

Regulatory Considerations from Europe

ASGCT Policy Summit 2019

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Overview

- What is an ATMP?
- Regulatory framework in Europe
- Specific procedures for ATMP
- EMA support for developers

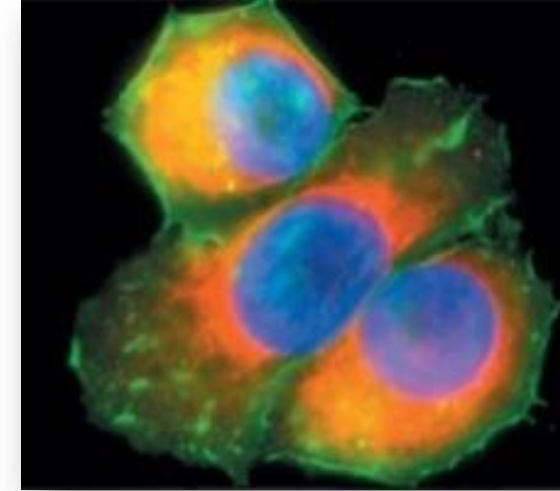
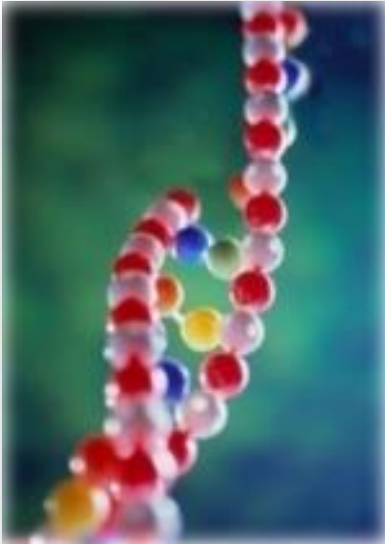
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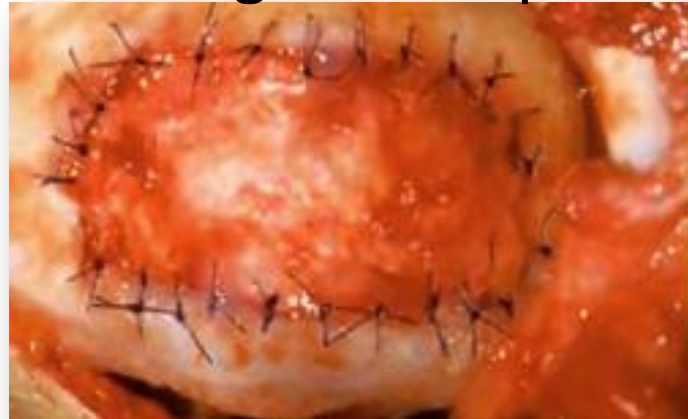
What is an ATMP?

Somatic cell therapy medicinal product

Gene therapy medicinal product



Tissue engineered product



What is an ATMP?

- **Gene therapy medicinal product**
 - Biological medicinal product
 - Contains or consists of recombinant nucleic acids
 - Used/administered with a view to regulating, repairing, replacing, adding or deleting a genetic sequence
 - All of the above has to apply
- Exception: vaccines against infectious diseases



! Under the EU framework medicinal products consisting of synthetic nucleotides is not classified as gene therapy and is thus not considered an ATMP

What is an ATMP?

- **Somatic cell therapy medicinal product**

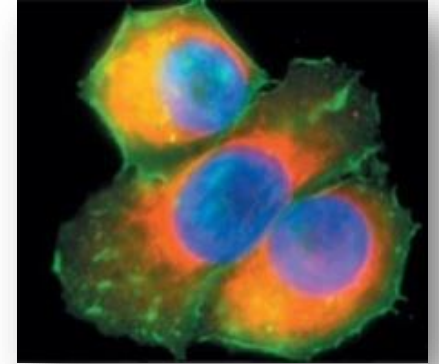
- Contains or consists of cells or tissues that have been subject to substantial manipulation

Or

- Contains or consists of cells or tissues that are not intended for the same essential function in the recipient and the donor

- **Tissue engineered product**

- Consists of engineered* cells or tissues
- Administered with a view to regenerate, repair or replace a human tissue
- *engineered: cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved

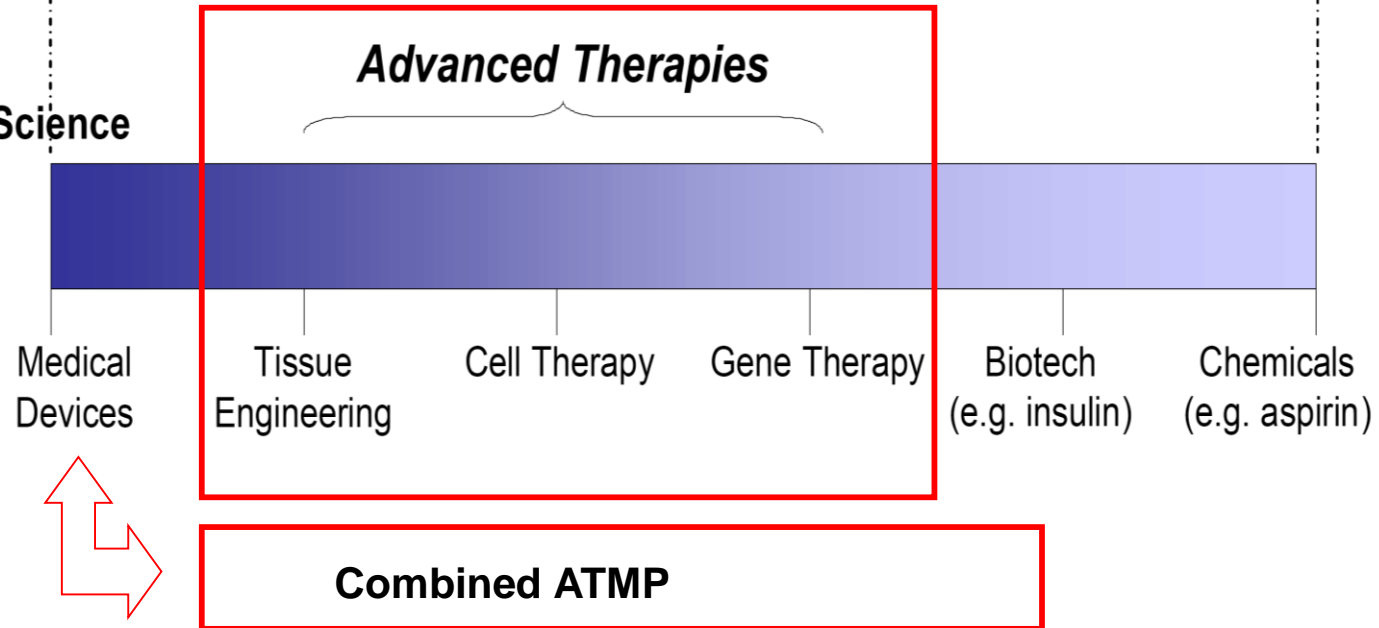


Advanced Therapy Medicinal Products Regulation (EC) 1394/2007

Legislation



Science



Committee for Advanced Therapies (CAT)

- Established by ATMP regulation
- One expert per EU member state (+ Island and Norway)
- Two patient representatives, two physician representatives
- Decision-making preferably by consensus, if necessary by voting (simple majority)

Tasks

- Draft opinion for marketing authorisation
- Responsible for classification and certification of ATMP
- Advise CHMP on any matter related to ATMP
- Advise Paediatric Committee on any matter related to ATMP
- Contribute to scientific advice provided by CHMP

Marketing authorisation of ATMP

Assessment of quality, safety, efficacy -> Benefit/Risk appraisal

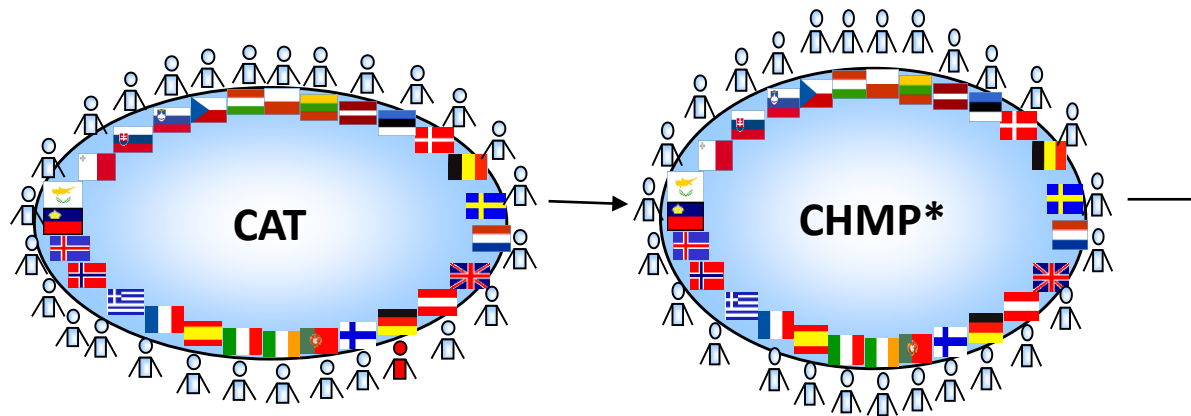
Draft opinion



Final opinion



Marketing authorisation



5 „double members“
CHMP und CAT

European Commission

*Committee for Medicinal Products for Human Use



Reality in 2019



Marketing authorisation

Alofisel (anal fistula)

