

Applying Quality by Design to Cell and Gene Therapies

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:



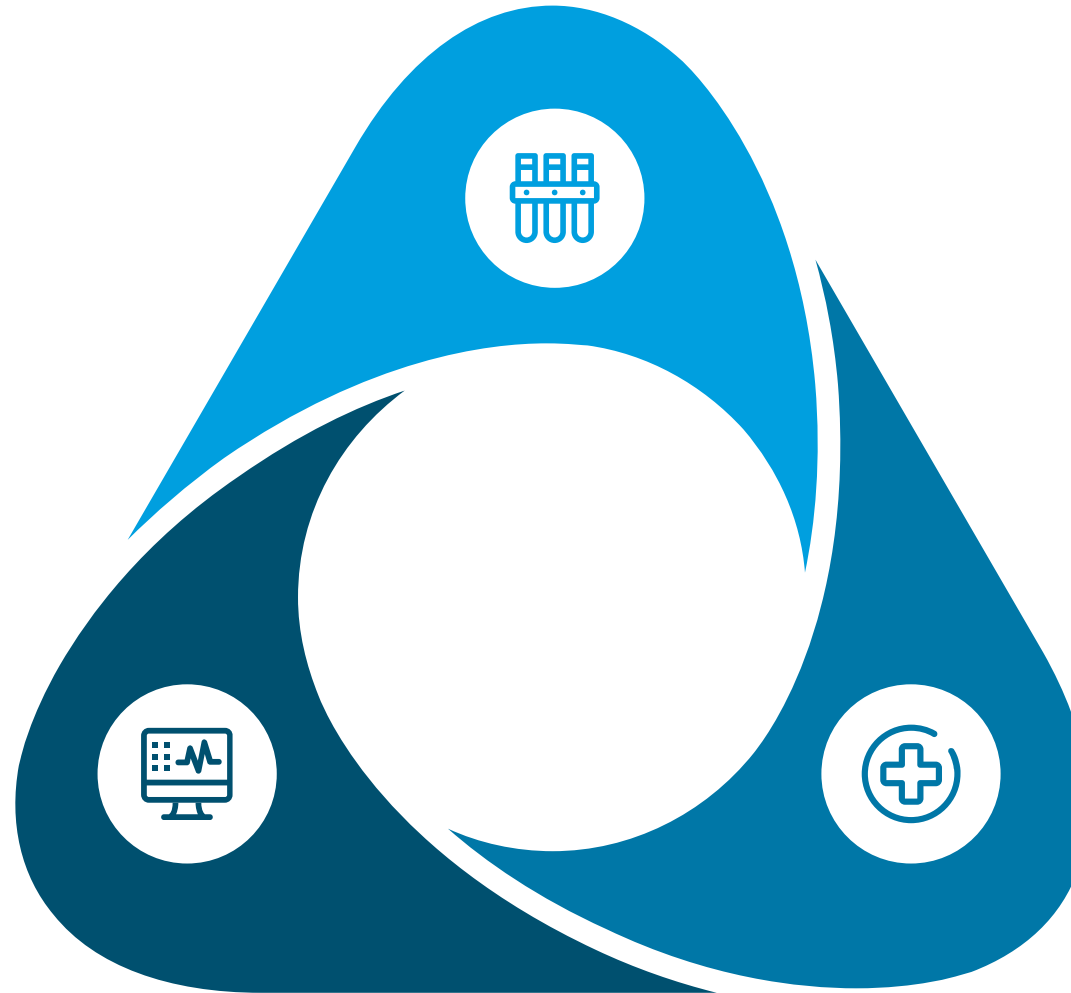
Breaking down industry barriers

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

The challenge

Developing a reliable and robust manufacturing process.



How we can help

Identifying ways to lower the costs of manufacturing your product.

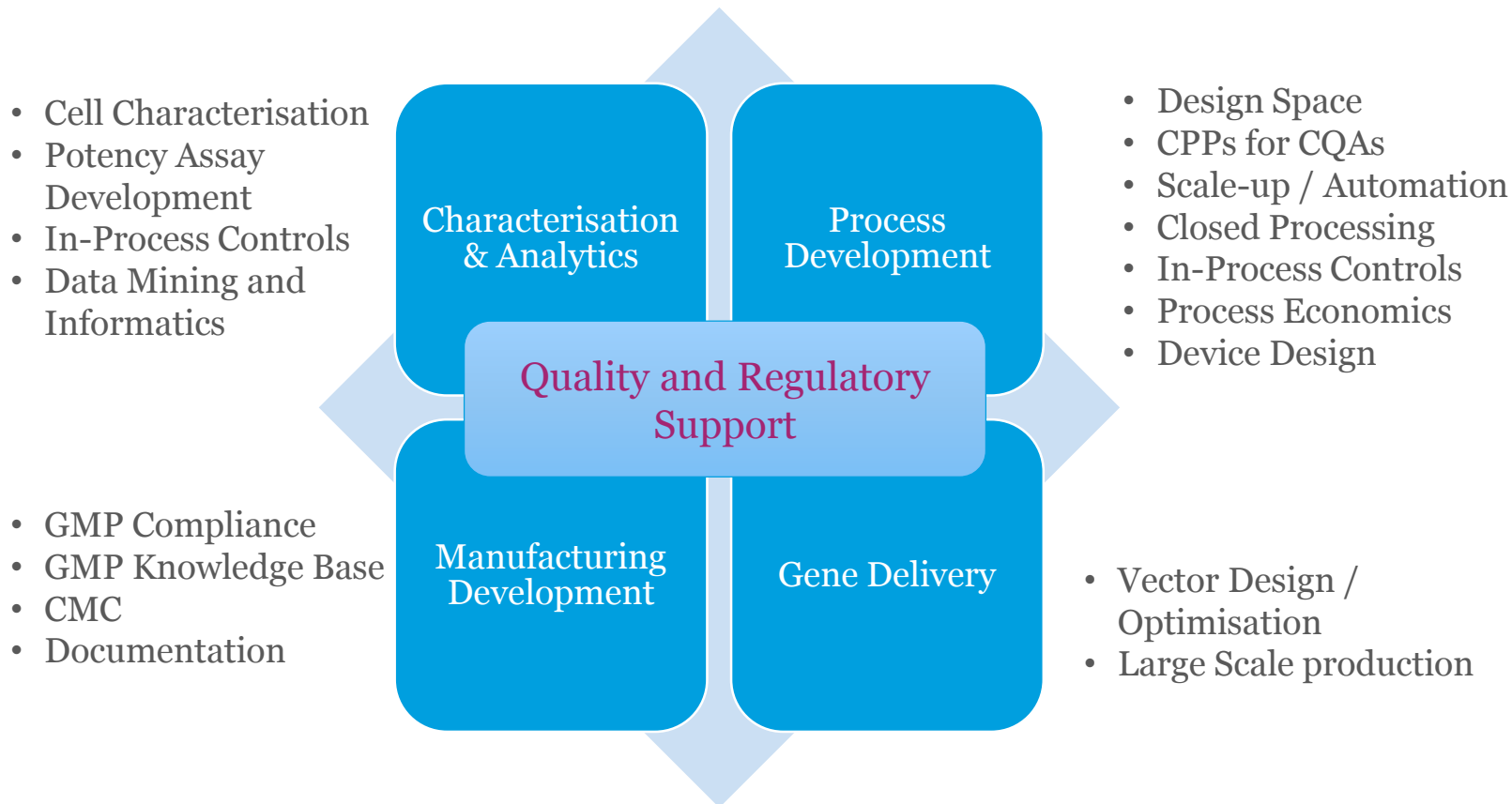
Finding innovative ways to make your process more efficient and robust.

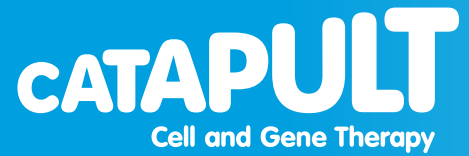
Providing methods to accelerate and support clinical trials.

