

### **About CGT Catapult**







Part of a **world-leading network** of technology and innovation centres



Provide access to unique technical **facilities** and **expertise** to help adopt, develop and exploit innovations



**Bridge the gap** between businesses and academic research



Established by Innovate UK as a **not-for profit**, independent centre

It is our vision for the **UK** to be **a global leader** in the development, delivery and commercialisation of cell and gene therapies.

Where businesses can start, grow and confidently develop advanced therapies, delivering them to patients rapidly and effectively.

### **CGT Catapult Capability:**



#### Accelerate

the commercialisation of innovations from research

#### **Complement**

industry and academia with unique technical facilities and expertise

#### **Innovate**

in collaboration with academia and industry

#### **Facilitate**

operating in UK as a global centre; working with Government, the NHS and international regulators

#### **Development laboratories**

- 1200m² purpose built centre
- Analytical characterisation
- Process development
- Viral vector



#### **Manufacturing centre**

- 7000m<sup>2</sup> manufacturing centre designed specifically for cell and gene therapies
- 12 segregated large clean room modules
- Secure supported collaboration model
- Centre of a cell and gene therapy cluster



#### Cell and gene therapy specialists (>180)

#### **Industrialisation**

- Process development
- Analytical development
- Manufacturing systems
- Supply chain

#### Regulatory and clinical development

- Regulatory
- Non clinical safety
- Clinical delivery
- Programme management

#### **Engagement**

- Collaboration formation
- Intellectual property and patent
- Health economics
- Reimbursement

# **Breaking down industry barriers**

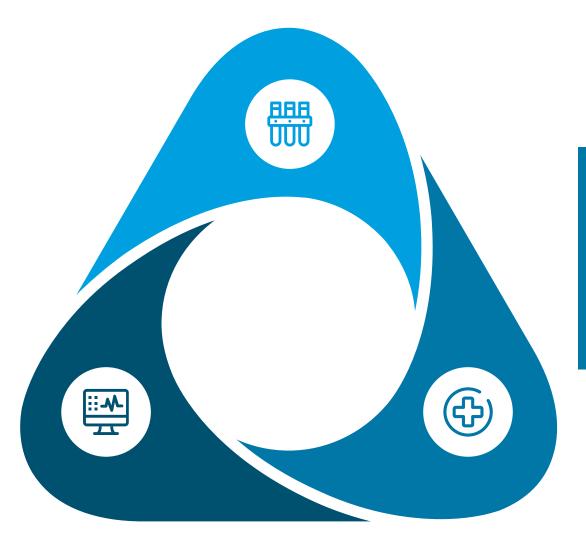


# Manufacturing and supply chain

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

#### **Health economics**

- Uncertainty on reimbursement
- Poorly understood health economics
- Unproven business models



# Regulatory and clinical framework

- Uncertain, complex regulatory environment
- Clinical trial site ability to handle live products
- Cautious hospital research committees

### **Industrialisation**



#### The challenge

Developing a reliable and robust manufacturing process.



### How we can help

Identifying ways to lower the costs of manufacturing your product.

Finding innovative ways to make your process more efficient and robust.

Providing methods to accelerate and support clinical trials.

Helping ensure your process and product are controlled and quality compliant.

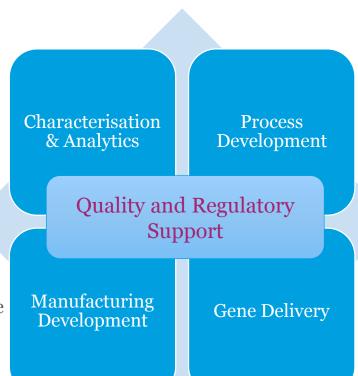
Using tried and tested methods to transfer seamlessly to Good Manufacturing Practice (GMP) manufacturing.

### The Industrialisation Team - Our team is your team



- Cell Characterisation
- Potency Assay Development
- In-Process Controls
- Data Mining and Informatics

- GMP Compliance
- GMP Knowledge Base
- CMC
- Documentation



- Design Space
- CPPs for CQAs
- Scale-up / Automation
- Closed Processing
- In-Process Controls
- Process Economics
- Device Design

- Vector Design / Optimisation
- Large Scale production















































### **Maturation of the Field**



### Yescarta

\$373,000

Strimvelis

€600,000

- (axicabtagene ciloleucel)
- Kite's CAR-T therapy for forms of Diffuse large B-cell lymphoma (DLBCL) in adults. Type of non-Hodgkin lymphoma (NHL).

• GSK's treatment for a very rare disease called ADA-SCID (Severe Combined Immunodeficiency due to Adenosine Deaminase

# Kymriah

- (tisagenlecleucel)
- Novaritis's CAR-T therapy for B-cell precursor acute lymphoblastic leukemia (ALL) in children and young adults.

