# Lentiviral vector CMC considerations for clinical and commercial use

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# The LentiVector® Platform Company

## A leader in gene and cell therapy

# Oxford Biomedica – an overview

**>20 years as a specialist in lentiviral vectors**

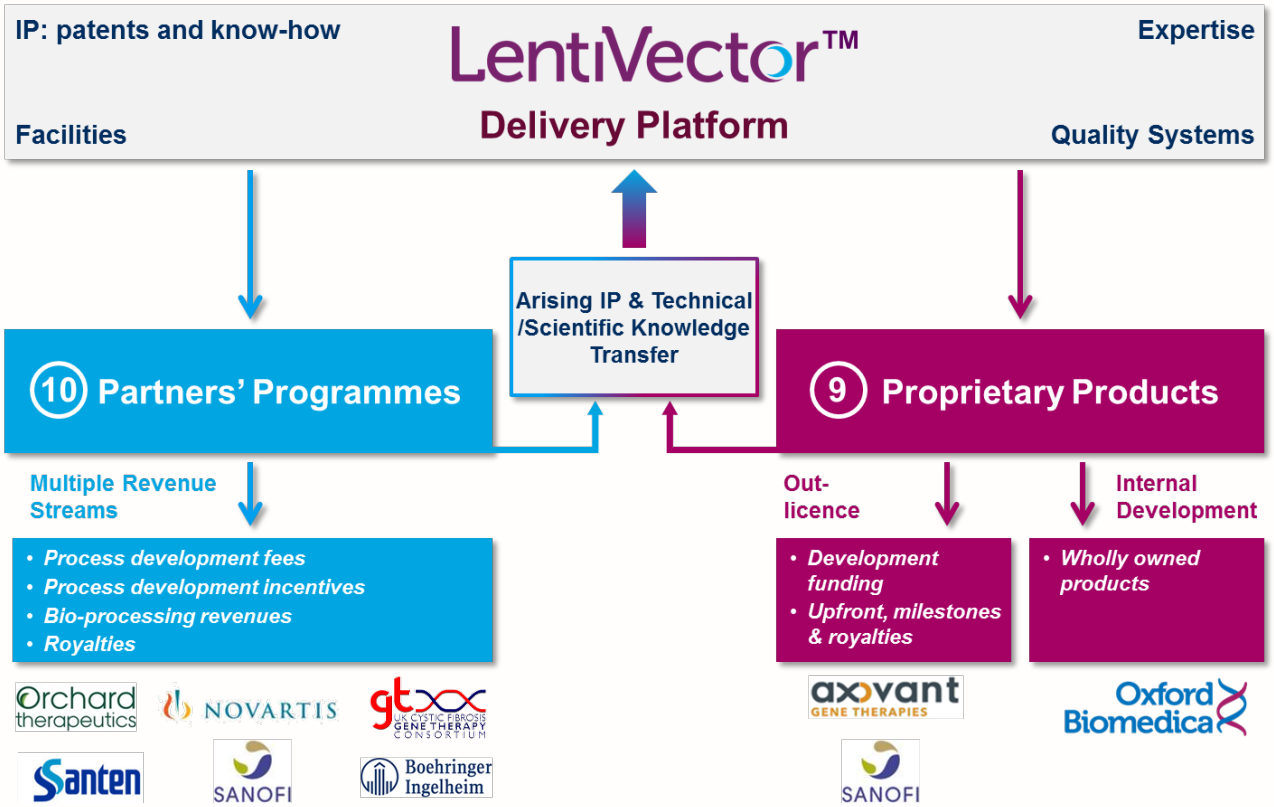
- **1st** world-wide to administer lentiviral vector gene therapy *in vivo* (both brain and eye)
- **1st** approved advanced therapy in the US using LentiVector® enabled technology, [Novartis's KYMRIAH® (tisagenlecleucel)]
- **1st** commercial supplier of lentiviral vectors, post CAR-T approval
- **100's** patients treated by Oxford BioMedica or by its partners

**Founded** in 1996

**Mission** – Delivering life-changing gene therapies to patients

**Employees** – >480 staff

**Core LentiVector® technology platform** based on lentiviral vector *in vivo* and *ex vivo* gene delivery system



# Oxford Biomedica - facilities

## Current

## Future

**WINDRUSH COURT**

State of the art laboratories

**HARROW HOUSE & CHANCERY GATE**

FDA and MHRA approved facilities

**YARNTON**

FDA & MHRA approved GMP manufacturing facility

**WINDRUSH INNOVATION CENTRE (2019)**

Non GMP research laboratories

**OxBox (2020)**

4x cGMP production & 2x filling facilities under construction

**Current 110,000 sq ft + 32,000 sq ft 84,000 sq ft***

* Initial phase 45,000 sq ft

# Lentiviral vectors are one of the most common viral vectors

- Lentivirus (LV), a member of the retrovirus family
- Enveloped
- Size ~80-120 nm diameter
- Transduces non-dividing and dividing cells
- Clinical success *in-vivo* and *ex-vivo*
- Can be pseudotyped to broaden their tropism [vesicular stomatis virus (VSV-G) envelope]
- Reduced insertional mutagenesis potential

**Lentiviral vectors vs. AAV vectors**

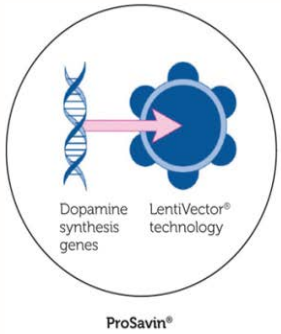
| | Lentiviral Vectors | AAV Vectors |
|---|---|---|
| • Efficient *in vivo* gene delivery | ✓✓✓ | ✓✓✓ |
| • Safe and well tolerated | ✓✓✓ | ✓✓✓ |
| • Large therapeutic payload | ✓✓✓ | ✗ |
| • No pre-existing immunity | ✓✓✓ | ✗ |
| • Permanent modification of dividing cells | ✓✓✓ | ✗ |
| • IP protection | ✓✓ | ✓ |
| • Ease of manufacture | ✓ | ✓✓ |

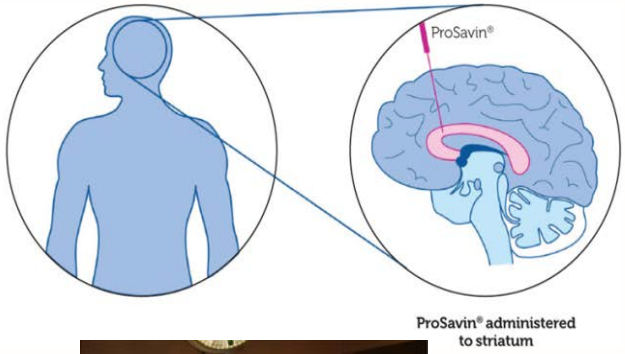
*Source*: https://www.uvm.edu/sites/default/files/UVMRisk-Management-and-Safety/lentiviral_vectors_fact_sheet.pdf

# Advanced therapy case examples: Potential for “one off” treatment

## Parkinson’s disease

e.g. OXB-102 (AXO-Lenti-PD)

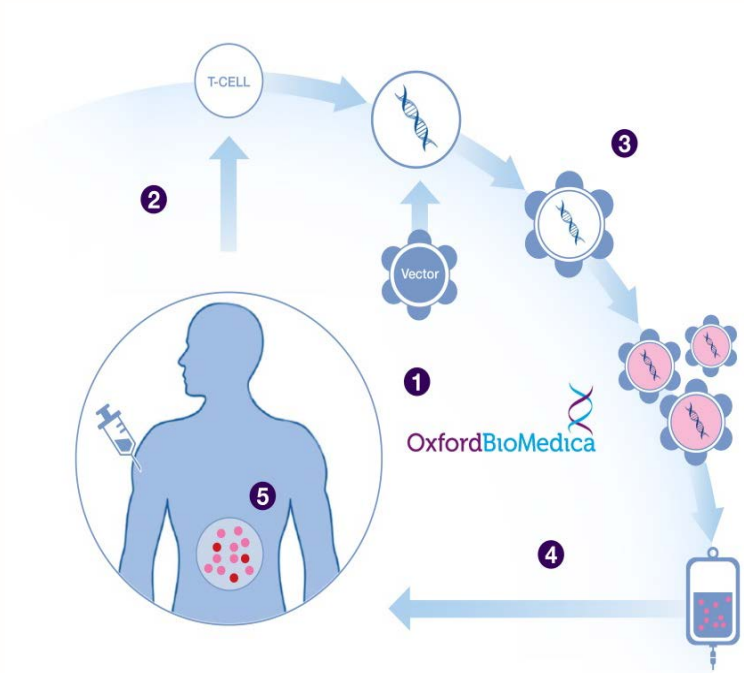



- Direct *in vivo* administration to the brain through surgery
- Encouraging signs of efficacy from ProSavin® clinical trial in 15 patients; >7 years of safety data – no related Serious Adverse Events (SAEs)
- OXB-102 - increased potency

## Adoptive T-cell immunotherapy

e.g. KYMRIAH® (Novartis)




