WHAT ARE ATMPs?

Clarifying misconceptions

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12th June 2020

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Why are we here?

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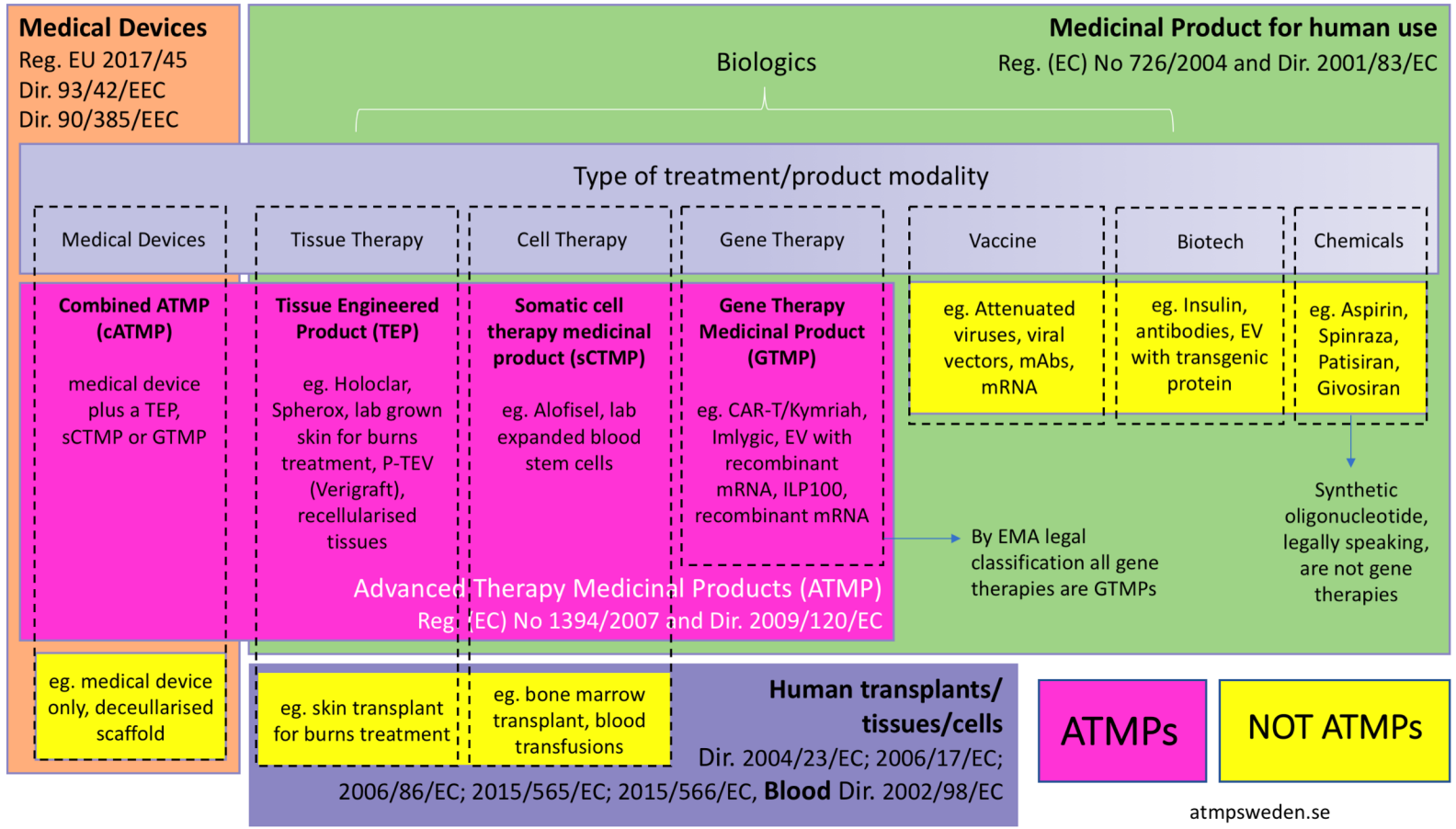
Regulatory language can be difficult to understand

This presentation attempts to clarify common misconceptions in what is classified as an ATMP

By the end of this presentation we hope you will be able to;

- understand this schematic (atmpsweden.se)
- have the chance to ask questions

We start by breaking down the schematic…



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Defining treatment modalities

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What types of technologies are we discussing?

Increasing complexity

Biologics

Type of treatment/product modality

Medical Devices	Tissue Therapy Ø > 100 µm	Cell Therapy Ø 10-50 µm	Gene Therapy	Vaccine	Biotech Ø 10 nm	Chemicals Ø 1 nm
Addition of non-biological structure • Scaffolds • Medical device	Addition of tissues; • Autologous • Allogeneic • xenogeneic	Addition of cells; • Autologous • Allogeneic • xenogeneic	Addition of; • recombinant genetic sequence • Genetic modification	Attenuated viruses, viral vectors, mAbs, mRNA	Recombinant proteins eg. mAbs, insulin, drug-antibody conjugates, fusion proteins	Synthetic small or complex molecules

Not all ATMPs

By EMA legal classification all gene therapies are ATMPs

Synthetic oligonucleotides, legally speaking, are not gene therapies

Regulations around ATMPs

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Medical Devices
Reg. EU 2017/45
Dir. 93/42/EEC (medical device)
Dir. 90/385/EEC (active implantable medical device)

Borderline heirarchy consideration GTMP > TEP > sCTMP

Medicinal Product for human use
Reg. (EC) No 726/2004 and Dir. 2001/83/EC

Biologics

Type of treatment/product modality

Medical Devices	Tissue Therapy	Cell Therapy	Gene Therapy	Vaccine	Biotech	Chemicals
Combined ATMP (cATMP)	**Tissue Engineered Product (TEP)**	**Somatic cell therapy medicinal product (sCTMP)**	**Gene Therapy Medicinal Product (GTMP)**			

Advanced Therapy Medicinal Products (ATMP)
Reg. (EC) No 1394/2007 and Dir. 2009/120/EC

Human transplants/ tissues/cells
Dir. 2004/23/EC; 2006/17/EC; 2006/86/EC; 2015/565/EC; 2015/566/EC, **Blood** Dir. 2002/98/EC

ATMPs

NOT ATMPs

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Legal definition - Medicinal Product

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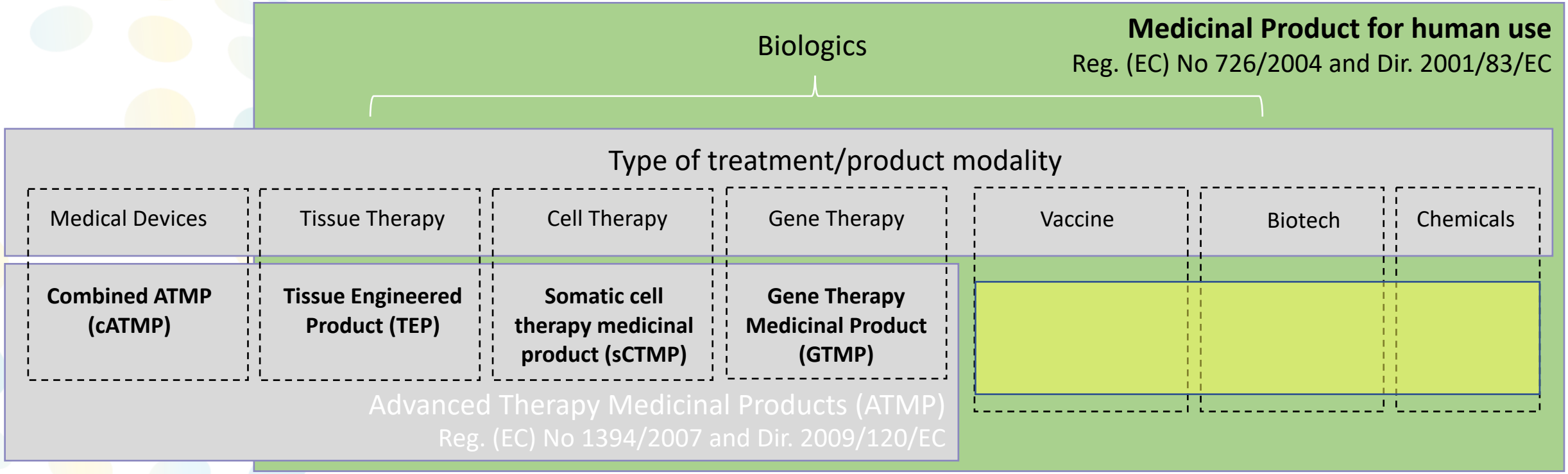
a) any substance or combination of substances presented for treating or preventing disease in human beings; or
b) any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings.

