ATMP R&D and Commercialisation 2020 - Maximising the Value of Innovation

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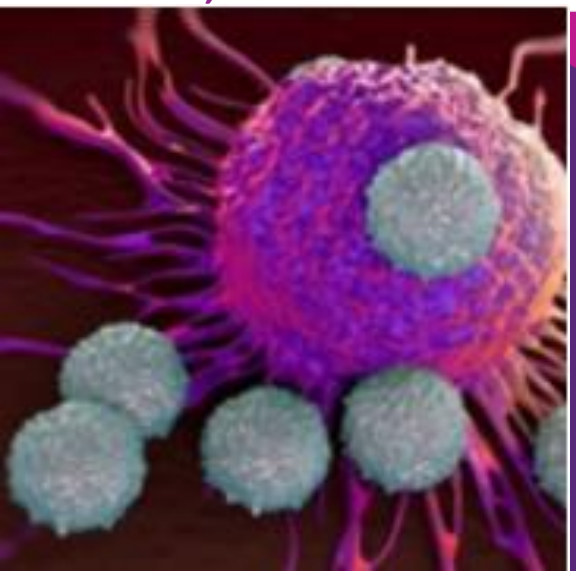
Advanced Therapies – Opportunities and Challenges

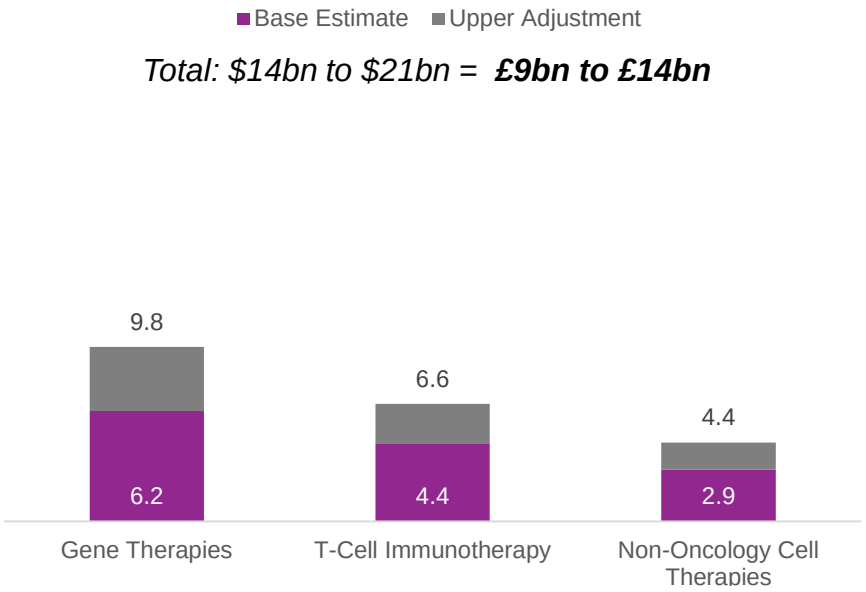
London, November 2017



The global Cell & Gene Therapy market is forecast to be £9 -14bn by 2025, growing to £21-32bn by 2030

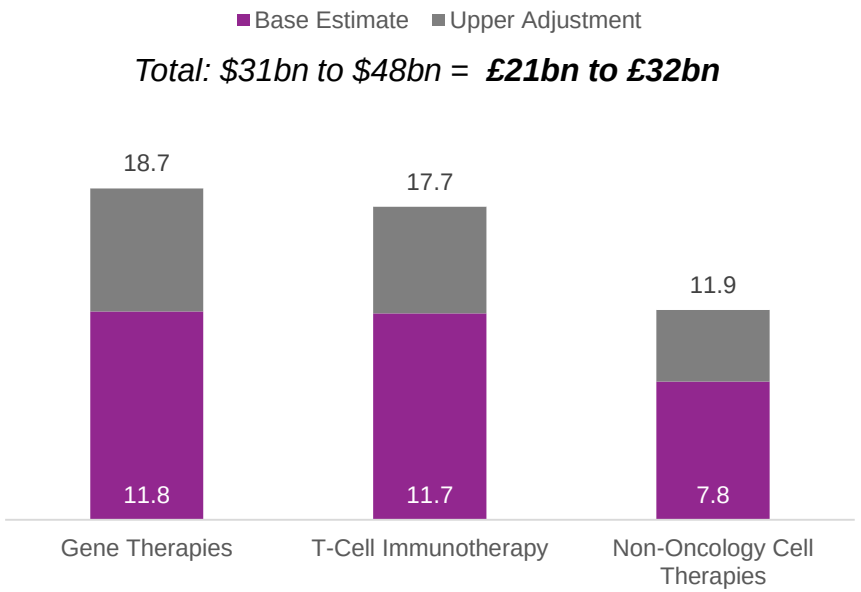
Overall Cell & Gene Therapy Market Sizes, by segment including price ranges

