



## **Taking Advanced Therapy Medicinal Products (ATMPs) to Market**

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EU Regulatory  
Network

# EU Regulatory Network



- **European Commission (EC) (DG SANTE)**

- Propose and amend legislation for the entire sector;
  1. *Regulations – self-executing and binding to all Member States (MS), no national changes allowed*
  2. *Directives – required output is binding but transposition up to MS to interpret locally (more leeway)*
- Grants legally binding marketing authorisation valid in all EU

- **European Medicines Agency (EMA)**

- Coordination of scientific evaluation for Marketing Authorisation (ATMPs)
- Developing guidelines in cooperation with expert committees and working groups
- Product-specific scientific advice and early access pathways

- **National regulatory authorities (31 EEA Member States)\***

- Authorisation and oversight of clinical trials, blood, tissues and cells as well as GMO approval
- Grants national marketing authorisations (**not applicable for ATMPs in Europe**)
- Grants use under hospital exemption
- Product-specific scientific advice to developers

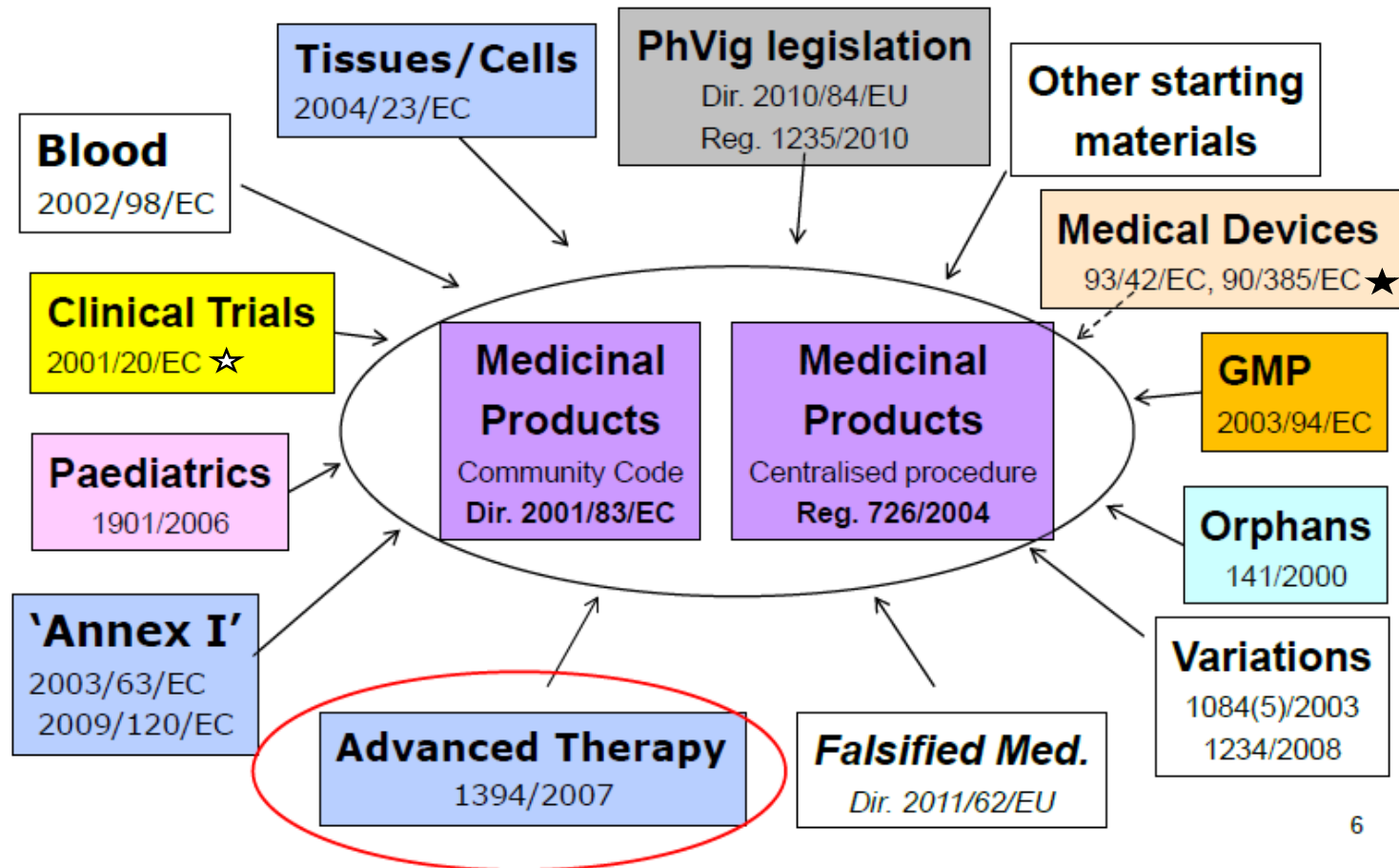
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\* Pricing and reimbursement is established with each EU Member State

CONFIDENTIAL



# EU Regulatory Framework



☆ Reg 536/2014

★ Reg 2017/745

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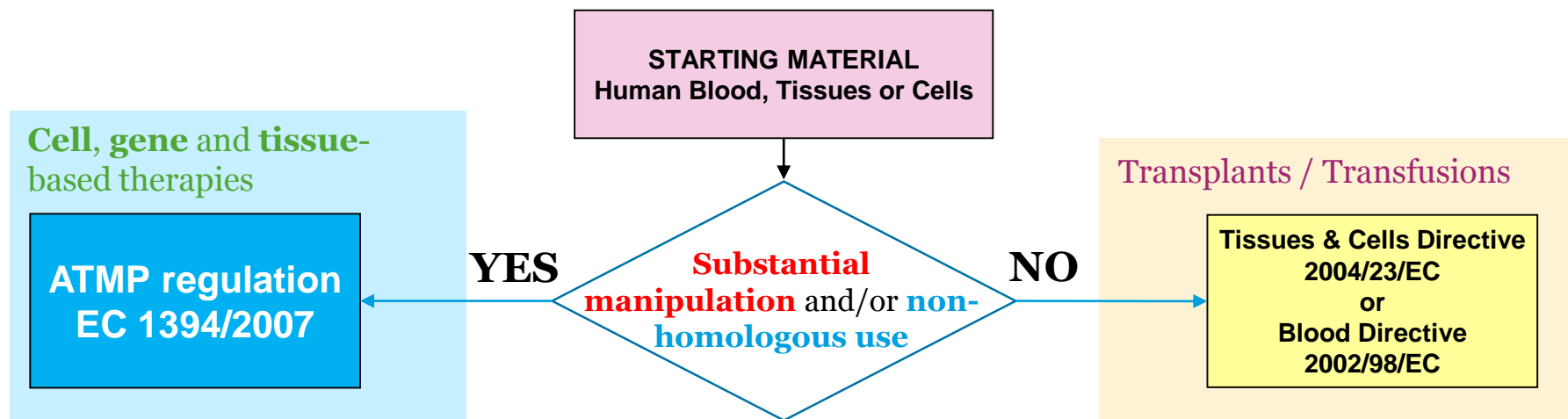


# ATMP Regulation 1394/2007

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- Established a novel legislative framework for advanced therapies (includes **Gene Therapy Medicinal Product** (GTMP), **somatic Cell Therapy Medicinal Product** (sCTMP), **Tissue Engineered Medicinal Product** (TEP) and **Combined-ATMP**)
- Requires a centralised marketing authorisation application (MAA) for all ATMPs within the EU (not nationally authorised)
- Formed a new Committee for Advanced Therapies (CAT) within the EMA, with particular responsibility for:
  - Evaluation of ATMP MAA for recommendation to EMA's CHMP
  - Providing scientific advice and generating technical guidelines
  - ATMP classification
  - 'Certification' of quality & non-clinical IMPD
- Further detail on the marketing authorisation procedure, post-authorisation requirements and incentives is also described within the regulation

