UCL eXmoor Workshop: Manufacturing Strategies for Successful ATMP Development

6th March 2024

Introduction to eXmoor

Trusted Cell & Gene Therapy Partner

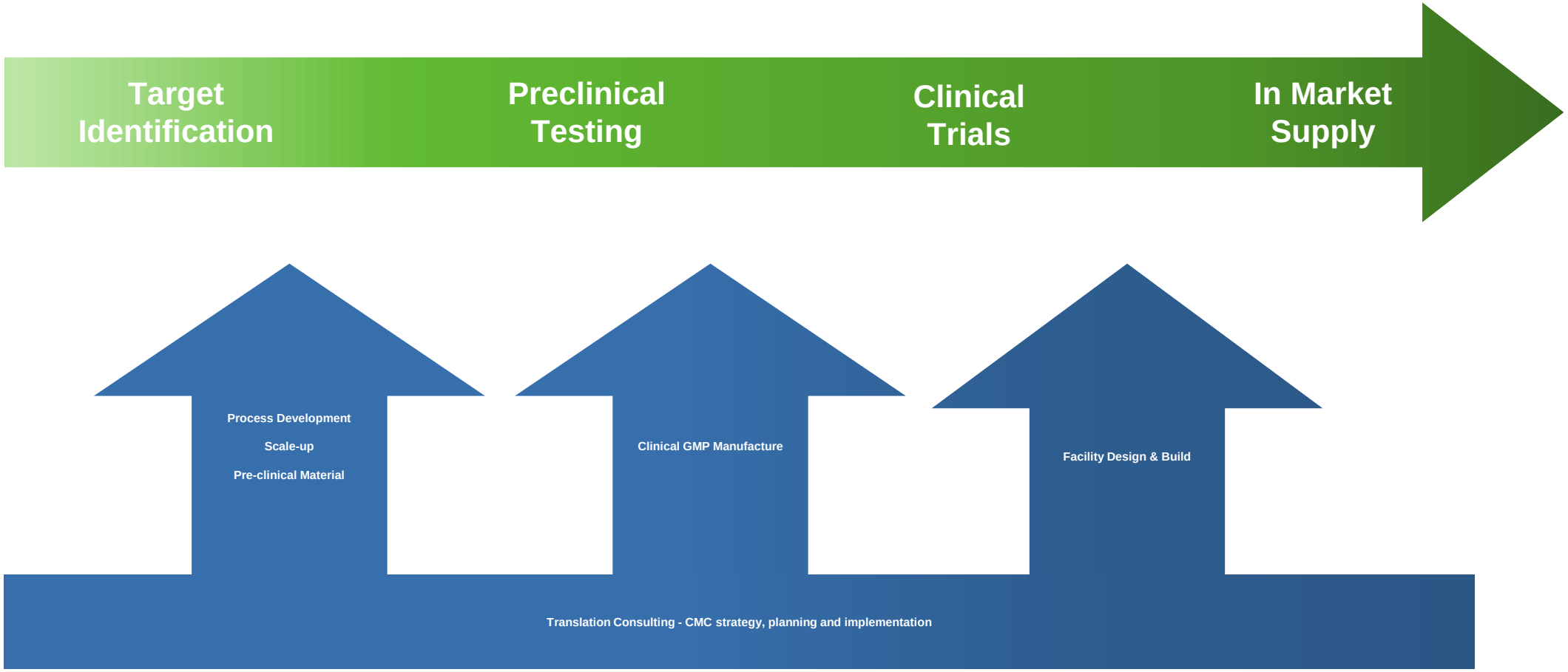
Full service CDMO accelerating therapies from research to patients

- >20 Years' Experience
- 85+ Employees
- 65,000 ft^2 GMP Facility
- Global Customer Base
- Dedicated to ATMPs

Our Services:

- CMC Consulting
- Process & Analytical Development
- GMP Clinical Manufacturing
- Facility Design & Build Consulting

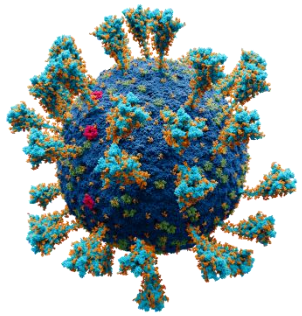
Accelerating your Commercialisation Journey



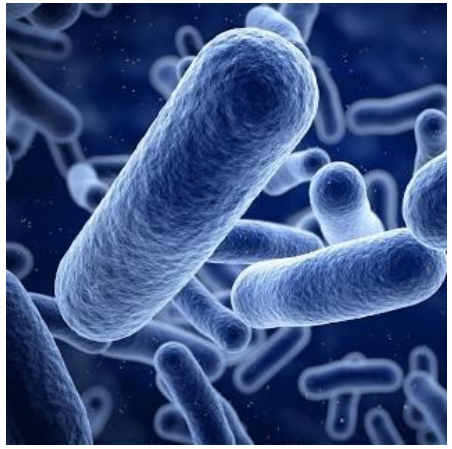
How CMC Expertise Early in Development Can Maximise Chances of Product Success

