EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CAT's views on classification of ATMPs

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European body of legislative texts

The definition of ATMPs is laid down in Reg 1394/2007 modifying Dir 2001/83

Four Different types of ATMPs:

1. **Gene Therapy medicinal products** (defined in Annex I part IV of Dir 2001/83 amended by Dir 2009/120)
2. **Cell Therapy medicinal products** (defined in Annex I part IV of Dir 2001/83 amended by Dir 2009/120)
3. **Tissue engineered products**
4. **Combined ATMPs**

1. Gene Therapy Medicinal Product (GTMP)

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

(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.**

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,

— vitrification.

3. Tissue engineered product

— 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:

— the cells or tissues have been **subject to substantial manipulation**,

— the cells or tissues are **not intended to be used for the same essential function** or functions in the recipient as in the donor.

4. Combined advanced therapy medicinal product

— 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.

Specific issues from art 2 REG 1394/2007

In case a product falls within the definition of a gene therapy medicinal product **and** a somatic cell therapy medicinal product **or** a tissue engineered product:

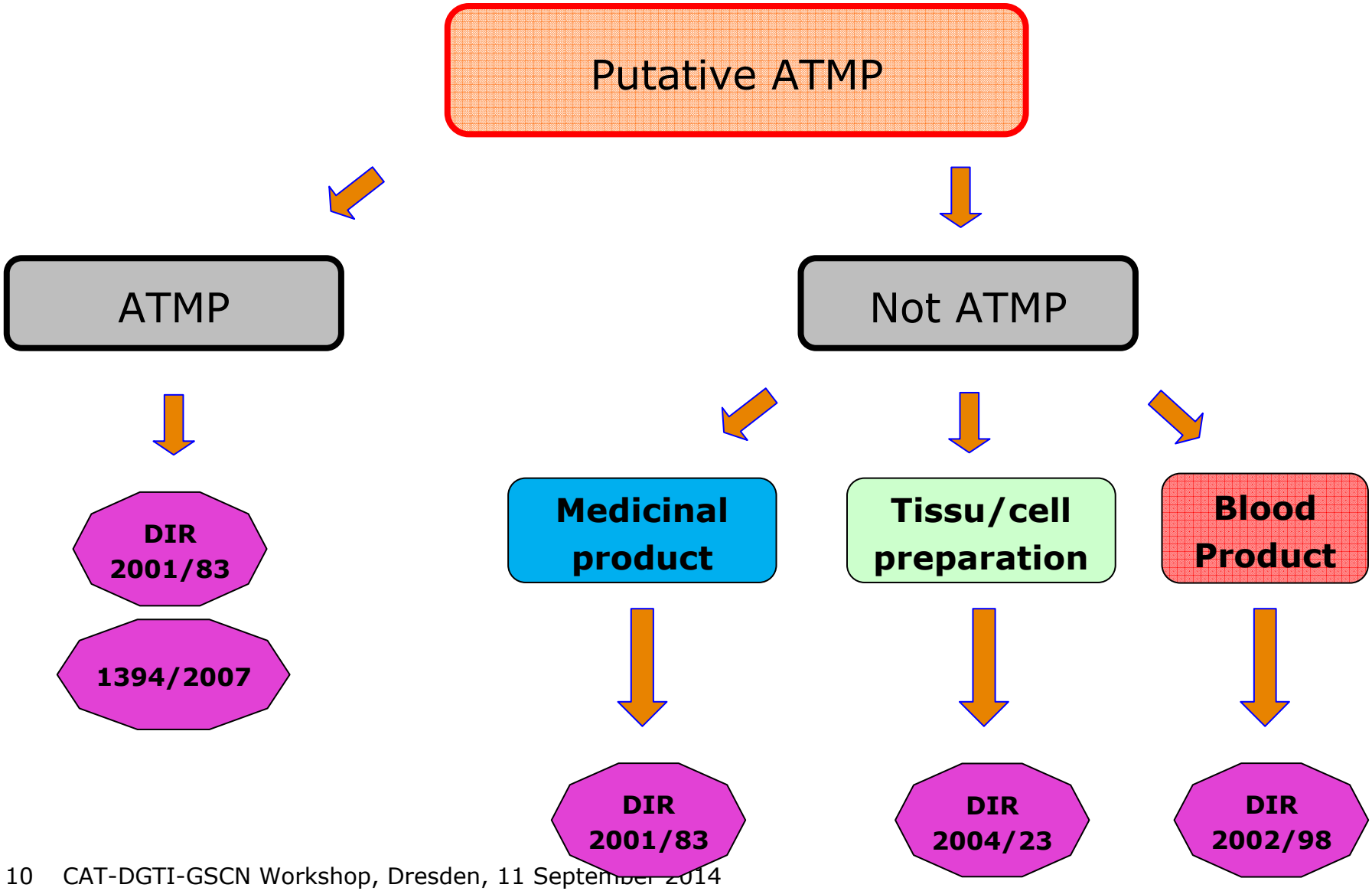
GTMP > CTMP / TEP

In case a product falls within the definition of a somatic cell therapy medicinal product and a tissue engineered product:

TEP > CTMP

CAT is responsible for classification of ATMPs.

