Scientific Recommendation on classification of Advanced Therapy Medicinal Products Request Form and Briefing Information Article 17 - Regulation (EC) No 1394/2007

The request for scientific recommendation should be sent to AdvancedTherapies@ema.europa.eu (no fee required).

Submission of scientific recommendation should follow the submission dates listing here.

Please send this form in Word format as it is. Do not convert it to PDF.

Note that all the fields followed by a red asterisk (*) are mandatory. If any of the mandatory fields is missing, the request will not be processed.

Green text: additional guidance provided, based on the reflection paper on the classification on advanced therapy medicinal products.

A classification request can be filed with EMA in order to get a scientific recommendation from CAT on whether your product classifies as an ATMP, and more specifically, whether it is a

- *Gene therapy medicinal product*
- *Somatic cell therapy medicinal product*
- *Tissue engineered product*
- *Combined ATMP (combination with a medical device)*

This is a voluntary procedure, which is aimed to provide guidance on which legislation and guidelines are applicable.

There is no expectation that the product is already in nonclinical/clinical development.

The information provided below should be concise, but sufficiently informative to allow an understanding of the manufacturing of the product, its mechanism of action and how it is supposed to be used.

The EMA reflection paper on classification of ATMPs can be found here: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en-0.pdf

Information on the Request*

Company developing the product (applicant)	
Person authorised to communicate on behalf of the applicant	
Proposed product invented name or identifier[1]	
Short descriptor (or name when available) of the proposed active substance[2]	
Brief description of the proposed finished product[3]	

[1] If an invented name is not available, use an adequate identifier (e.g. company internal code) followed by the company name.

[2] The descriptor should identify the key identifying features of the active substance such as, depending on its nature, the gene to be transferred, vector, cells or tissues.

[3] Including, when applicable, devices/structural components being an integral part of the product.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom

Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail AdvancedTherapies@ema.europa.eu **Website** www.ema.europa.eu

Proposed indication	
Proposed advanced therapy medicinal product classification	

Proposed Summary for Public Release

Product description	
Therapeutic area	
Outcome of the scientific recommendation	
Date	

The applicant presents hereafter its understanding of the regulatory definition of the product under development.

The document addresses scientific, legal, regulatory and medical aspects supporting or not the applicability of the pharmaceutical framework for the development and evaluation of the product.

The applicant discusses potentially overlapping aspects relevant to medical devices or cosmetics, human tissues and cells, blood products, borderline medical use or other issues as appropriate.

1. SCIENTIFIC ASPECTS

1.1. Active substance

- Description of active substance (including starting materials, when relevant)*
- Description of any additional substances (e.g. when applicable: structural component such as scaffolds, matrices, biomaterials, biomolecules and/or other components)
- Description of medical device or active implantable medical device (when applicable)

Include information to understand what the Active substance and Finished product is.

- *Information on the starting material – relevant especially for products based on cells/tissue*
- *Description of structural components (scaffolds, devices) and other substances are combined with the cells/tissue.*
- *If you consider that your product is a combined ATMP, make sure that sufficient information is provided on the medical device (MD) part. If the MD is not (yet) CE-marked, include a statement on the fulfilment of the definition of a MD (as per Regulation (EU) 2017/745)*

1.2. Finished Product*

- Qualitative & quantitative composition
- Mode of Administration
- Pharmaceutical form (use standard term as applicable) and description of the finished product ready for clinical use

Provide here information of the composition, pharmaceutical form and mode of administration of the finished product. A quantitative composition might not be possible for early developments.

1.3. Mechanism of Action / Proposed use*

- Claimed mechanism of action
- Properties (including pharmacological, immunological or metabolic, if applicable)
- Proposed use / Indication (including therapeutic, prophylactic, diagnostic)

Provide data and/or literature to substantiate the mechanism of action. The provided information should allow CAT to make a scientific assessment of the product, specifically

- *For GTMP and sCTMP, information on how the genes, cells or tissues act on the body to treat, diagnose or prevent a disease in humans;*
- *for a product based on genes, that the product consists/contains recombinant nucleic acid & that the therapeutic effect is directly related to the gene/gene product (as per the definition of a GTMP)*
- *for a product based on cells or tissues, that the cells/tissues are subjected to substantial manipulation and/or that the cells/tissues are used for a different essential function (as per the definitions of sCTMP / TEP).*
- *For TEP, information how the cells/tissues regenerate, repair or replace a diseased tissue in humans.*

1.4. 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 – see Reg. 1394/2007, Annex I)
- Outline of Non-Clinical development
- Outline of Clinical development
  Note: specify the current stage of development.

