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Regulation of ATMPs in Europe: Present and Future

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Disclaimer

The presenter does not have any conflict of interests

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SCIENCE MEDICINES HEALTH

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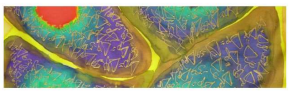
Overview

Part 1

Advanced therapy medicinal products (ATMPs): What they are, how they are regulated, and what support tools developers can use

Part 2

Future challenges, potential bridges and solutions



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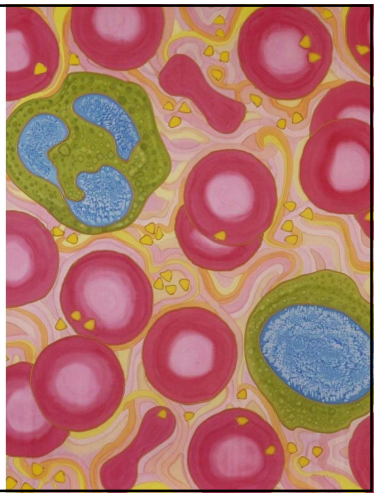
Part 1



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What are ATMPs?

ATMP classification may differ by world region

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What are ATMPs?

Gene therapy products

Somatic cell therapy products

Tissue engineered products

ATMPs are regulated as medicinal products/**authorised in the EU** via the centralised procedure

Transplant/transfusion of non-substantially manipulated cells for homologous use are well-established and are not regulated as medicines (e.g. bone marrow transplant)

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Different from traditional medicines

	Small molecule chemicals	ATMP
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 is the drug
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…
Treatments decision	Generally reversible	Cannot stop treatment if non-responder

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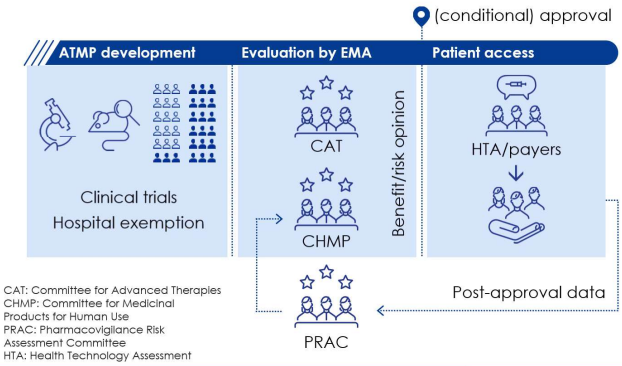
EMA's evaluation: Entry route of ATMPs to the EU market



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EMA's evaluation: 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

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EMA issues opinion and EC issues decision to grant marketing authorisation

The EMA committee/s issue/s opinion following assessment of data:

Medicinal products must have a **positive benefit-risk** balance based on scientific assessment of the **quality, pre-clinical and clinical data**

The European commission makes decision based on EMA committees' opinion in a process called 'Decision Making Process' which lasts approximately 2 months

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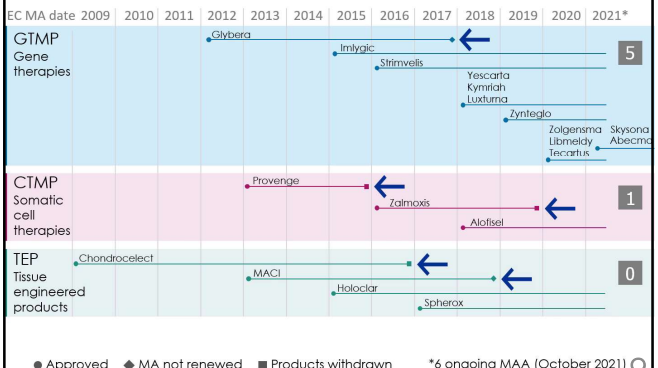
Approved ATMPs 2009-2021



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ATMPs: Challenges in their lifecycle

Innovative therapeutic approaches
High complexity

Specificities in development affect ATMP approvals and patient access

Product consistency

Proof of concept

Dose finding

Optimal study designs

Sustained efficacy

Retreatment

Real world data/ disease registries

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Innovative medicines: Challenges for regulators