Holoclar (corneal injury)

Imlygic (melanoma)

Kymriah (ALL, DLBCL)

Luxturna (retinal dystrophy)

Spherox (cartilage defects knee)

Strimvelis (ADA-SCID)

Yescarta (DLBCL)

Zalmoxis (adjunctive treatment allo HSCT)

Refused, retracted, suspended

Advexin (cancer)

CAOMECS (corneal injury)

Cerepro (brain cancer)

ChondroCelect (cartilage damage knee)

Contusogene ladenovec (cancer)

Glybera (LPL deficiency)

Heparesc (urea cycle disorder)

Hyalograft C (cartilage damage knee)

MACI (cartilage damage)

Provenge (prostate cancer)

Overview

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- **Specific procedures for ATMP**
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Special procedures: Classification

- Is my product an ATMP under European legislation?
- Typical issues:
 - Does the manufacturing involve substantial manipulation?
 - Is the use homologous or heterologous?
- Non-binding recommendation
- Classifications are published as [summary reports](#)

Special procedures: Certification

- Only for SME
- Evaluation of quality data and non-clinical data
- Aim: identify issues that would become relevant at the stage of marketing authorisation application (MAA)
- Possible outcome is „Certification“: confirmation that available data comply with standards for MAA

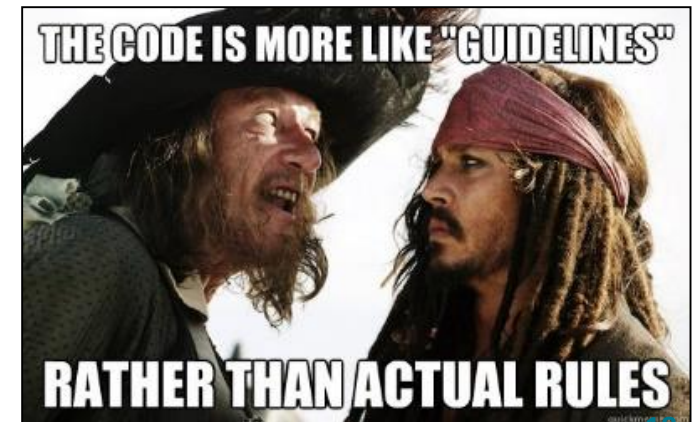
- 90 day procedure
- 14 Certification procedures finalised

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New scientific guidance to clarify regulatory expectations

- GMP specific to ATMPs → **EC Guideline, in effect since 2018**
- Non-substantially manipulated cell-based ATMPs → **Q&A, 2017**
- Gene therapy → **Updated EMA guideline, 2018**
- Safety & Efficacy follow-up and risk management → **Updated EMA guideline, 2018**
- Genetically modified cells → **Guideline under public consultation until July 2019**
- Investigational ATMPs → **Guideline under public consultation until July 2019**
- Comparability for ATMPs → **Planned for Q4 2019 (CAT Work Plan)**



