RARE IMPACT

Presentation of preliminary results & discussion

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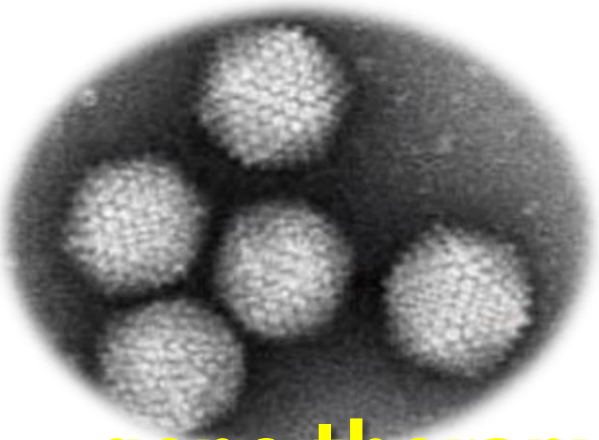
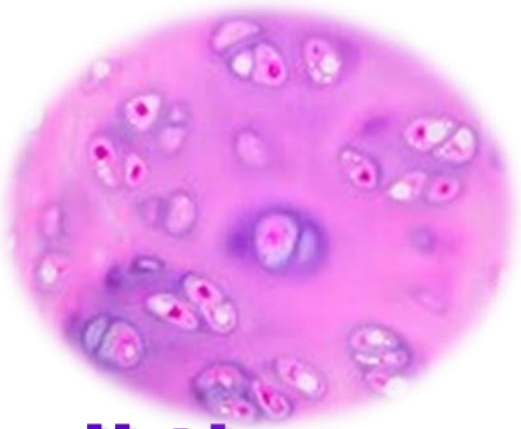
Advanced Therapies Medicinal Products (ATMPs) in the EU / Regulation (EC) from 2007



gene therapy



cell therapy

tissue engineering

ATMPs: what are they?

ATMPs are medicines for human use that are based on genes, tissues or cells. They offer **ground-breaking new opportunities** for the **potential cure and treatment of rare diseases**

Gene therapy

Contains genes that lead to a **therapeutic, prophylactic or diagnostic** effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including **genetic disorders**, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources.

Cell therapy

Contains cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be **used to cure, diagnose or prevent diseases**.

Tissue engineering

Contain cells or tissues that have been modified so they can be **used to repair, regenerate or replace human tissue**.

Questions are still asked about efficacy and safety of gene therapy

SAFETY ISSUES:

- **Immune response:** an unwelcome immune response could cause serious illness or even death
- Safety issues about: toxicity of the viral vector, gene control, cell targeting

OTHER ISSUES:

- **Ethics**: confusion about gene therapy and genetic engineering: gene therapy aims to eliminate disease at its source, not produce a 'better' class of human being!
- **Affordability**: many promising gene therapy approaches are individualized to each patient. This individualized approach may prove to be **very effective, but it's also costly**. The manufacturing process is also complex and costly.

Jesse Gelsinger, who had a rare liver disorder, participated in 1999 in a gene therapy trial.

He died of complications from an inflammatory response 4 days after receiving a dose of experimental adenovirus vector.

EU Regulatory Framework for ATMPs

European Commission (EC) (DG SANTE)

- Proposes and amend legislation for the entire sector (ATMP Regulation of 2007)
- Grants legally binding marketing authorisation valid in all EU countries

European Medicines Agency (EMA)

- Coordinates scientific evaluation for Marketing Authorisation (CAT)
- Develops guidelines in cooperation with expert committees and working groups
- Product-specific scientific advice and early access pathways

National regulatory authorities

- Authorisation and oversight of clinical trials
- Grants use under hospital exemption
- Pricing and reimbursement is established with each EU Member State

8 advanced therapies for rare diseases in the EU

Name	Indication	Approval Date Status	Status
STRIMVELIS (GSK) (orphan designation)	Adenosine deaminase deficiency (ADA-SCID)	APRIL 2016	APPROVED
HOLOCLAR (Chiesi) (orphan designation)	Severe limbal stem cell deficiency in the eye	MARCH 2015	APPROVED
ZALMOXIS (MoIMED) (orphan designation)	Stem cell transplantation I high-risk blood cancer	JUNE 2016	APPROVED
GLYBERA (UniQure) (orphan designation)	**Lipoprotein lipase deficiency (LPLD)**	**NOVEMBER 2012**	**WITHDRAWN (2017)**
IMLYGIC (Amgen)	Melanoma	OCTOBER 2015	APPROVED
PROVENGE (Dendreon)	**Metastatic prostate cancer**	**OCTOBER 2013**	**WITHDRAWN (2013)**
MACI (Vericel)	**Cartilage defects in the knee**	**JULY 2013**	**WITHDRAWN (2014)**

