar recommendation for classification as the EMA recommendation or be referred to the EMA CAT's process/decision . Notwithstanding the co existence of EMA-CAT and National processes for ATMP classification, EuropaBio would consider it highly beneficial if EMA-CAT could set up a central public database where EMA and National recommendations for classification are collected. The accountability of the accuracy of the data would reside respectively with EMA CAT for centrally assessed ATMPs or	As mentioned above, the CAT classification is not binding and thus, an appeal is not possible. Reclassification of a product is possible, if requested by the Applicant. However, additional information and data are the elements that are expected to change the original classification. ATMP classification is a voluntary procedure and this is written in the guideline. The national classifications are not within the remit of the CAT. It should be noted that all EU member states are represented in the CAT and that the CAT classifications are widely followed by the NCAs.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	with the NCA and for national/local opinions. This would be similar to the EU Clinical Trials Register, [2] Such database might increase transparency and allow ATMPs developers to compare different interpretations of product classifications across Europe. Additionally, this approach might help bridge the interpretation gaps that may arise between regulatory Competent Authorities. 4. Further elaborate and put the illustrative examples already used by EMA-CAT to help the readers' understanding of the classification procedure in a more reader-friendly "Q&A document" on ATMP classification. As expressed in the Report from CAT-Interested Parties Focus Groups (EMA/CAT/463795/2011), EuropaBio would be very happy to participate in the development of such a Q&A document.	Point taken, a Q&A document under preparation.
46.	The revision is welcomed by the HTA, as it consolidates the thinking that has been applied to ATMP classification over the last five years, as well as providing clarity on CAT's current approach to this activity.	Thank you.
47.	InGeneron, Inc. ("InGeneron") thanks the Committee for Advanced Therapies (CAT) for the opportunity to submit comments on the EMA's Reflection Paper on Classification of Advanced Therapy Medicinal Products ("Reflection Paper"). InGeneron believes that cellular therapy will be the future of medicine. Moreover, InGeneron believes that there is a need for guidance and stringent regulations for cellular therapies and devices related thereto. To that end, InGeneron appreciates the CAT's efforts in regulating advanced therapy medicinal products (ATMPs). InGeneron has carefully considered the proposals set forth in the Reflection Paper and respectfully submits the following comments with respect to those proposals affecting the regulation and use of autologous adult cells that are enzymatically processed.	Thank you. The comments on autologous cells treated with enzymes are addressed under the different headings below.
48.	The ISCT comments the CAT's attempt to provide insights into how they reach	Thank you. The proposed additions are to a large

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	classification opinions for ATMPs and borderline products. As a general comment, the ISCT suggests the EMA/CAT to review the document to make sure the text and figures are consistent with existing literature, like published classification recommendations and EMA guidance. To reach a classification recommendation, additional information should be added on the intended use, likely dose and route of administration and consequential likely mechanism(s) of action in the target indication(s). The ISCT understands that without disclosing confidential information with the classification summaries, they are very difficult to interpret. The ISCT would like to suggest that, in addition to publishing the classification recommendations, the EMA/CAT also provides guidance how to present the argumentation for a certain classification to the agency. Accepting that significant data may be needed in some instances to reach a classification recommendation, and that evolving scientific understanding could have an impact (84-85, 190-191), the ISCT feels the text in the document can be improved with regards to early classification (47-48, 60-61, 78-79). In addition, the ISCT suggests emphasizing the primary purpose: to provide a scientific recommendation on borderline products. It might be useful to include a statement that Regulation 1394/2007 is not intended to address transplants or to interfere with current clinical practices. This is consistent with the travaux preparatoires in respect of Regulation 1394/2007 . In the case of borderline products, ISCT suggests that the different competent authorities on blood and blood products, tissues and cells for transplantation, medicinal products for human use, as well as notified bodies, both at a national and at a central level should interact to prevent from potential bias in the categorization of products. Furthermore, the ISCT would like to see reflected in the paper that for many products there would be little or no doubt as to the classification, and the procedure does not necessarily include face-to-face contact. While provided free by the agency, the time and effort required to present a well-argued classification is not	extent confidential information of the Applicant, many times at a very early stage of development and thus cannot be published. The CAT classification is not only intended to classify borderline products, but to provide a recommendation whether a product fulfils one of the ATMP definitions given in the legislation. The aim is to give predictability and clarity for further development. Current clinical practise is not a justification for classification, nor has it been defined in any EU legislations. CAT classification of ATMPs has a legal basis (Reg.1394/2007) and follows the legal definitions. A classification is always triggered by an application.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	trivial and the value of the limited interaction with the CAT for a straightforward classification is questionable. In the opinion of the ISCT, the style of the document is too absolute in places and gives the impression that the CAT has developed a series of definitive rules (addressed in later specific comments). The usefulness of the document might be improved by providing relevant references to support certain rules, and if not available, softening the language. In particular, several examples mentioned in section 2.2.3 are presented with a generalised certainty that might not be supported by the science. Rather than focussing on attempting to explain existing classifications without being able to provide the necessary detail, the ISCT suggests to acknowledge that each classification needs to present a well-argued scientific position with, where appropriate, relevant quality, non-clinical and clinical data. Furthermore it should be emphasised that existing classification decisions may be based on completely different data packages or that the science may have evolved and led to new understanding. Furthermore, amongst others, the indication, presentation and route of administration could all impact the overall classification position.	As mentioned above, confidential information of the Applicant cannot be released in the classification summary.
	The ISCT is of the opinion that the discussion on minimally manipulated cells not used for the same essential function or functions in the donor as the recipient (286-307) should be strengthened because it is the most difficult ATMP classification concept. The ISCT is concerned that the way the term non-homologous use (15, 288, 301, 303, 305, 417, 419, 422, 425) is used in the document is confusing. In biology, homologous means corresponding in type of structure but not necessarily in function [see Oxford English Dictionary]. In the document, the EMA/CAT seems to suggest that anatomical or histological location (293-306, 421-425) is relevant in deciding whether minimally manipulated cells are intended to be used for the same essential function(s) or not.	Chapter for ´same essential function´ has been further clarified and wording ´non-homologous use´ has been removed.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	In summary, the ISCT suggests the EMA/CAT to consider the following. This document might be more useful if focussed on providing advice on how to present a classification argument to the agency, including an explanation of which data might be needed allowing the developer to understand when they might be ready. For example, under what circumstances data are needed to support classifications and what should the likely nature of those data be? The whole document could be more balanced by acknowledging that it is the responsibility of the developer to determine the right regulatory path for their product, including classification. While it may be desirable to be classified even in an early preclinical phase of development, this may not be possible and in some cases not even desirable, until sufficient data on the mechanism of action are available. Furthermore, changes to the product during preclinical development can also influence the classification, meaning it may be necessary to wait until close to (or after) clinical development is started before it would be useful to discuss the classification with the agency. The ISCT strongly suggests that the possibility for a briefing meeting is created. This would give developers the possibility to first accrue sufficient understanding of the product and discuss this with the agency before a formal classification opinion is requested. The ISCT suggests the EMA/CAT to provide guidance on the specific data packages needed in support of a classification procedure	Advice on the data/information needed for the classification is provided in the guideline. In unclear cases such briefing meetings are already arranged, however, the limited time of the CAT meetings does not allow extending briefing meetings to all applications.
49.	We know that the regulatory classification of cell based products is a difficult matter and we appreciate very much that CAT is proposing more clarifications and that it is giving us the opportunity to comment the draft of the revised reflection paper. It is our opinion that this new document should take into account the many new scientific data that have become available after the first publication of the paper in December 2012. To this regard as a general comment we think that the positions about non homologous use and about the implant of non manipulated cells into another	Thank you. Both chapters on ´substantial manipulation´ and ´same essential function´ have been further

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	anatomical or histological environment should be reconsidered. In some cases the mode of action of a cell product, as well as the mechanism of action are still unknown or may be multifactorial. Following are further general proposals we would like to express: 1) In addition to the products cited as examples in the paper it would be valuable to add some products to better illustrate the classification criteria of borderline products between ATMP and other products for which it is more critical to assign a regulatory classification. For example: the replacement of tissues compared to a transplant of tissues (as defined in directive 2004/23/EC). With both products you achieve a replacement which is interlinked with a regeneration and repair of the damaged tissue, as stated in line 317. It would be instructive to describe product examples that better clarify the criteria applied to qualify a TEP compared to a transplant. 2) Some borderline products have been classified differently in different Member States. In order to assure a more harmonized classification system of cell products and cell derivatives we believe that also European representatives of other competent authorities (e.g. Blood, Tissue and Cells, Medical Devices, Cosmetics) and experts of cell biology, molecular biology, etc. should be participating in the classification procedure of the CAT. In this way the evaluation of the product information submitted by the applicants and the criteria applied for the regulatory classification could be shared and become a useful tool to achieve a unique European classification system.	clarified. Please see the definition of a TEP in Reg.1394/2007. National classifications are outside the remit of the CAT and this guideline.
50.	none	
51.	none	
52.	The Reflection paper provides useful guidance from the Committee for Advanced	Thank you. Combined ATMPs are separately

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Therapies' (CAT) experience with the classification procedure on how borderline classification decisions are made. Additional guidance on the use of devices in relation to combined advanced therapy medicinal products (cATMPs) would be beneficial.	addressed in the guideline.
53.	none	
54.	Cell Therapy Catapult appreciate the opportunity to comment on the reflection paper of the Classification of ATMPs. The ATMP field is both relatively novel and rapidly evolving and as such, guidance of this type is welcomed. Furthermore the use of case studies/models are extremely helpful and Cell Therapy Catapult suggest more case studies are supplied. Furthermore this reflection paper should help to reduce the disparity between the various member states between the interpretation of the starting material legislation (EU Blood Directive 2002/98/EC and EU TCD 2004/23/EC) and the transition into the Medicines legislation (Regulation 1394/2007 and 2001/83/EC). We believe the reflection paper should provide more guidance on this, using exemplar case studies. In addition the Cell Therapy Catapult strongly recommend that the ATMP classification procedure should become, legally binding, centrally determined by the CAT. This change would act to provide certainty to developers and reduce disparity between member states thereby making the EU more attractive for developers of ATMPs and as such retaining internal investment whilst attracting external investment.	Thank you. As mentioned above, the national classifications are outside the remit of the CAT. Furthermore, making the CAT classification binding would require changes in the legislation, which again, is outside the scope and remit of this guideline.
55.	The BIRD-C GmbH&CoKG (BIRD-C) welcomes and appreciates the opportunity to submit comments on the Committee for Advanced Therapies (CAT) of the European Medicine Agency's (EMA) Reflection paper on classification of advanced therapy medicinal products (ATMPs) (further referred as CAT Reflection Paper). BIRD-C is a biotech company operating from facilities in Vienna, Austria. Utilizing its	Thank you. See comments above.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	patent-protected Bacterial Ghost platform technology the company is developing human and veterinary vaccines with the particular interests in cell therapies and immunotherapies in Europe and worldwide. BIRD-C would like to respond to the EMA's CAT Reflection Paper. BIRD-C submits the following comments and recommendations concerning the "Reflection paper on classification of advanced therapy medicinal products": <feedback ICCTI included here, see contribution nr. 10.>	
56.	The Austrian Cluster for Tissue Regeneration (Cluster) would like to appreciate the opportunity to submit comments on the Committee for Advanced Therapies (CAT) of the European Medicine Agency's (EMA) Reflection Paper on Classification of Advanced Therapy Medicinal Products (ATMPs) (further referred as CAT Reflection Paper). The objective of the Cluster is to better understand soft tissue, cartilage, tendons, ligaments, bone and neuroregeneration, and thereby enhance therapy through new and improved treatment methods. Research assignments arise from treatment necessities and proven benefits to patients. The Cluster includes 12 groups of 5 universities. We believe that the proposed classification needs some revision in order to balance the best interests of patients and, at the same time, properly address the regulatory's concerns regarding safety and efficacy of cell/tissue engineering therapies. We believe that ATMP classifications/requirements are endangered to reach a level, which could have detrimental consequences for public health as it could prevent the appearance of valid treatments for unmet medical needs and supports medical tourism at a continuosly increasing level. Such actually patients can be at greater risks, than by less demanding European rules. Furthermore it can act as a roadblock	Thank you. Both the requirements for ATMPs and the hospital exemption are outside the scope of this guideline, which provides advice on classification of ATMPs only.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	to translational research in the field of tissue engineering and regenerative medicine in Europe, especially for SME's and non-profit entities (like eg. Red Cross). It has some parallel features to partly overregulated animal protection issues, which can lead to loss of jobs in Europe and increase of experiments in less regulated regions with conditions below European standards. We emphasize the importance to apply a risk-based approach to determine the extent of quality, non-clinical and clinical data. We feel that enough flexibility should be applied, particularly in the area of quality, with a view to ensure that the marketing authorization application requirements take due consideration of scientific progress and specific characteristics of ATMPs. It also be realistic to lead to affordable therapy costs thereafter. We support the statement "that the realization of randomized controlled clinical trials may not always be feasible, for instance, if the administration of the product requires a surgical procedure (i.e. the majority of tissue engineering products), or where no alternative treatments are available" (Section 2, paragraph 4 of EC Report). It is therefore necessary to find a balance between the need to ensure that ATMPs are made available to patients only after quality, efficacy and safety thereof has been adequately demonstrated, and the need to facilitate early access for new treatments in case of unmet medical needs. Conditions of hospital exemption should be harmonized (eg. number of procedures/year), but be flexible and inclusive enough to allow innovative treatment approaches for unmet medical need or regional availability in low income regions despite otherwise unrealistic high price tags and not available commercially licensed ATMP products. In vitro fertilisation is available in all European countries with high quality but without ATMP regulations, therefore at least the autologous use of minimally manipulated cells should be made not further difficult with overstretched	See comments above.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	"homologous tissue use" ATMP rules- eg. adipose derived MSC have their perivascular niche in each musculo-skeletal and not only in fat tissue. For example, mesenchymal stromal cells should be used for the treatment of damaged tissues of mesenchymal origin and this should be considered as homologous use. It is good surgical practice to use bone marrow to support bone and cartilage repair (microfracture) – why should that considered now as ATMP (acc. CAT reflection paper) ? We believe that with autologous and minimally manipulated cells, the evidence based on case-control study with proper long-term follow up for safety and efficacy would bring enough evidence to justify such therapy as accepted standard without the need of hard to perform or impossible blinded randomized controlled trials.	Good surgical practise using manipulated cells as "concurrent treatment" is not defined in EU legislation. Regulation 1394/2007 was established to ensure that patients are not put into undue risk and that products without proven safety and efficacy are not used to treat patients.
57.	See 11.	
58.	TERMIS-EU would like to appreciate the opportunity to submit comments on the Committee for Advanced Therapies (CAT) of the European Medicine Agency's (EMA) Reflection Paper on Classification of Advanced Therapy Medicinal Products (ATMPs) (further referred as CAT Reflection Paper). TERMIS brings together the international community of persons engaged or interested in the field of tissue engineering and regenerative medicine and promotes education and research within the field of tissue engineering and regenerative medicine through regular meetings, publications and other forms of communication. The Society is committed to bringing you closer to key professionals to support your mutual understanding of the field, accelerate your research in the field and to enable you to contribute to the ultimate care of patients in this very important way. We believe that the proposed classification needs some revision in order to balance the best interests of patients and, at the same time, properly address the regulatory's concerns regarding safety and efficacy of cell/tissue engineering	Thank you. Please see comments above.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	therapies. We believe that ATMP classifications/requirements are endangered to reach a level, which could have detrimental consequences for public health as it could prevent the appearance of valid treatments for unmet medical needs and supports medical tourism at a continuosly increasing level. Such actually patients can be at greater risks, than by less demanding European rules. Furthermore it can act as a roadblock to translational research in the field of tissue engineering and regenerative medicine in Europe, especially for SME's and non-profit entities (like eg. Red Cross). It has some parallel features to partly overregulated animal protection issues, which can lead to loss of jobs in Europe and increase of experiments in less regulated regions with conditions below European standards. We emphasize the importance to apply a risk-based approach to determine the extent of quality, non-clinical and clinical data. We feel that enough flexibility should be applied, particularly in the area of quality, with a view to ensure that the marketing authorization application requirements take due consideration of scientific progress and specific characteristics of ATMPs. It also be realistic to lead to affordable therapy costs thereafter. We support the statement "that the realization of randomized controlled clinical trials may not always be feasible, for instance, if the administration of the product requires a surgical procedure (i.e. the majority of tissue engineering products), or where no alternative treatments are available" (Section 2, paragraph 4 of EC Report). It is therefore necessary to find a balance between the need to ensure that ATMPs are made available to patients only after quality, efficacy and safety thereof has been adequately demonstrated, and the need to facilitate early access for new treatments in case of unmet medical needs. Conditions of hospital exemption should be harmonized (eg. number of procedures/year), but be flexible and inclusive	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	enough to allow innovative treatment approaches for unmet medical need or regional availability in low income regions despite otherwise unrealistic high price tags and not available commercially licensed ATMP products. In vitro fertilisation is availble in all European countries with high quality but without ATMP regulations, therefore at least the autologous use of minimally manipulated cells should be made not further difficult with overstretched “homologous tissue use” ATMP rules- eg. adipose derived MSC have their perivascular niche in each musculo-skeletal and not only in fat tissue. For example, mesenchymal stromal cells should be used for the treatment of damaged tissues of mesenchymal origin and this should be considered as homologous use. It is good surgical practice to use bone marrow to support bone and cartilage repair (microfracture) – why should that considered now as ATMP (acc. CAT reflection paper) ? We believe that with autologous and minimally manipulated cells, the evidence based on case-control study with proper long-term follow up for safety and efficacy would bring enough evidence to justify such therapy as accepted standard without the need of hard to perform or impossible blinded randomized controlled trials	
59.	ARI believes the proposed classification needs some revision in order to balance the best interests of patients and, at the same time, properly address the European Medicine Agency’s (EMA’s) concerns. Therefore, ARI believes that allogeneic cells or tissues for the purpose of mass production and distribution should be regulated as a drug. To strike a balance, some allowance for patients to use either their own cells or donated cells for an individual therapy for one time use should be allowed under the classification without classification as a drug. This balance is needed, as it is highly unlikely that any one individual patient or clinic could economically afford or wait for the full Investigational New Drug (IND) process to take place to treat one	Thank you. We note your observation. However, current clinical practise is not a justification for classification, nor has it been defined in any EU legislations. CAT classification of ATMPs has a legal basis (Reg.1394/2007) and follows the legal definitions. A classification is always triggered by an application.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	patient each time, regardless of safety or efficacy concerns. There are many clinics and physicians around the world using autologous and allogeneic cellular therapies to treat several disease conditions and have produced overwhelming documentation showing safety and efficacy. Since these were individualized therapies for individual patients, the cell tissues were never intended to be mass-produced, distributed, or regulated as a drug. Select, individualized cellular therapies have been employed safely and effectively for many years in clinical translation. Authors such as Hernigou describes his use of Bone Marrow Concentrate (BMC) to help bone and rotator cuff tear repair since the late 90s. These procedures have had an excellent safety record. As of 2013, the publicly posted clinical trial database at www.clinicaltrials.gov has shown 359 clinical trials using Mesenchymal Stem Cells (MSCs) with a very wide range of therapeutic applications worldwide. Bone marrow transplants have been utilized to treat blood borne cancers for over 50 years. It must be noted that since 1986, in-vitro fertilization has become commonplace throughout the world as a regenerative procedure that has been completed safely and effectively and involves, in some cases, substantial manipulation of cellular tissues and risk to expectant mothers.	
60.	EBE welcomes the initiative of the CAT to provide clarification on how classification opinions for ATMPs are formed. As a general comment, EBE suggest that the present Reflection Paper should provide more guidance on the type and extend of the expected documentation and the presentation of the justification for the desired classification as this would be helpful for SMEs. It is understood that more information may be required to reach a classification recommendation in some cases, and that evolving scientific understanding could have an impact in the final recommendation. Several of the specific comments speak to additional information that could be provided if the	Thank you. The guideline includes advice concerning data/information to be provided (e.g. on mode of action). However, the final classification is always based on the data provided by the Applicant and on available scientific knowledge, which may differ between products.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	reflection paper was advanced to a draft guidance. In the case of borderline products, especially regarding combined ATMPs, EBE would like to propose that CAT consult with competent authorities on blood and blood products, tissues and cells for transplantation, as well as notified bodies in order to gain a broad input on the categorization of products. Further clarification would be needed on the concept of minimally manipulated cells not used for the same essential function or functions in the donor as the recipient (286-307) as this is the most complex concept in developing cell therapies. In general it would be useful (certainly to SMEs) to emphasize that it is the responsibility of the company to determine the right regulatory path for their product, including classification, that the timing of classification (early pre-clinical versus clinical stage) may be crucial to decide on the data package to be developed, and that the classification may change if major changes are introduced to the product during development. Recognizing that EMA and FDA offer coordinated orphan designation and scientific advice, where possible (given differences in the regulatory frameworks for devices), we encourage joint efforts or participation in forums seeking regulatory harmonization of the classification of cell, gene and tissue therapies.	ATMP classification has a legal basis and does not interfere with national classifications. Thus, it is the task of the CAT to decide if a given product fulfils one of the legal ATMP definitions. For further borderline cases (non-ATMPs), the CAT has no remit. Currently, non-manipulated cells used for other purposes than ´same essential function´ belong to ATMPs, as defined in the legislation. An international survey on classification aspects has been conducted (IPRF, see above) and the results will be published soon.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Comments on the introductory statement			
15	48	Comment: Non-homologous use does not appear in the EU legislation and as such might be misinterpreted. For instance the Oxford English dictionary states “Having the same relation to an original or fundamental type; corresponding in type of structure (but not necessarily in function)”. Proposed change (if any): use ‘same known essential function or functions’ or perhaps ‘same essential function(s)’ throughout the document and remove ALL occurrences of homologous use.	Accepted. The wording has been changed to better reflect the legal definitions.
Comments on the Executive summary			
41-49	54	Also applies to lines 62-63 Comment: The optional/voluntary nature of the CAT scientific recommendation for the ATMP classification procedure is established in article 17 of the Regulation (EC) 1394/2007. Cell Therapy Catapult believe that this procedure should become legally binding, centrally determined by the CAT. Proposed change (if any): as above	Not accepted. Such a change would require legal changes, which are outside of this guideline.
43	41	Comment: The optional nature of the ATMP classification procedure is	Not accepted. The procedure is voluntary and thus

