WHAT IS THE LANDSCAPE FOR APPROVAL AND LICENSING OF GENOMIC THERAPIES IN EUROPE?

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"Translation of genomics into routine cardiological practice"

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Disclaimer

- This presentation might not be the view of the EMA-CVSWP or AEMPS.
- The ideas expressed here represent my personal view and do not bind the organisations mentioned above or any other party.
- I have no conflict of interests to declare.

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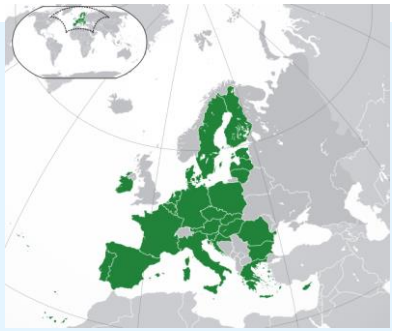
Regulatory agencies (1)

European Union + UK (28 countries, ≈ 32 regulatory agencies of medicines)

- **EMA - European Medicines Agency**
- HMA – Heads of Medicines Agencies
- Germany – BfArM, Federal Institute for Drugs and Medical Devices
- Germany – PEI, Paul-Ehrlich-Institut
- Austria – Austrian Medicines and Medical Devices Agency (BASG)
- Belgium – Federal Agency for Medicines and Health Products (AFMPS)
- Bulgaria – Bulgarian Drug Agency (BDA)
- Bulgaria – National Veterinary Service
- Cyprus – Ministry of Health
- Cyprus – Ministry of Agriculture, Natural Resources and Environment, Veterinary Services
- Denmark – Lægemiddelstyrelsen, Danish Medicines Agency (DKMA)
- Slovak Republic –State Institute for Drug Control (SUKL)
- Slovenia – Ministry of Health
- **Spain – AEMPS, Agencia Española de Medicamentos y Productos Sanitarios**
- Estonia – Ravimiamet, State Agency of Medicines
- Finland – Finnish Medicines Agency (FIMEA)
- France – Agence nationale de securité du médicament et des produits de santé (ANSM)
- Greece – National Organization for Medicines
- Hungary – National Institute of Pharmacy and Nutrition (OGYÉI)
- Ireland – The Health Products Regulatory Authority (HPRA)
- Italy – Agenzia Italiana del Farmaco (AIFA)
- Letonia – State Agency of Medicines of Latvia
- Lithuania – State Medicines Control Agency of Lithuania (VVKT)
- Luxemburg – Ministère de la Santé. Division de la Pharmacie et des Médicaments
- Malta – Medicines Authority
- Netherlands – Medicines Evaluation Board (MEB)
- Poland – Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
- Portugal – Autoridade Nacional do Medicamento e Produtos de Saude I.P. (INFARMED)
- Czech Republic – State Institut for Drug Control (SUKL)
- Romania – National Medicines Agency
- Sweden – Läkemedelsverket, Medical Products Agency

- United Kingdom – MHRA, Medicines and Healthcare products Regulatory Agency



Other countries of the European Economic Area (EEA)

- Iceland – Lyfjastofnun, Icelandic Medicines Agency
- Lichtenstein – Liechtensteinische Landesverwaltung Amt für Lebensmittelkontrolle und Veterinärwesen Kontrollstelle für Arzneimittel
- Norway – Legemiddelverk Norwegian Medicines Agency (NoMA)

North-America

- **United States - Food and Drug Administration (FDA)**
  - CBER – Center for Biologics Evaluation and Research (biological medicines)
  - CDER – Center for Drug Evaluation and Research (non-biological medicines)
- Canada – Health Canada

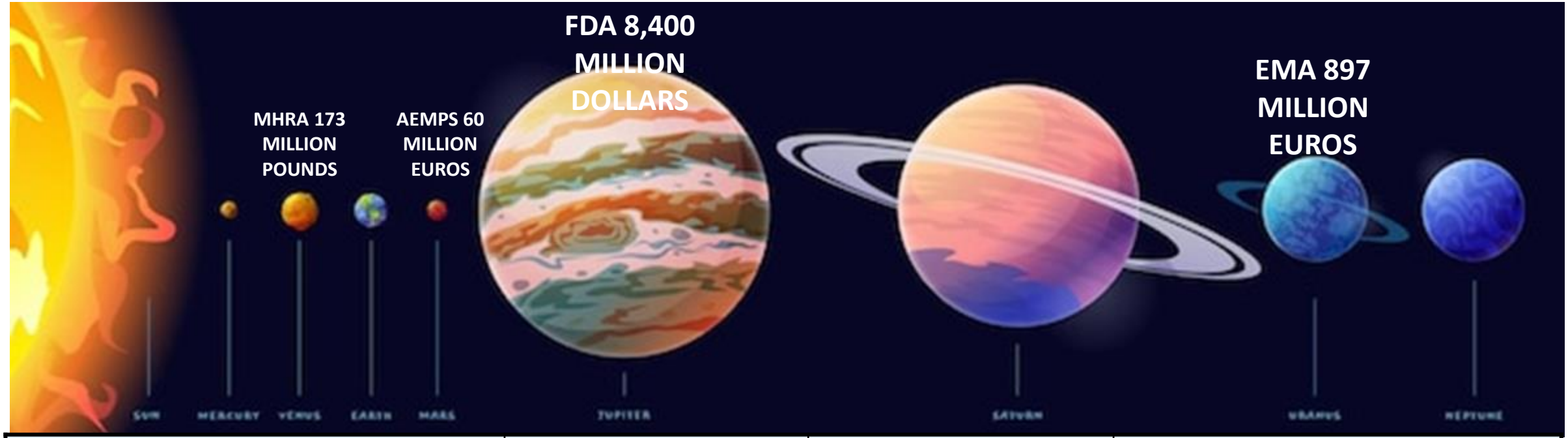
Latin America

- EAMI network: Red de Autoridades en Medicamentos de Iberoamérica

Rest of the world

- Australia – TGA. Therapeutic Goods Administration
- Japan – Pharmaceuticals and Medical Devices Agency (PMDA)