\$475,000

# Glybera

deficiency),

- (alipogene tiparvovec)
- UniQure's AAV-based gene therapy to treat the rare inherited disorder lipoprotein lipase deficiency (LPLD)

>€1,000,000

# State of Play in the EU – Since Regulation (EC) 2007/1394





- Approved 2015

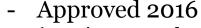


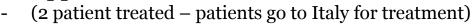
Holoclar





Strimvelis







Zalmoxis

- Approved 2016, Conditional MA



Spherox





Alofisel

- Approved 2018



Yescarta

- Approved 2018



Kymriah

- Approved 2018



Chondroselect

- Voluntary Withdrawal 2016



**MACI** 

- (Reimbursement challenges / Complex Logistics)



Provenge

Approved 2013, Suspended 2014
 (Manufacturing Discontinued)



Glybera

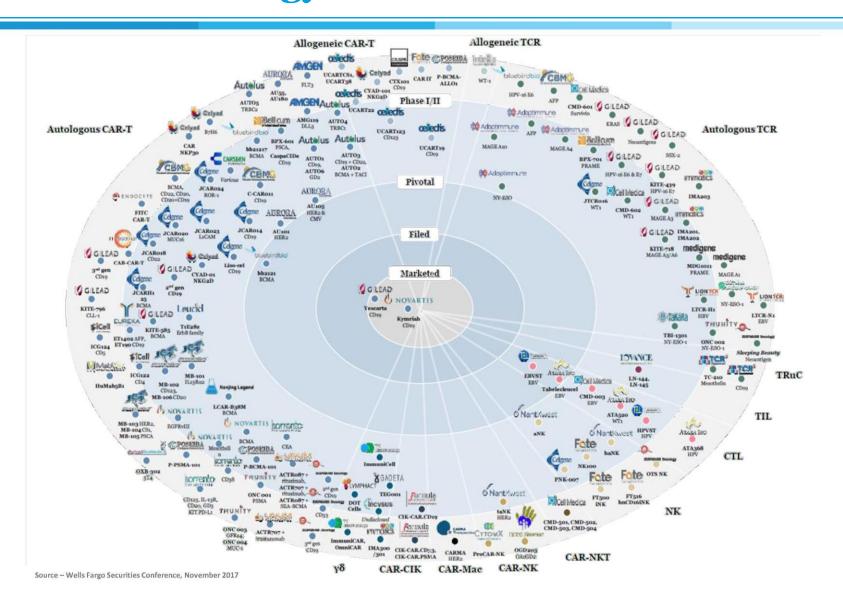
Approved 2013, Withdrawn 2015

(1 patient treated)

Approved 2012, Voluntary Withdrawal 2017

### **Immuno-Oncology Sector – The Next Generation!**



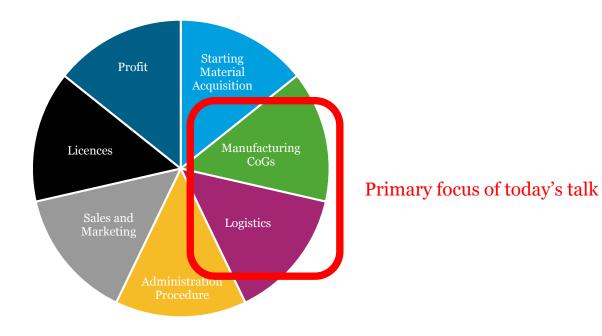


Need to deliver scalable, low cost manufacturing solutions to enable healthcare provider adoption of a diverse portfolio of therapies.

# What key factors influence therapy price?



### Key Cost Contributors – Product Manufacture and Administration



Key Cost Contributors – Perceived / Tangible value to the Healthcare System

- Can be very challenging to define
- What is the true cost (lifetime cost) of a patient to the healthcare system
- How do you engage a patient for their lifetime, especially if they are cured within a year?



# **Quality by Design**



A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (*ICH Q8(R2)*)

**Q8** 

# Pharmaceutical Development

Application of systems to support the development and manufacture of DS and DP throughout the product lifecycle Q9

### **Quality Risk Management**

- Bring risk management into Pharma industry
- Provide details of systematic approach to QRM
- Info on QRM tools to enable effective risk based decisions

Q10

### Pharmaceutical Quality Systems (PQS)

- Achieve Product Realisation
  - Establish and Maintain a State of Control
    - Facilitate continual improvement

# **Understanding your product**



# Target Product Profile

Indication, treatment, delivery mode, dose, formulation efficacy, side effects

# **Quality Target Product Profile**

Quality characteristics to ensure safety and efficacy as promised in the label

# Critical Quality Attributes

A physical, chemical or biological, property that should be within an appropriate limit, range to ensure product quality

