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Reflection paper on classification of advanced therapy medicinal products

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1. Executive summary

Further to the implementation of Article 17 of Regulation (EC) No 1394/2007ⁱ (hereinafter referred to as 'the Advanced Therapy Medicinal Products (ATMPs) Regulation'), applicants have access to an optional procedure which is the CAT (Committee for Advanced Therapies) scientific recommendation for the classification of ATMPs, hereafter referred to as "ATMP classification". It is underpinned by the ATMP Regulation which enables the European Medicines Agency (EMA) in close collaboration with the European Commission to determine whether or not a given product meets the scientific criteria, which define ATMPsⁱⁱ. The ATMP classification procedure has been established in order to address, as early as possible, questions of borderline cases where classification of a product based on genes, cells or tissues is not clear.

The CAT issues scientific recommendations determining whether or not the referred product falls, within the definition of an ATMP in the European Union.

The ATMP Regulation and the Directive 2001/83/EC Annex I Part IVⁱⁱ provide precise legal definitions for ATMPs.

The ATMP classification is based on the evaluation of whether a given product fulfils one of the definitions of gene therapy medicinal product (GTMP), somatic cell therapy medicinal product (sCTMP) or tissue engineered product (TEP) and whether the product fulfils the definition of a combined ATMP or not. However, it is also acknowledged that, due to the complex nature of these therapeutic products, the limited data package at an early stage of product development and the rapid evolution of science and technology, questions of borderline may ariseⁱⁱⁱ.

The ATMP classification is conducted by the CAT on request of and on basis of information provided by a developer of a product based on genes, cells or tissues and the outcome of the classification is therefore specific to the product under development. The examples¹ and the conclusions mentioned in this paper may not be directly applicable to other products which may be from a different origin or manufactured using different processes / undergoing different manipulation steps. The CAT classification examples in the reflection paper should not be understood as generic classifications for certain classes of ATMPs. Future applicants should apply caution when extrapolating the CAT classifications to their product and should consider applying for ATMP classification of their product.

The ATMP classification procedure is voluntary and free of charge. While the recommendation on classification provided by the Agency is not binding, the procedure can help developers to clarify the applicable regulatory framework. It also provides clarity on the development path and scientific-regulatory guidance to be followed. The ATMP classification may sometimes also be a useful tool for applicants to initiate a tailored dialogue on the product development with regulators. Indeed, the ATMP classification, along with other tools (e.g. ITF briefing meetings²), 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 (only for small and medium enterprises). The ATMP classification may also help developers to gain access to all relevant services and incentives offered by the EMA.

Although clinical trials are under the responsibility of the National Competent Authorities, it is important to stress that the classification recommendation made by the CAT may help when submitting a clinical trial dossier, as the applicant and the concerned competent authorities will be made aware of

¹ In order to protect the commercially confidential information provided by the applicants, the examples in this reflection paper are generalised, especially with regards to the manufacturing and manipulation steps.

² See EMA website: [European Medicines Agency - Human medicines - Innovation Task Force \(ITF\)](#)

a European classification position which can clarify and facilitate identification of the most relevant criteria and procedure to be applied.

Moreover, the ATMP classification can be applied for at any stage of the product development, even when non-clinical and clinical data are not available. It should be noted that scientific recommendations given by the CAT are always related to a defined product. It is thus not possible to classify scientific 'concepts' in the absence of a clear description of the product.

In addition, the ATMP classification procedure is only applicable when a product is based on genes, cells or tissues³.

If additional scientific information becomes available after the original ATMP classification that may impact the classification of the product, the applicant can submit a follow-up request. This should follow the same procedure as the original submission.

The summary outcome ATMP classifications assessed so far by the CAT is available on the EMA website⁴. Since 2011, summary reports of all ATMP classifications are published.

Scope

The aim of this reflection paper is to provide guidance on the ATMP classification procedure, as well as on the interpretation of key concepts of the definition of gene therapy medicinal product, somatic cell therapy medicinal product, tissue engineered product, and combined advanced therapy medicinal product. The guidance reflects the experience gained in the application of the classification procedure.

2. Discussion

2.1. Legal basis of ATMP classification

According to Article 2(1)(a) of Regulation (EC) No.1394/2007, an 'advanced therapy medicinal product' means any of the following medicinal products for human use:

- a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC, as amended
- a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC, as amended
- a tissue engineered product as defined in Article 2(1)(b) of Regulation (EC) No. 1394/2007.

Article (2)(1)(d) of the ATMP Regulation also gives a definition of 'Combined ATMP'. These products contain as an integral part of the product a medical Device (see below).

The definitions of a gene therapy medicinal product and a somatic cell therapy medicinal product according to Directive 2001/83/EC, Annex I, Part IV, as amended (implementing Directive 2009/120/EC) are as follows:

2.1.1. Gene therapy medicinal product

Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

³ Taking into account the remit of the European Medicines Agency, as stated in Article 17 of Regulation 1394/2007 i.e. "Any applicant developing a product based on genes, cells or tissues may request a scientific recommendation of the Agency with a view to determining whether the referred product falls, on scientific grounds, within the definition of an advanced therapy medicinal product"

⁴ The complete list of scientific recommendations on classification of ATMPs can be found at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000301.jsp&mid=WC0b01ac05800862c0

(a) 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, adding or deleting a genetic sequence;

(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.