2025 Market Sizes, Base and Upper Product Pricing Ranges



Total: $14bn to $21bn = ***£9bn to £14bn***

2030 Market Sizes, Base and Upper Product Pricing Ranges



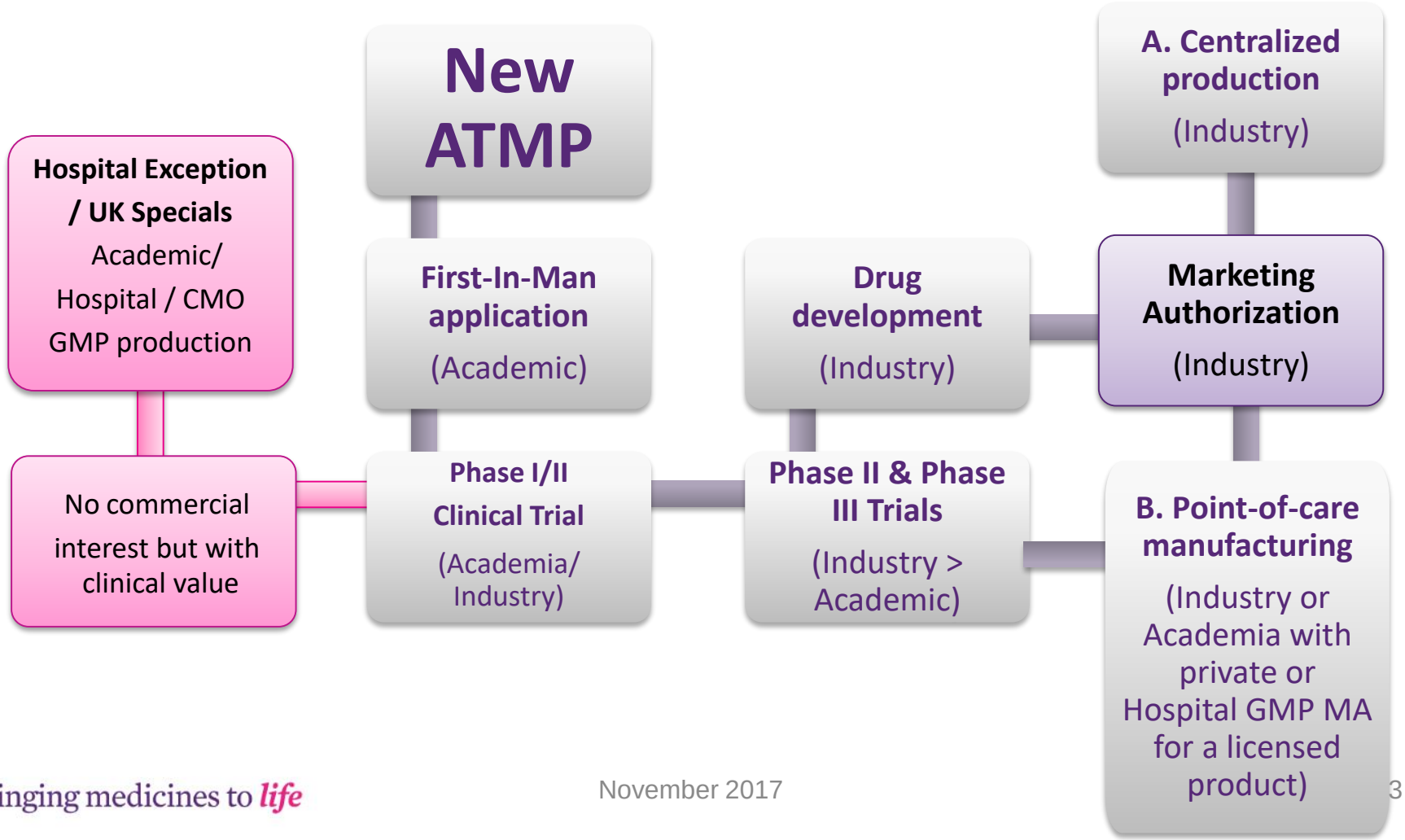
Total: $31bn to $48bn = ***£21bn to £32bn***