- *Ex vivo* autologous cell therapy
- Multiple diseases with CD19 target
- Initial Novartis target is paediatric ALL
- Manufacturing & logistics challenge for vector and cells

# OXB LentiVector® platform – safety features


| Benefit(s) | Feature |
|---|---|
| Safety—absence of replication-competent lentivirus (RCL)<br><br>Yield—efficient vector production | ***3rd Generation*** is geared towards clinical applications and is considered the safest method.<br>~10% (861 bp) of wild type genome |
| | Vector components segregated on 4 separate plasmids *(3 for EIAV as Rev-independent)* |
| | Open Reading Frames (ORFs) of nonessential accessory genes and Tat removed |
| | Codon-optimized Gag/Pol |
| | Self-inactivating long terminal repeat sequence (SIN LTR) to ensure transcription in the absence of Tat. |
| | VSV-G - Envelope protein required for cellular docking, membrane fusion and transduction |
| | Rev – Accessory protein required for transcription and nuclear export of full genomic RNA |
| High expression | Flexible promoter sequence – product specific |

Vesicular stomatitis virus G glycoprotein (VSV-G)

# Proprietary platform innovation/improved process understanding

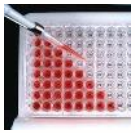
**Maximising data integration and analysis**

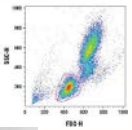
Microsoft

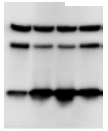
Synthace

**AI and machine learning**

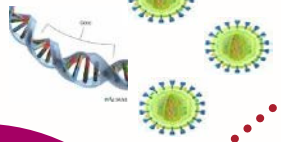
**Patient sample analysis**





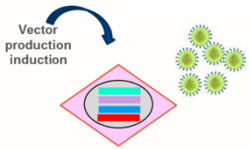


**Next gen. vectors: Regulation, targeting**

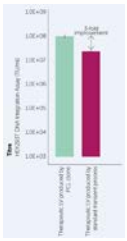


**Cell and vector engineering to increase bioprocessing yield**

LentiStable™

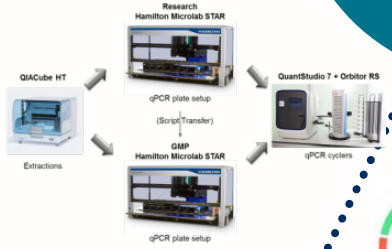



**Packaging and producer cell lines**





**USP and DSP**




**Automation**

**Proteomics/ transcriptomics**

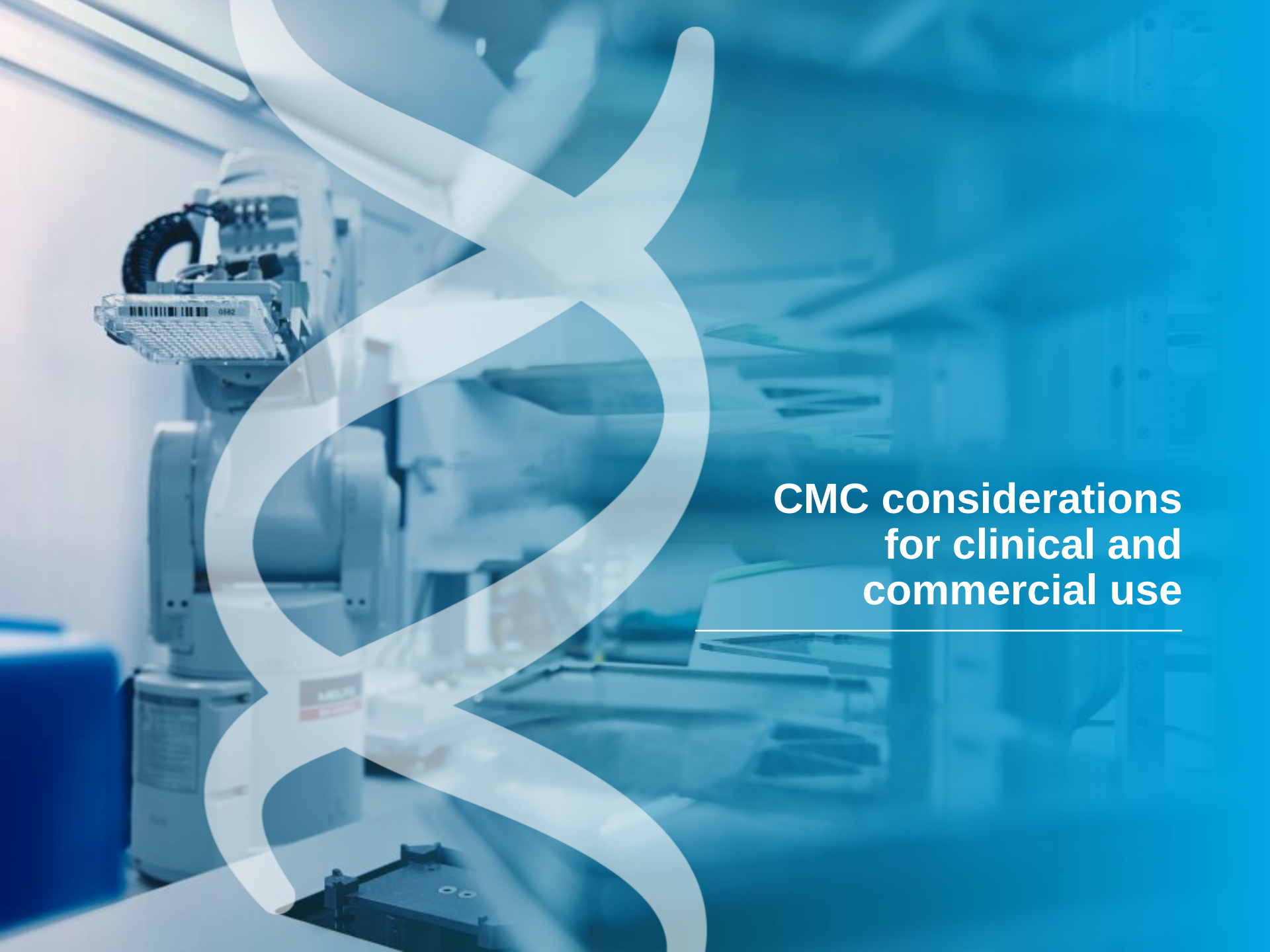
TRiPSystem™

SecNuc™

**Analytical dev. to characterise vectors (purity) and achieve rapid batch release**

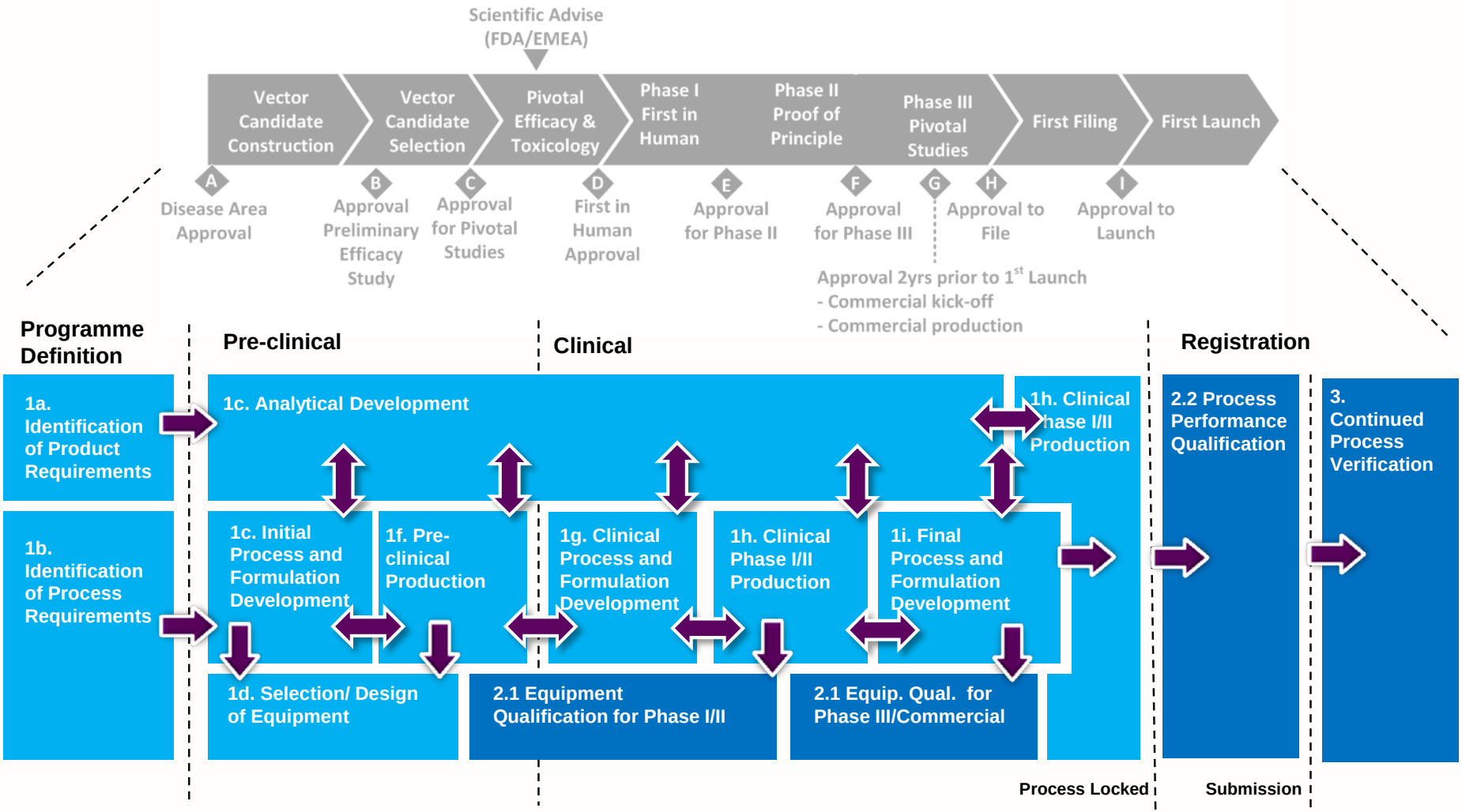
**Large scale bioprocessing: Increase yield and improve purity**

