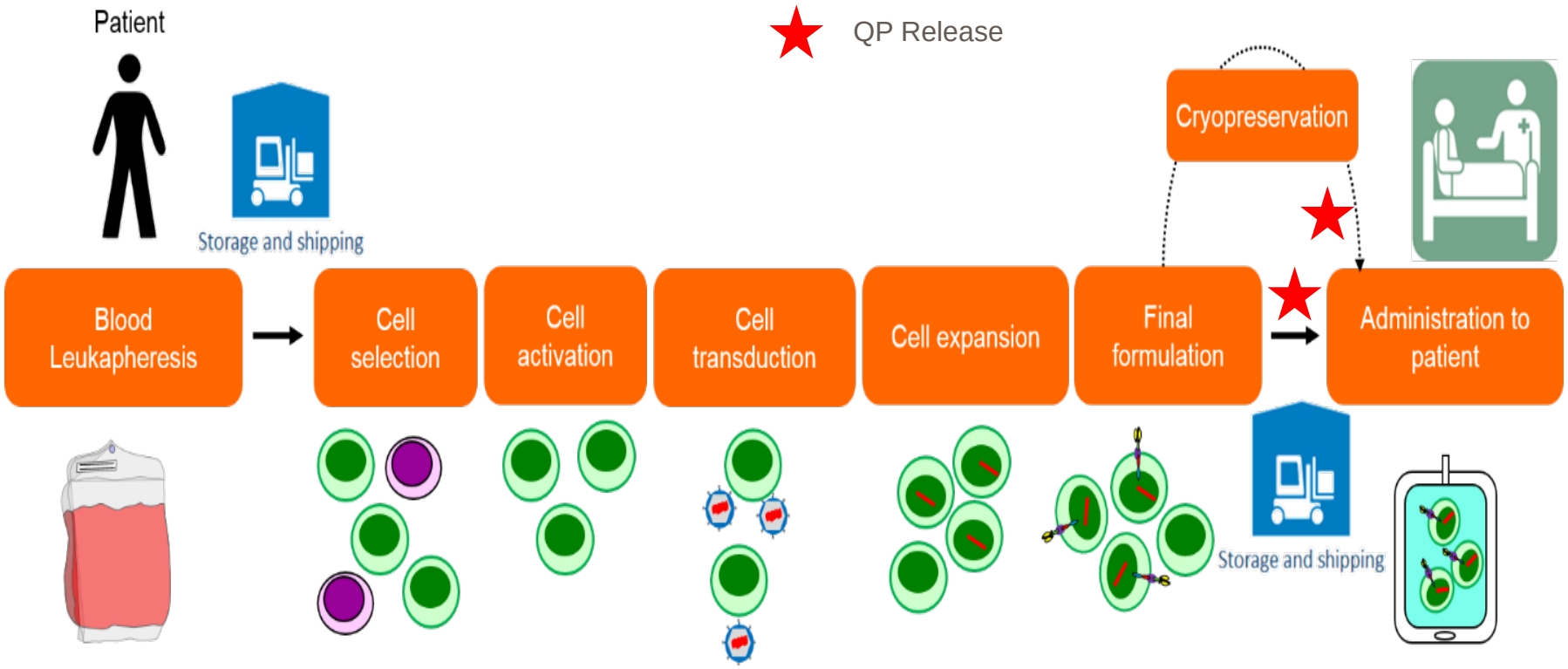
"Manufacturing challenges - now and future - how will we ensure patient access to these medicines?"

Bo Kara, Cell Gene Therapy: Process Development

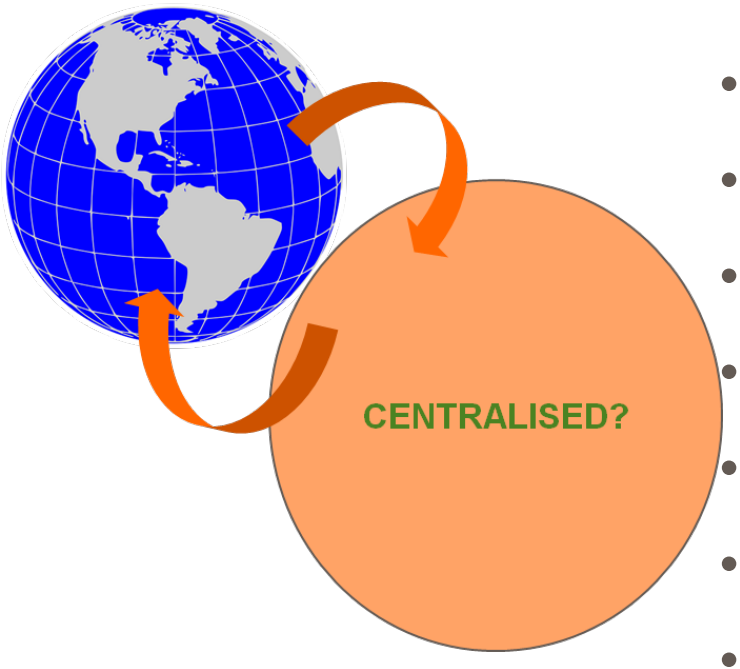
Workshop on Scientific and Regulatory Challenges of Genetically Modified Cell-based Cancer Immunotherapy Products

Generic process for genetic modification of autologous T cells



Manufacturing Models: T- Cell Processing – Current?

