EU & UK Challenges and opportunities for Gene and Cell Therapy products
Growing the UK cell and gene therapy industry, delivering health and wealth.
The big picture

- Licensed manufacturing and its supply chain creates sticky jobs
- Increase clinical trial pipeline
- Businesses created leading to Advanced Therapy companies that succeed and stay in the UK
- Demonstrating that the UK is the place to do this work, with increased inward investment
## Cross industry barriers

<table>
<thead>
<tr>
<th>Business</th>
<th>Manufacturing &amp; supply chain</th>
<th>Regulatory and clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Uncertainty on reimbursement</td>
<td>• Ability to scale up cost effective, robust and reliable manufacturing</td>
<td>• Uncertain, complex regulation</td>
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<tr>
<td>• Poorly understood health economics</td>
<td>• Meaningful quality and analytical assays</td>
<td>• Clinical trial site ability to handle live products</td>
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<tr>
<td>• Business models</td>
<td>• Storage and delivery systems</td>
<td>• Cautious hospital research committees</td>
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<td></td>
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<td>• Slow adoption</td>
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How we work

01 Projects
We work with the owners of promising technologies to accelerate their development into investible products.

02 Platforms
Identifying and tackling industry issues and creating technological innovation.

03 Environment shaping
Creating an advantageous environment in the UK for developers and manufacturers.

04 Infrastructure projects
Creating a robust supply chain for the industry in the UK.
European level

**European Union**
- 28 member states

**European Commission**
- Legislation - translated into MS law

**European Medicines Agency (EMA)**
- Approvals of EU MAA
- Guidance to developers
  - Guidelines
  - Advice meetings
National member states

Approved at MS level

• Clinical trials
• Blood, Tissues and Cells
• Unapproved/Compassionate use
• GMO
Related legislation

- Tissues/Cells
  - Dir. 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
- GMO
  - 2001/18/EC
  - 2009/41/EC
- Blood
  - 2002/98/EC
- Clinical Trials
  - 2001/20/EC
- Paediatrics
  - 1901/2006
- ‘Annex I’
  - 2003/63/EC
  - 2009/120/EC
- Advanced Therapy
  - 1394/2007
- Medicinal Products
  - Community Code
    - Dir. 2001/83/EC
- Medicinal Products
  - Centralised procedure
    - Reg. 726/2004
- Falsified Med.
  - Dir. 2011/62/EU
Related legislation

- **Blood** 2002/98/EC
- **Clinical Trials** 2001/20/EC
- **Paediatrics** 1901/2006
- **‘Annex I’** 2003/63/EC 2009/120/EC
- **Advanced Therapy** 1394/2007
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- **GMP** 2003/94/EC
- **Orphans** 141/2000
- **Variations** 1084(5)/2003 1234/2008
Approval

• CTA approval – very different timelines in MS
• GMO approval for Gene Therapy Products
  • Approval may be sequential or parallel
  • Different information requested
  • Non-English forms
Approval

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## GMO requirements

- Directive 2001/18/EC applies to the ‘**deliberate release**’ of GMOs
- EU Directive 2009/41/EC on the ‘**contained use**’ of GMOs
- Different implementation cross member states – some consider DR and some CU

<table>
<thead>
<tr>
<th>Member State</th>
<th>Contained use or Deliberate release</th>
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</thead>
<tbody>
<tr>
<td>Germany</td>
<td>Deliberate release</td>
</tr>
<tr>
<td>UK</td>
<td>Either (most studies are considered contained use)</td>
</tr>
<tr>
<td>France</td>
<td>Either</td>
</tr>
<tr>
<td>Sweden</td>
<td>Clinical studies are now normally considered as deliberate release</td>
</tr>
<tr>
<td>Spain</td>
<td>Deliberate release</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Deliberate release</td>
</tr>
<tr>
<td>Belgium</td>
<td>Either</td>
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</table>
GM for clinical study are generally Class 1. The acknowledgement of receipt is the approval.

GM application is submitted by the investigator site.