Clare Blue, Senior CMC Consultant

BioReliance®



nightstar THERAPEUTICS



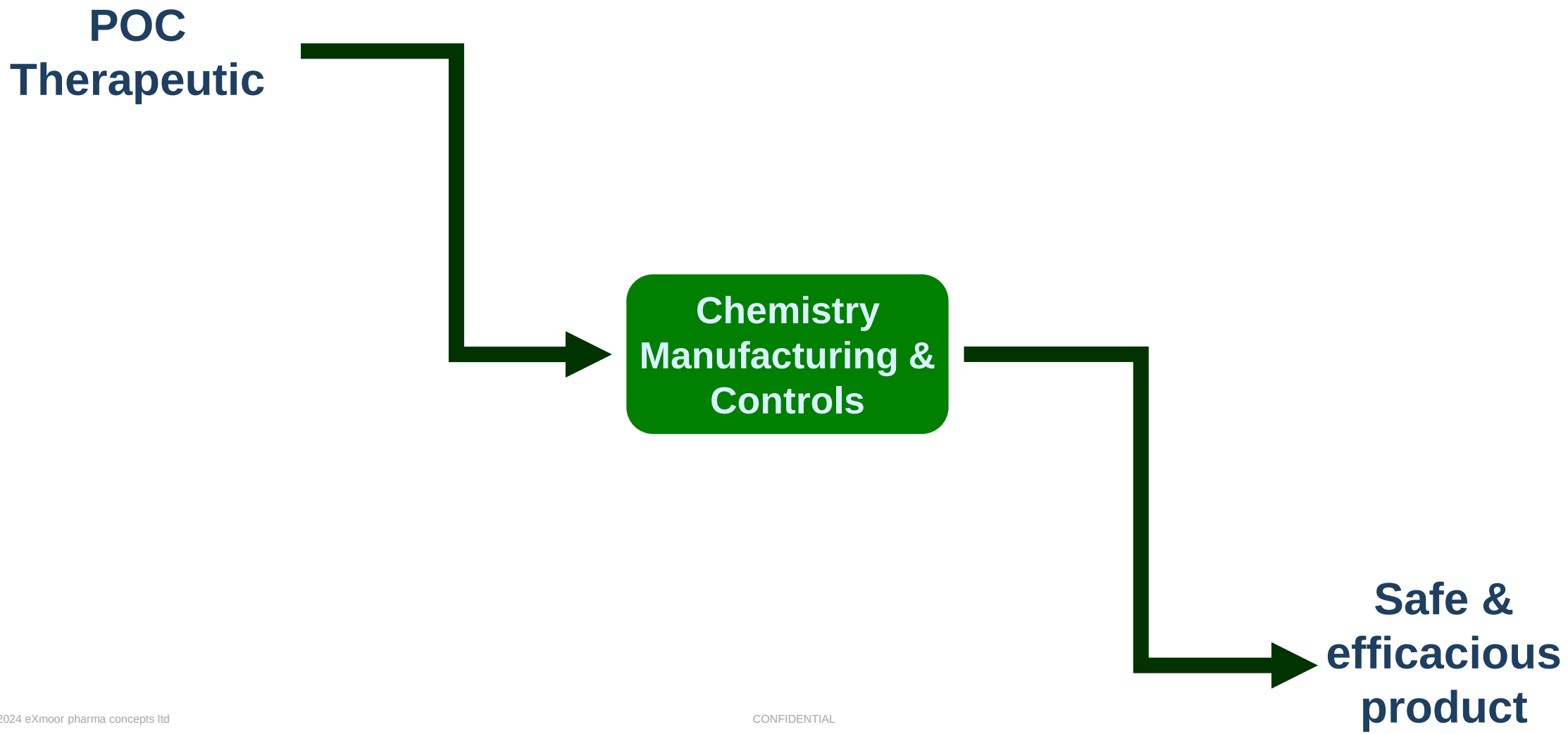
intercell
SMART VACCINES

eXmoor

Gene Therapy Expertise

- 10+ years AAV gene therapy products
- Predominantly within CMC
- Early to late stage
- Small team £ / large biotech £££
- Outsourced vs insourced
- Different AAV serotypes & disease indications
- Developing GMP manufacturing processes
- Developing analytical strategy
- Close interaction with regulators to define regulatory strategy
- Experienced many challenges!

What is CMC?



What is CMC?

POC Therapeutic

Equipment

Process Characterisation & Validation

Drug Formulation

Manufacturing Process

Raw Materials

Drug Stability

Impurity Removal

Consistent Product Quality

Chemistry Manufacturing & Controls

Container Closure

Product Specifications

Release Testing

Compliance, Quality & Safety

Labelling & Packaging

Product Characterisation

Assay Development & Validation

Safe & efficacious product

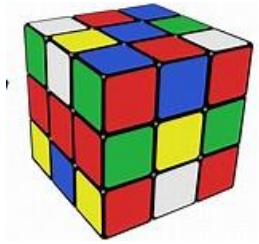
Compatibility

Comparability

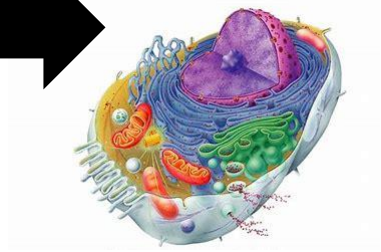
Why is Early CMC Expertise Important?

- Complex products
- No ‘one size fits all’
- Variation in AAV serotype, novel capsids, route of administration, formulation, delivery device
- Manufacturing process, scale, analytical testing, stability
- Separate considerations & development for different products
- Product understanding essential

From Concept to Clinic: Importance of QTPP



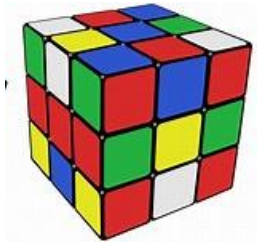
R2D



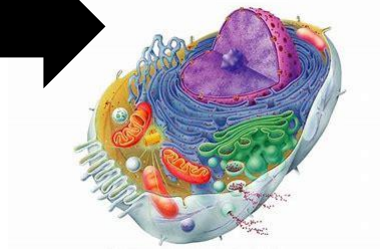
Research / Clinical / Preclinical → CMC → Supply Chain → Clinical

From Concept to Clinic: Importance of QTPP

R2D



QTPP
(Quality Target Product Profile)
A ‘design spec’ that defines critical attributes of a therapeutic



Research / Clinical / Preclinical → **CMC** → **Supply Chain** → **Clinical**

The Squeeze to IND Filing

IND Filing

Phase I Initiation

£££

???