# Critical Process Parameters

Process parameter whose variability should be monitored or controlled to ensure the process produces the desired quality

Product Characterisation & Baseline Process

**Process Optimisation & Scaling** 

**Process and Analytical Development** 

# Understanding the needs of your stakeholders





Clinic

Investors

Regulators

Manufacturing

Risk to Patient / Product Variations / Failed Manufacture

Not Cost Prohibitive

Safety / Understanding / Control

Design Space / Robust and Reproducible Ease-of-use

**Economic/ Commercial Viability** 

Full Characterisation / GMP Compliance / IPCs

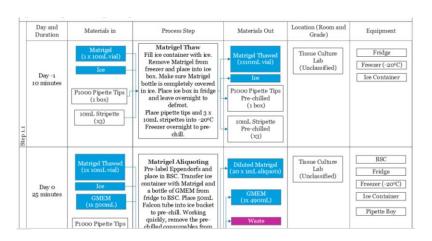
Automation and High-Throughput

# **Understanding your process**

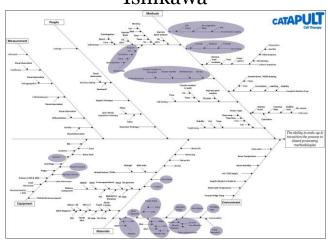


**Process Mapping** 

Areas of process currently undefined

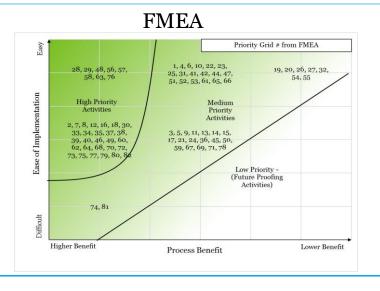


Ishikawa

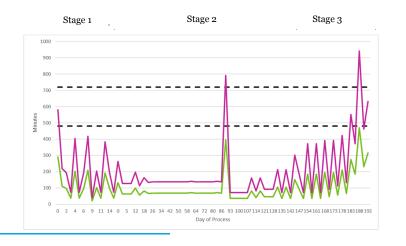


Root Cause of Failure

Risks and Mitigation Strategies



### Facility Utilisation and CoGs



Facility Utilisation Profile

# **Knowledge Space, Design Space and Control Space**



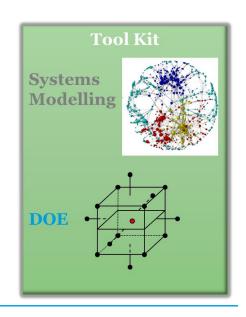


**Knowledge Space -** What you have tested and what you know.

**Design Space -** What works – the CPPs that give you the desired CQAs .

**Control Space -** Bandwidth allowed around optimal operation.

- **Documentation** SOPs / Working Instructions / Batch Manufacturing Records
- **Process Control** Monitoring / Analytics / IPCs / Decision Trees
- **Experimentation** Screening Studies / Optimisation / Alternative suppliers / New Technologies



# Identifying areas of development focus.





### Raw Material Supply

(e.g. Adventitious agent Testing/Supply agreements/licensing)



### Scalability

Needs of the clinic versus needs of the market / Skilled work-force



### **Closed Processing**

(e.g. Technology Selection/Room grade)



### Intermediate / Product Stability

Manufacturing strategy / Clinical population needs



#### Automation

(e.g. Throughput/accuracy/reproducibility/operator error reduction)



### Data Integrity and Storage

(e.g. Electronic Record Keeping and Tracking)



### Adaptive Control

(Process robustness and reduced failure rates)



### Facility Throughput



#### **Process Control**

(e.g. in line analytics / visual observation removal)



### Clinical Handling

(Specialised thaw-at-site systems)

# Accelerating your program development



### Structure

#### • Structured Development Program to meet Clinical Objectives

- Strategic development appropriate for clinical phase
- Decrease time to pre-clinical & clinical studies
- Focus on high priority areas

### Risk

#### • Reduce the risk of an expensive, failed GMP Manufacture

- Financial Risk Batch losses; Future investment
- Reputational Risk Company; Clinical uptake

#### • Reduce costs of the Development Program and GMP manufacture

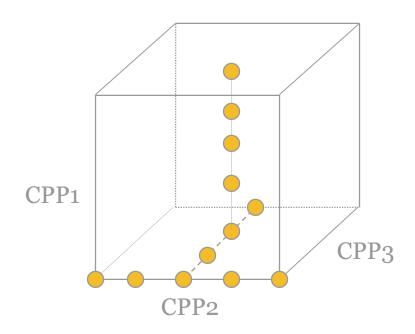
- Decrease CoGs / Increase the probability of achieving the reimbursement price-point
- Dendreon (Provenge) Manufacturing CoGs up to 77% of \$94,000 price tag.
- TiGenix (Chondroselect) Poor uptake in key markets Reimbursement challenges