# ATMPs are distinct to Transplants/Transfusions



## **Substantial manipulation\*** (Manufacture)

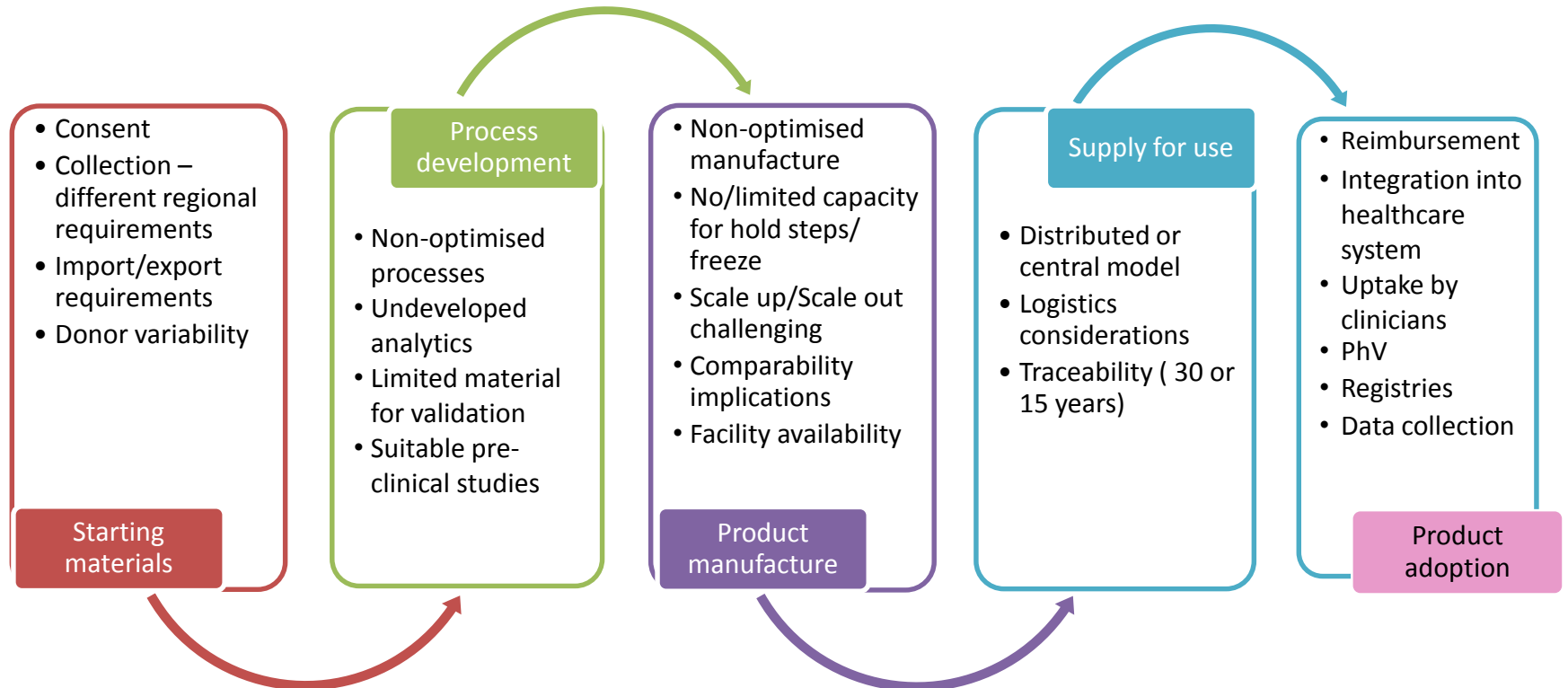
Manipulated during manufacturing process so that biological characteristics, physiological functions or structural properties have been modified to be relevant for their intended function

## **Non-homologous Use** (Function)

Cells or tissues not intended to be used for the same essential function(s) in the recipient and the donor (may relate to function and/or location)

\* Excludes: cutting, grinding, shaping, centrifugation, soaking in antibiotic/antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering...

# ATMP Regulatory Considerations

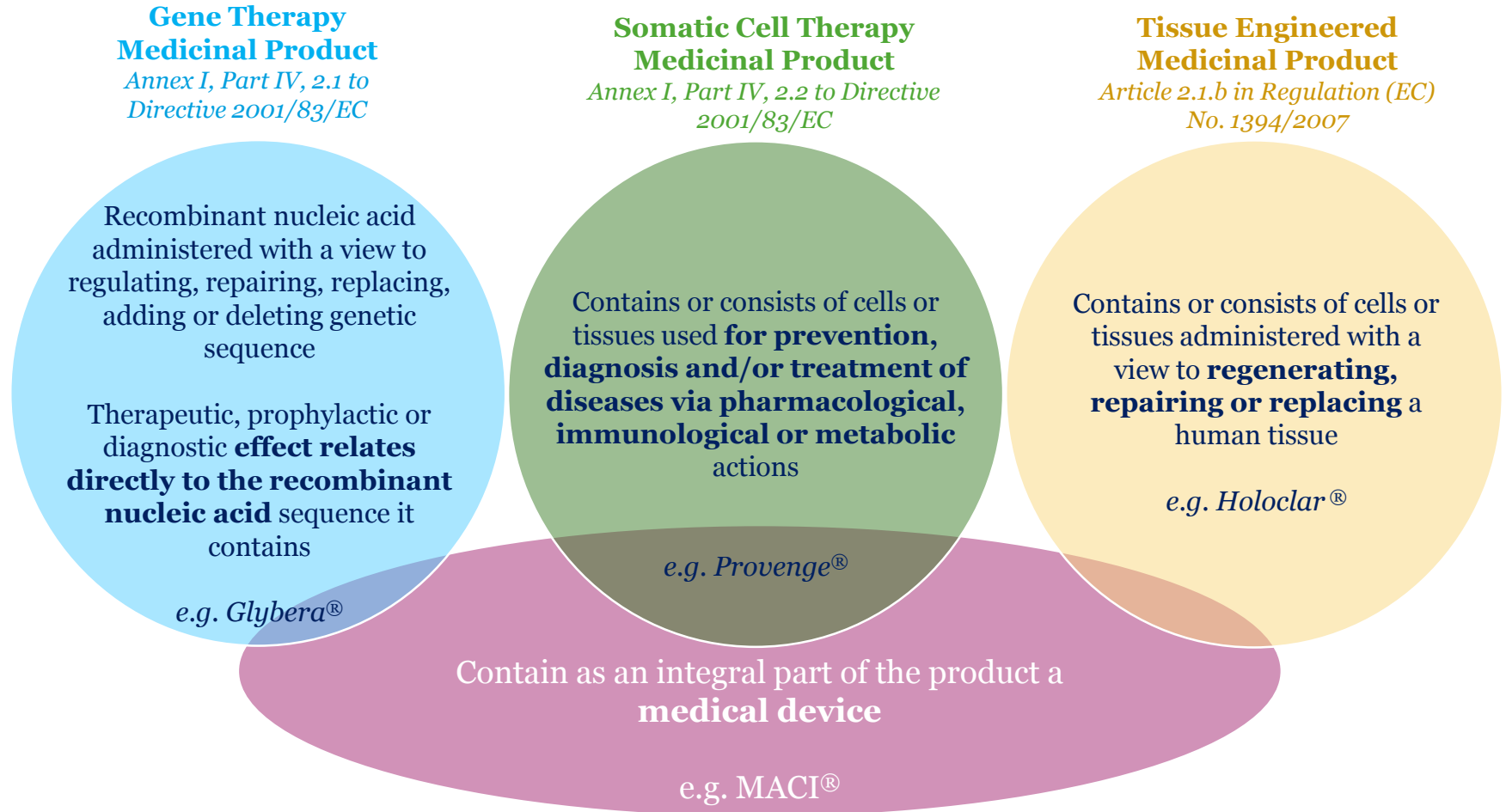


**From First-in-Human trials to market = significant jump in data requirements**

A microscopic view of numerous cells, likely oocytes or follicles, arranged in a grid-like pattern. The cells are circular and have a granular, textured appearance. They are set against a dark, almost black background, which makes the lighter-colored cells stand out. The lighting is even, highlighting the individual cells and their internal structure.