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		established in article 17 of the Regulation (EC) 1394/2007. However we believe the request for classification should be strongly encouraged in order to avoid the non-regulated development or use of products based on genes, cells or tissues that would actually fall under the definition of an ATMP. Proposed change (if any): remove the word 'optional'. Add that 'CAT advice on ATMP classification can be sought by national competent authorities.'	the word optional is maintained. Classification is triggered by an application; NCAs do not hold the data/information on products to be classified. However, CAT provides assistance to NCAs on classification issues, if requested.
50-51	48	Comment: Wording of this sentence seems to imply the classification procedure is more than just a scientific recommendation. Proposed change (if any): …scientific recommendations on whether or not the referred product…	Point taken, the text is revised.
50-51	48	Comment: It should be emphasised that the classification does not address whether the product falls within the scope (Title II) of the medicines directive (only the definition of an ATMP). By way of example, classification does not address whether the cells have been "placed on the market" or "prepared industrially". Further, classification does not address any of the statutory exemptions to obtaining a marketing authorisation. Proposed change (if any): Add sentence: The role of the CAT is limited	Point taken and text is revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		to scientific recommendations and it does not provide a scientific or legal recommendation as to whether the product falls within the scope of Directive 2001/83/EC. The ISCT suggests the EMA/CAT to add guidance reflecting the steps a drug developer can/should take in time to arrive at a certain classification (see also the summary on page 4). For example: Step 1. Product needs to be a medicinal product before classification as ATMP can be pursued. Step 2. Provide guidance on what information/data should be included in the data package. Step 3. Provide guidance on what the best timing in the drug development process is for submitting a classification request.	CAT classification is based on the legal definitions; the guideline provides assistance on the data/information required for the classification.
52	48	Comment: It seems that ATMP Regulation does not provide PRECISE legal definitions for ATMPs. In fact the reflection paper tries to clarify the interpretation of the definitions. Proposed change (if any): To remove the word precise: 'The ATMP Regulation and the Directive 2001/83/EC Annex I Part IV provide legal definitions for ATMPs'.	The references of legal definitions are exact copies from the legislation.
52-55	48	Comment: Unclear what the message is. If the intent is to clarify that the CAT classification does not consider whether the product is a medicinal product within the definition of article 1.2 of Directive	Definitions of gene therapy and somatic cell therapy medicinal products are in the Annex I, Part IV of Directive 2001/83/EC, as implemented by Dir.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		2001/83 this should be stated more clearly. Furthermore, since the definition of a biological medicinal product is contained within Annex I Part I (3.2.1.1.) the endnote (iii) referring to article 1.2 may seem confusing. Proposed change (if any): Modify text to make intended point clear; assumed to be that CAT classification doesn't cover article 1.2. Provide reference for biological medicinal product.	2009/120/EC. The reference to biological MP has been added to endnote iii.
62	41	Comment: The voluntary nature of the ATMP classification procedure should not be stressed for the same reason as mentioned above. Proposed change (if any): suppress the words 'voluntary and'	Not accepted, see comment above.
62-72	4	Comment: Although the classification procedure is voluntary, our experience suggests that this is a valuable procedural step, which triggers CAT involvement and the application of ATMP specific incentives. Therefore, we recommend this section of the guidance be rearranged to highlight this aspect of classification. Comment: If it is not possible to obtain the proposed ATMP Definition Recommendations via the ATMP Classification process as described above, it would be most helpful for EMA to provide guidance on the optimal path to obtain feedback on these issues. Proposed change (if any):	Not accepted, see comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Recommend reordering as follows: **The ATMP classification procedure is voluntary and free of charge. ~~Indeed, the~~ ATMP classification, along with other tools (e.g. ITF briefing meetings1), should be seen as a first opportunity to engage with regulators. Once the candidate ATMP classification has been clarified and confirmed, the dialogue can continue with the use of other regulatory procedures such as scientific advice and ATMP certification, the latter exclusively set up under the auspices of the dedicated committee (CAT). The ATMP classification may also help developers to gain access to all relevant services and incentives offered by the EMA.** While the recommendation on classification provided by the Agency is not binding, the procedure can help developers to clarify the applicable regulatory framework **and recommended pathway to define of the active substance, the pharmaceutical form and the units to be used for strength, as well as the wording to be used to define the final product for EMA procedures.**"	
62-67	46	Comment: We recognise that the opinion of CAT is not legally binding, but would welcome opinion on the implications of a Member State choosing not to recognise the recommendation of CAT.	Not accepted, see comments above.
69-70	4	Comment: Suggest clarifying that the ATMP certification procedure is intended for SME companies. Proposed change (if any): "… procedures such as scientific advice and ATMP certification for **Small Medium Enterprises (SMEs)**, the latter exclusively…"	Accepted, clarification included.
78-81	48	Comment: Repeated point (from lines 47-48) that classification can be sought early.	Point taken, the early time point is deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Move last two sentences to line 49, delete first sentence starting line 78.	
80	19	Comment: We do not understand the use of the adjective “scientific” with regards to the “recommendations” made by the CAT. Proposed change (if any): Replace “scientific recommendations” by “classification”.	Not accepted. Classification is based on evaluation of the scientific information/data e.g. on mode of action, manipulation of cells etc. Furthermore, this is how this procedure is described in the ATMP Regulation
82-83	48	Comment: This sentence seems redundant because of sentence 56-59, and footnote 2 is a repeat of endnote iv. Proposed change (if any): delete sentence.	Not accepted. This clarification is considered important.
84-85	19	Comment: We would appreciate a brief description of the procedure for a follow-up request on classification somewhere in the document. Proposed change (if any): Some information regarding the follow-up request opportunity might be put in section 2.4 “classification on procedural aspects information to be submitted by the applicant”.	Point taken and text has been revised.
84-85	60	Comment: It is not entirely clear from the sentence whether this can be done after a classification has been published (…previously submitted…) or during the procedure. It is not completely clear either whether the Applicant should submit a new classification request if new scientific insights become available or major changes are introduced that may impact the classification.	Point taken and text has been revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
86-87	30	Comment: The summary outcome ATMP classifications assessed so far by the CAT is available on the EMA website from July 2011. Yet, almost half of the recommendations were adopted before July 2014 and are not available. To fully comply with article 17 (2) of Regulation (EC) n°1394/2007 and in accordance with the proactive policy on transparency that the EMA is developing (EMEA/232037/2009- rev*), it will be relevant for stakeholders to access also the summaries of these older recommendations as soon as possible although their process of publication on the EMA website may already be ongoing.	Not accepted. The information published prior July 2011 is sufficient to fulfil the requirement in art 17(2). However, in order to further assist the ATMP developers, more information is published since then. Furthermore, most of the CAT considerations related to these early ATMP classifications are reflected in depth in this reflection paper.
87	30	Comment: This information is also summarised in the CAT monthly report. Proposed change (if any): "This information is updated on a monthly basis" and the general activity of the CAT regarding scientific recommendation on ATMP classification is also summarised each month in the CAT monthly reports.	Partly accepted: reference is made to the publication of the summary reports. Reference to the CAT monthly report is not added.
Comments on the scope			
90	42	Comment: There are several concrete cases mentioned in the paper that are given as examples of demarcation between combined or non-combined ATMP, homologous or non-homologous use, SCTMP and TEP, substantial or non-substantial manipulation, ATMP and transplants etc. Although the paper provides reasons for the decisions the current descriptions are not regarded as being sufficient to mark a clear border for future	Point taken and text revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		applications. The reason for that is that CAT has to protect commercially confidential information with regard to the manufacturing and or manipulation of developing products and hence cannot publish all relevant information for the rationale of a decision. In line 410ff. it is therefore mentioned that “this conclusion … is not directly applicable … to other products which may be submitted for classification as they may be derived from very different and more complex process and substantial manipulations.” As this is true for the other examples in the paper as well and this is a matter of principle it is suggested to include a similar sentence at the beginning of the paper within the scope in the executive summary. Proposed change (if any): It is proposed to add a sentence at the end of the scope like: “However, the examples and the conclusions mentioned in this paper are not directly applicable to other products which may be submitted for classification e. g. as they may be derived from different processes and manipulations.”	
90-93	48	Comment: Procedural advice is covered by EMA/CAT/99623/2009 Rev. 1, this reflection paper covers scientific concepts of classification. Proposed change (if any): The ISCT proposes to make the following change: ‘The scope of the document is to provide updated information about the principles underlying the ATMP classification.’	Not accepted. The two mentioned documents have different scope, one is procedural and one is scientific.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
90-93	54	Comment: Whilst it is extremely useful to further sub-classify if an ATMP is a Somatic, Gene Therapy or Tissue Engineered product since this allows subsequent more detailed guidance on the development of these product subtypes, Cell Therapy Catapult question whether the mode of action of these subtypes discussed in more detail further down in the document is slightly artificial and leads to confusion. In particular we find the definition of a TEP to repair, regenerate or replace human tissue slightly incongruous as somatic and gene therapy products could also act to do this. Proposed change (if any): Suggest that it is emphasised that the sub-classification is to allow developers to draw upon appropriate guidance for the development and testing of their products rather than requiring a different regulatory route to a MAA.	Not accepted. The definitions are set in the legislation and cannot be changed by the CAT.
90-93	60	Comment: It would be useful to add the type and type of information needed to reach a classification recommendation taking into account the experience of the CAT with the level of documentation submitted so far. Proposed change (if any): Modify sentence as follows “The aim of this reflection paper is to provide guidance on the ATMP classification procedure and the information to be submitted, as well as…”	Not accepted. The guideline cannot define what information has to be submitted. The minimum is, as described, that there is a clear product and some understanding how it works.
Comments on section 2.1. Legal basis of ATMP classification			
95	11 / 57	STEMSO believes that a new, working definition of ATMPs should be created to: a. *Exempt* both autologous and individualized allogeneic point of care cell therapies from the list of ATMPs. Specifically,	Not accepted. The ATMP definitions are given in the legislation and cannot be changed by the CAT.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		I. Bone marrow concentrate (BMC) used for purposes other than haematopoietic use, and II. Stromal Vascular Fraction (SVF) derived from adipose tissue by enzymatic digestion. Proposed change (if any): b. Exempt situations when individualized, non-homologous, autologous or allogeneic cell therapy may be performed with signed, informed consent of the patient or delegated informed consent for compassionate care situations.	
95	22	2. Human Med AG believes that a new, working definition of ATMPs should be created to: a. Exempt both autologous and individualized allogeneic point of care cell therapies from the list of ATMPs. Specifically, - Stromal Vascular Fraction (SVF) and Adipose Stem Cells (ASC) or Mesenchymal Stem Cells (adMSC)derived from adipose tissue after enzymatic digestion and subsequent removal of remaining enzyme to physiological leves before application of the SVF/ASC. b. Exempt situations when individualized, non-homologous, autologous or ☐llogeneic cell therapy may be performed with signed, informed consent of the patient or delegated informed consent for compassionate care situations. The scope of 2001/83/EC (Article 2) http://bit.ly/1uGJ2nN limits the regulation of cells and tissues in Europe as it defines the authority of regulated products when it states," the provisions of this directive shall apply to industrially produced medicinal products for human use intended to be placed on the market in member states." Since	Not accepted, see comment above. Not accepted, see comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Regulation 1394/2007 http://bit.ly/1vbtWrR is an amendment to Directive 2001/83/EC, the provisions of 1394/2007 are guided by the scope of 2001/83/EC, by definition. Therefore, it is clear that cells and tissues that are 'placed on the market' are regulated and, the inverse applies if such cells or tissues are not placed on the market. The term 'placed on the market' is not defined in 2001/83/EC, however, the medical device directive 98/42/EC http://bit.ly/1vbvm5L provides a definition of 'placed on the market' that provides guidance on the intent of such a term / condition. Specifically, article 1(2)h of 93/42/EC defines placed on the market as: " the first making available in the return for payment or free of charge…with a view to distribution and or use in the community market." The 2014 EU 'Blue Guide' also adds clarity to the meaning of 'placed on the market' when it states, "placing on the market is considered not to take place were a product is….manufactured for one's own use". Furthermore, the European Commission report of 28 March 2014 on Regulation 1394/2007 has acknowledged the absence of regulatory authority over point-of-care autologous cells and tissues when it stated, "new innovative products, which are not clearly captured by existing provisions, are emerging…….its reinjection into the donor with the same procedure raises question as to how these treatments should be regulated". The same report illustrates that Regulation 1394/2007 was not intended to apply to autologous point-of-care cells and tissues due to the practical realities of not being able to comply with the quality and GMP requirements of 1394/2007 when it stated, "requiring autologous products that are manufactured at the hospital prior to the administration to the patient to comply with the quality controls and manufacturing requirements of standardized chemical-based medicinal products would prevent the development of these treatments in practice as batch release certification would be required per treatment and a manufacturing license would be required per hospital". Therefore, it is abundantly clear that autologous cells and tissues	

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		produced in the same surgical procedure and at the point of care are not regulated in Europe due to the fact that they do not meet the minimal jurisdictional burden of being 'placed on the market', regardless of how the cells are used. We encourage the European Union to clarify the exemption of autologous same surgical procedure cells and tissues in much the same way as Directive 2004/23/EC (Article 2) and in a similar manner as the FDA's exclusion of autologous same surgical procedure cells and tissues (HCT/P) in 21 CFR 1271.15(b). http://1.usa.gov/1Dxo1Cb Human Med AG brings to the Committee for Advanced Therapy's (CAT's) attention that historical data from clinical studies have not shown serious adverse reactions associated with autologous and allogeneic MSC therapy. 1 For this reason, Human Med AG believes that single, individualized therapies to treat one patient with autologous or allogeneic cells for homologous or non-homologous use should be allowed under the practice of medicine.	
95	48	Comment: This isn't really discussion, just reproduction of the various legal articles. Given that recital 24 of Regulation 1394/2007 states that the classification opinion is to address questions of borderline with other directives if parts of the medicines directive are reproduced why not parts of the directives covering devices, tissues and cells etc.? Proposed change (if any): consider adding relevant text from other directives, e.g. medical device definition (for combined ATMP) or Directive 2004/23/EC on human tissues and cells or both.	Not accepted. The classification of devices, transplantation products etc. are not within the remit of the CAT.
103-104	48	Comment: Since combined ATMP is covered in section 2.1.4 (starting line 154) this could be redundant here.	Not accepted. This is an overview of the legal basis and the text later gives further details.

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		Proposed change (if any): delete line 103-104.	
109	48	Comment: compared to Directive 2009/120 an extra word 'two' has been inserted. Legal text should not be altered unless clearly identified. Proposed change (if any): delete word 'two' at end of line 109.	Accepted. Text amended accordingly.
112-113	8	Comment: 'Regulating, repairing, replacing and deleting' all refer to the endogeneous genetic sequence, while the verb 'adding' refers to the novel genetic sequence that is introduced. For reasons of consistency and clarity, 'adding' should not refer to the same genetic sequence as 'regulating, repairing, replacing and deleting'. Although this appears to be an issue related to the relevant Directive and is not subject to change in the current procedure, it still seemed worth mentioning. Proposed change (if any): This sentence could be modified as follows: it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing or deleting a[n endogenous] genetic sequence or adding a[n exogenous] DNA sequence.	Not accepted. The definition is from the legislation, which cannot be changed with this guideline.
119	48	Comment: compared to Directive 2009/120 an extra word 'two' has been inserted. Legal text should not be altered unless clearly identified. Proposed change (if any): delete word 'two' at beginning of line 119.	Accepted, see comment above.
124-126 136-137	4	Comment: Suggest clarifying the reasons behind the difference in language between somatic cell therapy which **"is presented as having properties for, or is used in or administered to human beings**	Not accepted, the legal definitions are not within the remit of the CAT.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		with a view to treating preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells and tissues" and a tissue engineered product which "**is presented as having properties for, or is used in or administered to human beings with a view to regenerating repairing or replacing human tissue".** Most people in the field would consider a tissue engineered product to be one where the cells are in a matrix whereas this definition does not require that a matrix is present, nor does a tissue engineered ATMP need to be used to treat a disease whereas it appears that a somatic cell ATMP needs to treat a disease.	
130-131	48	Comment: This last sentence reflects an interpretation and does not appear in the Directive or Regulation. This should be made clear. The ISCT would like to comment that any combination of manipulations that are considered to be non-substantial manipulations individually, which are used in the manufacturing process, could lead to a situation in which the cells are considered to be more than minimally manipulated. Whether or not a product is considered to be more than minimally manipulated should always be assessed on a case-by-case basis. The assessment should focus on the cells themselves and the impact of the manipulations performed rather than the steps per se. Enzymatic digestion does not always substantially alter the biological characteristics of the cells. Proposed change (if any): Delete the sentence.	First comment accepted: the referred sentence has been separated from the rest of the text. Second comment: Not accepted. The sentence is only clarifying the legal text and does not set any rules for the classification.
131	2	Comment: In the "Reflection" paper, under section 2.1.2 it describes several categories that "shall not be considered as substantial manipulations : cutting, grinding shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation,	Not accepted. The text on enzymatic digestion is further clarified. Furthermore, this paragraph is repeating the text of the Annex I to the Regulation 1394/2007. It is not

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		concentration or purification, filtering □aematopoietic, freezing, cryopreservation and vitrification." However, in section 2.2.3 the paper then gives examples of substantial manipulation. In particular, it notes "enzymatic digestion of tissue to release cells. This is most often done using fat tissue and the enzyme collagenase. We assert that this is inconsistent with the already noted list of acceptable manipulations – namely "cell separation" and it is by far less manipulative than irradiation or even soaking in antibiotic solution. Collagenase is already an FDA approved medication (e.g. Xiaflex for Peyronie's or Dupetryn's Contracture). Collagenase only affects collagen material and does not even enter the cell membrane or alter its characteristics. The problem with collagenase stems from its manufacturing which originally came from bovine based products that were only approved for laboratory use. Such products run the risk of transmissible spongiform encephalopathies (TSEs) and thus could pose the risk of disease transmission. Current FDA and GMP manufactured collagenases are free of any such disease transmission risk. Indeed, Cytori provides a proprietary based collagenase to process their SVF cells and has not been shut down by the FDA. Indeed, they currently have an approved Investigational Device Exemption (IDE) that could not be possible if their collagenase use was such a violation of minimal manipulation. When the FDA Tissue Reference Group (TRG) responds negatively to someone suggesting the use of collagenase this is because they have no knowledge of the particular collagenase and do not want to take any risk for approval under such simple circumstances. They can reference this as possibly more than minimal manipulation in order to assert their jurisdiction. If medical grade collagenase were really an issue, then they would shut down CSN, Cytori and any other organization using collagenase in the USA. This is not the case as there is no risk of disease transmission (e.g. CSN uses Roche GMP collagenase). In South Korea e.g., the official policy of the KFDA is that the use of collagenase constitutes "minimal manipulation".	possible to add here additional non-substantial manipulations

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Example of minimal manipulation should include “enzymatic (collagenase) digestion of tissue to release cells”	
142-144	51	Comment: materials, which are composed from processed non-viable parts of the cells, should be more likely excluded from TEP. Proposed change (if any): Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells and/or its parts or tissues and which do not act principally by pharmacological, immunological or metabolic action, are excluded from this definition.	Not accepted. The legal definitions cannot be changed with this guidance.
154	8	Comment: It might be stated more clearly that first it needs to be established whether the product is an ATMP (GTMP, SCTMP or TEP) and only after that, whether its combination with a medical device results in a combined ATMP.	Not accepted. All these aspects are considered during the classification procedure, not sequentially in separate procedures.
162-164	8	Comment: The following is stated:”[…] its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.” What is the rationale for demanding an action primary to that of the devices referred to? If it were to be considered “secondary” it is no longer an ATMP? In addition, this might be very difficult to establish and matter of debate, e.g. when the impact of the functionality of each part changes throughout time.	Not accepted. The definition is from legislation and cannot be revised with this guidance.
177-182	44	In lines 177-182 it is clearly stated that if a product falls between the definitions of a tissue engineered product and a somatic cell therapy product, it shall be considered a tissue engineered product. Similarly a	Not accepted. The regulatory framework is the same for all ATMPs, despite of the different

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		product that falls between the definition of a somatic cell therapy medicinal product or a tissue engineered product and a gene therapy medicinal product, it shall be considered as the latter. This begs the question as to whether different regulatory pathways should be followed depending on the type of classification of the ATMP in question. However no guidance is given in this paper on this matter. One is therefore left with the question of the reasoning behind these classifications. EBA believe they are very important, and therefore a paragraph or flow chart as to the different regulatory pathways to be followed would be extremely helpful. Proposed change (if any): Add a paragraph or flow chart as to the different regulatory pathways to be followed .	classifications. For different product related aspects the applicants can always seek scientific advice.
182	10 / 20 / 26 / 55 / 56 / 58	Comment: New paragraph 2.1.6. reflecting recommendations from the European Commission to the European Parliament and the Council issued on March 3, 2014 by the European Commission and the 1st Report of Session 2013-2014: Regenerative Medicine Report by the House of Lords published on July 1, 2013 in London, that different model for testing safety and efficacy of cell therapies that would be different from recent and broadly unacceptable system of randomized controlled clinical trials previously developed for chemical-based compounds, should be added. Such model should be mainly based on ethical aspects related to cell therapy products in agreement with the Declaration of Helsinki. Proposed change (if any): 2.1.6. Good clinical practice for cell therapies - Autologous cells minimally manipulated, homologous use – practice of medicine, case reports, case control studies (model adopted from	Not accepted. See responses to similar comments above.