Medicinal product for human use: most products Market authorization by EMA - Applicable for ATMPs



Medical Devices v combined ATMPs

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Medical Devices
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Addition of non-biological structure - scaffolds/Medical device

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Combined ATMP (cATMP) medical device plus a TEP, sCTMP or GTMP	**Tissue Engineered Product (TEP)**	**Somatic cell therapy medicinal product (sCTMP)**	**Gene Therapy Medicinal Product (GTMP)**			

Advanced Therapy Medicinal Products (ATMP)
Reg. (EC) No 1394/2007 and Dir. 2009/120/EC

Any medical device combined with a TEP, sCTMP or GTMP is a combined ATMP

Borderline heirarchy consideration
GTMP > TEP > sCTMP

Legal definition - Gene Therapy Medicinal Product (GTMP)

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Annex I, part IV of Dir. 2001/83/E

Biological medicinal product with 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.

GTMP: in-vivo v ex-vivo

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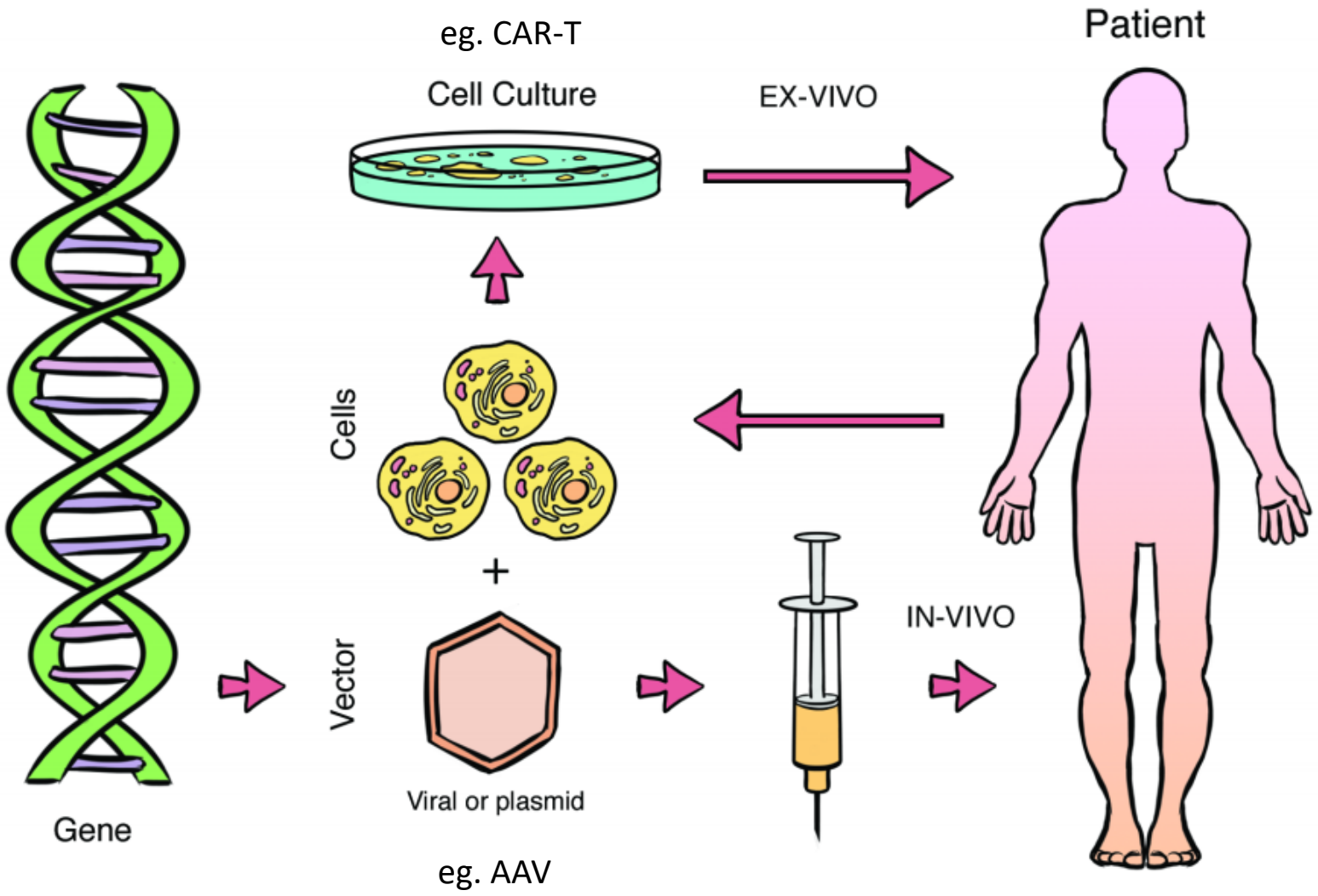
Borderline heirarchy consideration
GTMP > TEP > sCTMP

Cells gene modified in the lab and delivered to a patient are regulated as GTMP

CAR-T is an ex-vivo GTMP



Legal definition - Somatic Cell Therapy Medicinal Product (sCTMP)

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Annex I, part IV of Dir. 2001/83/EC & Reg. (EC) No. 1394/2007

- Substantially manipulated cells or tissues and/or not intended to be used for the same essential function(s) in donor and recipient;
- Administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action

Legal definition – Tissue Engineered Product (TEP)

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Reg. (EC) No. 1394/2007

- 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.

Legal definition – Combined ATMP (cATMP)

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Reg. (EC) No. 1394/2007

- 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.

