EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

October 30, 2014

Submission of comments on 'Reflection Paper on Classification of Advanced Therapy Medicinal Products' (EMA/CAT/600280/2010)

Comments from:

Name of organisation or individual
Association of Aesthetic Practitioners (AAP), http://aestheticpractitioner.org/

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Ladies and Gentlemen, 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. Below kindly find our comments on the CAT reflection paper on classification of advanced therapy medicinal products. Sincerely yours, DDr. Karl-Georg Heinrich, MD, President Herfried Wagner, MSc, Secretary Association of Aesthetic Practitioners (AAP) http://aestheticpractitioner.org/ info@aestheticpractitioner.org/	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The Regulation (EC) No. 1394/2007 on advanced therapy medicinal products (ATMP 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.	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	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 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	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	therapy needs to be available as it must always be the patient's choice (based on thorough information provided by the physician) 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 physician 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 physician. However, the physician 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	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	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. **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.	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Circumstances like long-distance flights, epidemiological and infection risk, cultural differences, language barriers, patients missing check-ups with the physician 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. 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	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	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	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	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) 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	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	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 for producing a cell therapy product, in some case leukapheresis is employed that may bring significant health risk to the donor.	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	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	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	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 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.	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	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,	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	adult, autologous, unexpanded, and uncultured regenerative cells of stromal vascular fraction from subcutaneous adipose tissue (EMA/500724/2012, EMA/129056/2013). **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	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	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. (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,	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	enzymatic digestion of tissue, and differentiation/activation with growth factors needs to be exempted from the list of substantial manipulations. **Scientific References** Casteilla L, Planat-Benard V, Laharrague P, Cousin B: *Adipose-derived stromal cells: Their identity and uses in clinical trials, an update*. *World J Stem Cells*. 2011;3(4):25-33. Cervelli V, Gentile P, De Angelis B, Calabrese C, Di Stefani A, Scioli MG, Curcio BC, Felici M, Orlandi A: *Application of enhanced stromal vascular fraction and fat grafting mixed with PRP in post-traumatic lower extremity ulcers*. *Stem Cell Res*. 2011;6(2):103-11. Culme-Seymour EJ, Davie NL, Brindley DA, Edwards-Parton S, Mason C: *A decade of cell therapy clinical trials (2000-2010)*. *Regen Med*. 2012;7(4):455-62. Dos-Anjos Vilaboa S, Navarro M, Llull R: *Age influence on stromal vascular fraction cell yield obtained from human lipoaspirates*. *Cytotherapy*. 2014;16(8):1092-7. Gentile P, Orlandi A, Scioli MG, Di Pasquali C, Bocchini I, Cervelli V: *Concise review: adipose-derived stromal vascular fraction cells and platelet-rich plasma: basic and clinical implications for tissue engineering*	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	therapies in regenerative surgery. *Stem Cells Transl Med*. 2012;1(3):230-6. Gimble JM, Guilak F, Bunnell BA: *Clinical and preclinical translation of cell-based therapies using adipose tissue-derived cells*. *Stem Cell Res Ther*. 2010;1(2):19. Hibbs MS, Hasty KA, Kang AH, Mainardi CL: *Secretion of collagenolytic enzymes by human polymorphonuclear leukocytes*. *Coll Relat Res*. 1984;4(6):467-77. Ichim TE, Harman RJ, Min WP, Minev B, Solano F, Rodriguez JP, Alexandrescu DT, De Necochea-Campion R, Hu X, Marleau AM, Riordan NH: *Autologous stromal vascular fraction cells: a tool for facilitating tolerance in rheumatic disease*. *Cell Immunol*. 2010;264(1):7-17. Jamiolkowski RM, Guo LY, Li YR, Shaffer SM, Naji A: *Islet transplantation in type I diabetes mellitus*. *Yale J Biol Med*. 2012;85(1):37-43. Jordan GH: *The use of intralesional clostridial collagenase injection therapy for Peyronie's disease: a prospective, single-center, non-placebo-controlled study*. *J Sex Med*. 2008;5(1):180-7. Koh YG, Choi YJ, Kwon SK, Kim YS, Yeo JE: *Clinical results and second-look arthroscopic findings after treatment with adipose-derived stem cells for knee osteoarthritis*. *Knee Surg Sports Traumatol Arthrosc*. 2013;14:337.	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Lee SK, Kim DW, Dhong ES, Park SH, Yoon ES: *Facial Soft Tissue Augmentation using Autologous Fat Mixed with Stromal Vascular Fraction*. *Archives of plastic surgery*. 2012;39(5):534-9. Lendeckel S, Jödicke A, Christophis P, Heidinger K, Wolff J, Fraser JK, Hedrick MH, Berthold L, Howaldt HP: *Autologous stem cells (adipose) and fibrin glue used to treat widespread traumatic calvarial defects: case report*. *J Craniomaxillofac Surg*. 2004;32(6):370-3. Mason C, Manzotti E: *Regenerative medicine cell therapies: numbers of units manufactured and patients treated between 1988 and 2010*. *Regen Med*. 2010;5(3):307-13. Pak J, Chang JJ, Lee JH, Lee SH: *Safety reporting on implantation of autologous adipose tissue-derived stem cells with platelet-rich plasma into human articular joints*. *BMC Musculoskelet Disord*. 2013;14:337. Ribes-Koninckx C, Ibars EP, Calzado Agrasot MÁ, Bonora-Centelles A, Miquel BP, Vila Carbó JJ, Aliaga ED, Pallardó JM, Gómez-Lechón MJ, Castell JV: *Clinical outcome of hepatocyte transplantation in four pediatric patients with inherited metabolic diseases*. *Cell Transplant*. 2012;21(10):2267-82. Riordan NH, Ichim TE, Min WP, Wang H, Solano F, Lara F, Alfaro M, Rodriguez JP, Harman RJ, Patel AN, Murphy MP, Lee RR, Minev B: *Non-expanded adipose*	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	stromal vascular fraction cell therapy for multiple sclerosis. *J Transl Med*. 2009;7:29. Rodriguez JP, Murphy MP, Hong S, Madrigal M, March KL, Minev B, Harman RJ, Chen CS, Timmons RB, Marleau AM, Riordan NH: *Autologous stromal vascular fraction therapy for rheumatoid arthritis: rationale and clinical safety*. *Int Arch Med*. 2012;5:5. Shi L, Carson D: *Collagenase Santyl ointment: a selective agent for wound debridement*. *J Wound Ostomy Continence Nurs*. 2009;36(6 Suppl):S12-6. Tallis A, Motley TA, Wunderlich RP, Dickerson JE Jr, Waycaster C, Slade HB: *Clinical and economic assessment of diabetic foot ulcer debridement with collagenase: results of a randomized controlled study*. *Clin Ther*. 2013;35(11):1805-20. Thomas A, Bayat A: *The emerging role of Clostridium histolyticum collagenase in the treatment of Dupuytren disease*. *Ther Clin Risk Manag*. 2010;6:557-72. Tomlinson MJ, Tomlinson S, Yang XB, Kirkham J. Cell separation: *Terminology and practical considerations*. *J Tissue Eng*. 2013;4:2041731412472690.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
264-266		Comment: Clarifying wording. 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.	
266-280		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~~	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		~~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 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.~~	
286-307		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.~~	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		~~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. 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.~~	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
339		Comment: The decision tree has to be adjusted to be consistent with other changes.	
415-425		Comment: These paragraphs have to be removed completely for consistency with the other changes. Proposed change (if any): ~~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 marrow at the site of bone injury with the aim of healing a bone lesion can be considered as non-homologous use.~~	

Please add more rows if needed.