Number of products in each segment

Gene Therapies: 21	T-Cell Immunotherapies: 19	Non-oncology Cell Therapies: n/a

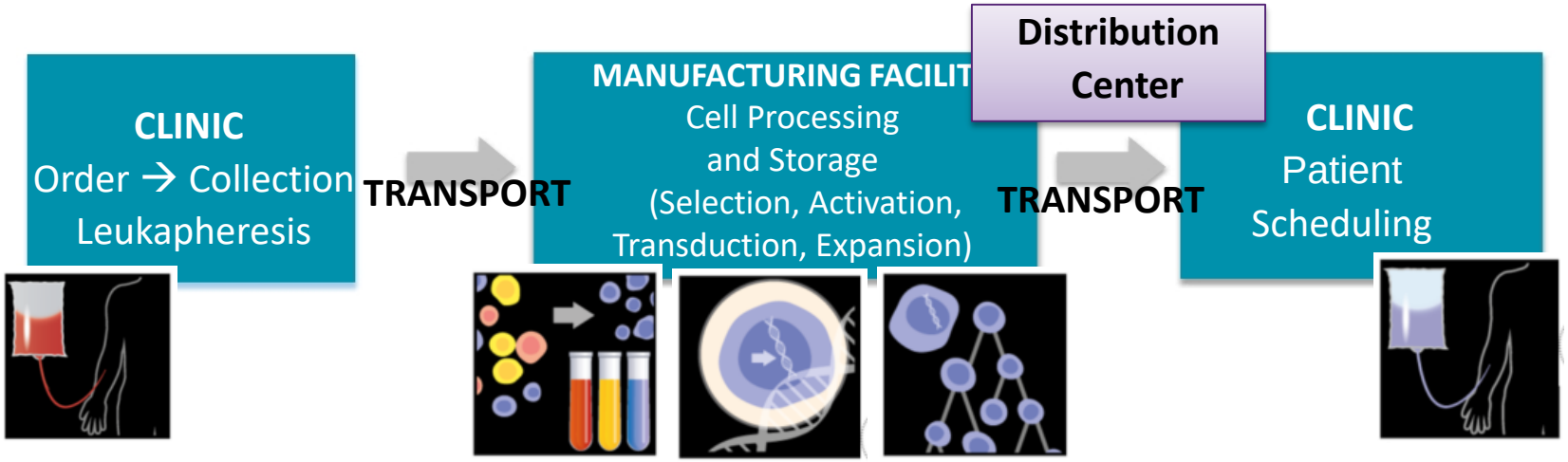
Note: *All values calculated in US Dollars, with 5 year average rate used to account for current volatility (1.5 USD: 1 GBP)*, sum totals rounded to nearest 1bn.
Number of products in the non-oncology cell therapies segment is not shown due to a top-down methodology approach base on overall market rather than individual products
Source: Roots Analysis, DataMonitor, Strategy& Analysis. See "Detailed Methodology" section for full breakdown

