EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Marketing Authorisations of Advanced Therapies in EU– a regulatory update by the EMA Committee for Advanced Therapies

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Disclaimer

The views expressed in this presentation are the personal views of the author and may not be understood or quoted as being made on behalf of the European Medicines Agency or the Paul-Ehrlich-Institut.

EU Marketing Authorisations (MA) 2009 – 2019

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Chondrocelect®	Cultured chondrocytes for repair of knee cartilage defects (2009)
MACI®	
Spherox®	
Holoclar®	Cultured corneal epithelial cells for treatment of corneal lesions
Provenge®	Metastatic prostate cancer
Zalmoxis ®	Stem cell transplantation, adjunctive treatment
Alofisel ®	Crohn`s disease, complex anal fistula
Glybera®	Familial LPL deficiency
Imlygic®	Injectable melanoma
Strimvelis®	Severe combined immunodeficiency ADA-SCID
Yescarta®	B-cell Lymphoma (DLBCL)
Kymriah ®	B-cell Lymphoma (DLBCL), B-cell acute lymphoblastic leukemia
Luxturna ®	Inherited retinal dystrophy, RPE65 mutation
Zynteglo ®	Transfusion-dependent β-thalassaemia, not β0/β0 (4.2019)

Tissue engineered products Somatic cell therapies Gene therapies

ATMPs in Europe (2009- 2019)

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~ 500 clinical trials using ATMPs in EU (2009-2017)

~ 350 ATMP classifications

~ 350 scientific advice requests
Dominance of gene therapies

22 MAAs reviewed

13 ATMPs approved, **1** decision by European Commission pending

2 withdrawn
2 ended

Market

9
licensed
ATMPs

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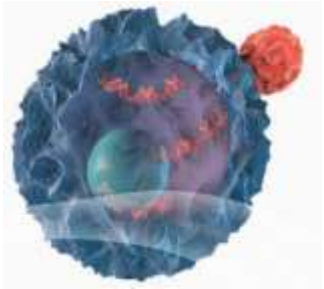
Legal Framework

Advanced Therapy Medicinal Products (ATMPs) Regulation (EC) No1394/2007

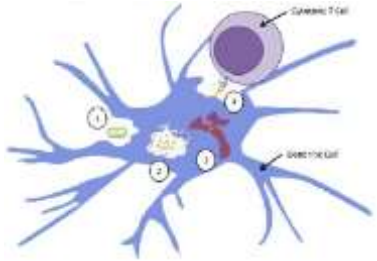
- ATMPs are medicinal products
- Are authorized in EU via the centralized procedure
- Are assessed by the Committee for Advanced Therapies