Oxford Biomedica



# CMC considerations for clinical and commercial use

# Product development lifecycle



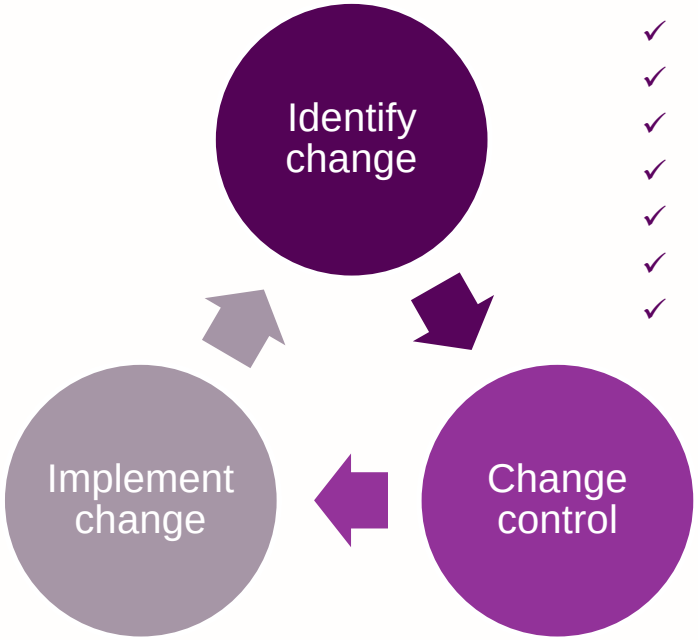

Processes, product characteristics, and product testing must be defined in order to ensure that the product is safe, effective and consistent between batches = CMC activities

# CMC critical elements

- We build QUALITY into the product by assuring that the product is safe, effective and meets the appropriate standards consistently
- The ability to consistently produce the same vector product to meet the same specifications time after time is answered by providing answers to:
  - How and where is the product being made?
  - How are raw materials tested and monitored?
  - What control procedures are in place to assure product consistency and quality?
  - Are quality attributes adequately identified and characterised for the product?
  - Are test methods used to monitor product quality  appropriate?
  - Does the product maintain its quality and stability after it is made?
  - What are the sources of variability in the process?

*Source*: Adapted from Cormier, E.P. (2014), www.slideserve.com/senona/elizabeth-pollina-cormier-ph-d-review-chemist-division-of-manufacturing-technologies

# Drivers for change are inevitable throughout product lifecycle…



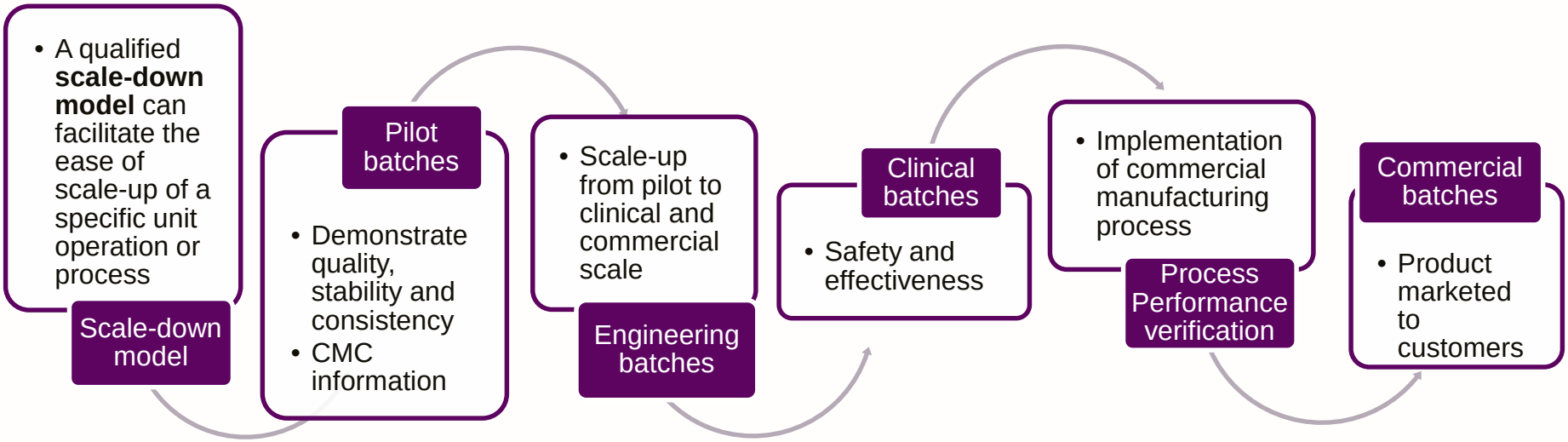

- ✓ Regulatory, post approval commitments
- ✓ Raw material specs/suppliers
- ✓ Method of manufacture, scale and controls
- ✓ Evolving platform and technology
- ✓ New manufacturing site, manufacturing flexibility
- ✓ Analytical improvements
- ✓ New reference standard, low inventory
- ✓ Specifications
- ✓ Supply/demand
- ✓ Reduce COGM

- ✓ Impact risk assessment
- ✓ Work up in PD lab
- ✓ Tech transfer from lab to GMP and/or CMO (inter-site and intra-site)
- ✓ Analytical method validation
- ✓ Control strategy refinement
- ✓ Process capability assessment
- ✓ Comparability studies
- ✓ Equipment qualification (EQ)
- ✓ Process performance qualification (PPQ)

- ✓ Amendments to SOPs/BMR/labels
- ✓ Amendments to IND/IMPD
- ✓ Variation to MAA/BLA
- ✓ Control strategy refinement
- ✓ Changes to CPV monitoring plans
- ✓ Effectiveness check

*Source*: Adapted from Markwick, L. (2019) Orchard Therapeutics, AMC 18th Technical Meeting Success Stories in Advanced Therapy Manufacturing

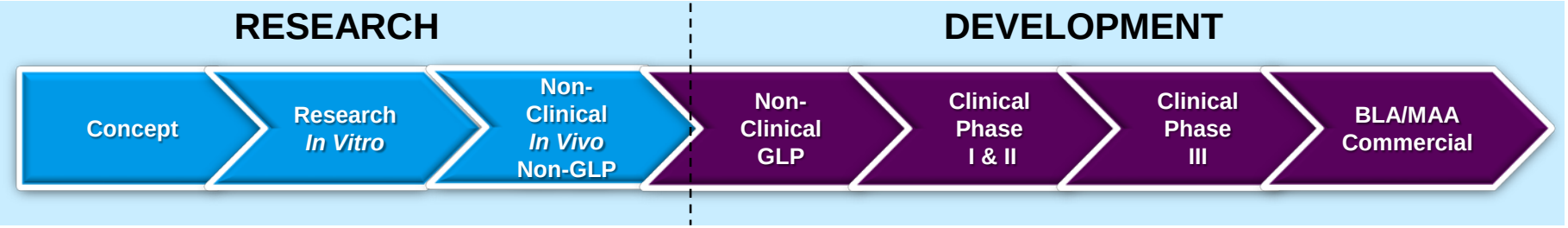
# Linking clinical batches to commercial batches




CMC helps maintain product safety, quality and efficacy during clinical development