The Squeeze to IND Filing

12-18 mth

IND Filing

Phase I Initiation

£££

The Squeeze to IND Filing

12-18 mth

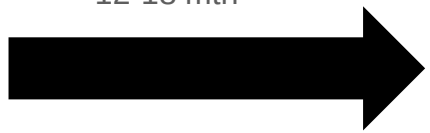
Research / Clinical / Preclinical / Supply Chain / Regulatory / Quality / CMC

Fix TPP/QTPP

- CMC activities often product specific & supporting development required
- Greater need for early cross functional expertise to ensure product understanding, informed decision making
- TPP to be fixed early to allow time for CMC activities
- **Quality by design**

The Squeeze to IND Filing

12-18 mth



Research / Clinical / Preclinical / Supply Chain / Regulatory / Quality / CMC

Fix TPP/QTPP

- Compressed timelines = hasty / poorly informed decisions
- Impact on product quality - may not be evident until later
- May require repeat of clinical and / or tox studies
- Limited development financing, low patient numbers, competition
- Potentially beneficial / life-changing product = terminated
- **Never too early to included CMC**

Why early collaboration is essential

Impact of Research Activities

- Vector Design
  - Size of payload – impact on product quality
  - Serotype selection / novel capsids – impact on yield, purification strategy
- Plasmids
  - Design – impacts yield and quality of vector
  - Cloning scars, poorly characterised stuffer sequence – quality / patient safety
- FTO – costly / prohibitory license requirements

Impact of Pre-clinical Activities on CMC

- Tox / In-life study ‘fixes’ subsequent CMC activities
  - Product concentration
  - Product quality (tox to be worse case)
  - Formulation
- **Changes later in development may require repeat of tox**

Case Study: Formulation

- 6+ months developing a process for AAV2 to overcome yield challenges
- Concurrent supporting studies to ensure chosen formulation suitable
- Material generated for tox studies
- Pre-clinical / clinical teams communicated new formulation requirement
- Additional PD / formulation studies
- New formulation caused product aggregation
- Revert to original formulation? Overcome aggregation?
- Significant program delay – avoided by appropriate QTPP

Impact of Clinical Strategy on CMC

Final product concentration, dosing strategy, delivery device, target tissue, PQA, locations of clinical trial sites

Selection of appropriate manufacturing process, analytical methods, final container, testing requirements

Case Study: Contamination of Plasmid Starting Material

Plasmid Starting Material

- Plasmids - a critical starting material for AAV manufacture
- Manufactured according to Principles of GMP
- Different grades of plasmid manufacture exist
  - Research grade
  - High Quality
  - GMP
- CMC / quality input essential to ensure correct quality & patient safety

Contamination of AAV Plasmid Starting Material

Sarepta Therapeutics Announces Clinical Hold of Phase 1/2a DMD Micro-Dystrophin Gene Therapy Trial

MDA STAFF 07/27/2018

Late on Wednesday, Sarepta Therapeutics announced that the Food and Drug Administration (FDA) has placed a clinical hold on their Phase 1/2a Duchenne Muscular Dystrophy (DMD) Micro-Dystrophin Gene Therapy Trial due to contamination of the manufacturing lot with plasmid DNA. No safety issues were reported for participants in the trial.

Sarepta has stated that they anticipate correcting the issue by manufacturing a new lot and are working with the FDA to resolve the hold. If the FDA accepts Sarepta's action plan, the company expects there to be no delay in dosing patients as originally planned by year-end 2018.

To read Sarepta's press release, click here.

CONTAMINATION DETECTED

There's nothing particular in the sequence that was troubling." The issue was essentially that the fragment was there, and shouldn't have been

Contamination of AAV Plasmid Starting Material

- Additional independent experience of contaminated plasmids, multiple products (incl HQ)
- No CMC oversight early in development
- Lengthy investigation to determine route cause
- Resynthesis of new plasmid
- Re-manufacture of new cell banks and HQ plasmid
- 3 -6 months minimum program delay
- Significant resource and £££ to correct
- Company reputation of a clinical hold
- **Potential impact on patient safety had contamination not been detected**

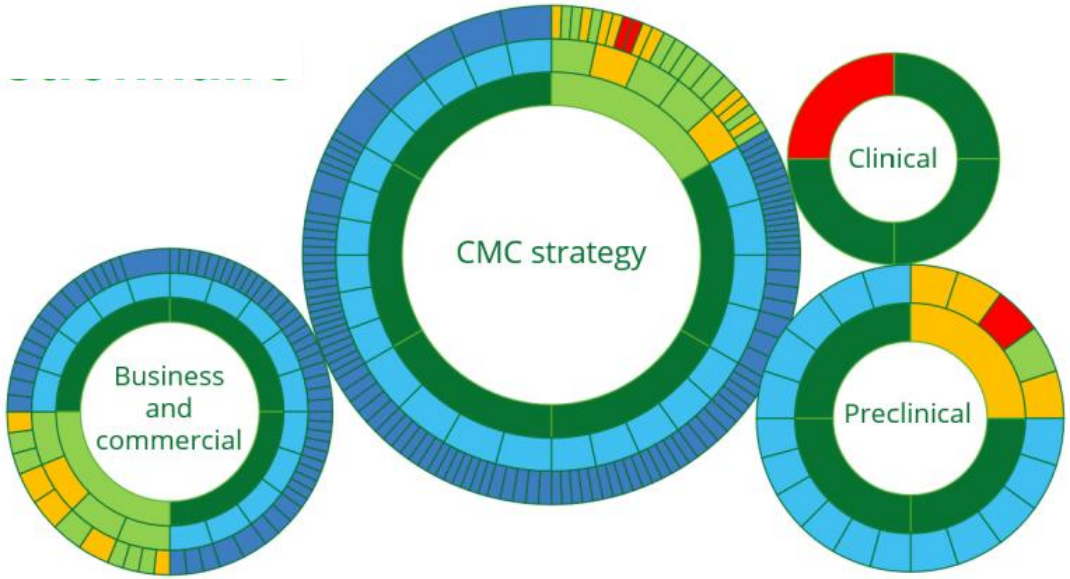
Summary

- CMC complexity, unique to individual products
- Importance of cross functional collaboration & expertise
- Never too early to involve CMC
- QbD to ensure PQ and avoid costly mistakes

Success depends on the correct design and assembly of individual pieces coming together to make a final product

Health Check Questionnaire

Bespoke strategic support at all stages of CGT product lifecycle



Business and commercial	Product quality (CMC)	Preclinical program	Clinical program
How to best set up the business, build precedent and acquire funding? What is the commercial viability of the products and is precedent built?	How to design the process so that a safe and robust product is suitable for clinical and commercial manufacturing according to scale?	What are the animal study designs minimally required to Proof-of-Concept and safety for the product?	How to get clinical data to achieve a commercially viable product accepted for reimbursement?