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 and Gene Therapies – a Brief Overview



Maturation of the Field

• Yescarta

\$373,000

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

• Strimvelis

€600,000

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

• Kymriah

\$475,000









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

• Glybera

>€1,000,000

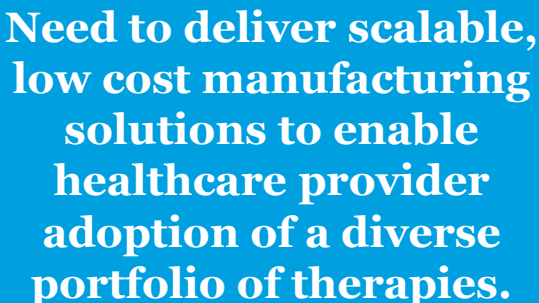
- (alipogene tiparvovec)
- UniQure's AAV-based gene therapy to treat the rare inherited disorder lipoprotein lipase deficiency (LPLD)

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

	Imylic	- Approved 2015		Spherox	- Approved 2017
	Holoclar	- Approved 2015		Alofisel	- Approved 2018
	Strimvelis	- Approved 2016 - (2 patient treated – patients go to Italy for treatment)		Yescarta	- Approved 2018
	Zalmoxis	- Approved 2016, Conditional MA		Kymriah	- Approved 2018

	Chondroselect	- Voluntary Withdrawal 2016 - (Reimbursement challenges / Complex Logistics)
	MACI	- Approved 2013, Suspended 2014 - (Manufacturing Discontinued)
	Provence	- Approved 2013, Withdrawn 2015
	Glybera	- Approved 2012, Voluntary Withdrawal 2017 - (1 patient treated)

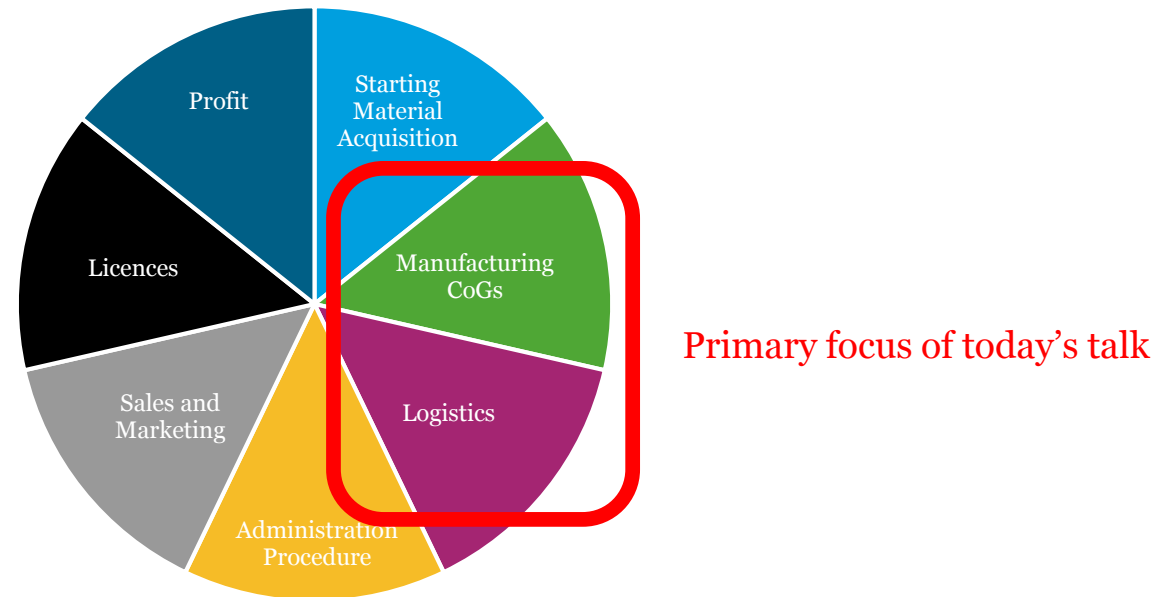
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*Adapted from the original presented at Wells Fargo Securities Healthcare Conference, Nov 2017

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?

Our Development Strategy

A Risk and Cost Based Approach

“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

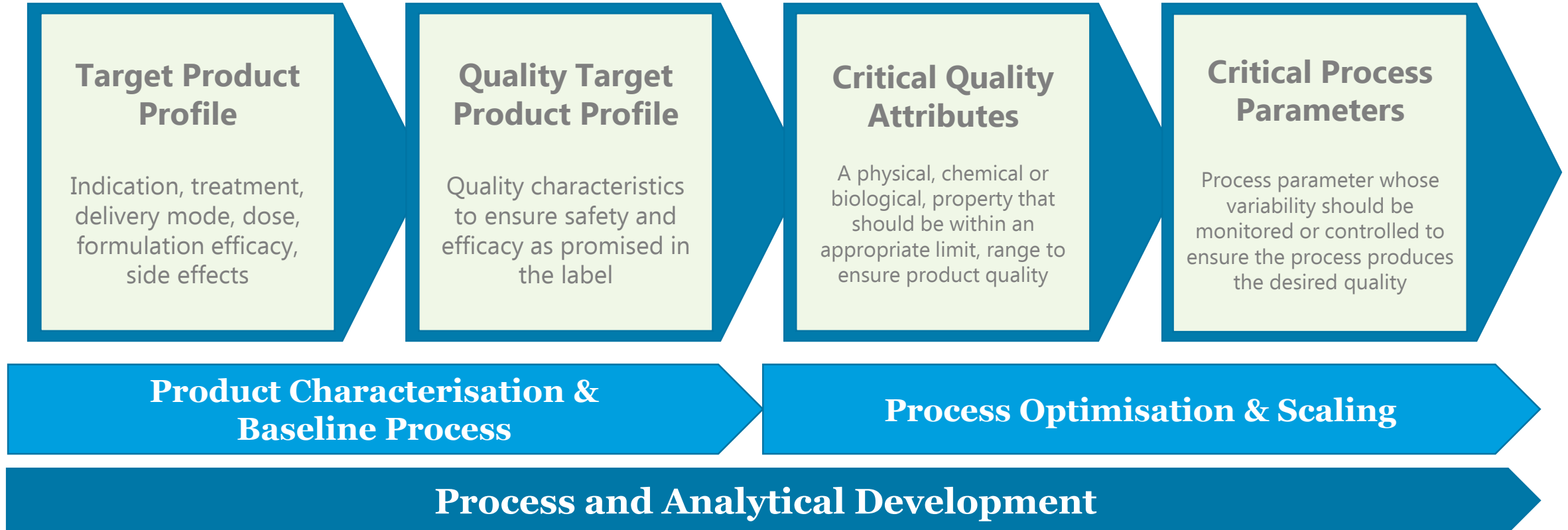
- Bring risk management into Pharma industry
- Provide details of systematic approach to QRM
- Info on QRM tools to enable effective risk based decisions

Q10

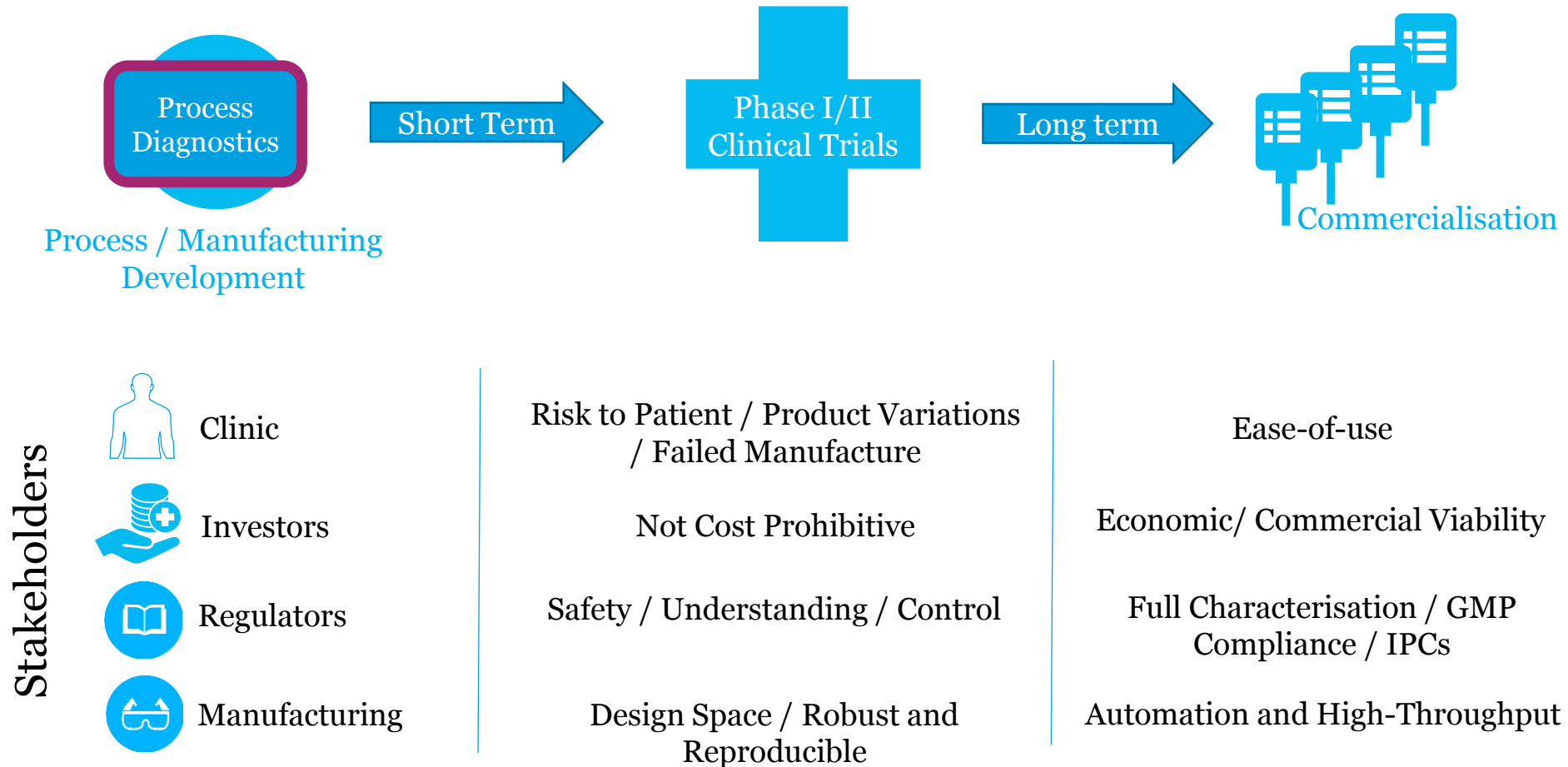
Pharmaceutical Quality Systems (PQS)