It should be noted that in order to be considered a gene therapy medicinal product, both the characteristics (a) and (b) have to be fulfilled.

2.1.2. Somatic cell therapy medicinal product

Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:

(a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;

(b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, 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, lyophilization, freezing, cryopreservation, and vitrification.

It should be pointed out that this list of non-substantial manipulations is non-exhaustive.

It should also be noted that in order to be considered a somatic cell therapy medicinal product, both the characteristics (a) and (b) have to be fulfilled.

2.1.3. Tissue engineered products

Tissue engineered products, according to Article 2(1)(b) of Regulation (EC) No. 1394/2007, means a product that:

- contains or consists of engineered cells or tissues, and

- is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.

A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices.

Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, are excluded from this definition.

Article 2(1)(c) of Regulation (EC) No. 1394/2007 also states that:

Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions:

- the cells or tissues have been subject to 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,*
- the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.*

2.1.4. Combined Advanced Therapy Medicinal Products

According to Article 2(1)(d) of Regulation (EC) No. 1394/2007, a 'Combined advanced therapy medicinal product' means an advanced therapy medicinal product that fulfils the following conditions:

- it must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC, and*
- its cellular or tissue part must contain viable cells or tissues, or*
- 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.*

For requirements for medical devices and implantable medical devices please consult the relevant European Commission guidelines and Medical Device Legislation, as appropriate.

2.1.5 Additional legal clarifications in Regulation (EC) No. 1394/2007

- With regards to **products containing cells or tissues**, Article 2(2) states that:

"Where a product contains viable cells or tissues, the pharmacological, immunological or metabolic action of those cells or tissues shall be considered as the principal mode of action of the product."

For Tissue Engineered products their Mode of Action is linked to regeneration, repair or replacement a human tissue, as described in Article 2(1)(b).

- In accordance with Article 2(3), an **advanced therapy medicinal product containing both autologous and allogeneic cells or tissues** shall be considered to be for allogeneic use.
- Demarcation rule between ATMPs:

Article 2(4) and 2(5) states that:

"A product which may fall within the definition of a tissue engineered product and within the definition of a somatic cell therapy medicinal product shall be considered as a tissue engineered product. A product which may fall within the definition of a somatic cell therapy medicinal product or a tissue engineered product, and a gene therapy medicinal product, shall be considered as a gene therapy medicinal product."

2.2. Scientific principles applied to the classification of ATMPs

According to Article 17 of the ATMP Regulation, products are classified according to the respective definitions of gene therapy medicinal product, somatic cell therapy medicinal products, tissue engineered product and combined ATMP, on the basis of scientific information provided by the applicant.

This section elucidates the scientific criteria applied for the classification of ATMPs. The following list of criteria is based largely on the experience gained by the CAT through recommendations on ATMP classification issued so far⁴. These should not be considered as exhaustive and might be subject to change as science evolves.

2.2.1. Definition of cell, viable cell and tissue for classification purposes

For the purpose of ATMP classification, the CAT considers that a cell is defined as follows: *'A typical cell is the smallest unit of an organism that has been generated directly through mitosis. A cell comprises a nucleus (eukaryotic cells) or nucleoid material (prokaryotic cells) and cytoplasm enclosed by a cell membrane. A viable cell should be capable to produce energy and synthesize new molecules from raw materials.'*

This definition is to be read in conjunction with the relevant legislation including Regulation (EC) No 1394/2007 and Directive 2001/83/EC including its Annex I, part IV (technical requirements for ATMP).

A viable cell is a cell that has a functional cytoplasmic membrane. The European Pharmacopoeia provides information on assays to demonstrate cytoplasmic membrane integrity and activity [Ph. Eur. General Chapter 2.7.29 (01/2008:20729)]. In particular the concerned method refers to cell staining by viability dyes and manual or automated analysis, under a light microscope or by flow cytometry, of a cell suspension in order to determine the percentage of viable cells. The same definition of viable cells is referred to in the 'Guideline on human cell-based medicinal products' (EMA/CHMP/410869/2006)

Tissues are defined in Directive 2004/23/EC (Art 3.b) as *'all constituent parts of a human body formed by cells'*.

2.2.2. Claimed mode of action (MoA)

Information on the claimed MoA is particularly important to ascertain whether the product is for treatment, prevention or diagnosis of a disease, and exerts its activity via a pharmacological, immunological or metabolic action, or whether the product is intended for regeneration, repair or replacement of cells/tissues. The possible MoA should be considered in relation to the intended indication.

For example, if mesenchymal stem cells are used to treat a diseased organ, this could act via a combination of mechanisms which can include metabolic, immunological, pharmacological, regeneration and repair. In such a case, the predominant mode of action claimed will affect whether this will be classified as somatic cell therapy or tissue-engineered product.

The claim can be based either on data and/or on current scientific knowledge, but it has to be sufficiently substantiated in each case. Otherwise, the CAT may only conclude that a product is an ATMP, but not yet if it is, for example, a tissue engineered product or a somatic cell therapy medicinal product.