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		Australia, Japan or South Korea); - Autologous cells substantially manipulated or heterologous use – case control studies (model adopted from Australia, Japan or South Korea) with defined long-term follow-up or simplified clinical trials without the need for randomization based on Ethical Commission consultation for ethically acceptable trial design; - Allogeneic cells – regulation as recently suggested by EMA in clinical trials including Ethical Commission consultation for ethically acceptable trial design.	
Comments on section 2.2. Scientific principles applied to the classification of ATMPs			
183-187	60	Comment: It would be helpful to add to this section an overview of the type and extent of details that are needed to reach a recommendation. Proposed change (if any): Add a sentence such as: "Examples of the type of information needed by the CAT to recommend a classification are given per section."	Not accepted. The classification is always triggered by an application and cannot be generalised.
184-196	50	Comment: Does the classification of ATMP apply, if a claimed mode of action of a cell product is not yet defined? Example: Adipose stem cells are isolated from fat tissue via collagenase treatment and stored for possible future application – both procedures without indication / claimed MoA.	Complete knowledge of MoA is not needed for classification, however such information would facilitate correct classification. If further knowledge of MoA is gained later, a reclassification is possible.
188	30	The direct consequences of the ATMP classification (i. e. which	Not accepted. This guidance concerns only the

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		guidelines should be followed after a recommendation on classification) should be underlined to facilitate the guidelines navigation, an issue for ATMP that has been relevantly identified by the CAT and its interested parties focus groups (EMA/CAT/463795/2011). This should be briefly mentioned regarding the two steps of the classification procedure: 1) ATMP or not? The classification as an ATMP implies that the general guidelines on ATMP should be followed. The classification as an ATMP does not necessarily involve the product to be covered by Regulation (EC) N°1394/2007 (hospital exemption). Indeed, the question of the industrial development of ATMP is not considered by the CAT yet. This question should be either considered by the CAT or it should be specified that “the classification as an ATMP does not necessarily involve the product to be covered by Regulation (EC) N°1394/2007, especially in case of hospital exemption”. 2) Which types of ATMP: GTMP, CTMP, TEP or Combined? The classification as one specific type of ATMP implies the following of the specific guidelines related to this specific type, but it does not necessarily exempt a product from the relevant and applicable regulatory requirements of other types of ATMP. This is very important for ATMP developers. Indeed, it may be thought that if a product is classified as a specific ATMP, it will have to follow only the guidelines linked to this specific ATMP. Moreover, this is specified only for the classification as CTMP regarding the requirement of GTMP that may apply (lines 235 236) whereas this is also true for: - a product classified as a tissue engineered products that is not necessarily exempted from the relevant and applicable regulatory requirements of CTMP;	ATMP classification, not product development. It should be also noted that products approved under ´hospital exemption´ are outside of the scope of this guideline, although they are ATMPs as defined by Article 28 of Reg. 1394/2007.

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		- a product classified as a tissue engineered products that is not necessarily exempted from the relevant and applicable regulatory requirements of GTMP; - a product classified as a GTMP that is not necessarily exempted from the relevant and applicable regulatory requirements of tissue engineered products; - a product classified as a GTMP that is not necessarily exempted from the relevant and applicable regulatory requirements of CTMP; - as well as for combined ATMP. Proposed change (if any): The scientific recommendation on the classification of ATMP helps developers to know which guidelines should be followed for the scientific development of their products. 1) If the concerned product is classified as an ATMP, the general guidelines related to ATMPs should be followed (to add a footnote towards these general guidelines on the EMA website). However, the classification as an ATMP does not necessarily require the product to be covered by Regulation (EC) N°1394/2007, especially in case of hospital exemption. 2) The classification as a specific type of ATMP implies following the specific guidelines related to this specific type of ATMP, but it does not necessarily exempt it from the relevant and applicable regulatory requirements of other types of ATMP: - a product classified as a tissue engineered products should follow the guidelines that are specific to tissue engineered products but it is not	

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		necessarily exempted from the relevant and applicable regulatory requirements of CTMP and/or GTMP; - a product classified as a GTMP should follow the guidelines that are specific to GTMP but it is not necessarily exempted from the relevant and applicable regulatory requirements of CTMP and/or Tissue engineered products; - a product classified as a CTMP should follow the guidelines that are specific to CTMP but it is not necessarily exempted from the relevant and applicable regulatory requirements of GTMP and/or Tissue engineered products; - This is also true for combined ATMP (to add a footnote towards the specific ATMP guidelines on the EMA website)	
191	10 /20 / 26 / 55 / 56 / 58	Comment: New paragraph 2.2.1. should be added. Proposed change (if any): 2.2.1. CAT EMA discussion with Scientific Societies. In the view of rapid scientific achievements in the field of cell therapies and regenerative medicine CAT EMA will initiate scientific discussion among Scientific Societies dealing with cell therapies and regenerative medicine (TERMIS, ISCT, IFATS, ICCTI, STEMSO, ICMS, etc.) with respect of novel clinical testing system for cell therapies.	Not accepted. The proposed text is not in the scope of this guideline.

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Comments on section 2.2.1. Claimed mode of action (MoA)			
193-196	11 / 22 /57	STEMSO believes that by its very definition, Regenerative Medicine intends to use living cells in order to repair, replace, and regenerate missing, damaged, or degenerating tissue. Proposed change (if any): The proposed classification of Advanced Therapy Medicinal Products by "Mode of Action" (MoA) criteria, which states: ". . . administered to human beings with a view to regenerating, repairing, or replacing a human tissue" should be struck from the regulation as a classification criteria. (Section 2.2.1 lines 193-196)	Not accepted, part of legal definition.
193-200	41	Comment: We believe that the use of words such as 'repair' and 'regeneration' may cause unnecessary confusion. Indeed these words are often used in the scientific literature or in other contexts to qualify the effect of advanced therapies, i.e. not limited to tissue engineered products but also somatic cell therapy and gene therapy. Even the European Commission – DG Research – refers to 'regenerative medicines' when publishing calls for proposals in the context of FP7 or Horizon 2020 whilst these calls are open to any type of advanced therapy. Proposed change (if any): We suggest to further define 'repair' and 'regeneration' in the context of the reflection paper for ATMP classification and to acknowledge that these definitions may be less	Not accepted, part of legal definition.

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		specific when used in other contexts.	
193-204	48	Comment: The MoA is not relevant for medicinal products used to make a medical diagnosis (See article 1.2b Directive 2001/83). For viable cells the MoA is always considered to be immunological, pharmacological or metabolic (Article 2.2 Reg 1394/2007), the issue is whether they are manipulated or used for the same essential function/s only. Whether a product is a gene therapy is dependent on the effect of the genetic modification and whether it is therapeutic, prophylactic or diagnostic. Proposed change (if any): Whether the product has an immunological, pharmacological or metabolic action is not an important consideration when considering if the product is a gene therapy or somatic cell or TEP except where any cells are non-viable. Since the difference between somatic cell and TEP is discussed in section 2.2.3 (starting line 258) this section should simply be deleted.	Not accepted, part of legal definition.
193-204	60	Comment: The (proposed) MoA is also extremely important to determine whether the product can be classified as ATMP or not (as illustrated by the example in lines 250-252) or whether cells are exerting the same metabolic or biological function as in the donor in relation to the targeted indication. Therefore the proposed MoA is crucial for a scientifically sound evaluation and should be central in the procedure.	Accepted.

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		Proposed change (if any): Add some wording to emphasize the importance of the proposed MoA in relation to the proposed indication.	
Comments on section 2.2.2. Criteria for GTMP			
205	48	Comment: It would likely be better to have the definition of a gene therapy within this section. Proposed change (if any): Move from section 2.1.1	Not accepted. All definitions are given in the beginning to facilitate understanding of the examples given later.
212-213	19	Comment: We would welcome a clarification on the words “biological origin”. Does that mean that no changes have been made to the wild-type sequence? Proposed change (if any): Please clarify if the wild-type sequence might be modified.	Partly accepted Reference is made to biological medicinal products and a cross reference to the definition of a biological Medicinal product has been added. The biological origin is not linked to the sequence itself. Mutations may be present in a wild type sequence that is biologically produced (i.e. mutated plasmids amplified in a bacterial system).
212-213	48	Comment: It should be clarified under what circumstances nucleic acids would not be considered to be of biological origin. Address whether (assuming possible) a cell genetically modified with nucleic acids not of biological origin would still be a gene therapy or only a CBMP.	See above

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		Proposed change (if any): The recombinant nucleic acids will always be considered of biological origin independently from their origin and of the vector system used (e.g. viral/bacterial vectors or micellar and liposomal formulations, etc.).	
212-213	60	Comment: It would be useful to clarify under what circumstances nucleic acids (e.g chemical synthesis) would not be considered to be of biological origin and whether, if used e.g. to create genetically modified cells, these cells would be a biological medicinal product. Proposed change (if any): Modify sentence.	see response above.
215-236	52	Comment: It would be helpful if the paper provided examples of products which the CAT has decided would be classified as a gene therapy medicinal product (GTMP) and then provided examples of non-GTMPs. Proposed change (if any): We propose the paper include additional examples of GTMP and non-GTMP.	Not accepted. The paper is not the place to put all examples of classified products.
229-230	30	This also applies to lines: 242; 249; 250; 267; 268, 278; 280; 282; 295; 299; 301; 304; 305; 327; 329; 333; 336; 362; 367; 377; 383; 397; 406; 414; 420; 425; 441; 456; 471; 477; 480; Comment: To enhance clarity and to limit potential lacks of understanding, it will be relevant to refer to the specific summaries of recommendations that are the basis of the CAT examples.	See response above.

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		To this end, the proposed change below should be followed for each example given in this reflection paper, or as much as possible. Proposed change (if any): For instance, the following footnote should be added to lines 229-230: **EMA, Summaries of scientific recommendations on classification of advanced therapy medicinal products, Allogeneic T cells encoding an exogenous TK gene, 2 March 2010.**	
235-236	30	Comment: The fact that the classification as cell therapy medicinal products does not necessarily exempt from the relevant and applicable regulatory requirements of GTMP, is very important for ATMP developers as it may be thought that if a product is classified as a specific ATMP, it will have to follow only the guidelines linked to this specific ATMP. Moreover, this is also true for a product classified as a tissue engineered products. Indeed such classification does not necessarily exempt from the relevant and applicable regulatory requirements of CTMP. Such information should appear at the beginning of section 2.2 after line 187 to be highlighted in a new paragraph from line 188. It should also be completed regarding other cases of definitions overlaps. (See general comment above and specific comment line 188).	Accepted. Agree with the comment, but consider not appropriate to include that statement in the beginning of section 2.2.
242-252	19	Comment: We would welcome an explanation as to why the legislation states that “gene therapy medicinal products shall not include vaccines against	Not accepted. The legal definitions are not within the remit of the CAT.

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		infectious diseases". Although the text seems comprehensive, some information are still missing. Indeed, we understand that: i. Prophylactic vaccines against infectious diseases are excluded from the ATMP scope; ii. Therapeutic vaccines administered in oncology can be considered as ATMPs. Hence, can, under some circumstances, therapeutic vaccines for infectious diseases or prophylactic oncology vaccines, be considered as GTMPs? Proposed change (if any): A table displaying the various cases (prophylactic/therapeutic; infectious diseases/oncology/others) and the potential classification would be useful. Add a statement that "classification is anyway performed on a case-by-case basis".	
245	30	Comment: Vaccines are covered by other regulations and guidelines, please specify which ones and/or refer to relevant webpage of the EMA in a footnote for more clarity in a complex regulatory landscape.	Not accepted. This guideline is dedicated for classification of ATMPs, not to provide any guidance concerning vaccines.
254	19	Flowchart GTMP: Add the word "prophylactic" within the diamond "vaccines against infectious disease?"	Not accepted: The GTMP definition does not restrict the exclusion to prophylactic vaccine against infectious diseases only.
253-255	8	Comment: In the first box the following is stated: "Product active substance contains or consist a recombinant nucleic acid sequence of biological origin." It is unclear what is meant with "biological": Does the nucleic acid sequence have to exist in nature or does it require that the nucleic acid sequence has been produced by a living organism? If it relates to the first condition, a fully artificially composed nucleic acid sequence with no known counterpart in nature is not considered to be of biological origin.	Accepted: reworded. Recombinant products are by definition biological MP. With biological MP (in the GTMP definition) the legislator means that synthetically made nucleic acids are outside the scope of ATMPs

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254-255	45	Comment: In view of the proposed Figure 1, EuropaBio is pleased to propose an improved version in either format per the EMA's needs. Proposed change (if any): Please see Figure 1 at the end of this response.	Thank you. The current figure is considered sufficient.

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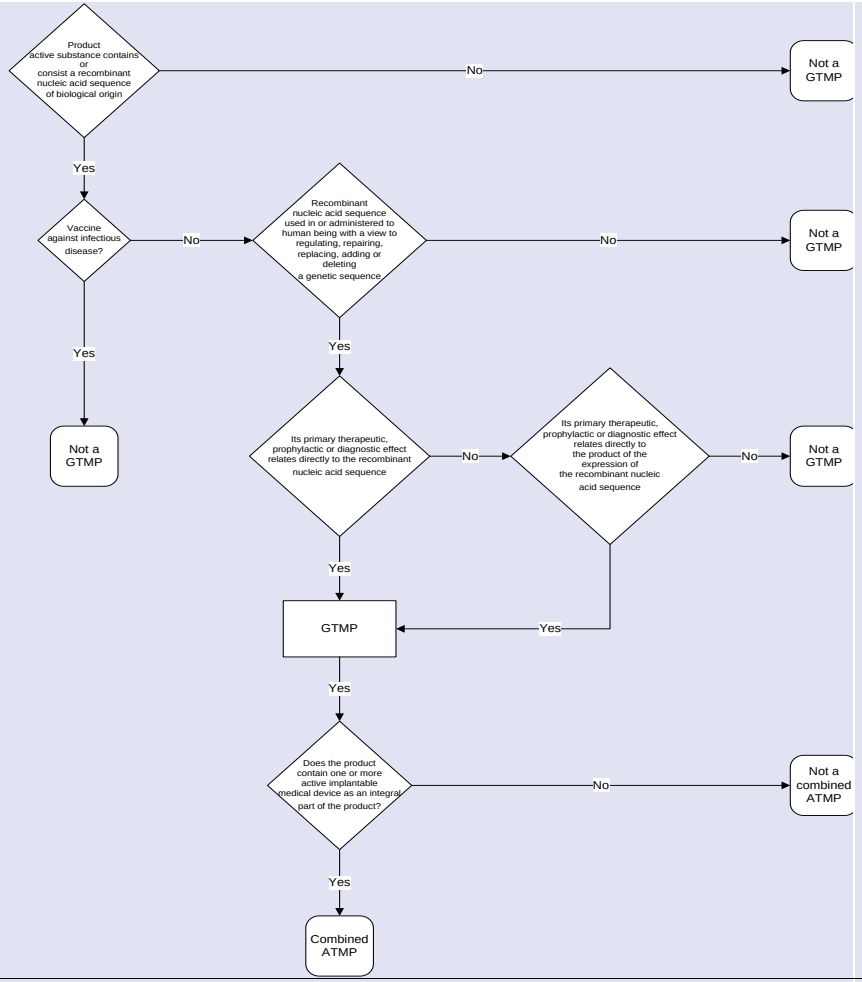

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254	52	Also applies to Decision tree for sCTMP and TEP (line 338) Comment: The decision trees refer only to active implantable medical devices, but other medical devices should also be included here. Proposed change (if any): We propose to edit the text to say: "Does the product contain one or more medical device/active implantable medical device as an integral part of the product?"	Accepted, flowchart amended.
Comments on section 2.2.3 Criteria for sCTMP and TEP			
258	1	In the "*Reflection"* paper, under section **2.1.2** it describes several categories that "*shall not be considered as substantial manipulations : cutting, grinding shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering ☐aematopoietic, freezing, cryopreservation and vitrification."* However, in section **2.2.3** the paper then gives examples of substantial manipulation. In particular, it notes "enzymatic digestion of tissue to release cells. This is most often done using fat tissue and the enzyme collagenase. We assert that this is inconsistent with the already noted list of acceptable manipulations – namely "cell separation" and it is by far less manipulative than irradiation or even soaking in antibiotic solution. Collagenase is already an FDA approved medication (e.g. Xiaflex for Peyronie's or Dupetryn's Contracture). Collagenase only affects collagen material and does not even enter the cell membrane or alter its characteristics. The problem with collagenase stems from its manufacturing which originally came from bovine based products that were only approved for laboratory use. Such products run the risk of transmissible spongiform encephalopathies (TSEs) and thus could pose the risk of disease	Not agreed concerning the first part of this comment dealing with enzymatic digestion of tissues to release cells using collagenase. Substantial manipulation is defined as any processing that alters the original relevant biological, physiological or structural characteristics of cells or tissues. Tissue dissociation to a single cell state usually requires several steps including Collagenase treatment (to digest extracellular matrix) and when needed, broad-specificity proteases (e.g. trypsin) to disperse tightly associated cells. These stable cell-cell interactions through gap junctions, tight junctions, adherent junctions and desmosomes play crucial role for the biological activity or structural characteristics of

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		transmission. Current FDA and GMP manufactured collagenases are free of any such disease transmission risk. Indeed, Cytori provides a proprietary based collagenase to process their SVF cells and has not been shut down by the FDA. Indeed, they currently have an approved Investigational Device Exemption (IDE) that could not be possible if their collagenase use was such a violation of minimal manipulation. When the FDA Tissue Reference Group (TRG) responds negatively to someone suggesting the use of collagenase this is because they have no knowledge of the particular collagenase and do not want to take any risk for approval under such simple circumstances. They can reference this as possibly more than minimal manipulation in order to assert their jurisdiction. If medical grade collagenase were really an issue, then they would shut down CSN, Cytori and any other organization using collagenase in the USA. This is not the case as there is no risk of disease transmission (e.g. CSN uses Roche GMP collagenase). On a purely argumentative point, how can anyone claim that collagenase, which only affects collagen and not a phospholipid membrane, is substantially manipulative compared to irradiation which can completely change cell characteristics and one's DNA, or even antibiotics that can permeate a cell membrane? This is simply self-serving and based upon false representation and mis-interpretation of the FDA's motives in their TRG responses. Further, as a surgical procedure doctors have authority to use any approved device or drug any way they see fit. No drug or device manufacturer can possibly file for every possible claim that doctors or surgeons ultimately utilize. In passing, it should also be noted that while the FDA ruled that cell expansion fell into the category of more than minimal manipulation, the actual problem related to closure of a Colorado based US organization	cells or tissues. These types of intercellular interactions are distinguished from those between cells and the extracellular matrix and need specific proteases to cleave them. That being said, we have to keep in mind that recombinant collagenase used to digest extracellular matrix are contaminated with Trypsin-Like-activity due likely to copurification of clostripain which is responsible for most if not all this activity since it is difficult to separate clostripain from collagenase because of its charge heterogeneity. In addition, Enzyme-digested tissues might also induce cleavage of a wide variety of cell membrane receptors leading to alteration of cell biological activities. Therefore, CAT can consider that Enzymatic digestion will be assessed on a case by case basis and will depends on the nature of the tissue to be digested and deviation may always be possible when scientific evidence is provided. Not agreed regarding the second part of this comment: the classification has to be based on evidence-based medicine. Therefore empirical findings cannot be taken in account. Only results from randomized trials are acceptable. The point of care delivery of cells should be regarded as an potential application of hospital

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		performing cell expansion was due to lack of GMP laboratory facilities and thus their inability to demonstrate prevention of disease transmission. Only after the FDA closed them for failure to meet GMP criteria did this organization sue the FDA claiming the FDA had no jurisdiction over the practice of medicine. The FDA prevailed by using their own regulations to show that this organization produced a “drug” by virtue of “more than minimal manipulation” and thus they maintained jurisdiction and won in court and even appellate court. Indeed, this very organization that got sanctioned by the FDA bears the primary responsibility for obtaining the FDA TRG responses directed toward collagenase. We assert that the FDA will not nor should not approve anyone asking for such blanket approval without knowing specifics about their process. Such approval puts the FDA at risk. On the opposite note, one should realize that while the FDA can’t approve this procedure, they also have no jurisdiction to disapprove it – at least not when done under a surgical environment. On a further note, in keeping with the basic FDA guidelines you have also adapted the necessity to be “of homologous use.” If this jurisdiction really existed over a surgical procedure, then your organization and the FDA as well, would have jurisdiction over a multitude of surgical procedures. For example, we’ve been using fat grafts for years – these are usually processed through liposuction and a variety of filtration techniques and then while commonly used in areas where fat is missing (homologous) it is not infrequently used to repair a variety of defects where fat is not the homologous tissue (e.g. contour defects following muscle trauma, as a plumping graft for a variety of sphincter repairs or as a filler substance for breast tissue defects). Coronary artery bypass is frequently done using vein grafts (not homologous). A bladder can be reconstructed using ileum (not homologous). Neither the FDA nor the EMA intends to police such	exemption.