A CGT Phase I clinical trial is the beginning

(not the end)

Drew Hope

drew.hope@exmoorpharma.com

Drew Hope, PhD, MRSB, UK QP

Finding a cure for cancer and not curing cancer is worse than doing nothing

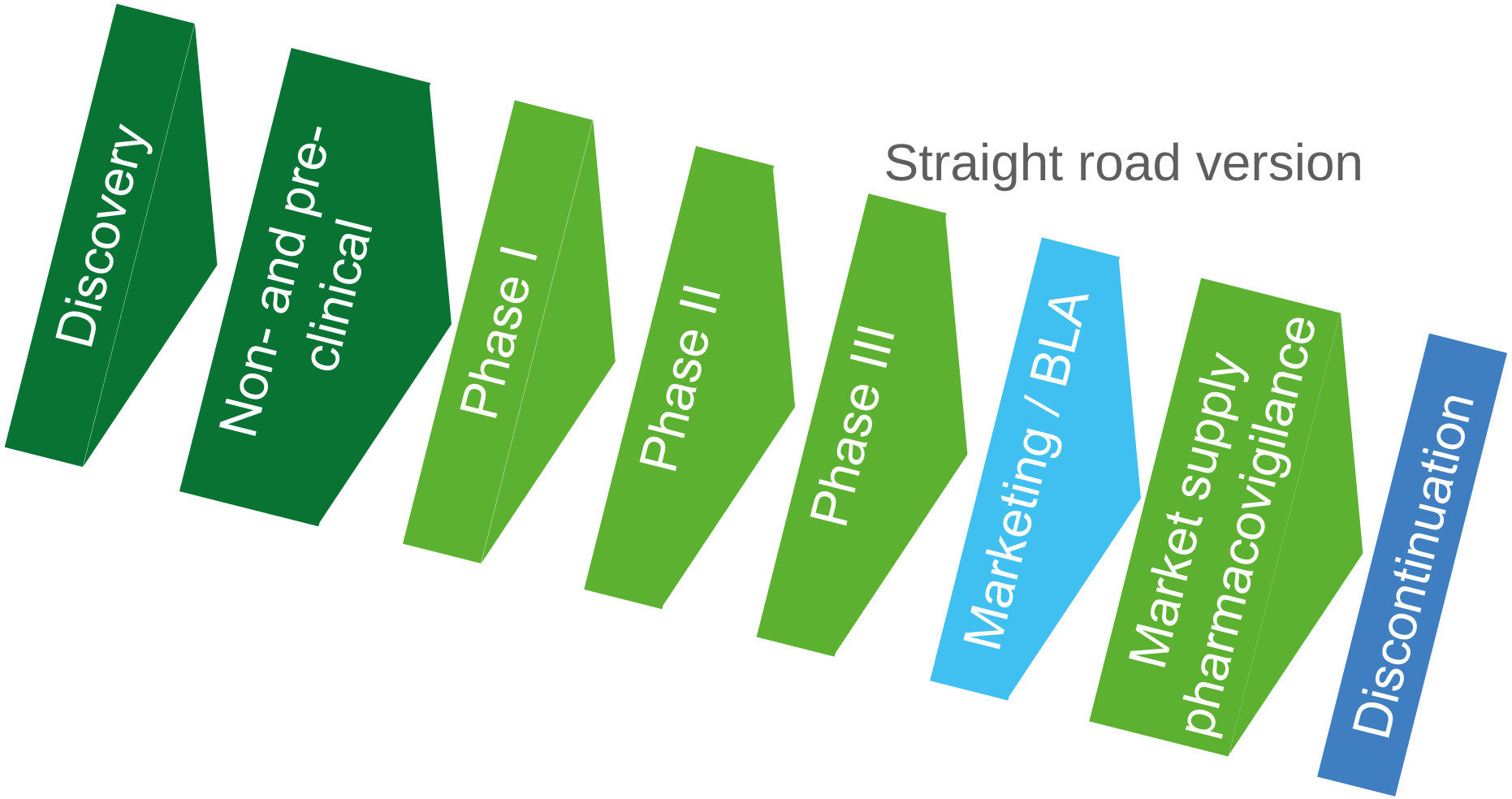
Anon.

Metaphor alert!

JOURNEY

FORESIGHT

Pharmaceutical product lifecycle



Straight road to success

Is that horizon your destination?