Name	Indication	Approval Date Status	Status
ChondroCelect (TiGenix)	**Cartilage defects**	**NOVEMBER 2009**	**WITHDRAWN (2016)**
SPHEROX (CO.DON)	Cartilage defects in the knee	MAY 2017	
ALOFISEL (TiGenix) (orphan designation)	Complex anal fistulas in adults with Crohn's disease	MARCH 2018	APPROVED
LUXTURNA (Novartis) (orphan designation)	Vision and ability to move around obstacles (particularly dim light)	NOVEMBER 2018	APPROVED
KYMRIAH (Novartis) (orphan designation)	2 types of blood cancer: diffuse large B-cell lymphoma (DLBCL); primary mediastinal large B-cell lymphoma (PMBCL)	AUGUST 2018	APPROVED
YESCARTA (GILEAD/KITE) (orphan designation)	2 types of blood cancer: diffuse large B-cell lymphoma (DLBCL); primary mediastinal large B-cell lymphoma (PMBCL)	AUGUST 2018	APPROVED
ZYNTEGLO (bluebird bio) (orphan designation)	blood disorder known as beta thalassaemia in patients 12 years and older who require regular blood transfusions	MARCH 2019	APPROVED (conditional marketing authorisation, PRIME 150 days assessment)

Today: ATMPs and clinical trials studies

- Investment in advanced therapies' clinical research
- Concerns: the price of these products and ensuring patients get access
- US market prediction by 2030 : 40-60 marketed advanced therapies products
- EU market prediction by 2022: 40 marketed advanced therapies products

Crowdfunding campaigns in MSs

Baby Pia: Almost 1mln Belgians paid for life-saving drug

More than 950,000 Belgians have responded to a couple seeking €1.9m to cover the cost of their baby's life-saving treatment.
Nine-month-old Pia, who has spinal muscular atrophy (SMA) has been treated with Zolgensma, which has not been approved for use in Europe but is available in the US.

Rare Impact collaboration set up in 2018

EURORDIS RARE DISEASES EUROPE + DOLON

16 manufacturers
2 patients' organisations
+ trade unions

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Rare Impact: 2018-2020 and beyond…

- Discussions started in 2017
- Rare Impact first meeting ECRD 2018
- 6 consortium meetings until today
- 2 consortium meetings planned for 2020
- Final event June 2020 (TBC)
- Next activity…

RARE IMPACT.

Improving patient access to gene and cell therapies for rare diseases in Europe

Rare Impact: objectives

RARE IMPACT.
Improving patient access to gene and cell therapies for rare diseases in Europe

- Identify **challenges** that are preventing rare disease patients accessing gene and cell therapies (ATMPs as defined in EU Regulation) at European and country level
- Propose actionable **solutions** to address these challenges
- Shape change to **improve patient access** to gene and cell therapies
- Prepare **external stakeholders** and companies for the access challenges that are likely to be faced with gene and cell therapies
- **Educate** external stakeholders on gene and cell therapy technology and terminology
- Provide a pre-competitive forum in which manufacturers can **share experiences and ideas**

Challenges and solutions: methodology

SECONDARY RESEARCH

Conceptual challenges → Literature search/ review other initiatives

EU and Market-specific challenges → Patient and P&R pathways → Analogue assessment and targeted literature searches

PRIMARY RESEARCH

Stakeholder engagement

Preparation
- Stakeholder identification
- Recruitment
- Discussion guide preparation

Execution
Combination of F2F and WebEx discussions

Refinement
- Insights and recommendations from stakeholders
- Working group

Challenges and solutions: Methodology – challenge identification

Country/region	10 countries plus EU in scope (AU, ES,DE, IT, FR, CZ, DK, NL, SE, UK)
Level of decision maker	National, Region, Hospital/Prescriber
Type of challenge	**Assessment, Affordability, Availability, Accessibility**
Product characteristics	Technology type and disease prevalence

- We analysed in this way because:
  - Makes assessment manageable
  - Makes output more applicable

