Guidance on Classification of Advanced Therapy Products

Version 1.0

(Draft for comment)

Drug Office

Department of Health

CONTENTS

1. Purpose and Scope

1.1 The aim of this document is to provide guidance on the advanced therapy product ("ATP") classification and on the interpretation of key concepts of the definitions of gene therapy product ("GTP"), somatic cell therapy product ("SCTP") and tissue engineered product ("TEP").

1.2 The scientific information and examples in this guidance are based largely on the experience gained by overseas regulatory authorities so far. These should not be considered as exhaustive and might be subject to changes as science evolves.

1.3 While the general principles for classification of ATPs are set out in this guidance, there are certain products or preparations based on genes, cells or tissues which are generally not classified as ATPs. Examples include:

(a) Whole human blood; or any blood cells unless they have been subject to substantial manipulation or are not intended to be used for the same essential function. Please refer to Section 3 of this guidance for the interpretations of substantial manipulation and same essential function.

(b) Human organs[1], tissues or cells, such as bone marrow, cord blood, cornea, bone, skin, and liver, for transplantation (i.e. use for same essential function), other than those processed with substantial manipulation.

(c) Live human embryo[2] and gametes in human reproductive technology.

(d) Cosmetics, beauty and skin care, and hair products which do not contain any viable cells or tissues, such as topical cosmetics derived from plant or animal stem cell extracts.

(e) Genetically modified organisms used in food.

[1] Under Section 2 of the Human Organ Transplant Ordinance (Cap. 465) ("HOTO"), "organ"— (a) means, except in relation to sections 5 to 7— (i) any human bodily part which— (A) consists of a structured arrangement of tissues; and (B) if wholly removed, cannot be regenerated by the body; (ii) any human bodily part specified in the Schedule; or (iii) any structured arrangement of tissues forming part of any human bodily part mentioned in (a)(i) or (a)(ii); (b) means, in relation to sections 5 to 7— (i) any human bodily part mentioned in paragraph (a)(i) and not specified in the Schedule; or (ii) any structured arrangement of tissues forming part of any human bodily part mentioned in (b)(i). Products or preparations falling within the aforementioned definition of "organ" are subject to the control under the HOTO.

[2] According to Section 2 of the Human Reproductive Technology Ordinance (Cap. 561), except where otherwise stated—(a) embryo means a live human embryo where fertilization is complete; and (b) references to an embryo include an egg in the process of fertilization, and, for this purpose, fertilization is not complete until the appearance of a 2-cell zygote.

1.4 However, products which are not classified as ATPs may still fall within the definition of pharmaceutical product and subject to the regulatory control of the Pharmacy and Poisons Ordinance, CAP. 138 ("PPO") and other relevant ordinances. It is advised to read "*Guidance Notes on Classification of Products as 'Pharmaceutical Products' under the Pharmacy and Poisons Ordinance (Cap. 138)*"[3] on the classification of pharmaceutical products. Below are some examples of products based on genes, cells or tissues, which are generally considered as pharmaceutical products but not ATPs:

(a) Products for medicinal use which are derived from blood or blood constituents and do not contain or consist of cells, such as albumin, coagulating factors, and immunoglobulins.

(b) Vaccines containing viable bacterial cells against infectious diseases, such as BCG vaccine and typhoid vaccine.

(c) Lactobacillus (not genetically modified) for the treatment of diarrhoea.

1.5 Products for veterinary use that are based on genes, cells or tissues are not considered as ATPs. However, they would be subject to the regulatory control of the PPO and relevant ordinances if they fall within the definition of pharmaceutical product.

[3] "*Guidance Notes on Classification of Products as 'Pharmaceutical Products' under the Pharmacy and Poisons Ordinance (Cap. 138)*" is available at https://www.drugoffice.gov.hk/eps/do/en/doc/guidelines_forms/Guide_on_PRClass.pdf.

