EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Advanced Therapies (ATMPs)

Awareness raising on the development and evaluation of ATMPs

PCWP-HCPWP Joint meeting

Presented by Patrick Celis & Ana Hidalgo-Simon on 3 March 2022
Advanced Therapies Office

Content

1. **Authorisation of ATMPs in the EU** – Patrick Celis
   - What are ATMPs & why we regulate them differently from other medicines?
   - Approval of ATMPs
   - Support to ATMPs developers

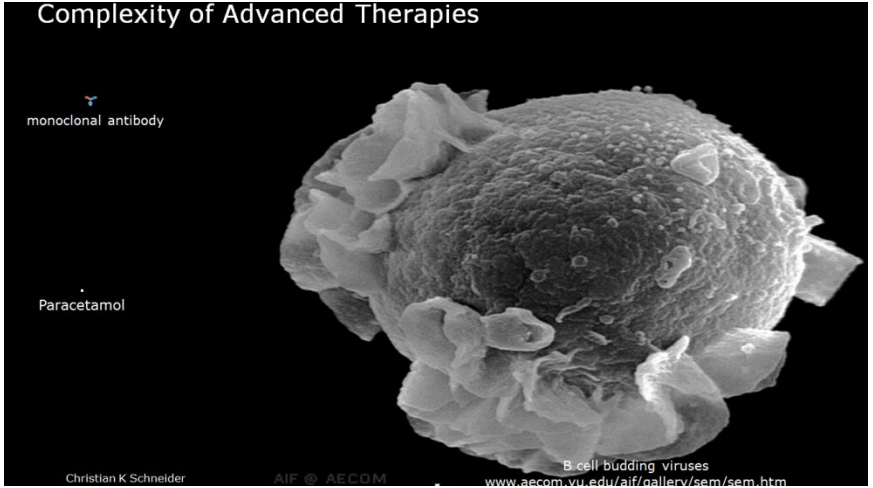
2. **How to support & improve patients' access to ATMPs** – Ana Hidalgo-Simon
   - Interaction with HTAs and payers
   - Access, price and the long-term view
   - How can patients and health care professionals help regarding access to ATMPs?

1. **Authorisation of ATMP in EU**

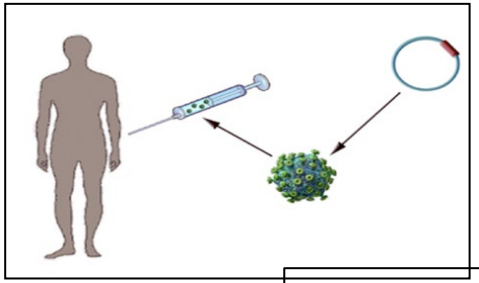
2. How to support & improve patients' access to ATMPs

What are ATMPs

- 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



Examples of approved ATMPs: gene therapy MP

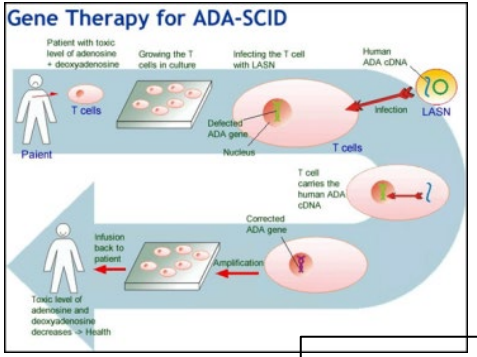


In vivo gene therapies

Other in-vivo GTs: Zolgensma, Luxturna

Example: Glybera

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



Ex-vivo gene therapies

Other ex-vivo GTs: CAR-T cells

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)

CAR T cells - from apheresis to infusion

EU hospital/trial site → EU preselection site → US manufacturing site → EU hospital/trial site