# **Design of Experiments (DoE) Philosophy**



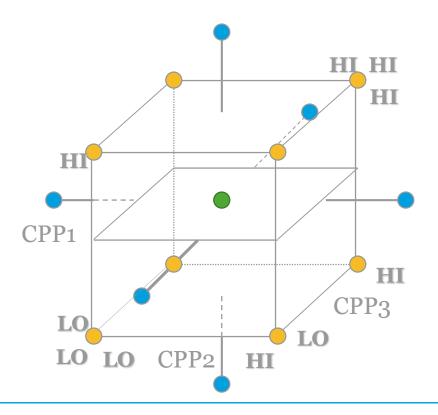
### One Factor At a Time (OFAT):

- Poor coverage of experimental space
- May miss optimal solution



### **Design of Experiments:**

- Good coverage of experimental space
- High efficiency designs



# **Theoretical Example of DoE**



### **Knowledge Space**

### Design Space

Control Space

Time in culture

Vessel Type

**Detachment Agent** 

**Buffer Wash** 

Surface Type

Hold Time

Feed frequency

Wash Method

Centrifugation Parameters

Choose factor ranges

Screening

**Hold Time** 

Centrifugation Parameters

Wash Method

Determination of relevant factors

Optimisation

2-4h 200-500g, 10-15min

1-3 volumes

Adjust factor ranges accordingly

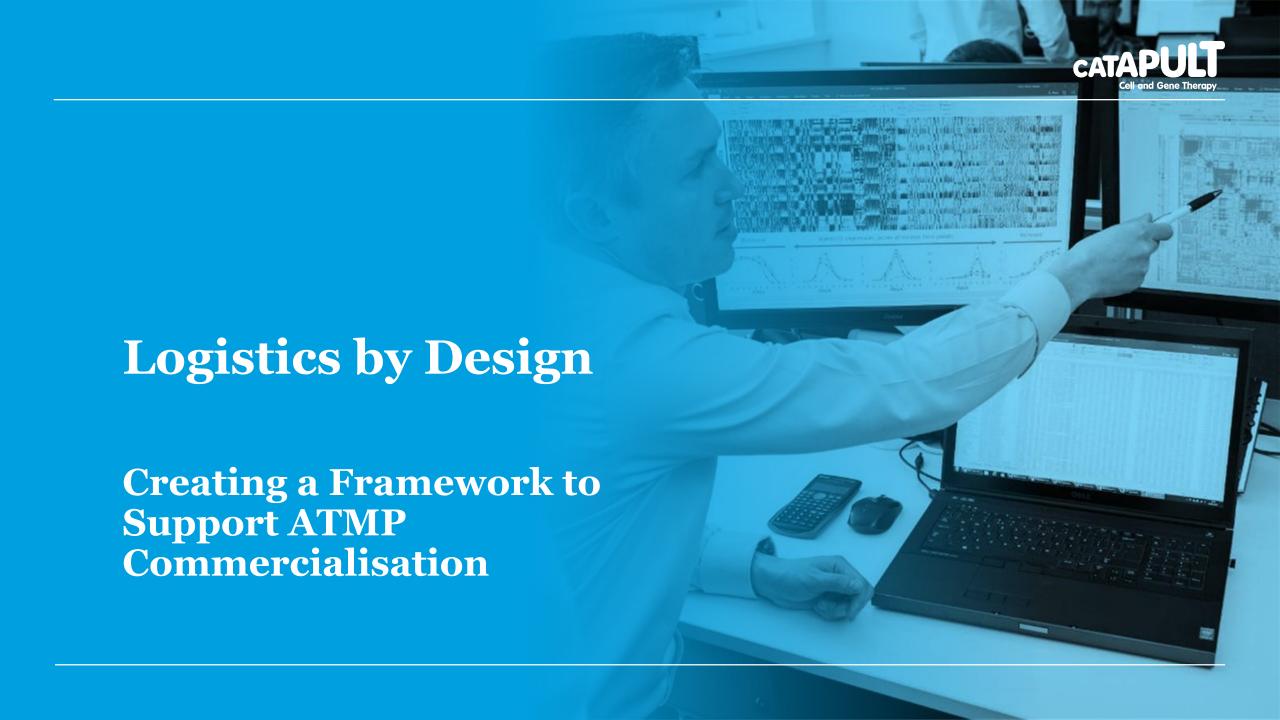
Lock-down

3+/-o.5h

400g, 12 min

2+/-0.5 volumes

Setting Operation
Bandwidth



### Why do we need a Framework?





"Surely it's just a case of picking up the phone and "voila", next day delivery"