2.2.3. Criteria for GTMP

The definition of gene therapy medicinal product according to Annex I, part IV, section 2.1 of Directive 2001/83/EC, as amended, is articulated into two conditions that have both to be fulfilled simultaneously: 1) the product has to be a biological medicinal product^{IV} and contains recombinant nucleic acid(s) and 2) the recombinant nucleic acid(s) should be directly involved in the mechanism of action (and hence therapeutic action of the product. In this respect the following observations can be made:

- Indent (a) of the definition of Gene therapy medicinal product:

the recombinant nucleic acids should be of biological origin independently from the origin of the vector system used (e.g. viral/bacterial vectors or micellar and liposomal formulations, etc.)

- Indent (b) of the definition of Gene therapy medicinal product :

“its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence”: the MoA and proposed indication, as claimed by the applicant are of essential to assess if there is a “direct” relationship between the therapeutic, prophylactic or diagnostic effect of the product and the delivered genetic sequence or the expressed product. As an illustration, the CAT provided two scientific recommendations for classifications for genetically modified T cells encoding an exogenous thymidine kinase gene. The T cell preparations were intended for immune reconstitution as adjunct treatment in haematopoietic stem cell transplantation.

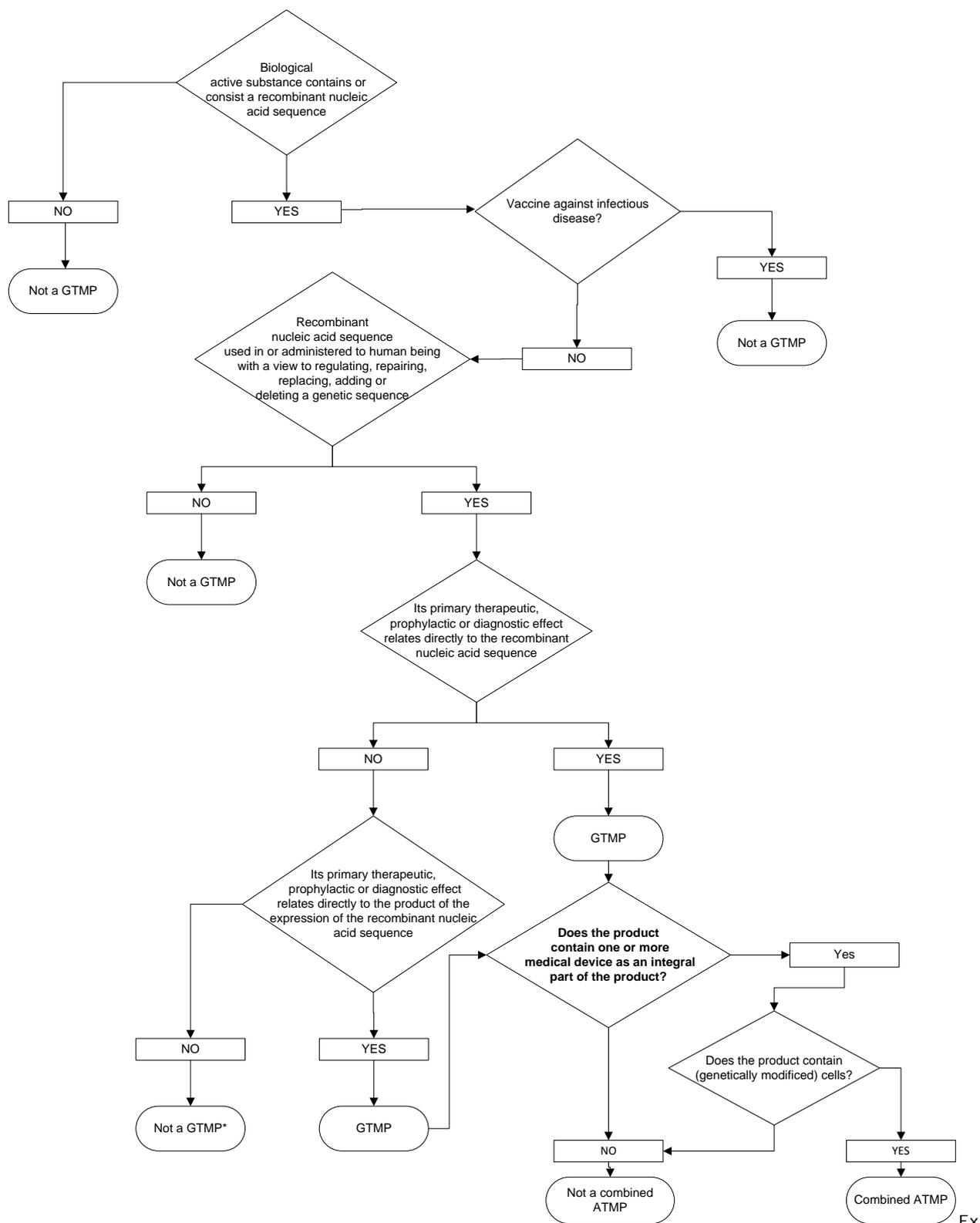
These T cell preparations have been classified as somatic cell therapy medicinal products considering that the treatment was adjunctive T-cell therapy supporting immune reconstitution of leukaemia patients who underwent bone marrow transplantation after myeloablative conditioning regime. In both cases, the genetic modification leading to the expression of the exogenous gene herpes simplex virus thymidine kinase - by the addition of the corresponding genetic sequence - relates to the treatment (with ganciclovir administration) of a potential graft versus host disease that may occur in some patients undergoing Haematopoietic Stem Cell Therapy (HSCT). The recommendation on the classification as somatic cell therapy considered that the primary role of the cells was the “immune reconstitution” of the patients, while the genetic modification was limited to a secondary role of controlling the potential risk of graft versus host disease. However, it should be stressed that being considered as a genetically modified somatic cell therapy product, most of the principles and requirements that normally apply to gene therapy medicinal products, may also apply for these products (i.e. the classification does not necessarily exempt from the relevant and applicable scientific requirements of GTMP).