Freeze -> thaw

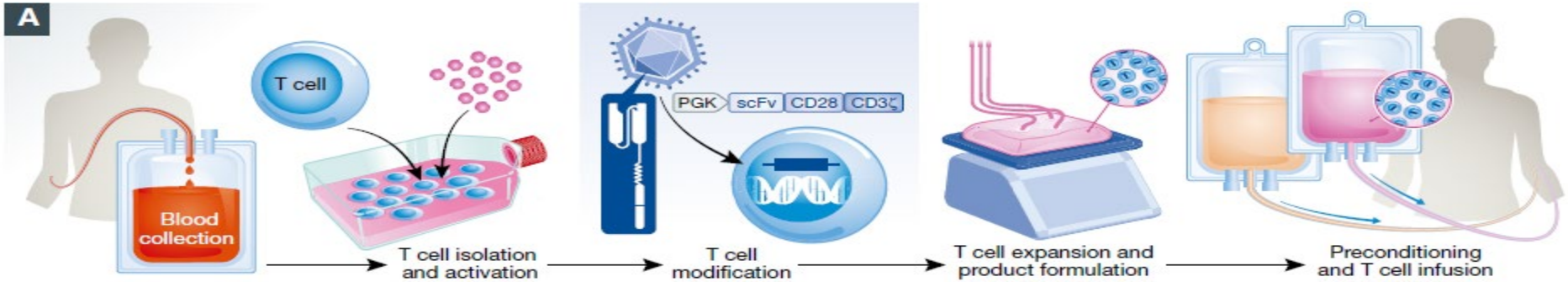
EU manufacturing site

Freeze -> thaw

Apheresis PBL

Lymphodepletion/ Conditioning

Infusion

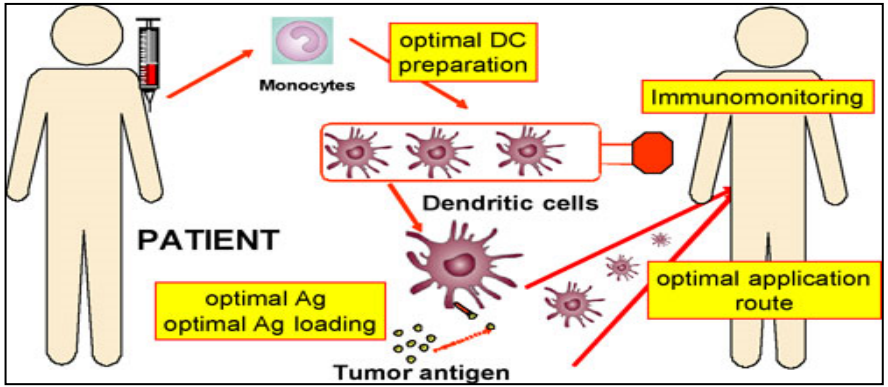


Hartmann J, **Schüßler-Lenz M**, Bondanza A, **Buchholz CJ,** *EMBO Mol Med* , 8 2017.

Examples of approved ATMPs: somatic cell therapy MP

Example: Provenge

- Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (sipuleucel-T)
- Treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer

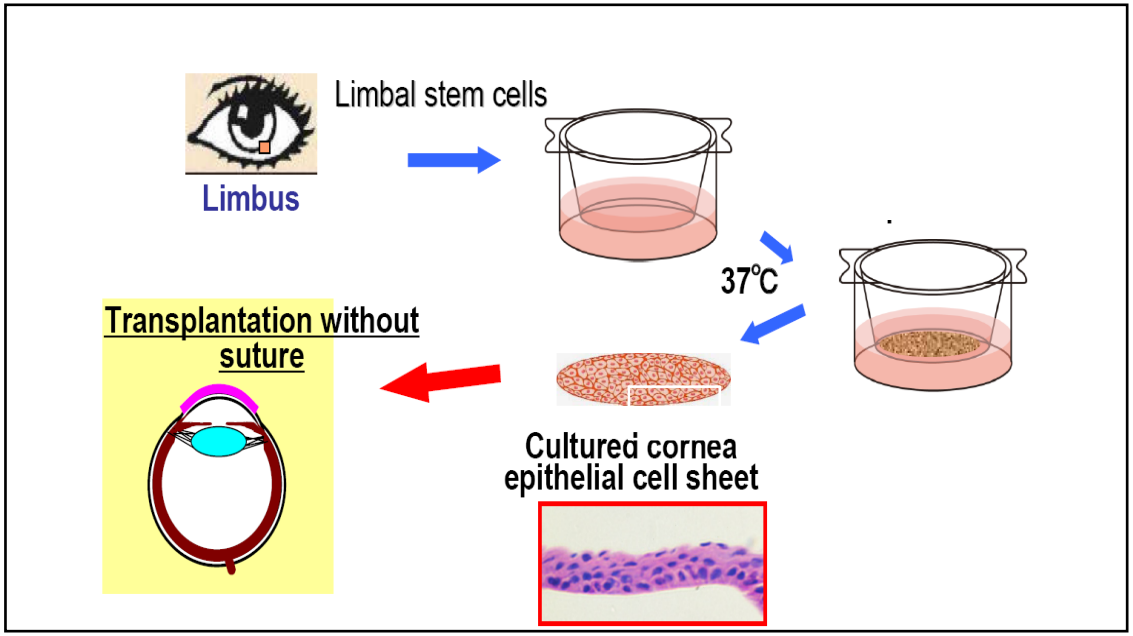


Other approved sCTMP: Alofisel (Allogeneic expanded MSCs for treatment of anal fistula)