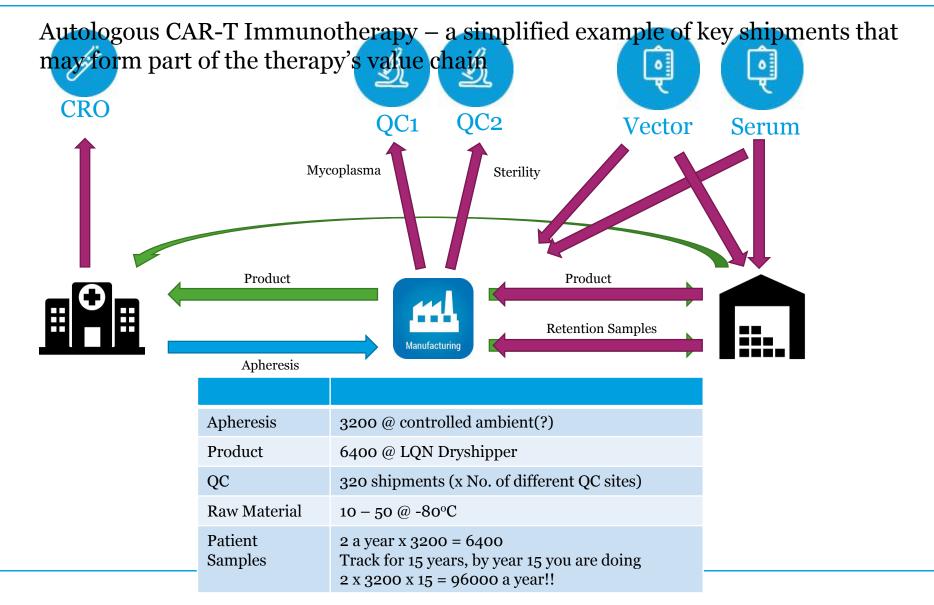
Unfortunately not - the logistics complexity surrounding ATMP manufacture and subsequent connection of final product to patient requires significant planning!

Logistics success will be influenced and impacted by several key stakeholders both internal and external to the therapy developer throughput the development lifecycle.

To be successful, the vision for a commercial logistics strategy needs to be planned early & have quality designed-in from the start.

# **Logistics – How complex can it be?**





### **Logistics - What could possibly go wrong?**







**AUTOMATED THERMAL PACKAGING RETURN** 

STABLE THERMAL PACKAGING

SENSOR + COMMUNICATION EMBEDDED PACKAGING





SECONDARY THERMAL PACKAGING for SITE LOCAL TRANSPORT to BEDSIDE

# **Logistics - What could possibly go wrong?**









**CHAIN OF CUSTODY MANAGEMENT** 



#### **Excursion Statistics**

Section

Value	
15.0	
04d 20h 00m 00s	
04d 08h 45m 02s	
25.0	
00d 00h 00m 00s	
00d 00h 00m 00s	
	15.0 04d 20h 00m 00s 04d 08h 45m 02s 25.0 00d 00h 00m 00s

Event Type	Time	Duration in Minutes
Excursion Below Threshold	11-Jan-2018 04:13:34 GMT-0700	6,285
Excursion Below Threshold	15-Jan-2018 23:43:40 GMT-0700	675

#### **AUTOMATED DATA ANALYTICS**

#### Unique Challenges Posed by Cell and Gene Therapy Logistics and Packaging



- Manufacturing
- Site
- Patient
- Logistics provider
- Logistics vehicle
- Data integrator
- Qualified person
- To name a few...