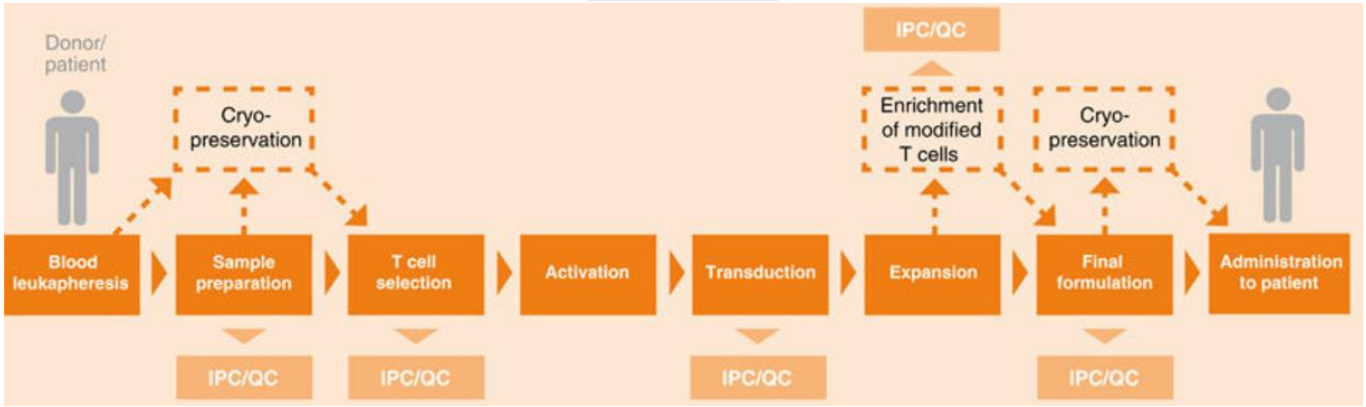
ATMP DEVELOPMENT: moving from research to commercial production



Process constraints:
The example of autologous CAR-Ts

- **Interaction of clinical and manufacturing sites**





A D Kaiser, et al. **Towards a commercial process for the manufacture of genetically modified T cells for therapy.** ***Cancer Gene Therapy (2015)***

Current Supply in numbers

- **Kymriah: B cell ALL:** 20% of 650 or 3000 new pts /pa (UK/US)
- **Supply shortages**
  - Central Infrastructures:
    - U Penn, CHOP: only 5 patients/month
    - Seattle Children's Hospital: 10 batches a month
    - Triage plans in place: sickest patients first
  - Private Investment: Novartis invested $43m in N. Jersey → New freezing method→ shipping across 10 countries
  - Defining scope and specifications for **Centres of Excellence**
    - Patients already travelling abroad to access novel therapies, ie. Milan San Raffaele for Strimvelis

THE CAR-T REVOLUTION:
Gilead's $12B Acquisition of Kite Pharma & FDA Approval of Novartis' Kymriah Signal Tipping Point for Promising Cancer Immunotherapies

GILEAD Kite Pharma NOVARTIS

BIOMEDICINE

Supply of promising T cell therapy is strained

Surging demand for modified immune cells causes some cancer trials to run short

By **Jennifer Couzin-Frankel**

Science 16 Jun 2017:
Vol. 356, Issue 6343, pp. 1112-1113
DOI: 10.1126/science.356.6343.1112

Tipping point for the UK

- UK companies attracted over £400 million investment in 2015
- At least 53 ATMP developers in the UK – (50% actively growing)
- By the end of 2015 over 1,000 jobs had been created in the UK
- Over 50% growth in UK Clinical trials in UK since 2013 (>66)
- 22 GMP facilities
- Conservative estimate is for 400-600 additional skilled staff being required over the next two years

- **UK LSO: 250 overseas-based companies to invest in the next 2-3 years**
- **8-10 investment opportunities bringing in £350 million of internationally mobile investment.**

ATMP pathway to commercialization and clinical use

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Bringing medicines to *life*