Defining your  
product

# The EU ATMP Framework



## Combined Device-ATMP

*Article 2.1.d in Regulation (EC) No. 1394/2007*

# Snapshot of ATMPs approved (Jun 2018)

- **Gene Therapy Medicinal Products**

- Imlygic, Strimvelis, **Glybera**, (Kymriah and Yescarta pending EC adoption)

- **Somatic Cell Therapy Medicinal Products**

- **Provenge**, Zalmoxis, Alofisel

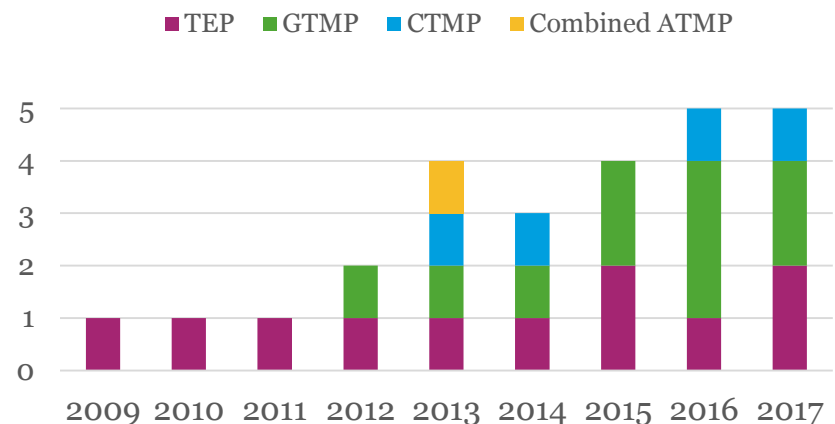
- **Tissue Engineered Products**

- Serox, Holoclar, **ChondroCelect**

- **Combined-ATMP**

- **MACI**

Licensed ATMPs in Europe



\* Withdrawn or suspended for use

# ATMP Classification at the EMA

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- Process established in particular to clarify questions on borderline classification areas
- Conducted by the Committee for Advanced Therapies (CAT)
  - Not obligatory (but advisable) and free
  - Procedure = 60 days
- Developers can apply at any point during product development (even when you have no data) but the recommendation should be based on a defined product i.e. not on a scientific ‘concept’
  - Can submit a follow-up request using the same procedure if new data comes to light.
- EMA publishes [non-confidential summaries](#) of previous ATMP classifications online

## Benefits for early development:

- First opportunity to engage with regulators
  - Position the product in the ATMP category and clarify the applicable regulatory framework(s)
  - Can help with clinical trial applications (NCAs will be made aware of classification so it will help them to identify most relevant criteria and procedure to apply)
  - Opens the door to other incentives designed for ATMPs
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## Default Decisions

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1. **Pharmacological, immunological or metabolic** action of viable cells or tissues are considered as the **principal Mechanism of Action (MoA)** of the product
2. ATMP containing both **autologous and allogeneic cells** shall be considered an **allogeneic** product
3. Products meeting the definition of both a **sCTMP + TEP** shall be considered a **TEP**
4. Products meeting the definition of a **sCTMP + TEP + GTMP** shall be considered a **GTMP**
5. Must be a **biological medicinal product**

# Case Study 1

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*Allogeneic T cells, genetically modified with a  $\gamma$ -retroviral vector to express HSV-TK ('suicide gene'). Used as an adjunctive treatment to support immune reconstitution during haploidentical haematopoietic stem cell transplantation (HSCT) in leukaemia patients.*

**Gene Therapy  
Medicinal Product**

*Annex I, Part IV, 2.1 to  
Directive 2001/83/EC*

**Somatic Cell Therapy  
Medicinal Product**

*Annex I, Part IV, 2.2 to Directive  
2001/83/EC*

**Tissue Engineered  
Medicinal Product**

*Article 2.1.b in Regulation (EC)  
No. 1394/2007*

**Combined ATMP**  
*Article 2.1.d in Regulation  
(EC) No. 1394/2007*

- Genetic modification to 'prevent the onset of GvHD' after transplant is a MoA
- Primary MoA is immune reconstitution
- But... because it is still a genetically modified sCTMP, most of the principles of a GTMP will still apply.

## Case Study 2

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*Nuclease resistant, synthetic, double-stranded, siRNA, delivered via liposomes, designed to inhibit the expression of the collagen-specific chaperone HSP47 for treatment of hepatic fibrosis.*

**Gene Therapy  
Medicinal Product**  
*Annex I, Part IV, 2.1 to  
Directive 2001/83/EC*

**Somatic Cell Therapy  
Medicinal Product**  
*Annex I, Part IV, 2.2 to Directive  
2001/83/EC*

**Does not fulfil the  
definition of an ATMP**

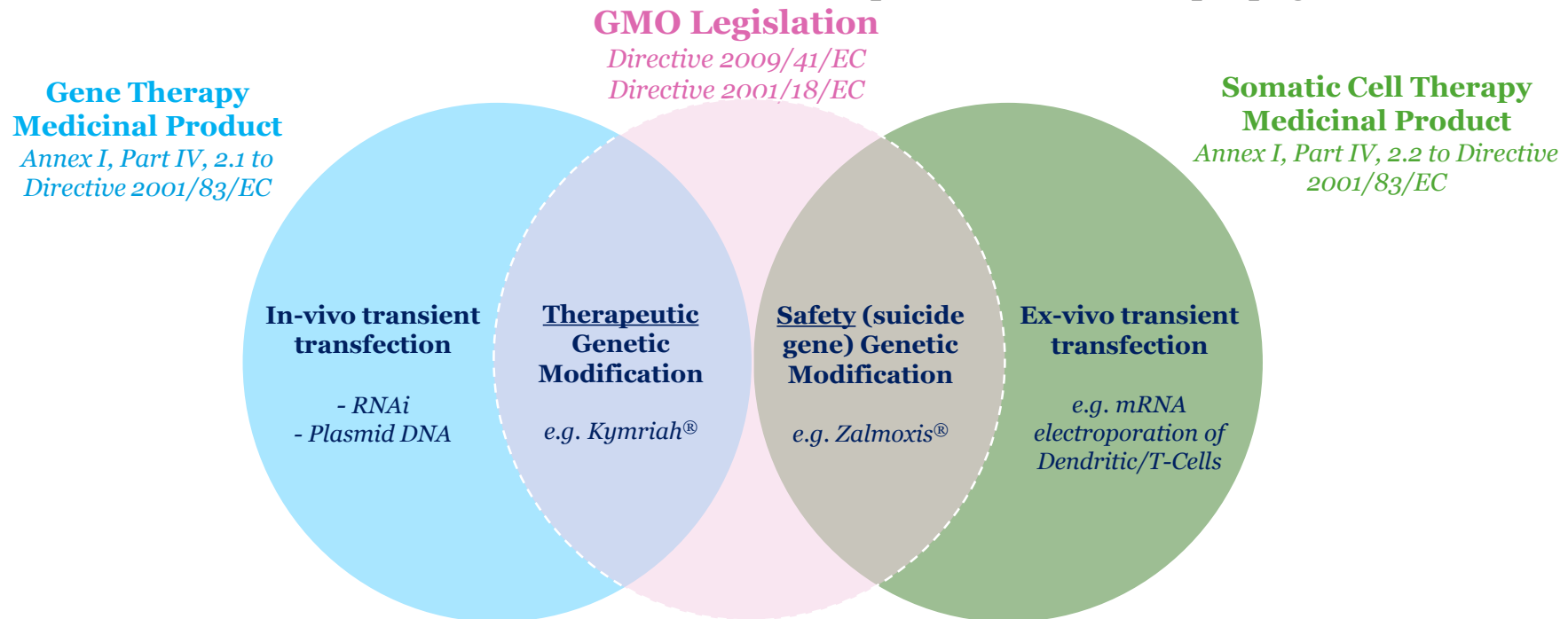
**Tissue Engineered  
Medicinal Product**  
*Article 2.1.b in Regulation (EC)  
No. 1394/2007*

**Combined ATMP**  
*Article 2.1.d in Regulation  
(EC) No. 1394/2007*

- The product is not of biological origin as it is chemically synthesised
- But... as the primary MoA is that of a GTMP most of the principles will apply

# Gene ‘Therapy’ versus Genetic ‘Modification’

- Unlike the EMA, the EU definition of genetic modification of organisms (GMOs) is based on the technology used, not on the mechanism of action
- ‘Medication’ could therefore also be considered ‘modification’ when applying heritable material or recombinant nucleic acid molecules capable of continued propagation\*



National regulatory bodies may interpret the definition of genetic modification differently leading to variation across EU Member States