European vs. National

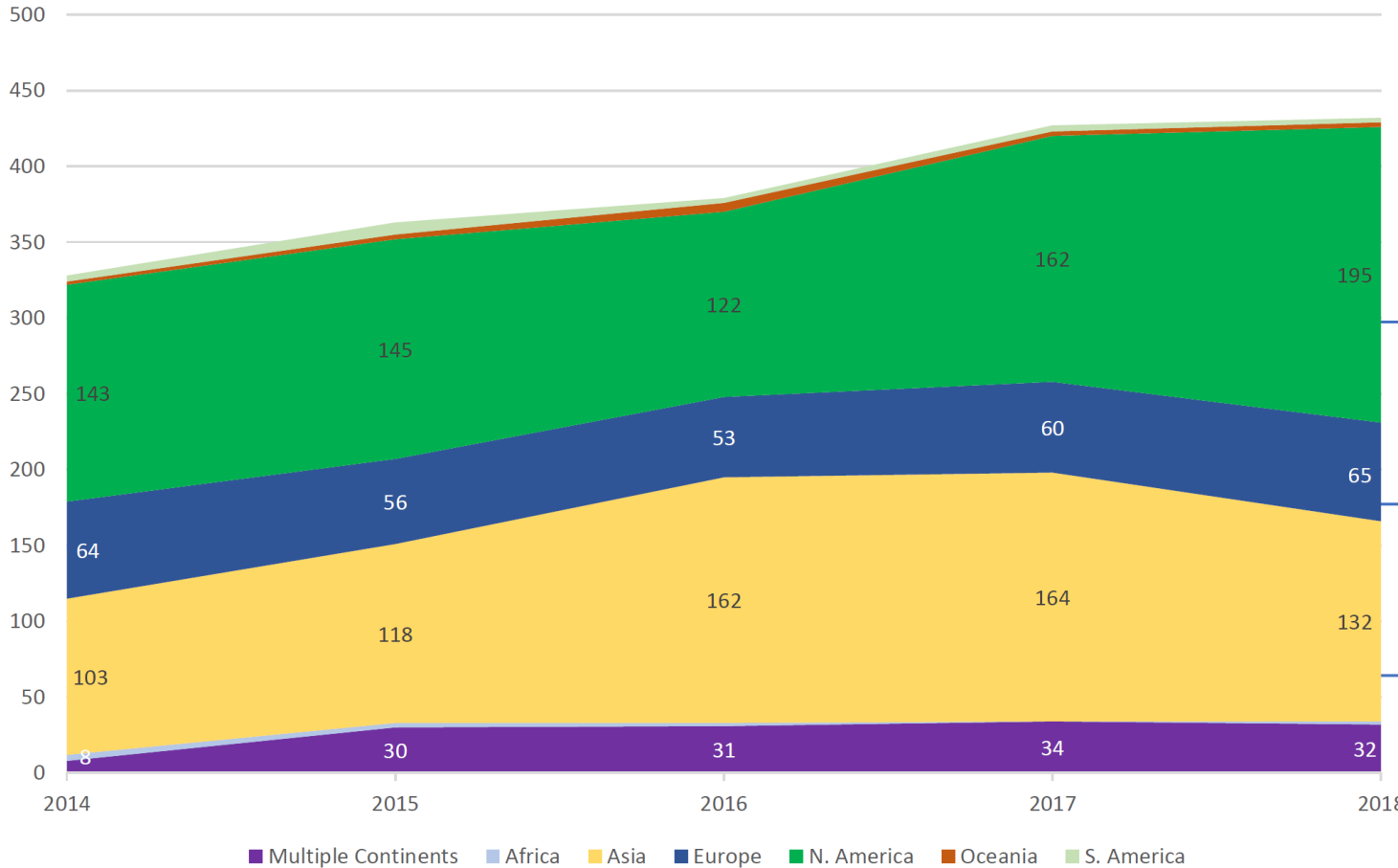
- Europe is growing together and European procedures become increasingly important

BUT

- Clinical trials are authorised by national agencies
- ERA assessment for medicinal products classified as GMO's

Over a 4 year-period, the increase in the number of new clinical trials is lower in Europe than in N. America and Asia

N° new Cell & Gene Clinical Trials started, by Continent and by Year



Growth 2018 vs 2014:

Total: +32%

N. America: +36%

Europe: <2%

Asia: +28%

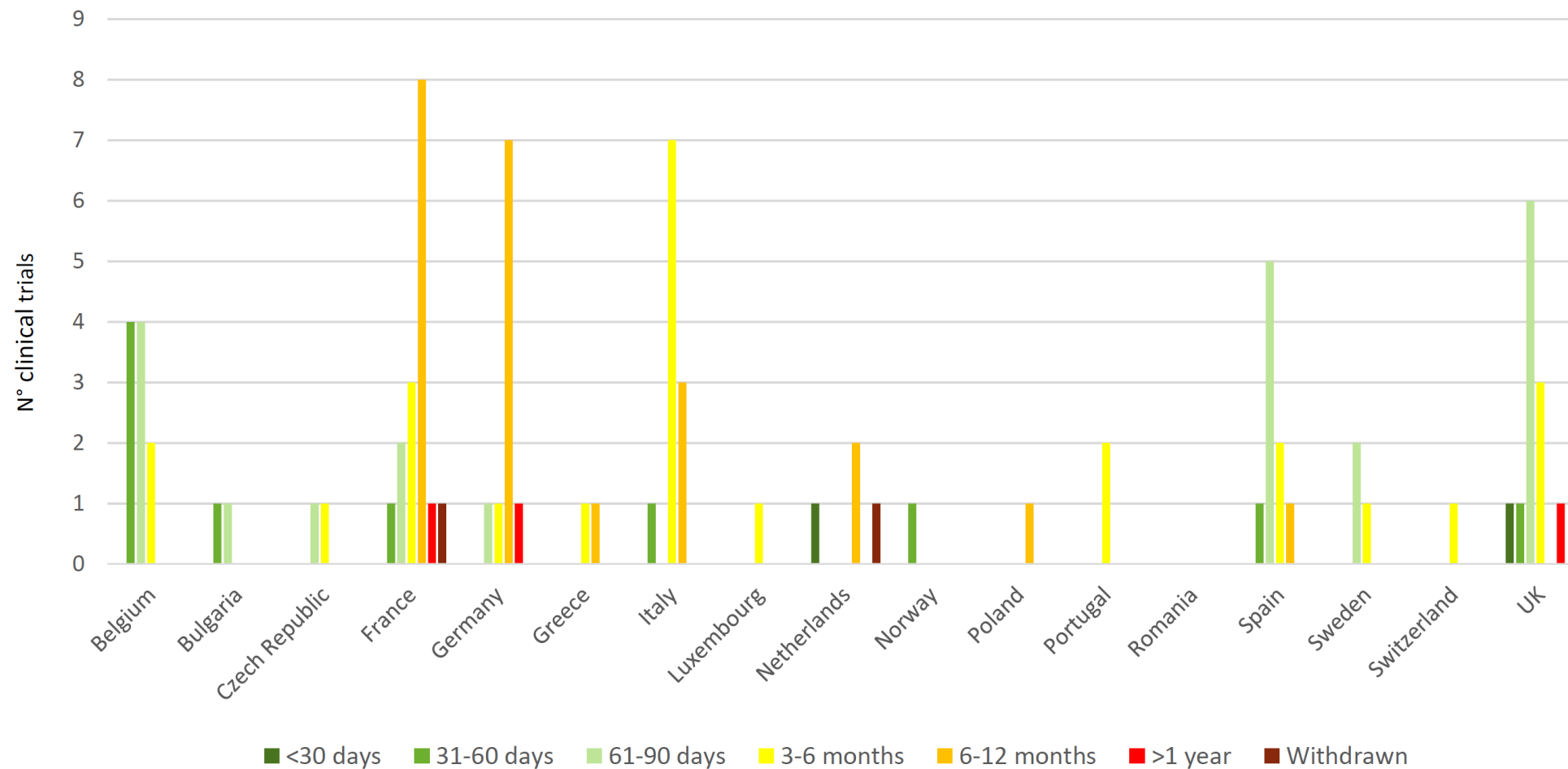
Total new trials started during the 2014-2018 period = 2097

(All new trials started in more than 1 continent are under Multiple Continents category)