Tissues and cells v drug/device

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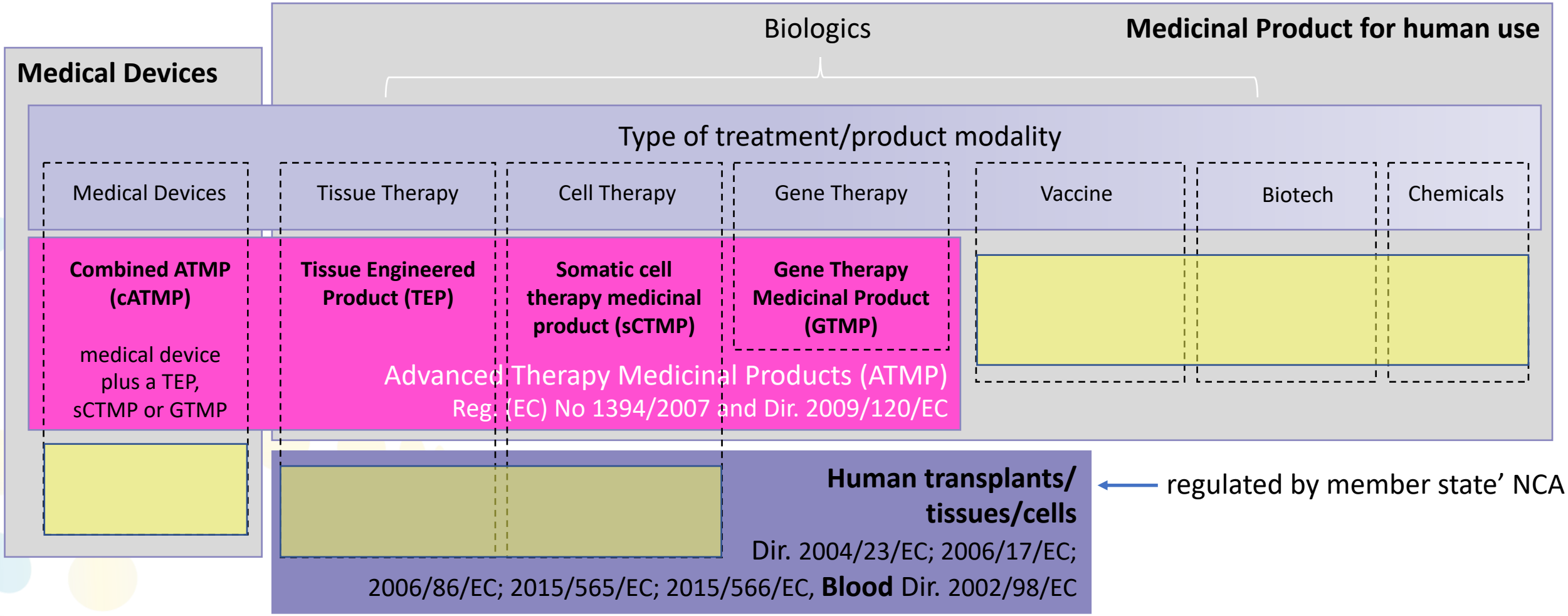

Why are cell based ATMPs different to traditional transplants?

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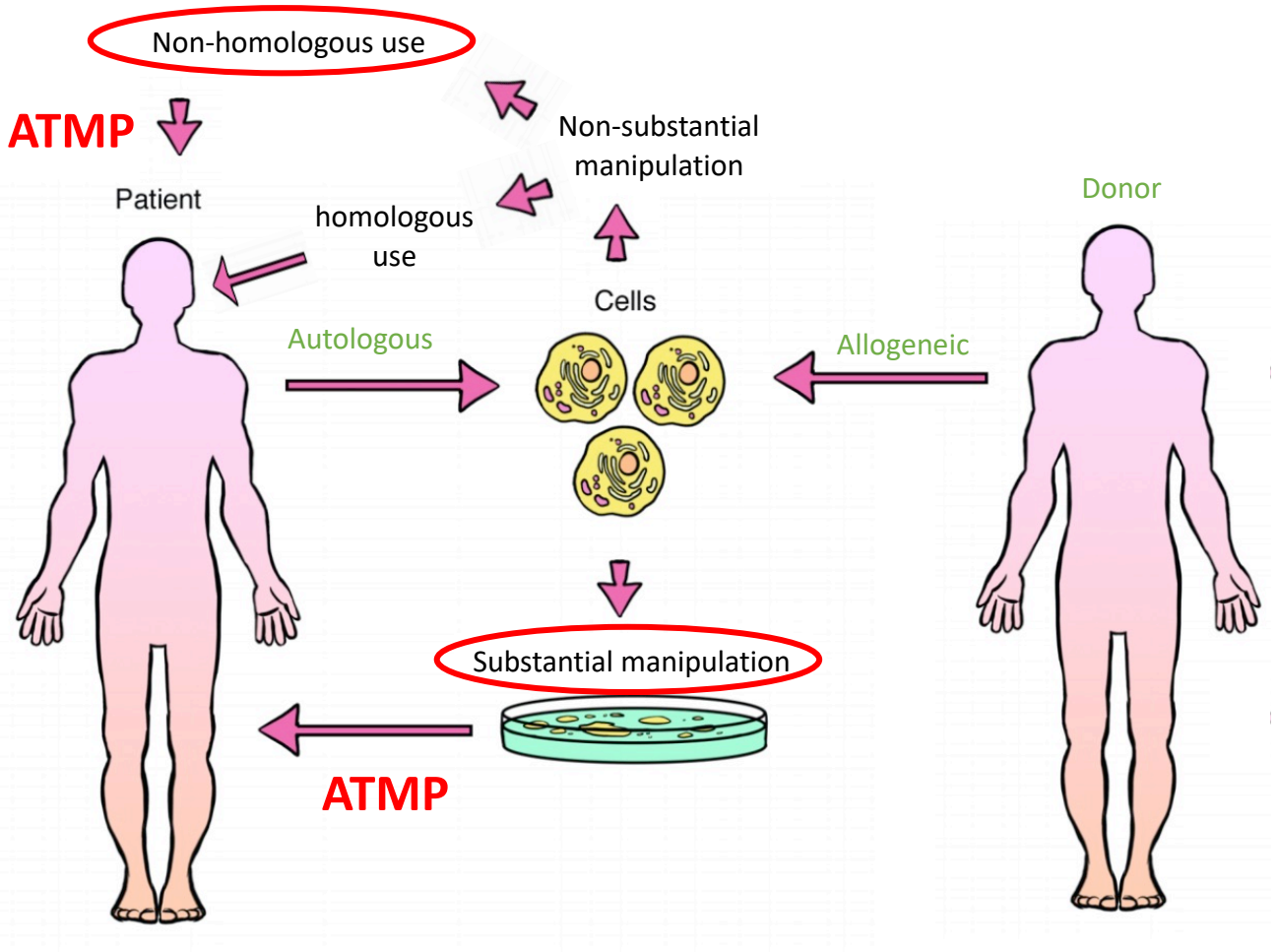
Annex I, part IV of Dir. 2001/83/EC &
Reg. (EC) No. 1394/2007

Cells **deemed to behave differently** in the patient than donor due to;

- "substantial manipulation" (quality definition) and/or
- different essential function (clinical definition)

are regulated as ATMPs.



Substantial v non-substantial manipulations

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Non-substantial manipulations			
Cutting Grinding Shaping Centrifugation	Sterilization Vitrification Soaking in Antibiotic or antimicrobial solution	Filtering Lyophilisation Freezing Cryopreservation	Cell separation, concentration, isolation or purification Irradiation

Substantial manipulations
Cell expansion (culture, *ex-vivo*)
Differentiation and/or activation with growth factors
Ex-vivo modification of cells (viral vector transduction; genome editing)