Early development  
support

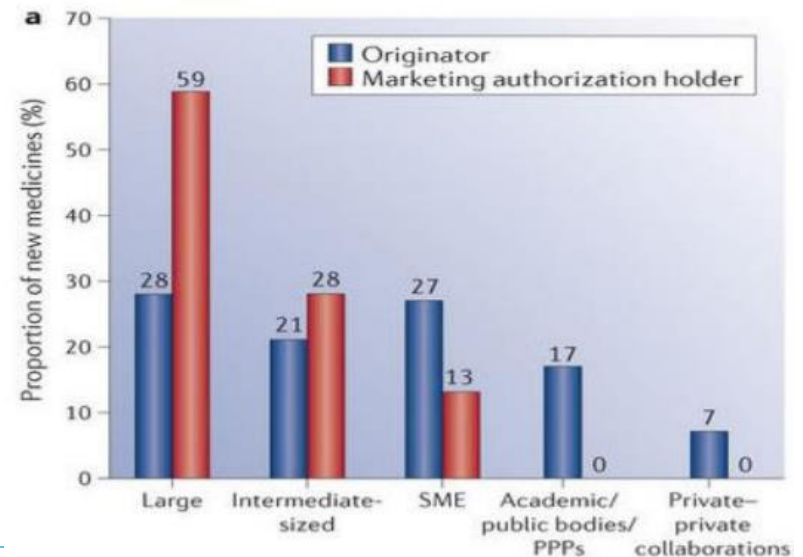
# EMA - Early interactions on innovation

- EU Regulatory Network is open for early, non-binding discussions on scientific, regulatory and technical aspects of innovative developments
  - Regulators from gatekeepers to **enablers**
- EMA's Innovation Task Force (ITF) is a multidisciplinary platform for preparatory dialogue and orientation on innovative methods, technologies and medicines

## EMA ITF briefing meetings

- From a total of 41 meetings in 2016, 40% were on innovative ATMPs
- Establish a platform for early dialogue with applicants, to identify scientific, legal and regulatory issues relating to emerging therapies and technologies
- Orientate applicants towards eligibility of medicines for Agency procedures

Originator and the marketing authorization holder for 94 approved products evaluated, divided according to organization type



Regulatory watch: Where do new medicines originate from in the EU? Nature Reviews Drug Discovery Volume: 13, Pages: 92–93; Published online 31 January 2014

# UK Support for Early Innovation

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- ‘Enhancing innovation’ is part of the MHRA’s corporate plan for 2018-23\*
- *We will support and enhance innovation and accelerate routes to market to benefit public health and be a magnet for life sciences including:*
  - Support innovation and growth in Life Sciences
  - Develop and deliver innovative regulatory and legislative measures
  - Responsive to priority areas of scientific development (new products, types and methodologies)

## **MHRA Innovation office** (*Launched, 2012*)

- Free, non-binding regulatory advice aimed at academic/SME stakeholders:
  - Information and guidance clarifying UK and EU requirements (manufacturing, preclinical, clinical) for early stage product development.
- Regulatory Advice Service for Regenerative Medicine: specific information and guidance, reviewed by 4 independent and UK-based agencies, for queries about regenerative medicines.

## **Early Access to Medicines Scheme (EAMS)** (*Launched, 2015*)

- Initiative aimed at making ‘promising innovative medicines’ which is likely to offer a significant advantage over existing options, available to patients in the clinic prior to full licensure.
- Helps to ensure clinical plan satisfies regulators (MHRA) and HTA (NICE) reimbursement data requirements, supporting real-world adoption

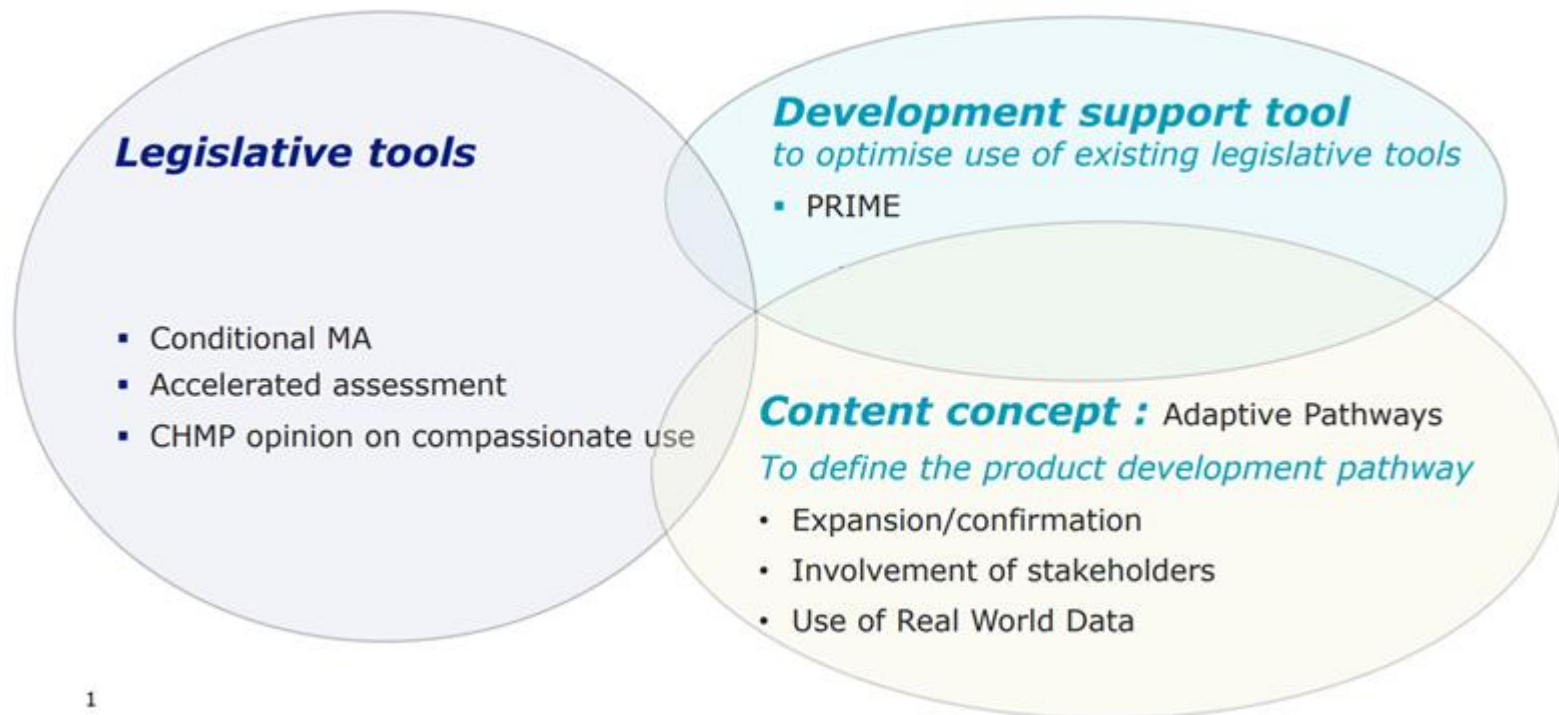
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\* MHRA Corporate Plan 2018

A microscopic view of numerous cells, likely lymphocytes, showing their characteristic round shape and internal structure. The cells are densely packed, with some showing prominent nuclei and others appearing more uniform. The overall color palette is dominated by shades of green and blue, giving it a scientific and clinical feel.