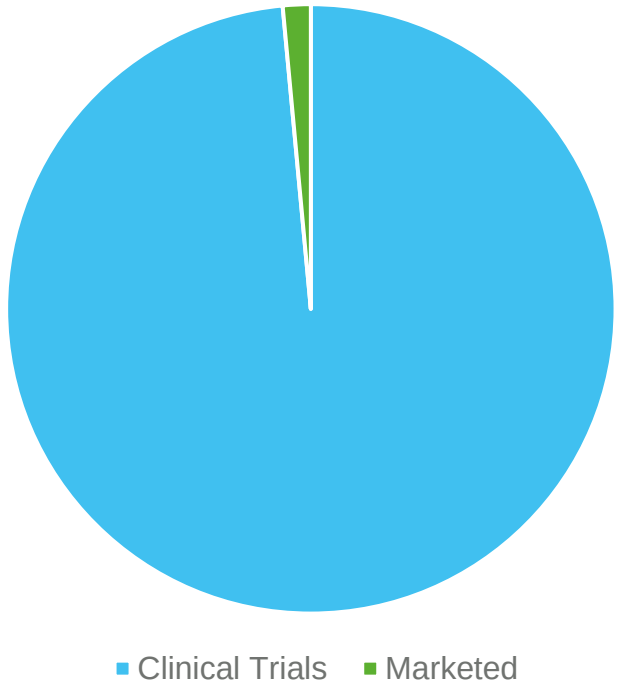
Is this the right road?

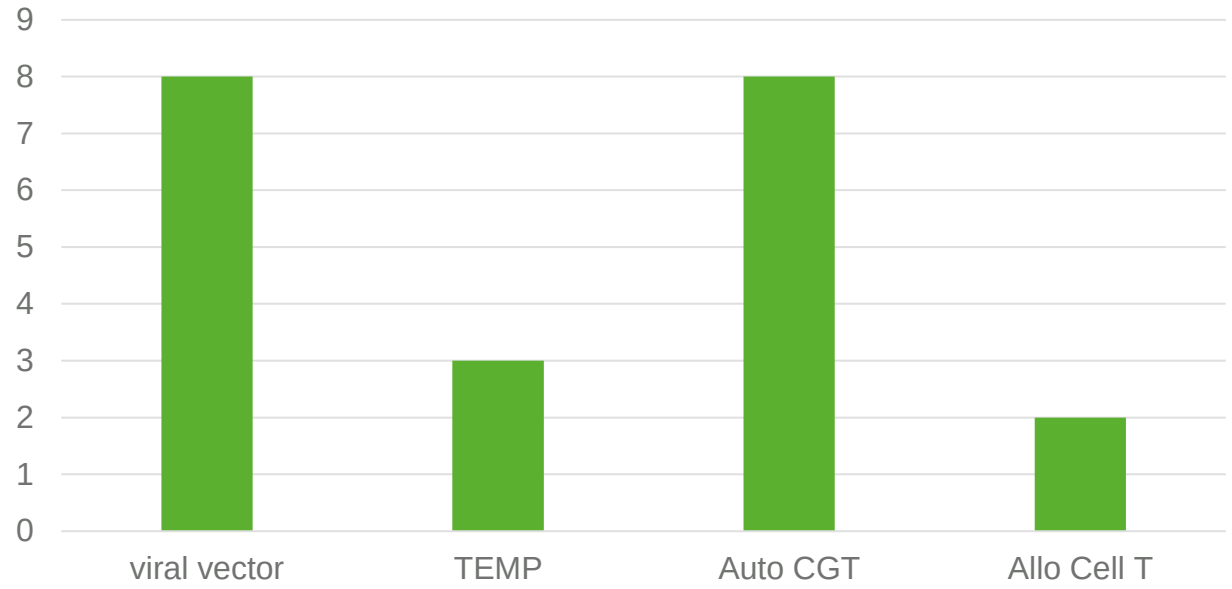
Is this heading in the right direction?

The reality

The evidence – Marketed << Trials

- 1400 active CGT trials ongoing (Clinicaltrials.gov)
- As of Sep 2023, since August 2017 (Kymriah) **21** ATMPs successfully marketed in USA





The evidence – market failure

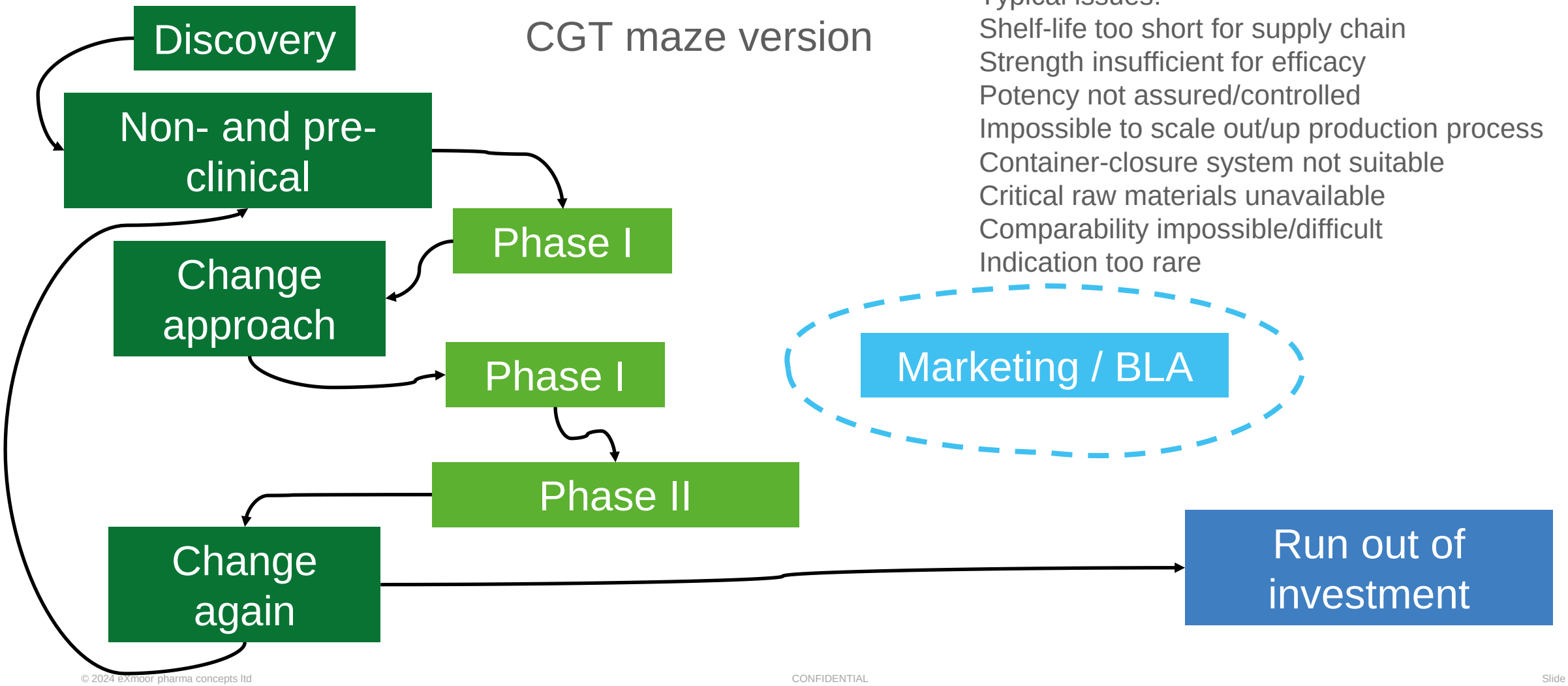
- 16 EU ATMP Marketing Authorisations since 2009, six have been withdrawn from the market