# Manufacturing strategy considerations

## Potential impact of indication and clinical development phase on production capacity requirements

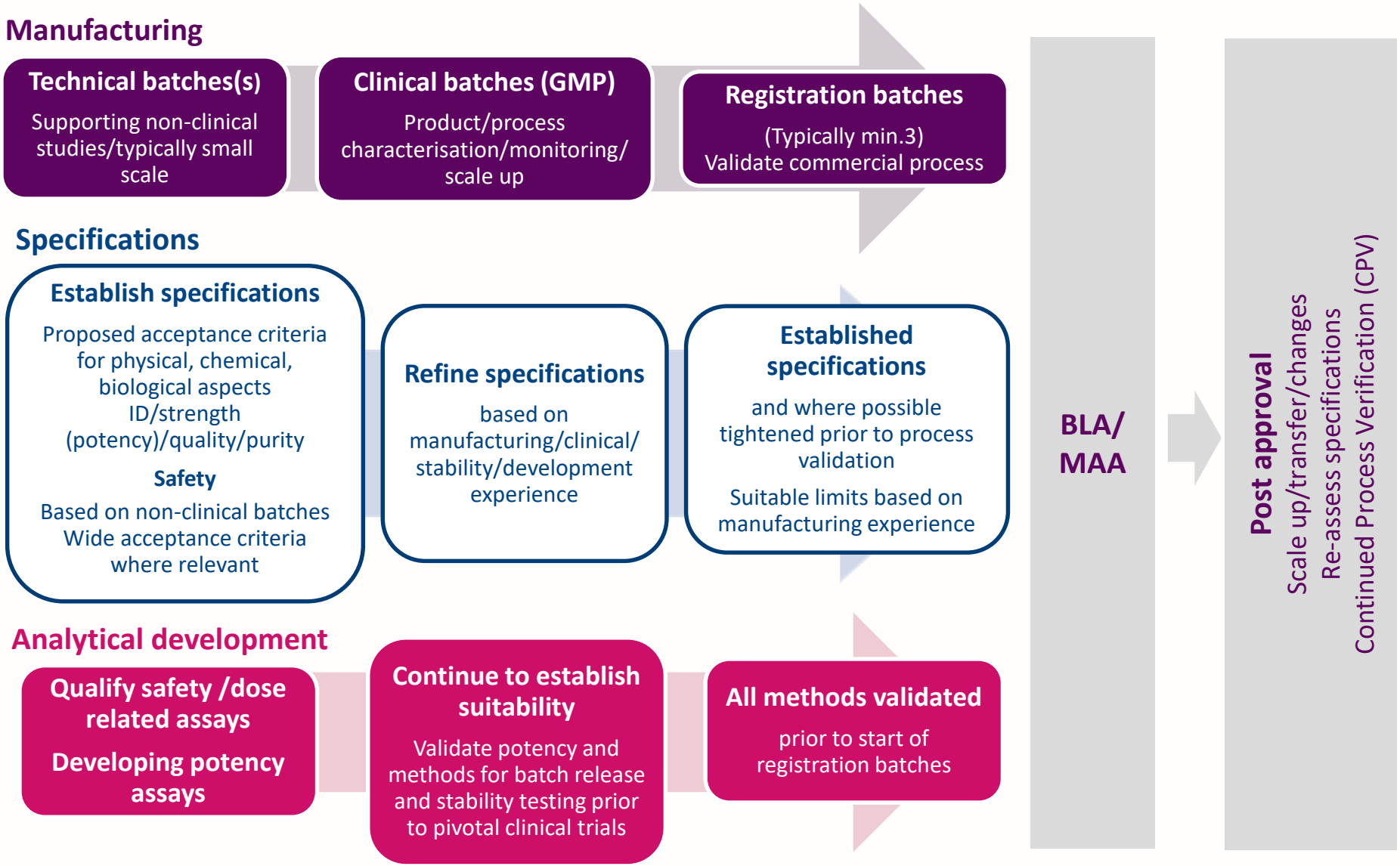



| Phase of clinical development | 'Low demand' indication | | 'High demand' indication | |
|---|---|---|---|---|
| | No. of subjects | Volume (L) | No. of subjects | Volume (L) |
| Preclinical | 12 primates<br>30-60 rodents | 10-20L | 12 primates<br>30-60 rodents | 10-20L |
| Phase I/II | 10 -15 patients | 100L | 10-20 | 100-200L |
| Phase II | 20 | 200L | 50-100 | 500-1000L |
| Phase III | 50 | 500L | 100-500 | 1000L-5000L |
| BLA/MAA Commercial | 100's | ≥1000L | >1000's | >10,000L |

- Manufacturing strategies are influenced by indication and development phase
- Major driver for process design/development/improvements in upstream volumetric productivity, recovery/downstream purification, sterile manufacturing, % step recoveries etc.

Assumptions: 1L gives approximately one dose to account process losses, testing etc.
USP yield improvements targeted to realise benefits in COGS and access to high demand indications

# Graded nature of CMC information during clinical development



# Changes to manufacturing process

## Shift from 2D planar technologies to 3D suspension culture

### Adherent + 1st Gen DSP


- Serum-containing
- 1L - <100L total harvest
- Manual unit operations
- Batch to batch variation
- Scale-up limited
- Low DSP recovery
- **“1’s to 20’s” w.r.t. lentivirus ‘dose’ per batch**
- **Cost per dose v.high**

### Suspension + 2nd Gen DSP

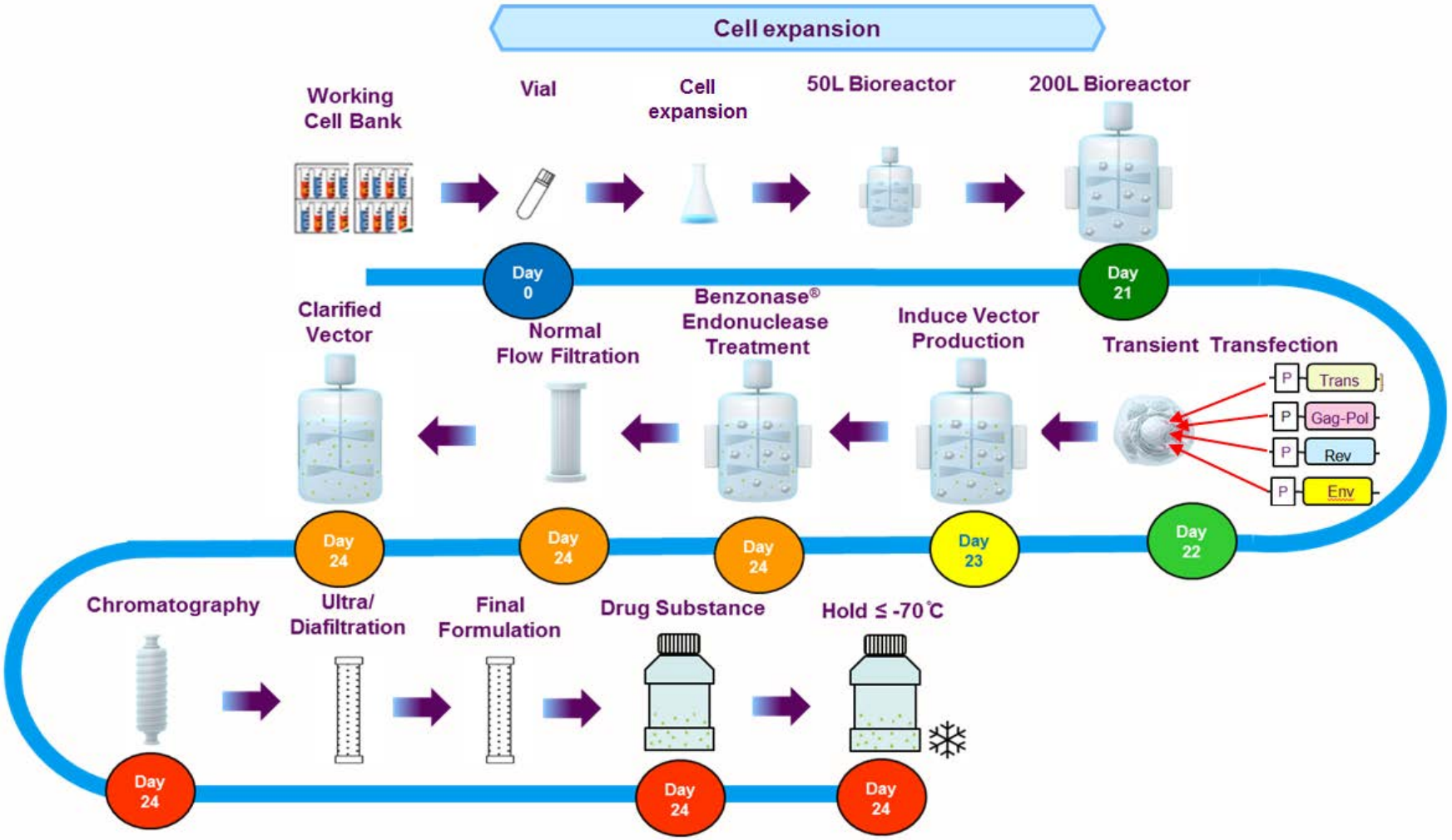


- Serum-free
- 50-2,000L harvests: scale to match vector market needs
- Closed processing – automation of unit operations
- Robust and consistent performance improved DSP recovery/quality
- **“100s-1000s” of doses per batch**
- **Cost per dose reduced**

*Source*: Adapted from Kara, B. (2017) Lentiviral Vector Manufacturing – Challenges and Solutions, AMC, Cardiff