- Genetic manipulation does not necessarily have to take place in the human body, since for example products consisting of genetically modified cells generated *ex-vivo* have also been classified as a gene therapy medicinal product (e.g. autologous CD34+ haematopoietic stem cells (HSCs) transduced with lentiviral vector encoding the human ABCD1 cDNA and autologous CD34+ haematopoietic stem cells (HSCs) transduced with lentiviral vector encoding the human β A-T87Q-globin gene).
- The legislation provides that *“Gene therapy medicinal products shall not include vaccines against infectious diseases”*. For classification purposes, vaccines are expected to have prophylactic mode of action, i.e. prevention of an infectious disease in humans. If a product is intended to treat pathologies caused by the infection (e.g. malignancies), it is classified as a GTMP. Live recombinant viral vectors (delivering genes encoding specific antigen sequences into human somatic cells) could fulfil the definition of Gene Therapy Medicinal Products (GTMP) when administered for example in

oncology, but similar products would not be classified GTMPs when intended as prophylactic against infectious disease. In order to enable the classification of borderline products (treatment of infections or premalignancies) the therapeutic indication and target population should be clearly defined.

Figure 1. DECISION TREE FOR GTMP

The following questions can help applicants to classify their product:



planatory notes: *) The product can contain genetically modified cells for which specific requirements should be followed (see 'Guideline on human cell-based medicinal products' (EMA/CHMP/410869/2006).

2.2.4. Criteria for somatic cell therapy medicinal products (sCTMP) and tissue engineered products (TEP)

a) sCTMP and TEP both contain or consist of engineered cells or tissues (see definition in section 2.1 above). To be considered 'engineered', cells or tissue(s) should fulfil at least one of the following criteria:

- Substantial manipulation

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, differentiation/activation with growth factors.

Cell culturing leading to expansion is considered substantial manipulation. Induction of proliferation of cells during cell culture has to be regarded as changes of their biological characteristics and structural properties, either because of an immediate change in cell functionality or cell phenotype, or 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 (e.g. membrane receptors).

Enzymatic digestion of a tissue to release cells is also considered to be substantial manipulation, when the aim is to dissociate cell-cell contacts and the released cells are administered into patients with or without subsequent manipulation. An example would be keratinocytes from skin, for which enzymatic digestion would destroy the tissue architecture and functional interactions of the cells, which cannot be regained in the cell suspension: this would be considered as substantial manipulation.

If the enzymatic digestion leads to isolation of functionally intact tissue units (e.g. pancreatic islets) or there is scientific evidence that the original structural and functional characteristics are maintained, the procedure is not considered substantial manipulation.

In case a tissue is treated to remove cells and to be used without any cellular components (e.g. amniotic membrane, bone) the product is not an ATMP because it does no longer contain cells or tissue.

If the number of certain cells (e.g. MSCs in fat grafts) is enriched by selection and the processing does not change the characteristics of the cells, this is not considered a substantial manipulation. Additionally, based on scientific considerations, the CAT can also consider other manipulations as "non substantial". One example is the radiolabelling of leukocytes for diagnostic purposes. This technique has no significant impact on the functional properties of the cells and should thus not be considered a substantial manipulation.

- Different essential function (non-homologous use).

In case no substantial manipulation of the cells/tissues takes place, the classification is based on the essential function of the cells/tissues. Such non-substantially manipulated cells or tissues 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(s) in the same anatomical or histological environment. Examples of this category are bone marrow cells or peripheral blood cells used for haematopoietic or immune reconstitution. Other clinical uses of bone marrow cells would be considered to be ATMPs, unless the same essential function(s) and the same anatomical/histological environment can

be demonstrated for the cells/tissues both at the donor and administration site (tissue). The same principle 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.