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		surgical procedures. Such techniques come under the auspices of the state or national medical boards to determine if there's any reason to limit such procedures. While we appreciate the need to prevent unscrupulous practitioners from taking advantage of their patients, doctors, nonetheless, have the ability to safely perform a simple surgical procedure and provide SVF to patients on an investigational basis that may benefit from it. Please note the attached bibliography of articles that indicate the multitude of products that have been differentiated from SVF (see Addendum). If, as surgeons in multidisciplinary teams, we can deploy SVF to our patients in a properly monitored investigative format we can gain a wealth of empirical data that can support fine tuning and further research while potentially helping patients that currently have no further option for viable treatments. Our empiric findings demonstrate that we can reverse severe arthritis, repair COPD, repair heart disease, often correct or improve neurological degenerative conditions and much more. It's simply a violation of the Hippocratic oath to deny such treatment to properly well-informed patients. Ironically, while we have seen criticism emanating from a variety of PhDs hard at work at developing a variety of stem cell lines, it's ironic that the vast majority of the 261 strains of NIH approved stem cell lines being researched and commercialized in the USA have failed to meet FDA tissue screening guidelines and demonstrate sterility. Clearly, these cell strains actually place patients at greater risk while the work we do under completely sterile conditions has been unjustly criticized by some in the basic science community in the USA and unjustly regulated outside of the USA. We would recommend that you consider the approach taken by CSN and several of our colleagues working with point of care delivery of SVF	

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		– namely, at the current time, until adequate numbers and research has been completed to claim otherwise, patients should be allowed to procure SVF deployment a) as part of investigational studies; b) with proper acceptable informed consents consistent with experimental protocols as outlined by the US Office of Human Research Protections; c) as part of approved IRB protocols not commensurate with FDA approval (because they don't approve surgical procedures); and if possible, d) through transparent online data collection in cooperation with all international providers. As such, CSN currently has an extensive online database documenting extraordinary safety and excellent efficacy data on over 1,000 of our patients. CSN is indeed willing to share and improve our database with our worldwide colleagues giving us all the unique opportunity to share and stratify the very data that will help the scientists refine and improve their research. We know from our experience within our network that cooperation and sharing of data has helped us improve our outcomes and increase our understanding of real clinical situations. In well over 1,000 cases adverse events have been limited to a few liposuction concerns (mostly post-operative discomfort) and no direct problems related to SVF deployment. It would be in the public's best interest for the EMA to recognize these different avenues and not restrict doctors from progressing to help their patients to the extent that they currently can. Further, we are willing to meet in person should you find it useful to have additional discussions that can reasonably help set up appropriate standards without negating the surgical process and our current abilities to ethically perform investigational deployment of autologous cells.	
260-262	48	Comment: Somatic cell therapy medicinal products are NOT composed of engineered cells. Specifically engineered cells have been subject to substantial manipulation, so that biological characteristics, physiological	Not accepted The term "engineered" is defined in regulation

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		functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. Proposed change (if any): suggest you say they have both been subjected to substantial manipulation or are not intended to be used for the same essential function(s).	1394/2007. This term, even if not mentioned in directive 2009/120 for the definition of sCTMP , is equally applicable to sCTMPs.
Comments on section 2.2.3.1 Substantial manipulation			
263-307	54	Cell Therapy Catapult found this section on what constitutes substantial manipulation and non-homologous use extremely helpful and encourage the EMA to add some further pertinent examples.	Accepted
264-267	11 / 57	In order to accomplish the above referenced individualized “practice of medicine”, STEMSO requests that cell expansion with culture, enzymatic digestion of tissue, and differentiation/activation with growth factors be exempted from the list of substantial manipulations only for point of care, individualized therapies.	Not accepted. The section on substantial manipulation has been amended to reflect the current scientific knowledge and the comments received. The legislation does not allow for a differential treatment for individualised therapies.
264-267	22	In order to accomplish the above referenced individualized “practice of medicine”, Human Med AG requests that intraoperative, sterile, closed loop stem cell separation with enzymatic digestion from fat tissue and subsequent removal of enzyme by simple dilution and/or centrifugation processes, and concentration of the stem cell suspension to > 20 ml out of 100 ml fat aspirate by simple filtration and/or centrifugation processes, should be exempt from the list of substantial manipulations, and this mainly for point of care, individualized therapies.	Not accepted. The section on substantial manipulation has been amended to reflect the current scientific knowledge and the comments received. The legislation does not allow for a differential treatment for individualised therapies.
264-266	32	Comment: Clarifying wording.	Not accepted. The interpretation of concept of

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		Proposed change (if any): The cells or tissue(s) have been manipulated during the industrial manufacturing process so that their biological characteristics, physiological functions or structural properties have been modified to be relevant for their intended function.	industrial manufacture is not within the remit of the CAT.
264-267	38	The term “activation” is unclear and creates uncertainty. This is compounded by the use of “growth factors”, which covers a broad range of products with a range of effects on cells. There seems to be little value in adding to the statutory definition by using unclear terms. In fact, it might be useful to draw the reader’s attention to the list of manipulations (Annex I) that “shall not be considered as substantial manipulations”. The statutory test is whether the cells have been the subject of “substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations,” Proposed wording: The cells or tissue(s) have been manipulated during the manufacturing process so that their biological characteristics, physiological functions or structural properties have been modified to be relevant for their intended function. Examples of substantial manipulations include cell expansion (culture), genetic modification of cells and differentiation. The manipulations listed in Annex 1 of the ATMP Regulation shall not be considered to be substantial manipulations. This list includes ☐ cutting, grinding, shaping, ☐ centrifugation, ☐ cell separation, concentration or purification, ☐ filtering,	Not accepted. Context is clear.

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		☐ soaking in antibiotic or antimicrobial solutions, ☐ sterilization, irradiation, ☐ ☐ulfils☐sation, freezing, cryopreservation and vitrification.	
263-284	41	Comment: In order to further clarify what constitutes a substantial manipulation, it would be useful to have a non-exhaustive list of substantial manipulations, similar to the list of non-substantial manipulations in Annex 1 of the ATMP Regulation. Proposed change (if any): Consider adding an annexe to this reflection paper or a change to the annex 1 of the ATMP Regulation to list examples of substantial manipulations.	Not accepted. A list of substantial manipulations would need regular updating and substantiality of applied manipulations will be assessed on a case by case basis and some might be context-specific and cannot be considered as a general rule (e.g. duration of treatment).
266-267	27	Comment: We would welcome a clear list of manipulations that have been considered as substantial up to now even if not exhaustive. Proposed change (if any): Add an annex to this guideline with a list of all previous manipulations that have been considered as substantial	Not accepted (see above)
266-267	45	Comment: We would welcome a clear list of manipulations that have been considered as substantial up to now- even if not exhaustive. Such list would be mirroring the Annex 1 of the ATMP Regulation which outlines the non substantial manipulations. Once more, it would be worthwhile enriching this flexible list of manipulations by means of regular updates of the “Questions & Answers” document referred to during Interested Parties Focus Groups in July 2011. Refer to Comment 4 of General Comments. Proposed change (if any):	Not accepted (see above)

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		Add an annex to this guideline with a list of all previous manipulations that have been considered as substantial or make clear reference to that in the Q&A document.	
266-280	32	Comment: Enzymatic digestion of tissue and expansion by cell culturing have to stay within the definition of minimal manipulation without any exception. Proposed change (if any): ~~Examples of substantial manipulations include cell expansion (culture), genetic modification of cells, differentiation/activation with growth factors.~~ ~~Cell culturing leading to expansion is 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 cannot be ruled out that the biological characteristics, physiological function(s) or structural properties of the cells are changed by cell culture. Induction of proliferation of cells during cell culture has to be regarded as changes of their biological characteristics and structural properties, at least by increasing cell numbers to augment the desired function of the cells. Furthermore, most adherent cells, for example, are impacted by the repeated attachment and detachment cycles. It has been demonstrated that even the techniques applied for cell detachment might lead to different phenotypic changes especially on cell surface proteins.~~ Enzymatic digestion of tissue to release cells **and expansion by cell culturing are not ~~is also~~** considered to be substantial	Not accepted (see above)

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		manipulation. ~~When the aim is to dissociate cell-cell contacts. Only when the enzymatic digestion leads to isolation of functionally intact tissue units (e.g. pancreatic islets), the procedure is not considered substantial manipulation.~~	
267	8	Comment: It is confusing to list “genetic modification of cells” under the heading “substantial manipulation” as one of the criteria for sCTMP and TEP, since “genetic modification of cells” is THE criterion that needs to be fulfilled to assess the possible classification of the product as GMTP rather than sCTMP or TEP. Proposed change (if any): Genetic modification should not be listed under “substantial manipulation” but should be assessed independently from this criterion, perhaps before it is determined whether the cells have been subject to a process that can be considered substantial manipulation. This must be changed accordingly in the “Decision tree for sCTMP and TEP” on page 12.	Not accepted. The section on substantial manipulation has been amended to reflect the current scientific knowledge and the comments received.
267	48	Comment: The ISCT does not consider that activation with growth factors should necessarily always be considered manipulation, growth factors (including those in serum) are used to maintain stability, e.g. provide anti-apoptosis signals. It seems that the use of growth factors is referred to a) because these would be added ex vivo to promote an activation, expansion or differentiation of cells, or b) the cells would be endowed with the ability to express these growth factors to exert an effect on target, i.e. upon application. In any case, this must be specified. Duration of the activation might be relevant. Proposed change (if any): Given that the points made in the last sentence from lines 266-267 are repeated in the following paragraph the whole sentence could be removed. At the least, activation with	Not accepted. The section on substantial manipulation has been amended to reflect the current scientific knowledge and the comments received.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		growth factors should be removed or specified in more detail to avoid misunderstanding.	
267	60	Comment: The cumulative effect of various sequential manipulations that are individually not considered substantial may lead to alterations in the biological properties of the cell populations and thus may be considered as substantial in some instances. The argument that cell culture leading to expansion is considered substantial manipulation because it cannot be ruled out that the biological characteristics, physiological function(s) or structural properties of the cells are changed could also apply to a series of sequential non-substantial manipulations. This point is crucial and represents one of the grey zones that may lead to several interpretations. EBE suggest the CAT clarify the type of information to be provided by applicants to justify whether or not cells may be displaying modified biological characteristics. Proposed change (if any): Add a paragraph clarifying that a series of non-substantial manipulations may lead to changes in the biological properties (that in turn may lead to the conclusion that the cells have been substantially manipulated) and that the applicant should provide information as to whether the proposed sCTMP would display modified biological properties.	Not accepted. It is not possible to define which combination of non substantial manipulations could result in a substantial modification of the cells.
268	8	Comment: It is unclear why cell culture without expansion cannot be considered substantial manipulation: this might also result in (a substantial) enrichment of the desired cell type, including a profound change of the biological characteristics of these cells.	Accepted. Any culture step without expansion could be considered as a substantial manipulation.
268-280	44	Comment: CAT states that cell culturing is always considered as substantial manipulation. EBA agrees with this. The reasoning is based on the fact	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		that it cannot be ruled out that the biological characteristics, physiological functions and/or structural properties have not been changed by cell culture. On the other hand in lines 404-414 it is stated that islet cells have been classified as NON ATMPs (with which EBA agree) because there is no change in their biological characteristics. Clinically we know that they function as insulin producing cells and one can therefore assume that their biological functions have not been changed. For any new products, EBA believe that culturing should be considered as a substantial manipulation unless it can be shown that the biological, physiological and structural characteristics have not been changed.	
268-271	48	Comment: The reasoning that cell culturing leading to expansion is considered substantial manipulation because it cannot be ruled out that the biological characteristics, physiological function(s) or structural properties of the cells are changed does not seem sufficient. It could be argued the same in several non-substantial manipulations, as it is the case of vitrification or □ulfils□sation. Objection: Cell culturing leading to expansion should be considered substantial manipulation when biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered or when biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. Risk associated with cell expansion should be evaluated case by case by following a risk-based approach.	Not accepted. These manipulations can be considered of high risk and cleavage of a wide variety of cell membrane receptors during passage can lead to alteration of cell biological activities. A case by case basis is not feasible. It is not possible to define the modifications of the cell during or after the culture step on a case by case basis.
274-276	48	Comment: The ISCT accepts that cell expansion usually is more than minimal manipulation, however they do not agree that exposure to enzymes necessarily leads to permanent cell changes. Since this is clearly a concern of the CAT, it would be helpful (if the point is retained) if some example literature could be referenced. Again, a risk-based	Partly accepted. The section on substantial manipulation has been amended to reflect the current scientific knowledge and the comments received.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		approach should be used in the context of the entire production process. But more importantly, we do not see the relevance of mentioning this in the context of a classification; this is an issue for manufacturing strategy and development. Proposed change (if any): Delete sentence, the use of enzymes for cell passage is not directly relevant to classification.	
277-278 264-266	6	Comment: The Paul-Ehrlich-Institut acknowledges the advantage of applying clear-cut criteria with respect to differentiation between substantial and non-substantial manipulation. In according with revision 2 of the reflection paper enzymatic digestion of tissue to release cells is considered to be substantial manipulation, when the aim is to dissociate cell-cell contacts. Strict application of that criterion implies that it is more likely that a product will be classified as ATMP. It could be considered to add a reference that on a case-by-case basis deviation from that principal might be feasible, e.g. in case that the applicant is able to provide scientific evidence, that enzymatic digestion does not influence any properties of the cells (e.g. cell surface molecules) having relevance for the intended purpose/indication. Alternatively, deletion of the reference to the 'intended function' in line 266 would make the criterion even more clear-cut thereby reducing the leeway for dispute. **Proposed change (if any):** 277 Enzymatic digestion of tissue to release cells is also considered to be	Accepted. The section on substantial manipulation has been amended to reflect the current scientific knowledge and the comments received.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		substantial manipulation, when the aim is to dissociate cell-cell contacts. Deviations from that principal may be possible, in case applicants provide scientific evidence that the enzymatic digestion does not affect any cell properties having relevance with respect to the intended purpose/indication. **Alternative proposal:** 264 The cells or tissue(s) have been manipulated during the manufacturing process so that their biological characteristics, physiological functions or structural properties have been modified ~~to be relevant for their intended function~~.	
277-280	2	Comment: See above under 131…. Further details commenting and reflecting on line 131 and 277 – 280 are below…. Proposed change (if any): “enzymatic (collagenase) digestion of tissue to release cells” has no significant impact on the biological properties of the cells and should thus not be considered a substantial manipulation.	Not accepted (see above)
277-280	2	SVF While we appreciate the need to prevent unscrupulous practitioners from taking advantage of their patients, doctors, nonetheless, have the ability to safely perform a simple surgical procedure and provide SVF to patients on an investigational basis that may benefit from it. Please note the attached bibliography of articles that indicate the multitude of products that have been differentiated from SVF (see	Not accepted (see answers to comment from contributor 1 on line 258 and contributor 6 on line 264-266)

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		Addendum). If, as surgeons in multidisciplinary teams, we can deploy SVF to our patients in a properly monitored investigative format we can gain a wealth of empirical data that can support fine tuning and further research while potentially helping patients that currently have no further option for viable treatments. Our empiric findings demonstrate that we can reverse severe arthritis, repair COPD, repair heart disease, often correct or improve neurological degenerative conditions and much more. It's simply a violation of the Hippocratic oath to deny such treatment to properly well-informed patients. Proposed change (if any): ADD: Stromal Vascular Fraction harvested from adipose tissues, minimal manipulated in a same day medical procedure with IRB approved protocols is not considered as ATMP	
277-280	33 / 34	Comment: Enzymatic digestion of tissue to release cells should be considered as non-substantial manipulation. The final product – decellularised tissue in some clinical applications seems to be safer and more effective and it can easily be processed in tissue establishments. Some tissues could be decellularised either enzymatically or mechanically/physically (LN2 do remove epithelial cells from skin) Proposed change (if any): Remove the paragraph classifying enzymatic digestion of tissues to release cells as substantial manipulation	Partly accepted. The section on substantial manipulation has been amended to reflect the current scientific knowledge and the comments received.
277-280	10 / 20 / 26 / 56 / 58	Comment: "Enzymatic digestion of tissue to release cells is also considered to be substantial manipulation, when the aim is to dissociate cell-cell contacts. Only when the enzymatic digestion leads to isolation of	Not accepted (see answer to comment 1 in line 258).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		functionally intact tissue units (e.g. pancreatic islets), the procedure is not considered substantial manipulation." Why is this discrimination taken? What is the scientific basis for this decision? Stem cells will be found within a microenvironment and will need to be isolated on a single cell level and not within a microtissue. Collagenase is an enzyme that targets collagens, s compounds of the ECM not cell-cell contacts." Enzymatic digestion of tissue (without any exceptions for Langerhans´ islets) should stay within the definition of minimal manipulation, if the scientific data proofs that such technique does not harm cells that are further used in an autologous setting. Proposed change (if any): Enzymatic digestion of tissue to release cells is considered to be minimal "non substantial" manipulation, if the scientific data proofs that such technique does not harm cells and their physiological functions and the cells are further used in an autologous setting .	
277-280	39 / 40	**"Enzymatic digestion of tissue to release cells is also considered to be substantial manipulation, when the aim is to dissociate cell-cell contacts. Only when the enzymatic digestion leads to isolation of functionally intact tissue units (e.g. pancreatic islets), the procedure is not considered substantial manipulation."** We propose the following changes to the language of EMA's proposal: **"*Ex vivo* enzymatic digestion of tissue to release cells from extracellular matrix of a tissue for autologous application is**	Not accepted (see above).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		classified as a cell separation method (non-substantial manipulation listed in Annex I to Regulation EC No. 1394/2007) when such method utilizes enzymes that digest components of the extracellular matrix to release cells from the extracellular matrix. **Enzymatic digestion for purposes other than *ex vivo* release of cells from extracellular matrix is classified as a substantial manipulation."** Cell separation by enzymatic digestion of tissue is a universally accepted method that releases cells from the extracellular matrix of solid tissues, thus allowing for isolated cell *in-vitro* experimentation and characterization. Nearly all biological, physiological, and structural properties of cells that histologically populate solid tissues have been described using cells that have been obtained from enzymatically dissociated tissues. Consistent with the above, cells obtained from tissues digested with collagenase enzymes have been proven to be safe and friendly to the cells' essential function (i.e. insulin secretion of pancreatic islet cells), as used in a historically validated therapy such as pancreatic islet transplantation (5). Accordingly, EMA-CAT has previously considered that other cell populations derived by collagenase digestion of tissue *do not* fall within the definition of an sCTMP. Examples include cryopreserved adipose-derived stromal vascular fraction cells or regenerative cells and suspensions of viable, adult, autologous, unexpanded, and uncultured regenerative cells of stromal vascular fraction from subcutaneous adipose tissue (6-7).	
277-280	38	This conflicts with CAT decisions regarding cell products derived from adipose tissue, which it is assumed used enzymatic digestion to deliver the cell-assisted lipotransfer ("CAL") procedure. In a recommendation	Not accepted. The section on substantial manipulation has been amended to reflect the current scientific knowledge and the comments

