The future of medicine
Cell and gene therapy
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Foreword

by Adam Bird
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While advanced therapeutic medicinal products (ATMPs) have started to gain momentum in recent years, cell and gene therapy is not new, having undergone decades of trials and regulatory scrutiny.

The success of clinical data and eventual approval of multiple CAR-T therapies in the area of blood cancers, has led to an uptick of interest in the field. This interest has resulted in many large pharmaceutical companies turning their attention to innovations coming from small ATMP producers (academics), buying up patents/inventions as promising candidates for similar applications.

The next expected paradigm is that this success will lead to a trampoline effect for ATMP developments into solid tissue cancers or genetic disease affecting increasingly large organs and human biological systems such as the liver, lungs etc. It has already been shown that gene therapy applications for certain ocular diseases can also be very effective, but producing a gene therapy for larger organs (at the right strength/volume/presentation) is likely to be the next challenge.

There are also advances in the form of bioinformatics, which mean some of these autologous ‘personalised medicines’ (i.e. same patient cells but transformed with a generic gene therapy) could start becoming ‘personalised-personalised medicines’ (i.e. same patient cells but transformed in a custom way based on bioinformatics dependant on the patient-specific gene mutation). However, for the latter to achieve its potential, a robust regulatory framework around decentralised/point of care manufacture will be key.

Post-Brexit regulation

When the UK voted to exit the EU in 2016, there were fears about what this would mean for the UK life sciences sector, which had become strongly embedded within Europe.

Now, several months post-Brexit, the long-term impact of the break is still unclear.

A positive result has been the localised (MHRA rather than EMA) vaccine applications. Those in the industry will know that localised approval was still possible when UK was part of EU, however the agility shown by UK regulators during the height of the pandemic may not have been the case pre-pandemic.

Nevertheless, Brexit is not without challenges; the importing of finished products into EU and the associated batch testing and QP certification is still a concern.

In general, the supply chain for raw/starting materials has become more cumbersome. This could possibly see companies operating on a ‘just in time’ basis in terms of material holding, adding risk to continuity of supply/ongoing manufacturing.

This is somewhat exacerbated at the moment by the increased demand due to the pressure on the industry from new COVID-19 vaccine/therapies.

Lessons from COVID-19

Looking at the specific impact of the COVID-19 pandemic on ATMPs, for obvious reasons many clinical trials have had to pause recruitment, but it has become very evident that companies invested in ATMP research and production jumped into the fight against COVID-19, diversifying, adapting, collaborating, partnering, acquiring, to switch focus to vaccine production.

A huge amount can be learnt by the industry (and regulators) about the vaccine response, and the truncated timelines for product development of what are being shown to be world-changing medicinal products.

A new precedent has been set and the industry is engaged in serious discussion around how to make under 12-months development nearer the norm, rather than the often-quoted 12 years - not just for emergency vaccines, but also for life-changing treatments for smaller populations than a global pandemic.

A ‘lessons learnt’ exercise by all pharmaceutical companies that successfully navigated the pandemic (and regulators) could completely reshape how medicines are (or could be) developed.

With new ground opened for cell and gene therapy in the UK, I am confident ATMPs are the future of medicine and we hope you find this white paper not only insightful but also exciting!

Adam Bird
Introduction

While cell and gene therapy (CGT), also known as advanced therapy medicinal products (ATMPs) has been around for decades, advanced therapies were introduced into the EU regulatory framework as a new classification of biological medicinal products in 2003.

The regulatory framework is established principally in Directive 2001/83/EC, and a number of other Directives and Regulations (e.g., on clinical trials, manufacturing, orphan medicinal products, paediatric research, and ATMPs) establish its principles.

In late 2008, Directive 2001/83/EC and Regulation (EC) No. 726/2004 (on procedures for human medicinal product authorisation and supervision within the EU and EEA) were amended by a specific Regulation on ATMPs: Regulation (EC) No. 1394/2007. This regulation (which known as the ATMP regulation) defines ATMPs as three specific types of medicinal products, including gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (SCTMPs), and tissue-engineered products (TEPs).

It’s only in recent times that it has gained momentum for having the power to revolutionise the future of medicine and how we treat various chronic and life shortening illnesses that had previous been seen as incurable.

ATMPs are a fast growing field of novel therapies that are based on genes, tissues or cells that hold promise as treatments for a variety of previously untreatable and high-burden diseases.