Gene therapy
e.g.CAR T cells



➔ **Recombinant nucleic acid**

Somatic cell therapy



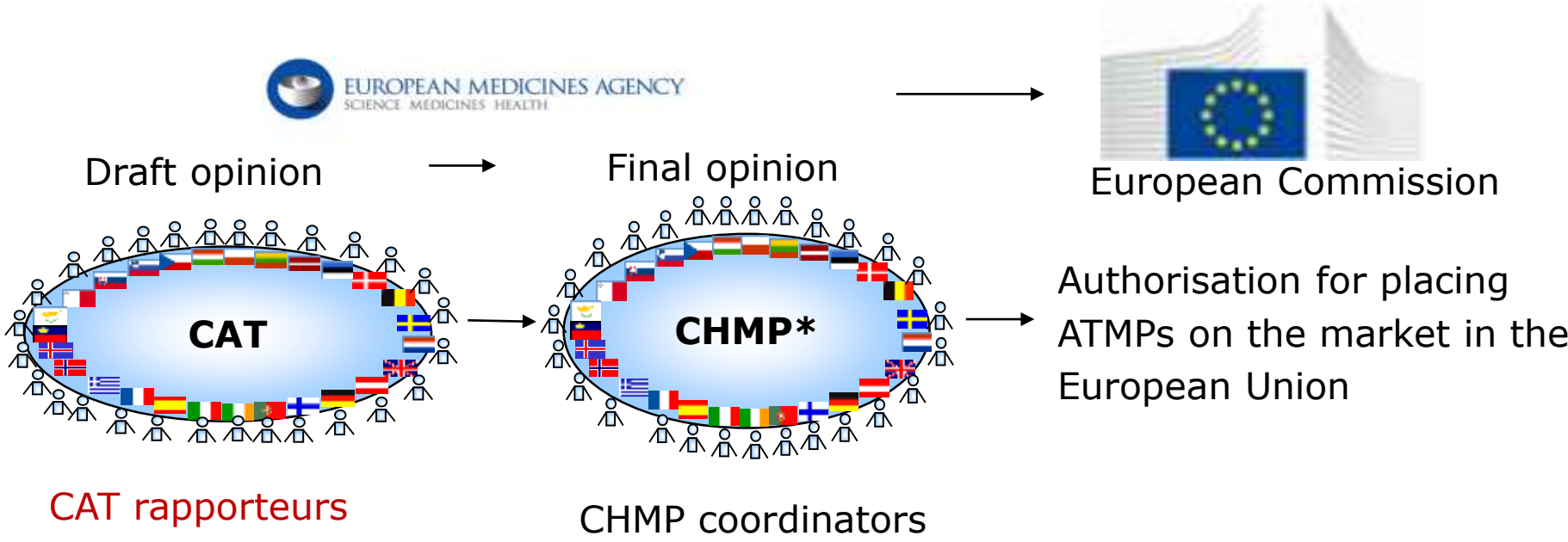
➔ **Pharmaco-immunological…**

Tissue engineered product

➔ **Regeneration, repair….**

EMA Committee for Advanced Therapies (CAT)

Quality, safety, efficacy -> positive benefit-risk assessment



*Committee for Medicinal Products for Human Use

The CAT – tasks and composition

Evaluation of marketing authorisations

Classification -> ATMP or not

Certification

Scientific advice (via SAWP) and Priority Medicines (yes/no)

Support to other committees (e.g. Pediatric Committee PDCO)

Publications, guidelines

Interaction with stakeholders

Full house - 34x2

Clinicians, scientists from 28 EU member states plus Norway, Iceland, clinician and patient representatives

Genetically modified cells - CD19-CAR T cells

EU authorised (8/2018)

Yescarta™
(Axicabtagene ciloleucel)

- γ-RV (scFv.CD28.CD3z)
- Non-Hodgkin Lymphoma (DLBCL , PBMCL)
- Manufacturing site: US

Kymriah™
(Tisagenlecleucel)

- LV (scFv.4-1BB.CD3z)
- Pediatric B-ALL, Non-Hodgkin Lymphoma (DLBCL)
- Manufacturing site: US, Germany

Points to address at marketing authorisation

Several rounds of questions to applicant (210 days review time)

To substantiate the Benefit-risk assessment

- Is the treated patient population representative for the target population?
- Are frequency and durability of tumor responses (OR, CR) meaningful (single arm trial setting)
- Is large scale product manufacturing and supply chain assured?
- Is safe and effective use assured under real world conditions?
- How are risks identifed, characterised, managed post-marketing?
- How is safety and efficacy follow-up ensured?
- Which specific post-marketing studies are intended to complement missing information

⟹ Risk Management Plan

Regulatory tools

to address uncertainties at marketing authorisation

Post-approval commitments and obligations ->part of B/R

- Commitments in Risk Management Plan
  - Risk minimisation measures
    - Site/hospital qualification/certification process, availability of tocilizumab
    - Patients in proximity of treatment center
    - Educational material for Health care professionals, patients
- Conditions to the marketing authorisation
  - Post-authorisation safety studies: data from registries EBMT, CIBMTR
  - Ovservational study for efficacy and safety follow-up, manufacturing turnaround time

➢ Assessed by Pharmacovigilance Risk Assessment Committee (PRAC) in cooperation with CAT, Annexed to the CAT/CHMP opinion, legally binding

Regulatory tools

to recommend marketing authorisation with less complete data

Conditional marketing authorisation

> On the basis of the CAT's assessment and positive opinion, EMA's committee for human medicines (CHMP) recommended a conditional approval for this medicine. This is one of the EU's regulatory mechanisms to facilitate early access to medicines that fulfil an unmet medical need. This type of approval allows the Agency to recommend a medicine for marketing authorisation with less complete data than normally expected, in cases where the benefit of a medicine's immediate availability to patients outweighs the risk inherent in the fact that not all the data are yet available.