Example of approved ATMPs: Tissue engineered products

Example: Holoclar

- Ex vivo expanded autologous human corneal epithelial cells containing stem cells
- Treatment of adult patients with moderate to severe limbal stem cell deficiency unilateral or bilateral, due to physical or chemical ocular burns.

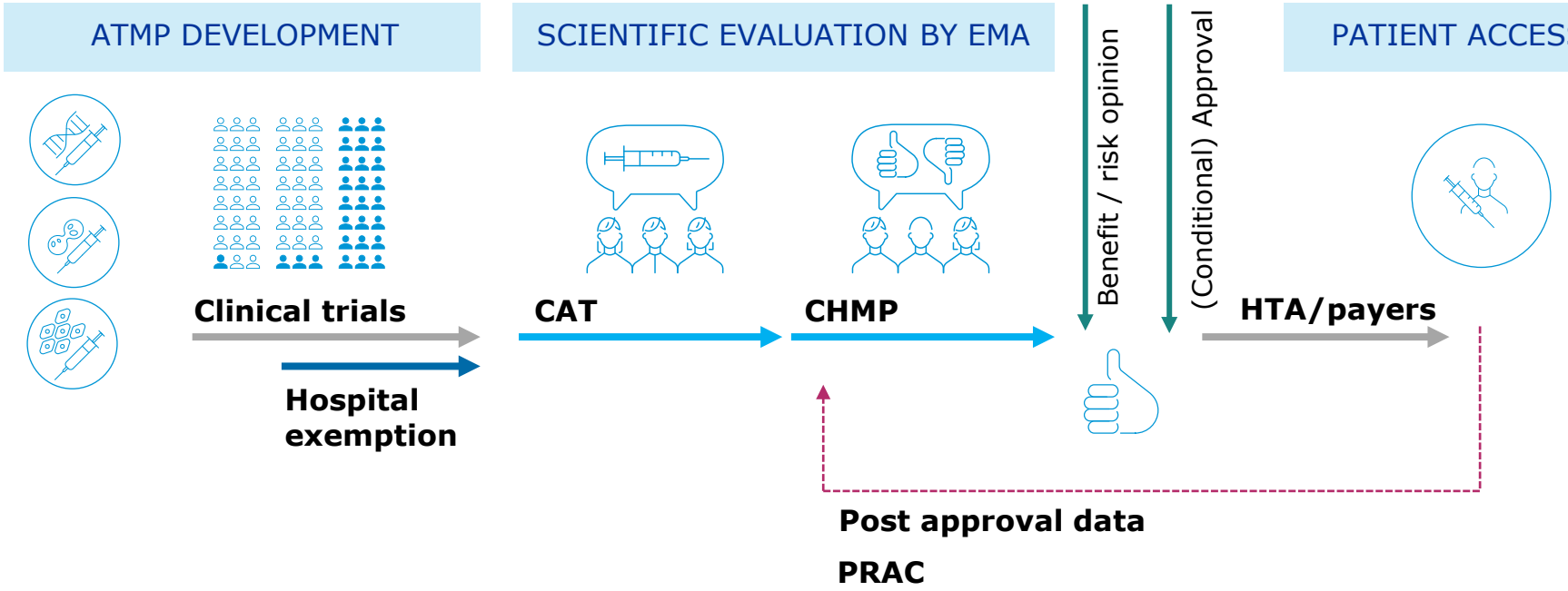


Other approved TEPs: chondrocyte containing product (cartilage repair)

What are the key differences from other medicines?

