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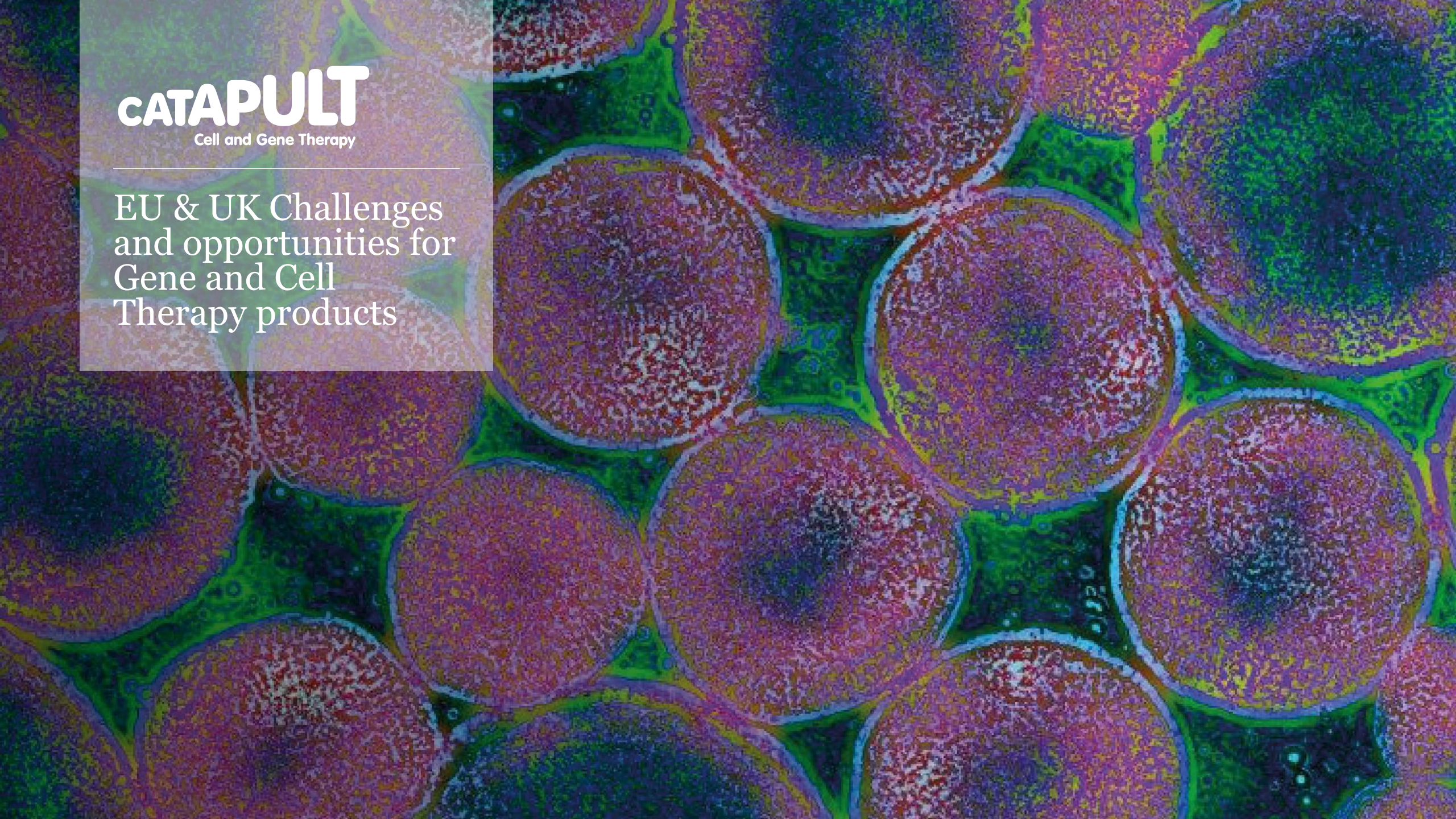
EU & UK Challenges and opportunities for Gene and Cell Therapy products



Cell and Gene Therapy Catapult

Growing the UK** cell and gene therapy industry, delivering **health and wealth

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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

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Cross industry barriers

Business

- Uncertainty on reimbursement
- Poorly understood health economics
- Business models

Manufacturing & supply chain

- Ability to scale up cost effective, robust and reliable manufacturing
- Meaningful quality and analytical assays
- Storage and delivery systems

Regulatory and clinical

- Uncertain, complex regulation
- Clinical trial site ability to handle live products
- Cautious hospital research committees
- Slow adoption

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.

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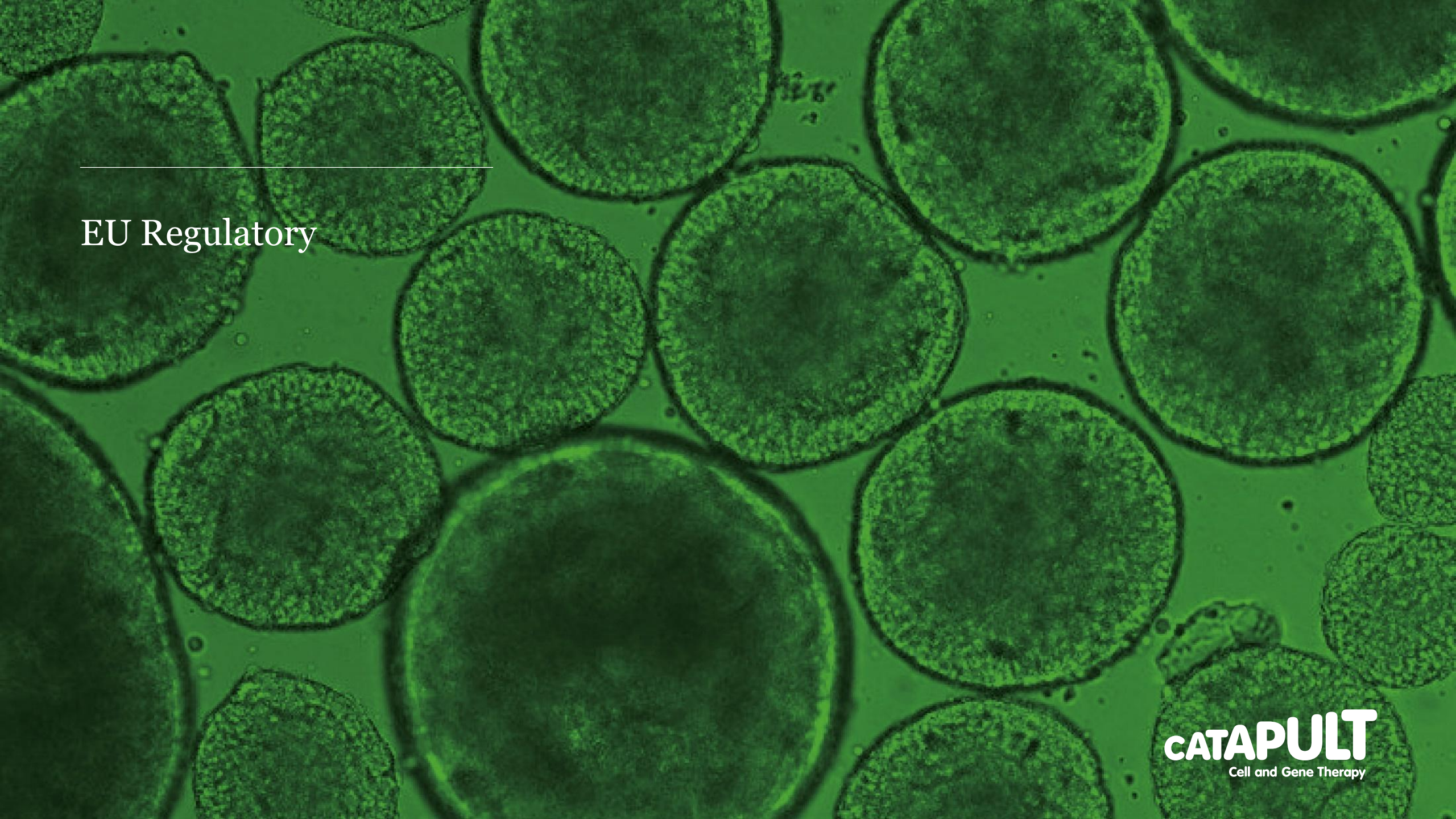
EU Regulatory