Replacement of a tissue as its whole or functional unit of a tissue (such as cornea or pancreatic islets) is regarded as use for the same essential function. Similarly, transplantation of a non-manipulated tissue to another location in the same anatomical or histological environment is also considered to achieve the same essential function. This is the case for skin transplantation from one part of the body to another part, subcutaneous implantation of pancreatic islets or replacement of arteria by veins. However, in the case of pancreatic islets, the classification will also depend on the manipulation and functional integrity of the islets.

b) Differentiation between sCTMP and TEP

The main difference between sCTMP and TEP is determined on the basis of the intended function of the product as claimed by the Applicant. The sCTMPs are intended for the prevention, diagnosis and/or treatment of diseases via pharmacological, metabolic actions, whereas TEPs are used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue. The decision, whether a product fulfils the requirements of a sCTMP or a TEP, is taken on the basis of the claimed mode of action in association with its associated claimed intended function.

The therapeutic action of the product i.e. "regeneration– repair – replacement" is an important component in determining the classification as TEP. These may be interlinked processes that cannot be defined separately but have to be considered together. The three processes may occur concomitantly or sequentially (e.g. implantation of chondrocytes to replace missing cartilage followed by repair and induction of regeneration).

The CAT considers that a product consisting of engineered cells that induces regeneration, repair or replacement in the native tissue e.g. via secretion of paracrine factors (by the engineered cells/tissue), also fulfils the definition of a TEP. In many cases, such products would also fulfil the definition of a sCTMP, and therefore the classification as TEP is based on the demarcation rule in art. 2(4) of the ATMP Regulation.

Isolated pancreatic beta cells embedded in an alginate matrix may serve as example for the delineation between somatic cell therapy and tissue engineering: This cell-based product was intended to be administered to patients with a view to restoring, correcting or modifying physiological function via a metabolic action of the cells it contains (secretion of insulin). As the claimed MoA of the product was the transient restoration of beta cell activity (the "replacement of the function"), but not the regeneration, repair nor the replacement of the human tissue itself, it was concluded that the product was a somatic cell therapy product. In line with this approach, human liver-derived progenitor cells were also classified as somatic cell therapy, since the cells serve to primarily replace a function (treatment of inborn errors of liver metabolism) rather than the tissue itself.

In contrast, a preparation of cells derived from adult skeletal muscle tissue, intended for the treatment of stress urinary incontinence, was classified as a TEP because the cells were administered primarily with a view to regenerating, repairing or replacing a human tissue (the replacement of urethral sphincter muscle cells, or to repair respective injured tissue).

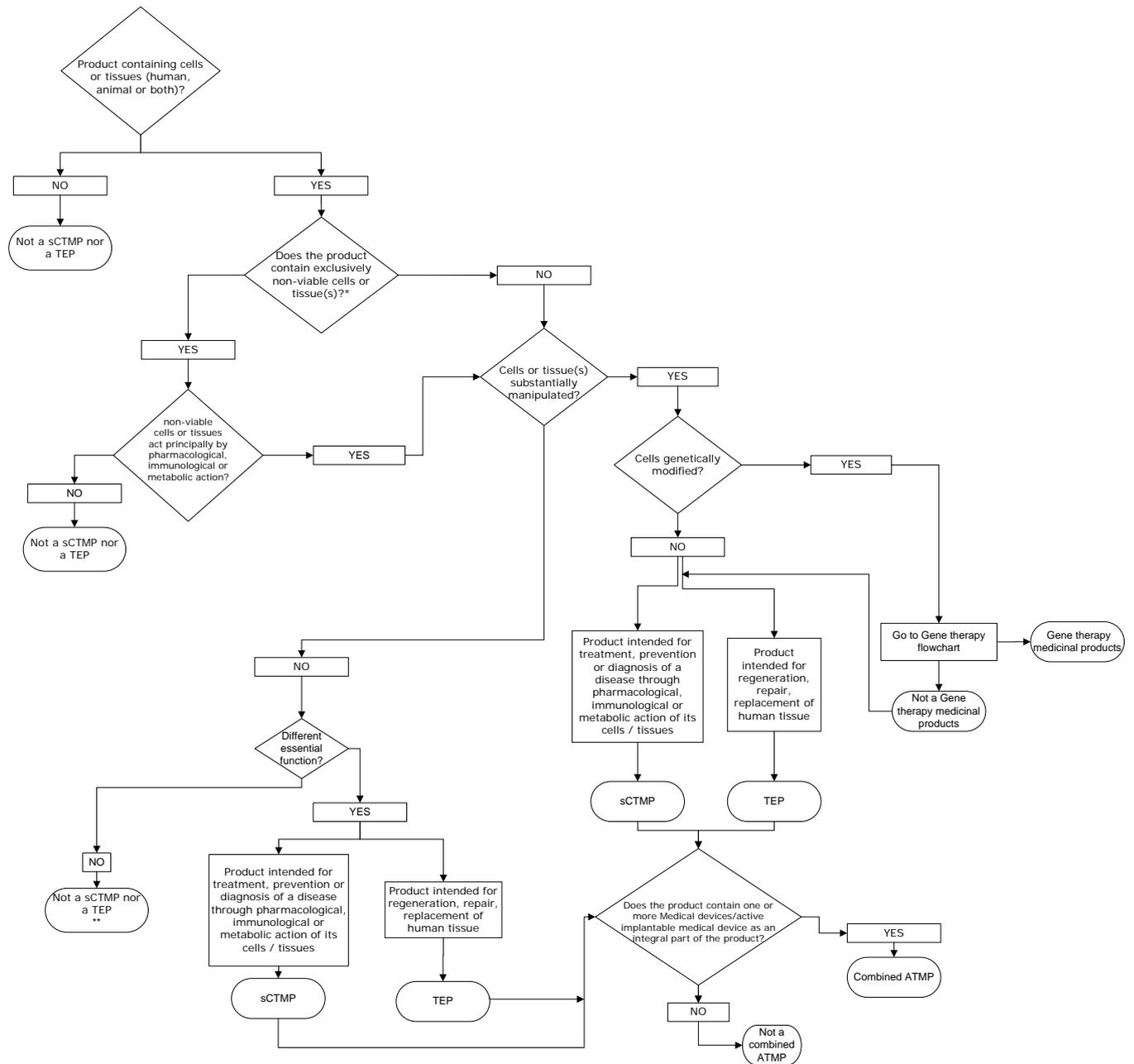
It should be noted that the effect of a tissue engineered product can be transient, e.g. autologous human keratinocytes intended for the treatment of acute burns may only transiently repair the underlying structure and later be replaced.