Stakeholders' feedback

Top challenges	
Assessment	• *"HTA is the biggest problem. Need to look for solutions when the treatment benefit is not realised until far in the future"* – ***UK patient group*** • *"Short trial duration is problematic for HTA along with recognition of primary endpoints e.g., clotting factor levels at 6 months are very clear"* – ***EU/NL CAT member***
Affordability	• Price and affordability are significant concerns for all stakeholders, especially patient groups. *"Price is a major concern"* – ***NL patient advocate*** • *"The pathway to patients is too long, regulatory framework, GMP etc., all problematic and this is reflected in the reimbursement"* – ***UK Patient advocate***
Availability	• Patients need a specialist in there own country to refer to a cross-border specialist centre. ERNs play a role in this, but not all countries have a specialist in the disease area of interest
Accessibility	• *"Expertise with ATMPs is limited…means products will be in the hands of few"* – ***EU/UK patient advocate*** • There are patient safety concerns, ethical concerns and unknowns *"Am I my own guinea pig?"* – ***SE Patient advocate***

Rare Impact: European level challenges to patient access to ATMPs can be split into two levels

European level challenges that require EU *level* solutions

Country challenges that are common across European countries

Country challenges that are common across European countries

Uncertainty in the evidence:

Assessment

- Pathways are unsuitable and uncertain
- Different comparators required for clinical benefit measurement across countries
- Acceptance of surrogate endpoints
- Duration of follow-up is scrutinized and acceptance of extrapolation is varied

Affordability

- Barriers to annuity payments and innovative funding options
- Cross-country collaborative initiatives for joint procurement are beginning to become operational

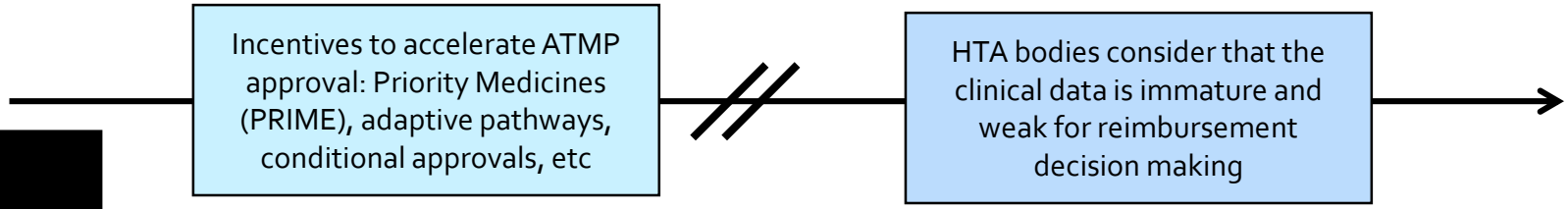
Availability

- Procedural expertise may not be available in home countries, requiring cross-border collaboration

Accessibility

- National health services' 'readiness' to adopt novel technologies, or ability to adapt existing infrastructure and care delivery, can pose hurdles to adoption

European level challenges that require EU level solutions



Assessment

- Registry-type data required for post-approval regulatory requirements differs from that required by payers for MEAs or other innovative payment models

Affordability

- EU-level federal funds have been proposed in the past; however, the appetite and feasibility for such funds is uncertain

Availability

- There is variability with the use of cross-border healthcare initiatives (Form S2 and E112) across markets and the sustainability of this pathway is uncertain
- Hospital exemption legislation interpretation can vary across markets which impacts patient access to licensed products

Accessibility

- Short shelf life of ATMPs require patients to be treated in centres with close proximity to GMP facilities