If a product is not considered an ATMP, it is not in CAT's remitt to classify this product

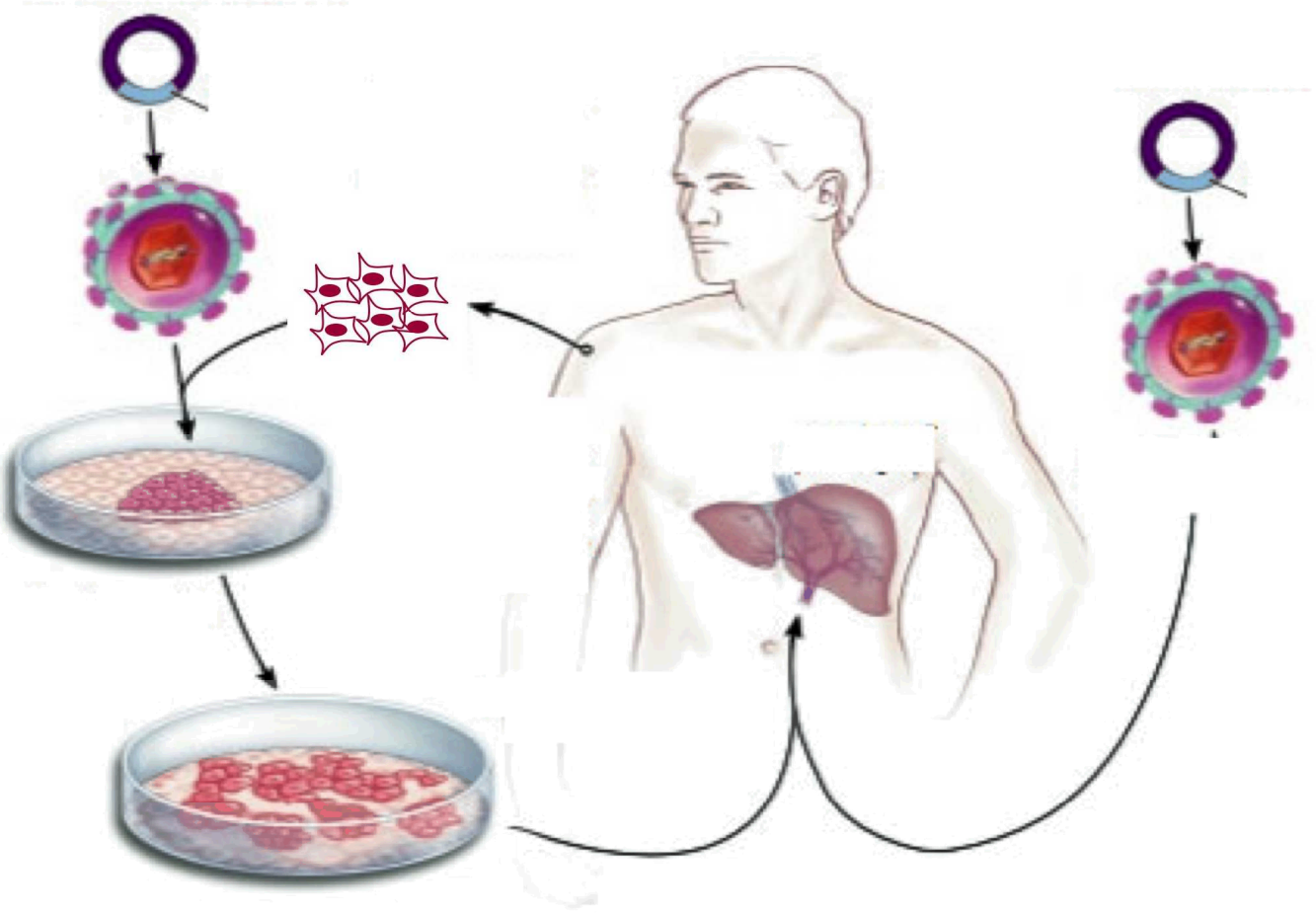

Putative ATMP
ATMP
Not ATMP
DIR 2001/83
1394/2007
Medicinal product
Tissu/cell preparation
Blood Product
DIR 2001/83
DIR 2004/23
DIR 2002/98