According to the MHRA metrics the average time before they send the GNA is 12.4 days.
GMO approval is a precondition for CA submission, the official timeline of 3 months is not currently reliable.

EC submission can be done as soon as the CTA package is ready, submission must then take place 2 weeks prior to meeting.

CNOM submission is compulsory but does not impact initiation.

http://ansm.sante.fr/var/ansm_site/storage/original/application/db5d829a71b0a28c91b014547a45052c.pdf
http://www.enseignementsup-recherche.gouv.fr/cid66789/declaration-utilisation-demande-agrement-utilisation-m.html
A single CTA and GMO submission is reviewed by the competent authorities (AIFA and ISS).

If more than one site: central Ethics and local ethics submission must be sent at the same time. A single opinion will be provided by the leading ethic committee that combines all the LEC comments.

BsF submission can be avoided if all German sites agree that scanning schedule isn’t above SOC (unlikely for these trials).

EU regulatory support systems
REGULATORY PATHWAY FOR ATMPs

Q. Is my product an ATMP?

ATMP Classification Procedure

- EUTCD ('Transplants')
- Non-clinical studies
- Clinical trials

Q. Will my clinical trials provide full efficacy data?

- MAA is required
- CHMP

Q. Does my product address an urgent need?

- PRIME Adaptive pathways
- Accelerated Assessment
- Conditional Approval
- Exceptional Approval
- Standard MAA

EMA Innovation Task Force
- Platform for early dialogue on scientific, regulatory and legal requirements
- Informal, not binding

SME office
- Administrative / regulatory and financial support to SME companies

Incentives
- ATMP incentives
- Orphan incentives
- Paediatric development incentives
- SME incentives
EU early access schemes - PRIME

The basis of PRIME is “Enhanced early dialogue to facilitate Accelerated Assessment of PRIority MEdicines”

- product has to show its potential to benefit patients with unmet medical needs based on early clinical data (or potentially compelling non-clinical and tolerability data for academic/SME applicants)

Early engagement between regulators

- **Scientific Advice** at key development milestones, including HTA bodies
- **Continuous support** led by a CAT rapporteur with input from a multidisciplinary group of experts drawn from EMA committees (CHMP, CAT, COMP, PDCO, SAWP...)
- Identification of **other early access routes**: Accelerated Assessment (210d – 150d) OR Compassionate Use and Conditional Approval
PRIME – 1 year on

108 applications
• 31 were ATMPs
• >50% from SMEs
• mainly for oncology products (25 received) – likely as it is easier to substantiate unmet medical need in this area
• 20 applications granted

Developers find particularly beneficial;
• (1) briefing document was easy to put together and had encouraged the companies to think more widely about the development of their product;
• (2) the kick-off meeting was tailored to discuss points they needed to work to move forward (i.e. mainly discuss things they were less familiar with);
• (3) having an informal relationship with the Rapporteur – support network
EU early access schemes - Adaptive pathways pilot

pilot project between March 2014 and August 2016

for treatments in high medical need where collection of data via traditional routes is difficult and where large clinical trials would unnecessarily expose patients who are unlikely to benefit from the medicine.

It relies on the targeted development of a medicine in a restricted patient population as an initial step but a gradual extension of the target population.

Real-world data collection is prospectively planned, as a supplement to clinical trials data and with the view to expand the patient population in which the medicine can be used.

Most likely will be approved under Conditional Route.

EMA received 62 applications, 6 of the applicants had received parallel advice from EMA and HTA bodies and 1 benefited from EMA scientific advice.

Now integrated in the parallel EMA /HTA advice process.
Future challenges for cell and gene products

Clinical Trial Regulation - (EC) 536/2014
- Published May 2014, due to come in 2018
- Portal
- Impact of GMO MS requirements

Supply under Hospital Exemption

EC GMP for ATMP document
- 2 rounds consultation, apparently due for release soon

Main Guideline undergoing revision
- Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products
Science translating into therapies - UK pipeline increasing year on year

50 % increase in clinical trials, 2013-16

>60 % increase in preclinical projects 2013-16

- Ongoing Trials (Cell Therapy)
- New Trials
- Closed Trials
Cell therapy clinical trials by year and phase (UK)