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

Understanding your product

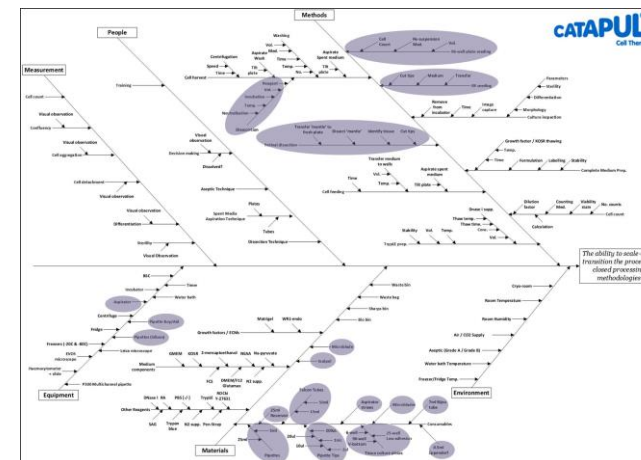


Understanding the needs of your stakeholders



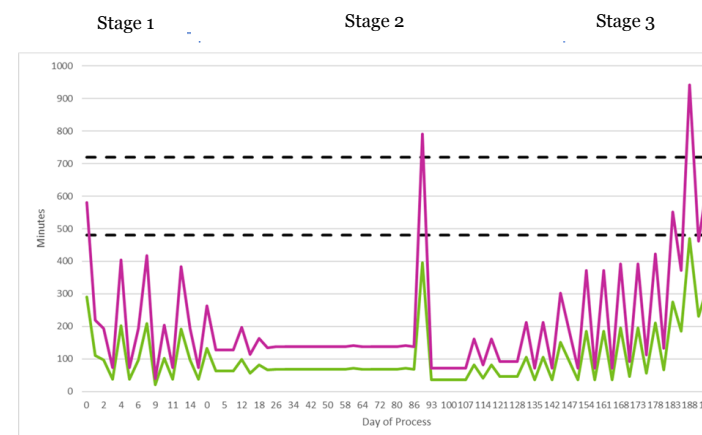
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Ishikawa



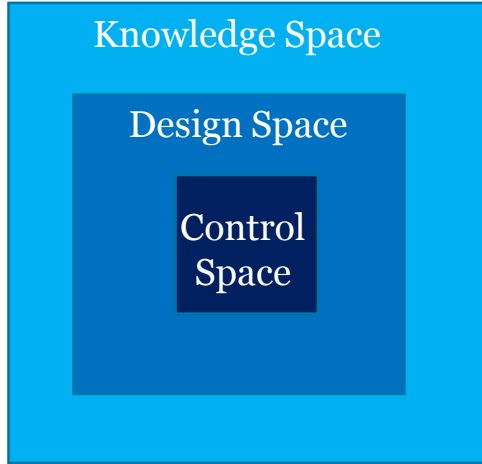
Root Cause of Failure

Facility Utilisation and CoGs



Facility Utilisation Profile

Knowledge Space, Design Space and Control Space

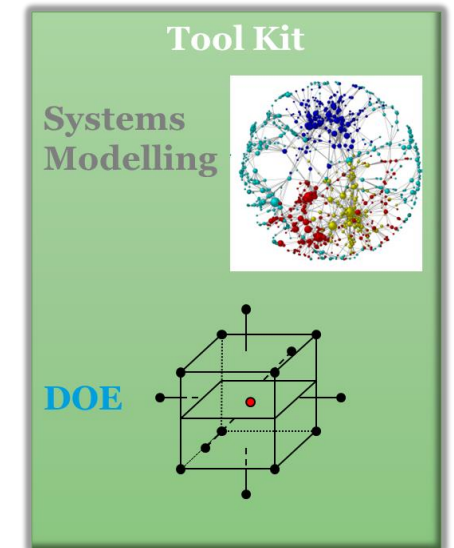


Knowledge Space - What you have tested and what you know.

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)



Closed Processing
(e.g. Technology Selection/Room grade)



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



Adaptive Control
(Process robustness and reduced failure
rates)



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



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



Intermediate / Product Stability
Manufacturing strategy / Clinical population needs



Data Integrity and Storage
(e.g. Electronic Record Keeping and Tracking)

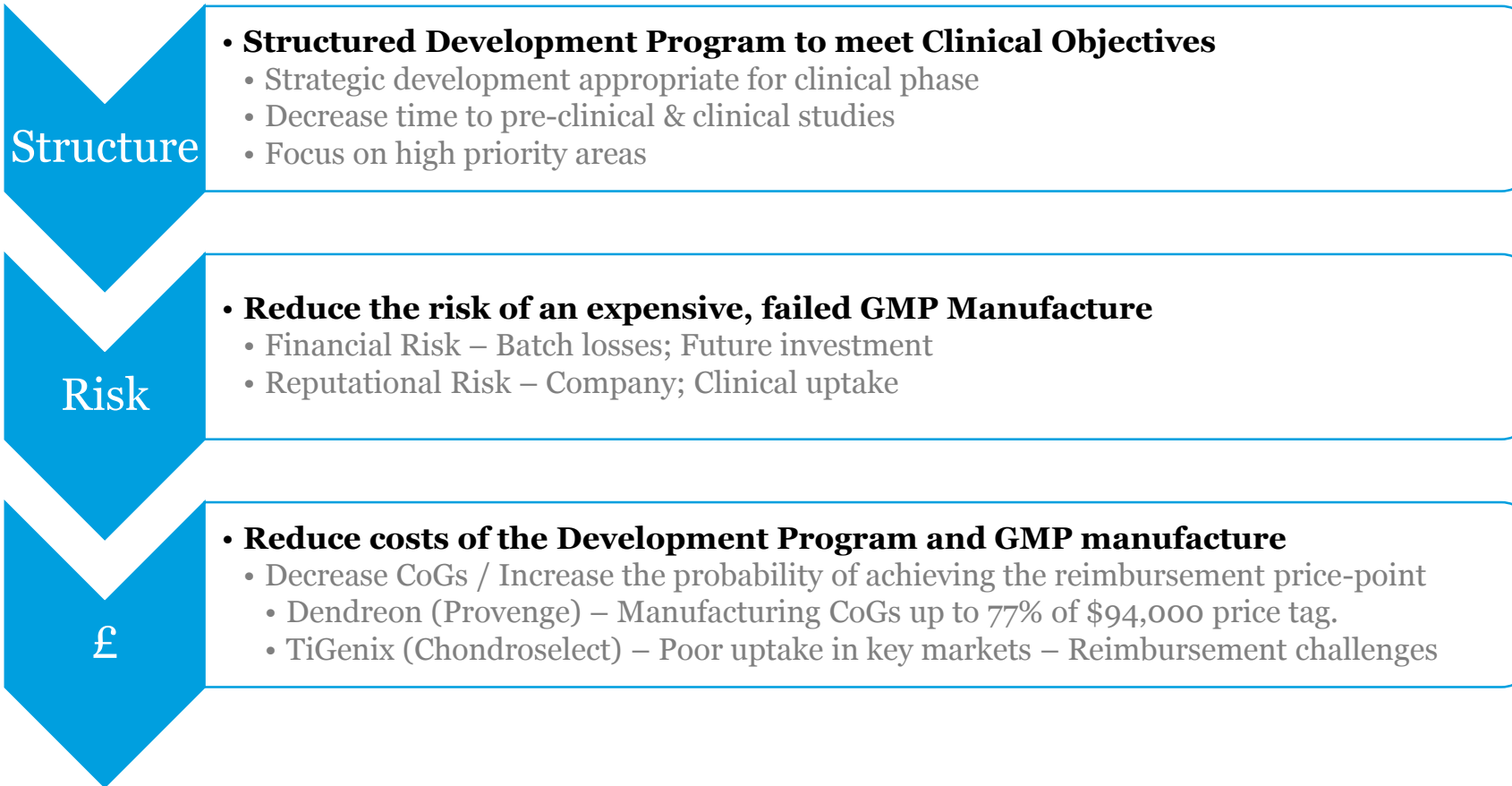


Facility Throughput



Clinical Handling
(Specialised thaw-at-site systems)