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		dated 24 July 2012 (regarding Autologous cells of Stromal Vascular Fraction (SVF) of adipose tissue), the CAT stated that “CAL contains viable cells but these cells have not been but these cells have not been subjected to a substantial manipulation”. The CAT repeated this conclusion twice in decisions published on 4 April 2013 in respect of Adult Autologous Regenerative Cells for subcutaneous administration and Adult Autologous Regenerative Cells in Autologous Cell-Enriched Matrix for Subcutaneous Administration . As set out in the Reflection Paper, the ATMP Regulation outlines “manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations.” As a result, any manipulation listed in Annex I cannot be considered to be a “substantial manipulation”. The list includes “cell separation, concentration or purification”. Clearly one (of many) means of achieving cell separation will be enzymatic digestion. Whether the relevant (clinical) biological characteristics of a particular cell have been manipulated will depend on the biology of the cell and the impact of the procedure. In turn, this requires an analysis of scientific and clinical factors. Proposed wording: In certain circumstances, enzymatic digestion could also be considered to be substantial manipulation. By way of example, if	received.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the enzymatic digestion is intended to alter the essential biological characteristics of the cells by virtue of changing cell-cell communication structures which are crucial to the intended clinical function of the cells, However, enzymatic digestion shall not be considered to be substantial manipulations if it is intended to lead to isolation of functionally intact tissue units (e.g. pancreatic islets). In this case, the digestion is not intended to alter cell-cell communications that are irrelevant to the clinical application of the cells. In any event, it would be prudent to gather data regarding the impact of any enzymatic digestion on the relevant clinical biological characteristics of the cells.	
277-280	44	Comment: In this paper CAT considers enzymatic digestion of tissue to release cells as substantial manipulation. This classification would have a major impact on the field and would therefore need a deeper scientific reasoning and clarification. Some questions and examples rising: - Is enzymatic digestion always categorically considered as substantial manipulation or is it possible on scientific basis to show that the probability of risk on the biological characteristics is unsubstantial? - For example, in the case of autologous human keratinocytes used for the treatment of e.g. acute skin burns (homologous, autologous): what is the assumed risk to the biological characteristics of the keratinocytes when trypsin is used for separation of keratinocytes from skin tissue? - With the new classification for substantial manipulation, is marketing	Not accepted (see above)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		authorization needed for a) a bed-side device intended for the enzymatic processing of tissue to release cells and/or b) for the resulting ATMP cell product in the hospital operating theatre? Or would the user of the device need a manufacturing license?	
277-280	46	Comment: This text clarifies when enzymatic digestion will be considered substantial manipulation, but does not explain the reasoning behind for this distinction. Proposed change (if any): The procedure is not considered substantial manipulation when the enzymatic digestion leads to isolation of functionally intact tissue units (e.g. pancreatic islets), or it is demonstrated that this cell-cell dissociation does not affect the biological characteristics, physiological functions, or structural properties of the cells.	Accepted: The section on substantial manipulation has been amended to reflect the current scientific knowledge and the comments received.
277-280	48	Comment: It is appreciated that the CAT is attempting to provide an understanding of how they are reaching a scientific opinion on classifications, however this paragraph is presented like a rule and might therefore be over interpreted as such by the reader. Scientifically the argument that dissociated cell-cell contacts are somehow different from dissociated organ units such as islets is difficult to follow. The implication of this paragraph certainly could not be that pancreatic islets were minimally manipulated but hepatocytes would be more than minimally manipulated even though they are both isolated with	Not accepted (see answer above)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		collagenase. Proposed change (if any): The CAT should clarify the need to provide evidence as to whether the process of cell dissociation alters the biological characteristics, physiological functions or structural properties relevant for the intended clinical use.	
277	49	The text states that “Only when enzymatic digestion leads to isolation of functionally intact tissue units (e.g. pancreatic islets), the procedure is not considered substantial manipulation”. We are of the opinion that enzymatic digestion of cells should not be considered a substantial manipulation when the aim is to prepare decellularised skin, heart valves or other tissues. The tissues remain functionally intact and the rational of this enzymatic treatment is to make the graft safer and more effective. Proposed change: Add the case of enzymatic digestion as a non substantial manipulation if the aim is to decellularize tissues.	Accepted (see answer to contributor 33-34 on line 277-280)
277-280	50	Comment: The enzymatic digestion of tissue to release cells should be considered as non-substantial manipulation, if the purpose of the enzymatic digestion is to release cells from their extracellular matrix. Such a separation / isolation process should not change the properties and	Partly accepted. The section on substantial manipulation has been amended to reflect the current scientific knowledge and the comments received.)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		function of cells. Proposed change (if any): Enzymatic digestion of tissue to release cells is also considered to be substantial manipulation, when the aim is to dissociate cell-cell contacts. Only when the enzymatic digestion leads to isolation of functionally intact tissue units (e.g. pancreatic islets), the procedure is not considered substantial manipulation. **Enzymatic tissue dissociation, i.e. release of cells from their extracellular matrix is considered to be non-substantial manipulation**.	
277-280	60	Comment: It is not completely clear from this paragraph why cells collected by tissue dissociation e.g. with collagenase would be in some cases minimally manipulated (pancreatic islets) whereas in other cases more than minimally manipulated (e.g. hepatocytes). It may be useful to add some more clarification on the need to provide information on whether the process of cell dissociation is expected to alter the biological characteristics, physiological functions or structural properties of the cells. Proposed change (if any): Clarify the need to provide data supporting whether the process of cell dissociation is expected to alter the biological characteristics, physiological functions or structural properties in conjunction with the proposed mode of action.	Not accepted The section on substantial manipulation has been amended to reflect the current scientific knowledge and the comments received.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
281-284	48	Comment: The idea that radiolabelling would not substantially manipulate the cells seems a surprising conclusion since depending on the label and labelling method this could quite easily have a major impact. More importantly whether radiolabelling is substantial manipulation or not in the context of a cell as an in vivo diagnostic is irrelevant, it will be a medicinal product (see article 1.2b Directive 2001/83). Proposed change (if any): Paragraph should be removed since it is irrelevant; all in vivo diagnostic products are medicinal products.	Not accepted. It is acknowledged that radiolabelled cells are medicinal products.
285	30	Comment: The substantial manipulation of cells and tissues is a key criterion that has been raising major concerns. A general summary of what is considered as non substantial manipulations by Regulation (EC) n°1394/2007 should be re-stated. It should be followed by a summary of what the CAT considered as substantial or non substantial manipulations according to its experience gained so far. It will be relevant to refer to the specific summaries of recommendations that are the basis of each CAT example in footnotes. It should be specified here again that these lists providing examples, are indicative as the scientific recommendations given by the CAT are always related to a defined product. Proposed change (if any): ***Non substantial manipulation according to Annex I of Regulation***	Not accepted (see above)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(EC) n°1394/2007: cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilisation,freezing, cryopreservation, vitrification. So far, the CAT considered the following manipulations as substantial: cell culturing leading to expansion/proliferation, Enzymatic digestion of tissue to release cells with the aim to dissociate cell- cell contacts, genetic modification of cells, differentiation/activation of growth factors… *(to add footnotes mentioning the summaries of recommendations that are the basis of each example given)* ***So far, the CAT considered the following manipulations as non substantial:Enzymatic digestion leading to isolation of functionally intact tissue units (e. g. pancreatic islets), radiolabelling of leukocytes for diagnostic purposes, …*** *(to add footnotes mentioning the summaries of recommendations that are the basis of each example given)* **These examples are indicative and non exhaustive as the scientific recommendations given by the CAT are always related to a defined product.**	
285	30	Comment: The CAT has discussed whether a succession of non substantial manipulations should be considered as a substantial manipulation. Please indicate what the present position of the CAT is according to its experience gained so far.	Not accepted. It is not possible to define which combination of non-substantial manipulations could result in a substantial modification of the cells.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): **According to its experience gained so far, the CAT considered that a succession of non substantial manipulations should be considered as ……(***if possible and/or available, to add a footnote mentioning the summaries of recommendations that are the basis of this position)*	
Comments on section 2.2.3.2 Different essential function (non-homologous use)			
286	10 / 20 / 26 / 56 / 58	Comment: Better definition of homologous use for autologous cell therapies should be implemented; i.e. based on histology, physiology and cell biology and Scientific Societies definitions and recommendations, such as already published position papers of ISCT (Dominici, et al. Cytotherapy, 2006,8:315-317), IFATS (Bourin, et al. Cytotherapy, 2013,15:641-648), etc. For example, mesenchymal stromal cells should be used for the treatment of damaged tissues of mesenchymal origin and this would be considered as homologous use. We suggest to include new paragraph “2. Homologous use” into the line 285. Proposed change (if any): 2. Homologous use Homologous use as defined in Regulation (EC) No 1397/2007 should be applied also in agreement with ISCT and IFATS Reflection Papers (Dominici, et al. Cytotherapy, 2006,8:315-317; Bourin, et al. Cytotherapy, 2013,15:641-648), i.e. mesenchymal stromal cells used for the treatment of damaged tissues of mesenchymal origin are considered as homologous use.	Not accepted: it is neither under the remit of the CAT nor the classification paper to change the legislation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
286	48	Comment: As mentioned previously (comment on line 15), the term (non-) homologous use should not be used since it does not appear in the legislation. Furthermore, to avoid interpreting legal text the heading should read 'Not same essential function(s)' Proposed change (if any): Replace the title by '2. Not same essential function(s)'.	Accepted
286-307	32	Comment: Homologous vs. non-homologous use is an unsuitable criterion to determine if the cells are used for the same essential function or functions. The potential of stem cells to develop into certain cell types due to tissue hormones and other mechanisms is an inherent natural biological capability of stem cells; the like applies to tissues. Proposed change (if any): ~~2. Different essential function (non-homologous use).~~ ~~Cells harvested and separated by a simple selection method, and re-administered to fulfil their same essential function will generally be regarded as homologous use. However, depending on whether or not the selection process/method will alter the original characteristics of the cells may result in classification as ATMPs.~~ ~~In case no substantial manipulation of the cells takes place, the classification is based on the essential function of the cells. Such non-substantially manipulated cells used for the same essential function are not considered ATMPs. The same essential function for a cell population~~	Not accepted: different essential function is one of the criteria in the legislation for classification; it is neither under the remit of the CAT nor the classification paper to change the legislation.

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		~~means that the cells when removed from their original environment in the human body are used to maintain the original function in the same anatomical or histological environment. An example of this category is bone marrow cells used for haematopoietic reconstitution. All other clinical uses of bone marrow cells are considered to be ATMPs. The same principal applies to other non-substantially manipulated cells from various origins, for example adipose cells transplanted to other than fat tissue are considered to be ATMPs.~~ ~~Similarly, the replacement of an organ or tissue as its whole or functional unit of a tissue (such as cornea or pancreatic islets) is regarded as homologous use. Transplantation of a non-manipulated tissue to another location in the same anatomical or histological environment to achieve the same essential function is also considered as homologous use. This is the case for skin transplantation from one part of the body to another part. Along the same line, subcutaneous implantation of pancreatic islets is considered as homologous use. However, the classification will depend on the manipulation and functional integrity of the pancreatic islets.~~ ~~Animal cells administered to humans will always be considered as ATMPs.~~	
286-299	56 / 58	Also for line 424 2. Different essential function (non-homologous use). “All other clinical uses of bone marrow cells are considered to be ATMPs.“	Not accepted The section on different essential function has been amended to reflect the current scientific knowledge and the comments received. The legislation does

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"Comment": This is against standard clinical practice in bone surgery and should not be ATMP	not allow for a differential classification for individualised therapies / clinical practice.
287	60	Comment: The definition of a "simple selection method" is rather subjective and will lead to confusion. The concept either needs clarification or should be removed. Proposed change (if any): Change sentence into "Cells harvested and not subjected to substantial manipulation before administration …"	Partially accepted Clarification added.
287-290	33	Comment: This paragraph does not address procedures carried out during the same surgical procedure.	Not accepted. The section on different essential function has been amended to reflect the current scientific knowledge and the comments received. The same surgical procedure is not a criterion of classification of ATMPs.
287-290	38	It would be clearer if the statutory terms were used. Proposed wording: Cells harvested and separated by a simple selection method, and re-administered to fulfil their same essential function or functions will not be regarded to be ATMPs. However, this would not be the case if the selection process alters the biological characteristics of the cells relevant for their intended clinical purpose.	Accepted. The section on different essential function has been amended to reflect the current scientific knowledge and the comments received.
287-290	48	Comment: Manipulations other than selection may be applied (e.g. cryopreservation). A simple manipulation is subjective, e.g. some might consider collagenase digest simple but magnetic bead isolation as more complex. The second sentence relates to whether the cells are	Accepted. The section on different essential function has been amended to reflect the current scientific knowledge and the comments received.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		manipulated by the process, which was covered in the previous section. Proposed change (if any): Cells harvested and not subjected to substantial manipulation before re-administration …. Delete second sentence.	
286-307	48	Comment: Throughout this section essential function (singular) is used whereas the definitions make it clear these functions could be singular or plural. In fact, most cell-based therapies are likely to have a pleiotropic effect. Furthermore the definition also makes it clear it is the intended therapeutic use, which is to be considered. This point is ignored. Proposed change (if any): same essential function(s).	Accepted
287-297	44	Comment: Antigen specific donor lymphocytes are necessary as supportive therapy in stem cell transplantation and should not be classified as ATMPs in cases where these cells are not genetically engineered, and/or significantly expanded and are solely subjected to processes, which aim to deplete the alloreactive T cells from the graft. These therapies are important for a limited number of high risk patients (<100 per year) and used in a directed manner (donor-patient). In vitro antigen stimulation for periods of up to 16hrs to allow isolation of antigen specific T cells with subsequent immune-magnetic isolation should not constitute a substantial manipulation. Classification of antigen specific donor lymphocytes as an ATMP would unnecessarily make these therapies unavailable to the patients in need, since the hurdles of marketing authorization are too high for academic institutions currently responsible for these therapies.	Not accepted. The section on different essential function has been amended to reflect the current scientific knowledge and the comments received. The legislation does not allow for a differential classification for individualised therapies / clinical practice.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
288-293	48	Comment: These sentences appear to be rewording of the definition itself and as such are more confusing than useful. Proposed change (if any): Move the wording of the definition into this section or simply refer back to it and remove these 3 sentences.	Partly accepted: The section on different essential function has been amended to reflect the current scientific knowledge and the comments received.
291-297	45	Comment: Need to add in the section non-homologous use some statements to broaden the cited examples to other cell lines and not restricting to only bone marrow cells. Refer to Comment 4 of General Comments. Proposed change (see underlined text below): In case no substantial manipulation of the cells takes place, the classification is based on the essential function of the cells. Such non-substantially manipulated cells used for the same essential function are not considered ATMPs. The same essential function for a cell population means that the cells when removed from their original environment in the human body are used to maintain the original function in the same anatomical or histological environment. Examples of this category are <u>bone marrow cells used for haematopoietic reconstitution and mobilized peripheral blood stem cells widely used to reconstitute hematopoiesis</u>. All other clinical uses of bone marrow cells <u>or mobilized peripheral blood stem cells</u> are considered to be ATMPs.	Accepted. The section on different essential function has been amended to reflect the current scientific knowledge and the comments received.
292 – 295	2	Comment: …… in keeping with the basic FDA guidelines you have also adapted the necessity to be “of homologous use.” If this jurisdiction really existed over a surgical procedure, then your organization and the FDA as well, would have jurisdiction over a multitude of surgical procedures.	Partly accepted. The section on different essential function has been amended to reflect the current scientific knowledge and the comments received.

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		For example, we've been using fat grafts for years – these are usually processed through liposuction and a variety of filtration techniques and then while commonly used in areas where fat is missing (homologous) it is not infrequently used to repair a variety of defects where fat is not the homologous tissue (e.g. contour defects following muscle trauma, as a plumping graft for a variety of sphincter repairs or as a filler substance for breast tissue defects). Coronary artery bypass is frequently done using vein grafts (not homologous). A bladder can be reconstructed using ileum (not homologous). Neither the FDA nor the EMA intends to police such surgical procedures. Such techniques come under the auspices of the state or national medical boards to determine if there's any reason to limit such procedures. Proposed change (if any): ADD: In a surgical procedure with autologous stem cells, "homologous use" is defined by medical practices, i.e. performing the same basic function or functions, but does not have to go to the same site or homologous location.	
293-297	21	"The same essential function for a cell population means that the cells when removed from their original environment in the human body are used to maintain the original function in the same anatomical or histological environment. An example of this category is bone marrow cells used for haematopoietic reconstitution. All other clinical uses of bone marrow cells are considered to be ATMPs." Comment: The sentence in yellow is inexact. Bone marrow has a haematopoietic function; but haematopoiesis is not the only essential function of bone marrow cells. Bone marrow cells are active in replacing and building bone. Iliac crest bone graft, is the gold standard therapy	Not accepted. The section on different essential function has been amended to reflect the current scientific knowledge and the comments received.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		used in orthopaedic surgery; it is not used for haematopoietic reconstitution but for osteogenesis obtained from the osteoblasts on the graft surface as well as bone marrow stem and progenitor cells contained within the graft material. This function from a scientific point of view is known since 1869 [1], and is therefore as old as the haematologic function in knowledge. Furthermore it is well known that in orthopedic surgery the graft can be done on any an anatomical site (tibia, humerus,femur non-uion) with bone [2] coming from other sites (iliac crest, tibia, femur,….); therefore all the skeleton has to be considered as homologous in function. The classical technique of taking a “piece of bone” can be changed by bone marrow aspiration. To get the same number of bone precursors the bone marrow is concentrated [3,4]. Taking only the bone marrow by aspiration decreases the morbidity for the patient [5]. 1)Goujon E. Researches experimentals sur les proprietes phsiologigues de al moelle des os. Journal de l’Anatomie et de Physiologie Normales et Pathologiques de l’Homme et des Animaux 1869 ;6 :399. 2)Ebraheim NA, Elgafy H, Xu R (2001) Bone-graft harvesting from iliac and fibular donor sites: techniques and complications. J Am Acad Orthop Surg 9:210–218 3) Hernigou P, Poignard A, Beaujean F, Rouard H. Percutaneous autologous bone-marrow grafting for nonunions. Influence of the number and concentration of progenitor cells. J Bone Joint Surg Am 2005;87:1430-7. 4) Hernigou P, Poignard A, Manicom O, Mathieu G, Rouard H. The use of percutaneous autologous bone marrow transplantation in nonunion and avascular necrosis of bone. The Journal of bone and joint surgery British volume 2005;87:896-902. 5) Hernigou P, Desroches A, Queinnec S, Flouzat Lachaniette CH, Poignard A, Allain J, Chevallier N, Rouard H. Morbidity of graft harvesting versus bone marrow aspiration in cell regenerative therapy. Int Orthop. 2014 Sep;38(9):1855-60 Proposed change (if any): the change could be: “An example of this category is bone marrow cells used for haematopoietic reconstitution. Another example is use of bone marrow cells for bone and skeleton reconstitution that should not to be ATMPs.”	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Other possibility: delete this sentence	
293-297	36	"The same essential function for a cell population means that the cells when removed from their original environment in the human body are used to maintain the original function in the same anatomical or histological environment. An example of this category is bone marrow cells used for haematopoietic reconstitution. All other clinical uses of bone marrow cells are considered to be ATMPs." Comment: The sentence in yellow is inexact. Bone marrow has a haematopoietic function; but haematopoiesis is not the only essential function of bone marrow cells. Since the research of Asahara et al who discovered the Endothelial Progenitor Cell (EPC)(Asahara et al., 1999) the essential role of bone marrow cells to restore /repair the ischemic tissue and participate to the neoangiogenesis has been established (Burdon, Paul, Noiseux, Prakash, & Shum-Tim, 2011; Silvestre, Smadja, & Levy, 2013) (Maltais, Perrault, & Ly, 2011) Bone marrow stem cell interact with the resident stem cell and platelet to create new vessels and to switch the mechanism of the hibernated cell from apoptosis (Loffredo, Steinhauser, Gannon, & Lee, 2011) The fact that bone marrow has the function to restore/repair the ischemic tissue and promote angiogenesis is outlined by the fact that bone marrow stem cells are present in the vessel wall organized in niche similar to the bone marrow niche (Adamo & García-Cardeña, 2012) (Ergün, Tilki, & Klein, 2011) (Majesky, Dong, Hoglund, Daum, & Mahoney, 2012) (Torsney & Xu, 2011). The mechanism of mobilization from the bone marrow is impaired in diabetes and arteriosclerosis Since 2002 (Tateishi-Yuyama et al., 2002) bone marrow stem cell, have been use to treat the ischemic tissue in patient with critical limb ischemia an no option therapy with excellent results (Benoit, O apos	Not accepted, see responses for similar comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Donnell, & Patel, 2013). The concept underlyng the research and clinical application is to use the same function of the bone marrow for angiogenesis to restore the blood flow. Point of care device allow to use without manipulation bone marrow stem cell when implanted in the ischemic limb. The mechanism of mobilization from the bone marrow is impaired in diabetes and arteriosclerosis Essential function of bone marrow is to restore repair the ischemic damage and to maintain the homeostasis of the vessel wall reservoir of stem cell. References: Adamo, L., & García-Cardeña, G. (2012). The vascular origin of hematopoietic cells. *Developmental Biology*, *362*(1), 1–10. doi:10.1016/j.ydbio.2011.09.008 Asahara, T., Masuda, H., Takahashi, T., Kalka, C., Pastore, C., Silver, M., et al. (1999). Bone marrow origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization. *Circulation Research*, *85*(3), 221–228. Benoit, E., O apos Donnell, T. F., & Patel, A. N. (2013). Safety and Efficacy of Autologous Cell Therapy in Critical Limb Ischemia: A Systematic Review. *Cell Transplantation*, *22*(3), 545–562. doi:10.3727/096368912X636777 Burdon, T. J., Paul, A., Noiseux, N., Prakash, S., & Shum-Tim, D. (2011). Bone Marrow Stem Cell Derived Paracrine Factors for Regenerative Medicine: Current Perspectives and Therapeutic Potential. *Bone Marrow Research*, *2011*(3), 1–14. doi:10.1161/01.CIR.0000139340.88769.D5 Ergün, S., Tilki, D., & Klein, D. (2011). Vascular wall as a reservoir for different types of stem and progenitor cells. *Antioxidants & Redox Signaling*. doi:10.1016/j.jacc.2014.06.1175	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Loffredo, F. S., Steinhauser, M. L., Gannon, J., & Lee, R. T. (2011). Bone marrow-derived cell therapy stimulates endogenous cardiomyocyte progenitors and promotes cardiac repair. *Cell Stem Cell*, *8*(4), 389–398. doi:10.1016/j.stem.2011.02.002 Majesky, M. W., Dong, X. R., Hoglund, V., Daum, G., & Mahoney, W. M., Jr. (2012). The adventitia: a progenitor cell niche for the vessel wall. *Cells Tissues Organs*, *195*(1-2), 73–81. doi:10.1159/000331413 Maltais, S., Perrault, L. P., & Ly, H. Q. (2011). The bone marrow-cardiac axis: role of endothelial progenitor cells in heart failure. *European Journal of Cardio-Thoracic Surgery*, *39*(3), 368–374. doi:10.1016/j.ejcts.2010.04.022 Silvestre, J. S., Smadja, D. M., & Levy, B. I. (2013). Postischemic Revascularization: From Cellular and Molecular Mechanisms to Clinical Applications. *Physiological Reviews*, *93*(4), 1743–1802. doi:10.1152/physrev.00006.2013 Tateishi-Yuyama, E., Matsubara, H., Murohara, T., Ikeda, U., Shintani, S., Masaki, H., et al. (2002). Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. *Lancet*, *360*(9331), 427–435. doi:10.1016/S0140-6736(02)09670-8 Torsney, E., & Xu, Q. (2011). Resident vascular progenitor cells. *Journal of Molecular and Cellular Cardiology*.	
291-299	38	The reference to “the same anatomical or histological environment” is a disconcerting simplification and adds complexity and uncertainty to a challenging area. Neither of these terms (anatomical environment or histological environment) are defined or used in the ATMP Regulation (or the travaux preparatoires in respect of the ATMP Regulation). More specifically, the ATMP Regulation does not define the term same essential function by reference to anatomical location or histological	Not accepted. The ´same essential function´ has been further clarified.

