



Medicines & Healthcare products  
Regulatory Agency

# ATMPs in the UK: Routes to Market and Avoiding “Trees on the Track”

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# Outline

- ATMPs and the regulatory landscape in the UK
- National routes to market
- Early engagement/flexibilities for ATMPs
- Main Quality deficiencies at initial assessment
- State of the market

# MHRA

- Executive agency of the Department of Health and Social Care

## Size

- >1200 staff

## Location

- Head office at 10 South Colonnade, Canary Wharf
- NIBSC based at South Mimms, Hertfordshire
- A regional office at York
- British Pharmacopoeia and MHRA laboratories based at LGC in Teddington



# Advanced Therapy Medicinal Product (ATMPs)

- Somatic cell therapy medicinal products
- Tissue engineered products
- Gene therapy medicinal products (*In vivo* or *Ex vivo*)

Combined ATMPs (one of the above + device).

ATMP's as medicinal products are substances regulated under the medicinal products legislation.

# The ATMP regulatory framework in the UK

- **The Human Medicines Regulations 2012 (HMRs)** – fully incorporated EU medicinal products legislation by the 31<sup>st</sup> December 2021.
  - The main overarching medicinal products legislation is EU Directive 2001/83/EC.
  - The specific ATMP section in 2001/83/EC is Annex I - Part IV
  - In 2008 an ATMP-specific regulation came into force - Regulation 1394/2007 ('The ATMP regulation').
- For a product to be commercially available it must have a 'marketing authorisation' (a licence) granted by a 'competent authority' – the MHRA in the UK -
- MHRA regulates for both Northern Ireland (part of EU) and Great Britain (England, Wales, Scotland).

# Human Tissues and Cells

- Substances containing cells which do not fulfil the definition of a medicinal product are regulated under the **The Human Tissue (Quality and Safety for Human application) Regulation 2007** which incorporates the EU 'Tissues and Cells Directive' (2004/23/EC).
- ATMPs must comply with these tissues and cells regulations.
- The Human Tissue Authority (HTA) is the competent authority (does not regulate 'same-surgical-procedure')
- Human Fertilisation and Embryology Authority (HFEA) – CA for use of gametes and embryos which may be used in the derivation of cells.

# ATMP routes to market- Marketing Authorisation ('Licensed' products)

- **Reliance Routes**

Based on EC approval (Reg726/2004) or EU MS approval in MRDC.

- **Accelerated Assessment 150-day timetable**

Applicable for all national applications – new and existing active substances

- **Rolling Review**

For new active substances and biosimilars a modular approach to submission and assessment of the supporting dossier

- **Innovative Licensing and Access Pathway (ILAP)**

Innovation Passport – gateway, 3 criteria (clinical need and patient benefit).

Target Development Profile – roadmap to product development utilizing ‘toolkit’.

Toolkit to support all stages of the design, development and approvals process.

Pulls together expertise from regulatory and wider health-care system.

<https://www.gov.uk/government/publications/innovative-licensing-and-access-pathway-ilap-for-medicines>



# Routes to market in the UK- 'unlicensed'

- **Early Access to Medicines (EAMS)**
  - ✓ Life threatening or seriously debilitating conditions without adequate treatment options – High unmet need.
  - ✓ Aimed at medicines that have completed Phase III trials - nearing MAA.
  - ✓ MHRA makes benefit/risk decision based on submitted dossier.

<https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams>

- **‘Specials’ and Hospital exemptions:**
  - Specials apply to any medicine
  - Hospital exemption specific to ATMPs

### Hospital exemption

The ATMP must be prepared and used in the same EU Member State

The ATMP must be commissioned by a medical practitioner

The ATMP must be custom made to meet an individual prescription and preparation must be on a “non- routine basis”

The ATMP must be used in a hospital

### The “specials” scheme (UK)

Products meeting the requirements of the scheme can be manufactured in the UK or imported to the UK

Products can be prescribed by doctors, dentists and supplementary prescribers

There is a special needs test  
(interpreted to mean the absence of a pharmaceutically equivalent and available licensed product)

There is no stipulation as to location



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# Marketing authorisations, variations and licensing guidance: detailed information

From: [Medicines and Healthcare products Regulatory Agency](#) and [Department of Health and Social Care](#)

## New applications

- [Apply for a licence to market a medicine in the UK](#)
- [Medicines: apply for a parallel import licence](#)
- [Apply for the early access to medicines scheme \(EAMS\)](#)
- [Supply unlicensed medicinal products \(specials\)](#)
- [Advanced therapy medicinal products: regulation and licensing](#)
- [Decentralised and mutual recognition reliance procedure for marketing authorisations](#)
- [Unfettered Access Procedure for marketing authorisations approved in Northern Ireland](#)
- [European Commission \(EC\) Decision Reliance Procedure](#)
- [Procedural advice for Northern Ireland on applications for European Commission Centralised Marketing Authorisations](#)
- [150-day assessment for national applications for medicines](#)
- [Rolling review for marketing authorisation applications](#)
- [Guidance on Project Orbis](#)
- [Access Consortium](#)