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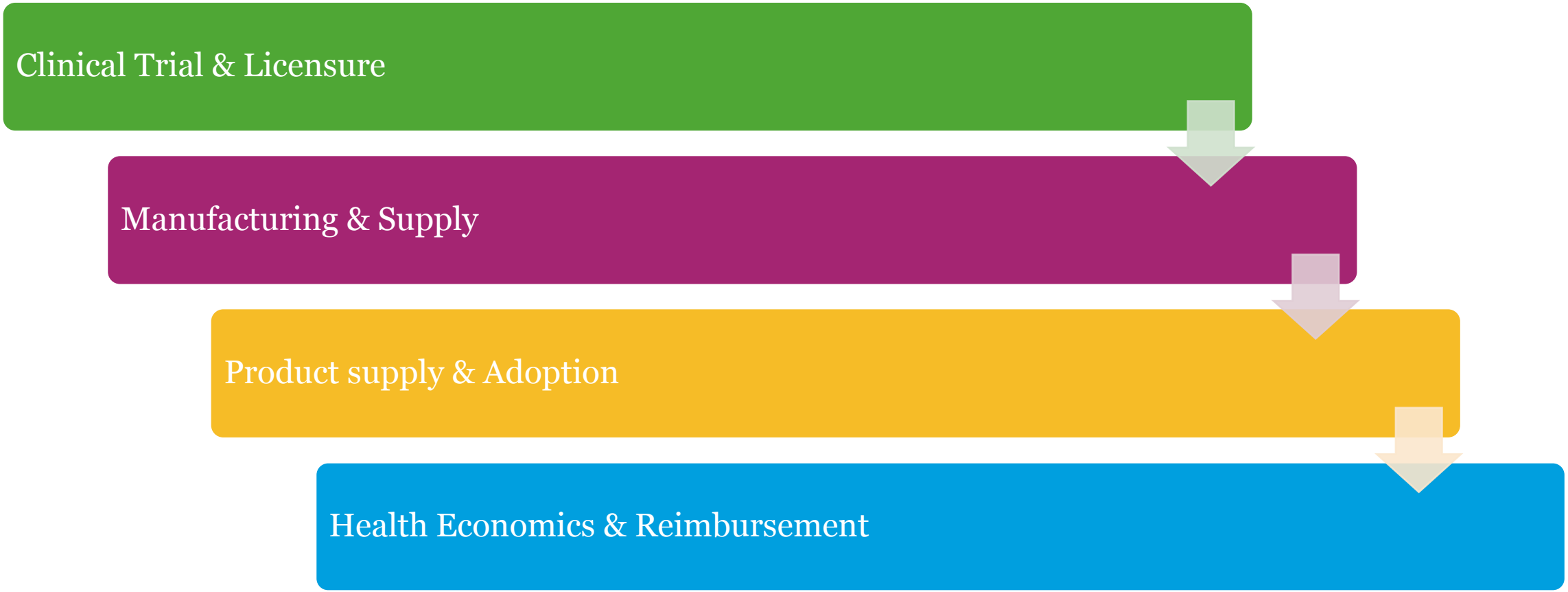
Regulatory challenges and opportunites



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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

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National member states

Approved at MS level

- Clinical trials
- Blood, Tissues and Cells
- Unapproved/Compassionate use
- GMO

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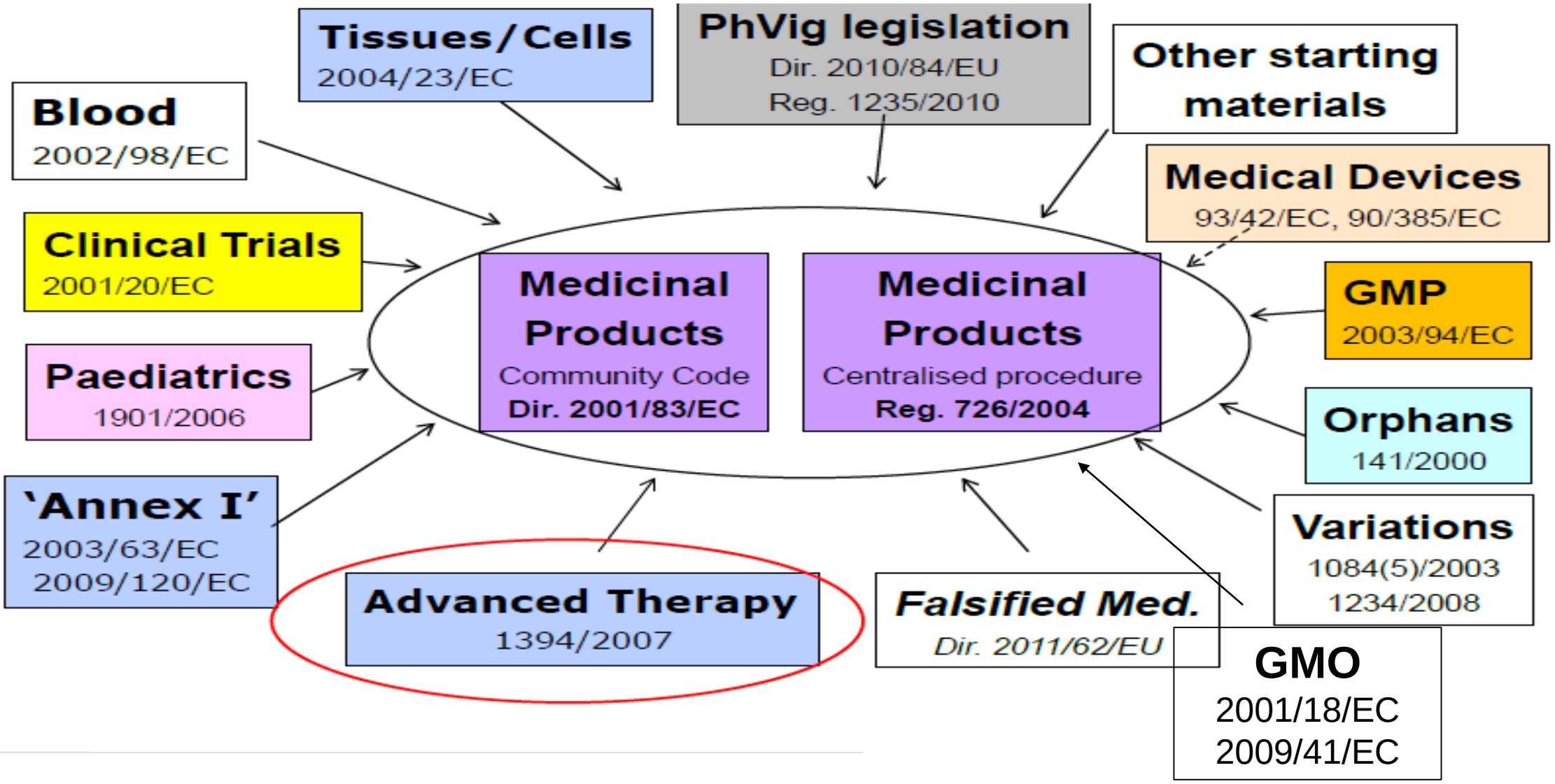
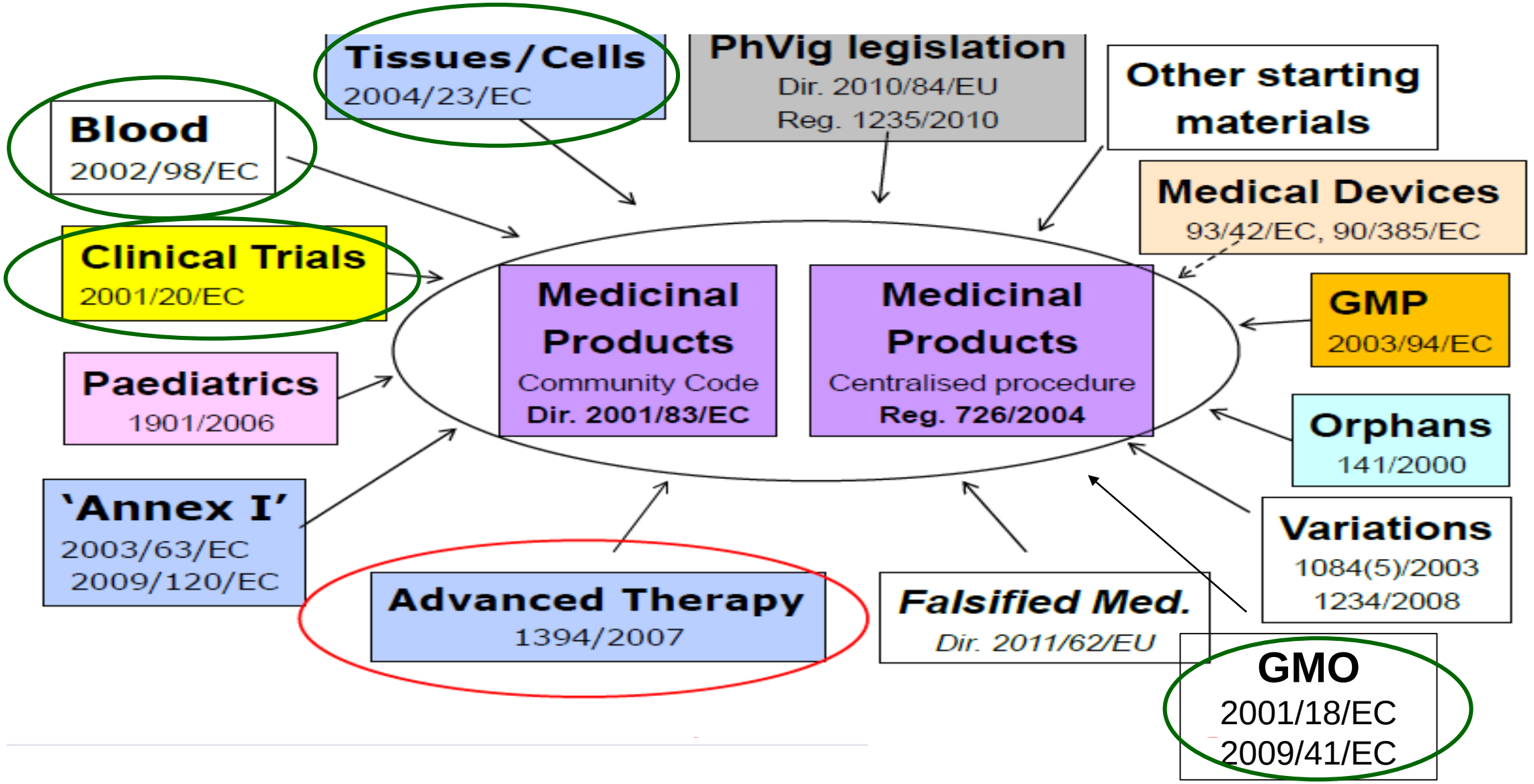
Related legislation