Example of sCTMP– Apligraf

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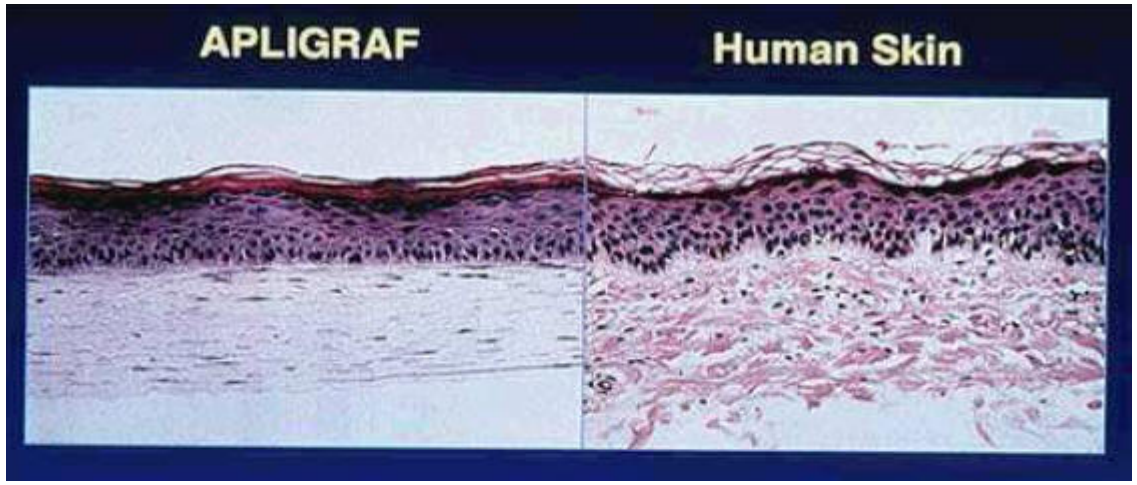
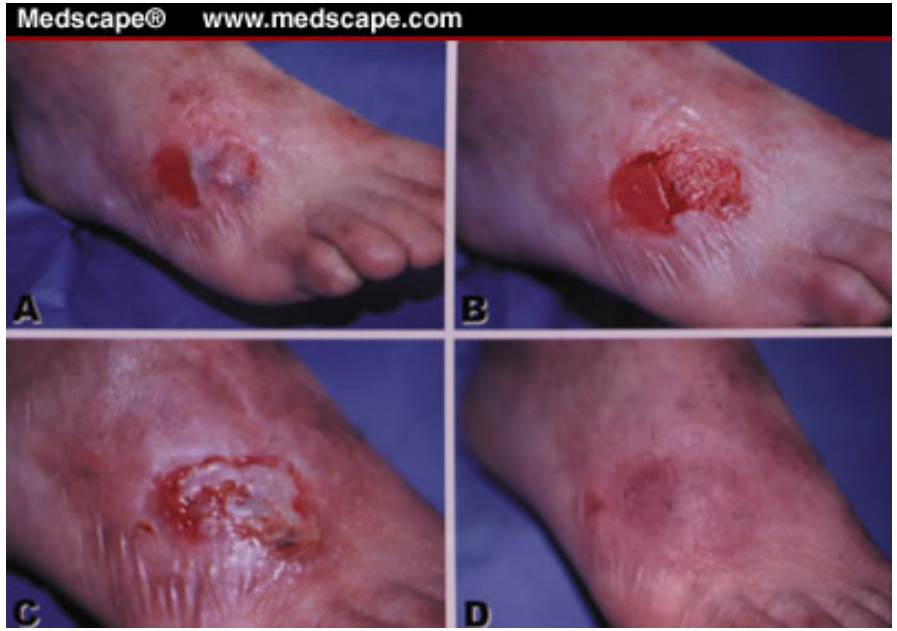
- Somatic Cell Therapy Medicinal Product

  Primary mode of action for treating wound ulcer: secreting growth factors by transplanted tissue to support formation new skin by patient

  Not a TEP





Advbiols

Example of a TEP – Holoclar®

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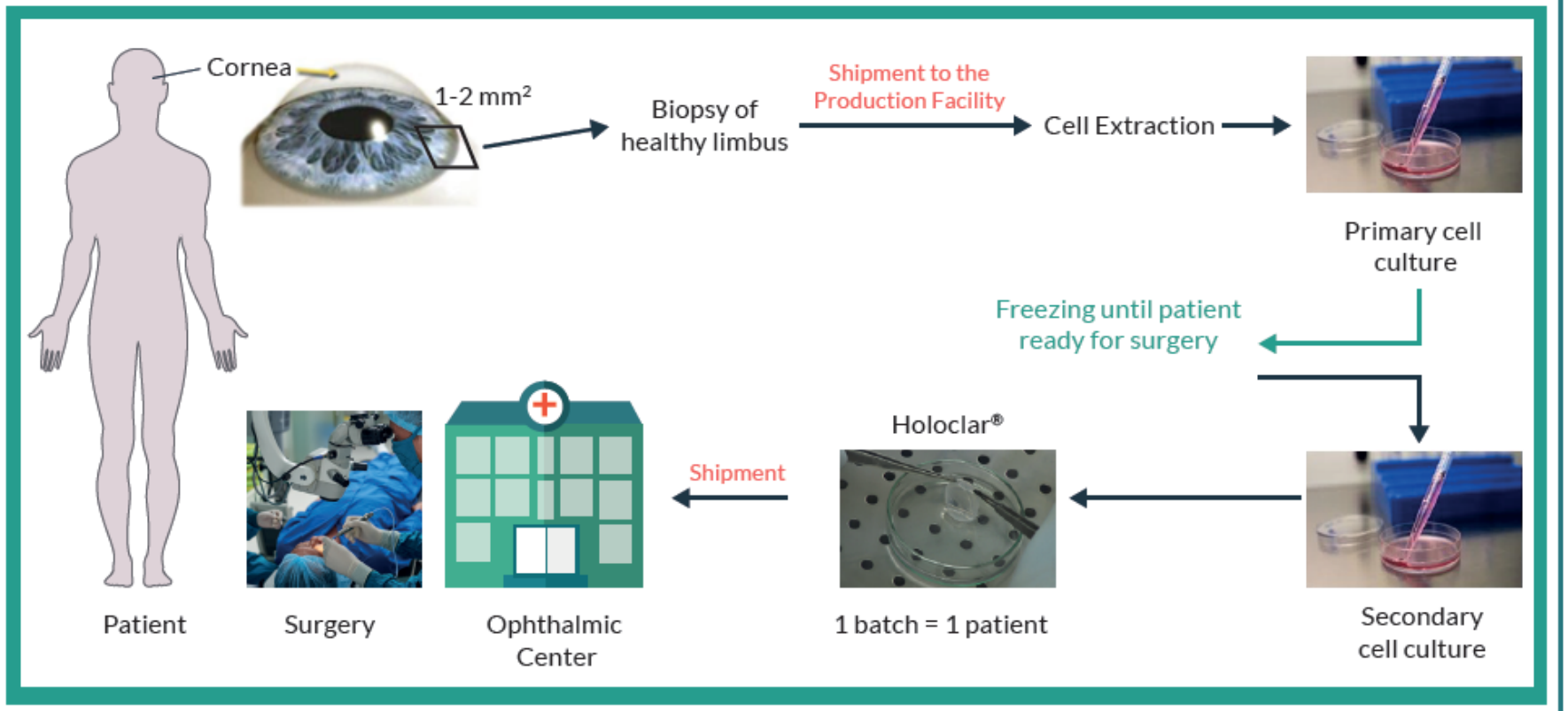
- Tissue Engineered Product
- Treat eye burns – EU MAA 2015

FIGURE 1

Manufacture and use of Holoclar.



http://insights.bio/cell-and-gene-therapy-insights/?bio_journals=holoclar-first-of-its-kind-in-more-ways-than-one

Example of a cATMP

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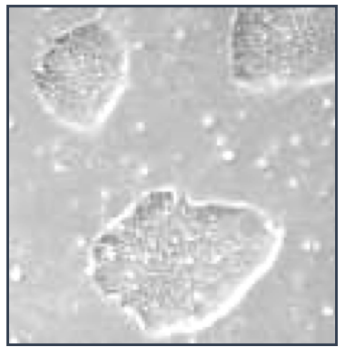
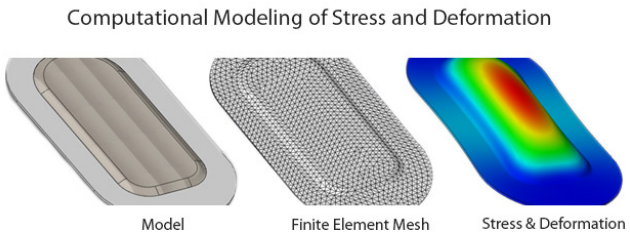
- Combined Advanced Therapy Medicinal Product

  sCTMP plus a medical device



Embryonic stem cells differentiated into pancreatic endoderm cells



Cells loaded into an immuno-protective device

Device transplanted subcutaneously into abdomen

- Cells mature in body, produce insulin
- Regulate glucose
- Eliminate the need for insulin therapy
- Reduce risk of hypo & hyperglycemic events
- Reduce long-term complications due to uncontrolled glycemia

http://viacyte.com/technology/stem-cell-engineering/

Can the same cells be an ATMP in one context and not in another?