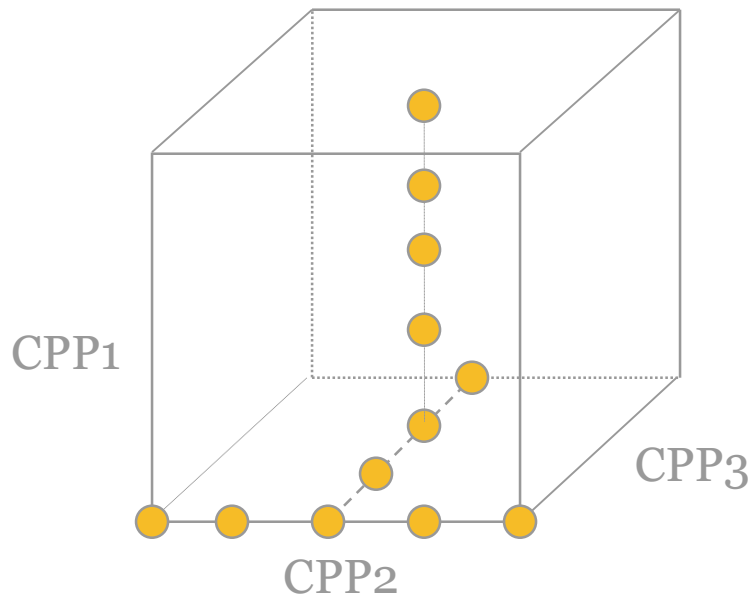
Accelerating your program development



Design of Experiments (DoE) Philosophy

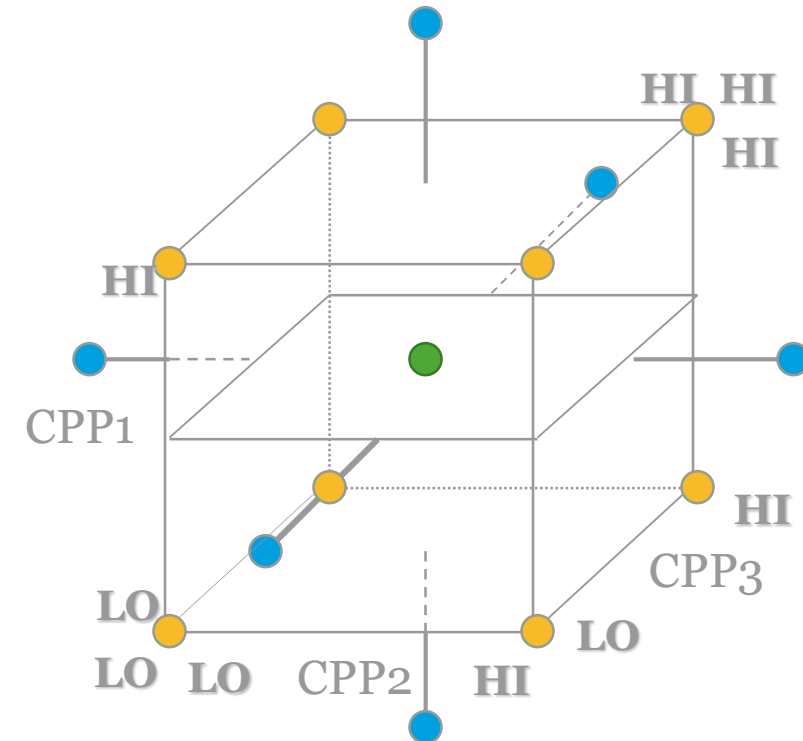
One Factor At a Time (OFAT):

- Poor coverage of experimental space
- May miss optimal solution

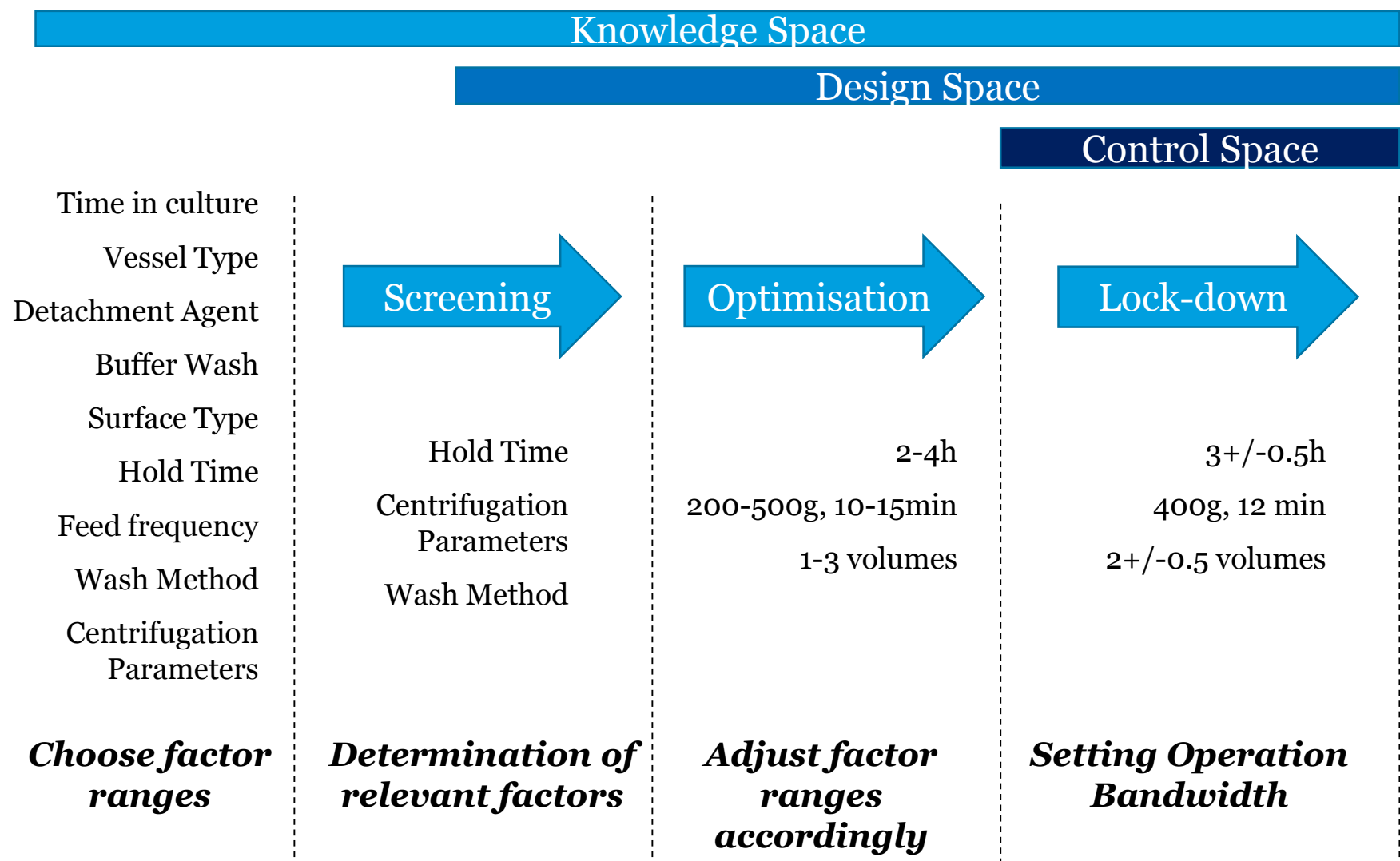


Design of Experiments:

- Good coverage of experimental space
- High efficiency designs



Theoretical Example of DoE



Logistics by Design

Creating a Framework to
Support ATMP
Commercialisation

Why do we need a Framework?