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		environment. Finally, neither of these terms are particularly clear. By way of example, few people would agree on the anatomical location of mesenchymal cells. This description could have the unintended consequence of classifying a number of well-established surgical transplant procedures as the creation of an unauthorised ATMP. • Heart transplant as an ATMP as the cells (or entire organ) are not placed in the exact same anatomical location: the donor heart may be placed in the chest cavity beside the original heart. This is known as an heterotopic transplant. • Saphenous veins used in the Cardiac Artery Bypass Graft procedure as veins from the leg are not from the same anatomical location as arteries near the heart. Each cell-based therapy should be considered on a case-by-case basis by reference to the underlying biology and the intended therapeutic application. This commentary is compounded by reference to the use of bone marrow cells. The statement is made that “all clinical uses of bone marrow cells” other than for “haematopoietic reconstitution” are considered by be ATMPs. Sweeping statements such as this are unhelpful and fail to take into account the fundamental obligation to consider each cell-based therapy on a case-by-case basis. This statement falls into the trap of assuming that a cell-type (or even a heterogeneous cell population) has a single essential function and that this function is defined by its physical position prior to procurement, as opposed to its biological embryological and developmental pedigree (an approach that would be more scientifically coherent) and any therapy which intended to use the cells for one of their other functions would require a Marketing Authorisation. As a result, this statement fails to recognise the pleiotropic or plastic nature of cells. This also fails to use the statutory test, which discusses function or functions.	

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		A recent Scientific Recommendation on the Classification of ATMPs published by the CAT directly contradicts this position on bone marrow cells . The CAT concluded that a concentrate of autologous, uncultured, custom-prepared bone marrow aspirate intended to treat avascular necrosis is not an ATMP. Manifestly bone marrow aspirate primarily comprises bone marrow cells. Clearly such cells are not intended to be used for “haematopoietic reconstitution”. In its recommendation, the CAT recognises the clinical and scientific reality that “bone marrow cells are actively involved in non-haematopoietic functions”. The CAT proceeds to describe these other functions in some detail. “Bone marrow cells have been shown to demonstrate Osteopoesis as follows: • Nonmesenchymal Bone Marrow stem/progenitor cells are active in osteoblast formation. • Bone Marrow hematopoietic stem and progenitors cells were able to differentiate in the both hematopoietic and osteocytic pathways. • Certain stromal cells do not contribute to hematopoietic reconstitution.” The same principle applies to other non-substantially manipulated cells from various origins. Thus, minimally manipulated cells extracted from adipose tissue which are intended to be used by clinician to deliver an effect that relies on one or more of the essential functions that those cells display in vivo should not be considered to be ATMPs. By way of example, if the clinician intends to take advantage of the angiogenic potential of the cells to promote angiogenesis at the point of administration, then the anatomical location of the target tissue should be irrelevant. Proposed wording 291-299: If cells have not been subjected to substantial manipulation, then the cells will only be ATMPs if they are not intended to be used for the same essential function (or functions) in the recipient as in the donor. This	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		question starts from a consideration of the intended therapeutic function of the cells. Once the intended function (or functions) has been identified, then such function needs to be compared with the function of the cells in the donor. If the intended therapeutic function of the cells employs an essential function that the cells display in the donor, then this may well constitute use within the scope of the same essential function. It is acknowledged that cells have pleiotrophic effects and that these vary by reference to the developmental stage of the cells as well as the proximity of the cells to other cells.	
293-306	48	Comment: As mentioned previously (comment on line 15 and line 286), the term (non-) homologous use should not be used since it is not mentioned in EU legislation. The ISCT suggests avoiding use of the word 'homologous 'in this document. It is also inconsistent with a recent decision of the CAT, which concluded that a concentrate of autologous, uncultured, custom-prepared bone marrow aspirate intended to treat avascular necrosis is not an ATMP. Manifestly bone marrow aspirate primarily comprises bone marrow cells. Clearly such cells are not intended to be used for "haematopoietic reconstitution". The CAT recognises the clinical and scientific reality that "bone marrow cells are actively involved in non-haematopoietic functions". The CAT proceeds to describe these other functions in some detail. "Bone marrow cells have been shown to demonstrate Osteopoesis as follows: • Non mesenchymal Bone Marrow stem/progenitor cells are active in osteoblast formation. • Bone Marrow hematopoietic stem and progenitors cells were able to differentiate in the both hematopoietic and osteocytic pathways. Proposed change (if any): The wording related to the use of bone marrow and fat should be	Accepted: comment on terminology. Not accepted (rest of the comment), see responses for similar comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		corrected to say that any intended uses of these cells should be for the same essential function(s), with a focus on the intended therapeutic function. The sentence “all other clinical uses of BM cells are considered to be ATMPs” should be removed.	
293-297	16	Comment: In our opinion, this statement should be changed. As we mentioned above, the hemangioblast is the common precursor cell for hematopoietic and endothelial lineages and therefore vasculogenesis should be considered the original function of bone marrow-derived mononuclear cells. Proposed change (if any): The same essential function for a cell population means that the cells when removed from their original environment in the human body are used to maintain the original function in the same anatomical or histological environment. An example of this category is bone marrow cells used for haematopoietic reconstitution and non-manipulated auologous bone marrow-derived mononuclear cells used for intramuscular injection into muscles of lower limb for treatment of chronic critical limb ischemia. All other clinical uses of bone marrow cells are considered to be ATMPs.	Not accepted (see above)
295-296	17	Comment: In the Scientific recommendation on classification of advanced therapy medicinal products published in your site on date 30 October 2013 (EMA/661080/2013), you commented: “The Bone Marrow Aspirate Concentrate is not an Advanced Therapy Medicinal Product according to the definition in Article 2(1) (b) of Regulation (EC) No 1394/2007”, and “Indeed bone marrow cells are actively involved in non-haematopoietic	Not accepted, see responses for similar comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		functions. Bone marrow cells have been shown to demonstrate Osteopoiesis as follows: • Nonmesenchymal Bone Marrow stem/progenitor cells are active in osteoblast formation. • Bone Marrow hematopoietic stem and progenitors cells were able to differentiate in the both hematopoietic and osteocytic pathways. • Certain stromal cells do not contribute to hematopoietic reconstitution." From what stated in your cited recommendation becomes clear that the essential function of the Bone Marrow is both the haematopoietic and the osteopoietic function. Proposed Change (if any): An example of this category is bone marrow cells used for ☐aematopoietic reconstitution, **and for Osteopoietic reconstitution**.	
295-297	18	Comment: there is a procedure called "Microfractures" that is very well known among the orthopaedic surgeons (Steadman J.R.-1999 -2003 -2004). This procedure is recommended as the gold standard by the International Cartilage Repair Society to repair the Grade II and Grade III Osteoarthritis. It consists in making small holes in the subchondral bone, once debrided the surface of a cartilage defect. Through these small holes the bone marrow can flow to fill up the cartilage defect site, and naturally clots as a natural elastic scaffold, essentially composed of the same bone marrow of the patient. In a more evolved version of this procedure a collagen membrane is superimposed to the cartilage defect site, with the aim to keep the bone marrow, as much as possible, close within the cartilage defect, in order for it to express all of its regenerative power where needed (AMIC – Behrens 2005, 2006). When we concentrate autologous MNC from the BM, with minimal manipulation, in order to collect more MSC in a small volume of blood, and put them into the cartilage defect, after the Microfractures	Not accepted, see responses for similar comments above.

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		procedure is performed, we are putting the MNC in touch with the BM of the same patient (homologous use). The apposition of a collagen membrane, or similar implantable device, over the site of the defect, has the only scope to keep the MNC in place after their implantation to obtain the maximum regenerative effect, just in the place of injury. Proposed change (if any): An example of this category is bone marrow cells used for haematopoietic reconstruction, **osteogenic reconstruction, and chondrogenic reconstruction.**	
295-297	23	Comment: The concept of BM as an exclusively hematopoietic organ changed more than a decade ago with the discovery of the existence of diverse nonhematopoietic stem cell populations, which share the same origin as hematopoietic cells and coexist in normal adult human BM (Shi Q, et al. 1998; Jackson KA, et al. 2001). Simultaneously, the concept of adult tissue renovation also changed, because until then it had been restricted to some specific organs and tissues known for their high regenerative capacity, but the ability to homeostatically renovate tissues such as myocardium, neural tissue, or blood vessels, among others, was then unknown. As a result of these discoveries, the view that, under physiological conditions, BM □ulfils an exclusively hematopoietic function has become obsolete. Over the last 13 years, it has been scientifically demonstrated that BM carries out a further regenerative function of remote tissues under homeostatic conditions. Proposed change (if any): An example of this category is bone marrow cells used for haematopoietic reconstruction. All other clinical uses of bone marrow cells are considered to be ATMPs. **These sentences should be cancelled.**	Not accepted, see responses for similar comments above.
295-297	23	Comment: several cells of nonhematopoietic lineage, or which can	Not accepted, see responses for similar comments

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		differentiate into nonhematopoietic cells, have been identified in the mononuclear fraction of normal human adult BM. Among these are the side population cells, which present a phenotype and functionality characteristic of primitive stem cells having multipotent capacity (Challen G, et al. 2006); mesenchymal stromal cells (Salem HK, et al. 2010); very small embryonic-like stem cells, which have characteristics similar to embryonic stem cells (Kucia MJ, et al. 2008); multipotent adult progenitor cells Ji KH, et al. 2008); hemangioblasts (progenitor cells that are common for hematopoietic and vasculogenic lineages) Park C, et al. 2005); endothelial progenitor cells (EPCs) Miyamoto Y, et al. 2007; and tissue-committed stem cells Kucia M, et al. 2005). Proposed change (if any): An example of this category is bone marrow cells used for haematopoietic reconstruction. All other clinical uses of bone marrow cells are considered to be ATMPs. **These sentences should be cancelled.**	above.
295-297	23	Comment: In the field of postnatal neovascularization, the discoveries of EPCs by Asahara et al. in 1997, and their origin in BM 2 years later by the same group constitute a genuine breakthrough. There exists growing evidence that postnatal neovascularization depends, to some extent, on the necessary contribution of mobilized marrow-derived EPCs (Koutna I, et al. 2011, Shintani S, et al. 2001, Takahashi T, et al. 1999). Besides the direct incorporation of EPCs to neovascularization foci and their subsequent differentiation into mature endothelial cells (Crosby JR, et al. 2000), both EPCs (Kocher AA, et al. 2001) and other types of mobilized BM-MNCs constitute a source of proangiogenic cytokines and growth factors (Kamihata H, et al. 2001).	Not accepted, see responses for similar comments above. The section on different essential function has been amended to reflect the current scientific knowledge and the comments received.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Therefore, the role of BM-derived cells in postnatal neovascularization can be summarized in two main functions: first, the direct mechanism by which EPCs differentiate into mature endothelial cells that incorporate into new vessels (vasculogenesis) (Crosby JR, et al. 2000) and, second, the indirect mechanism that involves, in turn, a paracrine-mediated stimulation of the local angiogenesis as well as a less known contribution of monocytes and/or macrophages to neoarteriogenesis (Gnecchi M, et al. 2008, Tongers J, et al. 2010). From the scientific point of view, all the above-mentioned functions of the bone marrow-derived cells that are mobilized by ischemia-induced stimuli (EPCs and probably other, less well known cell types) occur in a physiological way. Therefore, neovascularization should be considered an essential function of these types of cells. Proposed change (if any): An example of this category is bone marrow cells used for haematopoietic reconstruction. All other clinical uses of bone marrow cells are considered to be ATMPs. **These sentences should be cancelled**	
295-297	24	Attached is a manuscript, in pdf format, that has been submitted to a peer-reviewed journal and is currently in the review process. As the deadline to respond the the 20 June 2014 reflection paper of the EMA is rapidly approaching, we are sending the manuscript in its current state in hopes that it may provide additional dialog on the subject of regulating bone marrow cells used for treating bone. The paper is a	Thank you for submitting your manuscript. The section on different essential function has been amended to reflect the current scientific knowledge and the comments received.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		review of scientific (in vitro and in vivo) and clinical data of the several essential functions of bone marrow cells. Additionally, we provide a rationale for use of bone marrow cells for treating osteonecrosis (e.g., of the femoral head). Our hope is that EMA may find this manuscript a useful part of all the evidence as it relates to whether use of bone marrow cells for treating bone defects is or is not an ATMP. We hope that the decision reached by EMA:CAT in 2013, namely, that use of bone marrow cells for treating osteonecrosis (e.g., of the femoral head) is not an ATMP will stand. (pdf manuscript attached to e-mail 29.10.14 David D Harrell – USA)	
295-297	53	Comment: Regen Lab SA believes that the statement « All other clinical uses of bone marrow cells are considered to be ATMPs » is too broad and that there are clinical uses of bone marrow cells other than haematopoietic reconstitution which should not be considered ATMP's. In addition to haematopoiesis, bone marrow cells have been shown to demonstrate osteopoesis, which involves the proliferation and maturation of primitive precursor cells into functional osteoblasts. The bone cell lineage originates from mesenchymal stem cells that commit to the osteogenic cell lineage becoming osteoprogenitor cells, preosteoblasts, osteoblasts, and osteocytes. We refer specifically to autologous bone marrow concentrate, prepared in a point-of-care setting such as an operating theatre, through a simple centrifugation step and thus non substantially manipulated, and used clinically in an extemporaneous fashion to achieve bone repair. This cell preparation consists of concentrated viable cells from bone marrow aspirate suspended in the remaining plasma. The available evidence	Not accepted, see responses for similar comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		suggests that the cells that are fractionated from whole marrow preserve their phenotype and are identical to those in the native tissue, i.e. there is no evidence that they are phenotypically altered. The intended indication foresees the use of the cell preparation for the same function – namely bone repair – in the recipient site as in the donor site. Therefore, this non substantially manipulated cell preparation should be considered 'for homologous use´ and should not fall within the definition of an Advanced Therapy Medicinal Product. Proposed change (if any): Modify the following sentence (lines 5-6): "An example of this category is bone marrow cells used for haematopoietic reconstitution and bone repair". Delete the following sentence (lines 6-7): ~~All other clinical uses of bone marrow cells are considered to be ATMPs.~~	
295-298	37	Comment: Regarding to the wording: "An example of this category is bone marrow cells used for haematopoietic reconstitution. All other clinical uses of bone marrow cells are considered to be ATMPs. The same principal applies to other non-substantially manipulated cells from various origins, for example adipose cells transplanted to other than fat tissue are considered to be ATMPs." The statements "all other" and "other than" are claiming an absolute true that lacks from universal evidence. These statements specifically regarding joint cartilage should be taken in consideration. Recent preclinical and clinical data support the fact that cartilage	Not accepted, see responses for similar comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		improvement after treatment with bone marrow and adipose tissue derived cells (including MSCs) are, at least in part, due to a paracrine effect. An example are the positive clinical results of joint cartilage micro punctures, a common surgical practice producing the intraarticular bone marrow bleeding aiming the stimulation of cartilage repair. In this sense, at physiological level, and according to the literature, resident retro patellar fat and subchondral bone marrow cells have as one of their essential functions the support, through a paracrine mechanism, to cartilage vitality and repair. It cannot be excluded, thus, that the use of bone marrow or adipose tissue for cartilage defects treatment is based on their essential function. In this indication bone marrow concentrates and adipose tissue should not be considered sCTMP nor TEP Proposed change (if any): "An example of this category is bone marrow cells used for haematopoietic reconstitution. Other clinical uses of bone marrow cells, not demonstrating an essential function, could be considered to be ATMPs. The same principal applies to other non-substantially manipulated cells from various origins, for example adipose cells transplanted to other than fat tissue could also be considered to be ATMPs."	