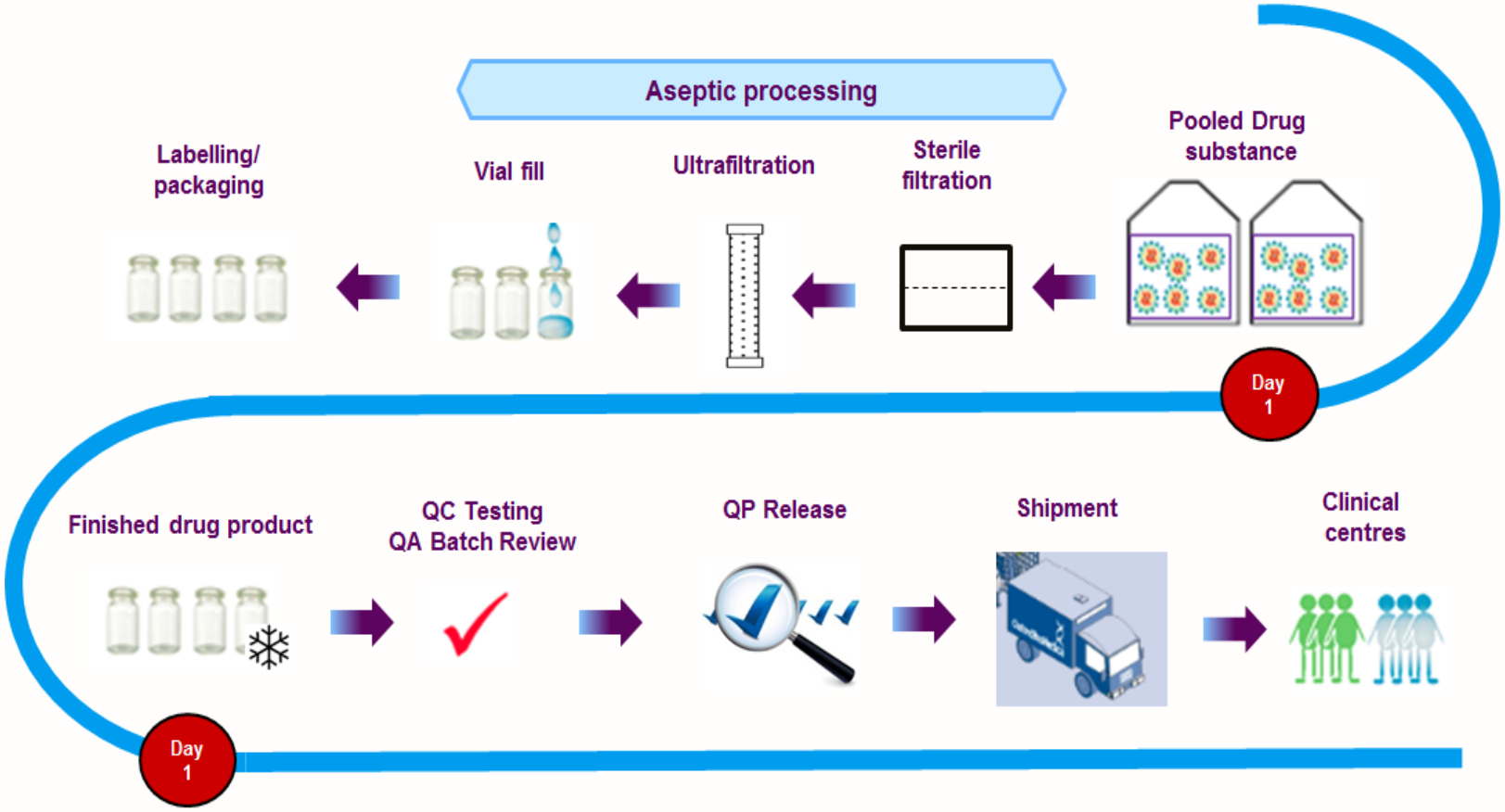
# Schematic of serum-free, suspension process (200L scale)

## GMP manufacturing process for clinical and commercial supply



# Sterile manufacturing process (aseptic fill & finish)

## GMP manufacturing process for clinical and commercial supply

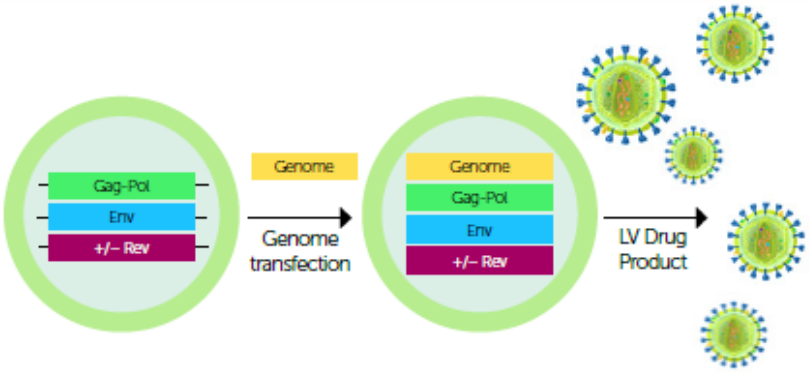



1. Vial to FDP: ~2000-fold volume concentration factor
2. Final volume determined by number of Ultra-diafiltered Drug Substance (UDFDS) lots and test data

# Changes to manufacturing process

LentiStable™

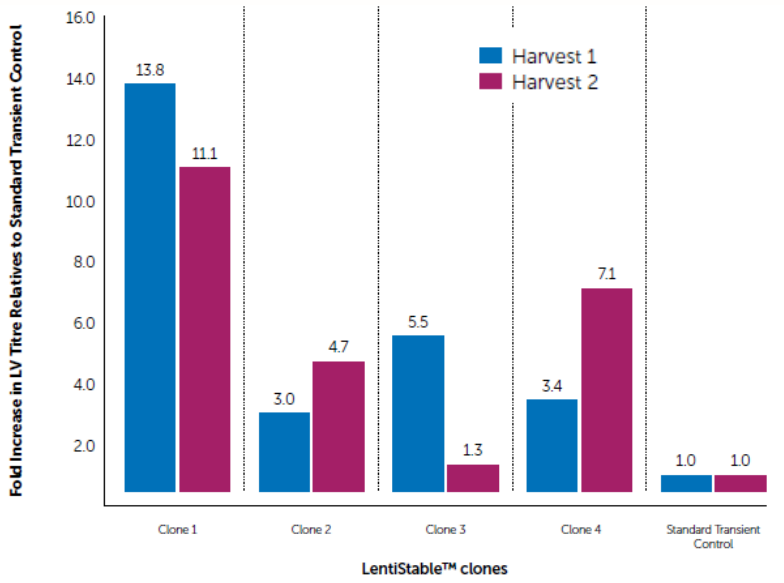
## Shift to GMP stable producer cell lines




Cassius™ robot for cell screening

### Advantages of LentiStable™

- High performing: Generates stable clones with high titres
- Scalable: Produces large amounts of vector over extended periods
- Reproducible: Eliminates variability of transient transfection
- Fast: Automation has drastically increased throughput to identify best clones
- Economical: Saves cost of plasmids and transfection reagents
- Ready-to-go: GMP compliant cell lines available