“Surely it’s just a case of picking up the phone and “voila”, next day delivery”

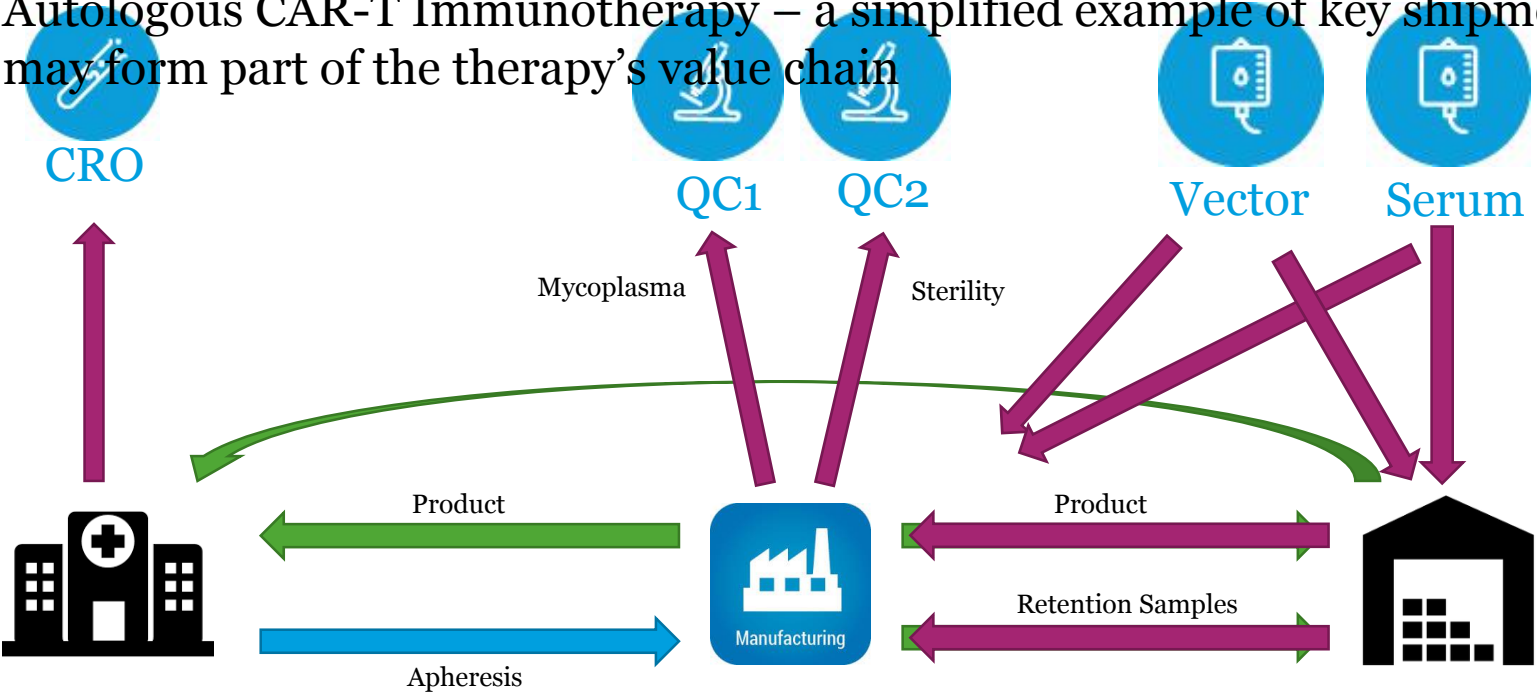
Unfortunately not - the logistics complexity surrounding ATMP manufacture and subsequent connection of final product to patient requires significant planning!

Logistics success will be influenced and impacted by several key stakeholders both internal and external to the therapy developer throughout 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?

Autologous CAR-T Immunotherapy – a simplified example of key shipments that may form part of the therapy’s value chain



Apheresis	3200 @ controlled ambient(?)
Product	6400 @ LQN Dryshipper
QC	320 shipments (x No. of different QC sites)
Raw Material	10 – 50 @ -80°C
Patient Samples	2 a year x 3200 = 6400 Track for 15 years, by year 15 you are doing 2 x 3200 x 15 = 96000 a year!!

Logistics - What could possibly go wrong?



STABLE THERMAL PACKAGING



SENSOR + COMMUNICATION EMBEDDED PACKAGING



AUTOMATED THERMAL PACKAGING RETURN



**SECONDARY THERMAL PACKAGING for SITE
LOCAL TRANSPORT to BEDSIDE**



DEDICATED THERMAL PACKAGING FLEET

Logistics - What could possibly go wrong?



PHYSICAL PAYLOAD PROTECTION



CHAIN OF CUSTODY MANAGEMENT



CHAIN OF IDENTITY MANAGEMENT

Excursion Statistics

Section 5

Type	Value
Low Alarm Threshold (°C)	15.0
Total Time Below	04d 20h 00m 00s
Longest Low Threshold Excursion Event	04d 08h 45m 02s
High Alarm Threshold (°C)	25.0
Total Time Above	00d 00h 00m 00s
Longest High Threshold Excursion Event	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



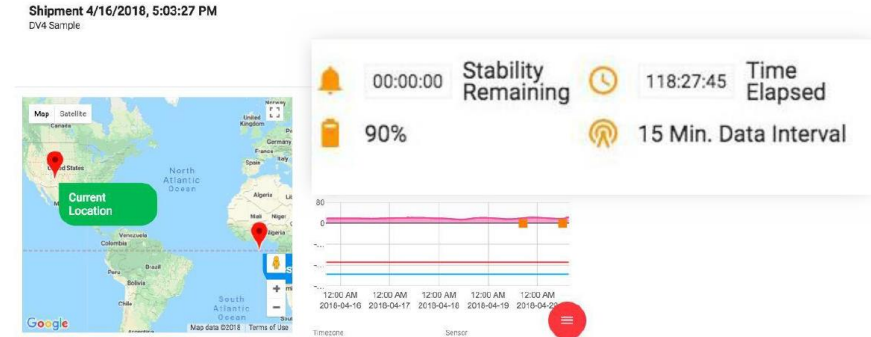
- Manufacturing
- Site
- Patient
- Logistics provider
- Logistics vehicle
- Data integrator
- Qualified person
- To name a few...

REAL TIME SYSTEMS INTEGRATIONS with PARTNERS

Logistics - What could possibly go wrong?