- Complex products to develop, manufacture, characterise, test
- Non-standard non-clinical & clinical development programmes
- Novel safety concerns
- Need for long-term safety & efficacy follow-up after approval
- New treatment options (orphan diseases, or patients with no/limited treatment options)
- Evaluation by expert Committee: Committee for Advanced Therapies (CAT)

Entry route of ATMPs to the EU market

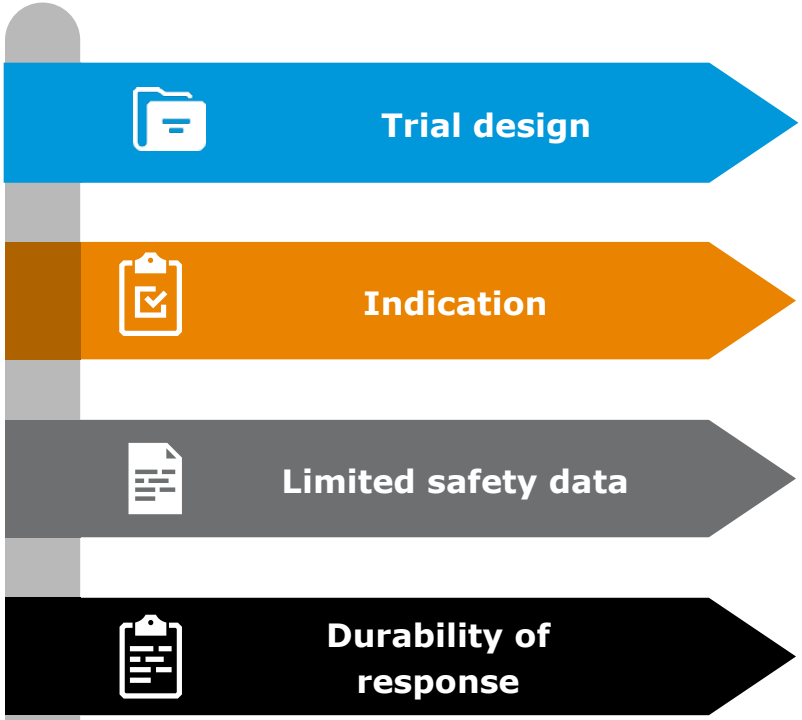


CAT: Committee for Advanced Therapies
CHMP: Committee for Medicinal Products for Human Use
PRAC: Pharmacovigilance Risk Assessment Committee

Specific safety and efficacy 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 FU
- Shedding, ERA, risk of HC professionals, care givers ….
- Allogeneic cells: risk of disease transmission, unwanted immunogenicity, GvHD…

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

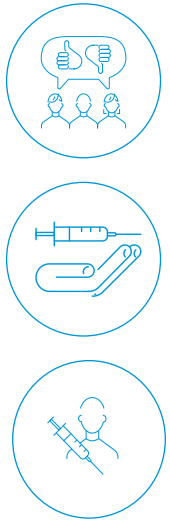
Limited study population, route of administration / surgical procedures, dose, tumorigenicity, biodistribution, integration, concomitant medication

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

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

ACCESS DECISION

POST-LICENSING EVIDENCE

Support to ATMP developers

<u>Classification of ATMPs</u>

- Incentive specific to ATMP developers – free of charge
- 'Is the product that I am developing an ATMP?'
  - Regulatory certainty

<u>ATMP Certification</u>

- Incentive specific for SME-ATMP developers
- 'Is my product development so far on track for a future Marketing Authorisation Application?'
  - Scientific certainty