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- Yes!
- If the cells are not substantially manipulated but are used for a different essential function in the patient they are classified as an ATMP
- eg. to transplant bone marrow from a donor to patient bone marrow is not an ATMP but to administer that same bone marrow to the patient's heart would now be considered an ATMP.

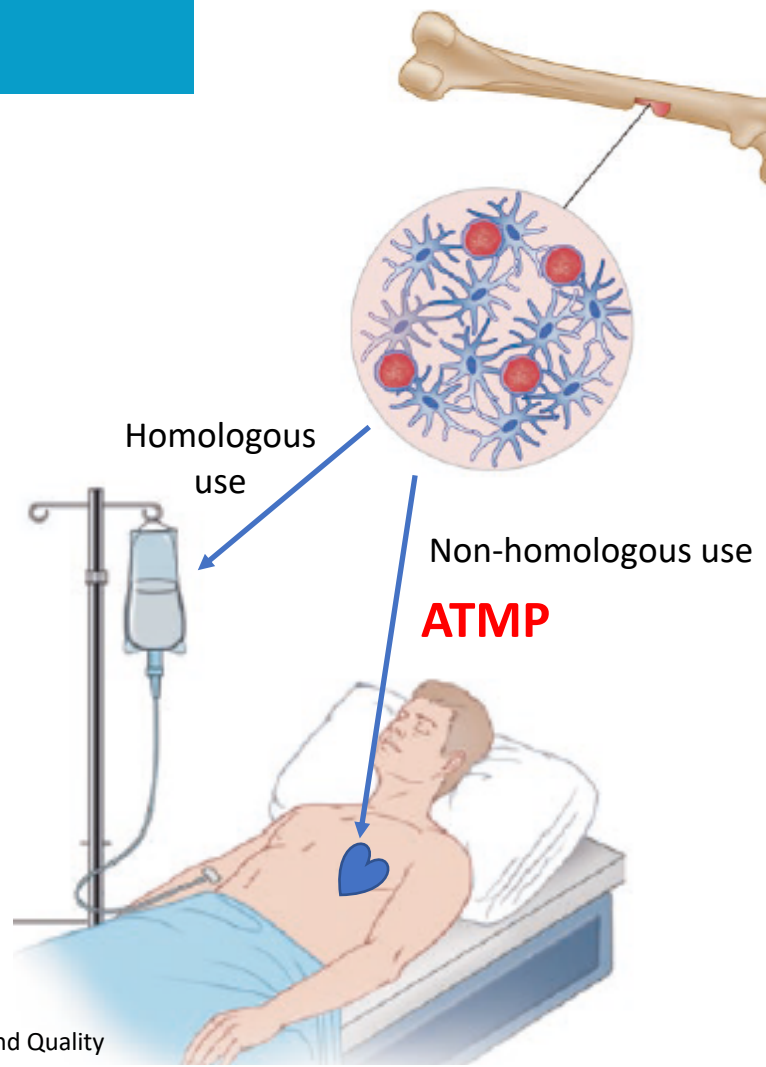
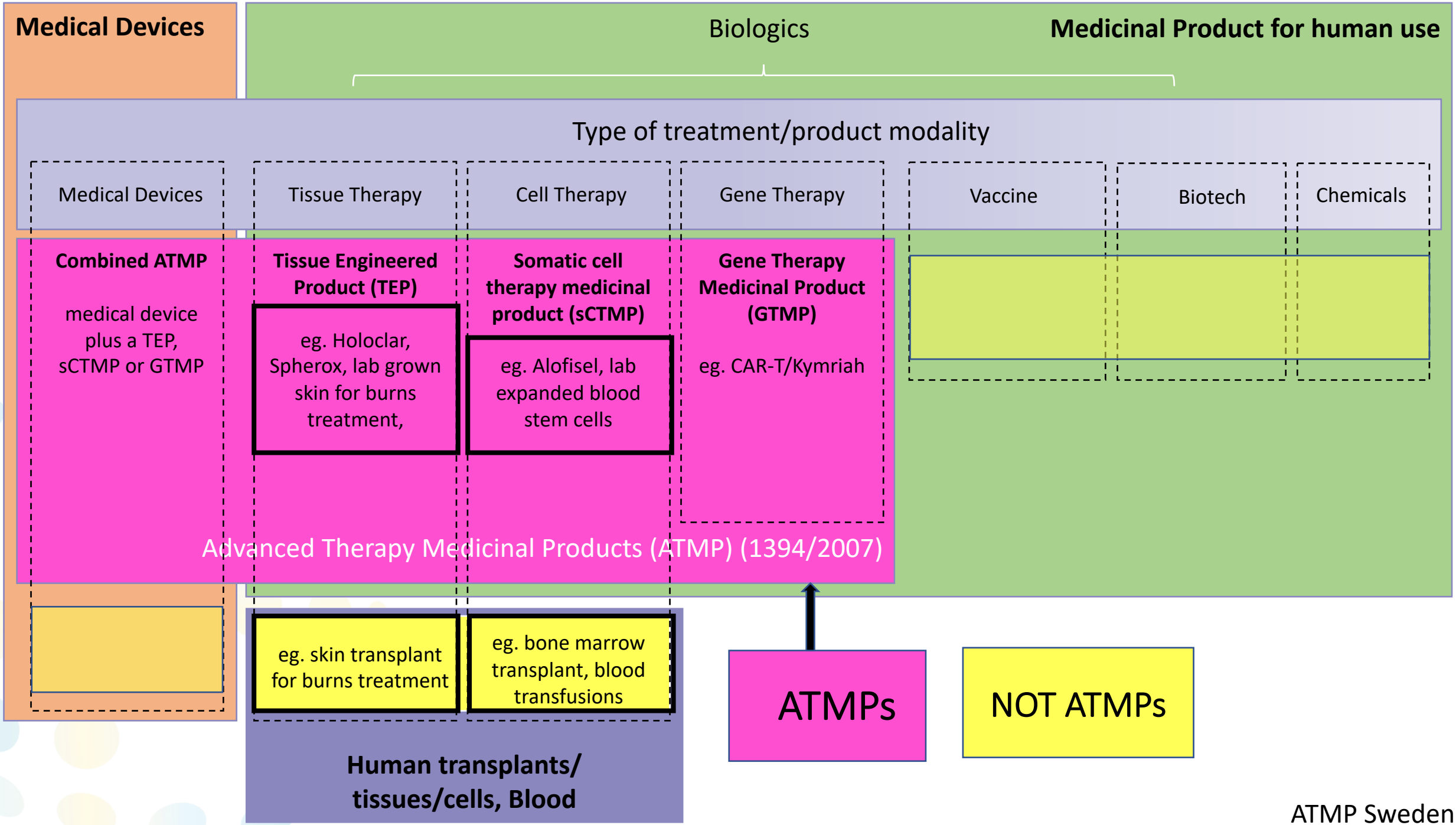


Figure adapted from: DJAC Crommelin *et al.* (eds), Pharmaceutical Biotechnology, 5th edition, Chapter 17-Advanced Therapies: Clinical, Non-clinical and Quality Considerations; K. Hoogendoorn


Medical Devices
Biologics
Medicinal Product for human use
Type of treatment/product modality
Medical Devices
Tissue Therapy
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Vaccine
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Combined ATMP
medical device plus a TEP, sCTMP or GTMP
Tissue Engineered Product (TEP)
eg. Holoclar, Spherox, lab grown skin for burns treatment,
Somatic cell therapy medicinal product (sCTMP)
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ATMPs
NOT ATMPs

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Are de-cellularised tissues delivered to patients ATMPs?