# European Pathways to Market

ATMP licensing 'pathways' overlap with the EMA's ***development support and early access for medicines addressing unmet need***



# ‘Legislative Tools’

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- **Accelerated Assessment**

- Justification that the medicinal product is expected to be **of major public health interest**, particularly from the point of view of **therapeutic innovation**
- Benefit - 210 day MAA procedure reduced to 150 days (same MAA requirements)
  - > Note: Submit request 2/3 months before MAA

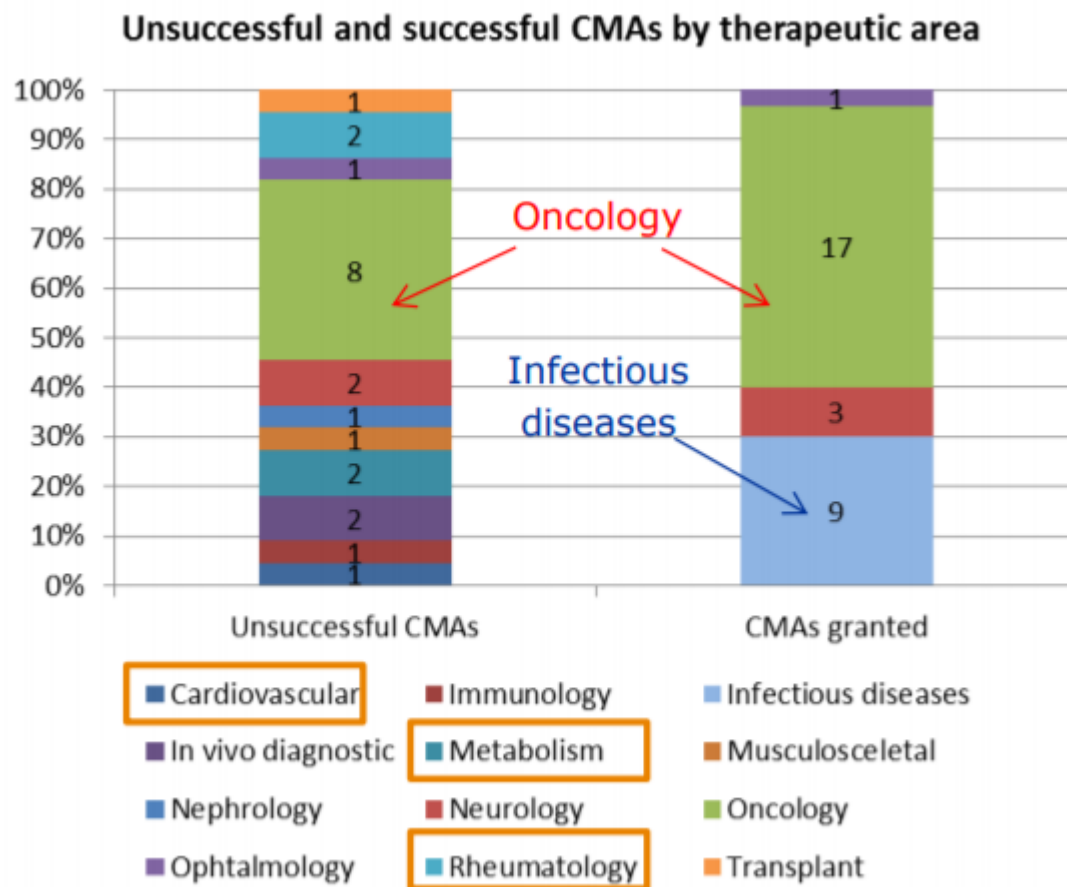
- **Conditional Marketing Authorisation**

- Eligible products include those
  - aimed at treating, preventing or diagnosing seriously debilitating or life-threatening diseases
  - intended for use in emergency situations (also less comprehensive pharmaceutical and non-clinical data may be accepted for such products)
  - designated as orphan medicines

- **Benefits**

- Product can be authorised several years earlier
- Comprehensive data are still generated after authorisation

# 'Legislative Tools'



[Zigmars Sebris. Conditional marketing authorisation - Report on ten years of experience at the EMA. June 2017](#)

# PRIME (Priority Medicines) Initiative

- Launched March 2016 - Early access tool, supporting patient access to innovative medicines to foster development of medicines with a **high public health potential**

## Key Features

- **Written confirmation of PRIME eligibility** and potential for accelerated assessment;
- **Early CHMP Rapporteur appointment** during development;
- **Kick off meeting** with multidisciplinary expertise from EU network;
- **Enhanced scientific advice** at key development milestones/decision points;
- **EMA dedicated contact point**;
- **Fee incentives** for SMEs and academics on Scientific Advice requests.

## General Benefits for Development

- Iterative Scientific advice
- Enhanced regulatory guidance
- Incremental knowledge gain
- Proactive dialogue
- Promote use of existing tools

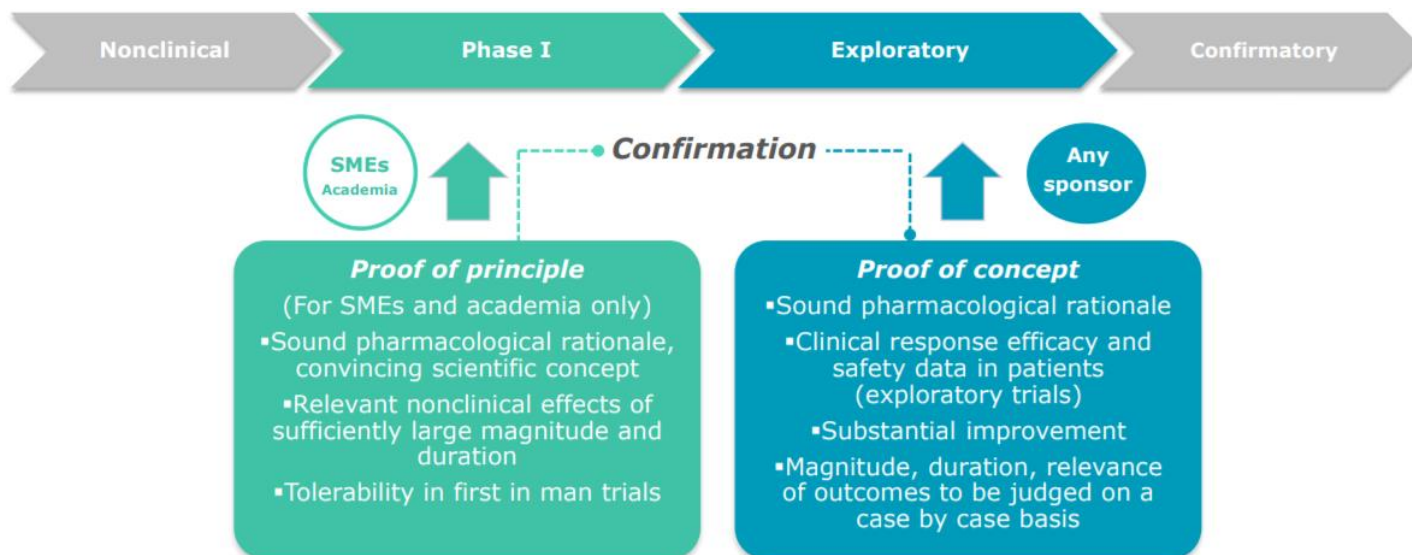


**Working towards  
an Accelerated  
Assessment (early  
confirmation)**

# PRIME (Priority Medicines)

- Eligibility based on accelerated assessment criteria:
  - An **unmet medical need** (a fancy new MoA or target is not enough!)
    - > 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)
- Justification must be based on
  - **What** is the unmet need; epidemiological data about the disease, description of available diagnostic, prevention and treatment options/standard of care, their effect and how medical need is not fulfilled
  - **How** will it be addressed (with evidence);
    - > Description of observed (how efficacious?/long-term?) and predicted effects including clinical relevant, added value and impact
    - > If applicable, expected improvement over existing treatments
    - > Data: nonclinical pharmacology, clinical data (exploratory efficacy + safety)

# PRIME (Priority Medicines)

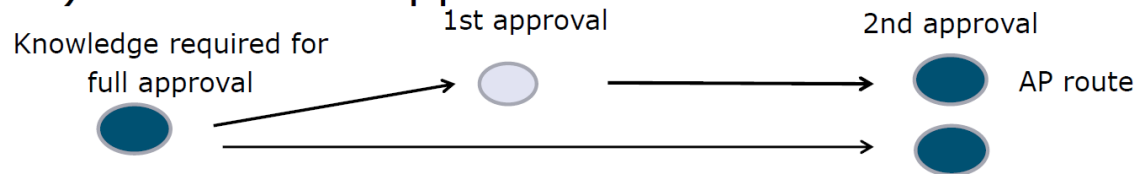


3 PRIME, SME workshop 2016

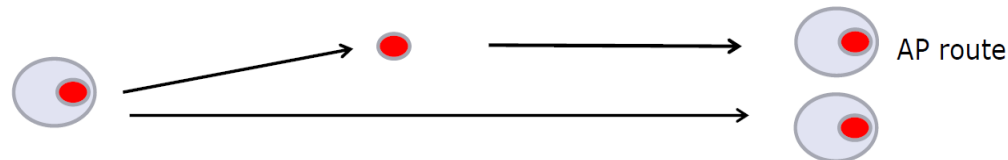
- SME/Academics versus sponsor distinction is a unique push in Europe and EMA have acknowledged PRIME designed with these developers in mind
- Currently 11/29 designations are for ATMPs: [List of products granted eligibility to PRIME](#)