Support to ATMP developers

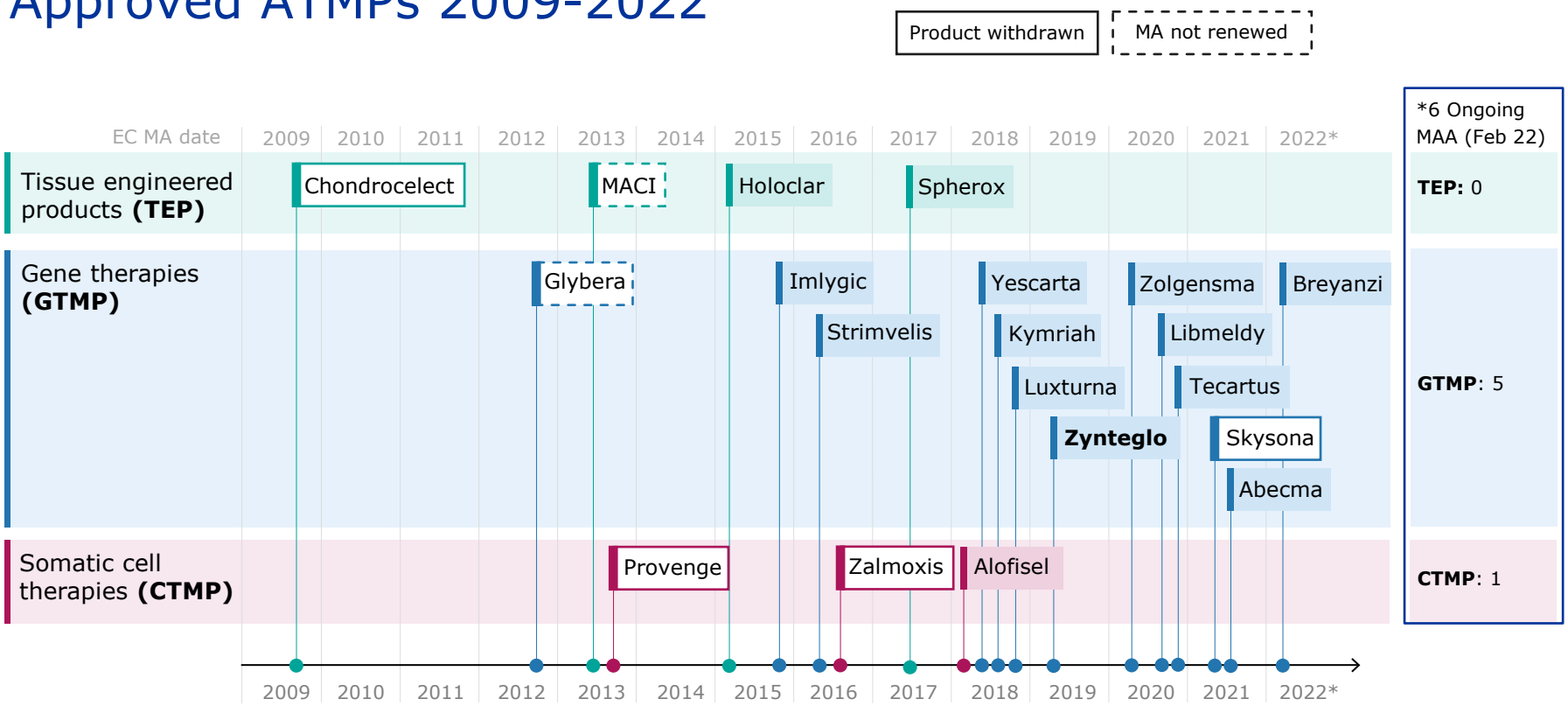
Scientific advice

- Not ATMP specific
- Scientific certainty on quality/manufacturing, non-clinical & clinical development
- Parallel SA with FDA
- Parallel consultations from regulators and HTA bodies

PRIME

- Enhanced support for the development of medicines for an unmet medical need
- Not ATMP specific, but high proportion of ATMPs designated as PRIME

Approved ATMPs 2009-2022



1. Authorisation of ATMP in EU

2. How to support and improve patients' access to ATMPs

Access to market versus access to patients

Once out of EMA remit….

…….Now very much in our sights

Regulatory science strategy

The European Medicines Agency's (EMA) 'Regulatory Science to 2025' strategy is a plan for advancing EMA's engagement with regulatory science over the next five to ten years, covering both human and veterinary medicines.

Regulatory science strategy | European Medicines Agency (europa.eu)

European medicines agencies network strategy to 2025

Protecting public health at a time of rapid change

European medicines agencies network strategy to 2025 - Protecting public health at a time of rapid change (europa.eu)

How ATMPs are different from traditional medicines

	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…

Current hot topics in ATMPs access to patients

- **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, outcome-based, annual payment model, conditional reimbursements, annuity/Netflix model…
  - Use of RWE
- **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

What EMA/CAT/EU network does to help patient access to ATMPs

- Aligning evidence collection with downstream stakeholders: talking and working with EUnetHTA, payers
- Revising the need, the type and the length of the post-authorisation commitments (without jeopardising public health), product by product
- Promoting the use of RWE and production and use of RWD
- Working with and on good registries
- Training and teaching: all stakeholders, including other decision-makers
- Other: warning of the dangers of unlicensed therapies, leveraging international collaborations, working with academic developers, supporting EC funding activities