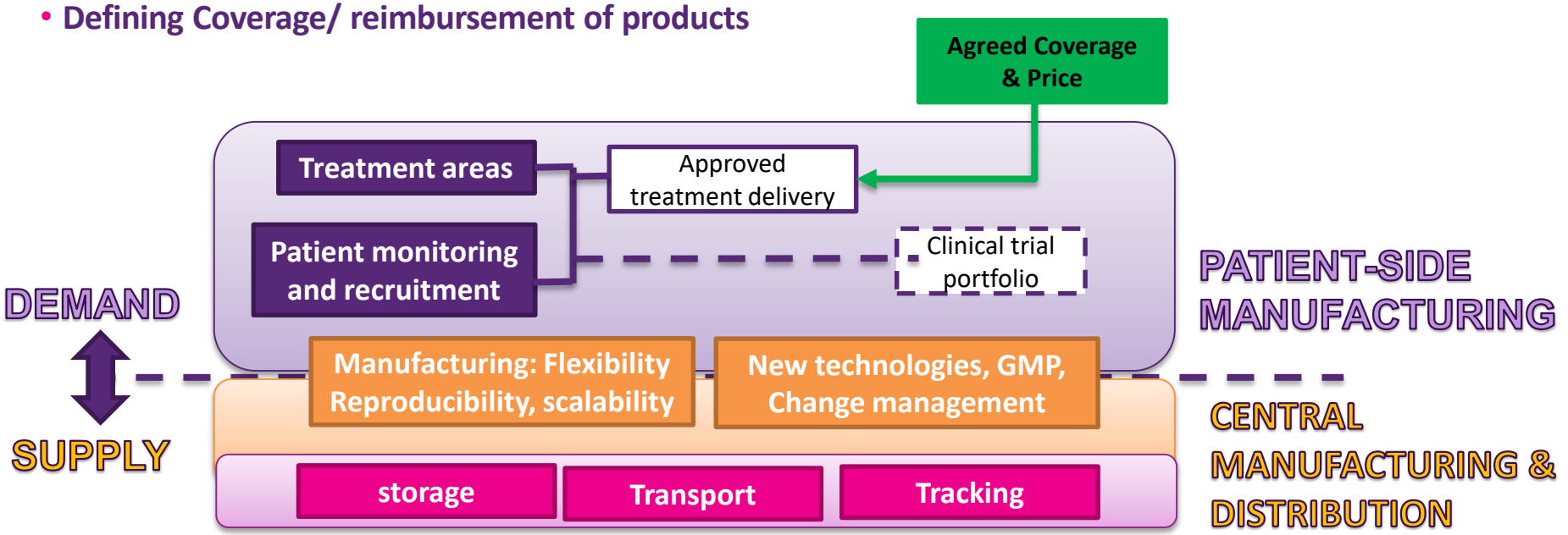
Systemic barriers to development and access

Research and Discovery | **Development and Manufacturing** | **Clinical Assessment and Delivery** | **Regulatory and Market Access** | **NHS Adoption & Use Optimization**

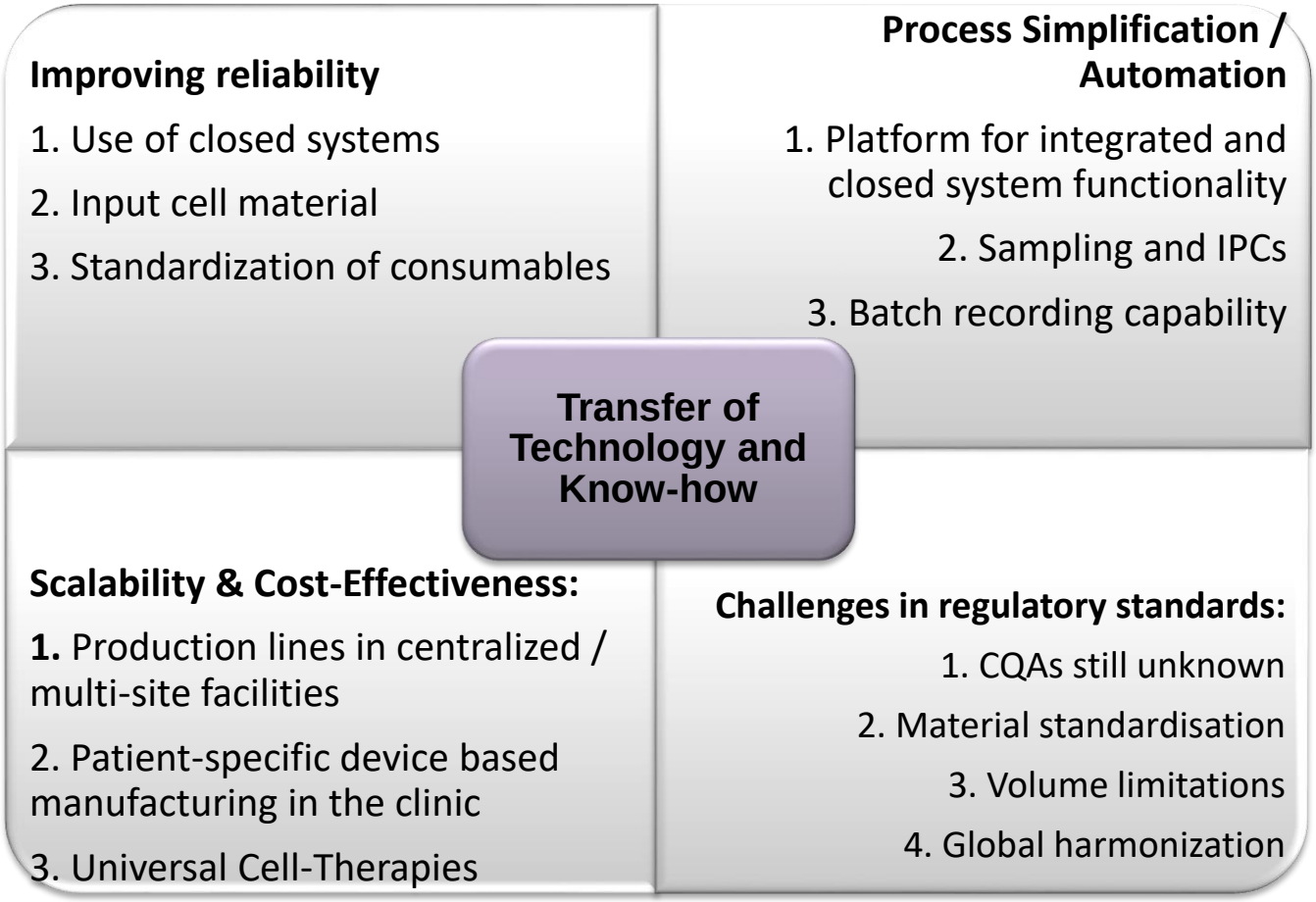
- **The 'process *is* the product':** Individual patient batches essentially corresponding to a different product
- **Standardization**: living materials as any change in manufacturing could affect a treatment's efficacy and safety – Unknown CQAs
- **Industrialization – COGs** challenges for production scaling-up to Phase 3 trials and commercial supply (product equivalence and cost control).
- **Clinical risks:** new CTs highly type and disease dependent, calling for new endpoints and trial designs (ie. for single-arm trials),
- **Coverage**: Promise for life-long effectiveness raises evidence availability challenges
- **Pricing**: Budget impact and affordability analyses – not capturing long-term health system benefits
- **Skilled human capital & cross-disciplinary talent pool**