Product	Licence Holder	Approval and Withdrawal Date	Reason for MA withdrawal
ChondroCelect	TiGenix	Oct 2009 – Jul 2016	Commercial
Glybera	UniQure	Oct 2012 – Oct 2017	Access restrictions and commercial
MACI	Vericel	Jun 2013 – Sep 2014	Closure of an authorized EU manufacturing facility
Provenge	Dendreon	Sep 2013 – May 2015	Commercial
Zalmoxis	MolMed	Aug 2016 – Oct 2019	Insufficient clinical efficacy
Zynteglo	Bluebird bio	May 2019 – early 2022	Commercial

- Strimvelis, GSK EU MA approved in 2016, sold to Orchard in 2017, five sales since. Future uncertain

If value < cost of supply → uneconomic

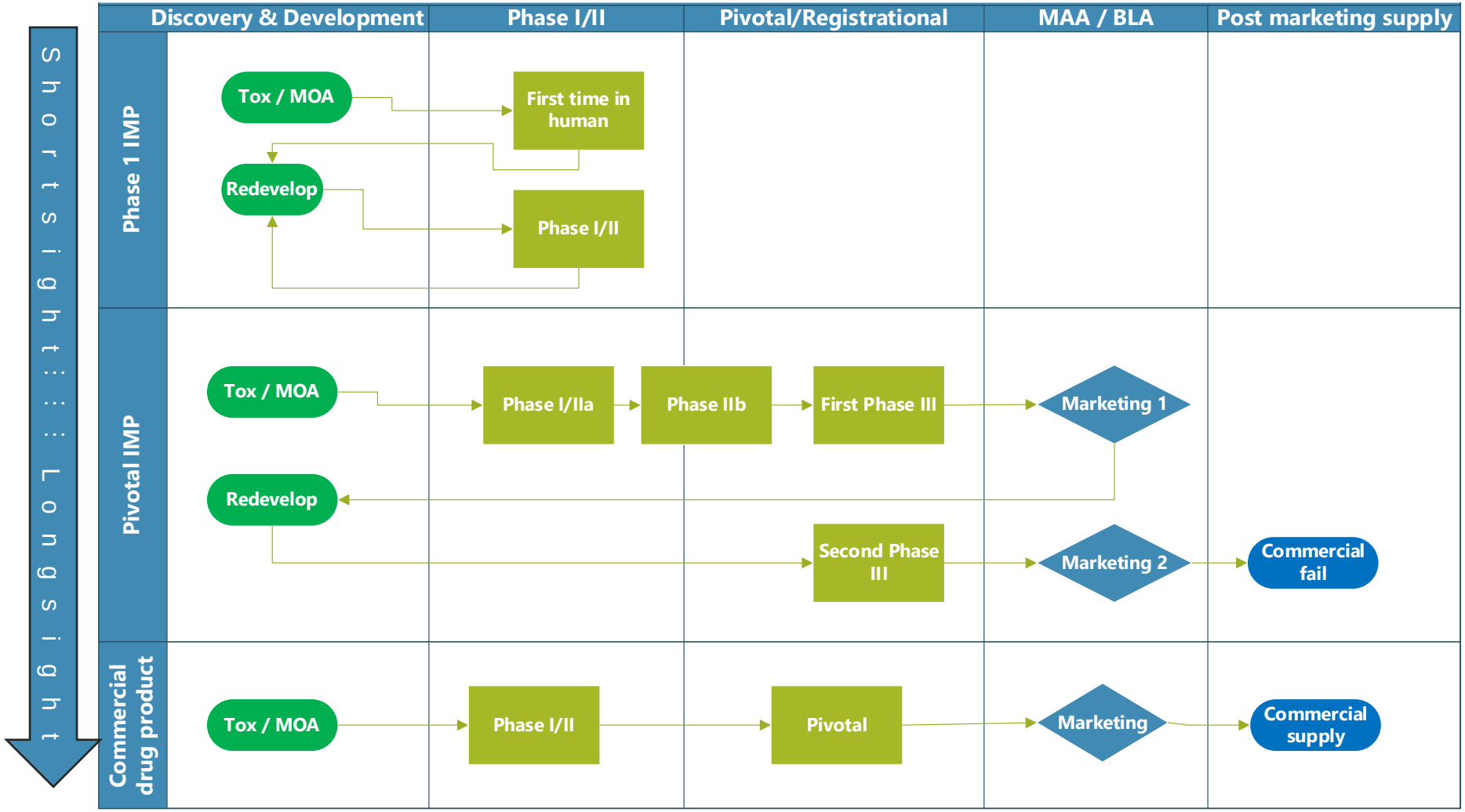
Pharmaceutical development lifecycle



CGT maze version

Typical issues:
Shelf-life too short for supply chain
Strength insufficient for efficacy
Potency not assured/controlled
Impossible to scale out/up production process
Container-closure system not suitable
Critical raw materials unavailable
Comparability impossible/difficult
Indication too rare

Foresight



What causes short-sightedness?