There is a large variation in approval times by country

Approval time by country – Overview

N = 26 ATMP Clinical Trials, of which 18 multinational trials

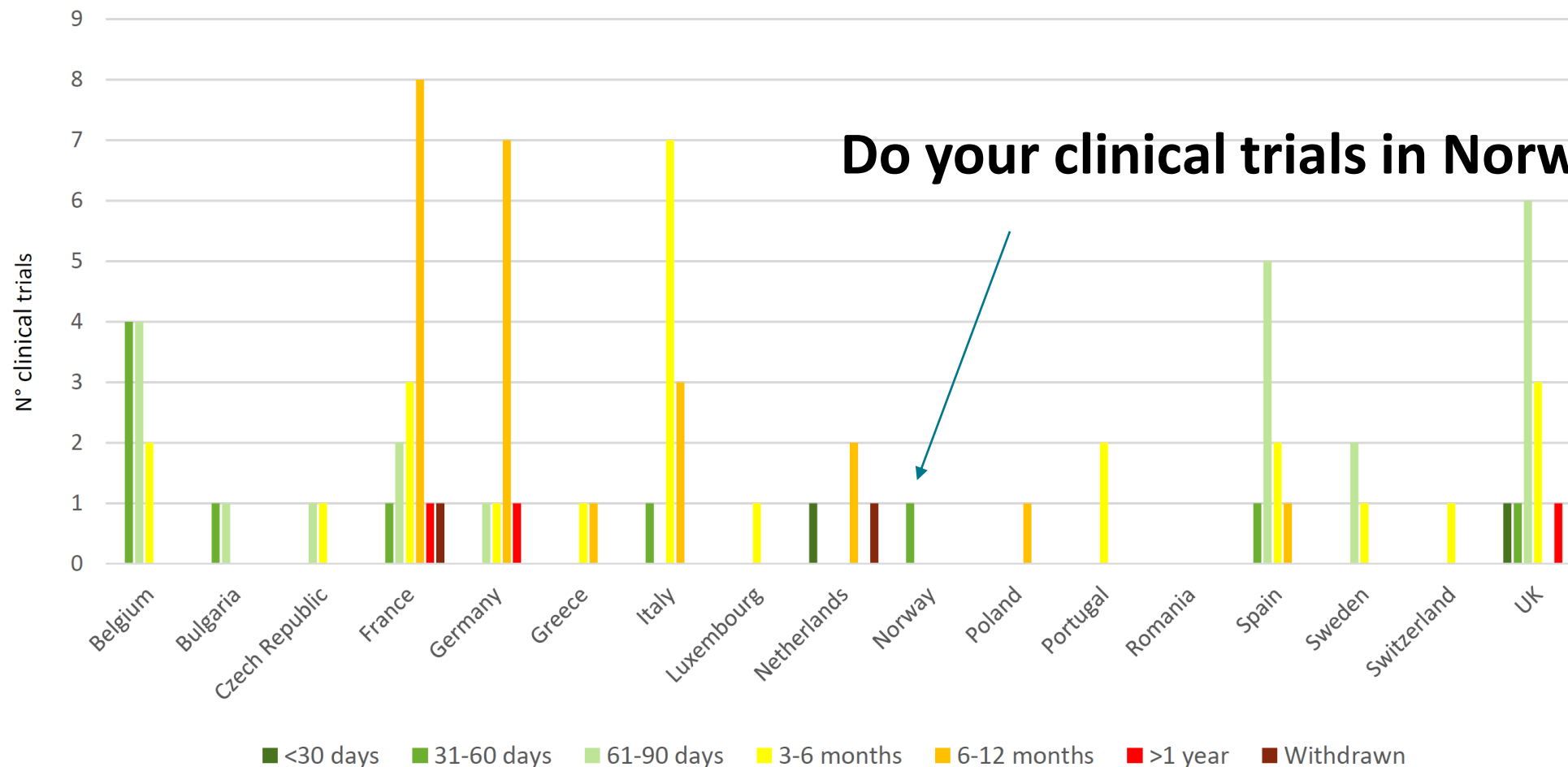


The majority of clinical trials are approved 6-12 months after application in France or Germany, whilst approval was obtained in 6 months or less in Belgium and the UK. The number of questions is also higher in France and Germany.

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Approval time by country – Overview

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Development of common approaches (within EU)

- Initiative for harmonised approach for clinical trials
- Development of harmonised approaches for Environmental Risk Assessment (ERA) for gene therapies