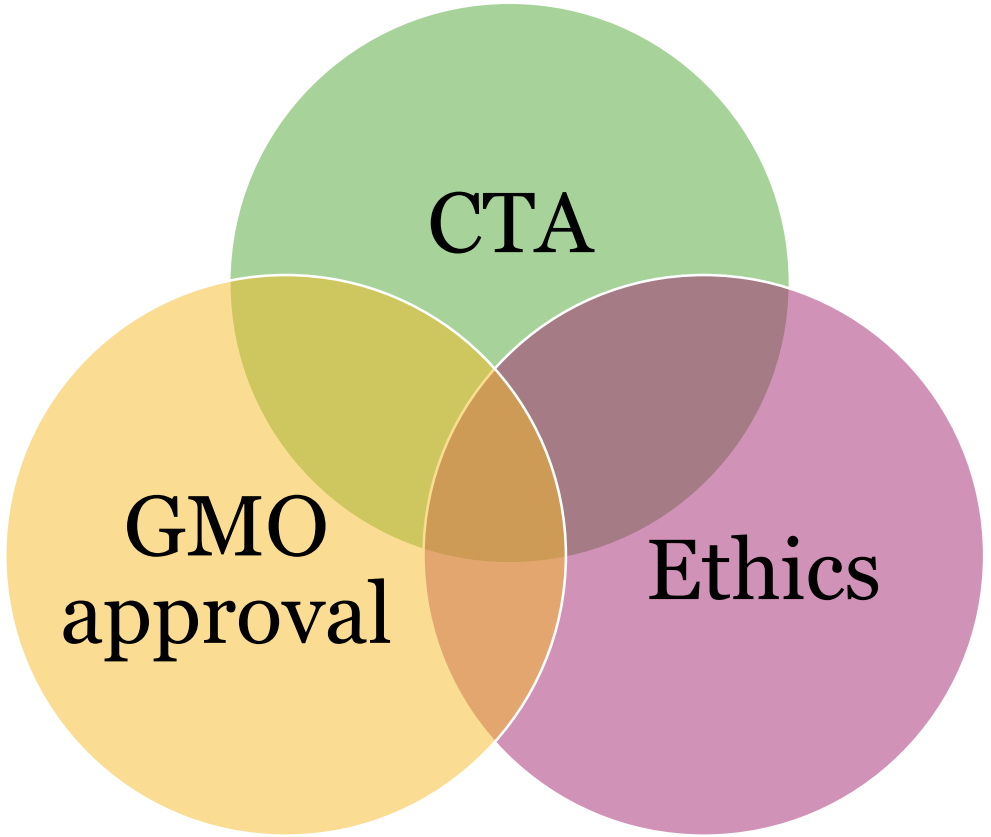


Related legislation



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



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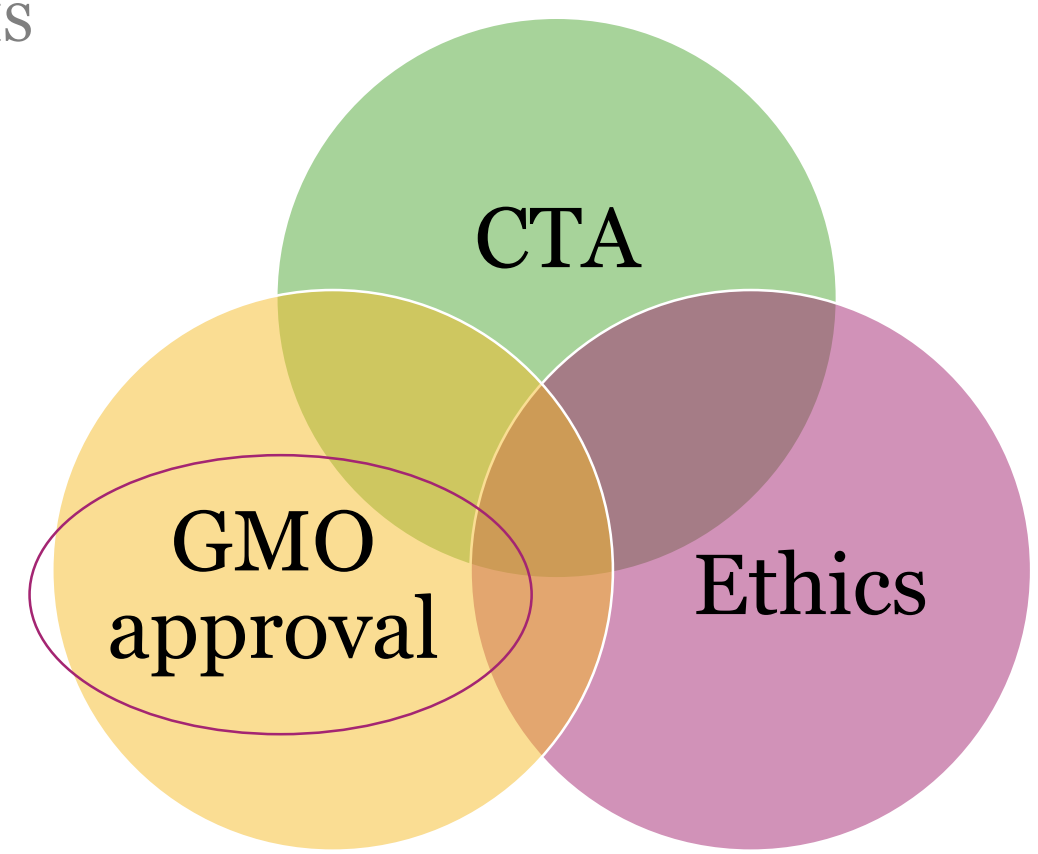

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GMO requirements

- 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

Member State	Contained use or Deliberate release
Germany	Deliberate release
UK	Either (most studies are considered contained use)
France	Either
Sweden	Clinical studies are now normally considered as deliberate release
Spain	Deliberate release
The Netherlands	Deliberate release
Belgium	Either

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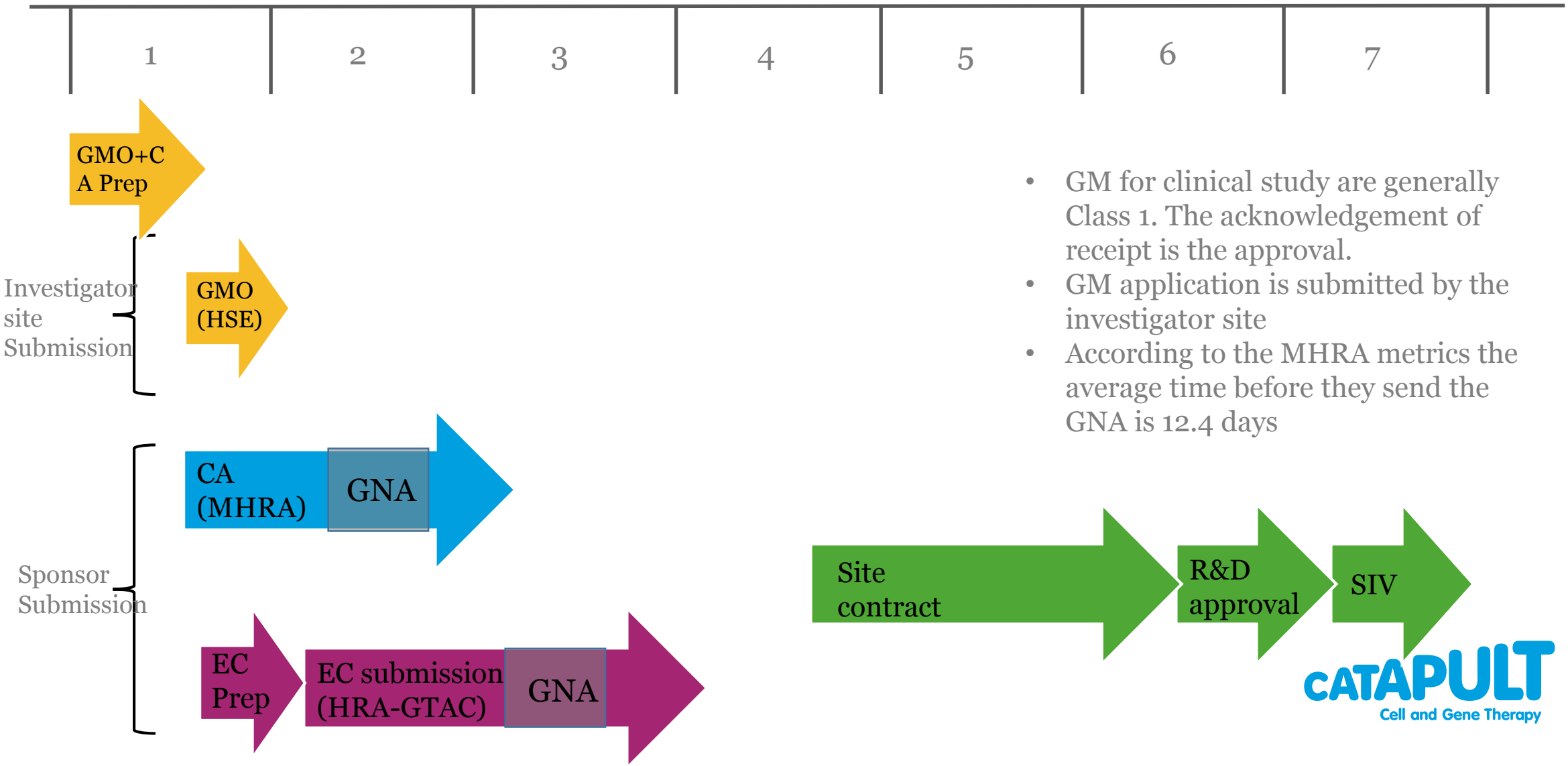
UK start-up map