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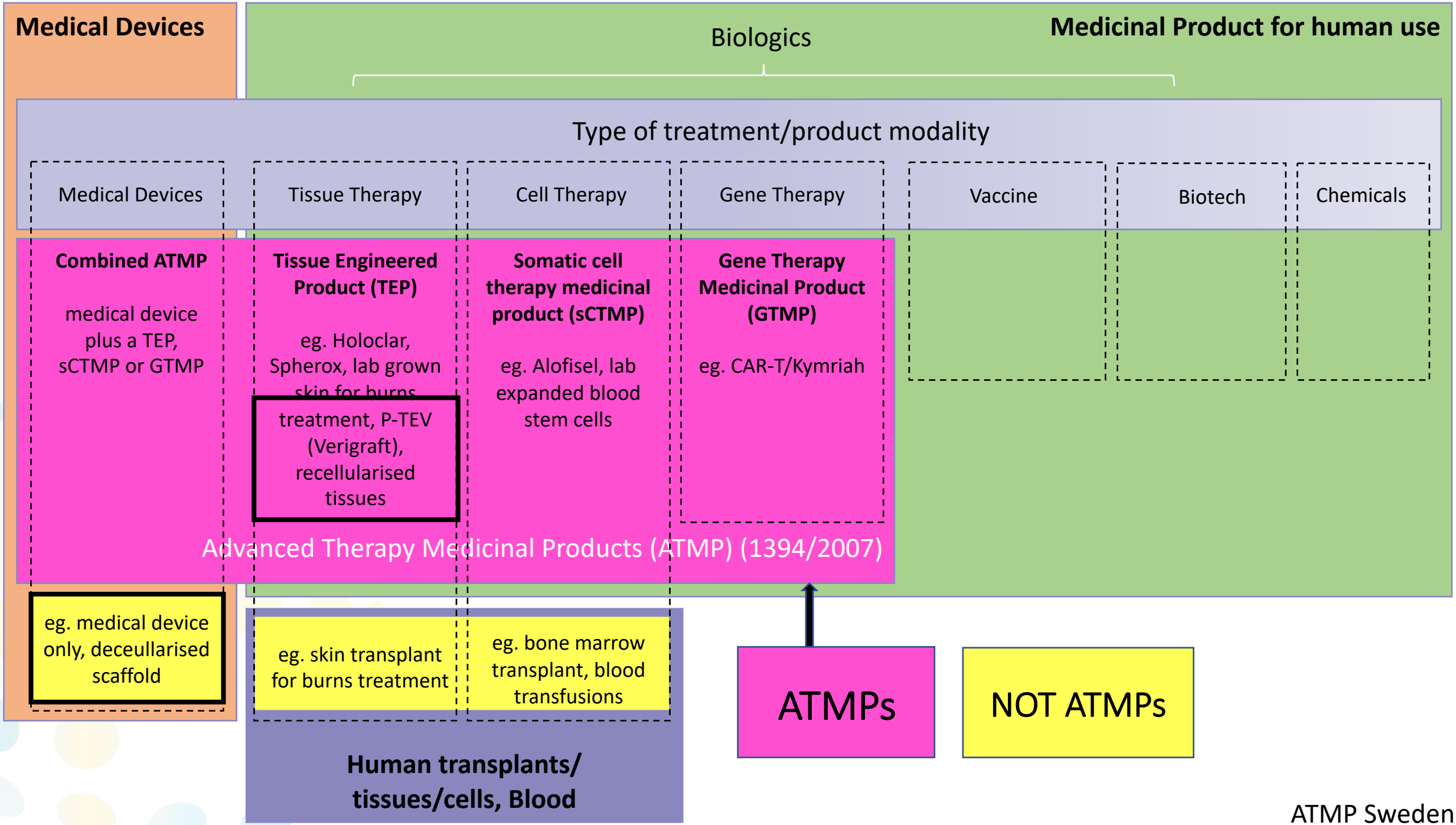
It depends.

- NO
  - If no addition of cells – medical device
  - https://www.ema.europa.eu/en/documents/report/scientific-recommendation-classification-advanced-therapy-medicinal-products-decellularized-porcine_en.pdf
  - If re-cellularised with cells that have not been substantially manipulated and if the tissue is to be used for the same essential function (theoretically).
- YES
  - If re-cellularised with cells that are substantially manipulated.
  - If re-cellularised with cells that have not been substantially manipulated but the tissue is to be used for a different essential function (theoretically).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Are recombinant technology vaccine products ATMPs/GTMPs?

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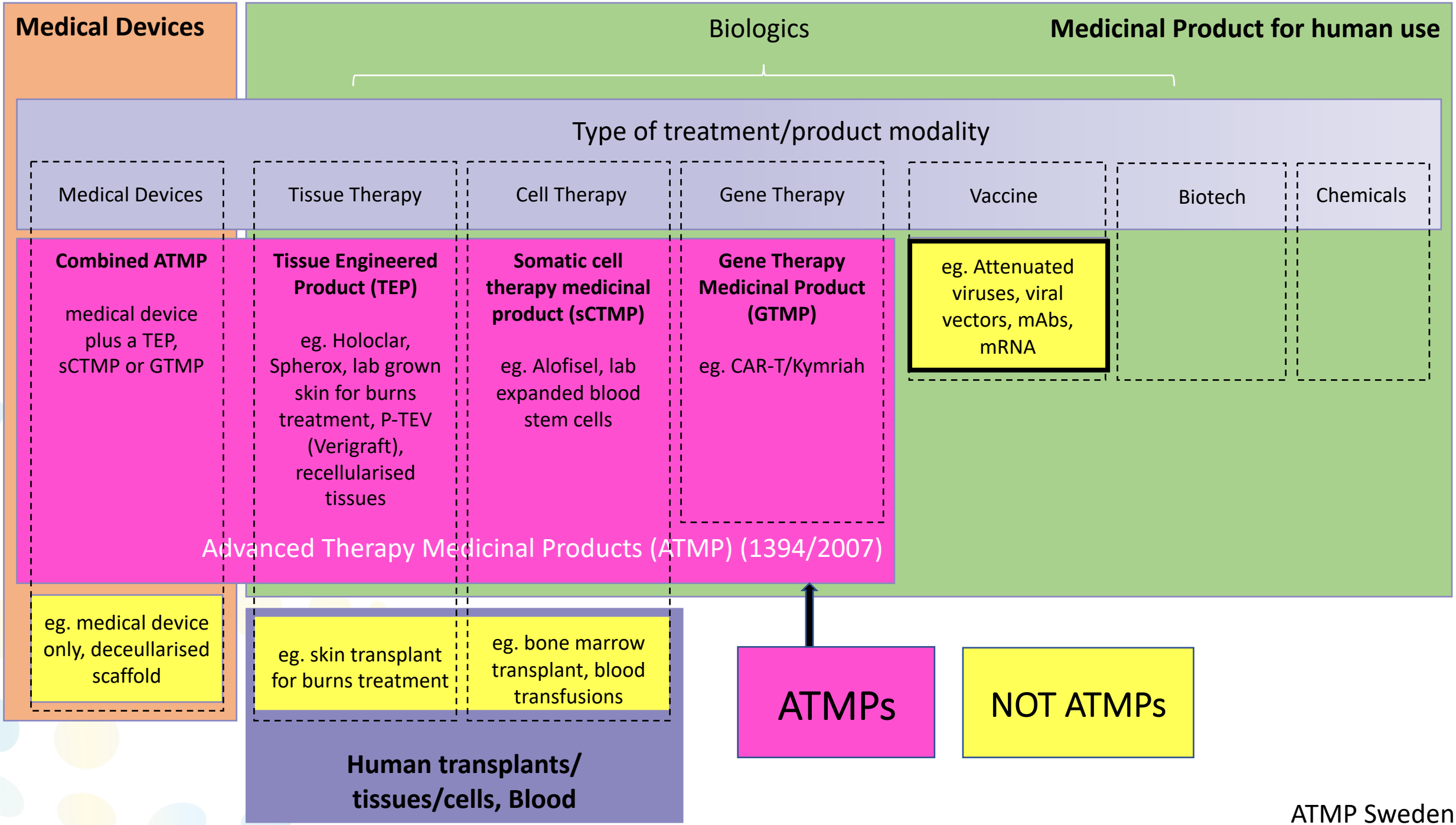
Annex I, part IV of Dir. 2001/83/EC

- No.