Zynteglo

Benefit-risk positive at marketing authorisation

Applicant to comply with specific obligations (complete ongoing studies or conduct new studies)

Marketing authorisation is valid for 1 year

EMA/CAT support to ATMP developers

PRIority Medicines (PRIME)

Early identification of therapeutic innovation in unmet medical needs.

MAA review under accelerated assessment

- Application to EMA
  - Exploratory Phase
  - NC (and tolerability) data – only academia and SME
- Criteria for Accelerated Assessment fulfilled
- Rapporteur from CAT
- Kick-off meeting with EMA/CAT
- Enhanced Scientific Advice including HTAs

PRIME kick-off meetings

with CAT rapporteur and experts from committees and EMA

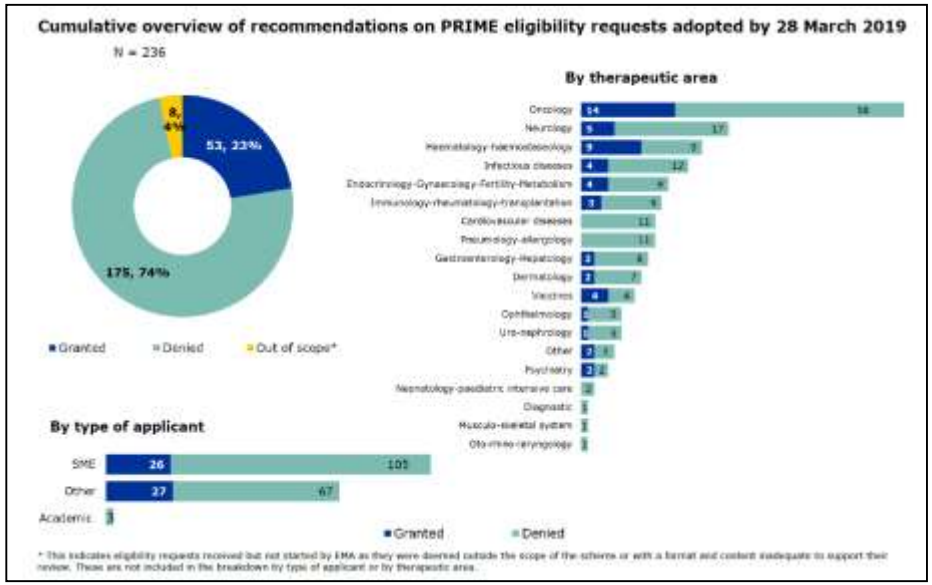
Discussion platform applicant – rapporteur – other experts

- Overview of development programme and milestones
  - Quality, non-clinical, clinical aspects
  - Changes to commercial manufacturing process and comparability analysis
  - Clinical data package at marketing authorisation, full versus conditional approval
  - Interaction with HTAs
  - Availability of disease registries
- Pediatric investigation plan PIP
  - Initiation of pediatric development, adolescent population and age subsets
- Orphan designation

➢ Gap analysis and next steps: scientific advice on key decision points

EMA/CAT support to ATMP developers

PRIority Medicines (PRIME) – focus on gene therapies



53 PRIME granted
23 were for ATMPs (43%)
- 21 are gene therapies
- 2 cell therapies
- 16 in hemato-oncology

3 medicines evaluated (accelerated procedure)
- all 3 are ATMPs
- 1 ATMP under evaluation

 CAT statistics 2009- April 2019, P. Celis

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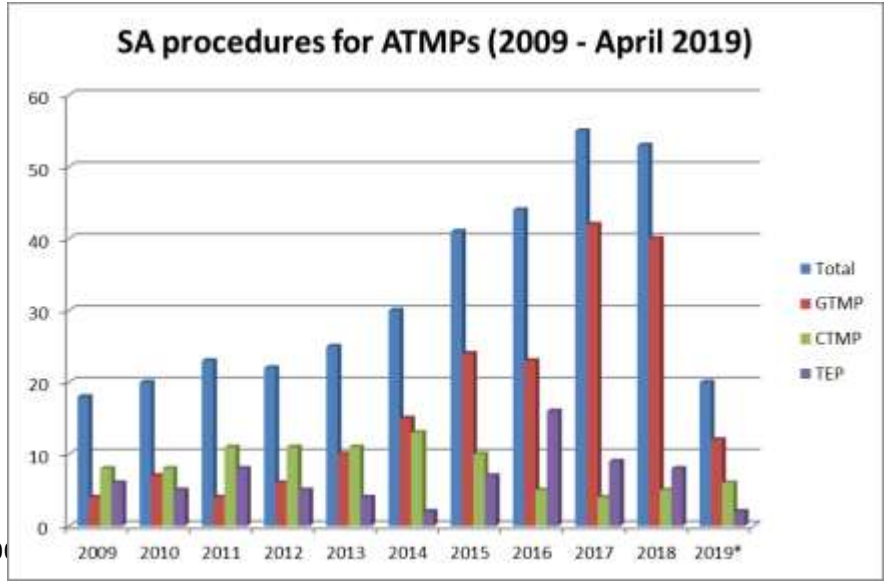
CAT
Other initiatives to support ATMP developers