- 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

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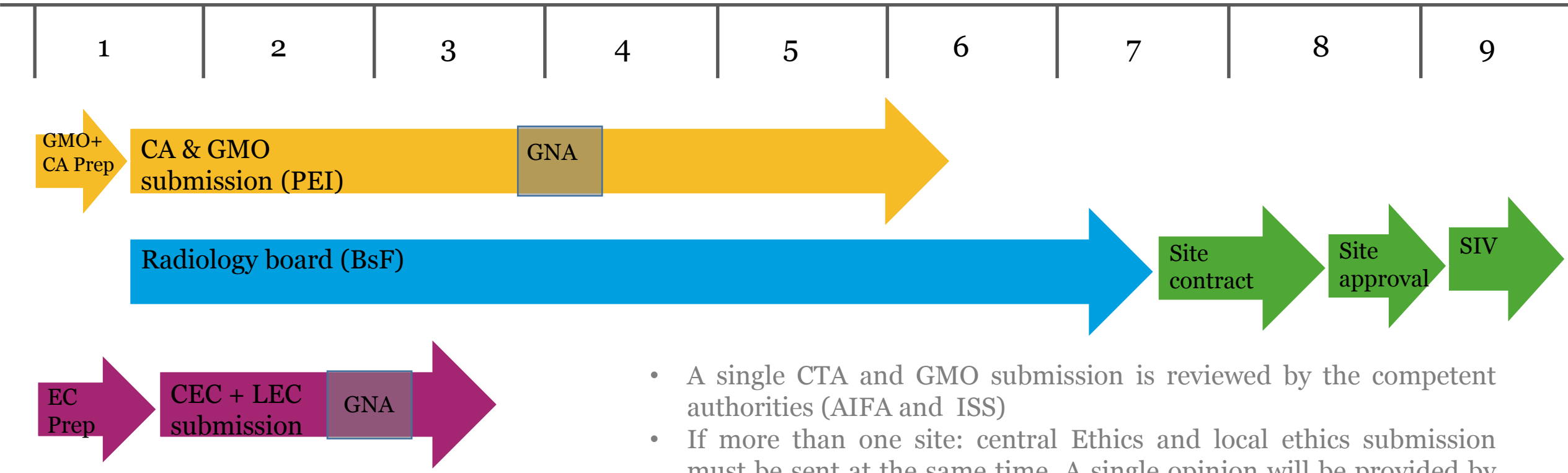
France start-up map

- GMO approval is a precondition for CA submission the official timelime of 3 months is not currently reli
- EC submission can be d as the CTA packag submission m prior to m
- CNOM sub but does not

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

Germany start-up map



- 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)

http://www.pei.de/SharedDocs/Downloads/EN/pu/clinical-trials/3rd-notification-clinical-trials-2006-08-10.pdf?__blob=publicationFile&v=1

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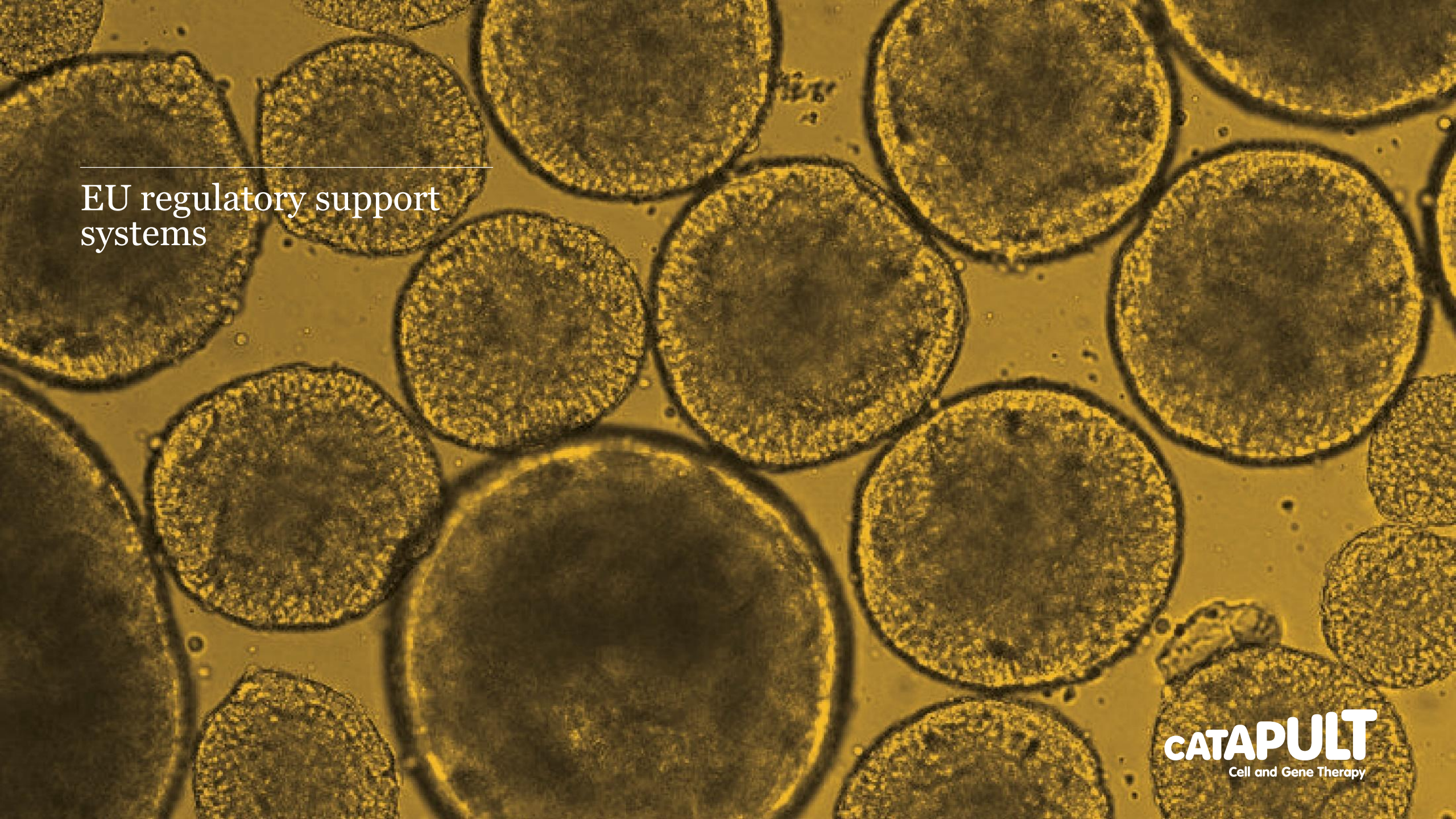
EU regulatory support systems



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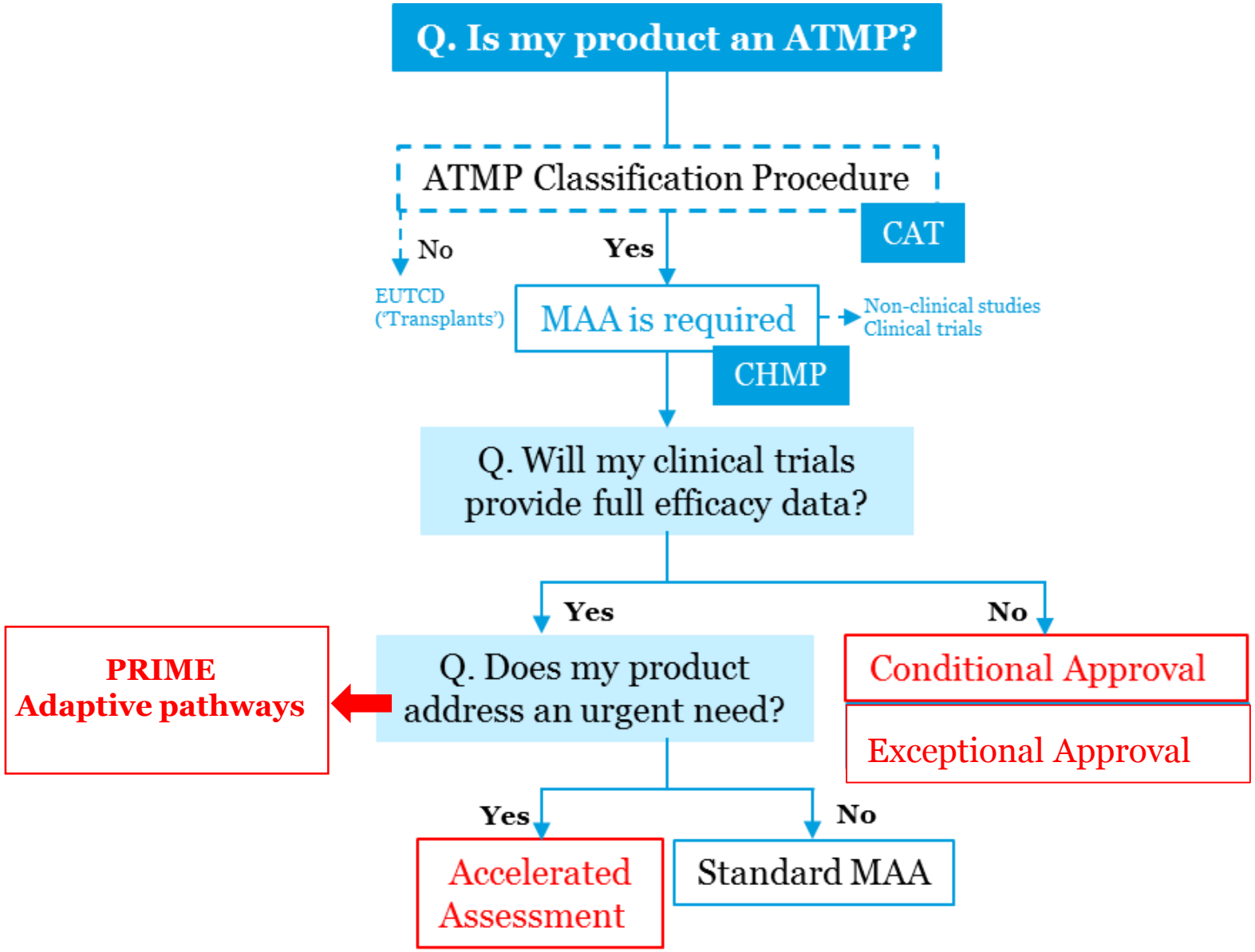
Regulatory pathway for ATMPs