One inflection point at a time, trial→funding (repeat)

Founded by passionate scientists lacking perspective

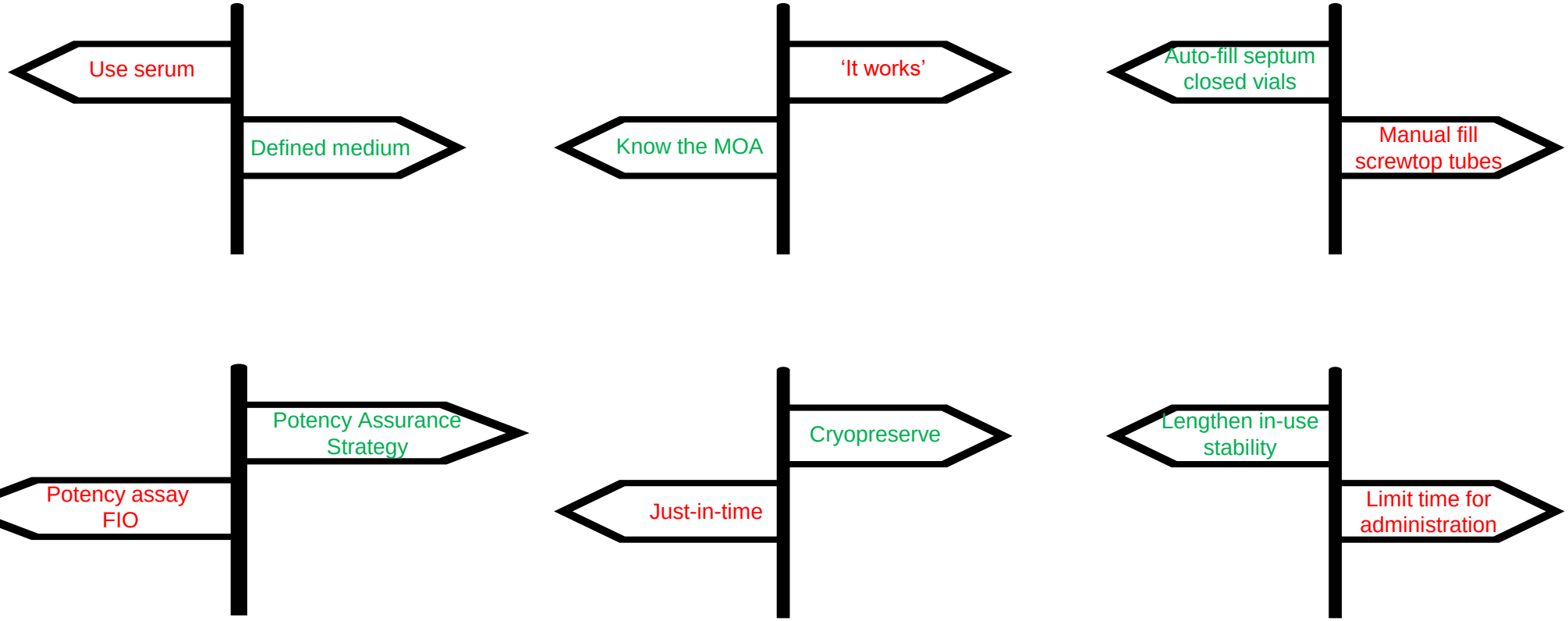
VC funding stage-gated

Focus on clinical product, blurred view of commercial product

No early funding for late-stage preparation

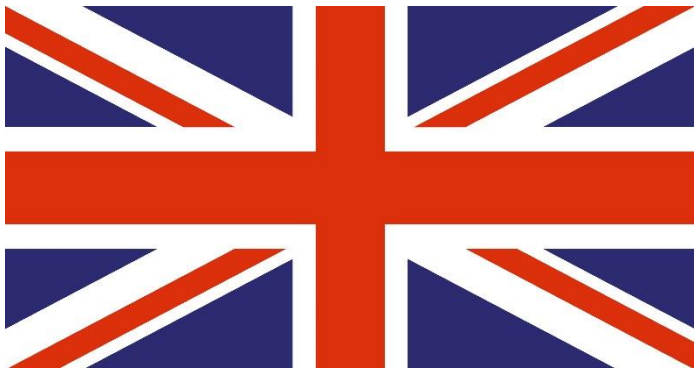
Foresight: Make the correct turns

- Know your Quality Target Product Profile
- General rule: quick-route to Phase I is in the wrong direction



Foresight: Know your regulations & territories

- CGT Cell line development cannot take place in an R&D laboratory (GMP Principles): UK & USA more flexible than EU
- Cell-donor serology with approved test kits (EU – validated; USA CLIA approved)
- USA cell-donor and BSE exposure risk unacceptable (lived in EU)
- Research Use Only materials only if no alternative
- IND GMP not inspected USA FDA (audit!)