Scientific advice in parallel with Health Technology Assessment bodies (HTAs)

→ **Aligning evidence-generation to serve both:**

→ ***Approval decisions (EMA)***
→ ***Reimbursement decisions (HTA, national level)***

- **Early dialogue** between regulators, HTAs and developers
- Simultaneous **feedback at an early stage** on R&D plans
- **Optimised development** plan ➔ **Improved access** for patients

EUnetHTA21

REGULATION (EU) 2021/2282 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 15 December 202 on health technology assessment and amending Directive 2011/24/EU

- EMA/EUnetHTA21 work plan
- the EUnetHTA21 consortium will consult EMA on some of their deliverables with relevance for EMA.

Post-authorisation requirements

- Post-authorisation requirements essential for long-term follow-up
- Early planning required to take full advantage of flexibility at marketing authorisation stage
- Essential to align with downstream stakeholders' needs

	Type of study and aims	**Final study report**	**Authorization**
Holoclar	Clinical study to evaluate Safety and Efficacy	31/12/2020	19/02/2015
	Long-term study to follow-up safety and efficacy	31/01/2023	
	Registry: primary long-term safety, secondary gain knowledge of the medicine and the disease	31/01/2025	
	Clinical study to evaluate efficacy and safety including patients from 2 years and adults	31/12/2020	
Strimvelis	Registry to evaluate long term safety and efficacy	31/12/2037	30/05/2016
	Long-term follow-up of patients treated in the clinical development programme.	31/03/2020	
	Evaluation of the effectiveness of additional risk minimisation measures	31/03/2021	
	Evaluation of insertion site analysis to predict malignancy due to insertional oncogenesis	31/12/2024	
Zalmoxis	Clinical study in children to assess safety in paediatric patients	31/12/2018	23/08/2016
	Clinical study in children to assess safety in paediatric patients	31/12/2022	
	Clinical trial to assess safety and efficacy	31/03/2021	
	Registry to assess safety and effectiveness in real clinical practice using the EBMT registry	31/12/2022	

Real World Evidence (and data)

Real world evidence complements evidence from clinical trials – used for:

- For regulatory decision-making
- For post-MA following

Converting data to evidence requires:

- Knowing the data quality and characteristics
- Applying robust methods
- Understanding the evidentiary value

Collaboration between regulators, HTAs and payers 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

RWE use: example of COVID-19

Review of study results

- **Daily triage** of published studies
- **Cumulative reviews** e.g. ACEi/ARBs and HCQ to support EMA Task Force
- Use of **EU PAS Register** to support transparency, collaborations and quality of studies

EMA-funded projects

- Infrastructure for COVID-19 **vaccine monitoring** and specific studies
- Framework for **multicentres collaboration** for multicentre observational studies
- **Pregnancy study** on effects of COVID-19 infection and treatments

International collaboration (ICMRA)

- Preparation for **vaccine safety monitoring** (lead MHRA)
- Building **international cohorts** facilitating multicentre observational studies (lead Health Canada) includes steroids and coagulation studies
- **Pregnancy research** to support regulatory decision-making (lead EMA)

ENCePP

- **Strengthened mandate** in the context of the COVID-19:
- Publication of **COVID-chapter** for the ENCePP Method Guide

Registries: bridging the gap to establish clinical effectiveness

- **Qualification opinion** of cellular module of **EBMT registry – Feb 2019**

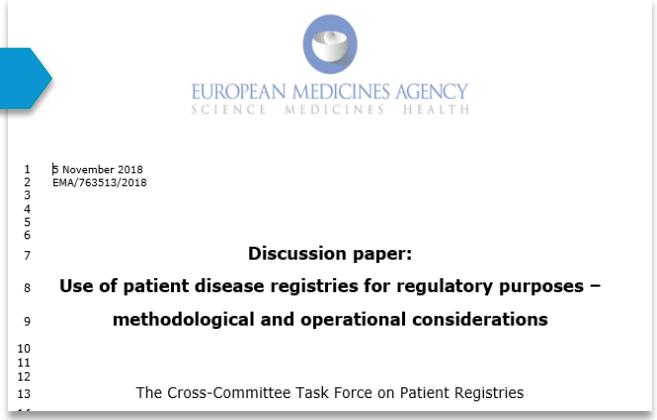
  ✓ opportunity to collect **long-term** real world data on CAR-T cells