AIRLINE RESTRICTIONS ON COMMUNICATION SYSTEMS

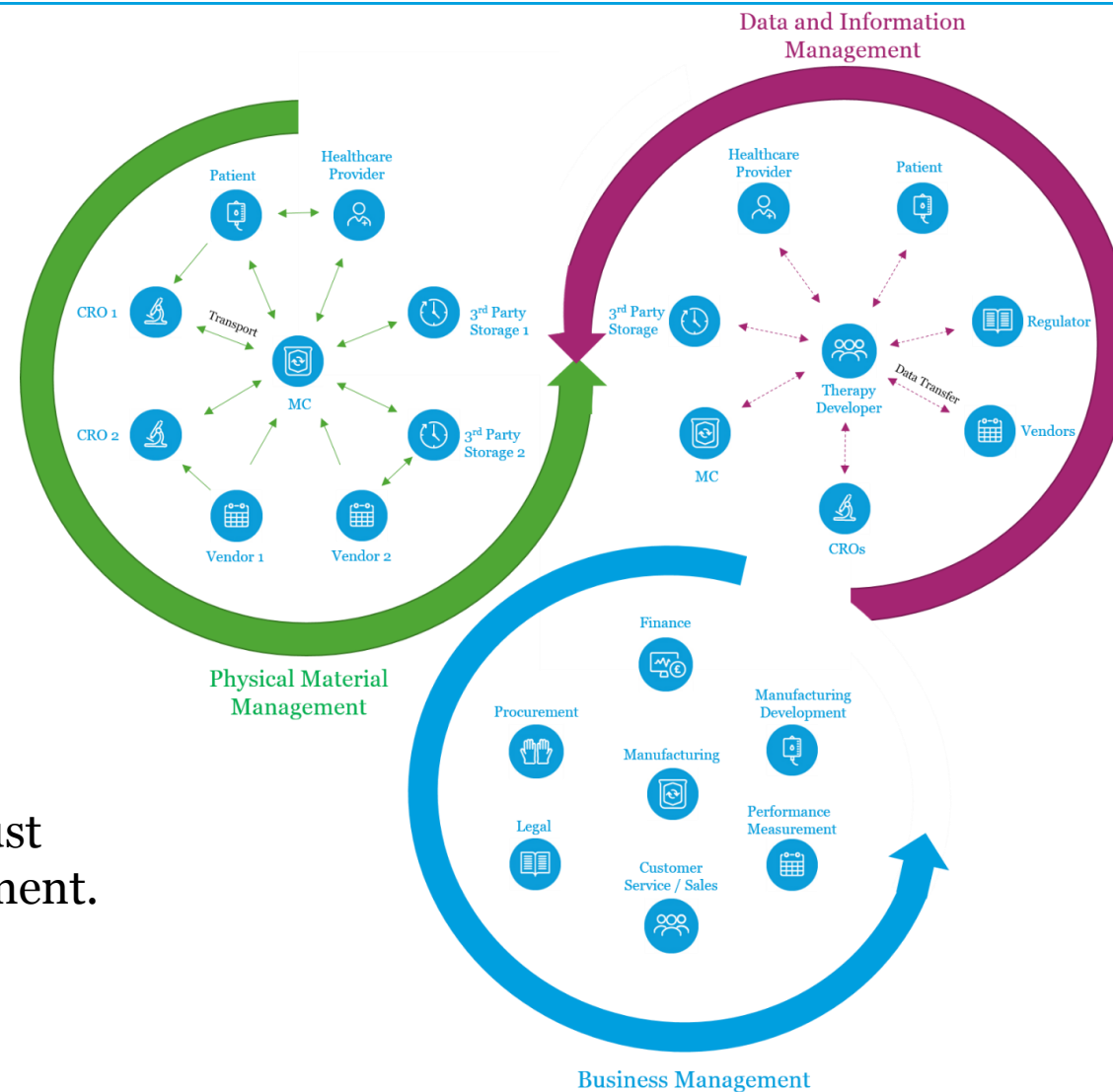


MANAGEMENT of TIME SENSITIVE SHIPMENTS



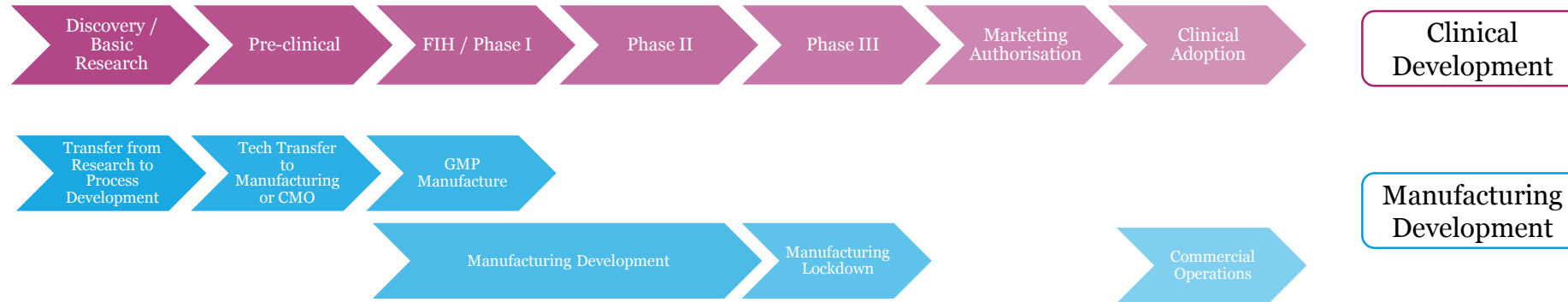
CLEANLINESS OF PACKAGING

The Key Elements



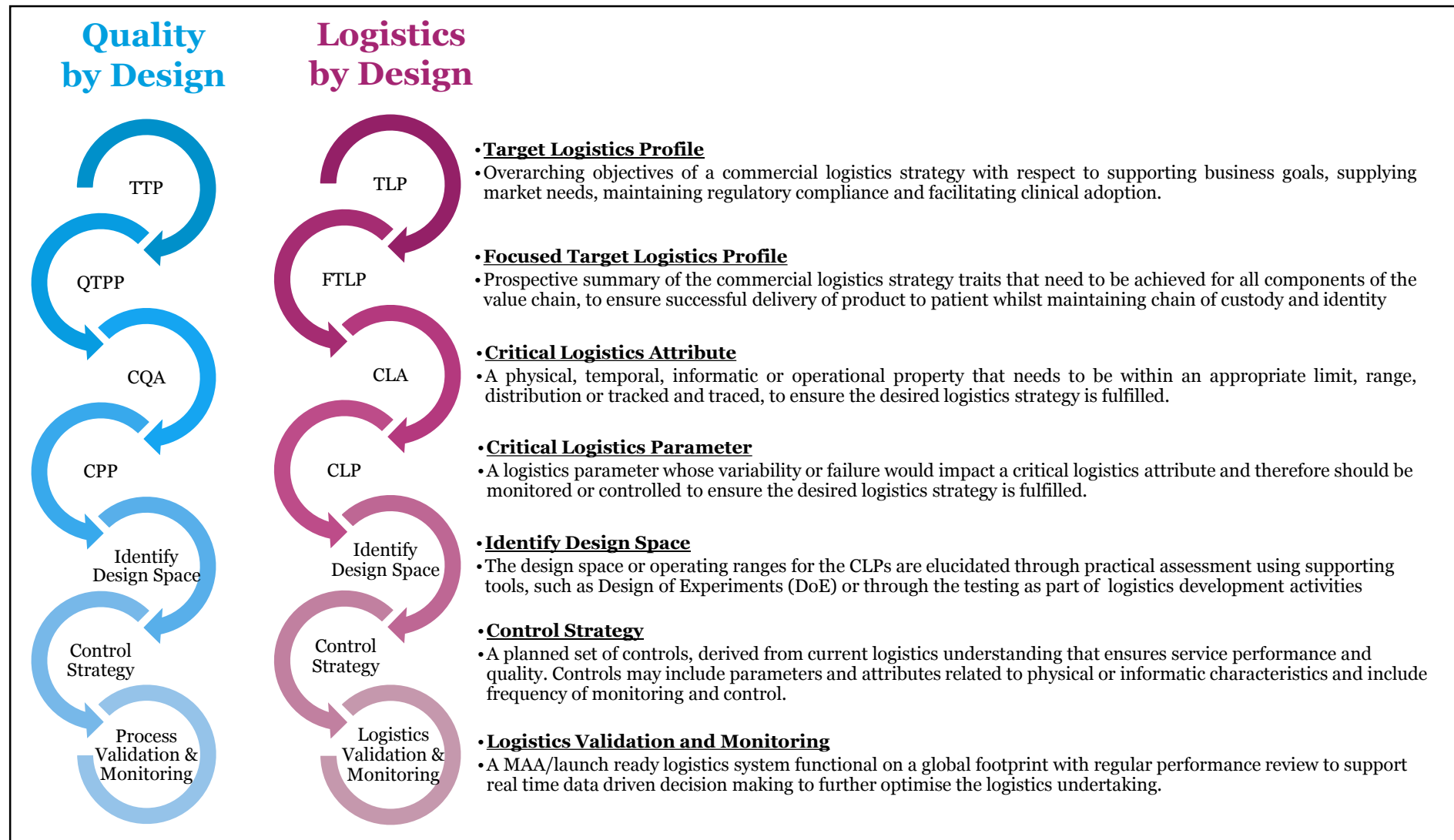
Logistics is more than just physical material movement.

When should I start planning?



