Taking Advanced Therapy Medicinal Products (ATMPs) to Market

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Content

1. EU Regulatory Network
2. Defining your product
3. Early development
4. Europe
5. USA
6. Japan
7. Conclusion
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

* Pricing and reimbursement is established with each EU Member State
EU Regulatory Framework

Clinical Trials
2001/20/EC

Blood
2002/98/EC

Tissues/Cells
2004/23/EC

PhVig legislation
Dir. 2010/84/EU
Reg. 1235/2010

Other starting materials

Medical Devices
93/42/EC, 90/385/EC★

GMP
2003/94/EC

Orphans
141/2000

Variations
1084(5)/2003
1234/2008

‘Annex I’
2003/63/EC
2009/120/EC

Paediatrics
1901/2006

Medicinal Products
Community Code
Dir. 2001/83/EC

Medicinal Products
Centralised procedure
Reg. 726/2004

Advanced Therapy
1394/2007

Falsified Med.
Dir. 2011/62/EU

★ Reg 536/2014
★ Reg 2017/745

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ATMP Regulation 1394/2007

- 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...

Confidential
ATMP Regulatory Considerations

From First-in-Human trials to market = significant jump in data requirements
Defining your product
The EU ATMP Framework

**Gene Therapy Medicinal Product**
*Annex I, Part IV, 2.1 to Directive 2001/83/EC*
- Recombinant nucleic acid administered with a view to regulating, repairing, replacing, adding or deleting genetic sequence
- Therapeutic, prophylactic or diagnostic *effect relates directly to the recombinant nucleic acid* sequence it contains
  - *e.g.* Glybera®

**Somatic Cell Therapy Medicinal Product**
*Annex I, Part IV, 2.2 to Directive 2001/83/EC*
- Contains or consists of cells or tissues used *for prevention, diagnosis and/or treatment of diseases via pharmacological, immunological or metabolic actions*
  - *e.g.* Provenge®

**Tissue Engineered Medicinal Product**
*Article 2.1.b in Regulation (EC) No. 1394/2007*
- Contains or consists of cells or tissues administered with a view to *regenerating, repairing or replacing* a human tissue
  - *e.g.* Hologlar®

**Combined Device-ATMP**
*Article 2.1.d in Regulation (EC) No. 1394/2007*
- Contain as an integral part of the product a *medical device*
  - *e.g.* MACI®
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
  – Sperox, Holoclar, ChondroCelect

• Combined-ATMP
  – MACI

Licensed ATMPs in Europe

* Withdrawn or suspended for use
ATMP Classification at the EMA

- 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
Default Decisions

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

Allogeneic T cells, genetically modified with a γ-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.

- 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

**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.**

Does not fulfil the definition of an ATMP

- 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

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**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**
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.*

### Gene ‘Therapy’ versus Genetic ‘Modification’

- In-vivo transient transfection
  - RNAi
  - Plasmid DNA
- Ex-vivo transient transfection
  - e.g. mRNA electroporation of Dendritic/T-Cells
- Therapeutic Genetic Modification
  - e.g. Kymriah®
- Safety (suicide gene) Genetic Modification
  - e.g. Zalmoxis®

GMO Legislation

- Directive 2009/41/EC
- Directive 2001/18/EC

Somatic Cell Therapy Medicinal Product

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

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
UK Support for Early Innovation

• ‘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:
  o Information and guidance clarifying UK and EU requirements (manufacturing, preclinical, clinical) for early stage product development.
  o 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

* MHRA Corporate Plan 2018
European Pathways to Market
EU ATMP Licensing

ATMP licensing ‘pathways’ overlap with the EMA’s development support and early access for medicines addressing unmet need.
'Legislative Tools'

• **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
Only few therapeutic areas have managed to use Conditional MAs

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**

- **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)**

- **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.
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)
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
Adaptive Pathways

- **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

Current scenario:
Post-licensing, treatment population grows rapidly; treatment experience does not contribute to evidence generation

Adaptive Licensing:
after initial license, number of treated patients grows more slowly, due to restrictions; patient experience is captured to contribute to real-world information