2. Legal Definitions

2.1 According to the Pharmacy and Poisons Regulations, CAP. 138A ("PPR"), a subsidiary legislation of the PPO, pharmaceutical products must be registered with the Pharmacy and Poisons Board before they can be sold, offered for sale or distributed or possessed for the purposes of sale, distribution or other use in Hong Kong.

2.2 In Hong Kong, ATPs are regulated as pharmaceutical products under the PPO.

2.3 Under the PPO, "pharmaceutical product"—

(a) means a substance or combination of substances that—

(i) is presented as having properties for treating or preventing disease in human beings or animals; or

(ii) may be used in or administered to human beings or animals with a view to—

(A) restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action; or

(B) making a medical diagnosis; and

(b) includes an advanced therapy product.

2.4 Advanced therapy product means any of the following products that is for human use—

(a) a gene therapy product;

(b) a somatic cell therapy product;

(c) a tissue engineered product.

2.5 Gene therapy product—

(a) means a product—

(i) that contains an active substance containing or consisting of a recombinant nucleic acid that may be used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; and

(ii) the therapeutic, prophylactic or diagnostic effect of which relates directly to—

(A) the recombinant nucleic acid sequence it contains; or

(B) the product of genetic expression of that sequence; but

(b) does not include a vaccine against an infectious disease.

2.6 Somatic cell therapy product means a product that—

(a) contains or consists of any of the following cells or tissues—

(i) cells or tissues that have been subject to substantial manipulation so that their biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered;

(ii) cells or tissues that are not intended to be used for the same essential functions in their recipient as in their donor; and

(b) is presented as having properties for, or may be used in or administered to human beings with a view to—

(i) treating, preventing or diagnosing a disease; or

(ii) restoring, correcting or modifying physiological functions,

through the pharmacological, immunological or metabolic action of those cells or tissues.

2.7 Tissue engineered product—

(a) means a product that—

(i) contains or consists of any of the following cells or tissues—

(A) cells or tissues that have been subject to substantial manipulation so that their biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement have been altered;

(B) cells or tissues that are not intended to be used for the same essential functions in their recipient as in their donor; and

(ii) is presented as having properties for, or may be used in or administered to human beings with a view to, regenerating, repairing or replacing a human tissue; but

(b) does not include a product that—

(i) contains or consists of exclusively non-viable human or animal cells or tissues; and

(ii) does not act principally by pharmacological, immunological or metabolic action.

3. General Principles for Classification of Advanced Therapy Product

3.1 ATPs are medicines for human use that are based on genes, cells or tissues. ATP classification is based on the evaluation of whether a particular product falls within one or more of the definitions of GTP, SCTP or TEP.

3.2 To determine whether a particular product is an ATP, all the available product information should be assessed which includes the following aspects:

(a) the active ingredient of the product;

(b) the preparation process of the active ingredient of the product;

(c) the use and mode of action of the product; and

(d) the presentation of the product.

3.3 All the above product information should be taken into account as a whole in the classification assessment. The following paragraphs illustrate how the above information would be assessed and the decision tree in **Appendix 1** can be used to assist in the assessment.

Active ingredient

3.4 In determining whether a product is an ATP, the active ingredient[4] of the product will be first considered.

3.5 For a product to be classified as a GTP, the product should contain an active substance containing or consisting of a recombinant nucleic acid. The nucleic acid sequence may be carried by a vector, by genetically modified cells, tissues or organisms, or by other means of delivery.

3.6 For a product to be classified as a SCTP or TEP, the product should contain or consist of cells or tissues. The cells or tissues may be from human[5] or animal origin, or both, may be viable or non-viable, and may or may not be substantially manipulated.

[4] ATPs may incorporate one or more medical device(s) as an integral part of the products.