The main ATMP therapeutic areas are oncology and regenerative medicine, particularly in the field of cardiovascular conditions and haematology. ATMPs offer revolutionary new prospects for the treatment of diseases or injuries, such as skin in burns victims, Alzheimer’s, Parkinson’s disease and cancer or muscular dystrophy. This offers huge potential for the future of medicine, which will allow healthcare providers globally to shift from a paradigm of illness management to one of cure.

Research from 2019, revealed that there were over 930 companies making advancements within the CGT arena¹ and projections by BIS Research has estimated the value of the global industry to be worth over $12 billion by 2021².

ATMPs are considered the therapies of the future but there are a myriad of not only legal but also ethical obstacles on the pathway from lab to patient, from; clinical trials and recruitment of patients, lack of investment, to the obscure regulations that have potential to slow the commercialisation of these products.

There are many different players in the CGT arena, most research and development of ATMPs is conducted by academics, academic spin-offs, not-for-profit organisations, and SMEs. Until recently, only a few larger pharmaceutical companies have engaged in the investigational phases of ATMP development, due to the perception that the early investigational phases of the development of ATMPs is a high-risk activity.

Typically, SME’s focus on production to the larger pharmaceutical and biotechnology companies, but with many players in the market including investors and the outsourcing partners with sometimes differing goals, harmonisation across regulatory aspects of the industry landscape is needed.

In this paper, we focus on the opportunities inherent in Europe, highlighting the landscape in the jurisdictions where Fieldfisher are leaders in supporting clients in this area – UK, Ireland, France, Italy and Spain. We also take a multifaceted view at the different areas of law that come into play, focusing on regulatory and commercialisation.

We are on the cusp of the future of medicine and research shows that those companies that made strides to pivot their business focus to gene and cell therapy are reaping the rewards. Fortunately, the industry still has an abundance of space for new players to position themselves to enter and Fieldfisher are well equipped to help businesses at all stages to unlock this opportunity.

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3 P. Hourd, A. Chandra, N. Medcalf and D.J. Williams, Regulatory challenges for the manufacture and scale-out of autologous cell therapies (June 30, 2014), StemBook, ed. The Stem Cell Research Community, StemBook, doi/10.3824/stembook.1.96.1.
What are ATMPs?

ATMPs are medicinal products that are prepared industrially or manufactured by a method involving an industrial process.

Over time, ATMPs have shifted the traditional strategy of “one-size fits all” to a more personalised medicinal approach as cell therapies, for example, can be allogeneic (universal) therapies where the therapy is dependent on a single source of cells (donor) to treat several patients.

To date many of the approved cell therapies have been autologous, where the cells are derived from the patient, modified, expanded and used to treat the same patient.4

There are three main types of ATMP:

1. Somatic cell therapy products consist of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered. Somatic Cell therapies include the use in humans of autologous (coming from the patient), allogeneic (coming from another human being) or xenogeneic (coming from animals) somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means.

2. Gene therapy medicinal products contain an active substance consisting of a recombinant nucleic acid used in, or administered to humans to regulate, repair, replace, add or delete a genetic sequence, with the therapeutic, prophylactic or diagnostic effect relating directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

3. Tissue engineered products contain or consists of engineered cells or tissues, and is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue. A tissue-engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices.

In addition, some ATMPs can be referred to as Combination ATMPs. Combination ATMPs incorporates as an integral part of the product, one or more medical devices or implantable medical devices as well as a cells or tissue component. The cells or tissue component of the product must contain viable cells or the non-viable cell or tissue component of the product must be liable to act on the human body with action that can be considered as primary to that of the device.

4 Farid and Jenkins, 2018, De Riva, 2020
The European landscape

Unsurprisingly, the CGT market is dominated by North America, with 60% market share\(^5\) : Europe follows but has a steep hill to climb. So why the disparity between North America and Europe?

There are currently only 10 ATMPs available within the European Union\(^6\), despite there being in excess of 386 current clinical trials being conducted across the EU. So, why with all the early stage activity are approved treatments so low?

In an article by Labiotech.eu, the journalist alludes to the youth of the European market\(^7\). In another article, the same publication asserts that EU regulations are what has stagnated the CGT market in Europe\(^8\).

Once a drug is granted marketing authorisation within the EU, it is then approved across the EU for use. However reimbursement, which is arguably the determining factor in the commercialisation of CGT, is still decided at a national level\(^9\).

Additional practical challenges are the limitations in the application of existing regulation and GMP guidelines to smaller scale batch manufacturing.

