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Reflection paper on classification of advanced therapy medicinal products

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7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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 1394/2007[i] (hereinafter referred as to '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 ATMPs[ii]. The ATMP classification procedure has been established in order to address, as early as possible, questions of borderline with other areas such as cosmetics or medical devices, transplants etc.

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 IV[ii] provide precise legal definitions for ATMPs. As a prerequisite to any further ATMP classification, the product under development has first to be qualified as a biological medicinal product for human use, according to the definitions in the Directive 2001/83/EC[iii]

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 arise[iv].

The ATMP classification is a non-mandatory, free of charge, legally non-binding procedure that helps 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, due to its easy and fast process, the ATMP classification, along with other tools (e.g. ITF briefing meetings[1]), 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). In addition, and depending on the type of product under development, liaison with other committees such as Committee for Orphan Medicinal Products (COMP) and/or Paediatric Committee (PDCO) may be recommended to the applicant. 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 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 at a very early stage 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' where a clear description of the product cannot be provided.

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

In addition, the ATMP classification procedure is only applicable when a product is based on genes, cells or tissues.[2]

If additional scientific information becomes available during the product development which could impact on the previously submitted ATMP classification, the applicant can submit a follow-up request.

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.

Scope

The aim of this reflection paper is to provide guidance on the ATMP classification procedure taking into account the experience gained so far:

- setting forth the legal basis for ATMP classification;
- providing clarification on the scientific grounds applied for the classification of ATMPs;
- providing further clarification on the information to be submitted by applicants for the purpose of the ATMP classification;
- communicating the current status of discussions on some borderline cases and on selected areas where scientific knowledge is fast evolving or experience is limited.

It should be noted that the products cases used in this reflection paper are limited to ATMP classifications assessed by the CAT so far; therefore there might be scenarios which are not covered in the document.

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.

The ATMP Regulation also gives a definition of 'Combined ATMP' which 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:

Gene therapy medicinal product

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

[2] 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 …."

(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.

Somatic cell therapy medicinal product

Somatic cell therapy medicinal product means a biological medicinal product which fulfils the following two 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 is non-exhaustive. Thus, based on scientific considerations, the CAT can also consider any other manipulation as "non substantial". As an example, this has already been done by the CAT for the radiolabelling of leukocytes. This technique, which has been used in clinical practice in a hospital setting since many years, and which has no significant impact on the biological properties of the cells, should not be considered a substantial manipulation. Therefore the CAT has concluded that radioactively labelled leukocytes should not be considered as ATMPs if not otherwise substantially modified.

Further, a '**Tissue engineered product**' 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."

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.

In addition, with regards to **products containing cells or tissues**, Article 2(1)(2) of Regulation (EC) No. 1394/2007 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."

However, 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).

Furthermore, an **advanced therapy medicinal product containing both autologous and allogeneic cells or tissues** shall be considered to be for allogeneic use.

Finally Article 1(5) of Regulation (EC) No. 1394/2007 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 grounds 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 far[3]. These should not be considered as exhaustive and might be subject to change as science evolves.

[3] 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

2.2.1. Claim on the mode of action (MoA)

In this context, the information on the claimed MoA is particularly important in order 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 intended MoA of the product is regeneration, repair or replacement of cells/tissues.

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.

2.2.2. 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 of biological origin 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"*: pending fulfilment of the indent (a) of the definition, the MoA and proposed indication, as claimed by the applicant for the defined products, are of importance when considering the "direct" relationship of the effect to 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 the primary role of the cells intended for the "immune reconstitution" of the patients while the genetic modification was restricted to a second 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 regulatory requirements of GTMP).