- Recombinant technology vaccines eg. DNA vaccines/recombinant virus against infectious disease used to be classified as gene therapies, this was updated in the mid 2000s.
- Where the mechanism of action is intended to treat or prevent a viral infection these technologies are not classified as an ATMP.
- If a 'DNA vaccine' or recombinant virus is intended to treat pathologies caused by the infection, for example malignancies, it is classified as an ATMP (GTMP).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Can recombinant bacteria being delivered to a patient be a GTMP?

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Yes!

- For example, bacteria genetically engineered and delivered to a patient to secrete recombinant therapeutic protein is regulated as a GTMP.
- The classification in this case is that the recombinant nucleic acid administered to human beings adds a genetic sequence that has the direct therapeutic effect.
- While the product does not modify the DNA of the patient or secrete therapeutic RNA, it is still legally classified as a gene therapy.
- https://www.ema.europa.eu/en/documents/report/living-genetically-modified-lactobacillus-reuteri-bacteria-plasmid-containing-gene-human-cxcl12-1a_en.pdf

Can recombinant mRNAs be ATMP/GTMPs?

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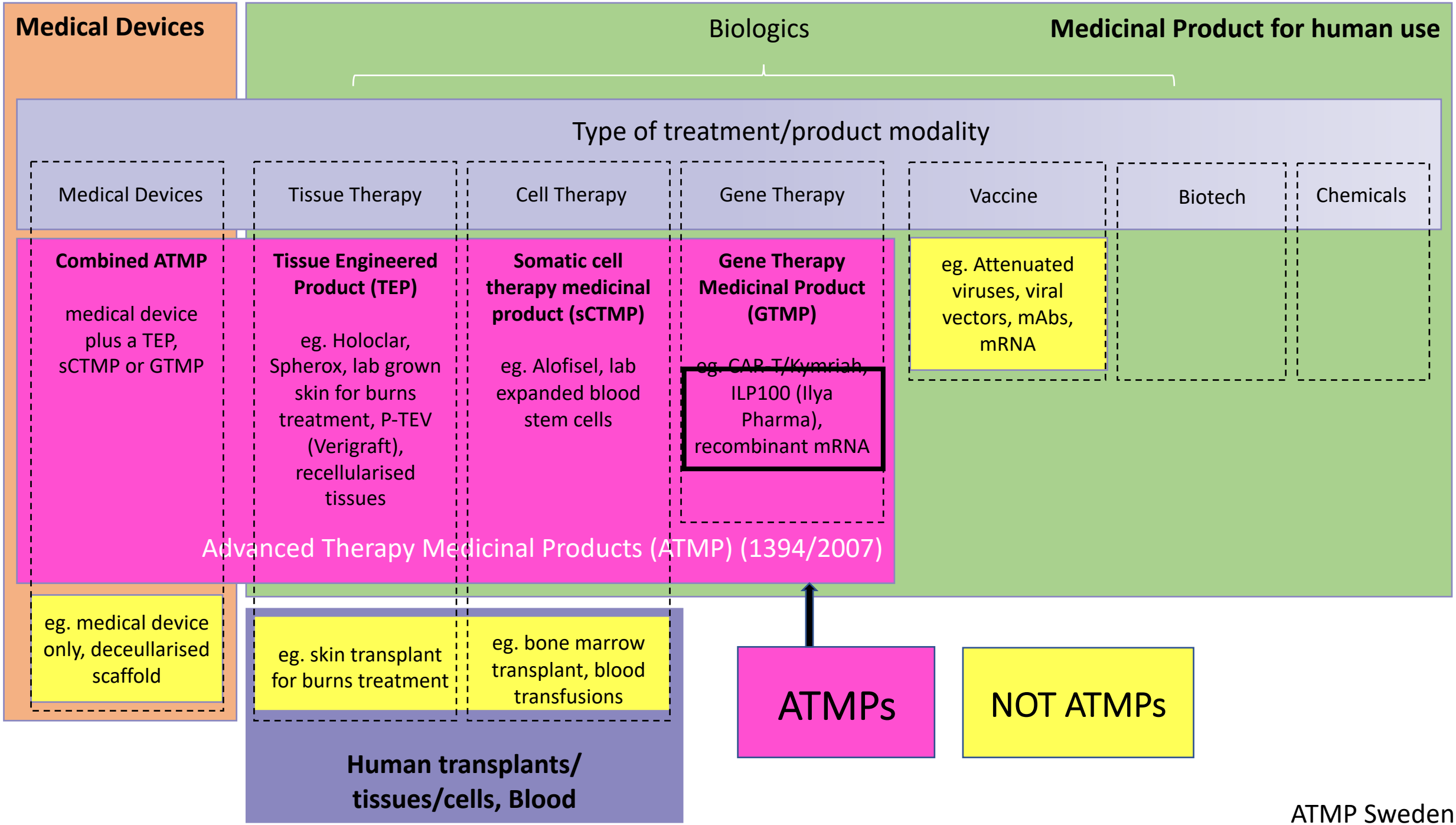
Yes!

- If the mRNA is produced from a recombinant source eg. linearised plasmid, and the resultant mRNA will be delivered to patients with a mechanism of action based on the mRNA or protein translated from it.
- https://www.ema.europa.eu/en/documents/report/scientific-recommendation-classification-advanced-therapy-medicinal-products-codon-optimized-mrna_en.pdf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Are synthetic oligonucleotide-based products ATMP/GTMPs?

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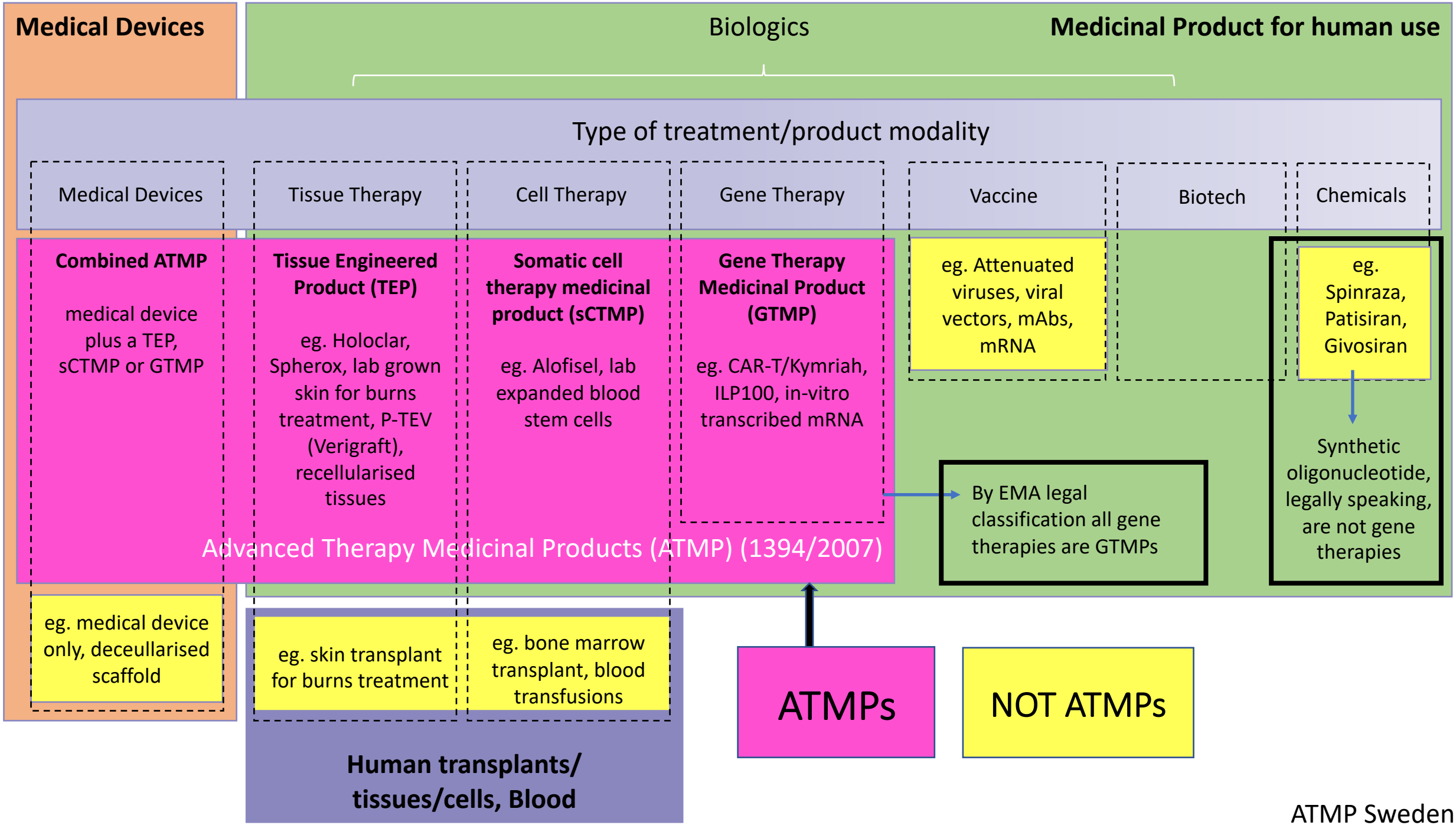
No