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

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EU early access schemes - PRIME

The basis of **PRIME** is "Enhanced early dialogue to facilitate **Accelerated Assessment** of **PRI**ority **ME**dicines"

- 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

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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

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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

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Future challenges for cell and gene products

Regulation

Clinical Trial Regulation - (EC) 536/2014

- Published May 2014, due to come in 2018
- Portal
- Impact of GMO MS requirements

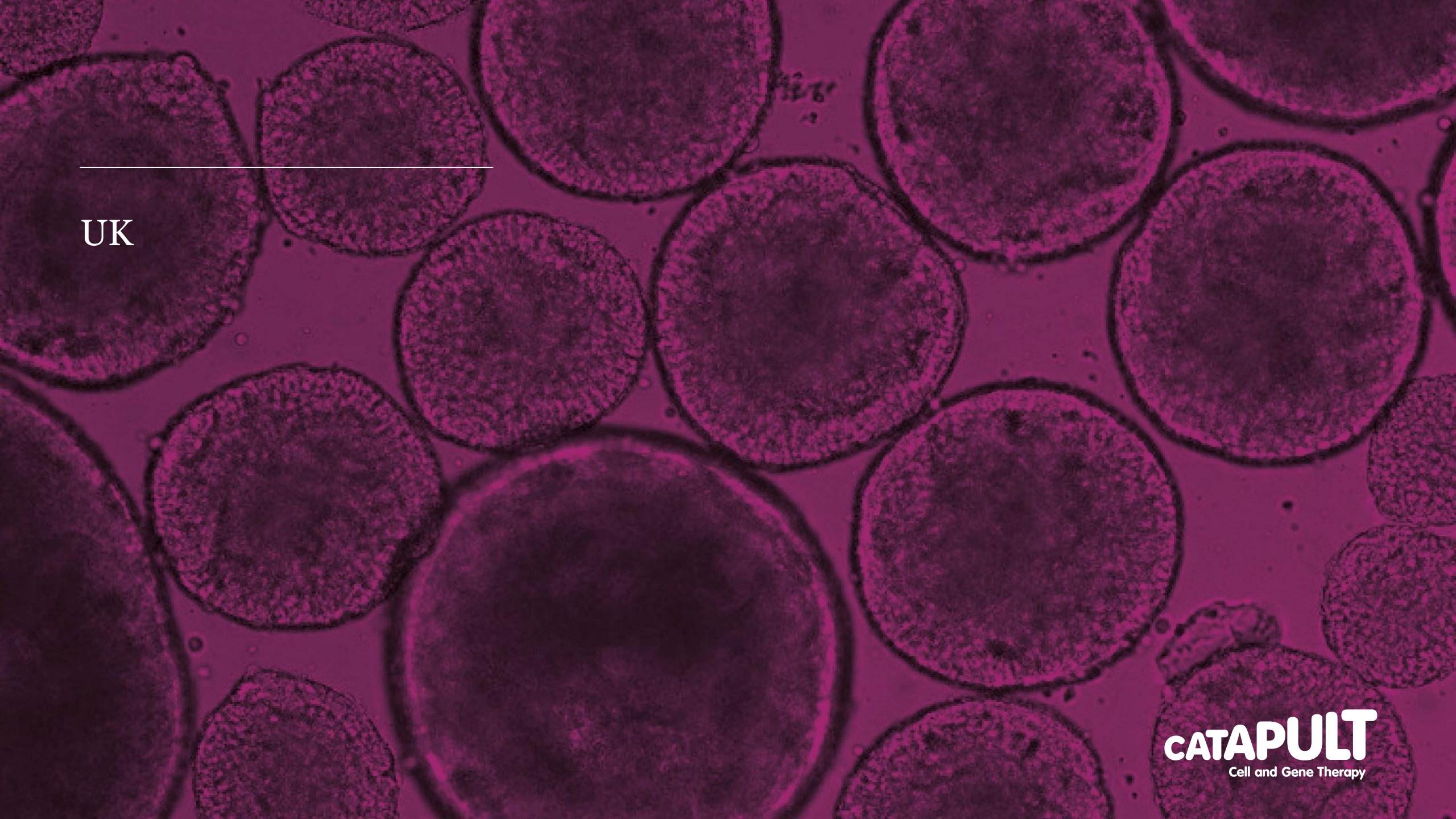
Supply under Hospital Exemption

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*


UK
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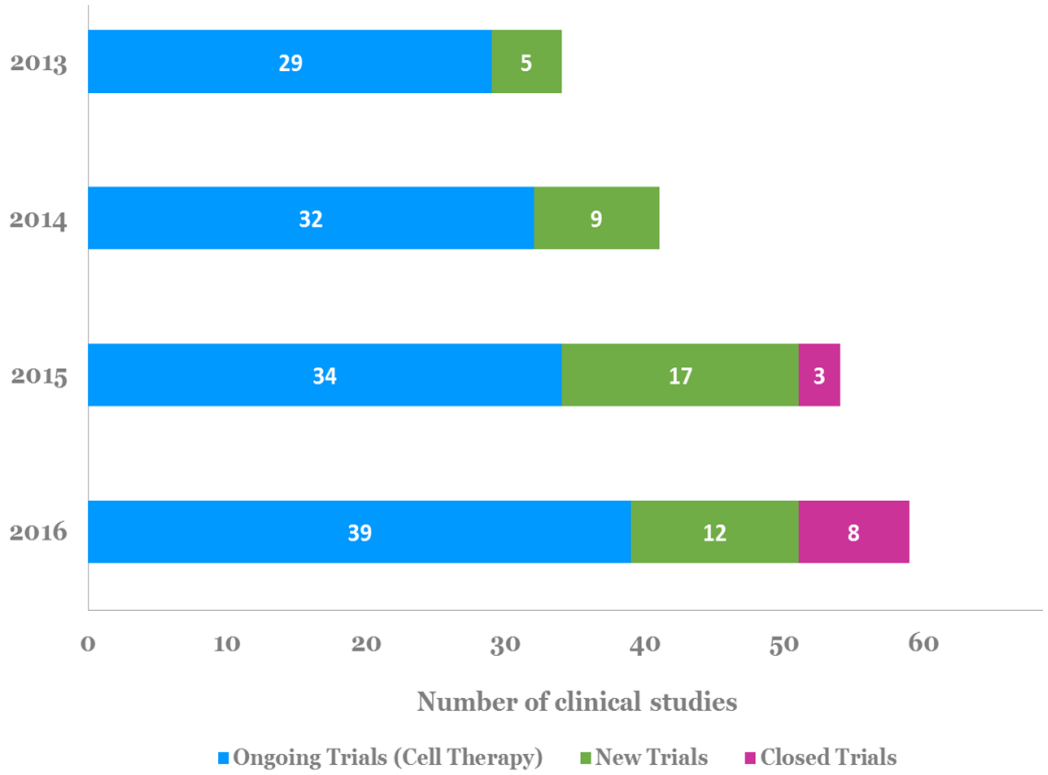
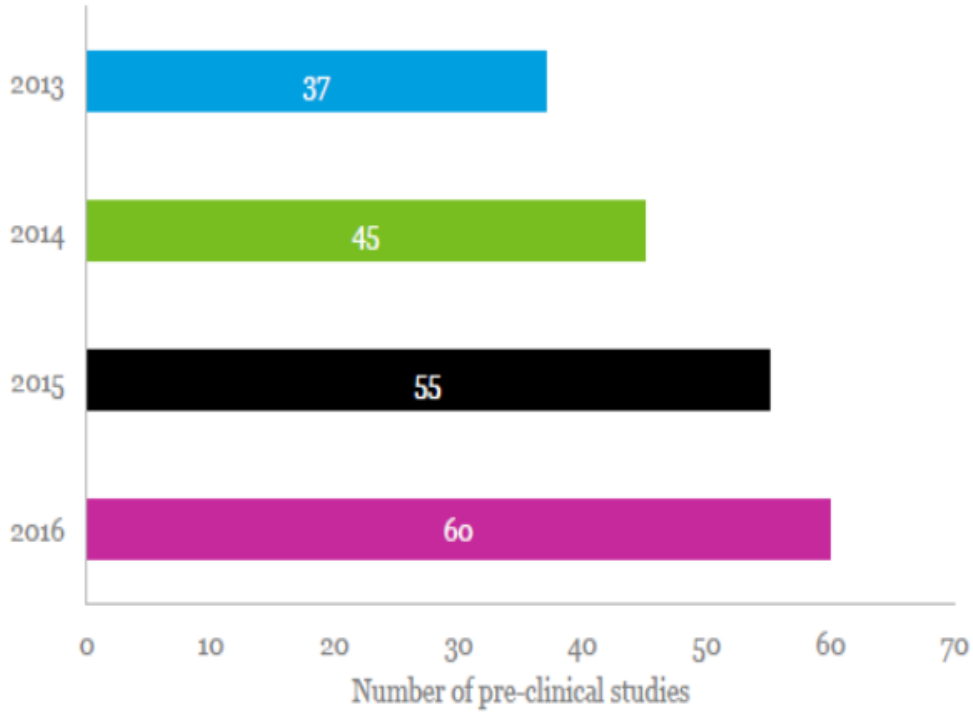
Science translating into therapies - UK pipeline increasing year on year