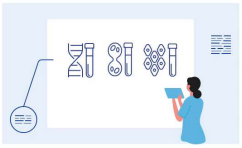
Novel technologies:
e.g. genome editing

Innovative manufacturing approaches:
Point-of-care manufacturing, release and control

Borderline products:
Contribution of each component to clinical benefit-risk

Data requirements:
Small patient populations/ comparators/registries

Evidence generation:
Approval/post-marketing/ market access



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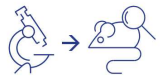
EMA tools to support drug development



Pre-authorisation | Post-authorisation

Scientific advice/protocol assistance/ qualification of novel methodologies

- Innovation task force
- SME/academia support
- Orphan drug designation
- Paediatric investigation plan
- ATMP classification and certification (ATMP specific tools)
- PRIME (PRIority MEdicines)
- Post-authorisation efficacy/safety studies (registries and observational studies)

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Preparing for a sound ATMP development: EMA support through scientific advice (SA)

Voluntary procedure

Fees according to the type of product and developer, indication, areas of advice

SA for ATMPs is provided by the Scientific Advice Working Party (SAWP) supported by the Committee of Advanced Therapies (CAT)

Questions on quality, non-clinical and clinical development

Questions on paediatric aspects of development (PDCO involvement)

Questions on significant benefit (COMP involvement)

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Critical aspects to be addressed during development

Quality	Nonclinical	Clinical
• Demonstrated comparability • Potency testing • Ensuring product consistency • Starting material challenges	• Proof of concept studies • Design toxicity studies, relevance • Bridging/ comparability studies • Bio-distribution and shedding • Non-clinical development data package	• Trial design • Indication/target population • Dose/regimen • Primary/secondary endpoints • Comparator • Study duration • Sample size/analysis • Extent of safety data • Durability of response

Tavridou A. *et al., Br J Clin Pharmacol.* 2021; **87**(6):2459-2464

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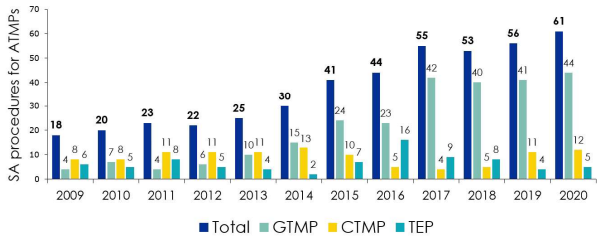
Increase in SA for ATMPs 2009-2020



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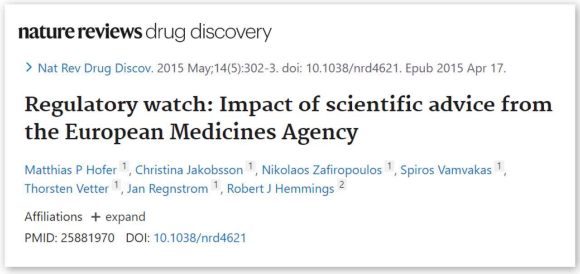
Positive impact of SA adherence on MAA procedure and outcome



nature reviews drug discovery

Nat Rev Drug Discov. 2015 May;14(5):302-3. doi: 10.1038/nrd4621. Epub 2015 Apr 17.

Regulatory watch: Impact of scientific advice from the European Medicines Agency

Matthias P Hofer [1], Christina Jakobsson [1], Nikolaos Zafiropoulos [1], Spiros Vamvakas [1], Thorsten Vetter [1], Jan Regnstrom [1], Robert J Hemmings [2]

Affiliations + expand

PMID: 25881970 DOI: 10.1038/nrd4621

Hofer M. *et al., Nat Rev Drug Discov.* 2015; **14**(5):302-3

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Positive impact of SA adherence on MAA procedure and outcome

MAA success rate:

74/88

compliant

MAA success rate:

13/30

non-compliant

Hofer M. *et al., Nat Rev Drug Discov*. 2015; **14**(5):302-3

EMA scientific advice in parallel with FDA

Aligning evidence-generation to serve both agencies

Best candidate products:

- Indications lacking development guidelines
- If guidelines exist, those for which EMA's & FDA's guidelines differ significantly

Early dialogue between regulators and developers

Clearer understanding of the agencies' respective requirements and perspectives regarding the development program

Simultaneous feedback on R&D plans

Harmonization and increased convergence between EMA and FDA

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Qualification of novel methodologies/ biomarkers/registries

Aim: speed up/optimise drug development and utilisation

Procedure to guide the development of new more efficient ways to develop drugs, e.g. development of new endpoints for clinical trials

Examples:

- Methods to predict toxicity
- Methods to enrich a patient population for a clinical trial
- Surrogate clinical endpoints: New sensitive scales to measure efficacy of a new drug instead of hard clinical endpoints
- Patient and caregiver reported outcomes
- Disease registries to support safety and efficacy of medicines

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Advice on RMPs, PASS and PAES

Advice on Risk Management plans (RMPs)

- Tabulated summary of safety concerns
- Justification for the inclusion of each risk
- For each of the proposed important identified risks, include a high level summary of the proposed pharmacovigilance and risk minimisation activities

- Does the CHMP agree that the proposed risks are appropriate?
- Does the CHMP agree that the proposed risks need to be further investigated and characterised?

Advice on post-authorisation safety and efficacy studies (PASS and PAES)

- Does the CHMP agree that a non-interventional cohort study design using data from registries would be appropriate to describe the long-term safety and effectiveness of product X after approval?

Uncertainty at the moment of marketing authorisation for ATMPs is **high**

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Need for additional data sources in pre- and post-approval phase

Pre-approval - need for external controls based on disease registries to contextualise results of SATs

Need for post-licencing evidence generation (PLEG) for safety and efficacy/long-term follow up due to ATMP characteristics (e.g. curative potential/loss of efficacy, safety concerns)

EMA encourages early discussions with developers on PLEG, involving relevant stakeholders

Disease registries

Data sources both in pre- and post-marketing phase

EMA registry qualification to assess the appropriateness of registry attributes for regulatory context of use (e.g. cystic fibrosis registry, cellular therapy module of EBMT registry)

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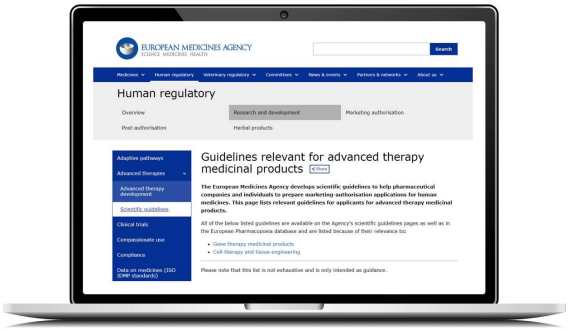
Further information



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Further information

Gene therapy

- ICH guideline S12 on nonclinical biodistribution considerations for gene therapy products - Step 2b (EMA/CHMP/ICH/318372/2021)
- Questions and answers on comparability considerations for advanced therapy medicinal products (ATMP) (EMA/CAT/499821/2019)
- The **overarching guideline** for human gene therapy medicinal products is the Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014)
- **Questions and answers** on gene therapy (EMA/CAT/80183/2014)
- Guideline on scientific requirements for the **environmental risk assessment** of gene therapy medicinal products (CHMP/GTWP/125491/06)
- Reflection paper on **design modifications** of gene therapy medicinal products **during development** (EMA/CAT/GTWP/44206/2009)
- Reflection paper on quality, non-clinical and clinical issues relating specifically to recombinat adeno-associated viral **vectors** (CHMP/GTWP/587488/07)
- ICH Considerations - **Oncolytic Viruses** (EMEA/CHMP/ICH/607698/2008)
- Guideline on quality, non-clinical and clinical aspects of medicinal products containing **genetically modified cells** (CAT/CHMP/GTWP/671639/2008)
- Guideline on the non-clinical studies required **before first clinical use** of gene therapy medicinal products (EMEA/CHMP/GTWP/125459/2006)
- Guideline on non-clinical testing for **inadvertent germline transmission** of the gene transfer vectors (EMEA/273974/2005)
- Reflection paper on management of clinical risks deriving from **insertional mutagenesis** (CAT/190186/2012)
- Guideline on **follow-up of patients** administered with gene therapy medicinal products (EMEA/CHMP/GTWP/60436/2007)
- Guideline on **safety and efficacy follow-up and risk management** of advanced therapy medicinal products (EMEA/149995/2008)