Overview Support by EMA

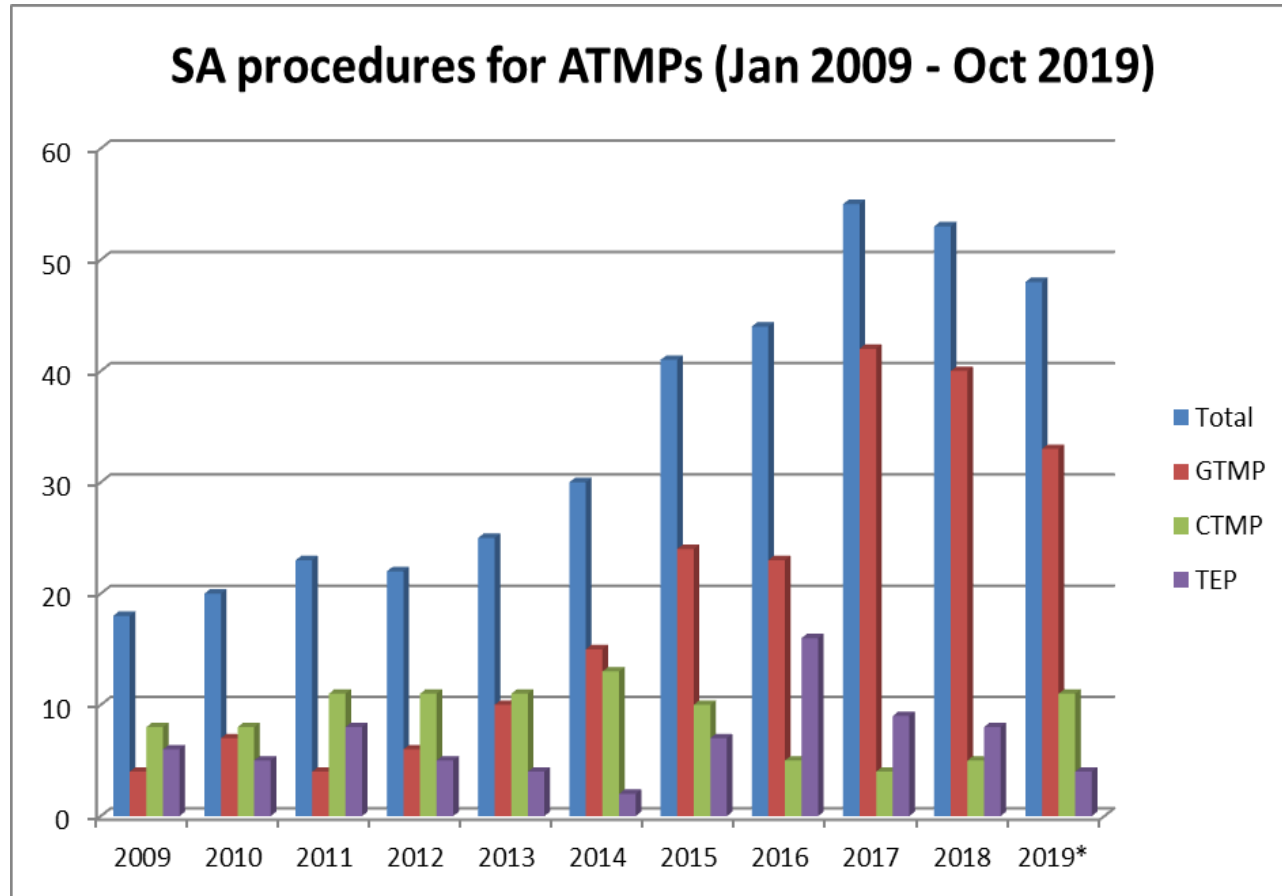
- Incentives for SME and orphan drugs
 - Special support office for SME at EMA
 - Fee reductions for scientific advice and marketing authorizations
- Innovation Task Force (ITF)
 - Informal early dialogue
- Scientific Advice
 - As with other medicinal products, but dedicated discussion and involvement of CAT
 - CAT/SAWP double members
- PRIME (PRiority MEdicine) scheme

Scientific Advice

- Incentive: early-late stage of development/scientific certainty
- Open to all applicants
- To provide regulatory input on issues not covered by current guidelines, or where deviation from guidelines are foreseen
- Scientific advice is given by the scientific advise working party (SAWP) with input from CAT (+ other committees & working parties)
- Qualification procedures on registries, platform technologies etc
- Parallel SA procedure with FDA possible
- EMA/HTA parallel scientific advice procedure

Scientific Advice for ATMPs (2009- June 2019)

- ~650 SA procedures 2019 – 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)