Regulatory agencies (2)



VARIABLE	AEMPS	EMA	FDA
Staff, n	800	879	18.000 (9.351 CBER, CDER, CDRH, CVM),
Annual Budget, millon euros/dollars	60 mill. € (20 mill. € Profit)	897 mill. €	8,400 mill. **$**
Population covered, million people	47	448	330
Budget per inhabitant	1.3	2.0	25.5

AEMPS = Spanish Medicines Agency; CBER = Center for Biologics Evaluation and Research; CDER = Center for Drug Evaluation and Research; CDRH = Center for Devices and Radiological Health; CVM = Center for Veterinary Medicine; EMA = European Medicines Agency; FDA = Food and Drug Administration

Activities of different regulatory agencies

ACTIVITIES	AEMPS	MHRA	EMA	FDA
Assessment of medicinal products (including gene therapies)	Yes	Yes (UK)	Yes (Coordination of Centralized procedures, CHMP)	Yes (US)
Team of assessors (quality, non-clinical, clinical)	Yes	Yes (UK)	No (National Agencies)	Yes (US)
Autorisation of medicinal products	Yes (National, DC, MRP)	Yes (UK)	No (European Commission)	Yes (US)
Scientific advice	Yesdecen	Yes (UK)	Yes (SAWP)	Yes (US)
Information to healthcare professionals, patients and users	Yes	Yes (UK)	Yes	Yes (US)
Pharmacovigilance	Yes (National, DC, MRP, Centralized)	Yes (UK)	Yes (coordination, PRAC)	Yes (US)
Assessment of medical devices	Yes	Yes (UK)	No	Yes (US)
CE marking (for medical devices)	Yes (AEMPS is also a notified body)	Yes (UK. MHRA works with notified bodies)	No	Yes (US)
Autorization of clinical trials	Yes	Yes (UK)	No (but coordination in COVID)	Yes (US)
Control of ilegal and falsified medicines	Yes	Yes (UK)	Yes (coordination)	Yes (US)
Control of food	No (AESAN)	No	No	Yes (US)
Control of poisons and biologic weapons	No (Ministries of Defense, Interior, Dpt. Public Health)	No	No	Yes (US)

AEMPS = Agencia Española de Medicamentos y Productos Sanitarios; AESAN = Agencia Española de seguridad alimentaria; DCP = decentralised procedures; EMA = European Medicines Agency; FDA = US Food and Drug Administration; MRP = mutual recognition procedure; PRAC = Pharmacovigilance Committee of the EMA; SAWP = Scientific Advice Working Party of the EMA-CHMP; **UK** = United Kingdom; **US** = United States of America.

Medicinal Products vs. Medical Devices

- Regulatory language sometimes difficult to understand.

Assessment: EMA, National Regulatory Agencies
Authorisation: European Commission, National Agencies

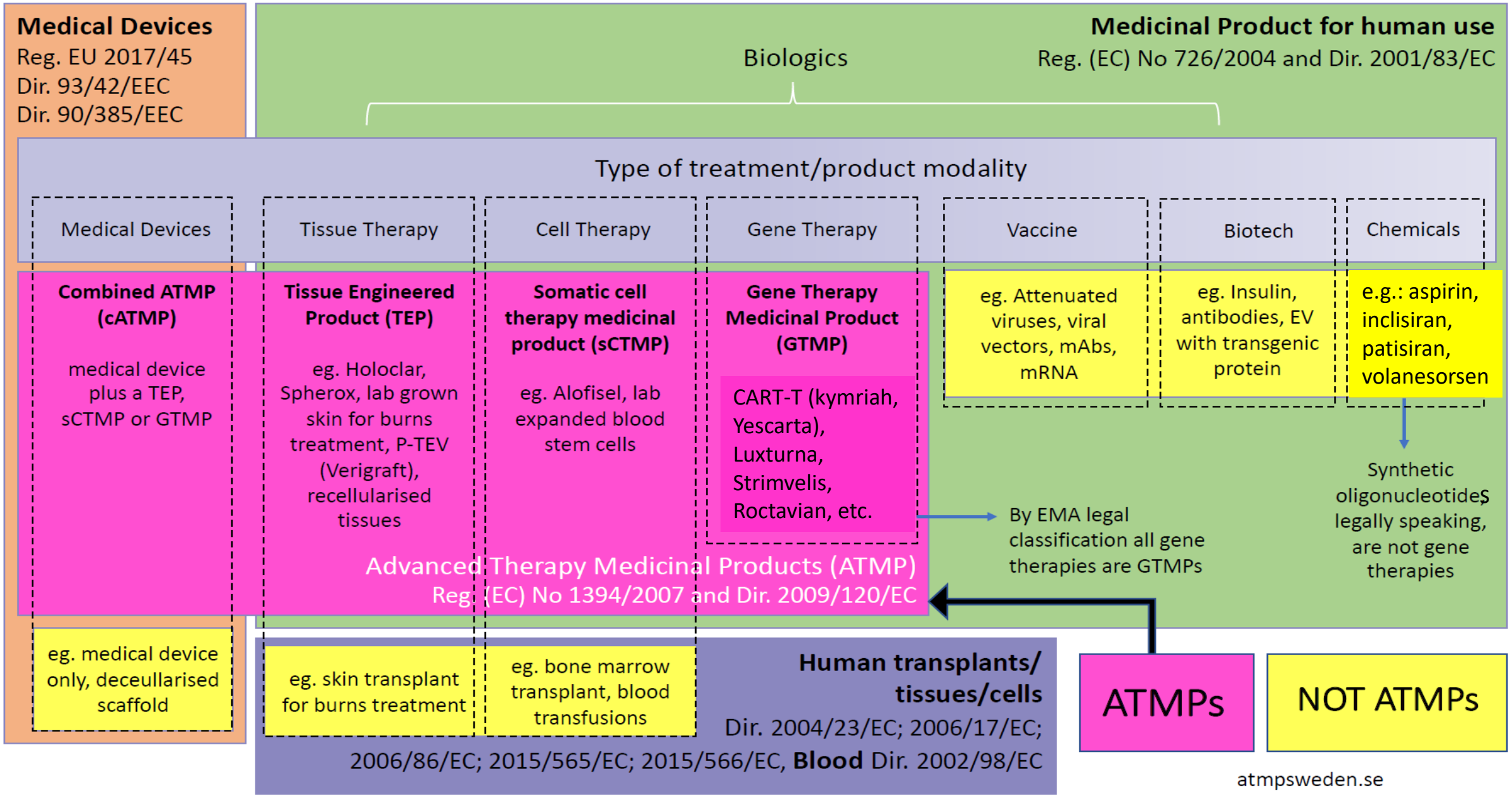
- **Medicinal product (MP):**
  any substance or combination of substances presented for treating or preventing disease in human beings; or any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings.
- **Advanced Therapy Medicinal Products (ATMP):**
  Medicinal products based on cells, tissues or genes. Very different from medicines based on chemical entities or biological / biotechnological origin but same requirement for testing / controlling each batch / GMP / GCP / PhVig/ RMP
  - Gene therapy medicinal products (GTMP).
  - Somatic cell therapy medicinal product (sCTMP).
  - Tissue engineered product (TEP).