Centralised



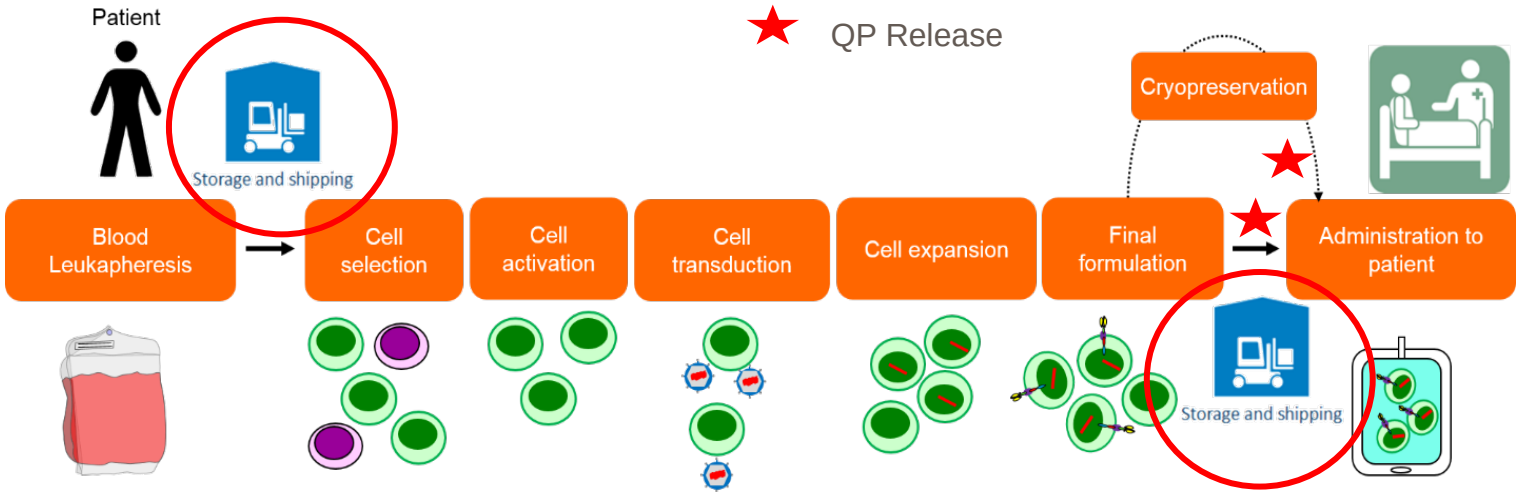
- Single product or single platform
- Lower CoG
- Product and process knowledge in one place
- Easier validation
- No tech transfers to other sites
- No duplication of QC across multiple sites
- Reduced ‘cost of testing’?
- Requires cryo in/out of facility
- Long(er), more variable distribution chain
- Security of ‘treatment’ supply’ if facility issues?

Autologous T-cell product manufacturing

- Heterogeneity - starting materials
- Manual steps, operator dependent, labour intensive
- Need: highly qualified operators
- Lack of automation and functionally closed manufacturing systems
- Scale-out: limited
  - Availability of adequate facilities and highly trained operators
- Centralised manufacturing: leukapheresis material/cellular product shipping – potential risks for the cell product?

Current - Manufacturing

Logistics



Centralised Manufacturing: Logistics

- Shipping: potential risks?
  - Leukapheresis material and final cellular product –
    - Short shelf-life (can have) or,
    - Critical delivery times - manufacturing timescales or patient conditioning regimens
- International borders
  - Bottleneck and source of potential risk
  - Inconsistencies in service levels for pharmaceutical products
  - Approach to security are a source of complication in logistics planning
  - Loss of shipments?
- Cryopreserved cell products?
  - Shipped on dry ice
  - Hospital receiving the cell product:
    - Handling frozen cell material and consistency?
    - Thawing process and consistency?

Meeting the demand/need: future – example

- Huge potential: 350 clinical studies studying the use of cell-based therapies in a number of haematological and solid tumours (clinicaltrials.gov accessed Sept 27 2016)
- Initial data confined to a subset of less common tumours (Acute lymphoblastic leukaemia, Chronic lymphocytic leukaemia and Diffuse and large B cell lymphoma):
  - Total incidence is ~60,000 patients per year in the US and a similar incidence in the EU5 (UK, Germany, France, Italy and Spain)
  - Commercialisation: What is the manufacturing model that ensures access to these medicines?
- As we work to extend cell-based therapies into solid tumours:
  - Potential population becomes significantly larger – non-small cell lung cancer alone affects nearly 200,000 individuals per year
  - Commercialisation: What is the manufacturing model that ensures access to these medicines?