Cost inflection points

- **Manufacturing Strategy:**
  - Standardization, scalability and productivity
- **Logistical constraints**
  - Speed, access and storage
- **Facility design** (patient-side vs centralised)
- **Regulatory compliance** paramount (Licensing/ GCP & Inspection / GMP & GMO)
- **Defining Coverage/ reimbursement of products**



Manufacturing: Process is the Product

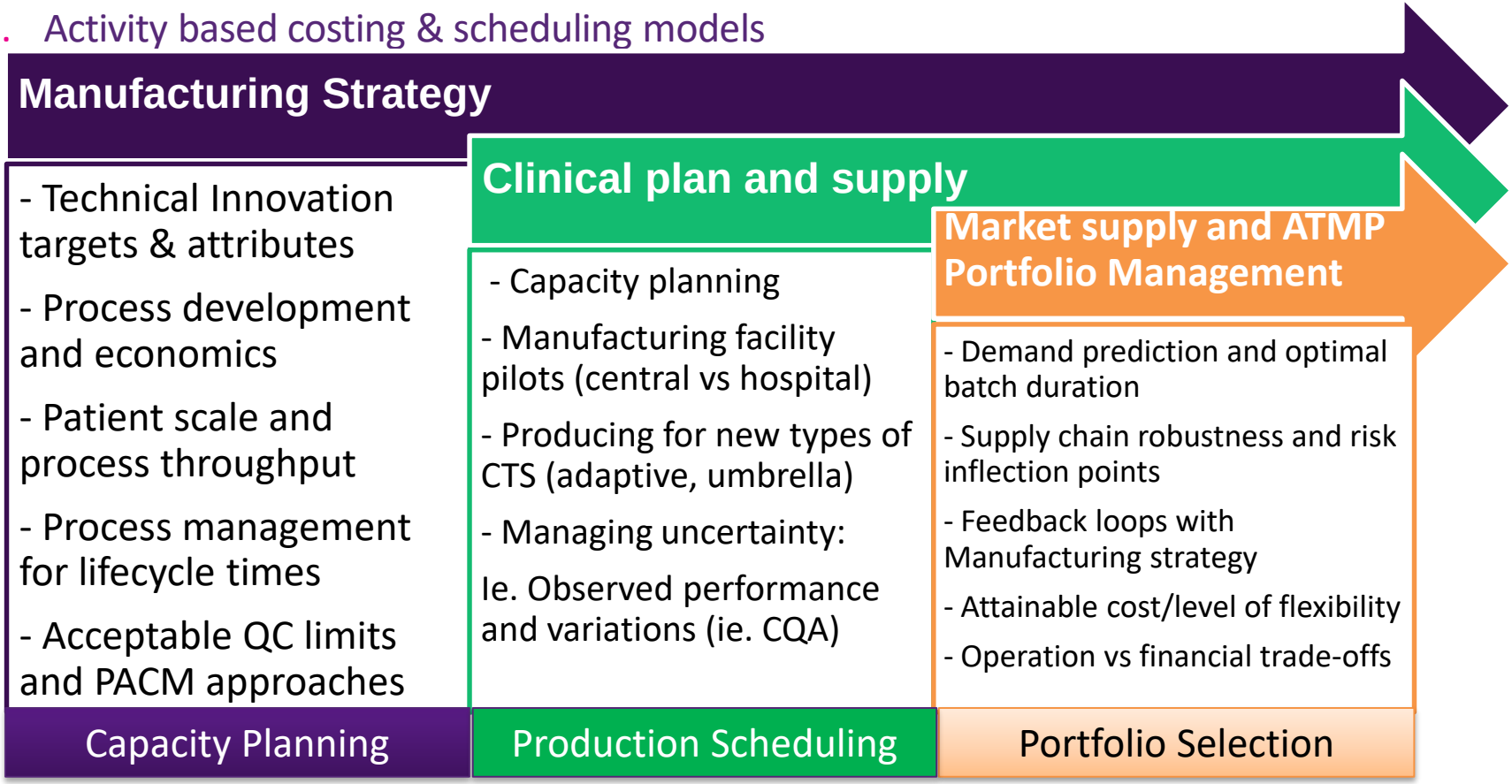


- **Early and continued engagement between scientists/manufacturers and regulators**

Clinical manufacturing / in-market supply

- **Production economies and Institutional / Clinical readiness**

1. Patient centric supply
2. Activity based costing & scheduling models



ATMP Sector Building Strategic intervention Opportunities

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Clinical Assessment and Market Access: Dealing with uncertainty

- **Small Patient cohorts**
  - Not easy to offset investment costs
  - Clinical evidence collection hard
- **Unavailability of evidence at the time of negotiations:**
  - hard to assess the value of 'cures → need for frequent re-assessment
- **Promise for long-term effect raise affordability concerns under existing payment / pricing examples**
- **Why high-upfront costs?**
  - Manufacturing technologies still lacking
  - Need for change in clinical delivery /infrastructure (ie. registries)
  - Need for continued monitoring /evidence generation

Integrated clinical production / trial and portfolio planning

1. **Improving manufacturing Infrastructure:** COGs control and reduction
2. **Accelerated/ Adaptive assessment strategies** (Regulatory and Clinical)
    1. Adaptive pathways, EAMS
    2. Small, single-arm, screening-aided clinical trials
3. **Early reimbursement consideration and discussions:**
    1. Acceptance of long-term safety/effectiveness evidence on a rolling basis
    2. Value-based pricing and control of patient access
    3. Use of novel payment, risk-sharing schemes (Annuity, pay for performance, lifetime leasing)
4. **Need for greater flexibility and management of uncertainty**

    → **Impact on expected demand:** More flexible production planning needed

    → **Impact on selected production mode:** additional trial needed if changes post assessment

1. Manufacturing process innovation

- **Novel manufacturing, analytical and control technologies**
  - I. **Clinical vs engineering** goals
  - II. **Technology** (Microfluidics, Continuous Processing, Single-use, Disposables)
  - III. **Process & Analytical** development
  - IV. **GMP proving** and **Change management** strategies

- **Which ones to use → Techno-economic analysis**
  - Desired capacity and product volume limits
  - Quality criteria
  - Material and sample availability
  - R&D investment budget

- **Engineering and knowledge IFR:**
  - Networks of academics /users and new tech suppliers: create and prototype new technologies