Conformity assessment: notified bodies (30 in the EU)
Authorisation: CE mark (not formal authorisation)

- **Medical Devices (MD). Many subtypes**
  - In vitro diagnosis (ej.: genotyping for CYP450: AmpliChip, Taqman; genotyping for APOE forms: DiaPlexQ)
  - Implantable devices: pacemakers, stents.
  - Medical device plus an ancillary chemical drug (i.e.: drug-eluted stents), plus GTMP, sCTMP or TEP.

A *notified body* is an organisation designated by an EU country to assess the conformity of certain products before being placed on the market.
EMA = European Medicines Agency; GMP = Good Manufacturing Practice; GCP = Good Clinical Practice; PhVig = Pharmacovigilance; RMP = Risk Management Plan

ADVANCED THERAPY MEDICINAL PRODUCTS (ATMPs) VS. OTHERS



atmpsweden.se

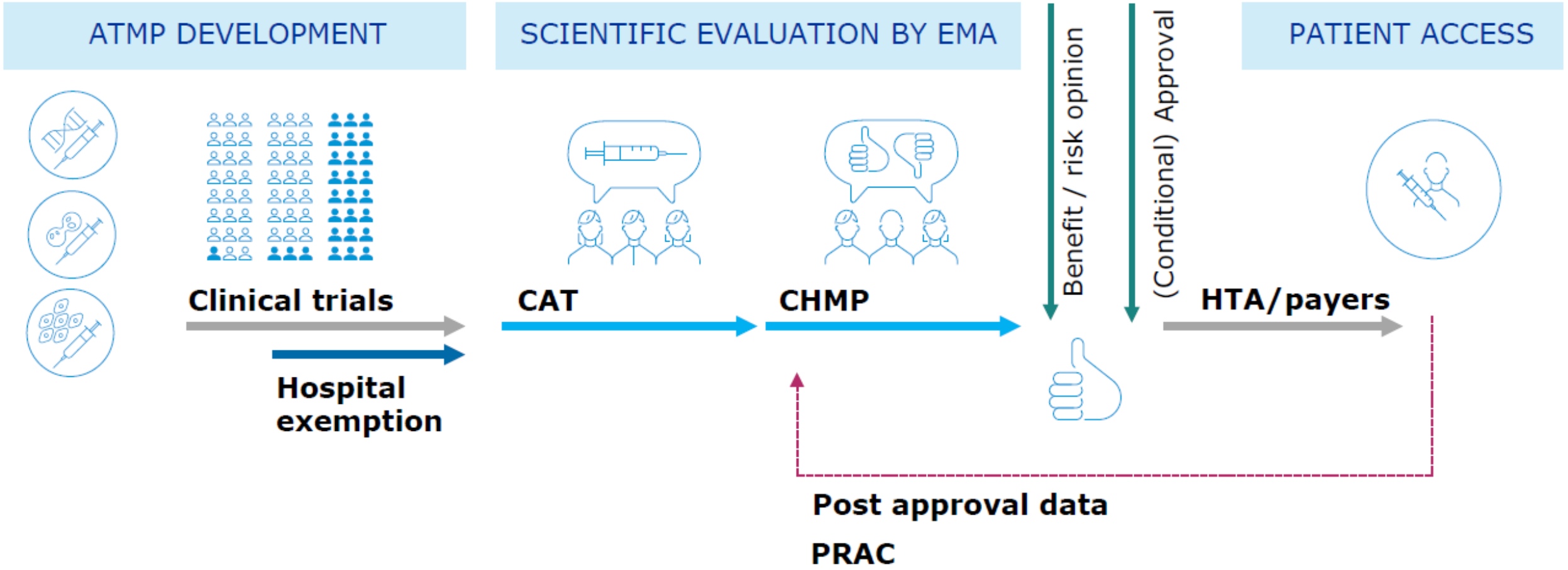
Traditional medicines vs. ATMPs

	Small molecule chemicals	ATMPs
Administration	Continuous/long-term	Single or few administrations
Where medicine is given	Home, GP, Ambulatory, hospitals…	Treatment centre - needs qualification
Easy to copy	Relatively easy to copy	Very difficult to copy
Definition	The molecule is the drug	The process plays a big role
Treatment decisions	Generally reversible	Cannot stop treatment if non-responder
Costs	Relatively cheap, but given long time, costs spread over time	High early costs
Access to market	Approval and market close in time	Not direct, delays frequent, HTAs, reimbursement etc…

GP = General Practitioner; HTAs = Health Technology Assessment Agencies

Patrick Celis & Ana Hidalgo-Simon. Advanced Therapies (ATMPs). 3 March 2022. Available from: https://www.ema.europa.eu/en/documents/presentation/presentation-awareness-raising-development-evaluation-atmps-pcelis-ahidalgo-simon-ema_en.pdf

Entry route of ATMPs to the EU market



CAT = Committee of Advanced Therapies; CHMP = Committee for Medicinal Products for Human Use; HTA = Health Technology Assessment Agencies; PRAC = Pharmacovigilance Risk Assessment Committee.

