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

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Base Estimate</th>
<th>Upper Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene Therapies</td>
<td>6.2</td>
<td>9.8</td>
</tr>
<tr>
<td>T-Cell Immunotherapy</td>
<td>4.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Non-Oncology Cell Therapies</td>
<td>2.9</td>
<td>4.4</td>
</tr>
</tbody>
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Total: $14bn to $21bn = £9bn to £14bn

2030 Market Sizes, Base and Upper Product Pricing Ranges

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<td>17.7</td>
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Total: $31bn to $48bn = £21bn to £32bn

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 each segment

<table>
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<tr>
<th>Segment</th>
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<tr>
<td>Gene Therapies</td>
<td>21</td>
</tr>
<tr>
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<td>19</td>
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<tr>
<td>Non-Oncology Cell Therapies</td>
<td>n/a</td>
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Source: Roots Analysis, DataMonitor, Strategy& Analysis. See “Detailed Methodology” section for full breakdown.

November 2017
ATMP DEVELOPMENT: moving from research to commercial production

New ATMP

- First-In-Man application (Academic)
- Phase I/II Clinical Trial (Academia/Industry)
- Phase II & Phase III Trials (Industry > Academic)

- Drug development (Industry)
- Marketing Authorization (Industry)

A. Centralized production (Industry)

B. Point-of-care manufacturing (Industry or Academia with private or Hospital GMP MA for a licensed product)

Hospital Exception / UK Specials
- Academic/Hospital / CMO
- GMP production

No commercial interest but with clinical value

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Process constraints: The example of autologous CAR-Ts

- Interaction of clinical and manufacturing sites

CLINIC Order → Collection Leukapheresis

MANUFACTURING FACILITY Cell Processing and Storage (Selection, Activation, Transduction, Expansion)

CLINIC Patient Scheduling

Distribution Center

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

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

November 2017
• 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
Systemic barriers to development and access

• 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

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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

Improving reliability
1. Use of closed systems
2. Input cell material
3. Standardization of consumables

Process Simplification / Automation
1. Platform for integrated and closed system functionality
2. Sampling and IPCs
3. Batch recording capability

Scalability & Cost-Effectiveness:
1. Production lines in centralized / multi-site facilities
2. Patient-specific device based manufacturing in the clinic
3. Universal Cell-Therapies

Challenges in regulatory standards:
1. CQAs still unknown
2. Material standardisation
3. Volume limitations
4. Global harmonization

- Early and continued engagement between scientists/manufacturers and regulators

Bringing medicines to life
Clinical manufacturing / in-market supply

- Production economies and Institutional / Clinical readiness
  1. Patient centric supply
  2. Activity based costing & scheduling models

Manufacturing Strategy
- Technical Innovation targets & attributes
- Process development and economics
- Patient scale and process throughput
- Process management for lifecycle times
- Acceptable QC limits and PACM approaches

Clinical plan and supply
- Capacity planning
- Manufacturing facility pilots (central vs hospital)
- Producing for new types of CTS (adaptive, umbrella)
- Managing uncertainty: ie. Observed performance and variations (ie. CQA)

Market supply and ATMP Portfolio Management
- Demand prediction and optimal batch duration
- Supply chain robustness and risk inflection points
- Feedback loops with Manufacturing strategy
- Attainable cost/level of flexibility
- Operation vs financial trade-offs

Capacity Planning  Production Scheduling  Portfolio Selection

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ATMP Sector Building Strategic intervention Opportunities
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
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

Bringing medicines to life

November 2017
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
EMA has opened several regulatory opportunities to evaluate assets in a 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:

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### TRADITIONAL LICENSING APPROACH

1. Focus on Licensing 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

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### 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:

<table>
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<th>R&amp;D Units</th>
<th>Cell production and CQ Units</th>
<th>Clinical Evaluation and Regulatory Advise</th>
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<tr>
<td>- Preclinical work</td>
<td>- Cell Preparation</td>
<td>- Patient / Donor registry</td>
</tr>
<tr>
<td>- Development</td>
<td>- GMP Processing</td>
<td>- Screening Facilities</td>
</tr>
<tr>
<td>- Analytical labs</td>
<td>- QC facility</td>
<td></td>
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<tr>
<td></td>
<td>- BioBanking</td>
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Investigating the role of ATMP Centres of Excellence

Advanced Therapies Treatment Centres

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 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
KEEP CALM AND INNOVATE

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