c) Inclusion and exclusions:

- Products containing or consisting of animal cells or tissues to be administered to humans will always be considered as ATMPs.
- Products containing or consisting exclusively of non-viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, will not be considered ATMPs.

Figure 2. DECISION TREE FOR sCTMP and TEP

The following questions can help applicants to classify their product:



Explanatory notes:

*) see section 2.2.1 on what are considered viable cells. It should be noted that a product containing exclusively non-viable cells/tissue and a medical device / active implantable medical device as an integral part, will be considered a combined ATMP when these non-viable cells/tissues exert the primary action of the combined product. This primary action should be based on the pharmacological, immunological or metabolic action of the non-viable cells/tissues.

***) See section 2.2.4. Criteria for somatic cell therapy medicinal products (sCTMP) and tissue engineered products (TEP)

2.2.5. Criteria for combined ATMPs

A product is classified as a combined ATMP when it fulfils the definitions provided in Article 2(1)(d) of the ATMP Regulation (EC) No 1394/2007 (See Section 2.1 above).

Combined ATMPs incorporate an active substance, i.e. a cellular or tissue 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 combination in the same way as its intended use without additional components. If cells or tissues are not viable these must exert the primary action of the combined product.

Examples of combined ATMPs:

- The expanded autologous chondrocytes seeded onto a collagen membrane and administered, fixed on this membrane, into the joint cartilage lesion. The primary action of the combined product is given by the viable cells that repair the damaged tissue, while the medical device part is a tool that is needed to retain the cells physically to the cartilage defect.
- Autologous osteoprogenitor cells, isolated from bone marrow, are grown within and around a bioresorbable scaffold that acts as physical support. The finished combined product is an integrated product consisting of a cellular component and a matrix. The repairing/replacing effect on the bone defect is accomplished by the living cells that continue to grow within the lesion while the biodegradable matrix is gradually eliminated. However, like in the first example, the matrix still has its intended function at the time of implantation.
- Genetically engineered cells - where a recombinant human gene in a mammalian expression vector is introduced into human cells through transfection and resulting cells are further cultured in vitro - incorporate as an integral part of the product two components, a semipermeable hollow fibre membrane (HFM) capsule and a scaffold of strands of polyethylene terephthalate (PET) yarn. Both components fulfil the definition of medical devices and/or active implantable medical devices as they are required for maintenance of the cells (growth support, delivery of nutrients) and the semipermeable capsule is needed for release of the therapeutic molecule. As the combined product fulfils both definitions of a tissue engineered product and a gene therapy medicinal product, it was classified as a combined gene therapy medicinal product.

It should be noted that normally the medical device should retain its intended purpose / mode of action in the combination to be considered as being "integral part" of the final product and thus qualify this product as a combined product. The CAT has therefore classified some products as non-combined ATMP, where the function of the matrix was no longer considered to be linked to its structural properties. This is discussed further in section 2.3.4 on Combined ATMPs versus non-combined ATMPs.

2.3. Evolving and borderlines areas

The ATMP classification procedure will also have to clarify borderline cases between ATMPs versus non-ATMPs as well as between the different product categories within the ATMP sphere. Below are given examples that illustrate the type of issues that are taken into consideration when assessing borderline cases.

2.3.1. Advanced therapies versus transplants/transfusion

Products consisting of cells or tissues may scientifically be at the border between Tissues and Cells directive (Directive 2004/23/EC) and the ATMP regulation. Cells/tissues harvested and separated by a simple selection method (that does not result in a substantial manipulation of the cells/tissue) and re-administered to fulfil their same essential function will generally be regarded as non-ATMPs. However, depending on whether or not the selection process/method will alter the original characteristics of the cells/tissues may result in classification as ATMPs. Similarly, cells derived from human blood (e.g. lymphocytes) that are substantially manipulated or use for a different essential function are classified as ATMPs.