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Part 1 summary

ATMP development is complex

The EMA acknowledges challenges in quality, non-clinical & clinical development

Early dialogue with regulators/ scientific advice

Make the best use for pre- and post-marketing evidence generation

Relevant/clear evidence from early stages

Smooth transition from quality to non-clinical and clinical development

Evidence needs to serve other downstream stakeholders (e.g. HTAs)

Timings are important, as it is to use regulatory tools

Critical to ensure optimal feedback from regulators

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Part 2

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Regulatory scientific strategy to 2025 - highlights for ATMPs

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Regulatory scientific strategy to 2025 - highlights for ATMPs

1. Support translation of ATMPs into patient treatments
2. Diversify and integrate the provision of regulatory advice
3. Foster innovation in clinical trials
4. Contribute to HTA's preparedness & downstream decision making
5. Bridge from evaluation to access through collaboration with payers
6. Promote use of high-quality RWD in decision making
7. Develop network-led partnerships with academic/research centres

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Current gaps and bridges

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Current gaps and bridges

Research centres	**Early bridges**	Traditional regulatory space	**Late bridges**	Patients
ITF; SA; protocol assistance; classifications; certifications; PRIME; stakeholders meetings; peer-review publications; academic engagement…			HTAs (EUnetHTA); payers; registries; RWE (DARWIN); patients' engagement; access to doc/information; combined SA with HTAs…	

Early bridges - academia liaison: The hub linking the agency and academia

Academia working framework 2017 | RSS 2025 | multi-annual work program

Liaison with many types of academic developers is important, for example, academics developing basic science methods, hospitals developing CAR T cell therapies, clinical research centres etc.

Developers should include those creating ATMPs or elements related to ATMPs, for example, diagnostic methods, companion diagnostics, viral vector development etc.

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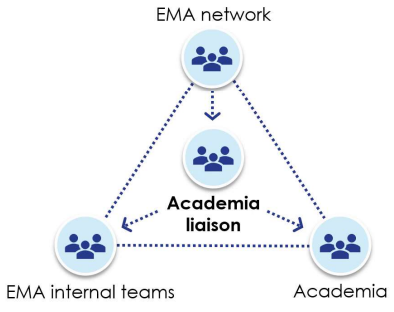
Early bridges - academia liaison: The hub linking the agency and academia

Academia working framework 2017 | RSS 2025 | multi-annual work program



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Early bridges - academia liaison: The hub linking the agency and academia

Academia working framework 2017 | RSS 2025 | multi-annual work program

MATRIX organised & coordinated approach

- Fostering mutual understanding to facilitate **supporting innovation**
- Provide optimal agency support to **research funding** programmes
- Facilitate regulatory **input into research initiatives**
- Ensuring that **excellent science is efficiently applied** to medicines development

Early bridges - PRIME scheme: Goal and scope

To foster the development of medicines with major public health interest

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Early bridges - PRIME scheme: Goal and scope

To foster the development of medicines with major public health interest

Reinforce scientific and regulatory advice
Foster and facilitate early interaction
Raise awareness of requirements earlier in development

Optimise development for robust data generation
Focus efficient development
Promote generation of robust and high-quality data

Enable accelerated assessment
Promote generation of high-quality data
Facilitated by knowledge gained throughout development

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Early bridges - eligibility to PRIME scheme: Based on accelerated assessment criteria