Quality of data for regulatory purposes

Qualification process
huge source of learning

EBMT European Society for Blood and Marrow Transplantation

Observed by eunethta


EUROPEAN MEDICINES AGENCY
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5 November 2018
EMA/763513/2018

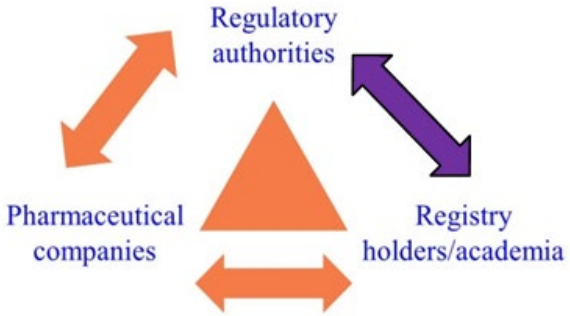
Discussion paper:

Use of patient disease registries for regulatory purposes – methodological and operational considerations

The Cross-Committee Task Force on Patient Registries

EMA Patient registry initiative

- Launched in September 2015
- To **facilitate the use of disease registries** by introducing and supporting a systematic approach to their contribution to the benefit-risk evaluation of medicines



Source: Nicola Ruperto, PRINTO

- Key components of the initiative

✓ To **promote dialogue** between regulators, companies and registry holders to understand barriers and opportunities of using disease registries

✓ To **provide guidance** to clarify methodological concepts and regulatory requirements

- EMA cross committee Task Force

Leveraging international cooperation

- Discussions with international partners on regulatory approaches to ATMPs

e.g. starting materials, ethical issues

e.g. joint EMA-FDA Workshop on quality development in early access approaches (PRIME)

e.g. Clusters with FDA

- Ad-hoc product-specific discussions with international partners
- Reflections ongoing at ICMRA

- hotspots in regulatory science
- leveraging collaboration

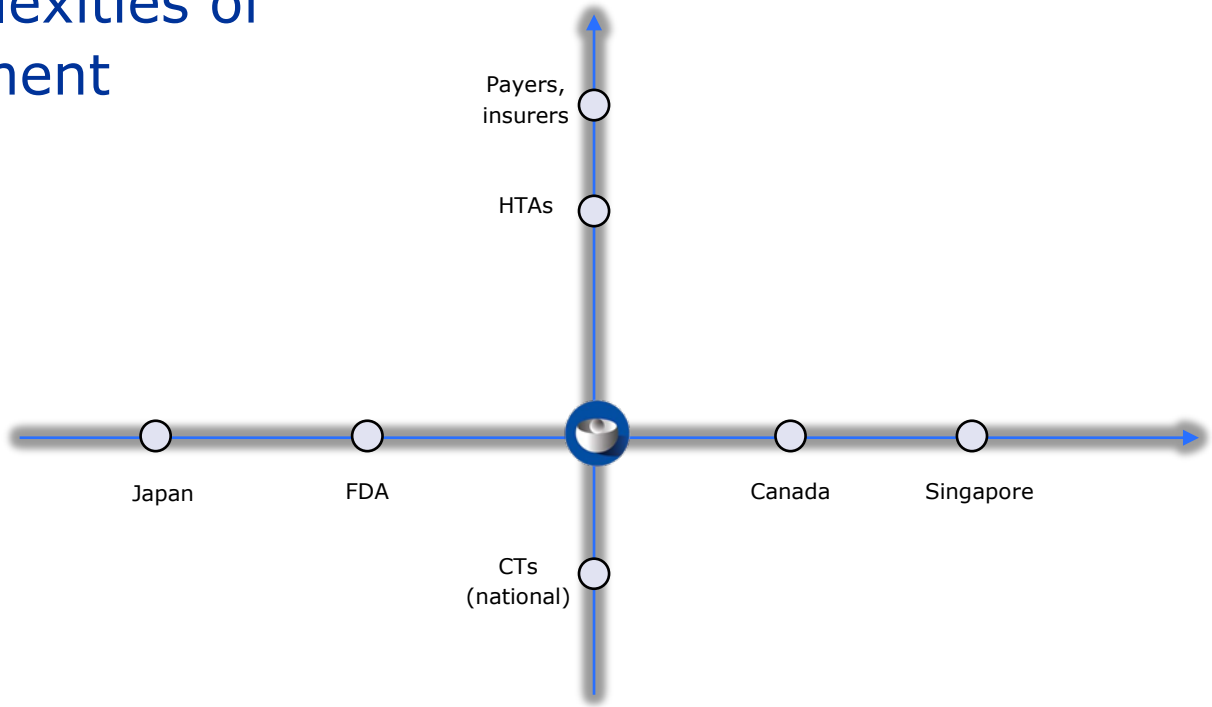
Advice for patients considering treatment with a cell-based therapy