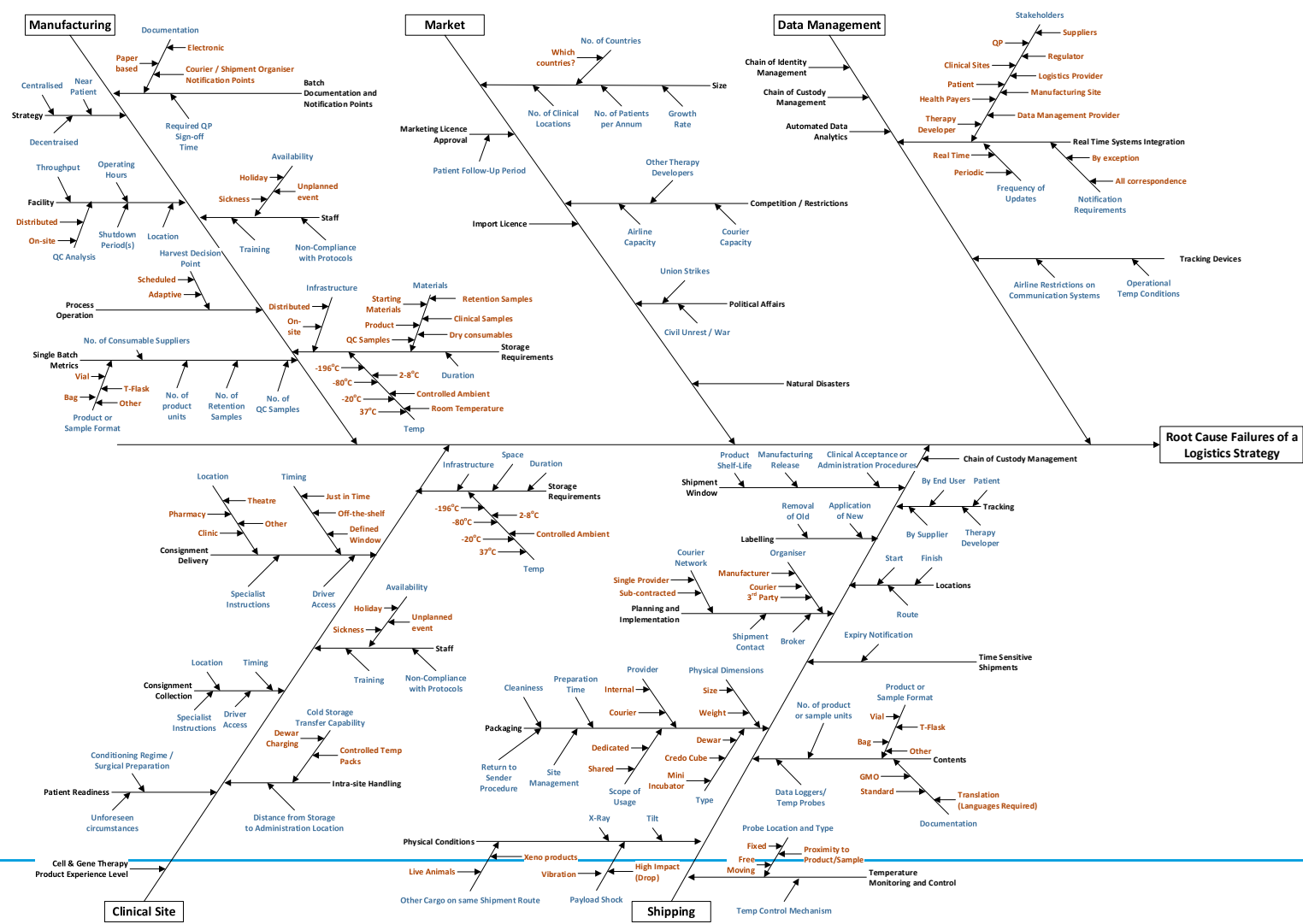
As early as possible – Logistics should have lifecycle management plans similar to clinical and manufacturing development