50 % increase in clinical trials, 2013-16



>60 % increase in preclinical projects 2013- 16



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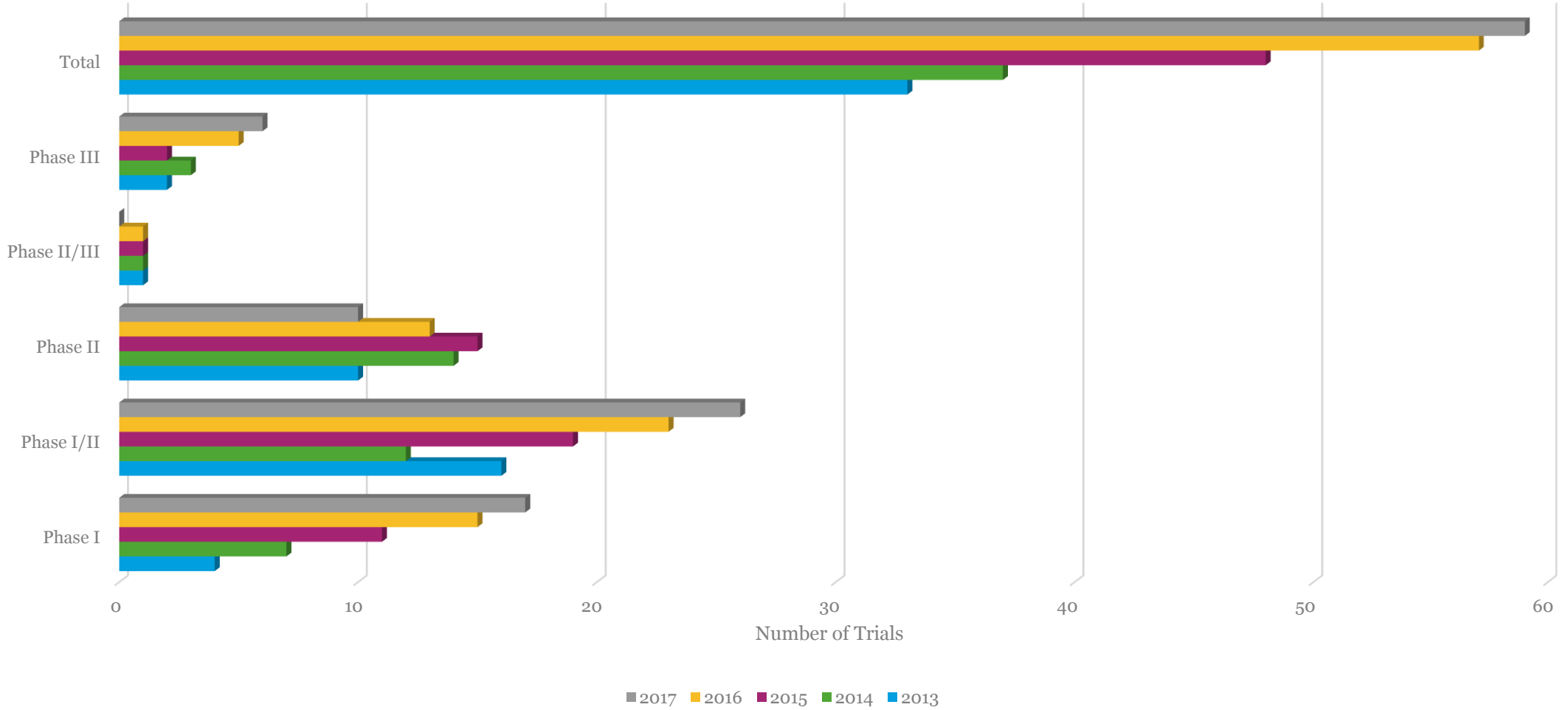
Cell therapy clinical trials by year and phase (UK)



Data from Cell and Gene Therapy Catapult Clinical databases

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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)

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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*

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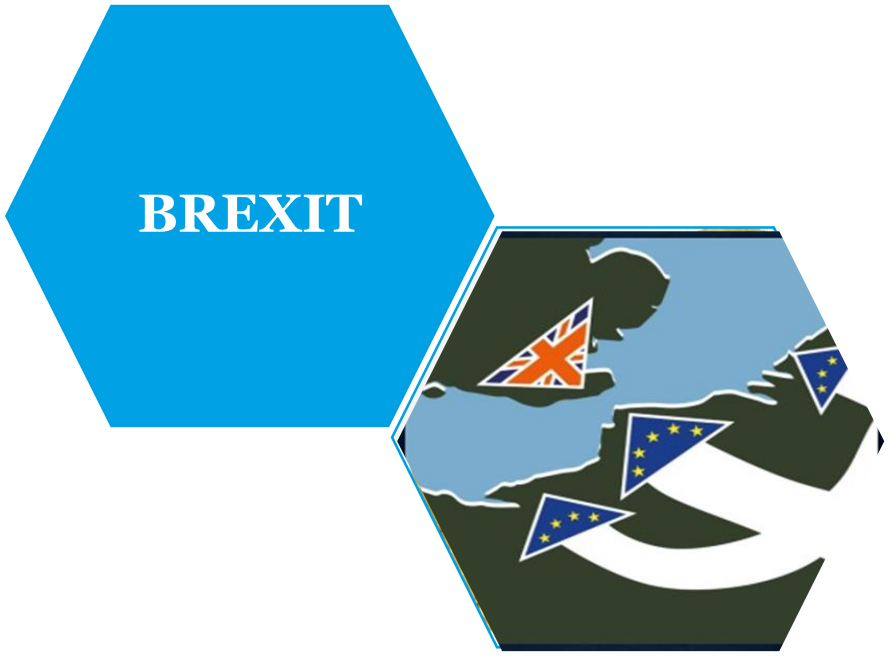
Future challenges for UK



- 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

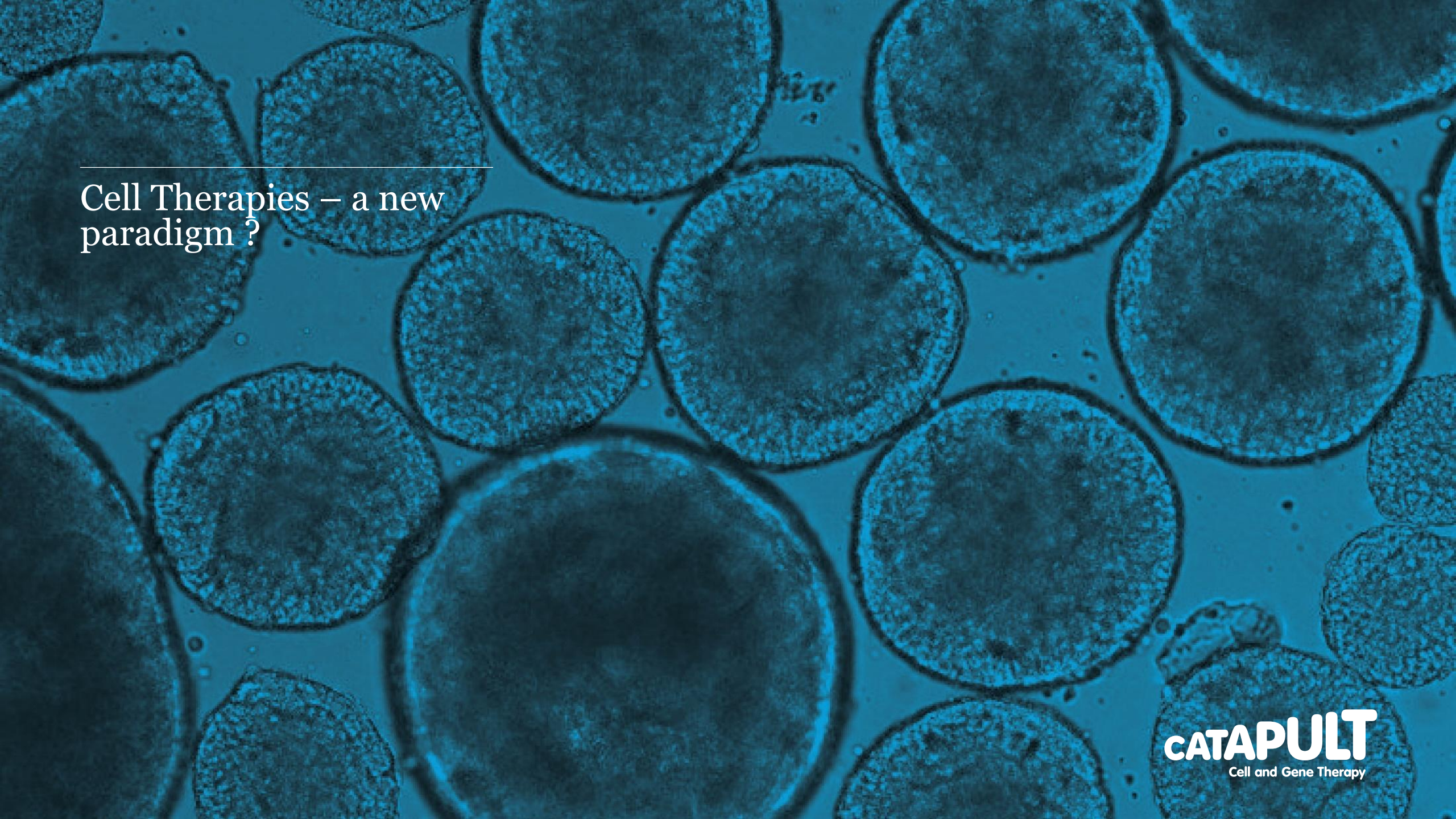
Streamlined regulation for entire supply chain for ATMP Regulatory