2. LIFECYCLE MANAGEMENT: New Paths For ATMPs

- **EMA has opened several regulatory opportunities to evaluate assets in more timely / iterative manner:**
  - **Tools:** Accelerated Assessment, Conditional Marketing Authorization, Compassionate Use
  - **Supportive Scheme for early dialogue:**
  - **Novel Development concepts**: Adaptive pathways, for gradual indication expansion and increasing use of real-world evidence:

ATMPS: 3/6 in Adaptive Pathways Pilot Phase 2

TRADITIONAL LICENSING APPROACH

1. Focus on Licencing approval
2. Single gated licencing decision
3. Main regulatory/reimbursement strategy is via B/R Prediction
4. RCTs are the main assessment tool
5. Aiming at Broad Populations
6. Goal is Open product utilization

LIFECYCLE MANAGEMENT APPROACH

1. Focus on Patient Access, at the outset
2. Life cycle management approach
3. Main regulatory/reimbursement strategy is via B/R Monitoring
4. Use of a much broader Toolkit for evidence generation: biomarkers, surrogates and health databases.
5. Aiming at Targeted Populations
6. Controlled access is essential

3. ATMP Centres of Excellence: Global Examples

Integrated structures for ATMP development, translation and commercialization

Combine several interacting units:

Clinical Centres of Excellence (Oncology, rare diseases, Autoimmune, CNS, etc)		
R&D Units - Preclinical work - Development - Analytical labs	**Cell production and CQ Units** - Cell Preparation - GMP Processing - QC facility - BioBanking	**Clinical Evaluation and Regulatory Advise** - Patient / Donor registry - Screening Facilities

CHARITÉ
Bringing medicines to life

C3i Center for Commercialisation of Cancer IMMUNOTHERAPY

SR-Tiget SAN RAFFAELE TELETHON INSTITUTE FOR GENE THERAPY

OSPEDALE SAN RAFFAELE

Investigating the role of ATMP Centres of Excellence

Advanced Therapies Treatment Centres

Building our #IndustrialStrategy

Proposals should:

- increase patient access to advanced therapy medicinal products (ATMPs) on a national level
- establish best practice for safe and effective delivery of ATMPs to patients
- establish best practice for ATMP near patient Good Manufacturing Practice (GMP) final preparation and manufacturing methods
- establish robust connected supply chains for the manufacture and delivery of ATMPs
- lay the foundations for traceability and tracking systems compatible with Regulatory expectations & suitable for dissemination throughout the NHS
- establish best practice for patient follow up and data capture

Advanced Therapies Treatment Centres

£30m

2016 ATMP Manufacturing Taskforce

Medicine Manufacturing Industry Partnership

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Advanced Therapies Manufacturing Action Plan

Retaining and attracting advanced therapies manufacture in the UK

Recommended actions to make the UK a global hub for manufacturing advanced therapies

1. Strengthen and secure an internationally competitive fiscal landscape to attract investment
2. Target and capture internationally mobile investments through a proactive and simplified process of engagement
3. Maintain science and innovation funding to support industry developing cutting-edge technologies
   - 3.1 Securing investment in manufacturing capacity through flexible funding
   - 3.2 Invest in viral vector manufacturing capacity in the UK
   - 3.3 Sustain the range of funding mechanisms to grow advanced therapies manufacturing technologies
4. Set out an end-to-end talent management plan to secure the relevant skills for emerging manufacturing technologies
5. Clearly set out a swift, predictable and viable route to market for these innovative products and give industry confidence that the UK is a progressive global hub
6. Develop a long-term regulatory strategy and plan for the MHRA to lead in global standards, supporting the scientific activities and international outreach of NIBSC

Take Home

- **New integrated development / manufacturing and commercialization business and costing models**
- **Regulating the Industry /Clinic translational interfaces:** new regulation, GMP/QP and QC challenges
- **Prospectively planning for capacity issues:**
  - Academic/Industrial/NHS collaboration: apheresis, stem cell labs, pharmacy,
  - NHS adoption – funding for appropriate training of delivery teams and clinical personnel
- **Scope and extent of ATMP Centres of Excellence**
- **New NHSE/ NICE reimbursement and pricing models**
- **Importance of addressing the entire value chain- HoC S&T Regenerative Medicine report (30 April 2017)**
  - linking with the Accelerated Access Review
  - NHS Personalised Medicine Strategy to include Regenerative Medicine and Cell Therapy

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