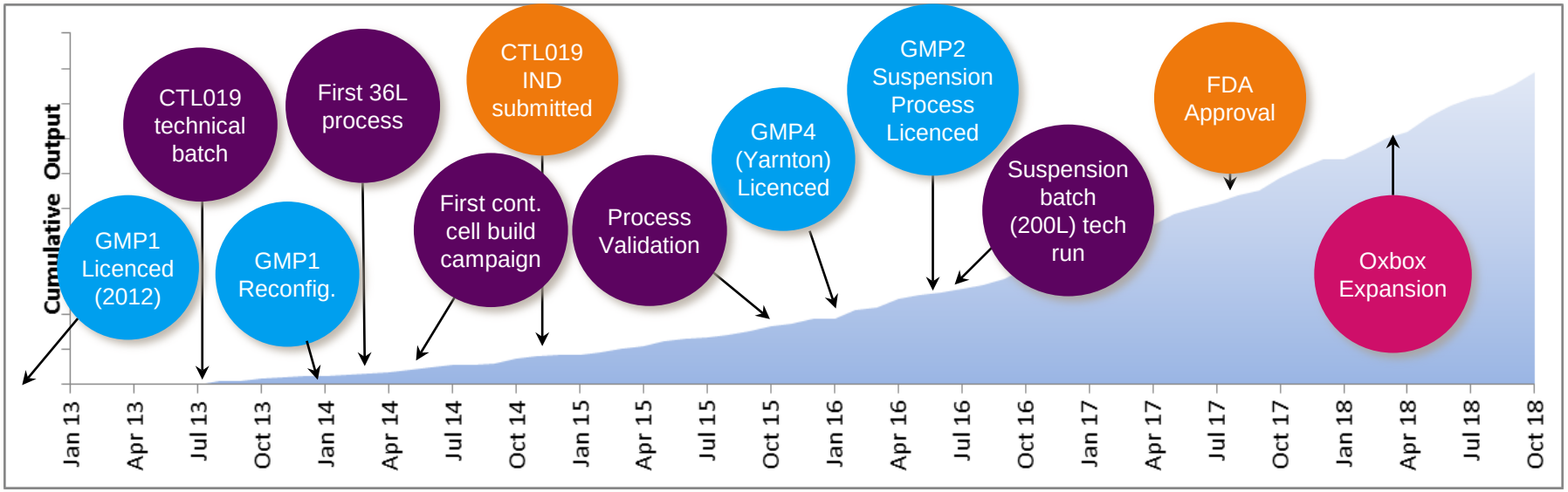



Screening of LentiStable™ clones for vector production

# Changes to manufacturing site

LentiVector Enabled

## Maintaining clinical and commercial supply



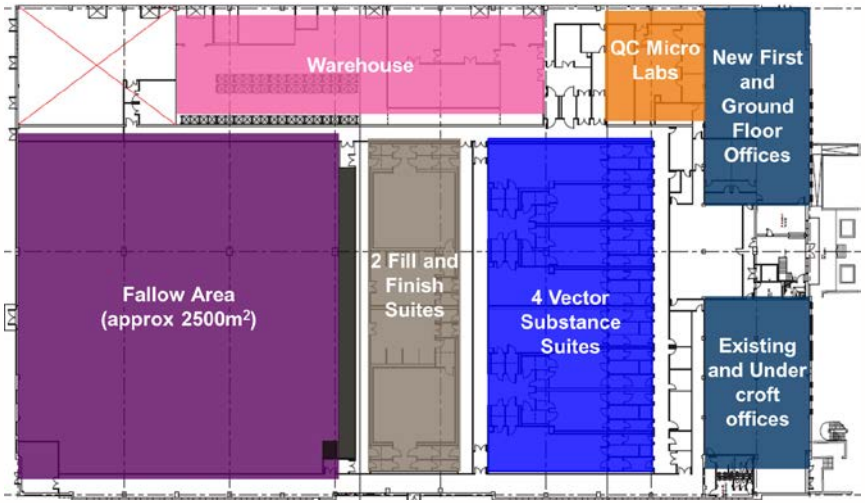

- Need to continue to develop and evolve technologies and CMC strategies to support anticipated level of patient demand
- Within the past 6 years:
  - FDA approval for CLT019 - Worlds first commercial LV manufacturer
  - Implemented the next generation serum-free suspension process
  - Increased yearly output 9-fold
  - Developed a network of CMO's/CTO's to improve manufacturing flexibility
  - Announced further expansion (OxBox) – doubling of capacity including in-house fill & finish

# Changes to manufacturing site

## Capacity expansion and increased manufacturing flexibility

New OxBox facility - approx. 84,000 sq ft (7,803 sq m)

- Phase I - 45,000 sq ft  (4,200 sq m)
- 4 x VS suites, 2 x  Fill & Finish suites
- Offices, GMP warehousing and QC micro labs
- Planned operational start date - 2020
- Phase II - future expansion (Fallow Area)




# Changes to the analytics

## Typical LV quality attributes used in clinical/commercial processes

- Comprehensive suite of in-house assays have been developed over time
- Includes full lentiviral vector characterisation, quality control and stability testing,

**Platform assays**

- pH
- Residual sodium butyrate
- Endotoxin
- Bioburden
- Sterility
- Mycoplasma
- Micro BCA Total Protein
- HCP ELISA
- Residual Benzonase
- PicoGreen Residual Total DNA
- 18S Residual Host Cell DNA
- KanR Residual Plasmid DNA
- VSV-G Residual Plasmid DNA
- SV40 Residual Host Cell DNA

**Lentiviral specific-assays**

- Vector titre
- FACS
- RNA copy number
- p24 ELISA
- RCL
- RCLCC

**Product specific-assays**

- Potency
- Vector ID

**In development**

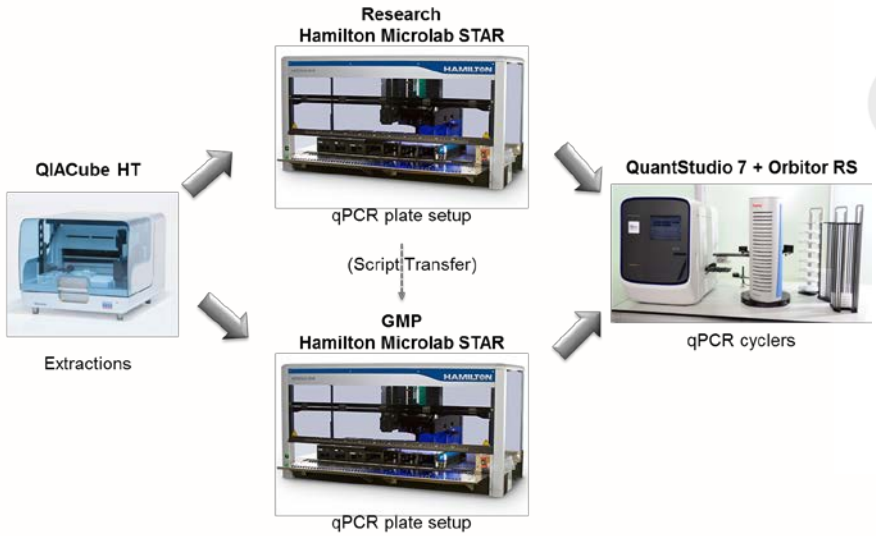
- Mass spectrometry
- Next-gen sequencing (NGS)
- HPLC based vector quantification

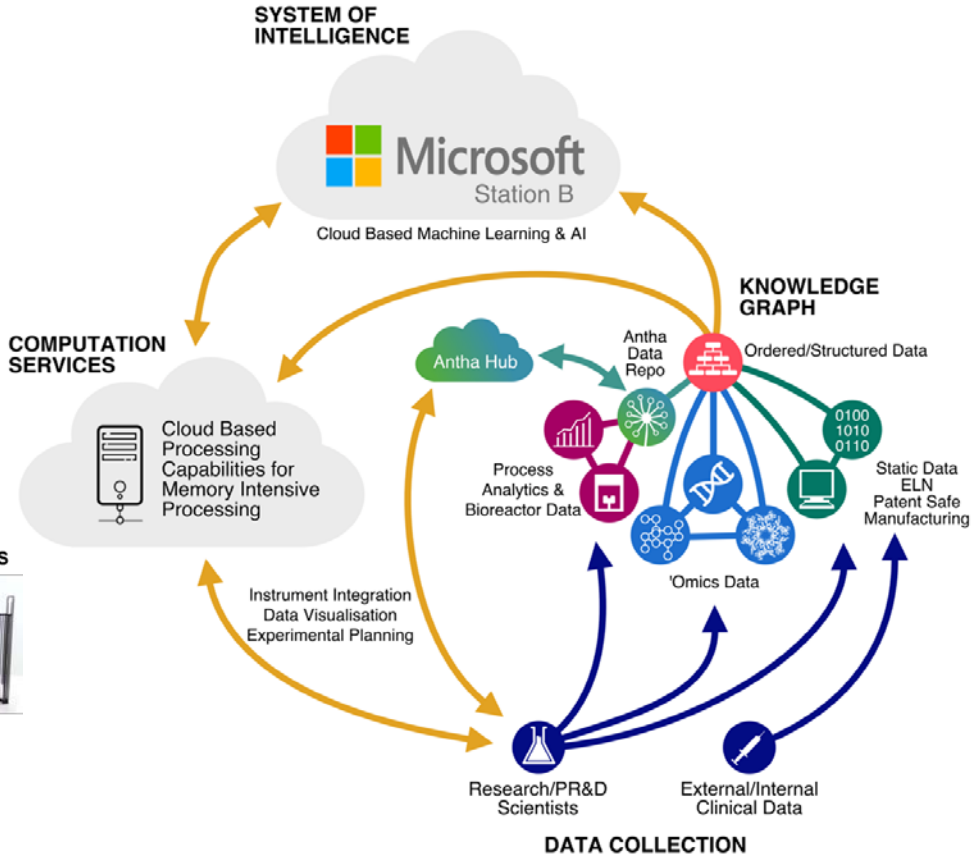
# Changes to analytical methods/ use of automation