Many of the current regulations/GMP guidelines in place are still tailored to large volume/batch manufacture of conventional small molecules. This can be restrictive for some ATMPs where a batch is for a one patient dose.

This presents a conundrum in that while the move to decentralised or point of care manufacturing may be productive, overcoming these more dated GMP guidance lines is likely to be a challenge.

For example, Qualified Person (QP) certification of an autologous, one unit batch within a hospital setting, could prove cost prohibiting.

Below we look at some of the key CGT hotspots across Europe.

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\(^7\) https://www.labiotech.eu/in-depth/atmp-cell-gene-therapy-ema/

\(^8\) https://www.labiotech.eu/trends-news/eu-regulations-cell-gene-therapy-trials/

The European landscape continued

United Kingdom

The number of ATMP clinical trials in the UK continues to increase year-on-year, with 154 trials reported as ongoing in 2020, indicating more than a 20% increase from 2019. This is representative of approximately 12% of all ATMP trials in progress globally.

Gene therapy trials currently account for 70% of the ATMP clinical trials in the UK, somatic-cell therapies account for approximately 20% of trials, whilst tissue engineered therapies make up the remaining 10%.

In 2020, there were 26 UK GMP manufacturing facilities and nine licenced ATMP products approved for use. Total financing for UK ATMP companies between the years 2018-2020 was £1.7bn contributing to over 3,000 people employed in the sector.

Alongside France, the UK leads in Europe for CGT but its potential has not been completely untapped. There is a real need to streamline the authorities that oversee CGT, for instance both the Medicines and Healthcare products Regulatory Agency (MHRA) and the Human Tissues Authority (HTA) are competent authorities in the process.

Multiple regulatory authorities for CGT is a theme that can be seen across Europe.

However, there was a significant breakthrough for CGT in May 2021, when the UK’s first patient received gene therapy treatment Zolgensma®, reimbursed by the NHS. As highlighted earlier reimbursement is a critical issue in getting product to market.

In this particular case, Novartis, producers of Zolgensma® struck a deal with the NHS, offering a discounted price, becoming only the second medical treatment for children with SMA to be available on the NHS, since Spinraza® became available in May 2019. This is a good indicator to those in the CGT space that the pathway to market for innovative treatments is getting clearer.

Regulations and Licenses in the UK

In the UK, the MHRA is the competent authority for clinical trial authorisation for all medicinal products, including ATMPs and for UK manufacturers or importers of ATMPs whilst the HTA is responsible for regulating human tissues and cells intended for human application.

Establishments which import, export or store tissues and cells intended to be used as the starting material in the manufacture may require an HTA licence for these activities. A licence for processing may also be needed if the tissues or cells are processed prior to the commencement of manufacturing.

Examples of where this could apply would be the derivation of early cell lines or banks prior to establishing a Master Cell Bank (MCB), or the banking of tissue where the future use is unknown but could include the manufacture of an ATMP.

Moreover, to undertake a research study involving gene therapy, embryonic stem cell therapy, the therapeutic use of genetically modified stem cells, or therapeutic xenotransplantation, researchers may also need to apply to an NHS Research Ethics Committee (REC) for approval prior to commencing studies. The Gene Therapy Advisory Committee (GTAC) is the UK national REC for gene therapy clinical research according to regulation 14(5) of The Medicines for Human Use (Clinical Trials) Regulations 2004.

There are two ways in which unlicensed ATMPs can be made available in the UK - namely under the Hospital Exemption or the ‘Specials’ schemes. Manufacturers need authorisation from the MHRA in order to use either scheme.

A Specials Licence (MS) is needed for the manufacture and supply of unlicensed ATMPs for human use outside of clinical trial whilst cell or gene therapies used in clinical trials must be manufactured under an MIA (IMP) Licence (Manufacturers Authorisation for Investigational Medicinal Products).

Post-Brexit

Now that the UK has left the EU, debate continues around how this will impact the future of CGT in the UK and new ventures in this area.

Since 1st January 2021, ATMPs have been regulated nationally in relation to Great Britain by the MHRA according to the same principles that previously applied. In Northern Ireland ATMPs will continue to be regulated according the European Medicines Agency’s (EMA) Centrally Authorised Procedure. This means that marketing authorisation applications for ATMPs will be assessed in accordance with the general provisions in place for the licensing of medicines, taking the specific requirements for this group of medicines into account.

Looking to the future at the manufacturing challenges for advanced therapies, the MHRA is developing a framework for point-of-care manufacture in 2021.