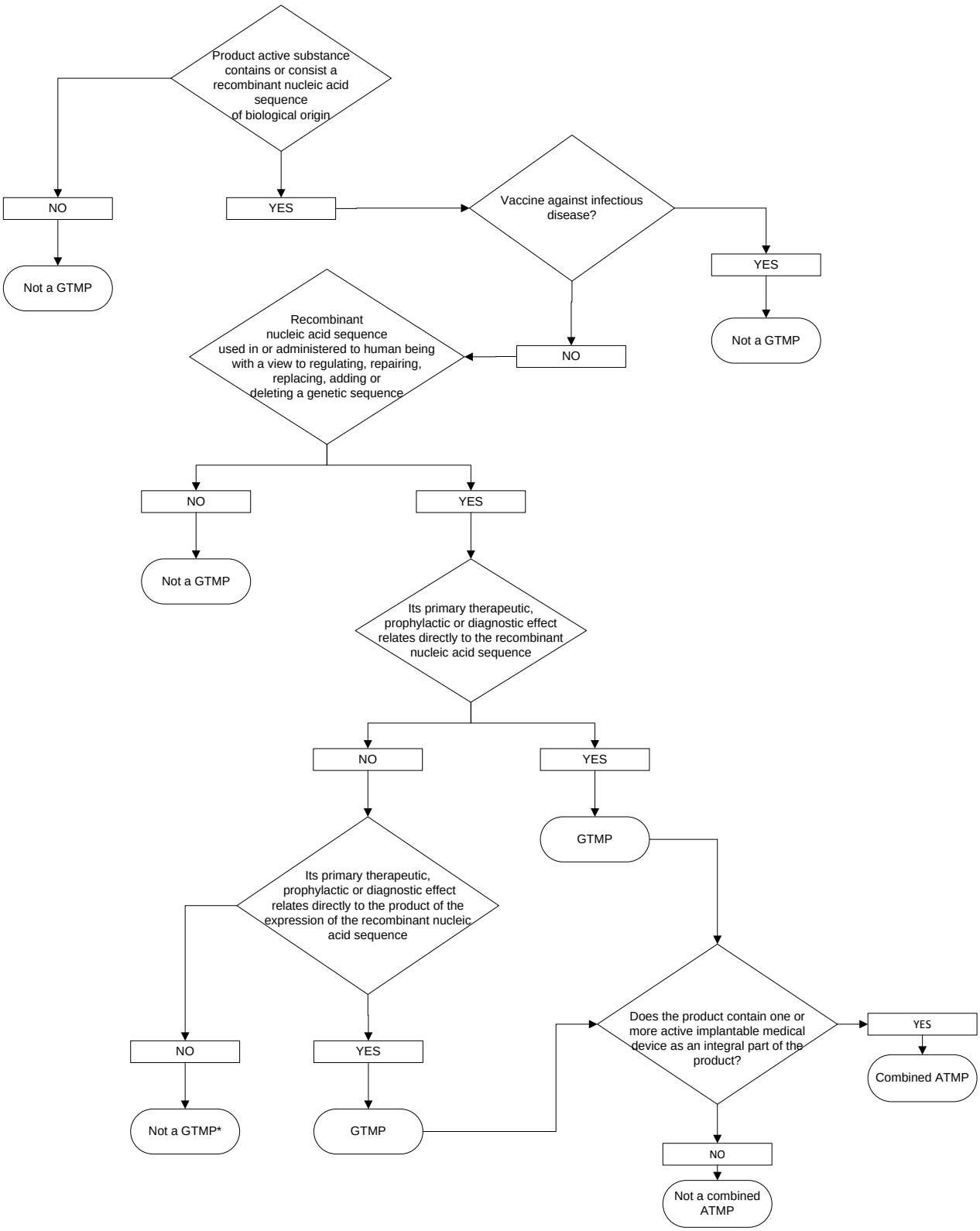
- Genetic manipulation does not necessarily have to take place in the human body, since for example products consisting of genetically modified cells generated *ex-vivo* have also been classified as a gene therapy medicinal product (e.g. autologous CD34+ haematopoietic stem cells (HSCs) transduced with lentiviral vector Lenti-D encoding the human ABCD1 cDNA and autologous CD34+ haematopoietic stem cells (HSCs) transduced with lentiviral vector LentiGlobin encoding the human βA-T87Q-globin gene).

- The legislation also foresaw that *"Gene therapy medicinal products shall not include vaccines against infectious diseases"*. 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 or therapeutic against infectious disease, based on this legal exemption.

  As example, CAT has classified a live recombinant lentiviral vector encoding viral epitopes for therapeutic vaccination against that virus as not being an ATMP in application of the above-mentioned exception. However, as for a previous case illustrated above, it should be stressed that being considered as a recombinant viral vector, the principles and requirements that normally apply to gene therapy medicinal products, may also apply for this product and should be taken into consideration during the development.

Figure 1. DECISION TREE FOR GTMP

The following questions can help applicants to classify their product:



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

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

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:

1. Substantial manipulation: during the manufacturing process the cells or tissue(s) have been manipulated so that their biological characteristics, physiological functions or structural properties have been modified to achieve their intended function. Examples of substantial manipulations include cell expansion (culture), genetic modification of cells, differentiation with growth factors, etc.

   Cell expansion by culturing is currently considered substantial manipulation. Although it may not necessarily lead to immediate changes in cell functionality or the phenotype of the cells before and after culture, it cannot be ruled out that the biological characteristics, physiological function(s) or structural properties of the cells are changed by cell culture. 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 permanent phenotypic changes especially on cell surface proteins. Another example is primary cells, where genotypic changes leading to senescence which begin to appear during in vitro cell culture. Some cell types are shown to be especially sensitive to culture conditions and prone to genotypic alterations.