## Use of digitisation & automation to improve productivity and quality

### Benefits of automation

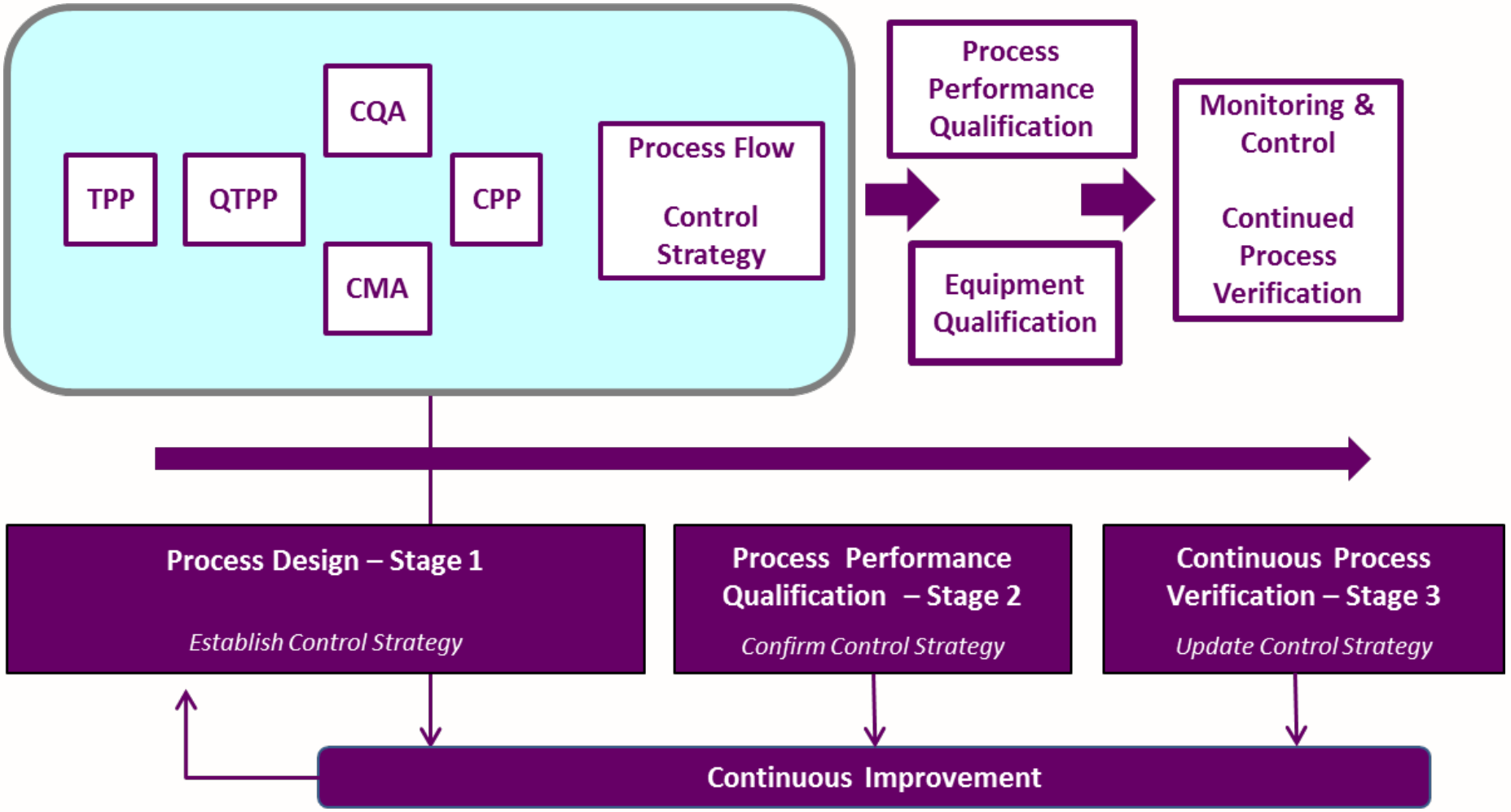
- Higher throughput
- Reduced turnaround times
- Cost savings per sample
- Improved reliability & reproducibility
- Reduced operator-to-operator variability
- Minimise risk of human error
- Streamlined data analysis
- LIMS integration



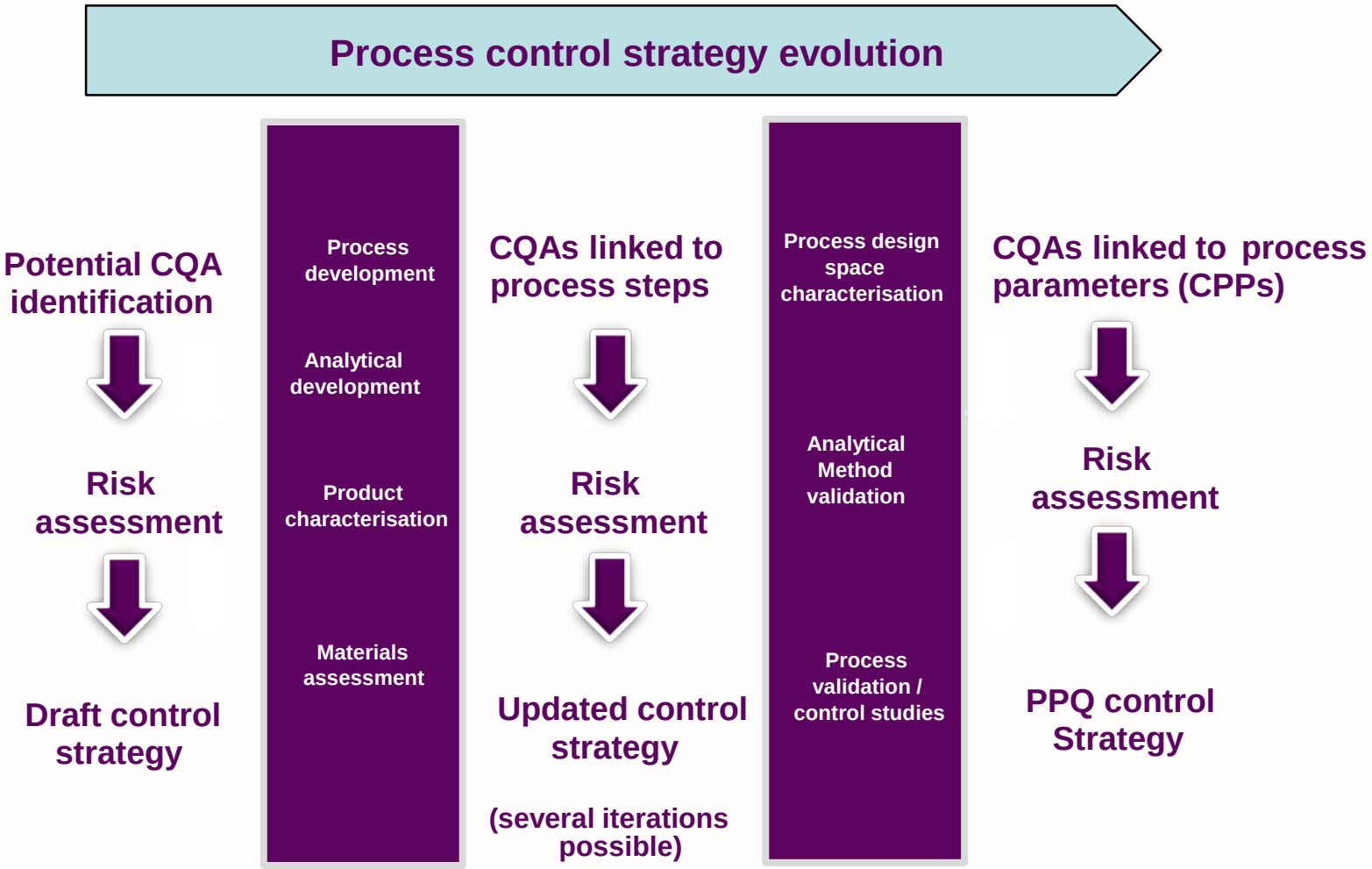




Automated qPCR workflow

# Process validation lifecycle



# Control strategy development



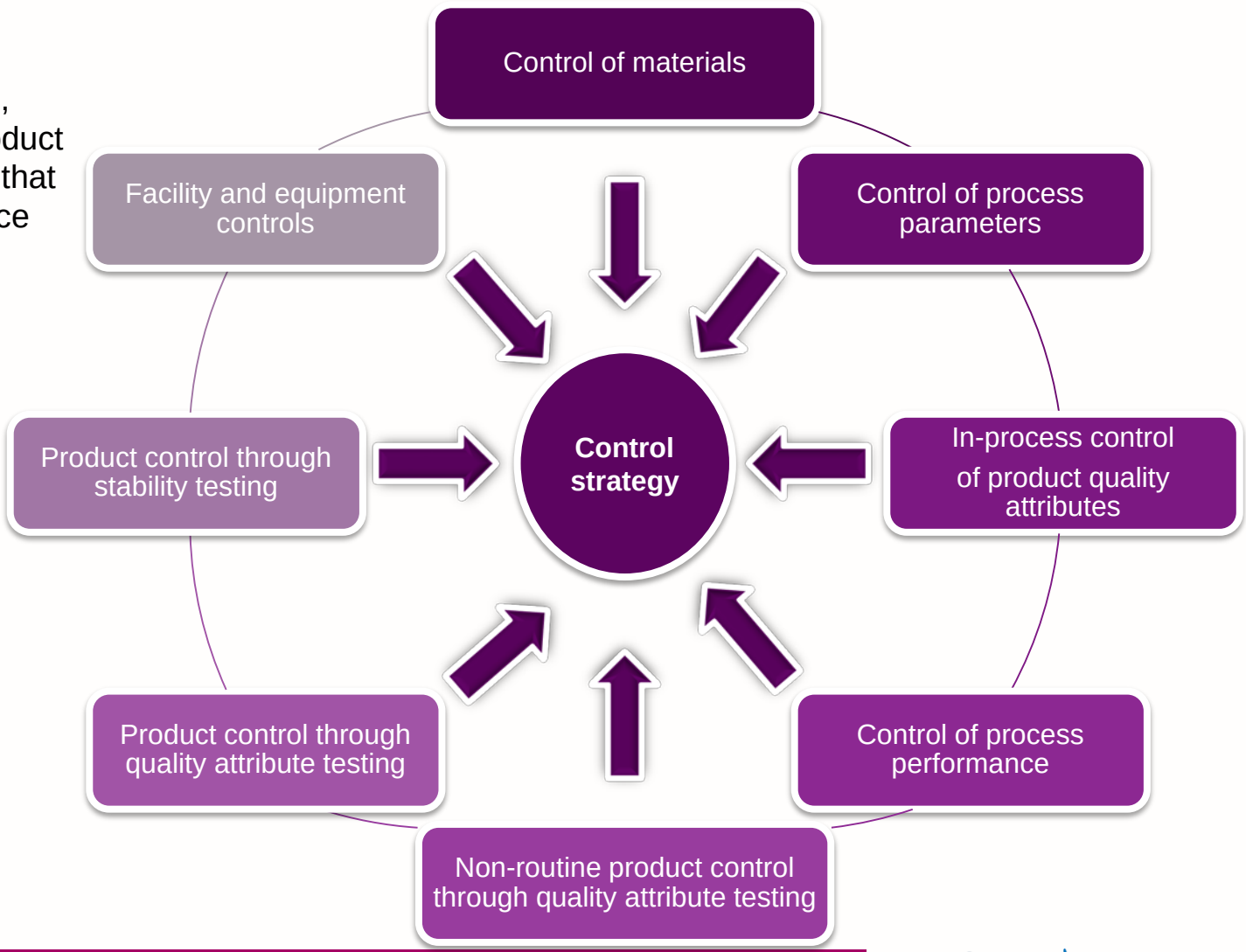
# Control elements for product quality and process performance