- **Prospectively planned, development approach** to commercialisation for medicines with high medical need
- Starting from an authorised (usually “niche”) indication, through phases of **evidence gathering** (controlled trials and real-world data) leading to **progressive licensing adaptation** to existing and/or new approvals

## 1) Conditional approval scenario

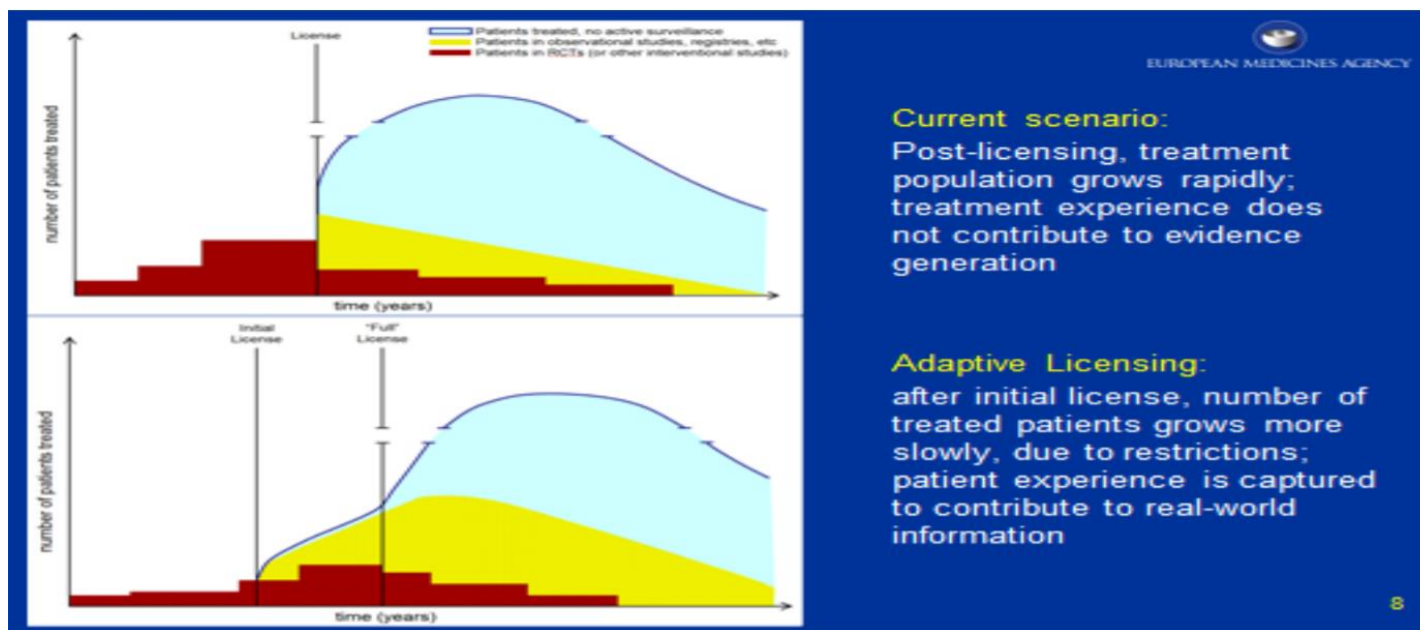


## 2) Expansion of indication scenario



- Balance **timely patient access** with the need to provide adequate **evolving information on risk vs benefit**

# Adaptive Pathways



- Patients treated, no active surveillance
- Patients in observational studies, registries, etc.
- Patients in RCTs (or other interventional studies)

# Case study: Bluebird's LentiGlobin BB305

## FierceBiotech

BIOTECH RESEARCH IT CRO MEDTECH

Biotech

### Bluebird Bio sees Europe as first market for its gene therapies



Bluebird Bio plans to bring its gene therapies to market in Europe before the U.S., thanks to a favorable regulatory pathway.



Bluebird's head of Europe, Andrew Obenshain, **told** the Daily Telegraph that the company is already in negotiations with the EMA and the U.K.'s Medicine and Healthcare products Regulatory Agency (MHRA) on possible regulatory filings.



The EMA's **adaptive pathways** process—which allows new therapies to be approved in stages based on stepwise collection of data—is a key part of that decision, as is the fact that the agency "works very closely with companies coming forward with new methodologies," said Morgan. And with Brexit looming, it makes sense to discuss these plans with the MHRA separately.



# Case study: Bluebird's LentiGlobin BB305

- LentiGlobin BB305 = gene therapy medicinal product for the treatment of transfusion dependent beta-thalassemia
- Once-only administration, initial conditional approval route foreseen in Europe  
= initial basis for labelling and the value proposition
- Long-term follow-up of trial patients will provide information on the duration of the effect and the long-term safety of the treatment to be used by regulators, HTA bodies and payers in their assessment and decision making.
- **Prospective discussion** taking place on the **data elements** and **design of long-term evidence generation** to collect relevant and 'high quality' data (RWD + other studies?) and on the corresponding feasibility of the proposed reimbursement schemes in the Member States

Note – prospective discussions of **post-authorisation data generation** and monitoring is what differentiates the adaptive pathways approach from EMA parallel scientific advice with HTA bodies and conditional approval alone, which generally focuses on the initial marketing authorisation

# A good candidate profile

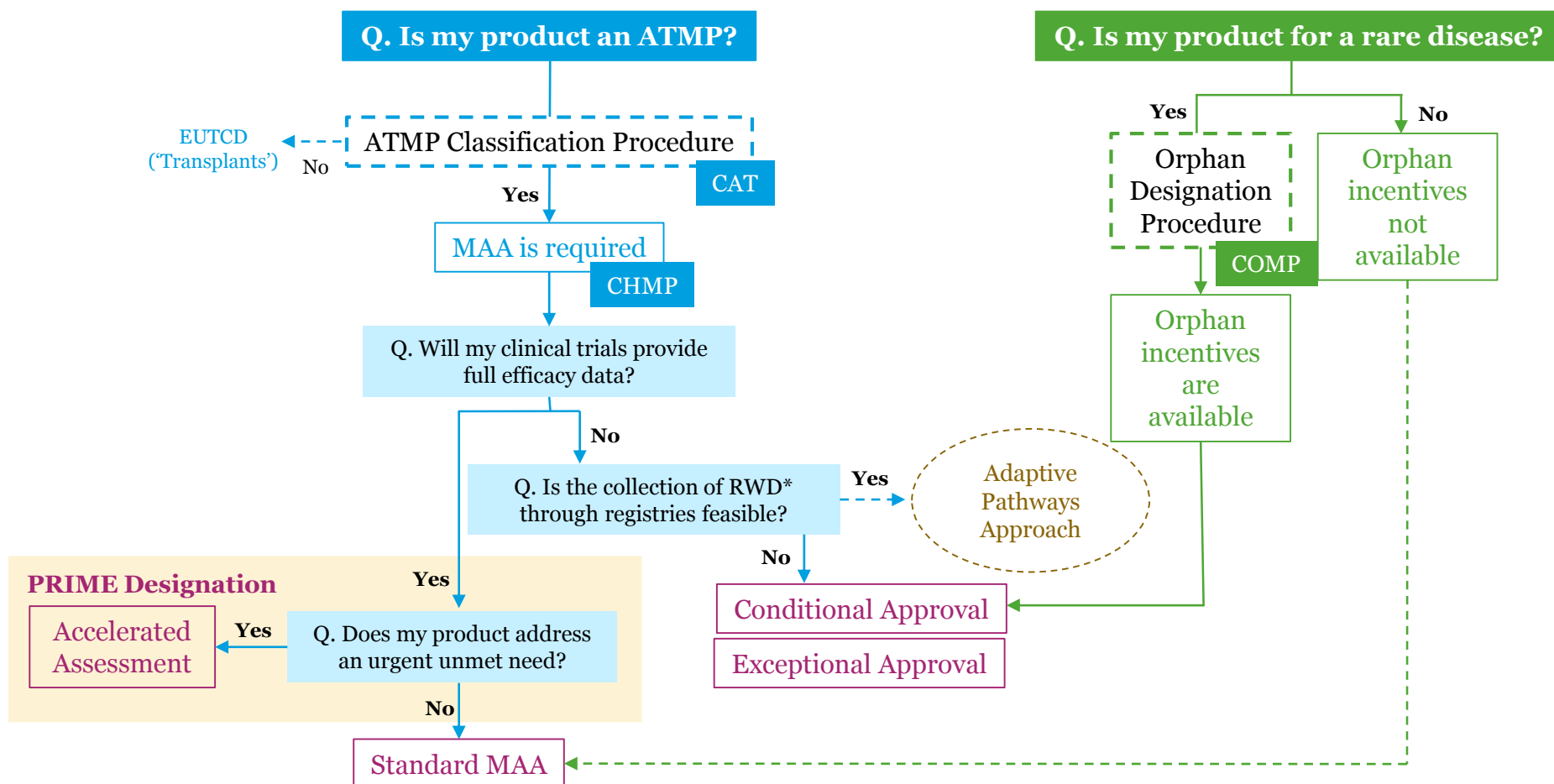
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1. An **iterative** development plan (staggered approval): start in a well-defined subpopulation with unmet medical need and **expand**, or have a Conditional Marketing Authorisation, maybe on surrogate endpoints and **confirm**.
2. **Real World Data** (safety and efficacy) can be acquired to supplement Clinical Trials, e.g. through well planned registries
3. Input of all **stakeholders**, particularly HTAs, is fundamental