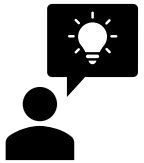


Foresight: Build your CMC data

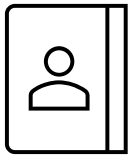
- CTA CMC supports MAA
- Material assessments of suitability – TSE, toxicity, particles, SAL
- Evidence of container integrity & leachables/extractables, particles
- Put down GMP lots for stability at Phase I for MAA/BLA

Foresight: Multidisciplinary approach

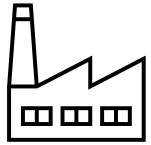
- Science & Medicine
  - Ideas
  - Product & Trail design



- Regulatory
  - Trial and Marketing planning
  - Fast track, Orphan Indication



- Technology
  - Closed aseptic process
  - Automation and scale



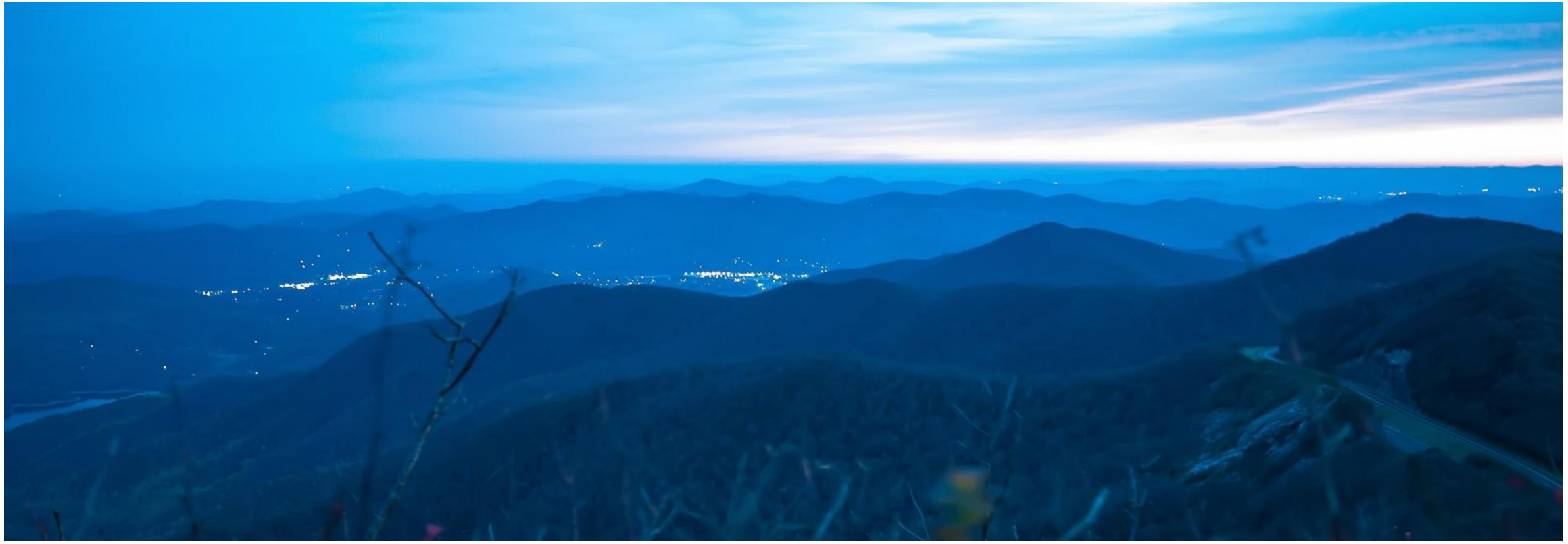
- Quality
  - Materials and Validation
  - Consistent, safe, potent

Stay on the direct route

GOOD

BAD

Recognise the horizons and destination



Strategize and fundraise wisely

1

Build a business case on commercial success

2

Build CMC data during the clinical phases

3

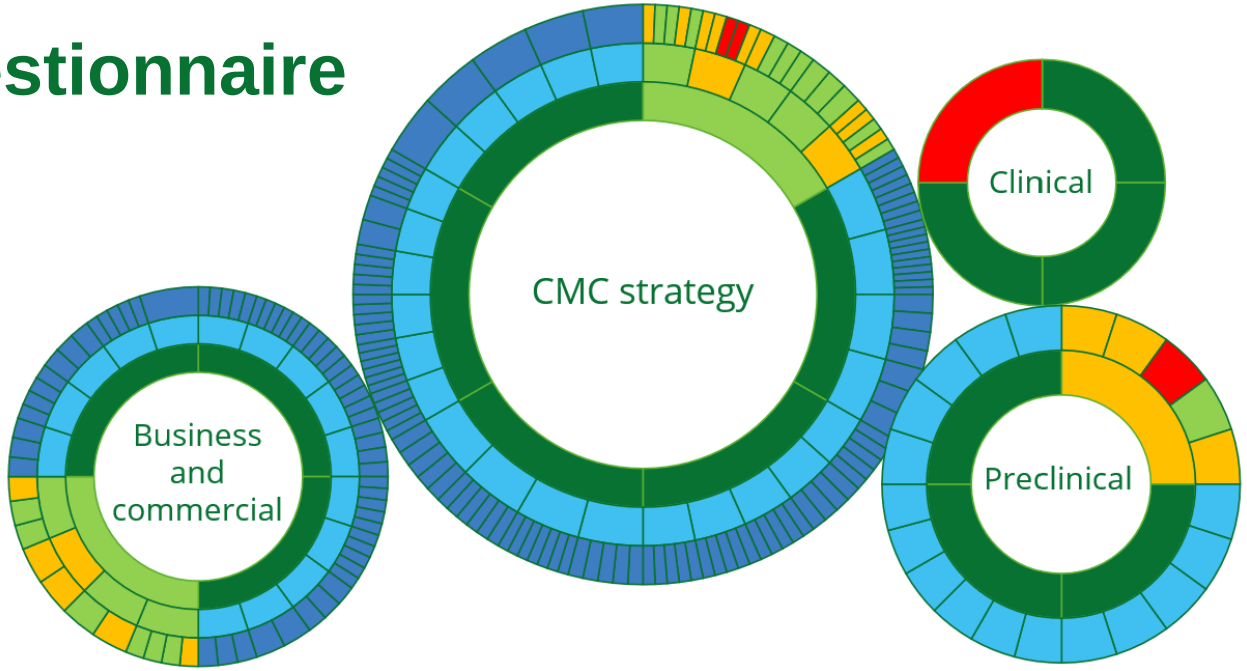
Avoid dead-end or return-to-start development

Thank you!
Any questions?

Structured Portfolio Assessment

Health Check Questionnaire

SCAN ME



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