[5] An ATP containing "organ" within the definition under the Human Organ Transplant Ordinance (Cap.465) ("HOTO") is also subject to the regulation under the HOTO. Definition of "organ" is set out in Footnote 2. If the ATP falls within the definition of "regulated product" under the HOTO, exemption from the application of the whole or any part(s) of the HOTO may be applied. According to Section 7A of the HOTO, "regulated product" means a product containing any structured arrangement of tissues that falls within the definition of "organ" and has been subjected to processing. Details regarding the application for exemption, please refer to the website at https://www.dh.gov.hk/english/useful/useful_hot_exemption/useful_hta.html.

Preparation process of the active ingredient

3.7 In determining whether a product falls within the definition of SCTP and TEP, the preparation process of the cells and tissues will be considered. If a product contains or consists of the cells and tissues that are substantially manipulated, the product may be classified as an ATP.

3.8 As stipulated in the Schedule of the PPO, the following processes are NOT substantial manipulations:

- Cutting
- Grinding
- Shaping
- Centrifugation
- Soaking in antibiotic or antimicrobial solutions
- Sterilization
- Irradiation
- Cell separation, concentration or purification
- Filtering
- Lyophilization
- Freezing
- Cryopreservation
- Vitrification

As such, preparation processes which are not listed in the Schedule are generally considered as substantial manipulation.

3.9 Substantial manipulation refers to a product preparation process which would alter the biological characteristics, physiological function or structural properties of the cells or tissues that the product contains or consists of.

3.10 Examples of common manipulation process that are considered substantial and the rationale behind are listed below:

- Cell expansion. Induction of cell proliferation during cell culture could change their biological characteristics and structural properties. The change could be immediate in functionality or phenotype of the cells, or augmentation in their desired function. Besides, some techniques applied for detachment of adherent cells during expansion might also lead to phenotypic changes especially on cell surface proteins.

- Enzymatic digestion for release of cells from tissues. In the process of releasing cells from a tissue by enzymatic digestion, functional integrity of tissue units are lost

and cell-cell contacts are disrupted. The digestion destroys tissue architecture and cells in a cell suspension cannot regain the destroyed functional interactions.

Other examples of substantial manipulation include genetic modification of cells and cell differentiation or activation by growth factors.

Use and mode of action

3.11 According to the definitions of GTP (i.e. the therapeutic, prophylactic or diagnostic effect of which relates directly to the recombinant nucleic acid sequence or the product of genetic expression of that sequence), SCTP and TEP (i.e. cells or tissues that are not intended to be used for the same essential functions in their recipient as in their donor), in determining whether a product is classified as an ATP, the use, the mode of action and the relevancy of the use and the mode of action of the product will be considered.

3.12 A product containing recombinant nucleic acid sequence will be classified as a GTP provided that the recombinant nucleic acid sequence it contains is used in or administered to human beings in order to regulate, repair, replace, add or delete a genetic sequence and; the therapeutic, prophylactic or diagnostic effect of the product directly relates to that sequence or the product of genetic expression of that sequence.

3.13 Regulation, repair, replacement, addition or deletion of a genetic sequence may take place after a GTP is used in or administered to the human body, such as using a viral vector to transfect human cells *in vivo*. The manipulation of a genetic sequence may also take place before a GTP is used or administered, such as addition of a genetic sequence to cells *ex vivo* before transfusion to human body.

3.14 The mode of action and proposed use are relevant 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.

3.15 For a product containing or consisting of cells or tissues, if there is no substantial manipulation involved in the preparation process, the classification would be based on the essential function of the cells or tissues. A product containing non-substantially manipulated cells or tissues that are used for the same essential function (i.e. homologous use) is not considered as an ATP, whereas it may be classified as a SCTP or TEP if the cells or tissues are not used for the same essential function (i.e. non-homologous use).

3.16 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.

3.17 Examples of homologous use and non-homologous use are illustrated below:

- Bone marrow cells or peripheral blood cells used for haematopoietic or immune reconstitution are homologous use, whereas other clinical uses of those cells such as applying to injured bone with a view to healing of bone lesion would be considered non-homologous use because the original function are not maintained.
- Adipose cells transplanted to fat tissue is homologous use, whereas the cells transplanted to other than fat tissue would be non-homologous use because function(s) of the cells applied to a different anatomical or histological environment cannot be assumed as the same as in the original environment.
- Replacement of cornea or pancreatic islets is considered homologous use because the tissue as a whole or the functional unit of the tissue is transplanted and their essential function are maintained.