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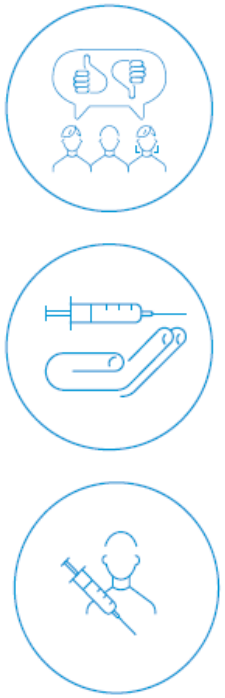
Supporting innovation to advance patient access

GENERAL SUPPORT

- Scientific advice
- Innovation Task Force
- Parallel consultation with HTAs
- ATMP Classification procedure
- ATMP Certification procedure
- PRIME (early access)
- Qualification of novel methodologies, e.g. registries
- Paediatric and Orphan framework
- Scientific guidelines
- SME support
- Academia cooperation
- Fee incentives



AUTHORISATION

Complete
Conditional
Exceptional circumstances

ACCESS DECISION

POST-LICENSING EVIDENCE

ATMP = Advanced Therapy Medicinal Product; HTAs = Health Technology Assessment Agencies; PRIME = Priority Medicines; SME = Small and Medium-sized Enterprises;

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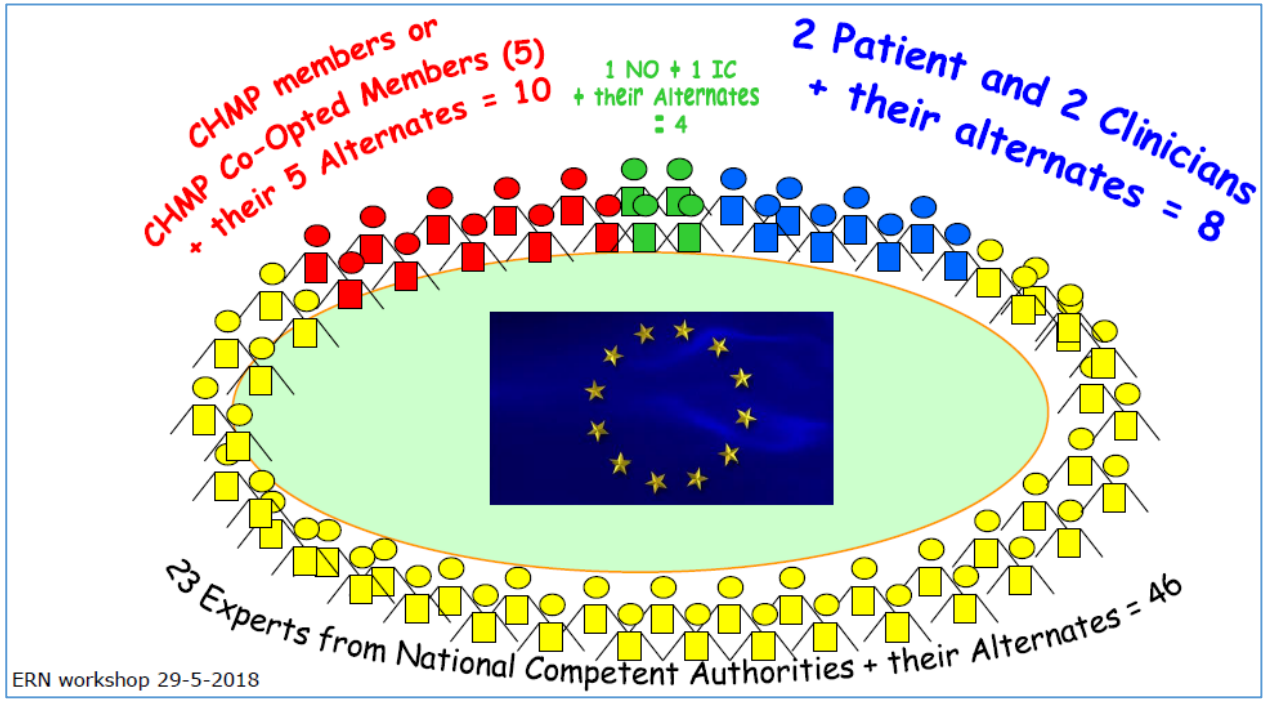
CAT: Committee of Advanced Therapies

- **The Committee for Advanced Therapies (CAT)** is the European Medicines Agency's (EMA) committee responsible for assessing the quality, safety and efficacy of advanced therapy medicinal products (ATMPs) before the Committee for Medicinal Products for Human Use (CHMP) adopts a final opinion on the marketing authorisation of the medicine concerned.
- At the request of EMA's Executive Director or the European Commission, the CAT can also draw up an opinion on any scientific matter relating to ATMPs.
- It was established in accordance with Regulation (EC) No 1394/2007.