It should be clear from the description whether the applicant considers that, in case of cells and tissues, the product is substantially manipulated or not. Also in case of 'minimal' manipulation of the cells, describe all steps. The criteria when a cell is/is not substantially manipulated is described in the legislation and can also be found in the reflection paper on the classification of ATMPs.

"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.".

For products based on genes, provide high level information on the plasmid / vector manufacturing and in case of genetically modified cells, cell processing and transduction steps.

- *It is not needed to include the (provisional) in-process or release test specifications.*

Detailed information on the non-clinical investigations and the clinical studies is not required.

- *A summary of the non-clinical studies (e.g. pharmacodynamic studies) can be used to substantiate the claimed mechanism of action.*
- *If clinical trials are ongoing, indicate the stage of development (e.g. first in man studies, exploratory studies, pivotal clinical trial).*

……..

2. LEGAL AND REGULATORY ASPECTS

2.1. Fulfilment of Article 1(2) of Directive 2001/83/EC (definition of medicinal product)*[4]

Indicate in this section why you are of the opinion that your product is a medicinal product.

For example;

- *Product 'A' fulfils the definition of a medicinal product because the product is intended to treat the following disease in humans: …*
- *Product 'B' fulfils the definition of a medicinal product because it given to human with the view to modify a physiological function via metabolic means. (This wording can be used for tissue engineered products the aim is to repair, replace or regenerate a diseased tissue rather than to treat a specific disease).*

2.2. Fulfilment of Article 2(1)(a-c) of Regulation (EC) No 1394/2007 (definition of advanced therapy medicinal product)*[5]

---

[44] 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"

[55] 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,
- a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,
- a tissue engineered product, i.e. a product which 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, shall be excluded from this definition.

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

Indicate in this section why you are of the opinion that your product fulfils the criteria for an advanced therapy medicinal product. It is important that you address in sufficient detail the different criteria in the definition of a GTMP, somatic CTMP or TEP.

For example;

- *Product 'C' fulfils the definition of an ATMP and more specifically that of a gene therapy medicinal product because it consists of a recombinant nucleic acid (e.g. AAV5 vector encoding the gene for XYZ) and the therapeutic effects of the patients is because of the expression of the XYZ protein.*
- *Product 'D' fulfils the definition of an ATMP and more specifically of a tissue engineered product because the cells are intended to be used for a different essential function: the cells are secreting paracrine factors that result in the regeneration of the tissue.*

Criteria of Substantial manipulation & different essential function: same for sCTMP & TEP
The main difference between sCTMP and TEP is determined on the basis of the intended function of the product. When the product is meant for induction of regeneration/repair eg via secretion of paracrine factors by cells = TEP.

2.3. Fulfilment of Article 2(1)(d) of Regulation (EC) No 1394/2007 (definition of combined advanced therapy medicinal product)[6]

Indicate here whether you consider that your product fulfils the criteria of a combined ATMP. Refer to footnote 6 for a description of the criteria.

For example;

- *Product 'E' is a combined ATMP because it contains living, substantially manipulated, cells and incorporates a scaffold that fulfils the criteria of a medical device.*

Note: As CAT will give a dual classification to combined ATMPs (e.g. TEP and combined ATMP), it is important that section 2.2. is duly completed.

2.4. Fulfilment of Article 2(1) of Directive 2001/83/EC[7] (products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process), if applicable at the current stage of development

This section can be left open in case of product in early development.

2.5. Applicability/Inapplicability of any other potentially relevant EU legislation (e.g Dir. 2004/23/EC on tissues and cells; Dir. 2002/98/EC on human blood and blood components; etc)

This section can be left blank.

- 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.

[66] '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.

[77] Article 2(1) of Directive 2001/83/EC provides that: "*This directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process*."

2.6. Other relevant aspects of European guidelines to be considered

This section can be left blank.

……..

3. REGULATORY STATUS AND CURRENT MEDICAL USE

3.1. Details of regulatory status (including medical (active implantable) device, when applicable) and marketing history in EU and non EU countries*

Note: including copies of decisions or minutes with regulatory authorities (EU and non-EU).

Include high level information only (if applicable)

3.2. Current medical use worldwide

Include high level information only (if applicable)

……..

4. OTHER ASPECTS / BIBLIOGRAPHY

You do not have to submit the articles that you refer to in the bibliography.

……..

5. CONCLUSIONS ON THE REGULATORY POSITIONING OF THE PRODUCT

This section is more relevant for borderline classification: You can include here your conclusion on the classification of your product, summarising the arguments included in sections 2.1 and 2.2 and making reference to specific finding as included in the sections 1.3 (mechanism of action) and 1.4 (manufacturing aspects).

……..