**REAL TIME SYSTEMS INTEGRATIONS with PARTNERS** 

# **Logistics - What could possibly go wrong?**





AIRLINE RESTRICTIONS ON COMMUNICATION SYSTEMS



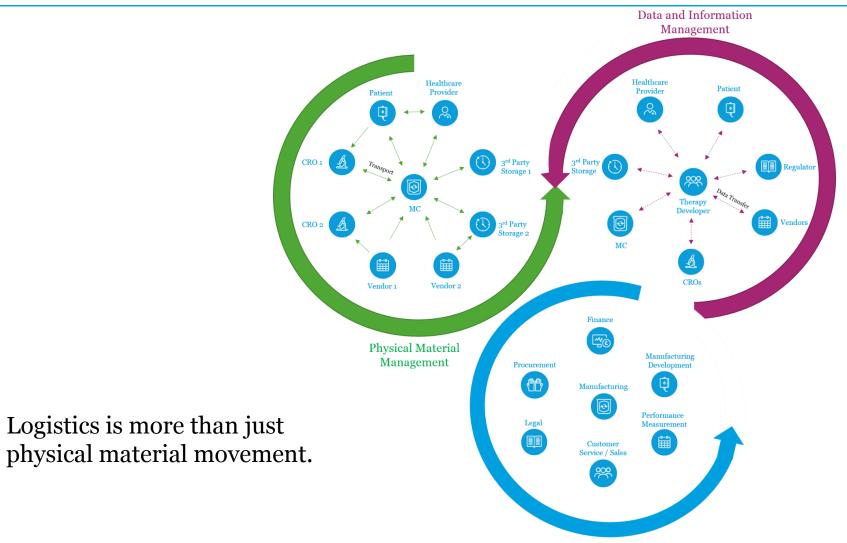
**MANAGEMENT of TIME SENSITIVE SHIPMENTS** 



**CLEANLINESS OF PACKAGING** 

# **The Key Elements**

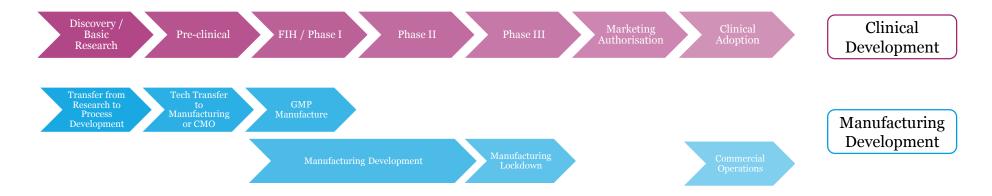




**Business Management** 

# When should I start planning?

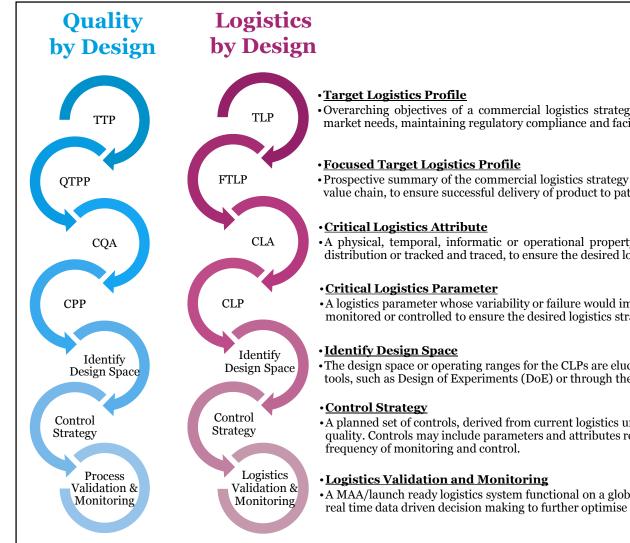




As early as possible – Logistics should have lifecycle management plans similar to clinical and manufacturing development

# Logistics by Design – Build in Quality from the Start CATAPU





•Overarching objectives of a commercial logistics strategy with respect to supporting business goals, supplying market needs, maintaining regulatory compliance and facilitating clinical adoption.

• Prospective summary of the commercial logistics strategy traits that need to be achieved for all components of the value chain, to ensure successful delivery of product to patient whilst maintaining chain of custody and identity

• A physical, temporal, informatic or operational property that needs to be within an appropriate limit, range, distribution or tracked and traced, to ensure the desired logistics strategy is fulfilled.

· A logistics parameter whose variability or failure would impact a critical logistics attribute and therefore should be monitored or controlled to ensure the desired logistics strategy is fulfilled.

• The design space or operating ranges for the CLPs are elucidated through practical assessment using supporting tools, such as Design of Experiments (DoE) or through the testing as part of logistics development activities