https://www.ema.europa.eu/en/committees/committee-advanced-therapies-cat

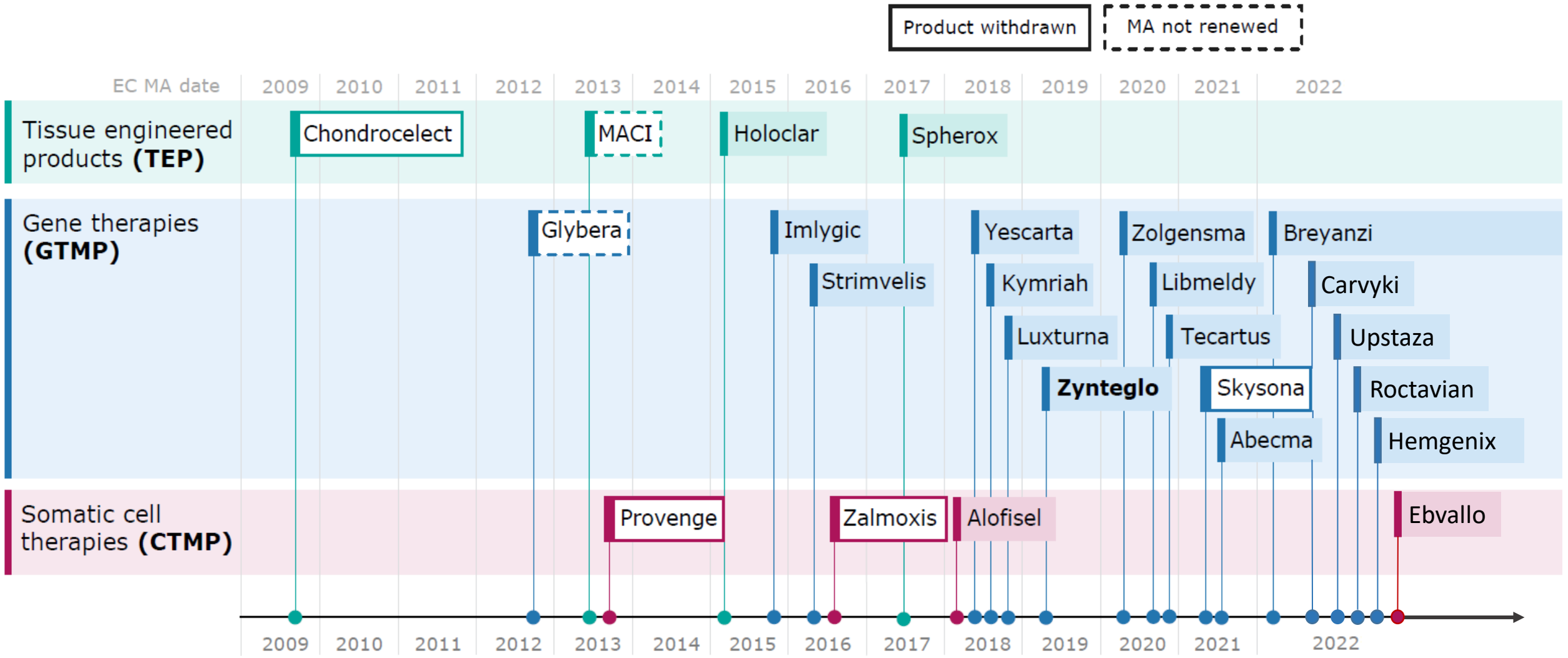
CHMP: Committee for Human Medicinal Products

- Chairman (Harald Enzmann, Germany DE) & Vice-Chairman (Bruno Sepodes, Portugal PT).
- 2 scientific expert members (CHMP member+alternate) nominated by each of the **27** Member States (56 co/rapporteurs; **27 votes**).
- 2 scientific expert members (CHMP member + alternate) from IS, LI, NO (EFTA, European Free Trade Association, observers)
- **5** co-opted members appointed by Management Board (2 biologic and advanced therapies, 1 statistician, 1 quality, 1 pharmacoepidemiology) (**5 votes**).

Co-opted = internal nomination, voted by CHMP members; **IS** = iceland; **LI** = Liechtenstein; **NO** = Norway.

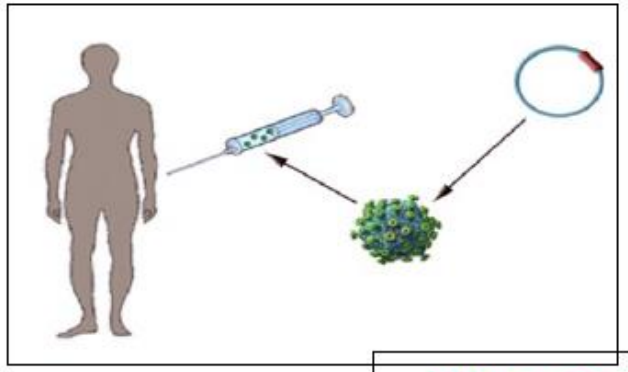
https://www.ema.europa.eu/en/committees/chmp/members

Approved ATMPs 2009-2022



Modified from: Patrick Celis & Ana Hidalgo-Simon. Advanced Therapies (ATMPs). 3 March 2022. Available from: https://www.ema.europa.eu/en/documents/presentation/presentation-awareness-raising-development-evaluation-atmps-pcelis-ahidalgo-simon-ema_en.pdf

What does a gene therapy look like?

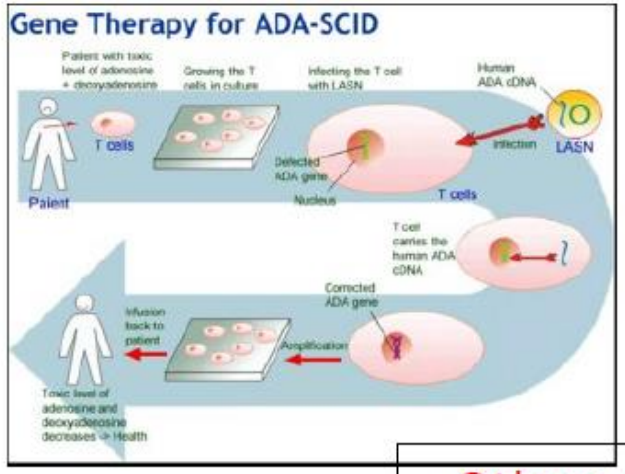


In vivo gene therapies

Example: Glybera

- Treatment of lipoprotein lipase deficiency
- Replication-deficient adeno-associated viral vector designed to deliver and express the human LPL gene variant LPLS447X

Other in-vivo GTs:
Zolgensma, Luxturna



Ex-vivo gene therapies

Example: Strimvelis

- CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence
- Treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID)