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 ?



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Cell and Gene Therapies – New and not so new

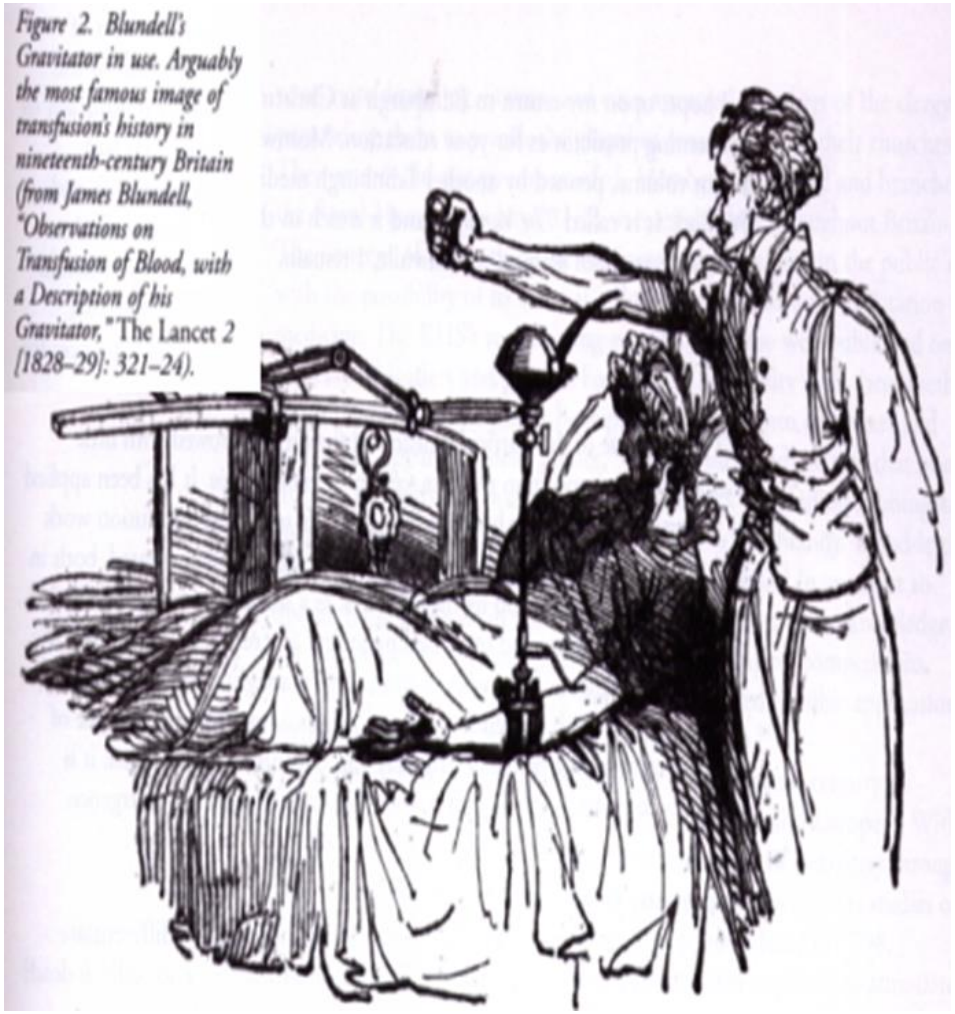

Figure 2. Blundell's Gravitator in use. Arguably the most famous image of transfusion's history in nineteenth-century Britain (from James Blundell, "Observations on Transfusion of Blood, with a Description of his Gravitator," The Lancet 2 [1828–29]: 321–24).

Blood Transfusion

The oldest cell therapy

BMT

Transplants

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Landmarks in blood transfusion

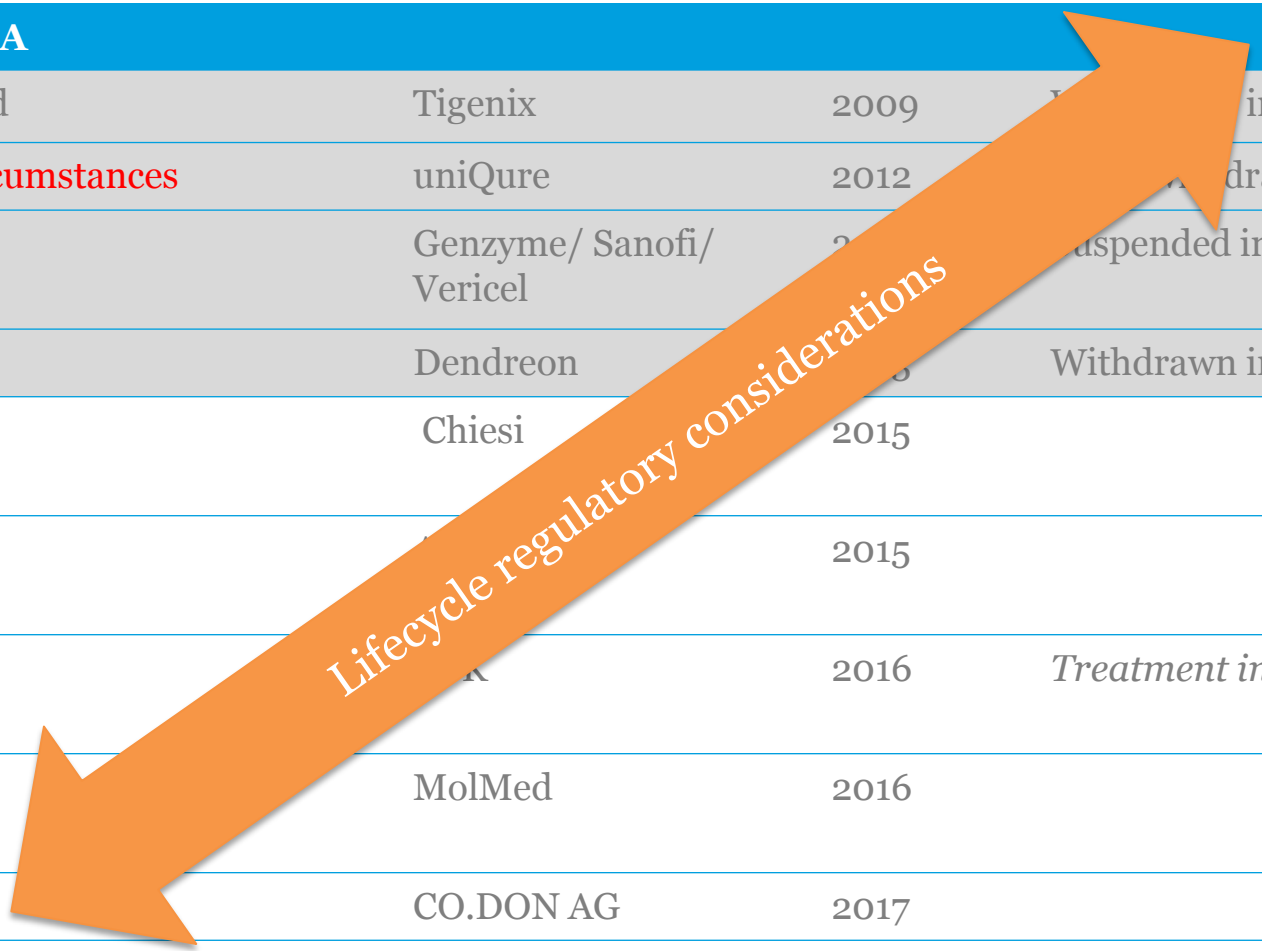
- 1628 William Harvey published the first description of the circulation of the blood.
- 1665 Richard Lower demonstrates dog to dog transfusion.
- 1667 Jean-Baptise Denis (France) transfuses humans with lambs blood. The patients experience severe reactions.
- 1668-70 blood transfusion banned in England 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