- Blue: Patients treated, no active surveillance
- Yellow: Patients in observational studies, registries, etc.
- Red: Patients in RCTs (or other interventional studies)
Case study: Bluebird’s LentiGlobin BB305

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

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)

Q. Is my product an ATMP?

- No: EUTCD (‘Transplants’)
- Yes: ATMP Classification Procedure

Q. Is my product for a rare disease?

- Yes: Orphan Designation Procedure
- No: COMP

Q. Will my clinical trials provide full efficacy data?

- No: Conditional Approval
- Yes: Orphan incentives are available

Q. Is the collection of RWD* through registries feasible?

- Yes: Adaptive Pathways Approach
- No: Exceptional Approval

PRIME Designation

- Yes: Accelerated Assessment
- No: Standard MAA

*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*
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
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”

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
## Breakthrough vs RMAT Designation

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<tr>
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<th>Breakthrough Therapy Designation</th>
<th>Regenerative Medicine Advanced Therapy Designation</th>
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<tbody>
<tr>
<td><strong>Statute</strong></td>
<td>Section 506(a) of the FD&amp;C Act, as added by section 902 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)</td>
<td>Section 506(g) of the FD&amp;C Act, as added by section 3033 of the 21st Century Cures Act</td>
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<tr>
<td><strong>Qualifying criteria</strong></td>
<td>A drug that is intended to treat a serious condition, <strong>AND</strong> preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies</td>
<td>A drug is a regenerative medicine therapy, <strong>AND</strong> the drug is intended to treat, modify, reverse, or cure a serious condition, <strong>AND</strong> preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition</td>
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| **Features**         | • All fast track designation features, including:  
    - Actions to expedite development and review  
    - Rolling review  
    • Intensive guidance on efficient drug development, beginning as early as Phase 1  
    • Organizational commitment involving senior managers | • All breakthrough therapy designation features, including early interactions to discuss any potential surrogate or intermediate endpoints  
    • Statute addresses potential ways to support accelerated approval and satisfy post-approval requirements |
| **When to submit**   | With the IND or after and, ideally, no later than the end-of-phase 2 meeting                     |                                                                                                                  |
| **FDA response**     | Within 60 calendar days after receipt of request                                                   |                                                                                                                  |
| **Designation Rescission** | Designation may be rescinded later in product development if the product no longer meets the designation-specific qualifying criteria |                                                                                                                  |
‘Preliminary’ Clinical Evidence

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\(^1\)
  - Requests: 27; Completed/Pending: 26/1; Denied: 17; Granted: 9; Orphan: 4 (at least)
- As of June 2018\(^2\) 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

\(^1\) Wilson W. Bryan, Director, FDA, Office of Tissue and Advanced Therapies, CBER. RMAT Designation - Cell and Gene Meeting on the Mesa, 5-Oct-2017

\(^2\) 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
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

SAKIGAKE Designation

• ‘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**
SAKIGAKE Benefits

General Timeframe of Forerunner Review Assignment

【Standard】
- Non clinical studies, Clinical studies
- Clinical trials I/II
- Consultation on Clinical trials
- phase III study
- Review
- Reimbursement
- Post Marketing

1. Priority Consultations
2. Prior-review
3. Priority Review
4. Review Partner System

【Forerunner】
- Non clinical studies, Clinical studies
- Clinical trials I/II
- Consultation on Clinical trials
- phase III study
- Review
- Reimbursement
- Post Marketing

Practical application of Innovative medical products

※ In some cases, may accept phase III data during review
Conclusion

- As a complex and heterogeneous 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

• European Medicines Agency – Support for advanced-therapy developers -

• Gene Therapy - Scientific Guidelines/Considerations, Reflection paper, Q&As etc. -

• Cell Therapy and Tissue Engineering - Scientific Guidelines/Considerations, Reflection paper, Q&As etc. -

• [Current] European Directive for Clinical Trials (excludes national (transposed) legislation) -
  European Clinical Trial Directive (EC) No. 2001/20/EC

• [Future] European Regulation for Clinical Trials, harmonising all European Member States -
  Clinical Trial Regulation EU No. 536/2014

• User guide for micro, small and medium-sized enterprises -

• MHRA Innovation Office - https://www.gov.uk/government/groups/mhra-innovation-office