No satisfactory method, or if method exists, bring a major therapeutic advantage	Medicinal products of major public health interest and in particular from the viewpoint of therapeutic innovation
Introducing new methods or improving existing ones	Potential to address an **unmet medical need** to a significant extent
Meaningful improvement of efficacy (impact on onset, duration, morbidity, mortality)	Scientific justification, based on the data and evidence available from nonclinical and clinical development

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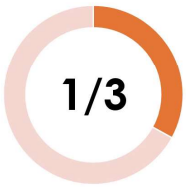
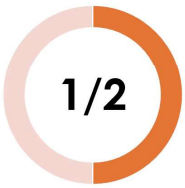
Early bridges - eligibility to PRIME scheme: Based on accelerated assessment criteria

Currently ATMPs represent:



Applicants to the PRIME scheme



Successful PRIME scheme applicants

Early bridges - the quality PRIME toolbox

Guidance on scientific elements and regulatory tools to support quality data packages for PRIME marketing authorisation applications	It aims to address common challenges with **quality** and **manufacturing** development data requirements during development and at the time of MA
Medicines supported by the EMA can use the PRIME scheme to generate robust **quality data** for an EU MA, to enable patients to benefit from these therapies as early as possible	It covers medicines containing **chemical, biological** or **biotechnologically derived substances** and advanced therapy medicinal products (ATMPs)

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HSTalks

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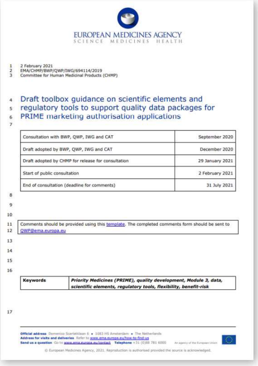
Early bridges - the quality PRIME toolbox



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2 February 2021
EMA/CHMP/BWP/QWP/IWG/694114/2019
Committee for Human Medicinal Products (CHMP)

Draft toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME marketing authorisation applications

Consultation with BWP, QWP, IWG and CAT	September 2020
Draft adopted by BWP, QWP, IWG and CAT	December 2020
Draft adopted by CHMP for release for consultation	29 January 2021
Start of public consultation	2 February 2021
End of consultation (deadline for comments)	31 July 2021

Comments should be provided using this template. The completed comments form should be sent to QWP@ema.europa.eu

Keywords	*Priority Medicines (PRIME), quality development, Module 3, data, scientific elements, regulatory tools, flexibility, benefit-risk*

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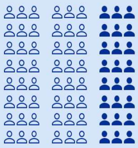
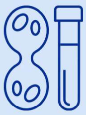
Early bridges - complex clinical trials



Complex clinical trials remain the **gold standard** for HTAs and developers



This is **not always possible** with ATMPs, especially when orphan drugs are being considered

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Early bridges - complex clinical trials

- Platform, basket, umbrella, multi-arm trials, master protocols, some adaptive trials etc.
- Combine elements of learn-and-confirm
- May provide a logistic framework that increases efficiency in terms of set-up, recruitment, conduct, monitoring and outcomes (e.g. same assays used)
- Can have advantages for research (e.g., richer data, more comparisons, more trials)
- Can have advantages for patients and clinicians (e.g. more options to take part)
- Concerns several therapeutic areas
- Accelerated experience with pandemic
- Decentralised clinical trials have taken centre stage - elements of this to be maintained in the future

- Always triggers a range of methodological concerns and questions, several without a trusted solution in trial as designed
- Methodological questions have been handled differently by international agencies
- Distinction needed between trial authorisation, supervision and assessment
- Competencies needed for using quality trial data, if collected for regulatory purpose or not

Draft Q&A on complex trials in development

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Late bridges - new EU framework for cooperation on HTA update

European Parliament — European Commission — Council of the European Union

EP opinion:
19 February 2019

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on health technology assessment and amending Directive 2011/24/EU

31 January 2018

Progress reports by BG, FI, AT, RO, DE, presidencies

Mandate for trilogues PT presidency

First meeting 26 April 2021

Trilogues

IF an agreement is reached → outcome is confirmed by the co-legislators

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Scientific advice in parallel with HTA bodies

Scientific advice in parallel with HTA's has previously been limited due to the availability of the HTA bodies

This should become more common in the future as the benefits to ATMP development are substantial

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Scientific advice in parallel with HTA bodies

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

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Other challenges - the global picture

How can we **harmonize** with other developers?