Manufacturing Models: Cell Processing

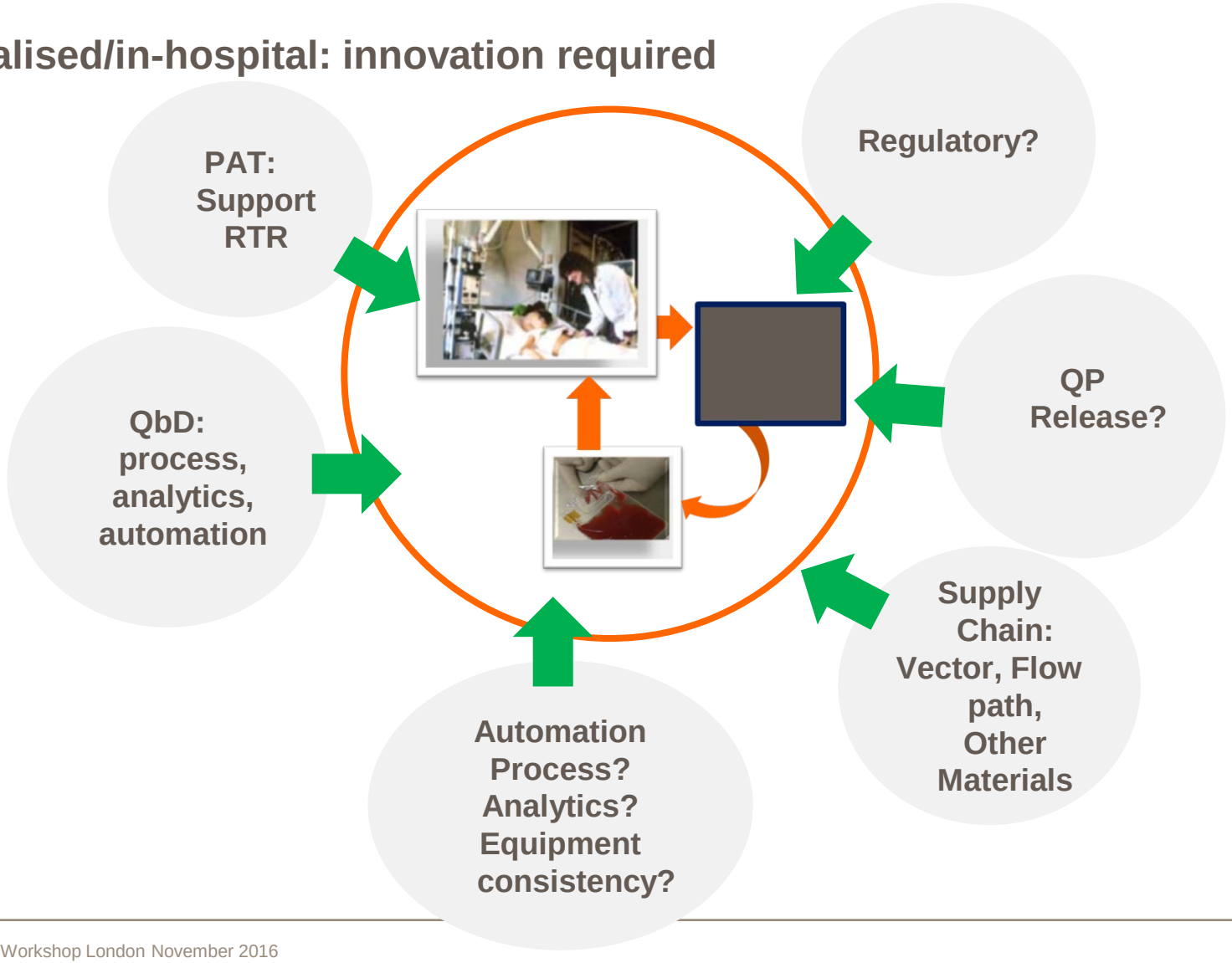
Decentralised?

- Shorter distribution chain
- Improved patient access to treatment
- Can align with local practises and needs
- Security of ‘treatment’ supply if one site has issues
- Could handle shorter shelf products
- Multiple capital investment
- Additional TT and validation time/costs
- RM/consumables supply chain
- Ensuring ‘same’ product across sites?
- QC replication: cost of testing
- Quality oversight replication

Manufacturing Models: Cell Processing

‘Localised’

Localised/in-hospital: innovation required



Discussion topics

- Localised manufacturing:
  - Regulatory framework?
  - GMP manufacturing – how do we bring into localised manufacturing?
  - Can we see new ‘bottlenecks’?
    - E.g. 100,000’s of patient batches – will QP’s be able to meet demand?
    - Other?

On a mission to make a difference

If we do these things well, we will do better by patients, our shareholders and society. And we will fulfil our mission: **to help people do more, feel better, live longer.**