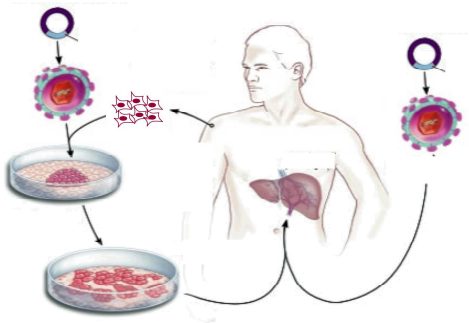
Examples

Gene Therapy Medicinal Products

Ex vivo Gene therapy

In vivo Gene therapy





- ✓ Live recombinant lentiviral vectors encoding HIV epitopes to be used for HIV vaccination
- ✓ Intended for the treatment of infectious diseases
- ✓ **Not ATMP**
- ✓ 27/05/2011

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

- ✓ Pseudomonas aeruginosa bacteria genetically modified to secret oncoproteins of Merkel cell carcinoma
- ✓ Intended for treatment of merkel cell carcinoma due to MCV infection
- ✓ **Gene-therapy medicinal product**
- ✓ 12/04/2013

Therapeutic treatment, not prevention against an infectious disease

- ✓ Haploidentical donor T lymphocytes genetically modified to express HSV-Tk gene
- ✓ adjunctive treatment post bone marrow transplantation in patients with high risk acute leukaemia
- ✓ **Somatic cell therapy medicinal product**
- ✓ 16/10/2009

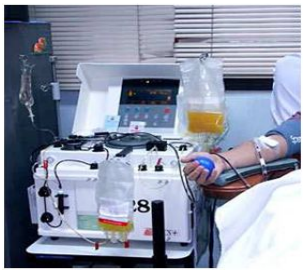
its therapeutic, prophylactic or diagnostic **effect relates directly to the recombinant nucleic acid sequence** it contains,

Examples

Cell Based Medicinal Products

- ✓ Substantial manipulation
- ✓ Homologous vs non-homologous use

Hematopoietic stem cells for bone marrow transplantation not manipulated for homologous use



Apheresis

Cell therapy unit

Non substantial manipulations

Thawing and washing

Administration

Homologous vs/Non homologous use

Reflection paper on classification of ATMPs EMA/CAT/600280/2010

- The classification is based on the essential function of the cells.
- The cells are used to maintain the **original function** in the **same anatomical or histological environment**
- Transplantation of a **tissue to another location** in the **same anatomical or histological environment** to achieve the **same essential function** is also considered as homologous use. (e.g. islets transplantation)

Stromal Vascular Fraction

- ✓ Autologous, non-manipulated lipoaspirate containing adipocytes and stromal vascular fraction
- ✓ intended to act as a natural autologous lipofiller
- ✓ **Was classified as Not ATMP in 2012**

Could be considered now as somatic cell therapy if manufacturing process is considered a substantial manipulation

Non homologous use

- ✓ Bone marrow-derived autologous CD34 cells
- ✓ Intended for improvement of heart function in patients with refractory angina and chronic myocardial ischemia

- ✓ **Tissue-engineered product**
- ✓ 22/03/2012

Non homologous use

- ✓ Autologous bone marrow cell aspirate in autologous plasma
- ✓ Intended for treatment of osteoarthrosis and osteochondral lesion
- ✓ **Now considered as Tissue-engineered product**
- ✓ 28/05/14

Formerly classified as non ATMP

Substantial manipulation Sorted lymphocytes (I)

- ✓ Product consisting of naturally occurring antigen-specific CD8+ donor lymphocytes isolated with streptamers
- ✓ Intended for the treatment of infectious diseases
- ✓ **Not an ATMP**
- ✓ 26/01/2010

Substantial manipulation Sorted lymphocytes (II)

- ✓ Naturally-occurring allogeneic donor lymphocytes (derived from a leukapheresis, bone marrow or a whole blood product) that are enriched for antigen-specific CD4+ and CD8+ T cells using the Cytokine Capture system (IFN-gamma) **after peptide stimulation**.
- ✓ Intended for treatment of therapy-refractory infectious and infection-related diseases and pre-emptive and prophylactic treatment of infectious and infection-related diseases
- ✓ **Somatic cell therapy medicinal product**
- ✓ 26/01/2010

stimulation is not a non substantial manipulation.

Examples of substantial manipulations

- ✓ cell expansion (culture),
- ✓ genetic modification of cells,
- ✓ differentiation/activation with growth factors
- ✓ enzymatic digestion (if it changes cell characteristics)

CONCLUSION

- ✓ CAT classification is not binding. However it will apply for marketing autorisation.
- ✓ CAT classification only applies to a defined product
- ✓ The applicants are encouraged to contact to the CAT as early as possible and to present their views on the classification of products under development

Reflection paper on classification of ATMPs
EMA/CAT/600280/2010 20 june 2014