2. Non-homologous use: the cells or tissues (substantially manipulated or not) are not intended to be used for the same essential function or functions in the recipient as in the donor. A relevant example is represented by autologous bone-marrow derived cells which are only minimally manipulated (e.g. bone-marrow aspirate) but injected in the patient's heart for regeneration of the myocardium. In this context it is important to mention that only the function and mechanism of action of the cells (or cell populations) is crucial with regard to the non-homologous use regardless of the anatomical region where they are applied.

   It is acknowledged that some products for transplantation purposes containing Hematopoietic stem cell (HSC) using either autologous or allogeneic cells do not fall under the ATMP remit, unless they are substantially manipulated and/or used for non-homologous use. However, when these products are not used for the same function in the recipient and the donor they are considered ATMPs. A typical example where a product is used for another function in the recipient as in the donor is not substantially manipulated bone-marrow derived stem cells injected in the myocardium intended for post-myocardial infarction cardiac repair.

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).

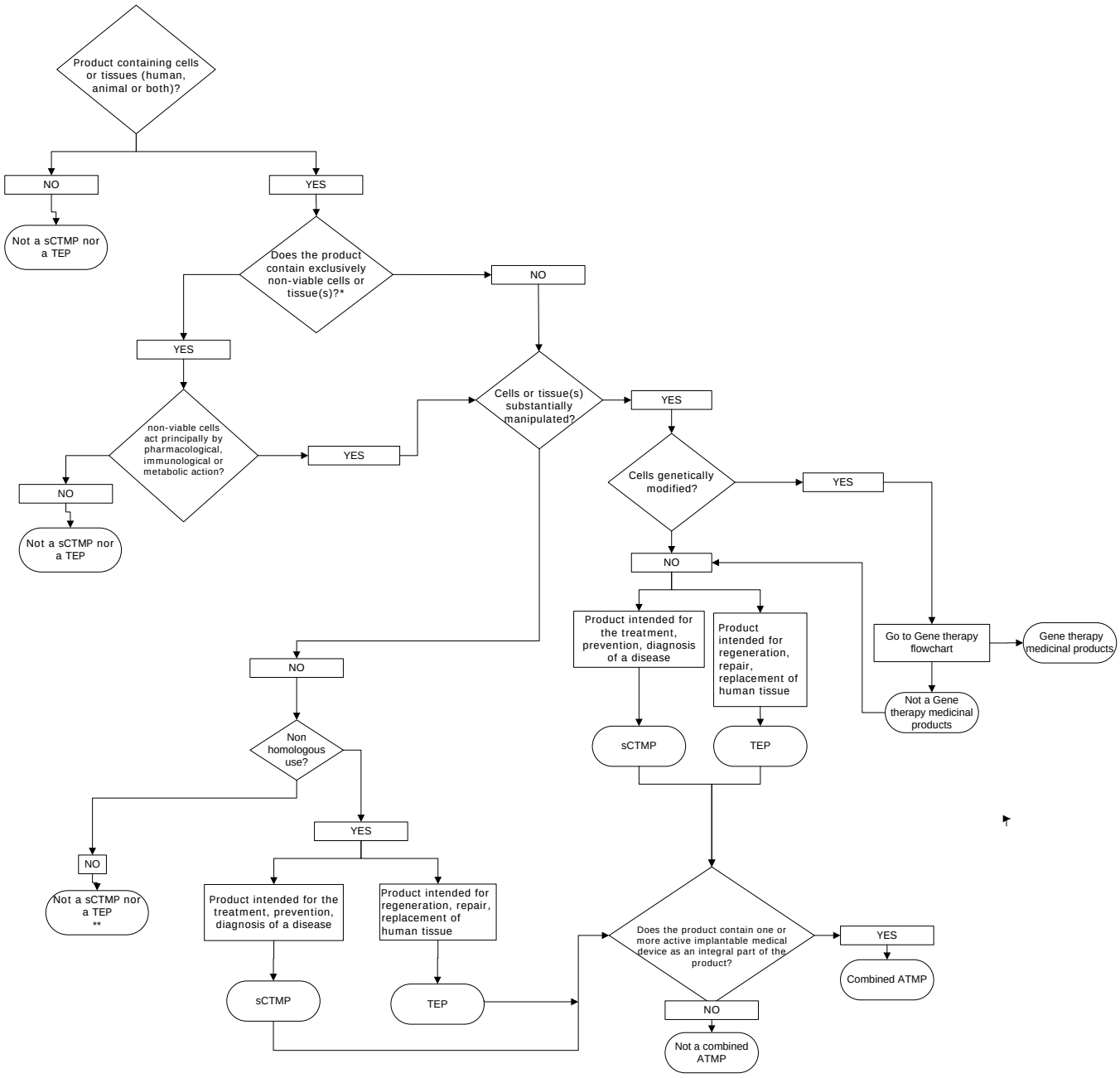
Isolated pancreatic beta cells embedded in an alginate matrix may serve as example for the delineation between somatic cell therapy and tissue engineering: This cell-based product is administered to patients with a view to restoring, correcting or modifying physiological function via a metabolic action of the cells it contains (secretion of insulin). The intended function is not to regenerate, repair or replace an organ or tissue. This decision was driven by the fact that 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. 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. Here, the cells are administered primarily with a view to regenerating, repairing or replacing a human tissue, in this case 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.