One example is the recommendation of the CAT that a preparation of human pancreatic Langerhans' islets should not be classified as an ATMP. The CAT considered that, for this preparation, the described process steps do not constitute substantial manipulations for the intended use so that there is no change in the biological characteristics of the islets. In addition, the product was intended to be used for the same essential function in the recipients, be it in the allogeneic or autologous conditions described. This conclusion is, however, not directly applicable to any other pancreatic beta cell products which may be submitted for classification, as they may be derived from very different and more complex process and substantial manipulations, as discussed also in section 2.2.4 (cell-based product consisting of isolated beta-cells embedded in an alginate matrix).

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 use based on (a) different essential function(s) of the cells/tissues. For example, the use of autologous bone marrow-derived progenitor cells intended for treatment of patients with myocardial infarction or other vascular diseases would be considered as different essential function and therefore such products are classified as ATMPs (in this case tissue engineering products) (see section 2.2.4).

It is possible that cell-based products administered in the same anatomical location fall under the definition of ATMP on grounds that it is used for a different essential function. 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, for example, the injection of concentrated bone marrow at the site of bone injury with the aim of healing a bone lesion.

2.3.2. Classification of genetically modified bacteria as Gene therapy medicinal product

The CAT has discussed several examples of genetically modified bacteria which express a human gene sequence in the patient after administration. These products raised difficult questions about the interpretation of the first indent in the definition of gene therapy medicinal product (i.e. that *"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, adding or deleting a genetic sequence"*). The following considerations are relevant in this regard: (i) it could be considered that the genetic sequence is not "added" to human cells, but remains in the bacteria, and equally also the protein it expresses; and (ii) it could be considered that the medicinal product is adding a genetic sequence into humans to elicit a pharmacological effect. However, given that the first indent of the definition does not include the requirement that the repair, replacement, addition or deletion of the genetic sequence is done "at the level of the human cell", the CAT classified this medicinal product as a gene therapy medicinal product. The consideration that prevailed was therefore that a genetic

sequence is administered to humans and that the effect is due to the product expressed from this added genetic sequence.

2.3.3. Gene therapy medicinal product versus cell therapy medicinal product

Another borderline scenario relates to products that are modified by adding a mRNA sequence, for example dendritic cells (DC) electroporated with mRNA in vitro and administered to the patient to elicit a specific immune response. One could argue that the claimed mechanism of action is directly related to the expression of the mRNA encoded antigens to stimulate e.g. tumour specific immune responses. However, due to its relatively short half-life there may be little or no residual mRNA at the time of re-administration of the dendritic cells to the patient. Thus, it can be claimed that a recombinant nucleic acid is not administered to human beings with a view to adding a genetic sequence, but rather the mRNA electroporated DCs could be seen as an intermediate in the manufacturing process where the phenotype is finally altered without alteration of the genotype of the cells. Therefore, the product was considered not to comply with the definition of a gene therapy medicinal product. Instead the CAT considered that the product was a somatic cell therapy product as it consists of cells which were administered to human beings with a view to treating a disease through the immunological action of the modified cell populations.

2.3.4. Combined ATMPs versus non-combined ATMPs

The border between combined or non-combined ATMPs is often discussed in classification procedures. This section should be read in conjunction with the section 2.2.5, which describes the criteria for combined ATMPs. In this regard it is relevant to consider if (i) the medical device is an integral part of the final product (combined) or (ii) if the combined component (although CE marked) is not or no longer used as a medical device but should be considered as an “excipient” in the final formulation of the drug (and therefore not combined).

Below are two examples where the matrix does not retain its original intended structure and/or does no longer function as a medical device and one example where the collagen matrix is acting as a medical device.

- An example of non-combined ATMP can be given with the human endothelial cells cultured in a gelatin matrix and used to treat vascular injury. The product was claimed to reduce the intimal thickening of vessels injured by the frequent procedures of artero-venous grafts and fistula placements in patients that undergo haemodialysis. The underlying mechanism of action is based on the concept that the allogeneic endothelial cells release biological factors that inhibit the intimal hyperplasia, reduce the graft thrombosis, and repair the vascular injury. The gel matrix is a CE marked medical device indicated in surgical procedures as an adjunct to haemostasis. The gel, which is seeded with the cells, contributes to the formulation of the final product. The gel matrix has the function to keep the cells around the vascular injury site to release the therapeutic factors, but it is also contributing in some way to provide the correct signals to the cells. The CAT considered that the porcine gelatine matrix, as a component of this medicinal product, is remodelled by the cells contributing to product efficacy. Thus, the manufacturing process uses the matrix in a different way than its intended use when considered as a medical device. In this formulation (e.g. the porcine gelatine matrix and the human aortic endothelial cells), the matrix was not considered to be a medical device any more. The CAT therefore classified the product as a sCTMP, not combined ATMP.
- A similar situation applies to another example, which is the mixture of pancreatic beta cells and their accompanying endocrine cell populations embedded in an alginate matrix intended for the

treatment of diabetes. The CAT was of the opinion that the inert alginate matrix is reworked by the cells during culture and becomes an integral part of the product that supports to contain/preserve the biological characteristics and functional activities of the cells. The function of the alginate matrix was no longer considered to be linked to its structural properties. The CAT therefore classified the product as a sCTMP, not combined ATMP.