Data from Cell and Gene Therapy Catapult Clinical databases
MHRA support for innovation

Strategic objective of the MHRA (#2 of 5) - Bringing innovation and new products speedily and safely to patients

Innovation office (Launched in March 2013)
• Provide regulatory / informal advice or scientific advice at an early stage
• Case studies published to encourage enquiries
• More than 300 enquiries received to-date

One Stop Shop (Launched in October 2014)
• Specifically ATMPs / cell therapies / regenerative medicines
• A cross agency advice source

Joint scientific advice MHRA/NICE Scheme
• To ensure clinical plan satisfies regulators and HTA reimbursement data requirements

Early Access to Medicines Scheme (EAMS)
EAMS Eligibility

• Ability to supply before licensure- accelerated adoption and real-world data collection, but no reimbursement

• Life threatening or seriously debilitating conditions, without adequate treatment options – high unmet need

• The medicinal product offers promise - *that it is likely to offer benefit or significant advantage over and above existing treatment options*

• Potential adverse effects likely to be outweighed by benefit. *i.e. the benefit: risk ratio is concluded as being positive*
Future challenges for UK

- Increased workload and cost due to duplication of MAA and CTA submission
- Reduced access to EU initiatives such as EMA fee reductions
- The MHRA has had a strong voice in the EMA and are often Rapporteurs for drafting and revisions of key documents. This input of the UK to crucial guidelines and rules will be lost
- Regulatory divergence from EU
Some possible advantages

Streamlined regulation for entire supply chain for ATMP Regulatory

Accelerated trials tailored for both regulatory approval and reimbursement

National Licensing which may be faster than Centralised approval with greater flexibility, this will be particularly advantageous if linked with reimbursement

- MHRA and NICE to provide joint advice from early advice meetings
- Greater use of the EAMS scheme with the introduction of a reimbursement initiative
- Gather real-world data
Cell Therapies – a new paradigm?
Cell and Gene Therapies – New and not so new

Blood Transfusion
The oldest cell therapy

BMT
Transplants
Landmarks in blood transfusion

- 1628 William Harvey published the first description of the circulation of the blood.
- 1665 Richard Lower demonstrates dog to dog transfusion.
- 1667 Jean-Baptise Denis (France) transfuses humans with lambs blood. The patients experience severe reactions.
- 1668-70 blood transfusion banned in England and France for the next 150 years
- 1818 First human to human transfusion carried out by James Blundell in Guys from a man to his wife undergoing post partum haemorrhage.
- 1900 ABO Blood Groups identified by Landsteiner. And in 1907 cross-matching is introduced.
- 1914 sodium citrate is introduced as an anticoagulant by Hustin transforming the transfusion process from direct to indirect.
- 1916 Rous and Turner introduce citrate-glucose that allows blood storage.
- 1921 first blood donor service (London)
- 1937 first hospital blood bank (Chicago)
- 2017 >100 million blood transfusions per annum worldwide
Landmarks in blood transfusion

• 1628 William Harvey published the first description of the circulation of the blood.  
  *Invention*

• 1665 Richard Lower demonstrates dog to dog transfusion.  
  *R&D*

• 1667 Jean-Baptise Denis (France) transfuses humans with lambs blood. The patients experience severe reactions.  
  *Trial*

• 1668-70 blood transfusion banned in England and France for the next 150 years  
  *Regulatory*

• 1818 First human to human transfusion carried out by James Blundell in Guys from a man to his wife undergoing post partum haemorrhage.  
  *Trial - POC*

• 1900 ABO Blood Groups identified by Landsteiner. And in 1907 cross-matching is introduced.  
  *Companion diagnostic*

• 1914 sodium citrate is introduced as an anticoagulant by Hustin transforming the transfusion process from direct to indirect.  
  *Enabling technology*

• 1916 Rous and Turner introduce citrate-glucose that allows blood storage.  
  *Enabling technology*

• 1921 first blood donor service (London)  
  *Improved supply chain - SM*

• 1937 first hospital blood bank (Chicago)  