## Important:

- AP should not be exclusively viewed as a tool for accelerated development
- AP is a long-term “life-cycle management” approach from the EMA
  - Still in early-stage → Buy-in from HTA bodies? How will the systems integrate?
- AP is different to PRIME, not mutually exclusive

# Navigating the European regulatory pathway(s)



\*RWD = Real World Data

# How does the yellow brick road look?

- **Standard MAA (6)**

GTMP: Imlygic, Strimvelis (Orphan)

CTMP: **Provenge**, Alofisel

TEP: Spherox, **MACI** (Combined), **CondroCelect**

- **Conditional MAA (2)**

CTMP: Zalmoxis (Orphan)

TEP: Holoclar (Orphan)

- **Exceptional Circumstances (1)**

GTMP: **Glybera** (Orphan)



\* Withdrawn or suspended for use

A microscopic view of numerous cells, likely oocytes or follicles, arranged in a grid-like pattern. The cells are circular and have a granular, textured appearance. They are set against a dark, almost black background, which makes the lighter-colored cells stand out. The cells vary slightly in size and focus, with some appearing sharper than others.

USA



- [Guidance to Industry: Expedited Programs for Serious Conditions](#) (May 2014)

## 1. Fast Track Designation

Eligibility – Serious condition + prelim. nonclinical/mechanistic/clinical to **show potential**

Benefits – Frequency of FDA meetings + written comms., rolling review?

## 2. Breakthrough Designation

Eligibility – Serious condition + prelim. **clinical evidence of substantial improvement**

Benefits – Above + development guidance + senior org. commitment, rolling review?

## 3. Accelerated Approval (approval pathway, post-approval commitments)

Eligibility – Serious condition + **meaningful** advantage + surrogate endpoint predictive of clinical benefit or endpoint that can be measured before morbidity/mortality

Benefits – Approval based on a surrogate endpoint or intermediate clinical endpoint

## 4. Priority Review

Eligibility – Serious condition **and** significant safety/efficacy improvement over available treatments if approved **OR** priority review voucher

Benefits – Shorter BLA review (6 months) compared with standard review time



## RMAT Designation\*

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- 21st Century Cures Act was signed into law December 2016 and *designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently*. Also established 2 **new expedited product development programmes**:
  1. [Regenerative Medicine Advanced Therapy](#) (RMAT) designation offers a new expedited pathway for certain eligible products
  2. [Breakthrough Devices program](#) designed to speed the review of certain innovative medical devices
- Includes cell therapy, therapeutic tissue-engineered product, human cell and tissue product and combination of the above
- **What about gene therapies?**

*“gene therapies, including genetically modified cells, that lead to a durable modification of cells or tissues may meet the definition of a regenerative medicine therapy”*

*Expedited Programs for Regenerative Medicine Therapies for Serious Conditions -  
[Draft Guidance for Industry](#)*

**Essential benefits:** interact with the FDA **earlier** in the clinical development process and **more frequently**, with the aim of maximising opportunity for **for priority review** and **accelerated approval**

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# Breakthrough vs RMAT Designation

	Breakthrough Therapy Designation	Regenerative Medicine Advanced Therapy Designation
<b>Statute</b>	Section 506(a) of the FD&C Act, as added by section 902 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)	Section 506(g) of the FD&C Act, as added by section 3033 of the 21 <sup>st</sup> Century Cures Act
<b>Qualifying criteria</b>	A drug that is intended to treat a serious condition, <b>AND</b> preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	A drug is a regenerative medicine therapy, <b>AND</b> the drug is intended to treat, modify, reverse, or cure a serious condition, <b>AND</b> preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition
<b>Features</b>	<ul style="list-style-type: none"> <li>• All fast track designation features, including: <ul style="list-style-type: none"> <li>▪ Actions to expedite development and review</li> <li>▪ Rolling review</li> </ul> </li> <li>• Intensive guidance on efficient drug development, beginning as early as Phase 1</li> <li>• Organizational commitment involving senior managers</li> </ul>	<ul style="list-style-type: none"> <li>• All breakthrough therapy designation features, including early interactions to discuss any potential surrogate or intermediate endpoints</li> <li>• Statute addresses potential ways to support accelerated approval and satisfy post-approval requirements</li> </ul>
<b>When to submit</b>	With the IND or after and, ideally, no later than the end-of-phase 2 meeting	
<b>FDA response</b>	Within 60 calendar days after receipt of request	
<b>Designation Rescission</b>	Designation may be rescinded later in product development if the product no longer meets the designation-specific qualifying criteria	

# ‘Preliminary’ Clinical Evidence

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Examples of preliminary clinical evidence that CBER considers sufficient to demonstrate potential to address unmet medical needs in those with a serious condition:

1. In a single-arm, open-label study conducted in a center treating patients with **severe and extensive skin burns**, use of allogeneic keratinocyte- and fibroblast-based cell therapy is associated with **rapid and substantial wound re-epithelialization** of deep partial thickness burns in the **majority of treated wounds**
2. In a phase 2, dose-finding study, intra-myocardial administration of allogeneic human mesenchymal precursor cells to patients with **advanced** chronic heart failure **refractory to available medical therapies** is associated with **dose-dependent improvement** in **several physiological measurements** of left ventricular performance.



# RMAT Designation

- October 2017<sup>1</sup>
  - Requests: **27**; Completed/Pending: **26/1**; Denied: **17**; Granted: **9**; Orphan: **4** (at least)
- As of June 2018<sup>2</sup> there have been 19 RMAT designations granted:
  1. CAR-T cell therapy in r/r NHL (Juno Therapeutics)
  2. Gene therapy for advanced Parkinson's disease (Voyager)
  3. Tissue matrix allograft for Osteoarthritis (Mimedix)
  4. Allogeneic human retinal progenitor cell suspension (jCyte)
- For the applications denied:

Administrative → inactive IND / No preliminary clinical evidence submitted

CMC Reasons → different product for designation VS evidence generated

Insufficient prelim. clinical evidence → study design, inconsistent product activity

<sup>1</sup> Wilson W. Bryan, Director, FDA, Office of Tissue and Advanced Therapies, CBER. RMAT Designation - Cell and Gene Meeting on the Mesa, 5-Oct-2017

<sup>2</sup> <https://www.bioinformant.com/rmat/#list> - Accessed 29-Jun-18



## RMAT Designation vs Europe

- Objective → interactions with FDA to expedite development and review of regenerative medicine advanced therapies



= PRIME designation (although PRIME agnostic on product type)

- *May* be eligible for **priority review**



= Accelerated Assessment

- *May* be eligible for **accelerated approval**



= Conditional Approval + Adaptive Licensing?