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295 ; 298	49	It is stated that cell population used to maintain the original function and moved to another anatomical or histological environment is considered ATMP. We do not agree with this proposal that is more restrictive to what was indicated in the previous published reflection paper. The reason is that we do not think that this new classification criteria would add any additional safety to treatments that have been used since many years. To this regard we list three examples: 1) Amniotic membrane used in eye lesions. This treatment has been recognised by the EU Tissue and Cell Competent Authorities and by the FDA as being a homologous use of the amniotic membrane because the function of the cells in their original site and in the new site does not change. 2) Transplant of adipose cells to replace mammary tissue after mastectomy 3) transplant of adipose tissue to repair bone lesions of the knee. In addition, considering that in line 305 the transplant of pancreatic islets subcutaneously has been considered non ATMP, the new position of CAT seems to be contradictory. Finally this paragraph does not address procedures carried out during the same surgical procedure. If a surgeon takes tissue from one anatomical site and uses it immediately in another, this should not become an ATMP – regulating it as such would be impossible and unnecessary.	Not accepted, see responses for similar comments above.
296	49	The text correctly excludes bone marrow used for haematopoietic reconstitution from classification as an ATMP but states that “All other clinical uses of bone marrow cells are considered to be ATMPs”. We do not agree on this statement and we cite a few examples for substantiating our opinion. 1) Many surgeons take autologous bone marrow during a surgical procedure and add it to bone graft material before implanting because it has an osteogenic activity in bone injury, bone defects and in osteonecrosis.	Not accepted, see responses for similar comments above. The statement on bone marrow has been modified to take comments into consideration.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		2) The application of autologous bone marrow to heal ulcers and promote angiogenesis in chronic limb ischemia. Although this treatment has been proven for many years to save the amputation in 70-80 % of patients, to date the precise mechanism of action has not yet been clarified, the population of progenitor cells is heterogeneous and the active substance cannot not be identified totally. Indeed it has been shown that this treatment is inducing the repair and regeneration of a lesion by the same biological mechanism that happens naturally when cells are recalled from other tissues to repair damaged tissues and to maintain the physiological homeostasis. 3) Bone marrow transplant is used as a prevention of rejection in kidney transplantation. Proposed change: Add more examples of bone marrow use that should be considered homologous use.	
296-297	25	Comment: The sentence “All other clinical uses of bone marrow cells are considered to be ATMPs.“ should be modified due to its generic nature. In fact, not all other clinical uses of bone marrow cells can be, by default, classified as ATMPs. For example, in the EMA/CAT recommendation EMA/661080/2013, autologous Bone Marrow Aspirate Concentrate for avascular necrosis has not been considered an ATMP since it was intended for homologous use. In the literature there are many studies demonstrating that mesenchymal bone marrow stem/progenitor cells are involved in osteogenesis (1). Therefore bone marrow concentrates used to repair bone can be intended to be used for their same essential function and in the same environment (2). Moreover, considering that bone and cartilage coexist in the joint, several studies demonstrated the ability of mesenchymal progenitors to differentiate also into chondrocytes (3) and that in the endochondral ossification a cartilage intermediate is formed (4), the use of bone	Not accepted, see responses for similar comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		marrow concentrates for osteochondral lesions (5, 6) should be taken into account for its homologous use, at least case by case. References: 1. Long MW. Osteogenesis and bone-marrow-derived cells. Blood Cells Mol Dis. 2001 May-Jun;27(3):677-90. 2. Perut F, Filardo G, Mariani E, Cenacchi A, Pratelli L, Devescovi V, Kon E, Marcacci M, Facchini A, Baldini N, Granchi D. Preparation method and growth factor content of platelet concentrate influence the osteogenic differentiation of bone marrow stromal cells. Cytotherapy. 2013 Jul;15(7):830-9. Doi: 10.1016/j.jcyt.2013.01.220. 3. Yoo JU, Barthel TS, Nishimura K, Solchaga L, Caplan AI, Goldberg VM, Johnstone B. The chondrogenic potential of human bone marrow-derived mesenchymal progenitor cells. J Bone Joint Surg Am 1998; 80:1745–1757. 4. Gilbert SF. Developmental Biology. 6th edition Sunderland (MA): Sinauer Associates; 2000. 5. Grässel S, Stöckl S, Jenei-Lanzl Z, Isolation, culture, and osteogenic/chondrogenic differentiation of bone marrow-derived mesenchymal stem cells. Methods Mol Biol 2012; 879:203-67 6. Cavallo C, Desando G, Cattini L, Cavallo M, Buda R, Giannini S, Facchini A, Grigolo B. Bone marrow concentrated cell transplantation: rationale for its use in the treatment of human osteochondral lesions. J Biol Regul Homeost Agents. 2013 Jan-Mar;27(1):165-75. Proposed change (if any): “The others clinical uses of bone marrow cells should be considered to be ATMPs, unless their homologous use is clearly demonstrated”.	
296-297	12	Comment: does CAT mean bone marrow cells or is the interpretation to be “hematopoietic progenitor cells from bone marrow” ? If so, it should be considered that bone marrow is not the ultimate source used	Not accepted. All cell types in BM are included, not only progenitor cells. See other comments above.

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		for hematopoietic reconstitution but more often progenitor cells from peripheral blood or Cord Blood. Proposed change (if any): Bone marrow derived hematopoietic progenitor cells	
296-297	15	Comment: “All other clinical uses of bone marrow cells are considered to be ATMP”. This assertion is too broad, and therefore incorrect. There are clinical uses of bone marrow cells, other than hematopoietic reconstitution, which are recognised as homologous, non-substantially manipulated preparation, and therefore non-ATMPs. See in particular Scientific recommendation EMA/661080/13 on “Autologous cell concentrate from bone marrow aspirate”. Proposed change (if any): Delete this sentence	Not accepted, see responses for similar comments above.
296-297	33 / 34	Comment: Not all other clinical uses of bone marrow cells should be considered to be ATMPs. If MSc are isolated from bone marrow and used for connective tissues/part of organs regeneration it would not be considered as non-homologous use. It is typical physiological (homological) regeneration. Only when other type of cell eg. CD34+ cells for regeneration of connective tissue are used, it may be considered as non-homological use. Proposed change (if any): Some clinical uses of bone marrow cells are considered to be ATMPs.	Not accepted, see responses for similar comments above.
296	43	Comment: The reflection paper establishes a definition of the same essential function of bone marrow derived cells. This definitive statement does not seem to be consistently applied and is in direct	Not accepted. Past classifications are non-binding and do not dictate future decisions after the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		contradiction to at least one classification procedure published in 2013 (EMA/661080/2013). It is also at odds with the accepted scientific understanding of the role of certain cell types within bone marrow. Proposed change (if any): This statement should be removed from the reflection paper.	revision of the guideline.
296-297	51	Comment: Bone marrow aspirate contains not only hematopoietic stem and progenitor cells but also • mesenchymal stem and progenitor cells which have been shown to differentiate into osteoblasts, chondrocytes, myocytes, adipocytes and beta-pancreatic islets cells • endothelial stem and progenitor cells Proposed change (if any): …bone marrow cells used for haematopoietic reconstitution. ~~All other clinical uses of bone marrow cells are considered to be ATMPs.~~ The same principal applies to other non-substantially manipulated…	Not accepted, see responses for similar comments above.
297-299	10 / 20 / 26	Comment: We would like to add another example. Proposed change (if any): The same principal applies to other non-substantially manipulated cells from various origins, for example adipose cells transplanted to other than fat tissue are considered to be ATMPs**, and connective tissue cells transplanted to other than connective tissue are considered to be ATMPs.**	Not accepted. Further examples are not considered necessary.
297-299	18	Comment: for what the fat is concerned: a consistent portion of fat is also present in the bone marrow, where it is easily separated by simple centrifugation. Depending on the bone district, and on the age of the	Not accepted, see responses for similar comments above.

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		subject, we can have fractions of fat into the bone marrow reaching up to 20% of total volume of the tissue. Insausti et al. on 2010 characterized this fat fraction, and apparently it was not distinguishable by the fat we can find in the sub-skin district, or in other stocking places in the body. Now, due to these evidences, added to the fact that this fraction seems to contain a relevant amount of Mesenchymal Stromal Cells, which demonstrated in many papers their high regenerative power in the mesenchymal cells lineages, I think the use of minimally manipulated fat cells transplanted in the bone marrow should not be considered as non-homologous use (not ATMP).	
297-299	45	Comment: As above, it would be beneficial to broaden the scope of cited examples as much as possible. Refer to Comment 4 of General Comments. Proposed change (see underlined text below): The same principal applies to other non-substantially manipulated cells from various origins, for example adipose cells transplanted to other than fat tissue are considered to be ATMPs <u>as well as other metabolic diseases</u>.	Not accepted. The classification procedure is not dependent on the intended clinical use, but only on the definitions given in the legislation.
301-303	10 / 20 / 26	Comment: We clarified the definition of a non-manipulated tissue. Proposed change (if any): Transplantation of a non-manipulated tissue, **including enzymatic digestion,** to another location in the same	Not accepted, see responses for similar comments above.

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		anatomical or histological environment to achieve the same essential function is also considered as homologous use.	
303-304	10 / 20 / 26 / 56 / 58	Comment: We would like to add another example. Proposed change (if any): This is the case for skin transplantation from one part of the body to another part**, or this is the case for connective tissue transplantation from one part of the body to another part.**	Not accepted, further examples are not considered necessary.
304-305	10 / 20 / 26 / 56 / 58	Comment: We do not believe that subcutaneous implantation of pancreatic islets can be considered as homologous use. Such exception would be inappropriate to the definition of homologous use. We recommend to remove this sentence. Proposed change (if any): ~~Along the same line, subcutaneous implantation of pancreatic islets is considered as homologous use.~~	The example has been further clarified.
304-305	39 / 40	Comment**:** We would like to point out that the following statement is not consistent with the definition of “same anatomical or histological environment to achieve the same essential function” provided in the EMA reflection paper: “Along the same line, subcutaneous implantation of pancreatic islets is considered as homologous use.” The subcutaneous space is tremendously different from the intra-pancreatic space where pancreatic islets are usually located, anatomically, histologically and with regard to tissue function and cellular microenvironment.	Not accepted, see responses for similar comments above.

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		Proposed change (if any): We would recommend the removal of this statement and a clear, scientifically substantiated definition of homologous and non-homologous use. In our opinion, there are no clear arguments in favour of this exception. However, if this is true or allowed for pancreatic islets, it should also be considered for other cell populations, such as autologous adipose tissue-derived stromal cells, e.g. being used for mesenchymal tissues. This injection has been previously reported in the scientific literature to be safe and effective in humans.	
Comments on section 2.2.3 Differentiation between sCTMP and TEP			
309-337	48	Comment: ISCT members consider that once the transitional period of the Regulation 1394/2007 has expired it is not really important determining whether a cell product is a sCTMP or TEP. Proposed change (if any): this section could be shortened.	Not accepted. ATMP classification has impact on the development of the products, i.e. concerning the choice of end points and potency tests for the products
309-336	54	As detailed above we find that the therapeutic action of a TEP as regeneration, repair or replacement" confusing as these are often properties of SC and GT products also. Furthermore these phrases are linked with general medicine.	Not accepted, see responses for similar comments above.
310-315	50	Comment: In particular in case of systemic application the actual cell colonisation of specific part(s) of the body with a view to regenerating, repairing or	The legal definitions cannot be changed with this revision. Implantation/administration site is not

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		replacing a human tissue, is not entirely predictable. Therefore also definitions, focussing on the place of implantation, are elusive and can be given in favour of or against a specific method.	important for the classification; however when considering the ´same essential function´ also the environment wherefrom cell/tissues are taken and further used plays a major role.
313-315	8	Comment: The document states: “The decision, …[…] claimed intended function. “ This is rather confusing when compared with the definition of cells and tissue given in directive 2004/23/EC which states that 'cells' means individual human cells or a collection of human cells not bound by any form of connective tissue, and 'tissue' means all constituent parts of the human body formed by cells. Function or mode of action is by no means a criterion to discriminate cells from tissue in directive 2004/23/EC, while it is in the ATMP reflection paper.	Not accepted. 1) Cells and tissues under Dir.2004/23/EC are not within the scope of this guidance. 2) Essential function is exactly one of the criteria (by legislation) to differentiate between tissues & cells and ATMPs.
316-317	33 / 34	Comment: The therapeutic action “regeneration– repair – replacement” is typical for some of the biostatic tissue grafts, eg. bone allografts. Bone allografts used as filling tissue of bone defect after eg, tumor removal, is gradually replaced by recipient own bone tissue (creeping substitution fenomenon). Proposed change (if any): Remove the sentence.	Not accepted. Legal definitions cannot be changed with this revision.
330-333	33 / 34	Comment: as above - regeneration– repair – replacement is not typical only for TEP.	Not accepted. Legal definitions cannot be changed with this revision.
338-339	45	Comment: As regards the proposed Figure 2, EuropaBio is pleased to propose an improved version in either format per the EMA’s needs. Proposed change (if any): Please see Figure 2 at the end of the document.	Thank you. The current figure 2 is considered sufficient.

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		Line 338-339 p 12/17 - Figure 2	

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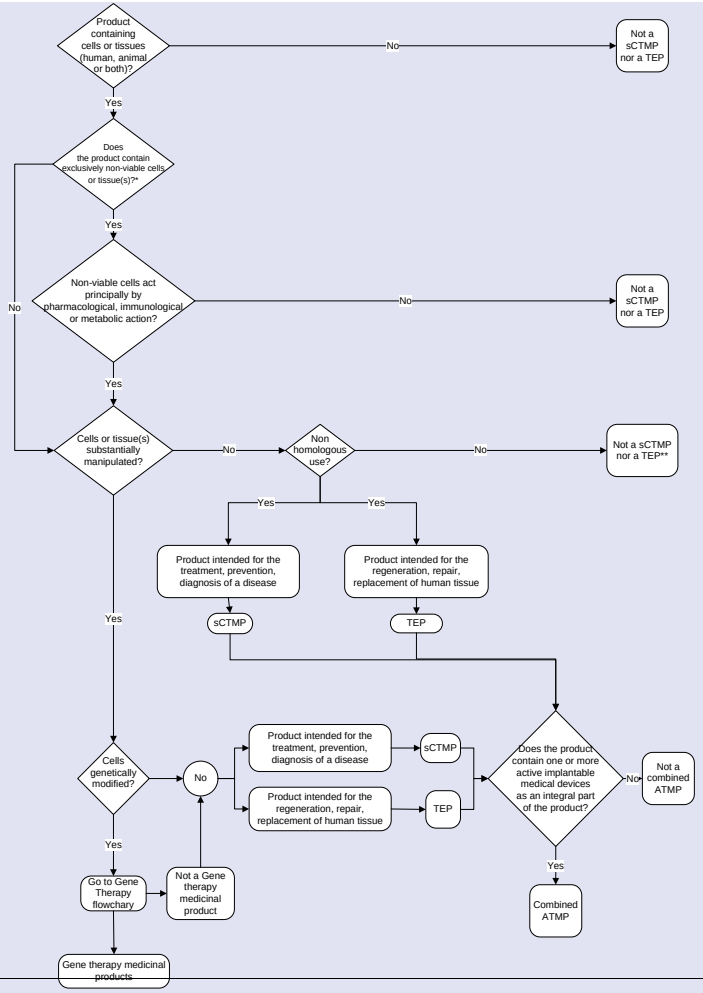

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
339	8	Decision tree sCTMP-TEP Comment: The document states: “The decision, …[…] claimed intended function. “ This is rather confusing when compared with the definition of cells and tissue given in directive 2004/23/EC which states that 'cells' means individual human cells or a collection of human cells not bound by any form of connective tissue, and 'tissue' means all constituent parts of the human body formed by cells. Function or mode of action is by no means a criterion to discriminate cells from tissue in directive 2004/23/EC, while it is in the ATMP reflection paper.	Not accepted, see response above.
339	32	Comment: The decision tree has to be adjusted to be consistent with other changes.	Not accepted, see response above.
339	48	Comment: There is no route in the figure for gene therapy (e.g. genetically modified cells) to be a combined ATMP. The algorithm should be implemented to allow classification of products containing cells exerting merely a function of carries (e.g. red blood cells loaded with specific drugs and then re-infused in the patients). In fact, following the algorithm, those cells should be classified as ATMP if one considers RBC as viable cells since the cell membrane is intact. It is also difficult to classify extracorporeal photo-aphaeresis (ECP) products. In fact, this product is a mixture of alive, apoptotic and death cells. But the therapeutic effect is likely exerted by apoptotic and death cells. Those cells exert a metabolic action. Proposed change (if any): Replace ‘homologous use’ with ‘same essential function(s)’. The algorithm should be improved in order to classify these border line	Homologous use is reworded In the flowchart Genetically modified cells are classified based on the purpose of the modification as clarified in the GTMP definition. This has been clarified in the flowchart of GTMPs.

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		products. Specify the product do non fall in the definition of ATMP when the main cell function of the cell is to carry drugs.	
341-347	48	Comment: it should be left to the developer's responsibility to justify whether their cells are viable or not in the small number of occasions where that might be necessary. Proposed change (if any): Remove reference to EMEA/CHMP/410869/2006 and reference to EP since it is not considered necessary to define for the purpose of the figure what is meant by viability.	Not accepted. This information is meant to clarify the basis of such classifications. The CAT will follow the existing definitions of viability.
Comments on section 2.2.4 Criteria for combined ATMPs			
351-397	54	Also applies to lines 457-480 (combined ATMPs) Comment: Cell Therapy Catapult welcome the additional detail provided on the distinction of devices acting as devices or excipients. This is an area of uncertainty currently and further exemplars and guidance on requirements for the 'device' component testing for progression through the development process would be welcomed. Proposed change (if any): As above, additional guidance on the distinction between device and excipient and accompanying testing requirements.	Not accepted, this guidance concerns ATMP classification, not definition of devices.
352	52	Comment: It is clear an advanced therapy medicinal product (ATMP) may be a cATMP as outlined in Section 2.1.	Not accepted, this guidance concerns ATMP classification, not definition of devices.

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		However, it is unclear if a device component of a cATMP always has to be separately authorised (i.e. have a CE mark) or not. Can a cATMP incorporate a component that falls within the definition of a medical device according to Directive 93/42 or 90/385 but which is not CE marked? If the 'medical device' has been manufactured specifically for use in the ATMP and its only use is as an integral part of the ATMP, is it a medical device within the meaning of Article 1(2)(a) of Directive 93/42/EEC or within the meaning of Article 1(2)(c) of Directive 90/385/EEC? Would it therefore need to be treated as a medical device under Directives 93/42 or 90/385 (e.g. CE marked), such that the ATMP is therefore classified as a cATMP? Or is the device component regulated under the ATMP regulation 1394/2007 (i.e. not separately treated as a device) and the ATMP is therefore a non-combined ATMP (ncATMP)? If the 'medical device' that is an integral part of the ATMP has not been manufactured specifically for use in the ATMP, and has not previously been treated as a medical device because it was not 'intended by the (device) manufacturer to be used for human beings for the purpose of: diagnosis, prevention, etc.' (see definition of a medical device within Directive 93/42), is the device component regulated under the ATMP regulation 1394/2007 and the ATMP therefore a ncATMP? Proposed change (if any): Please clarify or provide examples. We suggest a clearer definition of non-combined ATMP (ncATMP) be included as well.	According to the ATMP regulation (art 9), for a MAA of a combined ATMP, the evidence of conformity with the essential requirements for medical devices shall be included. This does not mean that the device needs to be CE-marked. The section on combined ATMPs has been amended.
354-355	8	Comment: The document states that "Combined ATMPs incorporate an active substance, i.e. a recombinant nucleic acid, cellular part consisting of viable or non-viable cells or tissues and one or more medical devices […]"	Not accepted, the definition is from legislation.

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		It is unclear why this definition needs to be that complex, since before a product can be considered a combined ATMP, it needs to be a confirmed ATMP. Proposed change (if any): Combined ATMPs combine an ATMP with one or more medical devices […]	
356-357	8	Comment: The document states “If cells or tissues are not viable these must exert the primary action of the combined product.” It appears that this criterion is not adequately reflected in the decision tree for sCTMP and TEP on page 12.	Partly accepted. The flowchart is primarily to make the differentiation between sCTMP/TEP, The situation for combined ATMP on basis of non-viable cells only is not fully depicted in the flowchart. A footnote is this respect is included in the flowchart.
357	30	Comment: If cells and tissues are not viable and exert an accessory action compared to the device, they should be covered by the future medical devices regulations once adopted. This should be added, at least in a footnote, for more clarity in a complex regulatory landscape.	Not accepted. Not within the remit of this revision.
358-397	48	Comment: Given that this section is fairly straightforward it could be shortened, they key message is contained in 378-397. Proposed change (if any):Add lines 378-380 to line 356 where integral has been stated to explain the term integral as this is an important factor in classification. Section under examples (359-397) can subsequently be shortened. Include an example for non-viable cells/tissues. Move the pancreatic beta cells in alginate matrix under non-combined ATMP.	Not accepted. The examples are demonstrating the differences between products. Some re-ordering of this paragraph has been done.