Logistics by Design – Build in Quality from the Start

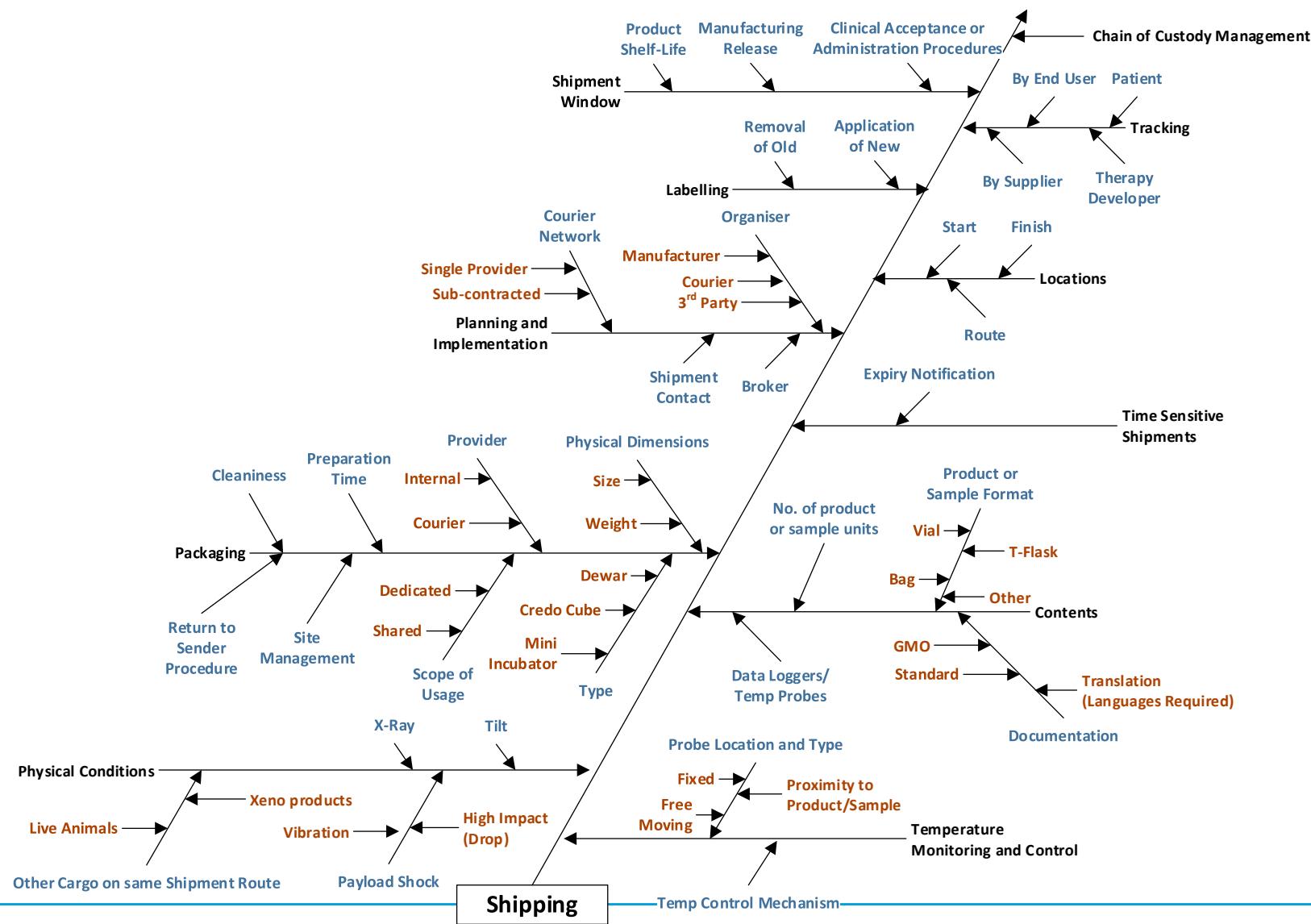


Examples of Route Cause Failures

Identifying root cause failures of the planned logistics strategy

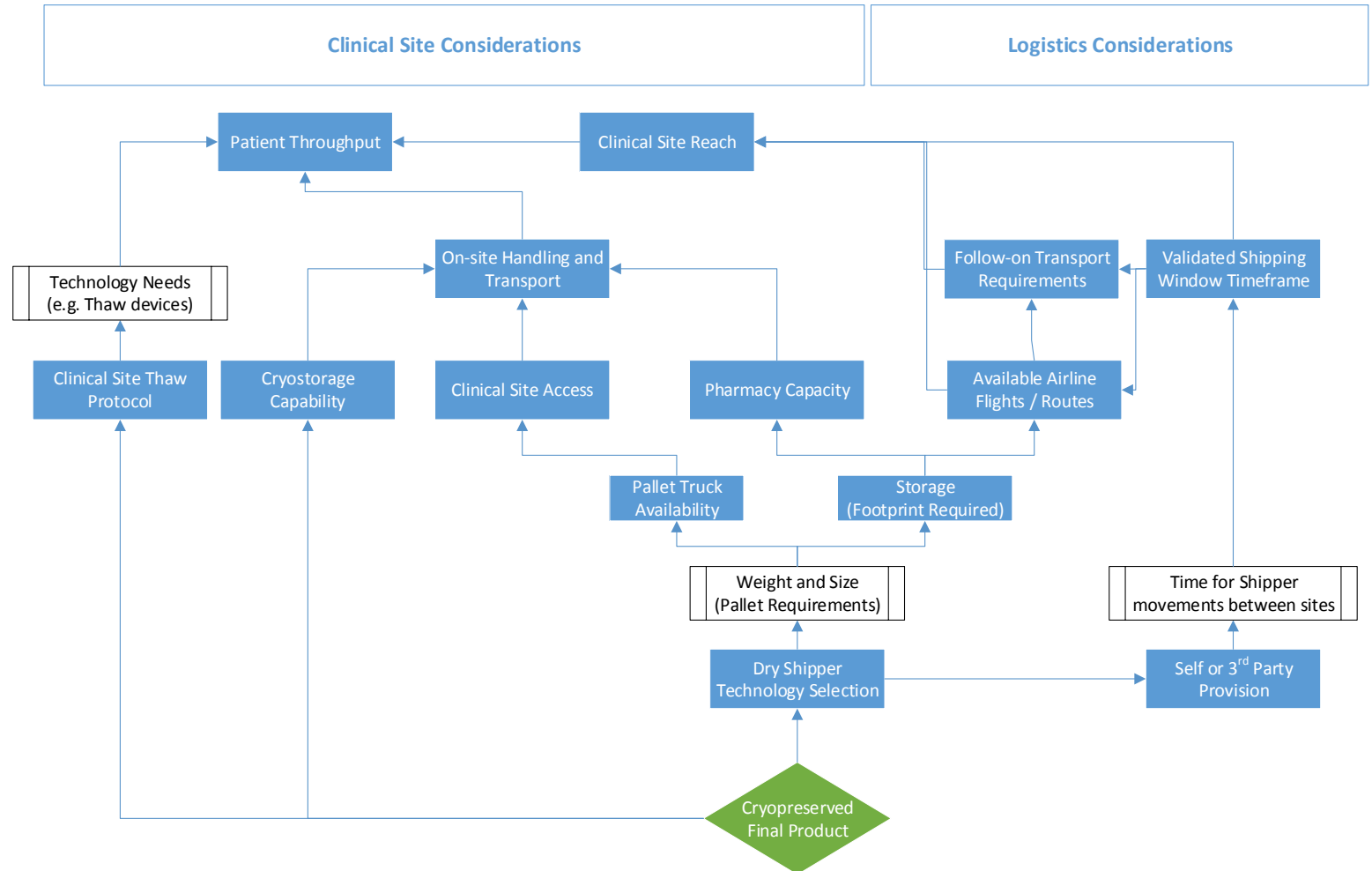


Examples of Root Cause Failures



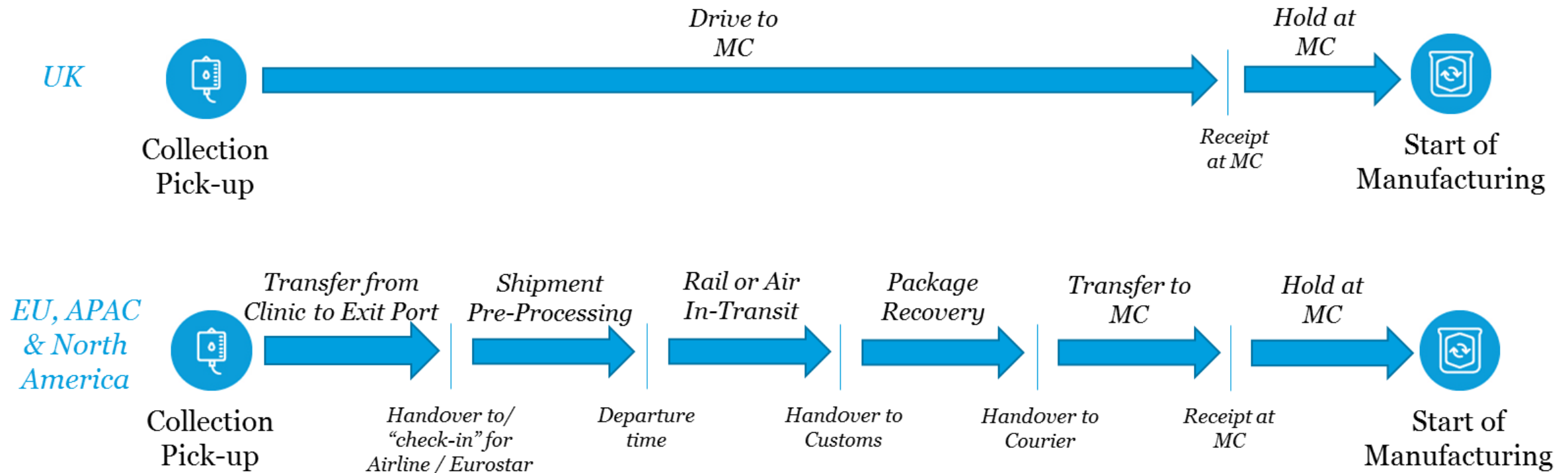
Case Study A: Mapping Complex Networks of Dependencies

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

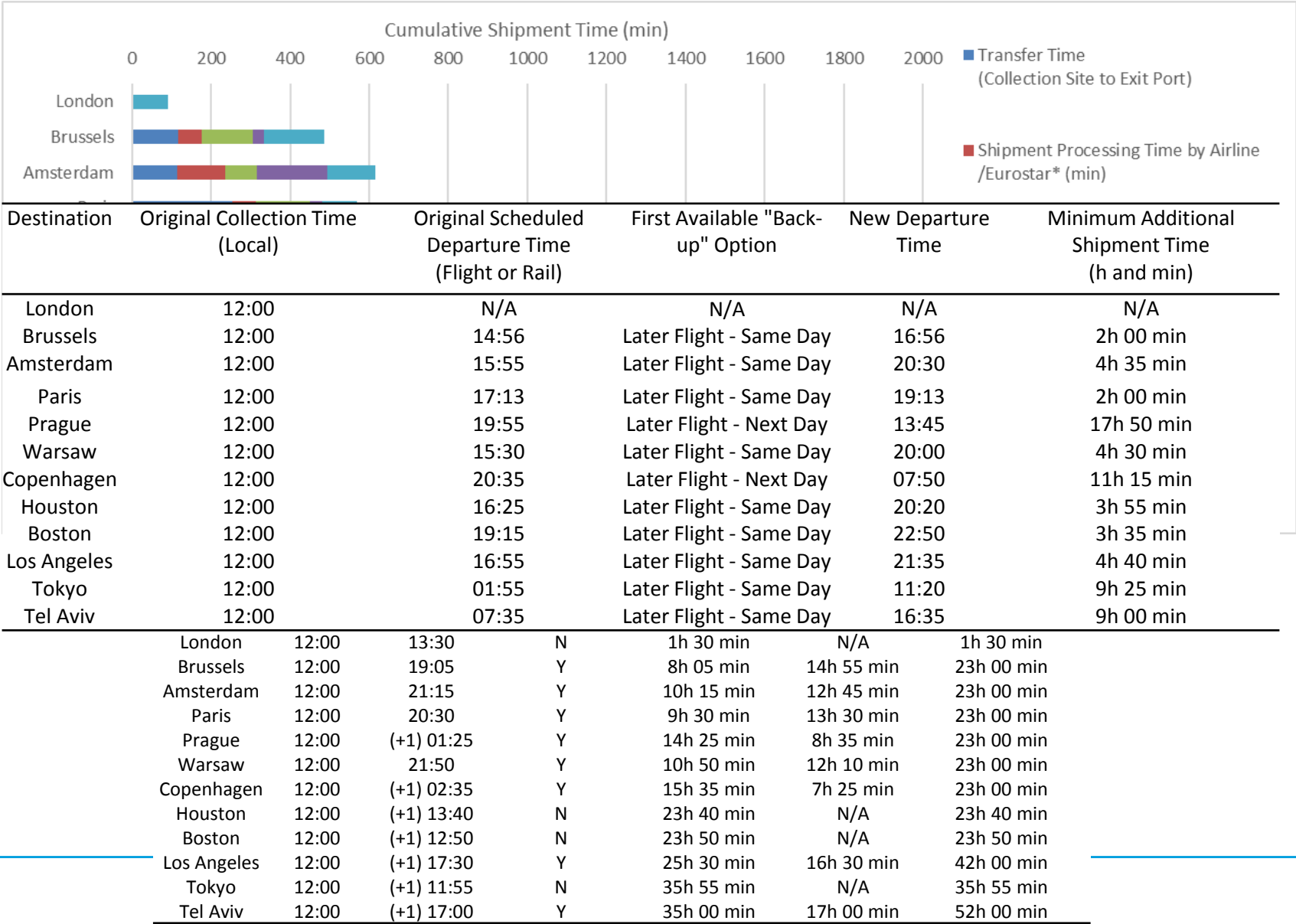


Case Study B: Mapping Shipping Lanes

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



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