<https://www.gov.uk/topic/medicines-medical-devices-blood/marketing-authorisations-variations-licensing>

# Early regulatory engagement

- **Innovation office:**
  - **Free** and expert regulatory information & advice for anyone developing innovative medicines, medical devices or manufacturing processes.
  - Hosts the **Regulatory Advice Service for Regenerative Medicine (RASRM)**:

## RASRM:

For ATMPs and regenerative medicine

Cross-regulatory agency advice service



- **MHRA Scientific Advice:**

- Provide advice on all aspects of development (regulatory, non-clinical, quality and clinical).
- Face-to-Face meeting - written response.

<https://www.gov.uk/guidance/medicines-get-scientific-advice-from-mhra>

- **ATMP classification:**

- Is my medicinal product an ATMP and if so which type?

<https://www.gov.uk/guidance/advanced-therapy-medicinal-products-regulation-and-licensing>

# Regulatory 'flexibilities' specific to ATMPs



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

11 February 2013  
EMA/CAT/CPWP/686637/2011  
Committee for Advanced Therapies (CAT)

Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products



Out of Specification  
Advanced Therapy  
Medicinal Products -  
Guidance for  
Healthcare  
Organisations

Pan UK Pharmacy  
Working Group  
for ATMPs

March 2020  
Version 1.2



EUROPEAN  
COMMISSION

**EudraLex**  
**The Rules Governing Medicinal Products in the European Union**  
**Volume 4**  
**Good Manufacturing Practice**

**Guidelines on Good Manufacturing Practice specific to Advanced  
Therapy Medicinal Products**

Document History	
Adoption by the European Commission	22 November 2017
Date for coming into operation	ATMP manufacturers should comply with these Guidelines no later than 22 May 2018.

These Guidelines are specific to ATMPs. Other documents developing GMP requirements for medicinal products which are contained in Volume 4 are not applicable to ATMPs, unless specific reference thereto is made in these Guidelines.

# Spotlight on 'Quality (CMC)'

## Common initial grounds for licence refusal



## Initial assessment phase: common major grounds for refusal

5 main areas where deficiencies identified:

- Comparability
- Release specifications
- Manufacturing process
- Sterility
- Stability



- **Comparability**
  - No assessments performed
  - Differences identified but non/inadequate discussion of efficacy/safety effects
  - Insufficient testing
  - Inappropriate statistics
- **Release specifications**
  - Acceptance criteria not clinically qualified
  - Absence of key CQA tests – identity – purity etc..
  - Potency/activity testing
  - Characterisation

- **Manufacturing process control/validation**
  - Missing GMP certificates
  - Insufficient manufacturing process description/ process validation/IPC's
  - Transport validation
  
- **Sterility and starting material control**
  - Non-compliance with Tissue and Cells legislation
  - Insufficient sterility testing points during manufacture
  - starting and raw material control (including scaffolds)

- **Stability**

- unclear storage conditions
- lack of real-time data to support shelf-life (inc. in-use stability)
- non-stability indicating parameters

# Licensed ATMPs in the EU

## Ex vivo gene therapy

Libmeldy (Dec 2020)  
Tecartus (Dec 2020)  
Zynteglo (May 2019)  
Yescarta (Aug 2018)  
Kymriah (Aug 2018)  
Strimvelis (May 2018)

## In vivo gene therapy

Zolgensma (May 2020)  
Luxturna (Nov 2018)  
Imlygic (Dec 2015)  
Glybera (Oct 2012)

17 licensed  
12 still on market

## Cell Therapy

Alofisel (March 2018)  
Spherox (July 2017)  
Zalmoxis (Aug 2016)  
Holoclax (Feb 2015)  
MACI (June 2013)  
Provence (Sept 2013)  
ChondroCelect (Oct 2009)

The screenshot displays the EMA website for Libmeldy. At the top, the EMA logo and name are visible, along with a search bar. A navigation menu includes categories like Medicines, Human regulatory, Veterinary regulatory, Committees, News & events, Partners & networks, and About us. The main content area features the product name 'Libmeldy' with share and RSS icons, and a green 'AUTHORISED' badge stating 'This medicine is authorised for use in the European Union.' Below this is a 'Table of contents' section with links to Overview, Authorisation details, Product information, and Assessment history. The 'Overview' section is currently selected and shows a brief description of the medicine's use for treating children with metachromatic leukodystrophy (MLD).



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