Other ex-vivo GTs:
CAR-T cells

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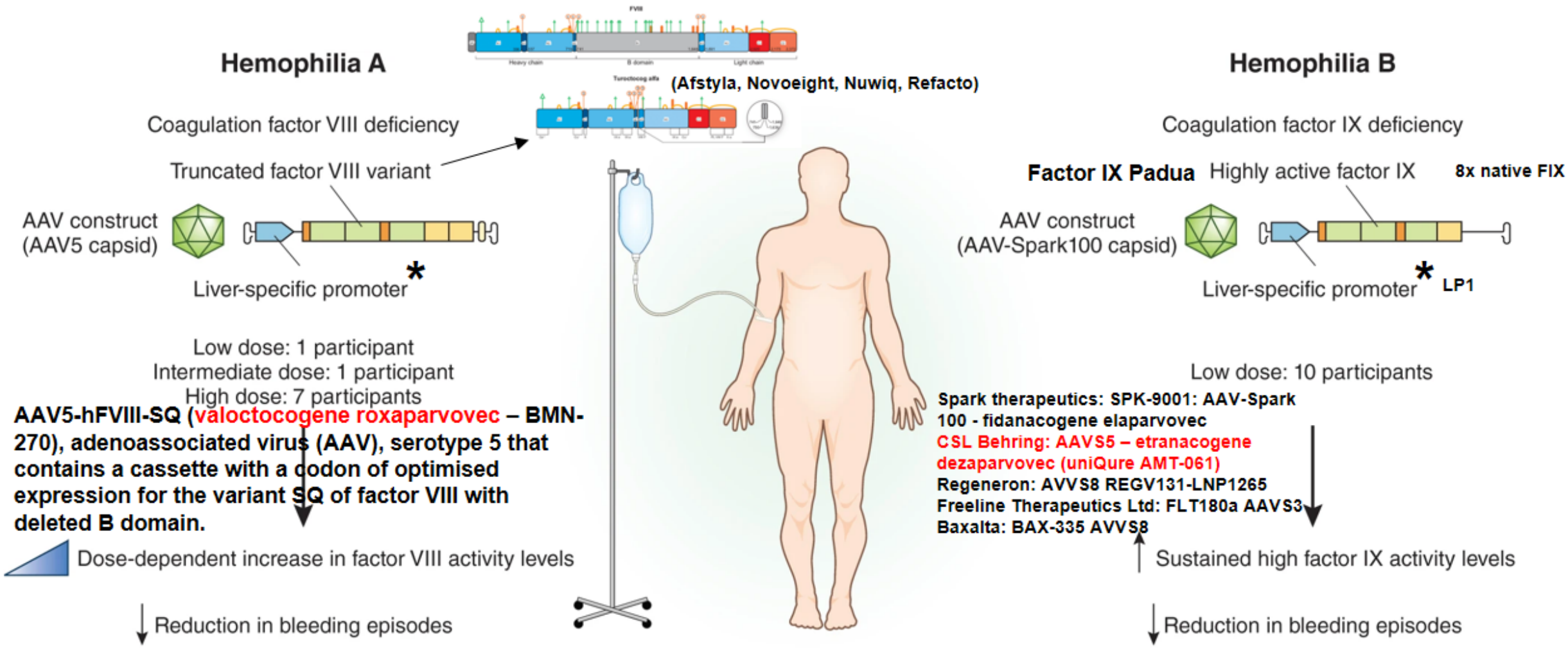
What does a gene therapy look like? (2)