3.18 If a product contains or consists of cells or tissues that have been subject to substantial manipulation or are intended for non-homologous use, the product will be classified as either a SCTP or TEP based on the claimed mode of action in association with its intended use. The product intended for treatment, prevention or diagnosis of a disease, or restoration, correction or modification of physiological functions through pharmacological, immunological or metabolic action is a SCTP, whereas the product intended for regeneration, repair or replacement of human tissues is a TEP. For example, a substantially manipulated adipose-derived mesenchymal stem cells product will be classified as a SCTP if it is used for treating an autoimmune disease through immunomodulation, whereas it will be classified as a TEP if it is used for repairing a bone fracture.

3.19 In case the product contains or consists exclusively of non-viable human or animal cells or tissues and it does not act principally by pharmacological, immunological or metabolic action, it will not fall within the definition of SCTP or TEP. For example, a non-viable animal heart valve for replacement of a heart valve in human body.

Presentation of the product

3.20 As considering whether the use of the product falls within the definition of ATP, the context in which the claims of usage made in the labelling, packaging/package insert, promotional materials and the overall presentation will be taken into account.

3.21 Some words or phrases may present the product as having properties for treating or preventing of disease, for restoring, correcting or modifying physiological functions, or for

regenerating, repairing or replacing a human tissue. These claims may indicate association of medicinal use.

3.22 The dosage form and instruction for administration should also be considered. For example, a cell and tissue product designed as parenteral dosage form and is indicated to be administered by injection or infusion (i.e. medical procedure) to human may indicate association of medicinal use.

3.23 It should be noted that the descriptions of the product are also subject to the regulatory control under the Trade Description Ordinance (Cap. 362). A product carrying a false trade description[6] may contravene the said Ordinance.

3.24 Each product should be assessed individually. ATP classification of one product may not be directly applicable to other products which may be from a different origin or prepared using different processes or manipulation steps, or for different indication, etc.