- Provide scentific guidance on Advanced Therapies
- Develop further guidance documents to address
  - Investigational ATMPs/Clinical Trials – see addendum slides
  - Comparability of ATMPs – quality/manufacturing –work in progress
- Address scientific considerations of genome editing technologies
- Pursue dialogue with European Commission and National Competent Authorities to reduce discrepancies for Genetically Modified Organisms/ATMPs in Clinical Trial Applications - see addendum slides
- Interact with EU Health Technology Assessment Organisations to increase understanding of added value of ATMPs

The ATMP pipeline

Scientific Advice for ATMPs (2009- April 2019)

- 345 SA procedures started – CAT involved (routinely) in all SA for ATMPs
- Increase in SA's for ATMPs over period 2012 – 2017
- Majority of SA nowadays for GTMP (76% in 2017; 75% in 2018)



SA requests until end April 2019

The ATMP pipeline

Expected ATMP marketing authorisation submissions 2019-2020

Gene therapies

- Glioblastoma
- Non Hodgkin Lymphoma
- Multiple Myeloma
- Cerebral adrenoleukodystophy, X-linked
- Sarcoma
- Haemophilia A/B (3-4 ATMPs)

Tissue enginieering Products (TEP)

- Chondrocyte containing product

~10 ATMPs submissions expected
Dominance of gene therapies

Conclusion

ATMPs offer new treatment options for rare diseases and patients with unmet medical need

CAT has granted positive opinion to 14 ATMPs, steep increase in gene therapies

We observe rapidly evolving scientific and technological innovation entering the field of ATMPs -> keep pace

We observe issues related to manufacturing process changes, large scale manufacturing and manufacturing failures

Single arm pivotal trials, small sample sizes, external controls increase uncertainty -> promote innovation/early patient access versus wait for confirmatory evidence?

Increased need for post-authorisation data/registries/commitments/obligations as regulatory tool

Where I work - Paul-Ehrlich-Institut

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The past - London, Canary Warf

Presence and future - Amsterdam

CAT support to ATMP developers

ATMP specific guidelines

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

- Finalised since 2012:
  - Guideline of risk-based approach for ATMPs - 2014
  - Reflection paper on clinical aspects of tissue engineered products - 2013
  - Q&A on minimally manipulated ATMPs - 2017
  - Revision of Gene therapy Parental guideline – 2018

Ongoing GLs

- Revision Guideline on safety and efficacy FU and risk management for ATMPs (Q1 2018)
- Guideline on requirements for investigational ATMPs (external consultation Q1 2019)
- Revision Guideline for genetically modified cells (external consultation July 2018)

CAT/European Commission initiatives

to support to ATMP developers (1/2)

- GMP for ATMPs: adapted framework entered into force in May 2018

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf

- GLP: pragmatic approach adopted in 2017

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/QAs_document_on_GLP_-_2017.pdf

- GCP for ATMPs – in progress

- Update of the definition of "similarity" for the purposes of the orphan framework to ATMPs. https://ec.europa.eu/health/human-use/advanced-therapies_en

CAT/European Commission initiatives

to support to ATMP developers (2/2) – Interplay with GMO legislation

- Repository of national requirements

https://ec.europa.eu/health/human-use/advanced-therapies/gmo_investiganional_en

- Adapted approach for GMO assessment of genetically modified cells
  - Streamlined data requirements, specific Environmental risk assessment
  - Common application form for CTA submissions to 19 member states

https://ec.europa.eu/health/human-use/advanced-therapies_en

- Q&A on the interplay between EU legislation on medicinal products and GM

https://ec.europa.eu/health/sites/health/files/files/advtherapies/2018_gmcells_qa_en.pdf