## Demonstrating “state of control”

### Control strategy

…“A planned set of controls, derived from the current product and process understanding that assures process performance and product quality”…

(ICH Q10)



# Control elements for product quality and process performance

| Control element | Type of control |
|---|---|
| Control of materials | • Specifications for raw materials<br>• Manufacture and testing of cell banks; cell bank controls<br>• Manufacture and testing of plasmid DNA; supplier controls<br>• Characteristics of incoming materials (raw materials, starting materials, intermediates, primary packing materials) that impact product quality attributes and their acceptable ranges |
| Control of process parameters | • Control implicit in the design of the manufacturing process or unit operations<br>• Manufacturing process controls<br>• Process parameters that impact product quality or process performance attributes/ control limits/acceptable ranges<br>• Process hold time limits<br>• Process step times<br>• Manufacturing process development and history for understanding and application of acceptable ranges |

# Control elements for product quality and process performance

| Control element | Type of control |
|---|---|
| Non-routine product control through quality attribute testing | • Elucidation of structure and other characteristics<br>• Non-routine tests for characterisation and demonstration of product comparability<br>• Reference standard qualification |
| Product control through quality attribute testing | • Routine release testing and acceptance criteria in product specification<br>• Justification of specification<br>• Analytical procedures and their validation<br>• Product attribute control through process performance qualification |

# Post approval CMC lifecycle management

- During development CMC changes are communicated and approved through IND/IMPD amendments
- Post approval changes are classified further depending upon their potential to have an adverse effect in the safety, identity, strength, quality, purity, potency and efficacy of the vector drug product
  - Major (Substantial) Change – Prior Approval Supplement (PAS) / Type II variation
    - New manufacturing site
    - Formulation changes
  - Moderate Change – Changes Being Effective in 30 days (CBE-30) / Type IB variation
    - Completion of post approval commitments
    - Reduction of expiration dating
  - Minor Change – Annual Report / Type IA variation
    - Increase or decrease in production scale if no equipment changes
    - Implementation of a new reference standard if the protocol is registered

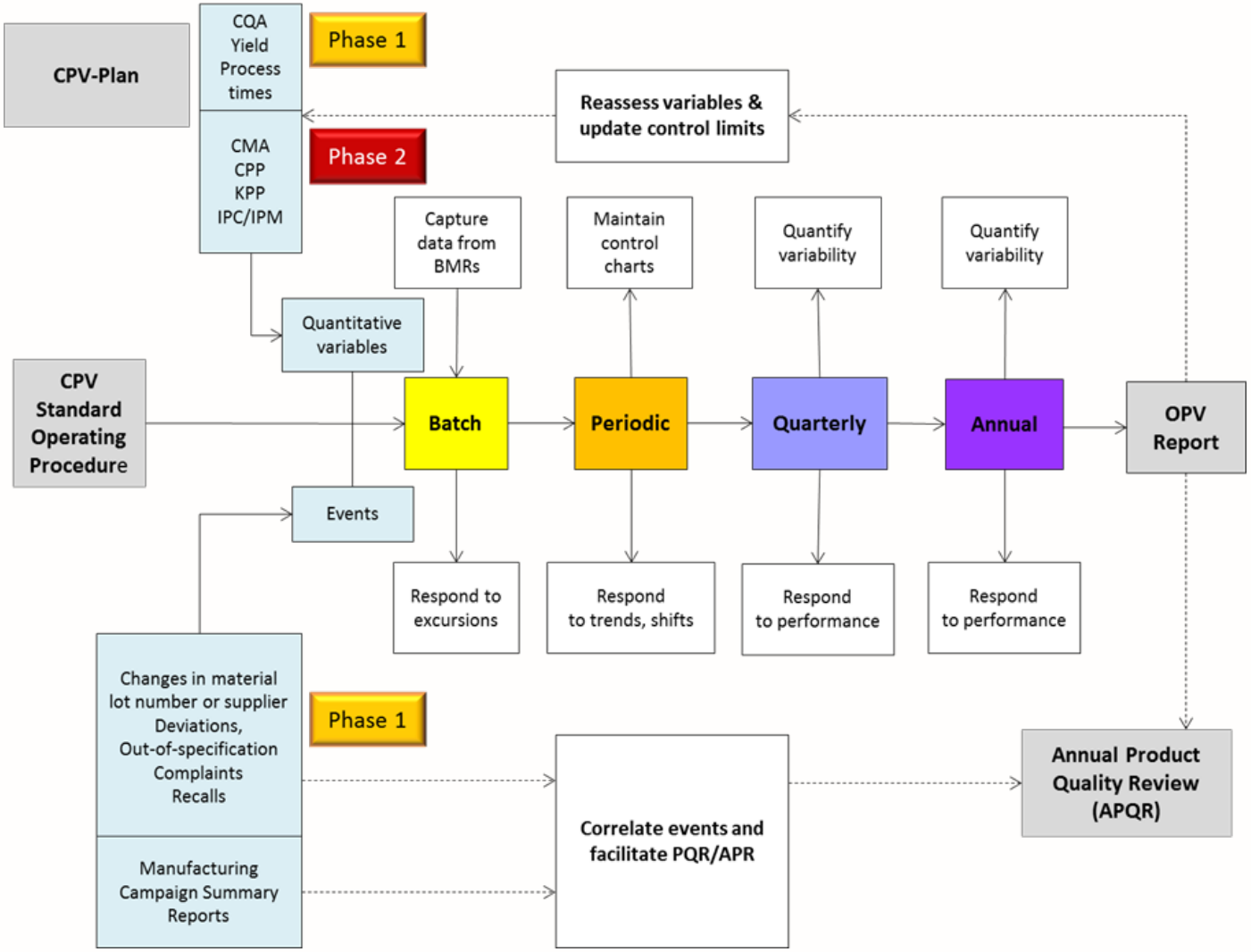
# Commercial supply

## Continued/On-going Process Verification (CPV/OPV)

- On-going assurance that the commercial manufacturing process remains in a state of control (stable and capable)
- Collection, trending and analysis of manufacturing performance data [through CPV Monitoring Plans (CPV-Plan)] to assure the state of control of the process (product/process/site)
- Identifies potential issues and determines whether action must be taken to correct or prevent problems so that the process remains in a state of control
- Manufacturing Robustness Review Board (MRRB) now established to provide:
  - Oversight of manufacturing performance and process robustness across the OXB manufacturing network (all internal and CMO sites, technology transfer)
  - Monitor and reports on the status of cGMP process performance (stability and capability) and any impact of process changes
  - Sponsor and drives cross-site process improvement efforts ensuring the appropriate use of capabilities and resources
  - Identifying areas of need for improvement, proposing improvement projects, prioritising and monitoring progress of project and process improvement actions

# Commercial supply

## Typical CPV/OPV Programme



# Concluding remarks

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- CMC considerations during clinical and commercial supply are driven by a variety of internal and external drivers
- A systematic approach is required to manage the inevitable changes during the product lifecycle, from process design and development to commercial use
- Within the past 6 years OXB has had to face and continues to face many CMC challenges to meet the growing demand for lentiviral vectors
- Developing better process understanding and know-how, new technologies and processes coupled with more sophisticated understanding of CQAs, will ultimately pave the way to the step change improvements needed to meet the future clinical and commercial needs

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