EMA			
Chrondocelect - Standard	Tigenix	2009	in 2016
Glybera- Exceptional circumstances	uniQure	2012	drawn in October 2017
MACI – Standard	Genzyme/ Sanofi/ Vericel		spended in 2014
Provenge – Standard	Dendreon		Withdrawn in 2015
Holoclar - Conditional	Chiesi	2015	
Imlygic- Standard		2015	
Strimvelis – Standard		2016	*Treatment in Italy only in one centre*
Zalmoxis - Conditional	MolMed	2016	
Spherox Standard	CO.DON AG	2017	



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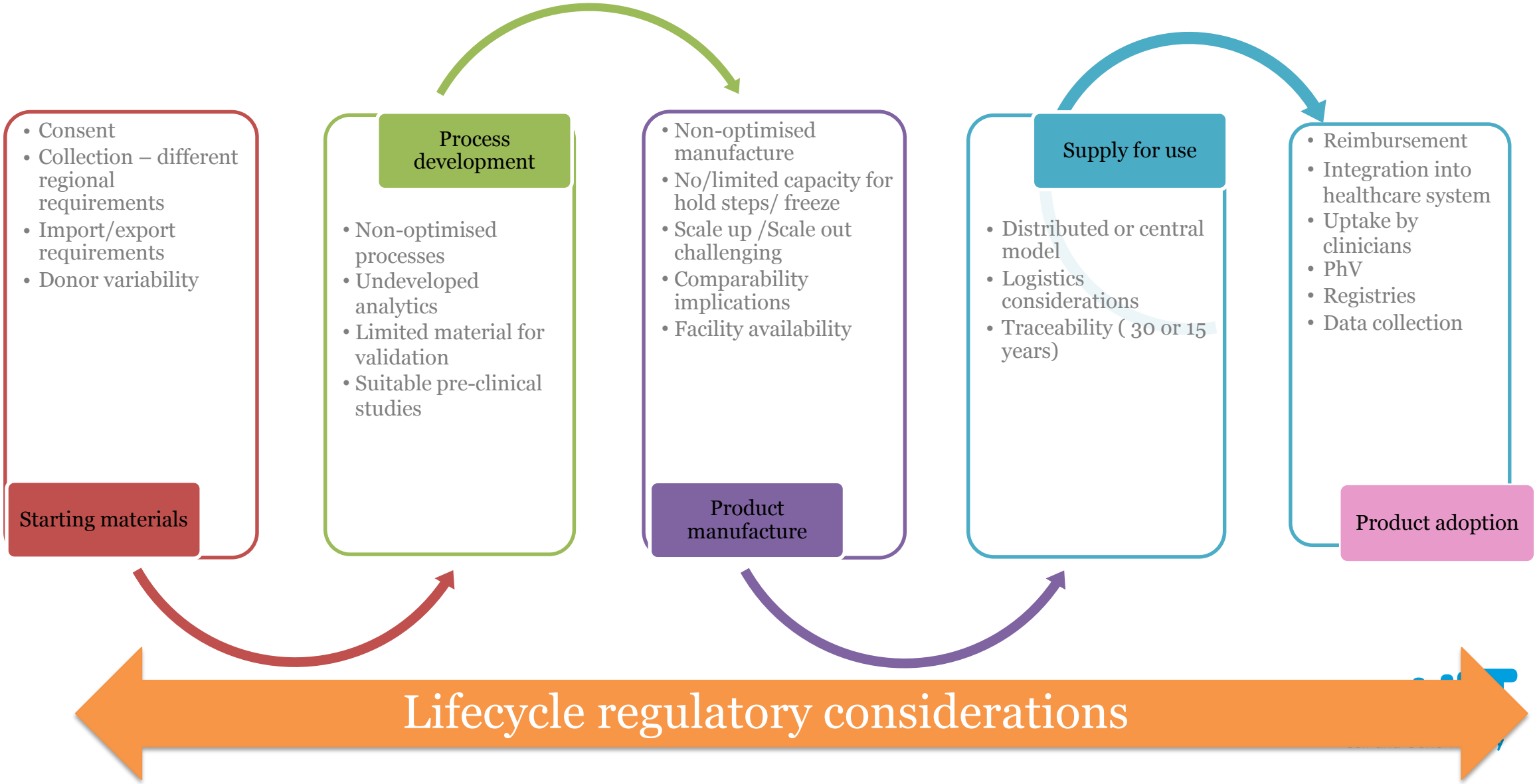
Lifecycle regulatory considerations



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)

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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

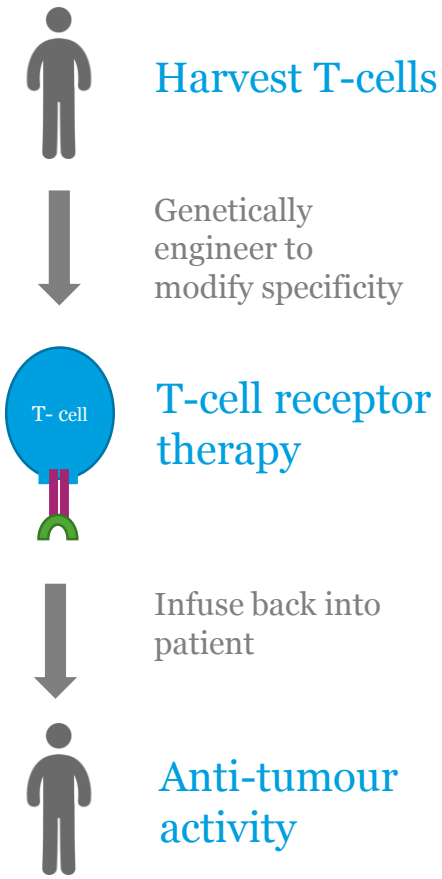
Supply chain

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



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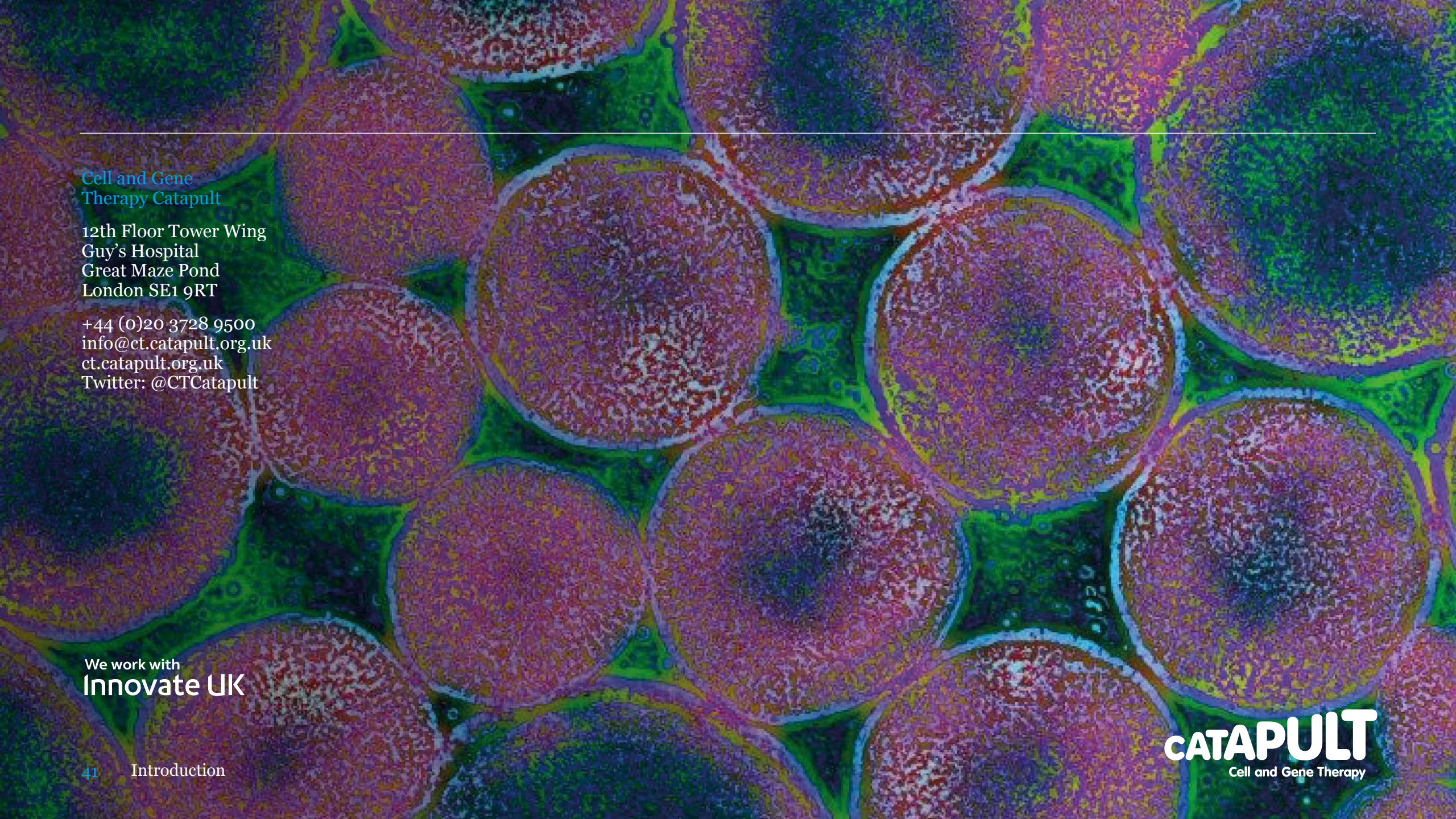

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