Germany: example of discussions

	Challenges	Solutions
Assessment	• AS1: Need to re-word as the trials don't generate the ITCs etc. • AS2: We could focus on the equity of access here that would apply in circumstances of two treatments, one administered weekly and one with a single administration. This makes the ATMPs pass the threshold much quicker • AS4: We should be stronger here. The issue is ethical, recruiting more when benefit has been shown to some patients, is denying some patients with access… • General: "one size fits all" approach to RCT to demonstrate additional benefit is the issue. Ethics of blinding or delaying treatment is important	• AS1: Should we focus on any RWE and not limit to just German RWE? Should we also address data protection here? Many stakeholders need to be involved in this. When discussing this data as part of re-assessment should mention opportunity for price to increase with better evidence • AS1: Need clarity on data can be presented after this 18-month period • AS1: Establish willingness to incorporate surrogate endpoints and how to implement changes • AS3: Better Solution for AS2 • AS4: Should we limit ourselves to just EU data? Could we include US? • AS4: Solution could be to engage G-BA to understand their willingness to explore RWE generation • General: Ideally, solution would be new legislation allowing greater flexibility for ATMPs to demonstrate additional benefit outside of the OD pathway, or a separate process for ATMPs. This would likely be in terms of accepting comparisons of the ATMP to the "appropriate comparator treatment(s)" using various statistical techniques
Affordability	• AF1: theoretical challenge rather than practical one • AF3: As used for CAR-T immediately, is it fair to say they are unlikely to be discussed in the first-year? • General: the AMNOG process only permits a price comparison to the annual cost of the appropriate comparator – big challenge	• AF1: Risk-sharing being explored in parliament. Should it be incorporated into law? • AF1: The "high-risk" pool was introduced and then removed – we need to understand the rationale for this • AF2: Is it possible/appropriate to suggest how sick funds might implement innovative annuity payments • AF3: Can we say CAR-T payment model is successful? • AF3: This only works for a rebate on the full payment – will this be possible for very expensive products?
Availability	• AV1: Not such an issue in Germany	• AV1: Legislation change in AMNOG review, or cross-border legislation? • AV2: Very important solution. In addition could add National-level requirement to strengthen requirements for exemptions within the EU regulation
Accessibility	• AC1; The key challenge is that the AMNOG and hospital processes have been put together without being integrated	

Italy: example of challenges discussed

	Challenges	Solutions
Assessment	• AS1: Should differentiate ATMP & orphan drugs. Phase II clinical trial is accepted only in case of orphan drugs. But in this case, due to the social impact, pts associations & scientific society could have a pivotal role in the negotiation with AIFA	• AS2: Registries are only for clinical governance only, usually the outcomes research is supported by the company through studies • AS3: Clarity on the timeline for re-assessment process is needed and what impact this will have on price
Affordability	• AF1: Innovative fund only covers the product. Needs to be an additional fund to cover technology delivery and support patient/family travel • AF1: The HCV drugs will lose innovative status which will free up budget	• AF1: Law 648 require robust clinical data and it is normal for doctors to ask manufacturers for the clinical data • AF1: Identifying funding requirements through horizon scanning is a very important point • AF3: Generic solution. Companies should drive education on business model
Availability		
Accessibility	• AC2: Regional variation in capacity and expertise to deliver ATMPs is an issue • AC3: Registry is really only used for clinical governance and are complicated to fill	• AC1: Reimbursement at national level to avoid regional variation in access is important in context of ATMPs due to complexity of administration • AC1: Most important delay is between EMA approval and AIFA reimbursement due to price negotiation – dialogue could help, but price is the main factor • AC2: Solution could go further by calling for more support hospital upskilling and infrastructure. There are no dedicated funds for implementing technology. Public-private partnerships could be proposed to identify patients and referral programs to ATMP centres

France: example of challenges discussed

	Challenges	Solutions
Assessment	• General: Reworking: 1. Strict evidence requirements. 2. Variation in guidance/methods relative to CAR-T assessments. Unwilling to extrapolate • AS1: Move first paragraph from Solution AS1 to challenge	• General: 1. Alternative process for ATMPs. 2. Clarity on CT requirements for ASMR for ATMPs 3. Capture RWE and use it to inform initial assessment (e.g .,via ATU) and re-assessment. 4. Guidance on acceptable extrapolation techniques • AS1: How does the magnitude of efficacy gain motivate decisions? Do we need/want a scale for this? • AS1: The need for RWE has been acknowledged and infrastructure is being developed • AS2: The Germany report articulates the same point better
Affordability	• AF1: Using reference pricing while conducting a cost-effectiveness analysis in the context of the national situation is contradictory. This suggests the CEA is rather a hurdle than a decision method • AF2: More focus on price-volume agreements vs agreements based on clinical value	• AF2: Public procurement may not work for ATMPs for rare disease
Availability		
Accessibility		

Rare Impact: next steps

- In depth discussions: **country meetings** (IT, ACHSE, UK), however there is a need to gather the experience from all EU Member States
- Revision of the Rare Impact national reports: **perspective of patients is key**!
- Preparation of the **EU solutions: please share with us your views!**
- **Publication** of the reports (Rare Impact website, others?)
- Reflection on the **post Rare Impact** activities (other EU projects)

EVENTS:

- Rare Impact meetings, including final meeting June 2020 (TBC)
- **ECRD conference (SWE):** 15-16 May 2020: sessions planned on innovation and access to ATMPs (Rare Impact to be presented)

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Thank you for your attention

More information:

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