3.25 Some illustrative examples of different ATP categories are provided in **Appendix 2**.

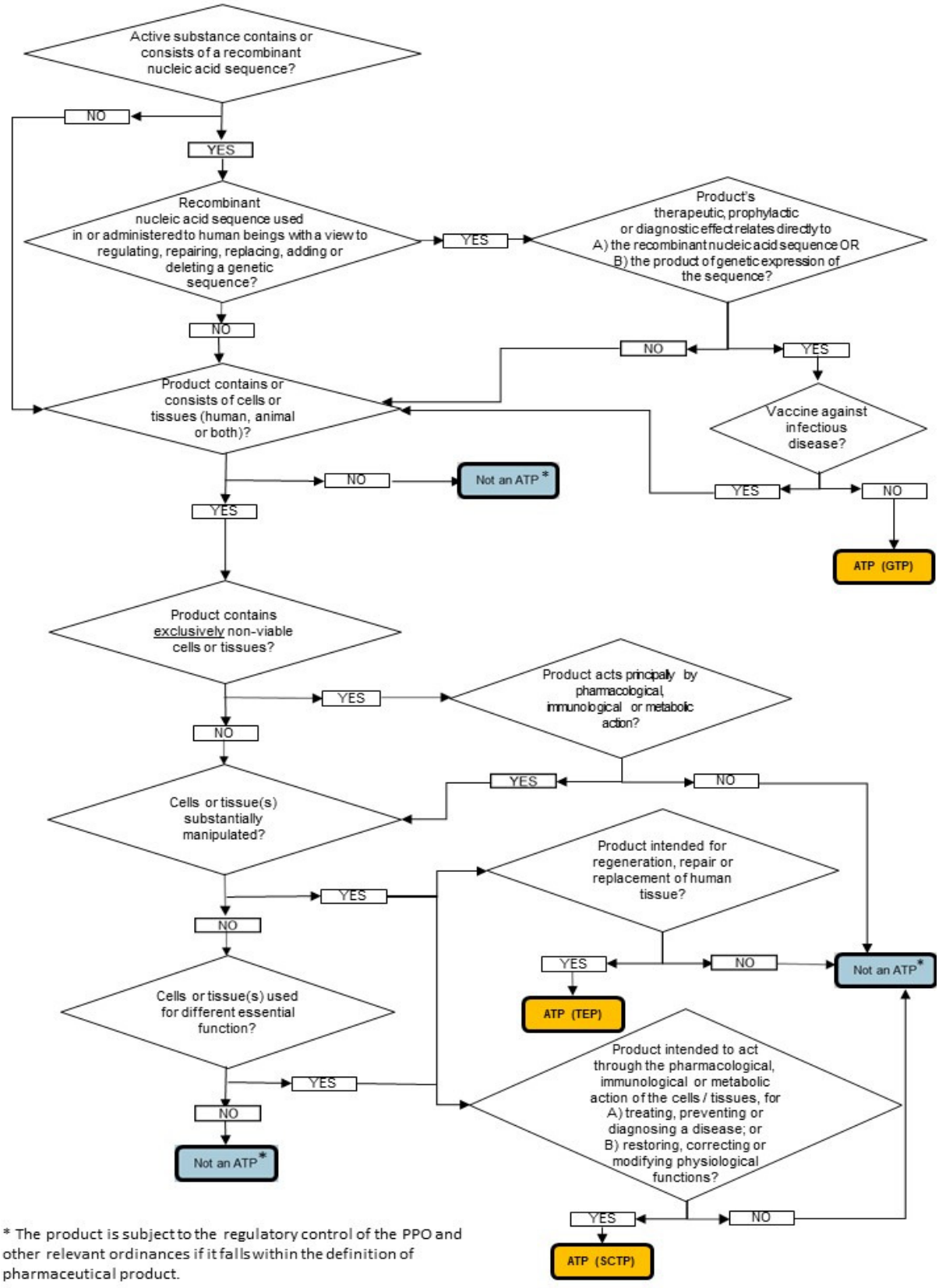
[6] Under Section 2 of the Trade Description Ordinance (Cap. 362), "false trade description" means (a) a trade description which is false to a material degree; or (b) a trade description which, though not false, is misleading, that is to say, likely to be taken for a trade description of a kind that would be false to a material degree.

Disclaimer

This guidance is only intended to provide general information on the classification of products as ATPs and should not be considered as a substitute for legal or other professional advice. Whenever necessary, please refer to the Pharmacy and Poisons Ordinance and Regulations for details of the requirements. The Department of Health accepts no liability for any loss or damaged caused, arising directly, or indirectly, in connection with reliance on the contents of this guidance.

Appendix 1 Classifying a Product as an ATP

The following decision tree may provide questions into consideration for classification of a product.



* The product is subject to the regulatory control of the PPO and other relevant ordinances if it falls within the definition of pharmaceutical product.

Appendix 2 Illustrative Examples

The examples are for illustrative purpose and should not be understood as generic classifications for certain classes of ATPs.

Some of the examples are taken from the European Medicines Agency website which aligns with our interpretation, while other examples demonstrate our interpretation of certain products. For those products which are not classified as ATPs, they may still fall within the definition of pharmaceutical product and subject to the regulatory control of the PPO and other relevant ordinances.

Examples of products that are classified as ATPs

Case 1	
Product Description	Lactobacillus, genetically modified with a plasmid containing a gene sequence for a protein promoting the healing of skin wounds and an inducible promoter. The product is intended for treatment of chronic skin wounds in diabetic patients.
Comments	• The active substance containing a recombinant nucleic acid administered to human beings with a view to adding a genetic sequence. • The product is not a vaccine against infectious disease. • Its therapeutic effect relates directly to the product of genetic expression of the recombinant sequence. The product falls within the definition of GTP.
Case 2	
Product Description	*In vitro* transcribed mRNA molecules encoding melanoma-associated antigens (mRNA vaccine). The product is intended for treatment of malignant melanoma.
Comments	• The active substance containing a recombinant nucleic acid administered to human beings with a view to adding a genetic sequence.