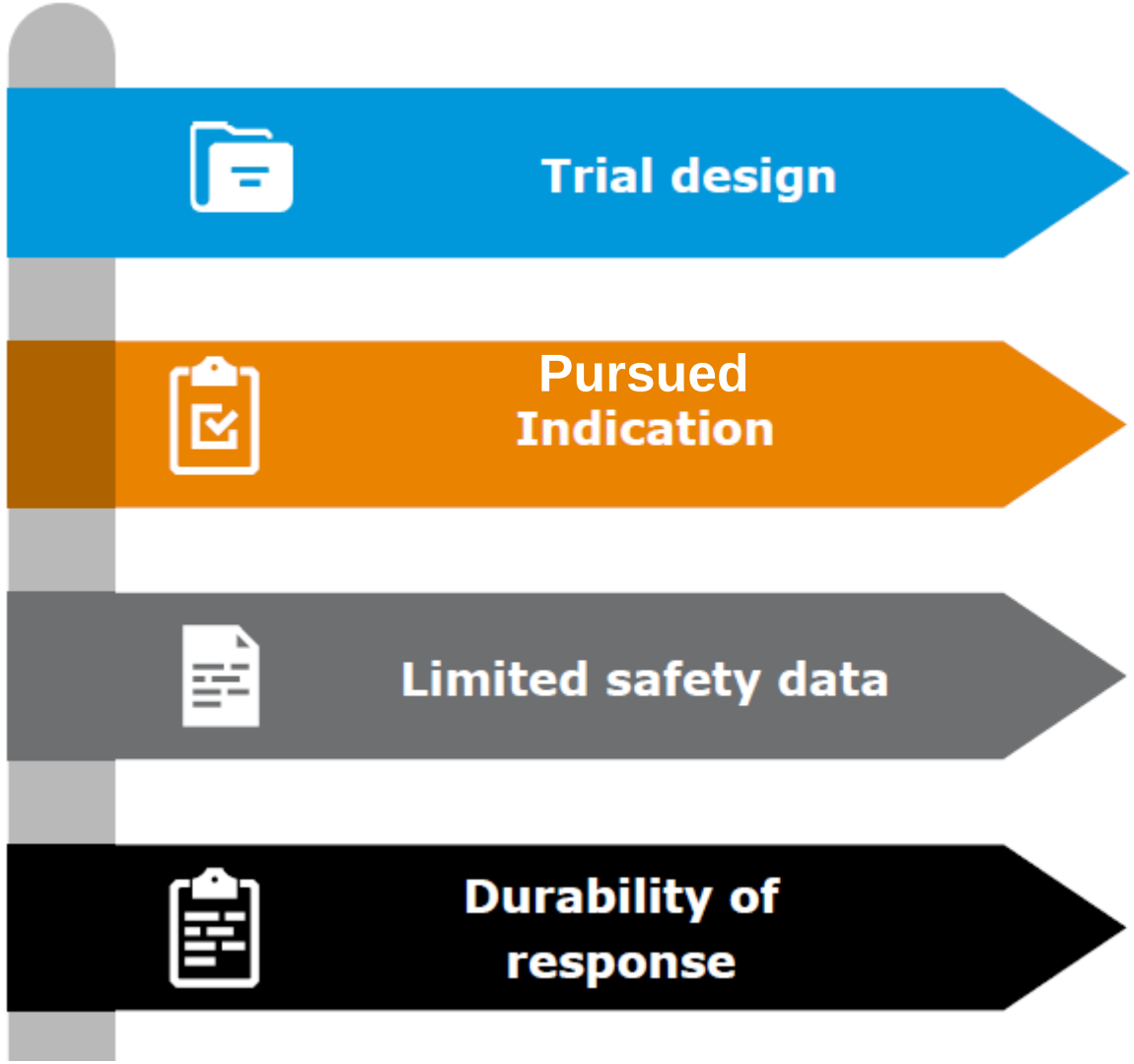


***liver specific promoter ensures that the gene is expressed only in hepatocytes after intravenous injection.**

Pickar, A., Gersbach, C. Gene therapies for hemophilia hit the mark in clinical trials. *Nat Med* 24, 121–122 (2018).

https://doi.org/10.1038/nm.4492

Challenges in clinical development of ATMP



Dose finding, lack of randomisation, non comparative trials (single arm trials), external controls, low patient numbers *

Not reflecting patient included in clinical trials (generally broader)

Limited study population, route of administration / surgical procedures, dose, tumorigenicity, biodistribution, integration, concomitant medication

Early planning of registries to bridge the gap on long term efficacy and safety is essential to build confidence for all stakeholders and demonstrate the magnitude of health benefit

*Cardiovascular Outcome Trials (CVOT) may be required for RNA terapeutics post-authorisation (e.g.: inclisiran, not an ATMP therapy)

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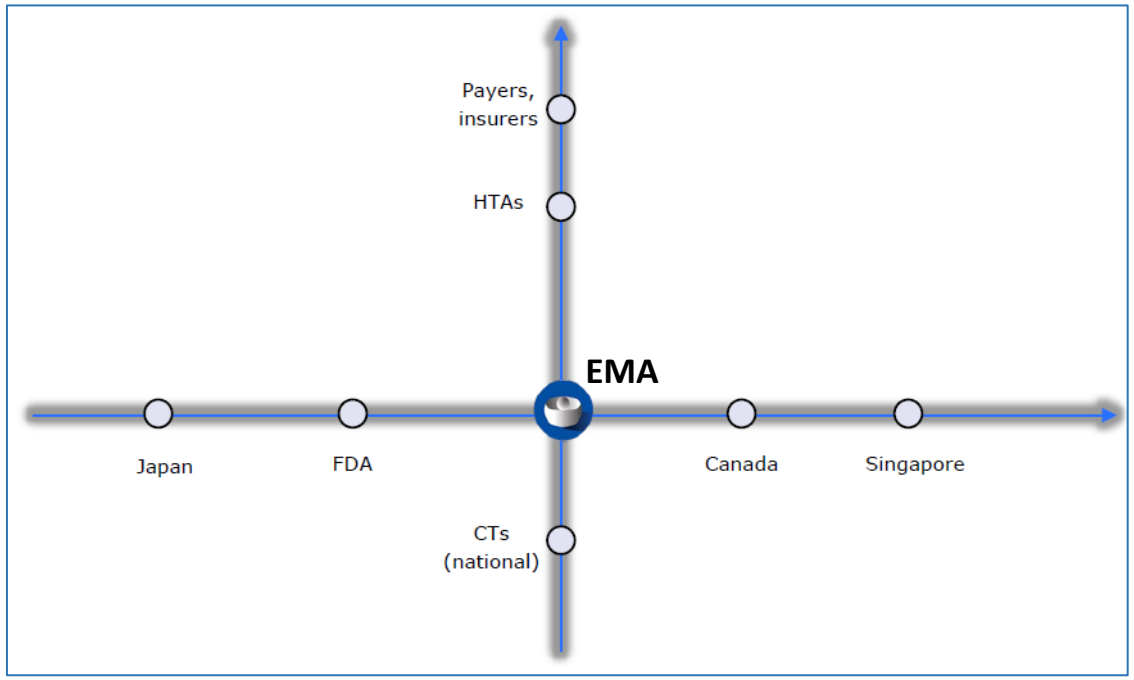
Alignment in requirements



- **ICH:** International Conference of Harmonisation: Europe (EMA), US (FDA) and Japan (PMDA). Agreement in principles.

•ICH guideline S12 on nonclinical biodistribution considerations for gene therapy products - Step 2b (EMA/CHMP/ICH/318372/2021).
•ICH Considerations - **Oncolytic Viruses** (EMEA/CHMP/ICH/607698/2008).
ICH Q5B Analysis of the **expression construct in cell lines** used for production of r-DNA derived protein products (CPMP/ICH/139/95).
ICH Q5D Derivation and **characterisation of cell substrates** used for production of biotechnological/biological products (CPMP/ICH/294/95).
ICH Q5A Viral safety evaluation of **biotechnology products derived from cell lines of human or animal origin** (CPMP/ICH/295/95).
ICH Topic Q5E Comparability of **biotechnological/biological products** (CPMP/ICH/5721/03).
ICH 5QC Stability testing of **biotechnological/biological products** (CPMP/ICH/138/95).
ICH Q6B Specifications: Test procedures and acceptance criteria for **biotechnological/biological products** (CPMP/ICH/365/96).
ICH Q7 Good manufacturing practice for **active pharmaceutical ingredients** (CPMP/ICH/4106/00).
ICH Q8 (R2) **Pharmaceutical development** (CHMP/ICH/167068/04).
ICH Q9 **Quality risk management** (EMA/CHMP/ICH/24235/2006).
ICH Q10 **Pharmaceutical quality system** (EMA/CHMP/ICH/214732/2007).
ICH E1 The **extent of population exposure** to assess clinical safety (CPMP/ICH/375/95).
ICH E3 Structure and content of **clinical study reports** (CPMP/ICH/137/95).
ICH E4 **Dose response information** to support drug registration (CPMP/ICH/378/95).
ICH E6 (R1) **Good clinical practice** (CPMP/ICH/135/95).
ICH E7 **Geriatrics** (CPMP/ICH/379/95).
ICH E8 General considerations for **clinical trials** (CPMP/ICH/291/95).
ICH E11 Clinical investigation of **medicinal products in the paediatric population** (CPMP/ICH/2711/99).
General principles to address the **risk of inadvertent germline integration of gene therapy vectors** (CHMP/ICH/469991/2006).
General principles to address **virus and vector shedding** (EMEA/CHMP/ICH/449035/2009).
ICH Q2 (R1) Validation of **analytical procedures**: text and methodology (CPMP/ICH/381/95).
ICH Q5A (R1) Viral safety evaluation of **biotechnology products derived from cell lines** of human or animal origin (CPMP/ICH/295/95).
ICH Q5C Stability testing of **biotechnological/biological products** (CPMP/ICH/138/95).
ICH Q5D Derivation and **characterisation of cell substrates** used for production of biotechnological/biological products (CPMP/ICH/294/95).
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ICH E11 Clinical investigation of **medicinal products in the paediatric population** (CPMP/ICH/2711/99).