If you are offered cell-based therapy, find out from your healthcare professional if it has been authorised by medicines authorities

- Ask your healthcare professional to explain the risks and benefits of the cell-based therapy and provide information in writing
- Ask your healthcare professional how you should report side effects resulting from the treatment
- Contact your national medicines authority or EMA if you have any questions*
- If you are considering taking a treatment in a non-EU country, check the regulations in that country

*ema.europa.eu/partners-networks/eu-partners/eu-member-states

Complexities of alignment



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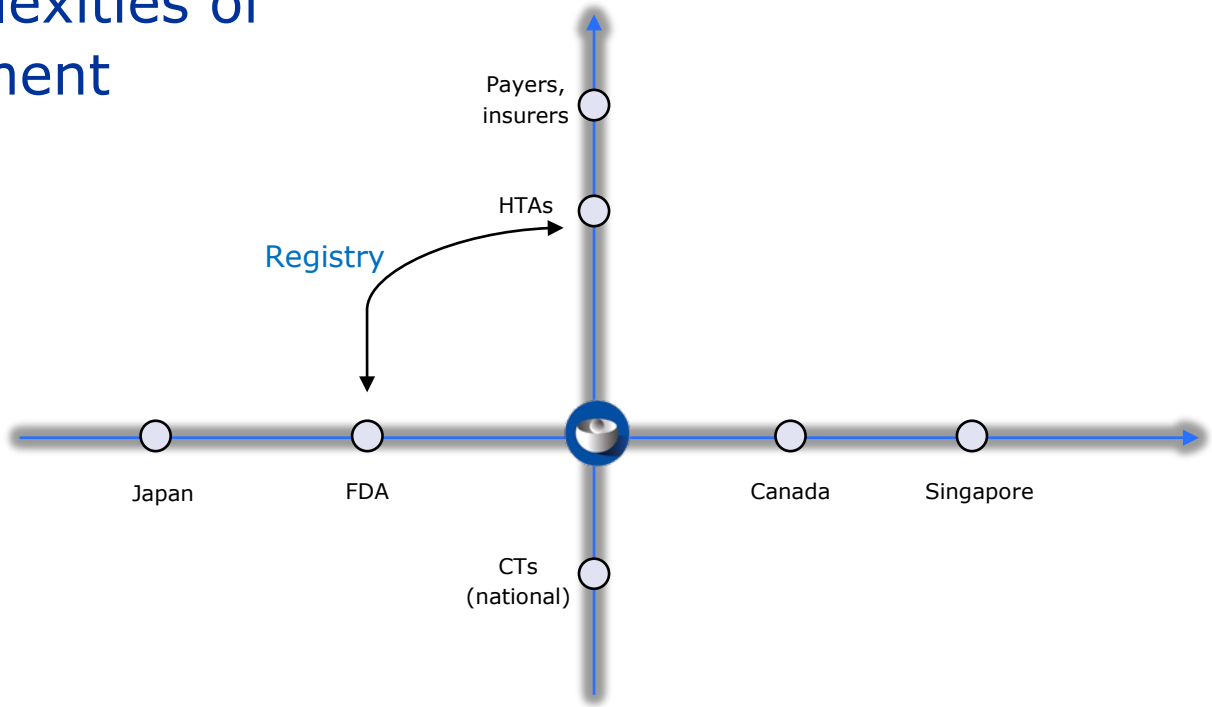

How Patients and HCPs can help - examples

Development:

- CT – participation, facilitation, logistics
- Promote early dialogue with HTAs/payers at national level

Regulatory process:

- Members of committees, WG, SAGs
- Training and education of beneficiaries, prescribers, decision makers

Post- MA:

- Feedback on protocols, end-points, scales…
- Registries: selection, funding, harmonisation initiatives…
- Awareness: authorised therapies, need for long follow-up…

Communication of news, needs and knowledge!

Any questions?

Further information

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