	• The product is not a vaccine against infectious disease. • Its therapeutic effect relates directly to the product of genetic expression of the recombinant sequence. The product falls within the definition of GTP.
Case 3	
Product Description	Human bone marrow-derived cells, *in vitro* cultured. The product is intended for allogeneic transplantation of treatment of leukaemia.
Comments	• The active substance does not contain a recombinant nucleic acid. • The product consists of viable human cells and the cells that have been subject to substantial manipulation (i.e. cultured and expanded). • The product is administered to human beings with a view to treating a disease through the pharmacological, immunological or metabolic action of the cells. The product falls within the definition of SCTP.
Case 4	
Product Description	T cells, genetically modified with additional genetic sequence for chimeric antigen receptor (CAR-T cells) against cell membrane protein specific to leukaemia cells. The product is intended for treatment of leukaemia.
Comments	• The active substance contains a recombinant nucleic acid administered to human beings with a view to adding a genetic sequence. • Its therapeutic effect relates directly to the product of genetic expression of the recombinant sequence. *At the same time* • The product consists of viable human cells and the cells that have been subject to substantial manipulation. • The product is administered to human beings with a view to treating a disease through the pharmacological, immunological or metabolic action of the cells.

	The product falls within the definitions of both GTP and SCTP.
Case 5	
Product Description	Human bone marrow-derived cells, *in vitro* cultured. The product is intended for treatment of articular cartilage damage and tendon injuries.
Comments	• The active substance does not contain a recombinant nucleic acid. • The product consists of viable human cells that have been subject to substantial manipulation (*in vitro* cultured) • The product is intended for regeneration, repair or replacement of human tissue. The product falls within the definition of TEP.

Examples of products that are NOT classified as ATPs

Case 6	
Product Description	Pancreatic islets isolated (in functionally intact tissue units) and directly encapsulated by biomaterials. The product is intended for treatment of severe form of Type 1 diabetes.
Comments	• The active substance does not contain a recombinant nucleic acid. • The product consists of viable human cells or tissues which have not been substantially manipulated. • The cells and tissues are used for the same essential function. The product does not fall within the definition of GTP, SCTP or TEP.
Case 7	
Product Description	Stem cell serum and essence with extracted peptides. The product does not contain or consist of any viable cells or tissues. The product is intended for moisturizing the skin and provide nutrients to the skin.
Comments	• The product contains peptides, which are extracted from stem cells, to provide nutrients to the skin. • It does not contain recombinant nucleic acid sequence, cells or tissues.

	The product does not fall within the definition of GTP, SCTP or TEP.
Case 8	
Product Description	Platelet-rich plasma. The product is intended for enhancing the healing process.
Comments	• The product does not contain recombinant nucleic acid sequence, cells or tissues. • Platelet-rich plasma contains mostly platelets which are anucleate and not considered as cells. The product does not fall within the definition of GTP, SCTP or TEP.
Case 9	
Product Description	Animal heart valve, dissected from pig and rendered non-viable. The product is intended for replacement of heart valve in human body.
Comments	• The active substance does not contain a recombinant nucleic acid. • The product consists of animal cells or tissues and are exclusively non-viable. • The non-viable cells or tissues provide structural support. They do not act principally by pharmacological, immunological or metabolic action. The product does not fall within the definition of GTP, SCTP or TEP.

Reference

1. European Medicines Agency. (2015). Reflection Paper on classification of advanced therapy medicinal products (EMA/CAT/600280/2010 rev.1).

Document Information

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1.0	23.10.2020	First version (Draft for comment)

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