EMA GUIDELINES: 35 for gene therapy (14 efficacy & safety aspects); 48 for cell-therapy and tissue engineering (11 E&S aspects):

https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products

Specific safety considerations

- Impact of manufacturing process on cells: e.g. on tumourigenicity profile.
- Storage, distribution and reconstitution of the product cells at administration site.
- Administration procedure (e.g. surgery) – both safety & efficacy.
- Patient pre-conditioning / immunosuppression.
- Long persistence of the product in the patient.
- GTMPs: risk of insertional mutagenesis ➡ Long term follow-up (FU)
- Shedding, Environmental Risk Assessment (ERA), risk of Healthcare professionals, care givers….
- Allogeneic cells: risk of disease transmission, unwanted immunogenicity, graft vs. Host Disease (GvHD)…

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EMA guidelines: Cardiovascular System

- Prepared by the Cardiovascular Working Party (**CVSWP**) of the EMA-CHMP.
- The EMA's scientific guidelines on the clinical evaluation of human medicines used in conditions affecting the cardiovascular system help medicine developers prepare marketing authorisation applications:
  - Hypertension
  - Lipid disorders
  - Pulmonary arterial hypertension
  - Arrythmias
  - Venous thromboembolism
  - Heart failure
  - Coronary artery disease
  - Other
- For a complete list of scientific guidelines currently open for consultation, see Public consultations.

EMA guidelines of efficacy and safety: cardiovascular system. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-efficacy-safety/clinical-efficacy-safety-cardiovascular-system

Specific efficacy considerations

- **Endpoints reflective of the drug effect.**
  - **Surrogate markers:**
    - **Laboratory:** LDL-C, triglycerides, NT-proBNP, levels of the defective protein before and after therapy (e.g.: levels of FVIII or FIX before and after gene therapy for hemophilia A and B, respectively).
    - **Hemodynamics:** ejection fraction, etc.
    - **Imaging endpoints:** infarct size, etc.
  - **Intermediate endpoints:** exercise capacity, improvement in clinical scores, etc.
  - **Outcome endpoints:** mortality, MACE, etc. Difficult to investigate in small populations.

- **Need to generate real world evidence (RWE).**
  - **Before authorization:**
    - Internal comparison: run-in period for setting baseline comparison (e.g.: annualized bleeding rate in haemophilia, consumption of coagulation factors).
    - External comparison: registry with a population similar to that enrolled in the pivotal study/ies.
  - **After authorization:**
    - Maintenance of the effect.

EMA = European Medicines Agency; LDL-C = low-density-lipoprotein cholesterol; MACE = major adverse cardiovascular events; NT-proBNP = N-terminal pro-hormone B-type natriuretic peptide;

EMA guidelines of efficacy and safety: cardiovascular system. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-efficacy-safety/clinical-efficacy-safety-cardiovascular-system

Post-authorization requirements and RWE

- **Real world evidence (RWE)** complements evidence from clinical trials:
  - For post-marketing authorisation (MA), but also before MA for regulatory decision-making.

- Converting data to evidence requires:
  - Knowing the data quality and characteristics.
  - Applying robust methods.
  - Understanding the evidentiary value.

- Collaboration between stakeholders (regulators, companies, HTAs, payers, clinicians/Academia and participation of patients) is critical:
  - To plan product development –use **EMA joint scientific advice**.
  - To build an EU network for accessing and analysing real world data: **DARWIN EU**.

DARWIN = Data Analysis and Real World Interrogation Network; EMA = European Medicines Agency; EU = European Union; HTAs = Health Technology Assessment Agencies;

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Current hot topics in patients access to ATMPs

- **How to assess the real value for patients and society.**
- **How to achieve the two main aims:**
  - Robust evidence.
  - Reduction of uncertainty.
- **Two main tools being discussed at many levels:**
  - **Innovative payment models:** single payment, risk-sharing, outcome-based (**payment by results, PbR:** contingent on the independent verification of results), annual payment model, conditional reimbursements, annuity/Netflix model…
  - **Use of Real world evidence (RWE):** measurement of clinical results/outcomes in real life. Linked to PbR.
- **Public risk versus company profits.**
- **Access in the wider sense:**
  - Within the EU, orphans vs large populations, across therapeutic areas.
  - Regulatory help for fast approval outside the EU.
- **Future trends:**
  - Crowdfunding.
  - **Global buyers clubs**.

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Conclusions

- Gene therapies have particular characteristics compared with other medical therapies:
  - Generally issued for rare orphan indications with small populations available. Need for suitable endpoints and attainable objectives.
  - Non-comparative trials, limited safety data and limited data on durability of response.
  - Need for RWE to generate evidence after and even before authorization.
- Regulatory landscape is heterogeneous but there is consensus in general principles for development and regulatory assessment (ICH).
- Patient access to ATMPs is complex. Need for collaboration between stakeholders is necessary:
  - To plan product development –use EMA joint scientific advice.
  - To build an EU network for accessing and analyzing real world data: DARWIN EU.

Thanks for your attention!

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