- Legally synthetic oligonucleotide-based medicines are not classified as gene therapies.
- Legally only those products with active substances based on recombinant DNA technologies that are delivered to patients to add or regulate gene sequences are gene therapies.
- Though synthetically produced oligonucleotides are widely referred to as gene therapies, they are better described as complex small molecule medicinal products or nucleotide based medicines.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ATMP Sweden

Are Extracellular vesicles (EVs) ATMPs?

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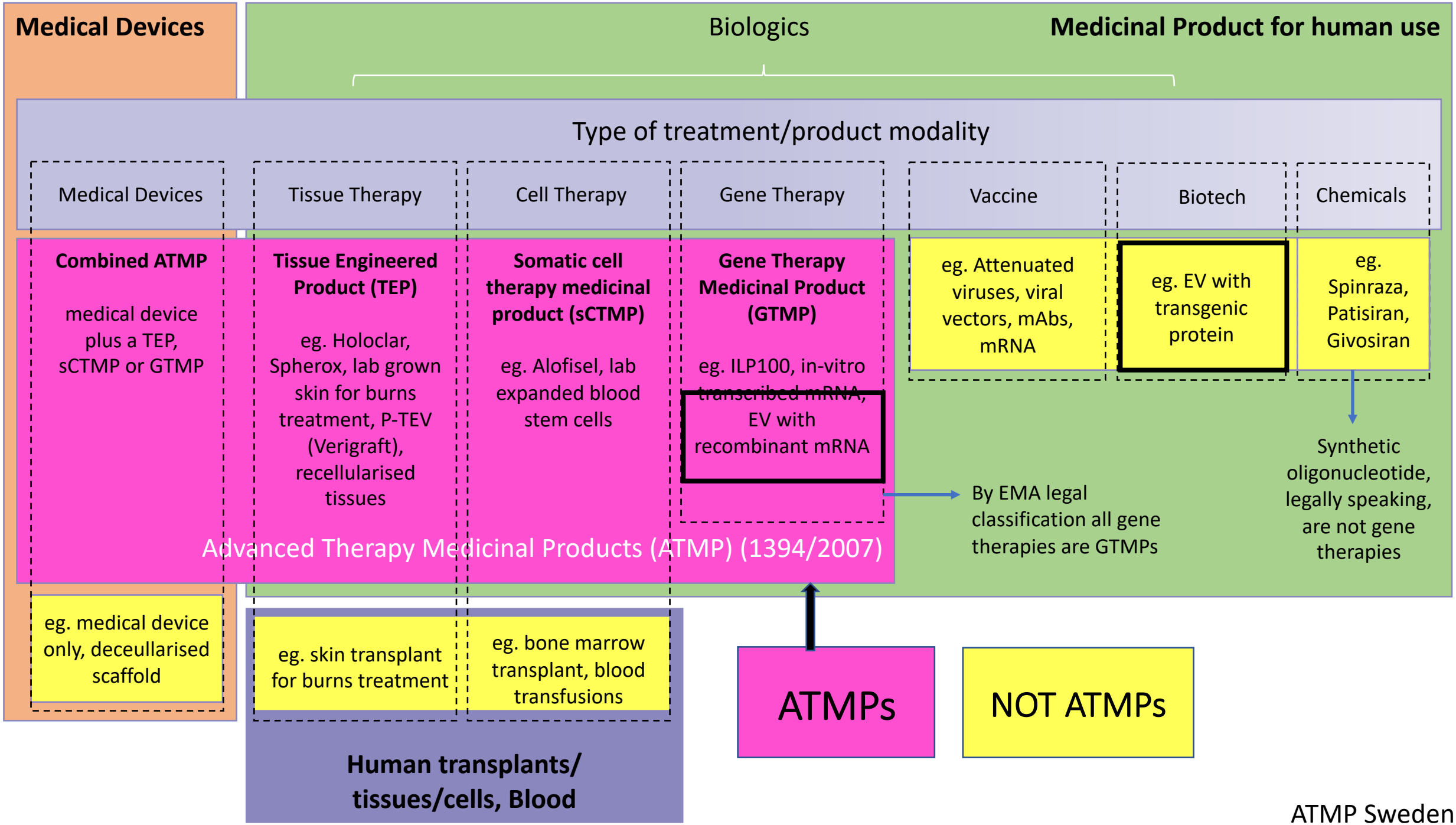
It depends

- If the product is EVs purified from non-modified cells or from genetically modified cells, but where the vesicles contain only functional transgenic protein, they are not ATMPs, but biologics.
- If the EVs contain functional transgenic mRNAs that will perform the intended therapeutic function in the patient they are classified as ATMPs (i.e. GTMPs).
- https://www.ema.europa.eu/en/documents/report/scientific-recommendation-classification-advanced-therapy-medicinal-products-exosomes-carrying_en.pdf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And the final schematic…

Find updated information and more at;
https://atmpsweden.se/resources/what-are-atmps/

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Why is it important these classifications are understood?

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So developers know what regulations they need to follow.

Applications to CAT for scientific recommendation/classification of borderline products are strongly recommended to be sure

EMA: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/advanced-therapies/advanced-therapy-classification#:~:text=Companies%20can%20consult%20the%20European,criteria%20for%20defining%20an%20ATMP.

MPA: https://www.lakemedelsverket.se/en/permission-approval-and-control/advisory/regulatory-advice

Thanks for taking this journey with us!.....questions/discussion

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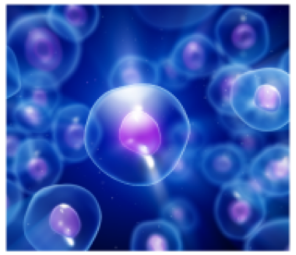

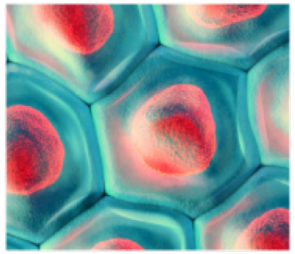

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