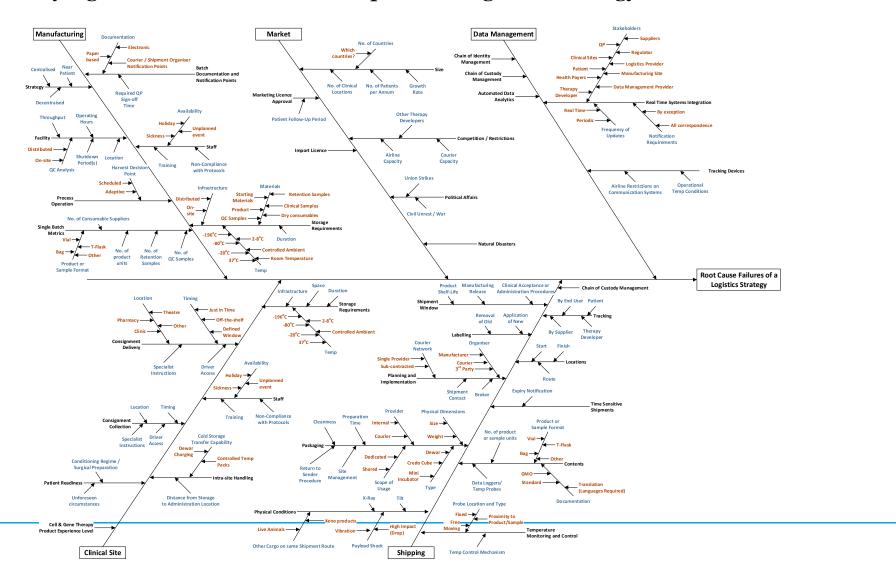
· A planned set of controls, derived from current logistics understanding that ensures service performance and quality. Controls may include parameters and attributes related to physical or informatic characteristics and include

• A MAA/launch ready logistics system functional on a global footprint with regular performance review to support real time data driven decision making to further optimise the logistics undertaking.