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Other challenges - the global picture

Harmonization vs. convergence:

- Different legal framework
- Common understanding of science
- Equivalent (or close) regulatory outcome with same development

Convergence initiatives:

- Advanced Therapy Cluster: FDA-EMA initially, now + (e.g., Canada, Japan), under confidentiality agreements
- International Pharmaceutical Regulators Programme (IPRP): regulators only information sharing forum
- International Council for Harmonization (ICH): First guideline for gene therapy (work in progress)
- WHO White Paper on ATMPs (work-in-progress)

Other challenges - international harmonization versus convergence EU July 2021

Country Regulatory Authority	Law/Regulation	Details
European Commission-European Union European Medicines Agency (EMA)	Regulation 1394/2007 on ATMPs	'Lex specialis' (only describing what is specific for ATMP)
	Directive 2001/83/EC	Main pharmaceutical legislation
	Regulation (EC) 726/2004	Regulation on the centralized evaluation procedure and EMA
	Directive 2009/120/EC	Scientific and technical requirements for ATMPs (dossier requirements)

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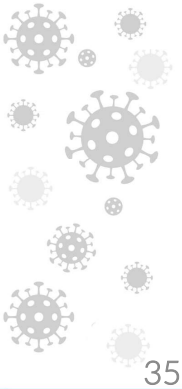
Other challenges - COVID: Lessons learnt

- Covid-19 has been an opportunity to learn and to improve - but systems are under stress and not all changes are sustainable
- ATMPs have been little affected from the regulatory point of view, but many delays in new submissions
- Increased international collaboration and increased transparency would be two gains from the crisis for the Advanced Therapies Community
- Regulators are open to new ideas that make good sense - early & effective engagement is recommended



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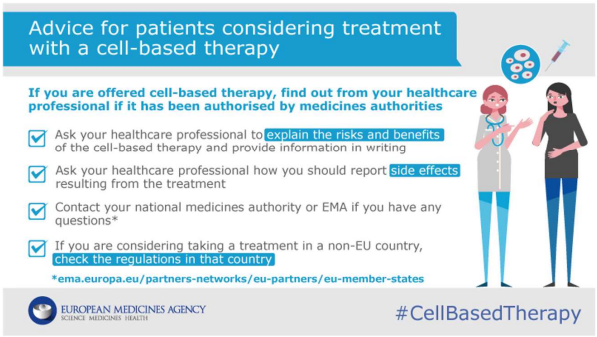
Other challenges - unproven cell-based therapies



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What developers can do

1. Use regulatory tools, and follow scientific advice given
2. Get yourself into PRIME
3. Plan your submission well and please keep to your plans - delays are more common than no delays for ATMPs
4. Make a submission with a mature dossier
5. Plan how you will use real world evidence
6. Explore a suitable registry (disease registries)
7. Support common codification activities
8. Think about downstream stakeholders and their data needs

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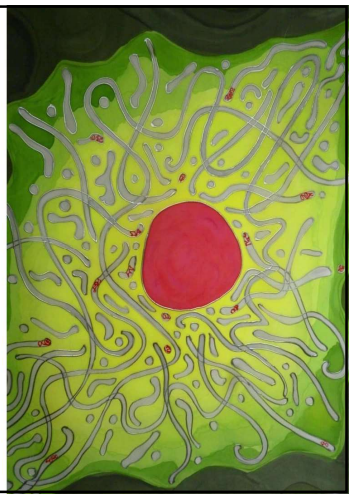
ATMPs can **cure** patients, but can also **kill** patients

Regulation is essential, **access** is critical, **pharmacovigilance** is crucial



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Thank you for your attention

Further information

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