- In contrast, human fibroblasts cultured onto a biodegradable collagen matrix were classified as a TEP, combined ATMP. Here, the matrix is an integral part of the product and it fulfils its function as CE marked medical device when administered to patients.

2.4. Clarifications on procedural aspects information to be submitted by the applicant

In order to facilitate the access to the ATMP classification, the CAT has published the procedural advice for the ATMP classification⁵, which describes the procedure and gives guidance for the steps to be followed by the applicant for the submission of an ATMP classification.

Upon receipt of a valid request⁶, the CAT delivers a scientific recommendation on an ATMP classification after consultation with the European Commission within 60 days.

Sufficient scientific information relevant to the decision is essential to be submitted in order for the CAT to classify a product, e.g. on following areas:

- Active substance: description of active substance (including starting materials, when relevant), any additional substances (e.g. when applicable: structural component such as scaffolds, matrices, biomaterials, biomolecules and/or other components), medical device or active implantable medical device (including information on the classification status of the Medical Device from a Medical Device Competent Authority when applicable).
- Finished Product: qualitative and quantitative (where available) composition, mode of administration, pharmaceutical form and description of the finished product ready for clinical use.
- Mechanism of Action/ Proposed use: claimed mechanism of action, properties (including pharmacological, immunological or metabolic, if applicable), proposed use / indication (including therapeutic, prophylactic, diagnostic). See also section 2.2.1. above. Applicants should provide an in-depth discussion on how the product works and what data are available to support the mechanism of action. This is essential, since the outcome of the classification will depend on the claim the Applicant provides and how strong the evidence is to support it. For example, the CAT was for one product not able to classify it as tissue engineered product or somatic cell therapy medicinal product, since the claim for the mechanism of action was not sufficiently defined, and not enough data (be it data with the product or what is published for that given product class) was presented to support the Applicant's claims.
- Summary of the status of the development of the product: key elements of manufacturing, quality aspects (including description and level of manipulations on cells and tissues, when applicable). Outline of Non-Clinical development and Clinical development relevant for the ATMP classification.

⁵ [Procedural advice on the provision of scientific recommendation on classification of advanced therapy medicinal products in accordance with Article 17 of Regulation \(EC\) No 1394/2007](#)

⁶ For the submission of an ATMP classification, applicants should complete a [Pre-submission request form](#) (selecting in the drop-down menu ATMP-ATMP classification) and the [ATMP Classification Request form and briefing information](#) and return both to: AdvancedTherapies@ema.europa.eu

Depending on the stage of development at which the classification advice is sought, some of the parameters or information requested above may not be finalised. In this case, the target profile and intended product description may suffice.

In addition to the qualitative and quantitative description of the product to be classified, applicants are encouraged to present their views on the classification of products under development. They should discuss any aspects supporting or not the applicability of the pharmaceutical framework for the development and evaluation of the product. Overlapping aspects relevant to medical devices, cosmetics, human tissues and cells, blood products, borderline medical use or other issues should also be highlighted if appropriate.

Details of the regulatory status of the product (including medical device/active implantable device, when applicable), marketing history in EU and non EU countries and information on the current medical use worldwide are requested to complement the overall understanding on the regulatory status of the candidate ATMP.

Applicants can include in the request any additional information or bibliographic references to further substantiate their positions on the classification of their product on the light of legal definitions in force.

ⁱ Article 17(1) of the ATMP Regulation: *Any applicant developing a product based on genes, cells or tissues may request a scientific recommendation of the Agency with a view to determining whether the referred product falls, on scientific grounds, within the definition of an advanced therapy medicinal product. The Agency shall deliver this recommendation after consultation with the Commission and within 60 days after receipt of the request.*
(2). *The Agency shall publish summaries of the recommendations delivered in accordance with paragraph 1, after deletion of all information of commercial confidential nature.*

ⁱⁱ Directive 2001/83/EC Annex I Part IV: *Web link to Directive 2009/120/EC:*
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:242:0003:0012:EN:PDF>

ⁱⁱⁱ Recital 24 of ATMP Regulation: *The Agency should be empowered to give scientific recommendations on whether a given product based on genes, cells or tissues meets the scientific criteria which define advanced therapy medicinal products, in order to address, as early as possible, questions of borderline with other areas such as cosmetics or medical devices, which may arise as science develops. The Committee for Advanced Therapies, with its unique expertise, should have a prominent role in the provision of such advice.*

^{iv} A medicinal product as defined in Article 1(2) of Directive 2001/83/EC, as amended, is:

(a) *Any substance or combination of substances presented as having properties for treating or preventing disease in human beings;*

or

(b) *Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis"*

A biological medicinal product as defined in section 3.2.1.1 (b) of the Annex I to Directive 2001/83/EC: *A biological medicinal product is a product, the active substance of which is a biological substance.*

A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physicochemical-biological testing, together with the production process and its control. The following shall be considered as biological medicinal products: immunological medicinal products and medicinal products derived from human blood and human plasma as defined, respectively in paragraphs (4) and (10) of Article 1; medicinal products falling within the scope of Part A of the Annex to Regulation (EEC) No 2309/93; advanced therapy medicinal products as defined in Part IV of this Annex.