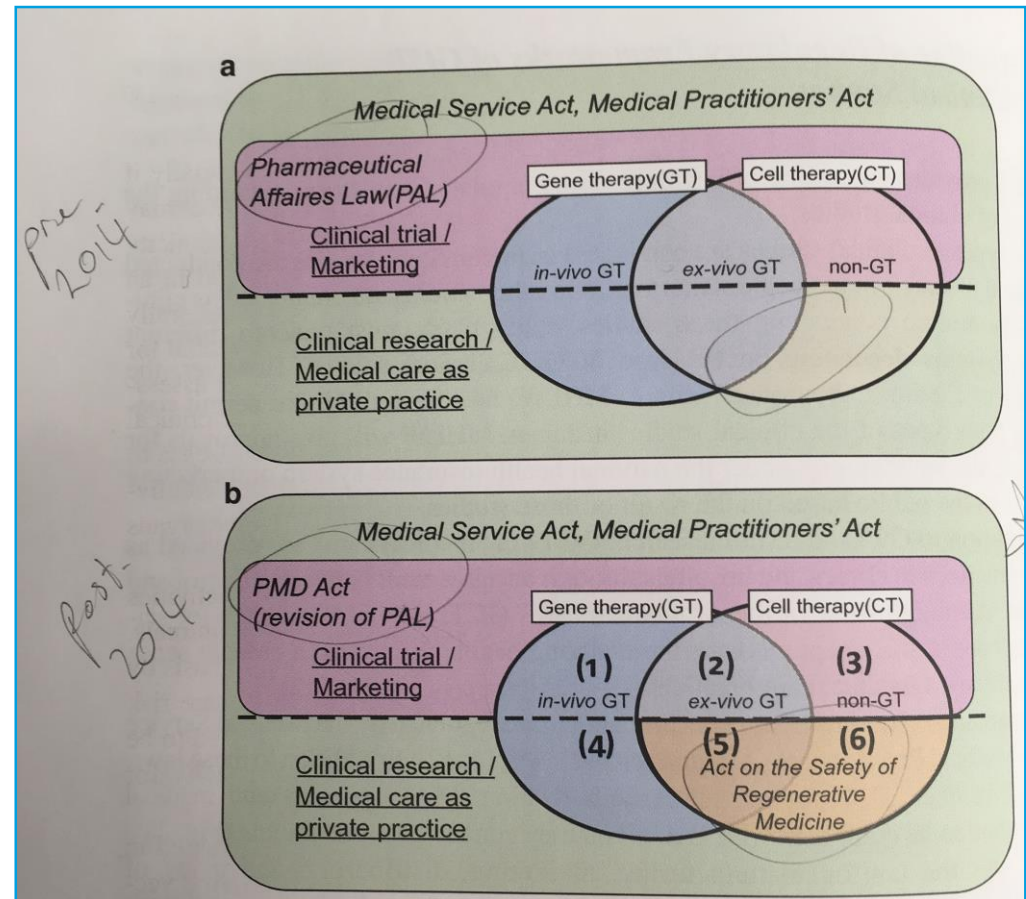
Japan

# Japan



In late 2014, new regulations accelerating the approval of 'regenerative therapeutics' took effect in Japan

1. Act on the Safety of Regenerative Medicine (Law No. 85/2013) - MHLW
  - Increasing clinical adoption of mainly of processed cells
  - **Outside a clinical trial**
2. Pharmaceuticals and Medical Device (PMD) Act (Law No. 84/2013) - PMDA
  - Revision for regen medicine products
  - '**Conditional approval**' based off Phase I and II data
  - 'Post approval' commitments or withdraw product after 7 years



\* Image: Regulatory Aspects of Gene Therapy and Cell Therapy Products (2016) Page 152

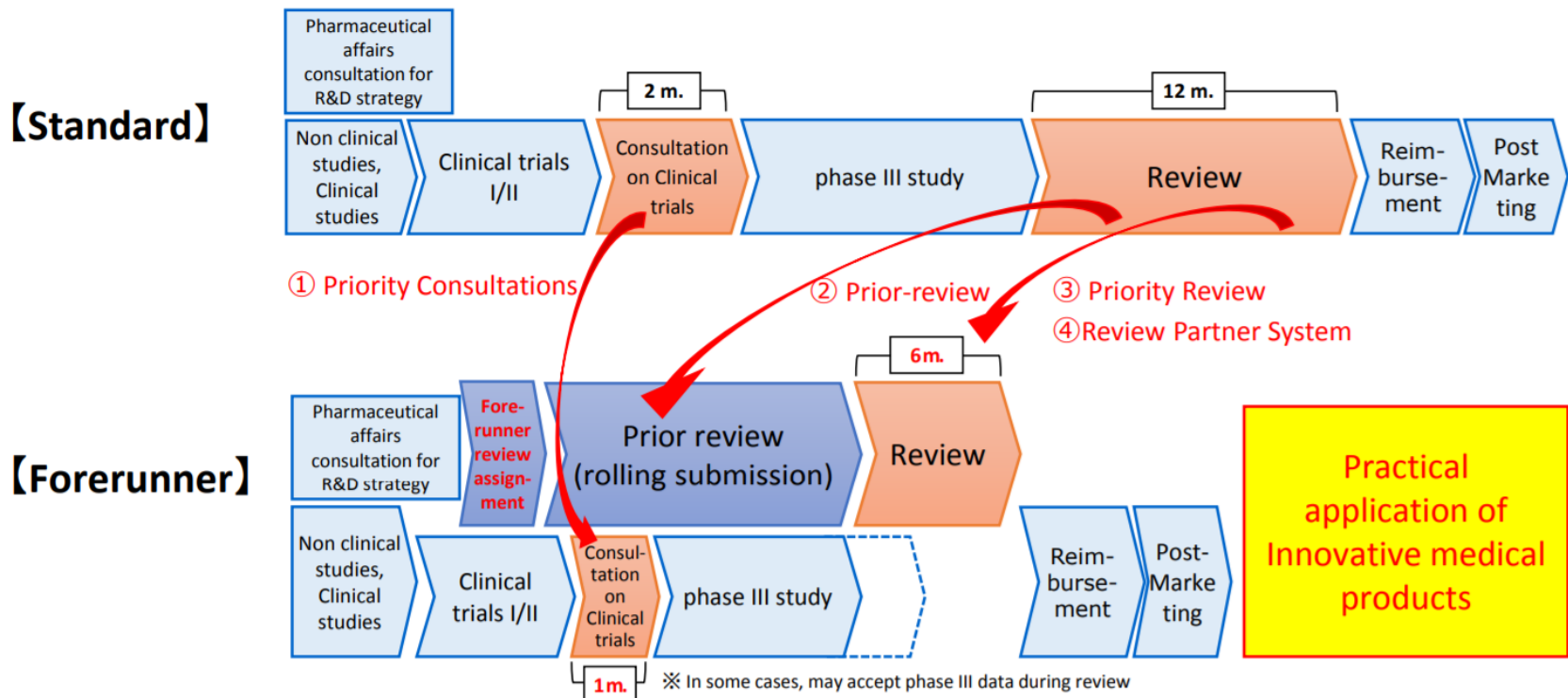
# SAKIGAKE Designation

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- *‘Charging ahead / frontrunner’*
- Similar objective to PRIME (EU) and RMAT/Breakthrough Therapy (US)
- **Eligibility**
  - Medical products for **diseases in dire need of innovative therapy**
  - Applied for **approval firstly or simultaneously in Japan**
  - Prominent effectiveness can be expected based on **non-clinical data** and **early phase of clinical trials**

## General Timeframe of Forerunner Review Assignment



# Conclusion

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- As a complex and heterogenous group of products, ATMPs sit within a **‘patchwork’ of European regulations** – context for product development
- Develop and discuss your ATMP regulatory strategy for market early – regulatory agencies (EMA and NCA) are gatekeepers and technology enablers
- **Range of pathways/designations available** to developers of innovative therapies that meet an unmet medical need **is growing**
- For many, deep experience is still lacking however the broad objectives are similar – **get innovative therapies to patients faster**
- Importantly, the way this is achieved varies in particular **eligibility** (products/data required), **methods** and **benefits...**
- **Understanding the interplay and differences** will be important to support planning and efficient development of exciting and novel therapies

## Further information

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- European Medicines Agency – Support for advanced-therapy developers - [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000641.jsp&mid=WCob01ac058007f4bd](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000641.jsp&mid=WCob01ac058007f4bd)
- Gene Therapy - Scientific Guidelines/Considerations, Reflection paper, Q&As etc. - [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000410.jsp&mid=WCob01ac058002958d](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000410.jsp&mid=WCob01ac058002958d)
- Cell Therapy and Tissue Engineering - Scientific Guidelines/Considerations, Reflection paper, Q&As etc. - [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000405.jsp&mid=Cob01ac058002958a](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000405.jsp&mid=Cob01ac058002958a)
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