• 2017 >100 million blood transfusions per annum worldwide  
  *Improved supply chain - Product*
### EU approved products

<table>
<thead>
<tr>
<th>EMA</th>
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<tr>
<td>Chronocelelect - Standard</td>
<td>Tigenix</td>
<td>2009</td>
<td>Withdrawn in 2016</td>
</tr>
<tr>
<td>Glybera - <strong>Exceptional circumstances</strong></td>
<td>uniQure</td>
<td>2012</td>
<td>To be withdrawn in October 2017</td>
</tr>
<tr>
<td>MACI – Standard</td>
<td>Genzyme/ Sanofi/ Vericel</td>
<td>2013</td>
<td>Suspended in 2014</td>
</tr>
<tr>
<td>Provenge – Standard</td>
<td>Dendreon</td>
<td>2013</td>
<td>Withdrawn in 2015</td>
</tr>
<tr>
<td>Holoclar - <strong>Conditional</strong></td>
<td>Chiesi</td>
<td>2015</td>
<td></td>
</tr>
<tr>
<td>Imlygic- Standard</td>
<td>Amgen</td>
<td>2015</td>
<td></td>
</tr>
<tr>
<td>Strimvelis – Standard</td>
<td>GSK</td>
<td>2016</td>
<td><strong>Treatment in Italy only in one centre</strong></td>
</tr>
<tr>
<td>Zalmoxis - <strong>Conditional</strong></td>
<td>MolMed</td>
<td>2016</td>
<td></td>
</tr>
<tr>
<td>Spherox Standard</td>
<td>CO.DON AG</td>
<td>2017</td>
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Lifecycle regulatory considerations

Starting materials
- Consent
- Collection – different regional requirements
- Import/export requirements
- Donor variability

Process development
- Non-optimised processes
- Undeveloped analytics
- Limited material for validation
- Suitable pre-clinical studies

Product manufacture
- Non-optimised manufacture
- No/limited capacity for hold steps/ freeze
- Scale up /Scale out challenging
- Comparability implications
- Facility availability

Supply for use
- Distributed or central model
- Logistics considerations
- Traceability (30 or 15 years)

Product adoption
- Reimbursement
- Integration into healthcare system
- Uptake by clinicians
- PhV
- Registries
- Data collection
Starting material

- Ensure have Licensed supplier
- Consider global consent, testing and traceability systems
- Build robust QTA
- CELL HISTORY FILE (https://ct.catapult.org.uk/whitepapers-and-resources)
- EU database of different MS requirements (TE (√) and GMO)
Process development and product manufacture

- CHF to capture procurement/early processing
- Development of early product with scale up/out in mind
  - Decentralised model - plan
- Process and assay standardisation
- Pain of early validation – gain of flexibility
- Gather data whenever, stability, QC, Validation
- Early engagement with regulators
- Engagement with industry bodies – work on common problems, standardisation
Product supply and adoption

• Companion diagnostics
• Different cryopreservation tools
• Engagement with healthcare network – understand what the clinician wants (not what you want to give them)
• Integrated delivery – RFID, integrated IT
  • Robust QTA with hospitals etc – to ensure traceability
  • Data collection, PhV, registries
  • Long term sample storage – ability to recall
High impact projects
WT1 t-cell therapy

1. Asset in academia
Identification of promising research not progressing to commercialization
TCR therapy directed at WT-1 for haematological conditions AML/MDS and potentially solid tumours

2. Spin out
Creation of innovative collaboration structure between Imperial, UCL, the researchers and CGT Catapult

3. Pathfinding
Regulatory feasibility
Technology transfer to CMO
European clinical trials

4. Technologies and knowledge
Manufacturing Process
Impedance Assay
European trials
Supply chain

5. Investable proposition
Purchased by industry leader Cell Medica in June 2017

6. Ongoing collaboration
Cell Medica collaborates in manufacturing centre to develop manufacturing systems

Harvest T-cells
Genetically engineer to modify specificity
T-cell receptor therapy
Infuse back into patient
Anti-tumour activity
We work with
Innovate UK