### **Examples of Route Cause Failures**

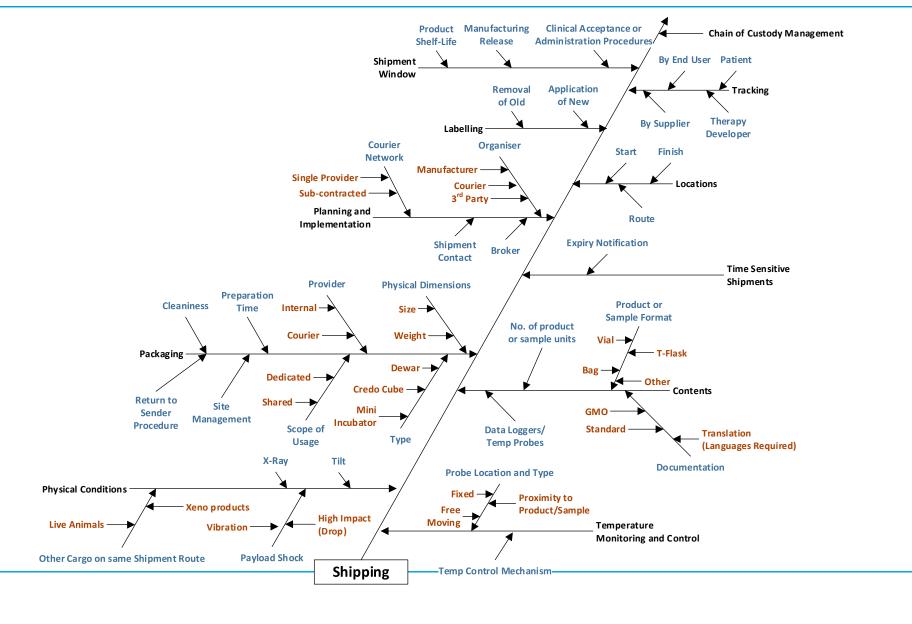


### Identifying root cause failures of the planned logistics strategy



### **Examples of Root Cause Failures**

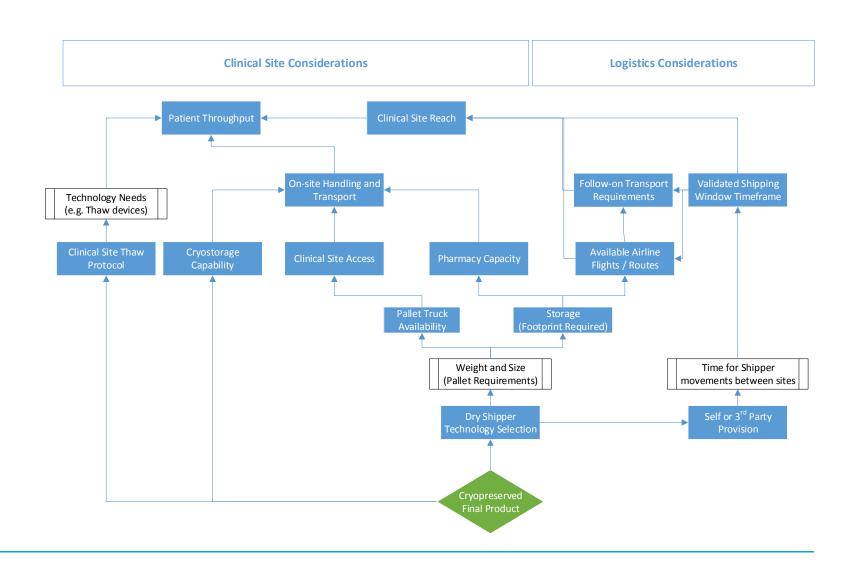




### **Case Study A: Mapping Complex Networks of Dependencies**



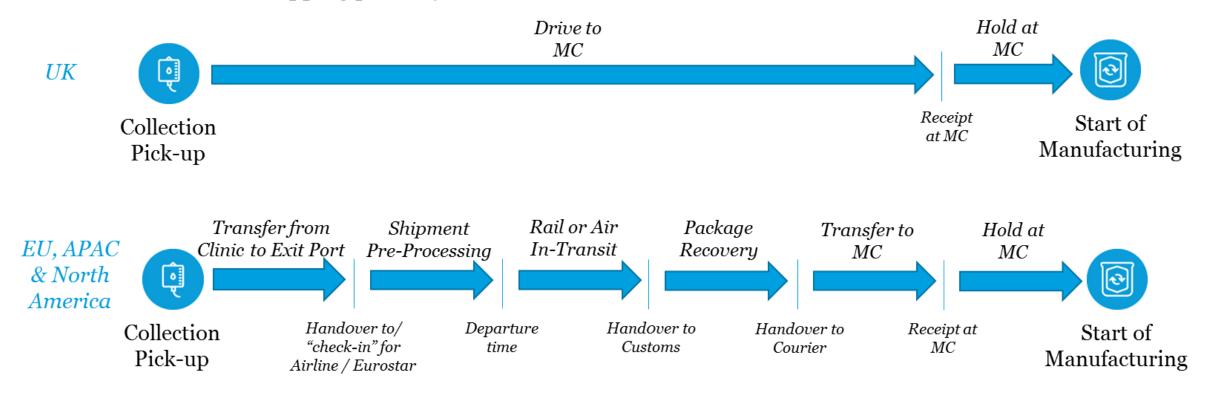
What's the impact of manufacturing or clinical development teams deciding the product should be cryopreserved?



# **Case Study B: Mapping Shipping Lanes**

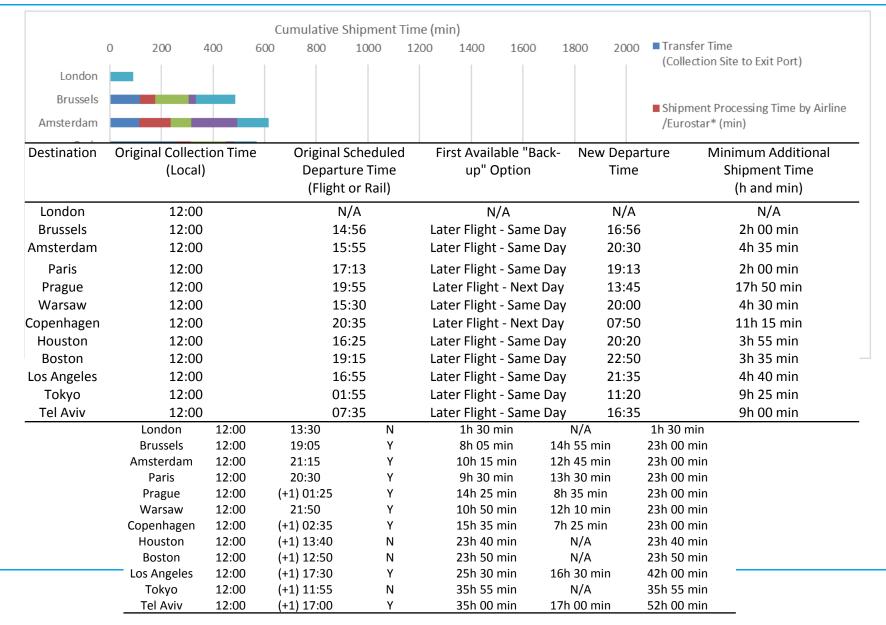


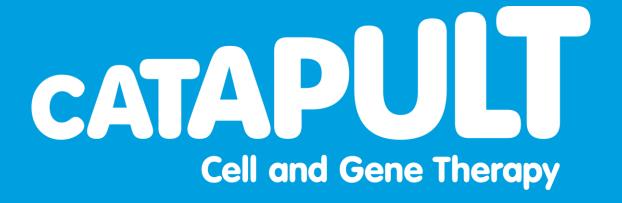
What's the impact on required shipping window / material shelf-life needs as a function of constrained elements within the shipping pathway?



# **Case Study B: Mapping Shipping Lanes**







Cell and Gene Therapy Catapult is committed to ensuring high standards of research integrity and research best practice in the activities we carry out. We subscribe to the principles described in the UK concordat to support research integrity.

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We work with Innovate UK