Recurring issues in Scientific advice

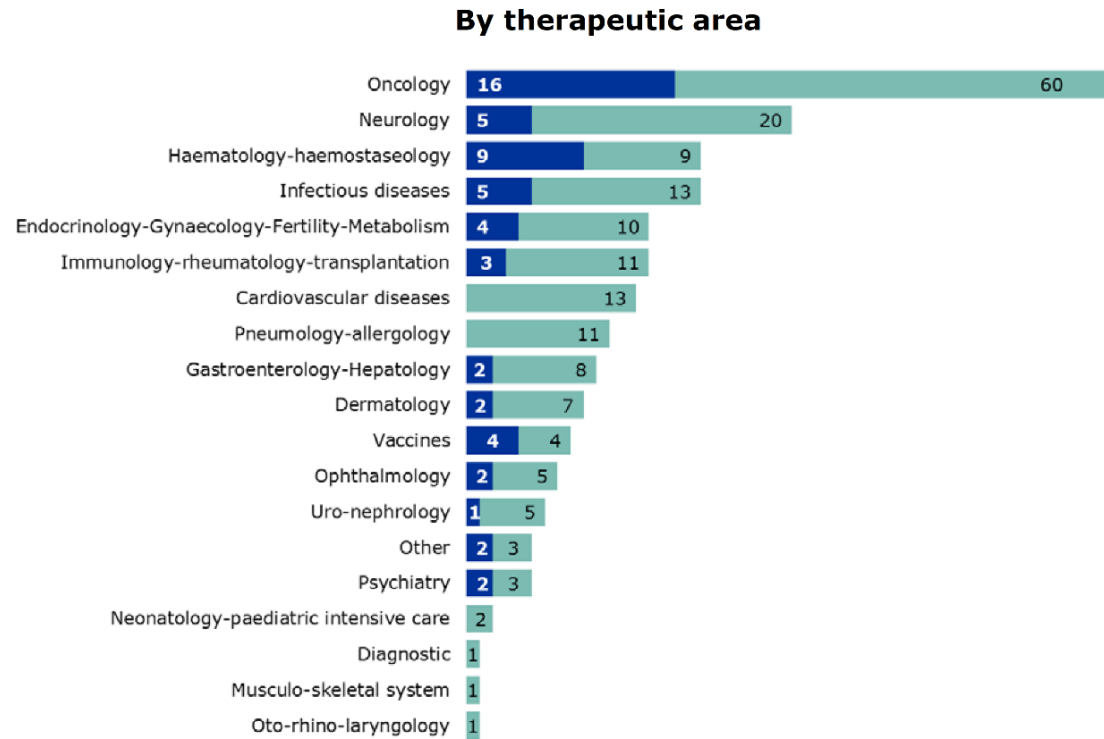
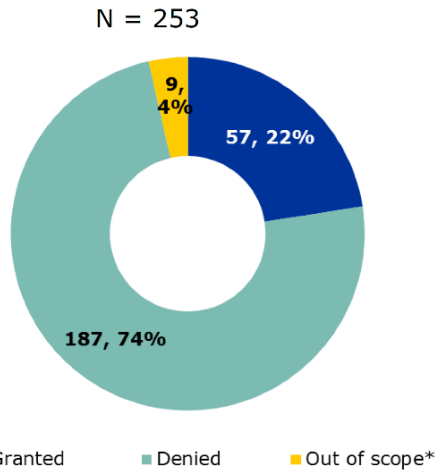
- Bridging quality from early development to commercial scale
- Nonclinical support for dosing & route of administration
- Overall trial design (e.g feasibility of RCT vs Single arm)
- Acceptability of natural history data
- Defining informative endpoints (including use of surrogate)
- Data sufficient to support full MA /CMA (feasibility of confirmatory trial)?
- If & when to start Pediatric development
- Data requirement for HTA?

Support to developers of ATMPs

Early access mechanisms in EU

- PRIME (Priority Medicines)
 - To foster development of medicines with a high public health potential
 - Reinforced scientific and regulatory advice
 - Optimise development for robust data generation
 - Enable accelerated assessment
 - Early appointment of Rapporteur, tailored support, iterative SA at major development time points.

Cumulative overview PRIME eligibility by September 2019



Out of the 57 PRIME granted, 25 were for ATMPs (44%):

- 20 are GTMPs, 5 CTMP
- 10 Oncology
- 7 Haematology
- 3 Immunology – rheumatology – Transplantation
- 1 Ophthalmology
- 2 Neurology
- 1 Other (X-linked myotubular myopathy)

By type of applicant



* This indicates eligibility requests received but not started by EMA as they were deemed outside the scope of the scheme or with a format and content inadequate to support their review. These are not included in the breakdown by type of applicant or by therapeutic area.

Eligibility to PRIME scheme



Medicinal products of major public health interest and in particular from the viewpoint of therapeutic innovation.

- Potential to address to a significant extent **an unmet medical need**
- Scientific justification, based on data and evidence available from nonclinical and clinical development

No satisfactory method or if method exists, bring a major therapeutic advantage

Introducing new methods or improving existing ones

Meaningful improvement of efficacy (impact on onset, duration, improving morbidity, mortality)

Eligibility to PRIME scheme



- *Entry to scheme at two different stages in development:*
 - *at the earlier stage of **proof of principle** (prior to phase II/exploratory clinical studies) focusing on SMEs.*
 - *at **proof of concept** (prior to phase III/confirmatory clinical studies).*
- *Must be based on adequate data to justify a potential major public health interest.*

Summary

EMA is committed to advance development and evaluation of ATMPs.

- Help to individualize product development
- Encourage new and innovative trial designs
- Collaborate to overcome manufacturing limitations
- Work towards harmonized regulatory standards globally

Early & continues dialog will benefit all stakeholders!

Acknowledgments

Jan Müller Berghaus

Patric Celis

Zahra Hanaizi

Anna Tavridou

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