Figure 2. DECISION TREE FOR sCTMP and TEP

The following questions can help applicants to classify their product:



Explanatory notes:

**) viable cells in the meaning of the 'Guideline on human cell-based medicinal products' (EMEA/CHMP/410869/2006); i.e.: viable human cells are defined by the European Pharmacopoeia monograph describing the biological assay for nucleated cell count and viability [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 methods provide information on the cytoplasmic membrane integrity which is an important factor to defining cell viability.*

***) See point 2 in section 2.2.3. Criteria for somatic cell therapy medicinal products (sCTMP) and tissue engineered products (TEP):*

2.2.4. 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) 1394/2007 (See Section 2.1 above).

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. 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 original form and function to be considered as being “integral part” of the final product and thus qualify this product as a combined product. CAT has, for example, classified a product containing pancreatic beta cells in an alginate matrix as non-combined ATMP (somatic cell therapy), as the function of the matrix was no longer considered to be linked to its structural properties (see also discussion on borderline cases further below).

Examples of non-combined ATMP:

An example of non-combined ATP can be given with the human endothelial cells cultured in a gelatin matrix and used to treat vascular injury. The applicant claims that the product reduces the intimal thickening of vessels injured by the frequent procedures of artero-venous grafts and fistula placements in patients that undergo hemodialysis. 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 as active substance, contributes to the formulation of the final product. The applicant is supposing that the gel matrix has the function to keep the cells around the vascular injury site to

release the therapeutic factors, but that it is also contributing in some way to provide the correct signals to the cells. The matrix is therefore acting as an active substance of the final product that is therefore considered to be a somatic cell therapy medicinal product and not a combined advanced therapy product.

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 where assigning ATMPs to their respective categories have been subject to debate and will be used as line of thinking for any future similar cases, unless new considerations have to be taken into account.

2.3.1. Advanced therapies versus transplant/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. One example is the recommendation of the CAT that a preparation of human pancreatic Langerhans' islets, in contrast with the previous example discussed above of a cell-based product consisting of isolated pancreatic beta cells embedded in an alginate matrix, should not be classified as an ATMP. 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 elsewhere also in this paper (see previous example in section 2.2.3).

In contrast, some products initially considered as non-ATMP because of an essentially minimal manipulation or maintenance of the initial biological properties and autologous origin have been classified by the CAT as ATMP due to their intended heterologous 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).

2.3.2. Gene therapy medicinal product versus biologicals containing or consisting of GMOs (genetically modified organisms)

CAT discussed several examples of genetically modified bacteria which express a human gene sequence. The decisive factor for classification was to determine whether the medicinal product is administered to human beings with a view to regulating, repairing, replacing adding or deleting a genetic sequence. One could in this case argue that the genetic sequence is not "added" to human cells, but remains in the bacteria, and equally also the protein it expresses. On the other hand, although there is no integration of the genetic sequence into human cells, it may still be claimed that the medicinal product is adding a genetic sequence into humans to elicit a pharmacological effect. It was clarified that the legal definition *"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"* should be read "as is", i.e. without adding for example "to the human body" when interpreting it. Accordingly, the CAT classified this medicinal product as a gene therapy medicinal product, since a genetic sequence is added and 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 is products that are modified by adding a mRNA sequence, for example dendritic cells (DC) electroporated with mRNA in vitro and administrated 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 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 cell-based medicinal products (device acting as “excipient” or no longer acting as device)

The border between combined or non-combined ATMPs is often discussed in classification procedures. Two situations have to be taken into account: first, the medical device is an active integral part of the final product (combined) and, secondly, the combined component (although CE marked) is not considered and used as a medical device but considered as an “excipient” in the final formulation of the drug (and therefore not combined).

Human aortic endothelial cells cultured in a porcine gelatine matrix and intended for the treatment of vascular injury were classified as sCTMP, not combined. The matrix alone has been made available in the European Union under the status of a medical device but 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, already discussed, 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 CAT therefore classified the product as a sCTMP, not combined.

In contrast, human fibroblasts cultured onto a biodegradable collagen matrix were classified as a combined TEP. Here, the matrix is an integral but not an active part of the product, but 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 classification[4], 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 request[5], 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 there 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, 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.

  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 understanding of the regulatory definition of the product 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

[4] 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

[5] 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

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.

References

[i] *Article 17(1) 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 as amended by Directive 2009/120/EC:
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 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"

[iv] 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.*