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Comments on section 2.3 Evolving and borderlines area			
398	10 / 20 / 26 / 55 / 56 / 58	Comment: New paragraph "2.3. Individualized treatment" should be added. Proposed change (if any): **2.3. Individualized treatment** **Exempt situations when individualized (non-industrial mass-production), autologous cell therapy may be performed with signed informed consent of the patient or delegated informed consent in agreement with the Directive 2001/83/EC and Regulation (EC) No 1394/2007 of the European Parliament and of the Council.**	Not accepted. Not within the remit of this revision. The legislation does not allow for a differential classification for individualised therapies / clinical practice.
Comments on section 2.3.1. Advanced therapies versus transplants / transfusion			
403-426	48	Comment: The ISCT feels that the importance of this section, similarly to the earlier section 2.2.3, lies in the consideration if the product is more than minimally manipulated and/or used for the same essential function(s) since that is the border between medicines and EUTCD. However, no mention is made of borderline with the blood directive for instance (suggested by heading). Another important point, which should be made also in the earlier section, is that existing classifications do not necessarily determine the outcome of a later application for classification (lines 410-414). It	Comment accepted: the paragraph has been amended. Accepted: past classifications are non-binding and do not dictate future decisions after the revision of the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		should be acknowledged that this same argument is applicable for future applications, whether cells are being used for the same essential function(s) or not. Lastly, a certain classification recommendation for a product does not imply that another similar product could be classified differently. Proposed change (if any): Section could be aligned with section 2.2.3, or alternatively be omitted while moving key message into section 2.2.3. It should be deleted the sentences “Autologous bone marrow-derived progenitor cells intended for treatment of patients with myocardial infarction, or other vascular diseases would be considered non-homologous use and therefore ATMPs.” And “Injection of concentrated bone marrow at the site of bone injury with the aim of healing a bone lesion can be considered as non-homologous use.”	Not accepted, see response to similar comments above.
403-426	60	Comment: This section describes important issues encountered by such products but would need some more clarification on where the border lies between the ATMP Regulation and the EU Tissues and Cells Directive. Furthermore, no mention is made of the borderline with the Blood Directive, although this would be welcome at this point. Proposed change (if any): Addition of information.	Accepted, clarification added.
406	4	Comment: We recommend the EMA clarify the classification of the human pancreatic Langerhans’ islets product (i.e., if not an ATMP was the product in the end classified as a “standard” biological medicinal product or not considered a medicinal product?)	Not accepted, see response to similar comments above. CAT’s remit is restricted to the classification as ATMP or not.
415-420	16	Comment: We assume, based on the common precursor hemangioblast, that vasculogenesis is one of the essential functions of bone marrow mononuclear cells as well as hematopoiesis. Therefore it should be	Not accepted, see response to similar comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		considered homologous use. Proposed change (if any): In contrast, some products previously considered as non – ATMP because of an essentially minimal manipulation or maintenance of the initial biological properties have been classified as ATMP due to their intended non-homologous use. For example autologous bone marrow – derived progenitor cells intended for treatment of patients with myocardial infarction~~, or other vascular diseases~~ would be considered non-homologous use and therefore ATMPs (in this case tissue engineering products) (see section 2.2.3).	
415-425	32	Comment: These paragraphs have to be removed completely for consistency with the other changes. ~~Proposed change (if any): In contrast, some products previously considered as non-ATMP because of an essentially minimal manipulation or maintenance of the initial biological properties have been classified as ATMP due to their intended non-homologous use. For example, autologous bone marrow-derived progenitor cells intended for treatment of patients with myocardial infarction, or other vascular diseases would be considered non-homologous use and therefore ATMPs (in this case tissue engineering products) (see section 2.2.3).~~ ~~It is possible that cell-based products administered in the same anatomical location fall under the definition of ATMP on grounds that it is for non-homologous use. This can be encountered when the mode of action of the cells is not identical to the one attributed to the cells by the scientific knowledge. As an example, injection of concentrated bone~~	Not accepted, see response to similar comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~marrow at the site of bone injury with the aim of healing a bone lesion can be considered as non-homologous use.~~	
415-420	33 / 34	Comment: same as comment regarding lines 296-297. Not all autologous bone marrow-derived progenitor cells can be classified as non-homologous use. Take also into consideration procedures carried out during the same surgical procedure.	Not accepted, see response to similar comments above.
417-420	12	Comment: are there any scientific evidence that the heterogeneous population of progenitor cells obtained from bone marrow, but used for treatment of patients with myocardial infarction, do not contain the relevant progenitor cell and if so why is this non-homologous use ? Proposed change (if any): revise /clarify the definition of homologous use	Not accepted, see response to similar comments above.
421-425	37	Comment: Regarding the statement: "It is possible that cell-based products administered in the same anatomical location fall under the definition of ATMP on grounds that it is for non-homologous use. This can be encountered when the mode of action of the cells is not identical to the one attributed to the cells by the scientific knowledge. As an example, injection of concentrated bone marrow at the site of bone injury with the aim of healing a bone lesion can be considered as non-homologous use" This is a confusing statement. Is is well known that after bone lesions a number of bone marrow components, including mesenchymal stem and	Not accepted, see response to similar comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		progenitor cells, vascular progenitors, platelets, leukocytes are recruited and, in addition to their variety of secreted molecules, contribute to bone healing. Bone marrow concentrates are mainly used when physiological mechanisms are impaired due to different causes. The rational include an accepted essential function and, obviously a homologous use, in addition to a non-substantial manipulation. Under this indication, bone marrow concentrates should not be considered sCTMP nor TEP. Proposed change (if any): Omit this paragraph: "As an example, injection of concentrated bone marrow at the site of bone injury with the aim of healing a bone lesion can be considered as non-homologous use"	
424-425	15	Comment: "As an example, injection of concentrated bone marrow at the site of bone injury with the aim of healing a bone lesion can be considered as non-homologous use". This example is inappropriate, since opposite decisions have been given by the CAT for products with very similar indications and modes of action: - Scientific recommendation EMA/82120/2013 on "Concentrate of autologous bone marrow seeded on a matrix consisting of cross-linked bovine type-1 collagen, coated with hydroxyapatite (HA)" : Tissue engineered medicinal product, combined ATMP - Scientific recommendation EMA/661080/13 on "Autologous cell	Not accepted, see response to similar comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		concentrate from bone marrow aspirate": **not an ATMP** - Decision of June 2014 on "concentrate of autologous, uncultured, custom prepared bone marrow aspirate" (Proposed indication: field of regenerative medicine: bone damaged by disease (e.g. ostenecrosis), fracture or ager elated loss of bone function): Tissue engineered product Autologous bone marrow concentrate injection for orthopaedic indication (osteonecrosis, pseudarthrosis "non-union") is performed in one step during surgery procedure. The treatment of the bone marrow requires a single centrifugation. It is a non-substantial modification process and the final product is for homologous use. It is therefore not an ATMP. Given that there is no clear interpretation of homologous and non-homologous use of bone marrow for bone repair, we would advise against using this this example. Proposed change (if any): Delete this sentence	
424-425	17	Comment: In the Scientific recommendation on classification of advanced therapy medicinal products published in your site on date 30 October 2013 (EMA/661080/2013), you commented: "The Bone Marrow Aspirate Concentrate is not an Advanced Therapy Medicinal Product according to the definition in Article 2(1) (b) of Regulation (EC) No 1394/2007", and "Indeed bone marrow cells are actively involved in non-haematopoietic functions. Bone marrow cells have been shown to demonstrate Osteopoiesis as follows: Nonmesenchymal Bone Marrow stem/progenitor cells are active in osteoblast formation.	Not accepted, see response to similar comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Bone Marrow hematopoietic stem and progenitors cells were able to differentiate in the both hematopoietic and osteocytic pathways. Certain stromal cells do not contribute to hematopoietic reconstitution." From what stated in your cited recommendation becomes clear that the essential function of the Bone Marrow is both the haematopoietic and the osteopoietic function. Proposed Change (if any): As an example, injection of concentrated bone marrow at the site of bone injury with the aim of healing a bone lesion can be considered as **homologous use, while injection of the same in the brain to sustain the nervous system's regeneration, can be considered as non-homologous use**.	
424-425	17	Comment: • If the Bone Marrow is concentrated by simple centrifugation, this is considered to be submitted to minimal manipulation (non-substantial manipulation) as stated in Annex I to Regulation (EC) No 1394/2007; • The fact that simple centrifugation of the human Bone Marrow will produce concentrated Mononuclear Cells that will keep their original biological characteristics, physiological functions, and structural properties relevant for the intended clinical use is demonstrated by several papers like, for example: Bara et al 2014; Carlos et al. 2012; Otsuru et al. 2012; de Girolamo et al. 2010; Jager et al. 2009; Gan et al 2008. • The fact that the Mononuclear Cells fraction maintains the same essential function both in the recipient and the donor, when engrafted in the bone, is demonstrated by several papers like, for example: Bara et al. 2014; the level I work of Prof. P. Bianco et al. (2001, 2011); and Prof. Dallari et al. (2007); the level II-1 paper of Ganji et al. (2004 & 2009); the papers of Prof. Hernigou et al. on 2002, 2005, 2006, 2008, 2009, 2010 and 2013 with 12,5 years	Not accepted, see response to similar comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		follow up; Otsuru et al. 2012; Gan et al. 2008. • The fact to inject the Concentrated Mononuclear Cells in the site of bone injury is intended to place BM derived cells in their own original place, i.e.: the BM itself. This is described in your Scientific recommendation on classification of advanced therapy medicinal products published in your site on date 30 October 2013 (EMA/661080/2013). Considering all the four points here above, how could it be the "injection of concentrated bone marrow at the site of bone injury with the aim of healing a bone lesion" be considered as "non-homologous use"? Proposed Change (if any): As an example, injection of concentrated bone marrow at the site of bone injury with the aim of healing a bone lesion can be considered as **homologous use, while injection of the same in the brain to sustain the nervous system's regeneration, it can be considered as non-homologous use.**	
424-425	18	Comment: there is a procedure called "Microfractures" that is very well known among the orthopaedic surgeons (Steadman J.R.-1999 -2003 - 2004). This procedure is recommended as gold standard by the International Cartilage Repair Society to repair the Grade II and Grade III Osteoarthritis. It consists in making small holes in the subchondral bone, once debrided the surface of a cartilage defect. Through these small holes the bone marrow can flow to fill up the cartilage defect site, and naturally clots as a natural elastic scaffold, essentially composed of the same bone marrow of the patient. In a more evolved version of this procedure a collagen membrane is superimposed to the cartilage defect site, with the aim to keep the bone marrow, as much as possible, close within the cartilage defect, in order for it to express all of its regenerative power where needed (AMIC – Behrens 2005, 2006). When we concentrate autologous MNC from the BM, with minimal manipulation, in order to collect more MSC in a small volume of blood,	Not accepted, see response to similar comments above.

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		and put them into the cartilage defect, after the Microfractures procedure is performed, we are putting the MNC in touch with the BM of the same patient (homologous use). The apposition of a collagen membrane, or similar, over the site of the defect, has the only scope to keep the MNC in place after their implantation to obtain the maximum regenerative effect, just in the place of injury. Proposed change (if any):"…, injection of concentrated bone marrow at the site of bone injury with the aim of healing a bone lesion can be considered **as homologous use**"	
425-425	21	The sentence: "injection of concentrated bone marrow at the site of bone injury with the aim of healing a bone lesion can be considered as non-homologous use" should be modified since it is not correct. Comment: injection of concentrated bone marrow at the site of bone injury with the aim of healing a bone lesion remains a homologous use. Bone union is obtained from cells coming from the bone marrow and non healing is related to absence of bone marrow when it occurs; Therefore taking bone marrow from the iliac crest to inject in another anatomical site as tibia, or humerus remains homologous even if the anatomy is not exactly the same. To treat a non union of the tibia it could be discussed to remain in the same anatomical homologous situation by taking the bone marrow from the pathological tibia (but there is a decrease of progenitors) or in the opposite normal tibia, but clearly this would not be an advantage for the patient; the morbidity and risk of taking bone marrow from a normal tibia would be higher (risk of fracture of the opposite normal tibia) than in the iliac crest; furthermore the number of osteogenic precursor is lower in the tibia than in the iliac crest. The scientific knowledge that the iliac crest is more osteogenic than the other bones is known since the end of 19th century and beginning of the 20th century (1890-1930).	Not accepted, see response to similar comments above.

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		Proposed change (if any): As an example, injection of concentrated bone marrow at the site of bone injury, bone osteonecrosis, or local bone defect with the aim of repair a bone lesion can be considered as **homologous use** Other possibility: delete this sentence	
424-425	25	Comment: The sentence: “injection of concentrated bone marrow at the site of bone injury with the aim of healing a bone lesion can be considered as non-homologous use” should be modified since it is not correct. In fact, bone marrow is present within the bone being one of the main constitutional components. Bone healing is due to the presence of cells in the bone marrow and many studies demonstrated that mesenchymal bone marrow stem/progenitor cells are involved in osteogenesis (1). Therefore, bone marrow concentrates used to repair bone can be intended to be used for their same essential function and in the same environment (2). References: 1. Long MW. Osteogenesis and bone-marrow-derived cells. Blood Cells Mol Dis. 2001 May-Jun;27(3):677-90. 2. Perut F, Filardo G, Mariani E, Cenacchi A, Pratelli L, Devescovi V, Kon E, Marcacci M, Facchini A, Baldini N, Granchi D. Preparation method and growth factor content of platelet concentrate influence the osteogenic differentiation of bone marrow stromal cells. Cytotherapy. 2013 Jul;15(7):830-9. doi: 10.1016/j.jcyt.2013.01.220.	Not accepted, see response to similar comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Comments on section 2.3.2. Gene therapy medicinal products versus biologicals containing or consisting of GMOs			
427-441	19	Comment: We would appreciate a more general discussion on the fact that GTMP might be at the same time GMOs or contain GMOs and that these are not exclusive. The title of the section is indeed confusing as the text (lines 429-441) is only a description of the considerations taken into account for the classification of genetically modified bacteria. Proposed change (if any): We would welcome a modification of the title of the paragraph or information added within the text with regards to GMOs & GTMPs.	Accepted: the title of this paragraph has been amended.
427-441	54	Comment: Cell Therapy Catapult welcome the EMA desire to expand on the definition of the distinction between GT products and GMO. Indeed there is a fair amount of uncertainty among developers of such products which is exacerbated by the differences in interpretation and requirements of the various member states. For example, some member states appear to be treating all genetically modified cell-based GT products as GMOs i.e. for the purposes of submitting a clinical trial authorisation application. This may incur additional fees, paperwork (such as GMO risk assessments, suitability of test sites under GMO aspects) and potentially extend the review time. Further to this, not all living cells can be classified as organisms i.e. unless they can function independently. Therefore, there remains doubt that a genetically modified cell can ever be classified as a GMO. Proposed change (if any): A clear statement of the CAT position should be provided with guidance on implementation for the Member states.	Not accepted. Not within the remit of the CAT. Other guidance is available on the EMA website discussing the regulatory considerations and requirements for GMOs.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
433-441	41	Comment: The considerations and the conclusion provided on the interpretation of the first indent in the definition of gene therapy medicinal product are not entirely clear and may not be sufficient to better understand the basis for classification into a gene therapy medicinal product. In addition, it would also be useful to clarify whether and when a product can be classified both as gene therapy product and a Genetically Modified Organism (GMO) and what the regulatory consequences are (see also general comment above regarding the overlapping of different regulations and requirements). Proposed change (if any): Reformulate lines 433-441 in order to clarify CAT position. Clarify situation regarding GMO status as this could help to drive harmonisation throughout the member states.	First comment: accepted. The paragraph has been clarified. Second comment: not accepted, not within the remit of the CAT.
437	30	Comment: The sentence appears unclear as it bases the classification as a GTMP on something (the repair, replacement, addition or deletion of the genetic sequence “to the human body” that does not appear in the legal definition of a GTMP. Proposed change (if any): To replace “Given that” by “Even though”	Partly accepted. The paragraph has been clarified..
Comments on section 2.3.4. Combined ATMPs verson non-combined cell-based medicinal products			
457-480	6	**Editorial Comment:** The section heading and lines 459-463 refers first to ‘combined ATMPs’ followed by ‘non-combined cell-based medicinal products’. In contrast	Not accepted. The flow of the paragraph would be disrupted by this editorial change.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the following paragraphs (line 464 to 480) provide first examples for 'not combined' products (line 464-477) followed by one example for a combined TEP. **Proposed change (if any):** Shift the text from lines 478-480 up to directly follow after line 463.	
457-480	27	Comment: We would appreciate more clarity on this section – in particular obtain more insight about when a matrix should be considered as an excipient and no longer as a medical device : is it only in the case it does not bring any structural properties?. Please note that the term "active" should be used carefully, because its usage in this section is misleading. Indeed, as per the directive 93/42/EC on medical devices, Annex IX, 1.4, "active" medical device means a medical device of which depends on a source of electrical energy or any source of power other than that directly generated by the human body or gravity and which acts by converting this energy. Moreover, our understanding is that it is not only when developers combine gene, cell or tissue with a CE marked product that final product could be a combined ATMP, but also when the ancillary product is not CE marked but falls under the definition of a Medical Device. If this is the case, this might be worth to be reminded here and therefore it does not mean that because a product is not used as per its original CE marking that the combined product might not be a combined ATMP – which seems to be meant in lines 468-469. Finally an insight on whether in case of a non-combined ATMP (line 469) the porcine gelatine matrix will be ruled as "novel excipient" and not as per Essential Requirements of MDD and how the regulation on novel excipient is adapted to this product would be greatly appreciated.	Not accepted. This guidance is dedicated for ATMPs, not on devices. The paragraph has been clarified.
457-480	45	Comment:	Not accepted. This guidance is dedicated for ATMPs,

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		We would appreciate more clarity on this section – in particular obtain more insight about when a matrix should be considered as an excipient and no longer as a medical device : is it only in the case it does not bring any structural properties? Overall, it would be very useful for ATMP developers to understand what criteria are used by EMA-CAT to make decisions on combined products. Please note that the term “active” should be used carefully, because its usage in this section is misleading. Indeed, as per the directive 93/42/EC on medical devices, Annex IX, 1.4, “active” medical device means a medical device of which depends on a source of electrical energy or any source of power other than that directly generated by the human body or gravity and which acts by converting this energy. Moreover, our understanding is that it is not only when developers combine gene, cell or tissue with a CE marked product that final product could be a combined ATMP, but also when the ancillary product is not CE marked but falls under the definition of a Medical Device. If this is the case, this might be worth to be reminded here and therefore it does not mean that because a product is not used as per its original CE marking that the combined product might not be a combined ATMP – which seems to be meant in lines 468-469. Finally, an insight on whether in case of a non-combined ATMP (line 469) the porcine gelatine matrix will be ruled as “novel excipient” and not as per Essential Requirements of MDD and how the regulation on novel excipient is adapted to this product would be greatly appreciated. Refer to Comment 4 of General Comments.	not on devices. Second comment: accepted. In case on non-combined ATMPs, Part IV of Annex I to Directive 2001/83/EC has to be followed.
457-480	48	Comment: It’s not clear why this wasn’t just discussed within section 2.2.4 particularly since the whole second paragraph is repeated text. Proposed change (if any): Work into section 2.2.4 or if retained trim out	Partly accepted: a clear cross reference to the the section on criteria for combined ATMPs has been included.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		repetition.	The entire discussion on combined vs non combined ATMP has been moved to this paragraph.
461-471	41	Comment: It would be useful to clarify whether the porcine gelatine matrix referred to in the example provided should be considered as an active ingredient (i.e. not as an excipient) as well as the human aortic endothelial cells.	Not accepted. This guidance is dedicated for ATMPs, not on devices.
468-469	52	Comment: This example indicates that when a medical device is used in the ATMP in a different way than its intended use when considered as a medical device, the ATMP would be a non-combined ATMP (ncATMP). Proposed change (if any): This seems to be an important distinction which should be clarified in the introductory section (lines 354-357) as follows: "Combined ATMPs incorporate an active substance, i.e. a recombinant nucleic acid, cellular part consisting of viable or non-viable cells or tissues and of one or more medical devices or one or more active implantable medical devices as an integral part of the product. The medical device or active implantable medical device(s) should be used in the same way as its intended use when considered as a medical device or active implantable medical device(s). If cells or tissues are not viable these must exert the primary action of the combined product."	Accepted. The paragraph has been amended.
472-477	41	Comment: Similarly, it would be useful to clarify whether the alginate matrix should be considered as an excipient in the example provided	Not accepted. In case on non-combined ATMPs, Part IV of Annex I to Directive 2001/83/EC has to be followed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Comments on section 2.4. Clarification on procedural aspects / information to be submitted by the applicant			
490-494	4	Comment: As mentioned above, we would welcome a recommendation from the CAT on the definition of the active substance, but also on the preferred wording to be used to define the active substance (actual written definition that could then be used for all future regulatory procedures with EMA).	Not accepted. Not in the scope of this guidance.
495-496	4	Comment: Similarly, advice from the CAT on the definition of the optimal wording to be used to define the finished product and the pharmaceutical form would be welcome.	Not accepted. Not in the scope of this guidance.
Main conclusions			
	48	MAIN CONCLUSION: IT IS SUGGESTED THAT THIS DOCUMENT WOULD BE MORE USEFUL IF FOCUSSED ON PROVIDING ADVICE ON HOW TO PRESENT A CLASSIFICATION ARGUMENT TO THE AGENCY AND WHICH DATA MIGHT BE NEEDED ALLOWING THE DEVELOPER TO UNDERSTAND WHEN THEY MIGHT BE READY. The ISCT view is that the document is an attempt to justify and provide framework to the classification and also some of the decisions taken so far. The first question is to attempt to strengthen the rational for a classification. Second that a classification is primarily a scientific discussion and that may, will, vary from case to case. There are a few	Classification of ATMPs is meant to provide regulatory predictability for developers and cannot be based on case-by-case decisions fluctuating along with increasing scientific data. Therefore strict rules are considered necessary. The classification cannot either correct possible current legal problems.

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		major guidelines and established points that we all agree where there is no discussion but also, a series of other ones where, borderline to not, we do not agree. We understand and value the attempt made with this document but the exercise failed to meet the objectives and the document could be more beneficial if based on the process, the scientific rationale and on the required documentation. The document rather than being so defensive and prescriptive it should be more conductive to the discussion and case analysis. Classification should be done case by case based on the process, the scientific rationale and on the required documentation.	
	60	MAIN CONCLUSION: This document is useful due to the examples provided. However, especially for SMEs with very innovative products, it does not sufficiently provide advice on how to build a case for classification and which kind of information would be useful to the CAT to reach a scientifically sound conclusion. EBE welcomes the attempt made by the CAT to illustrate its conclusions by adding examples to this document. However, it would be useful to build the Reflection Paper around the scientific rationale and the required type of information that is necessary to support the assessment.	Not accepted. The classification is always triggered by an application and cannot be generalised. If the information in the application is not sufficient, CAT will ask for further relevant information.