Despite the uncertainties that Brexit may have created in the sector, and as mentioned briefly above the Cell and Gene Therapy Catapult’s 2020 ATMP clinical trials database and report indicates that there has been in fact a 20% growth in the number of ATMP clinical trials in the UK since 2019.

One particular feature in the report is the increased number of commercially sponsored trials from 89 to 115 trials since 2019.

These figures suggest that international companies continue to invest in the UK as a location of choice for their ATMP trials, including those in late phase as commercialisation approaches. Businesses that continue to draw their attention to ATMP efforts will be setting themselves up to be ahead of positive change and benefit from inherent opportunities.

Focusing on the recently COVID-19 pandemic and the race to get a vaccine to the market we can see that some much needed agility has been applied to the UK CGT market. This is evidenced by the fact that the MHRA speedily approved the use of multiple COVID-19 vaccines (mRNA and Adeno vectors), whilst in contrast the EMA were arguably slower to act.

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11 The Medicines and Healthcare products Regulatory Agency (MHRA)-ATMP: Regulation and Licensing Guidelines
The European landscape continued

Will UK be the crown of Europe?

The UK is a world leader in the development of advanced therapies, contributing to the growth of the life sciences industry. There is a strong academic and commercial early-stage bioscience research base, in addition to access to clinical trial infrastructure and patients via the NHS.

Several UK government initiatives have helped foster innovation in the life sciences sector. For example, the Cell and Gene Therapy Catapult, supported by Innovate UK, was established in 2012 to bridge the translational gap between early stage research and late stage clinical development, and build a world-leading cell therapy industry in the UK. Furthermore, to help address manufacturing challenges, the MHRA is developing a framework for point-of-care manufacture due to be published at some point in 2021.

Challenges

At a meeting in June 2019, NHS England Accelerated Access Collaborative (ACC) identified three main issues in preparing for and securing sustained uptake of approved ATMPs:

(a) Lack of clinical data about patient outcomes;
(b) Limited experience in implementing ATMPs in joint pathways between the NHS and industry; and
(c) Variation in the clinical areas and use of ATMPs.

The ACC has a mandate for accelerating the adoption of promising products, which are early stage (pre-NICE approval), and late-stage (post-NICE approval) and regulatory systems are being put in place for these innovations.

The ACC highlighted that greater clarity and agreement on patient numbers, placement on the patient pathway, diagnostic requirements, and co-location is a recognised requirement in the AMTP sector. The variation of manufacturing and implementation including workforce-training requirements and on-boarding for providers also presents significant challenges and without collaboration ahead of value assessment, there are risks of delay to adoption downstream.

To facilitate the uptake of advanced therapies the UK government has developed a network of Advanced Therapy Treatment Centres (ATTCs). Established in 2018, the ATTC network is a world-first, UK-wide system of Advanced Therapy Treatment Centres (ATTCs) operating within the NHS framework. These centres are supporting the opening of multiple ATMP clinical trials in a range of diseases across the country, and are developing and sharing best practice with other hospitals to increase adoption of ATMPs across the UK.

Collaboration between industry and academia is vitally important in this sector area. For instance, The Advanced Therapy Manufacturing (Good Manufacturing Practice (GMP)) Platform at the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at Guy’s and St Thomas’ NHS Foundation Trust and King’s College London is a research platform designed the production of ATMP clinical studies, and early phase clinical trials.

Being located co-located on the 15th floor of St Guy’s Hospital with the MHRA Phase I Clinical Research Facility (CRF) and the BRC’s Flow Cytometry and Immune Monitoring Platforms provides a unique environment for ATMP studies to be undertaken. This unique co-location enables the manufacture and administration of ATMPs to patients within one site, and deliver trial endpoints.

Increasingly, industry is also participating in active collaboration with UK Universities for CGT research. Pfizer for example has joined with 15 of the UK’s leading universities to create the Rare Disease Consortium (RDC) and in 2015, Takeda joined forces with UCL to find new targets to treat a range of neurodegenerative diseases.

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12 NHS England: accelerated access collaborative advanced therapy medicinal products (ATMPs).
Commercial funding

From a commercial point of view, ATMPs present a different scenario to that of pharmaceutical medicines in that there is not a classic supply and demand model largely because ATMP therapies are more likely to have a patient pull to fulfil an unmet medical need.

In addition, the clinical development of ATMPs does not typically follow conventional clinical trial phases unlike traditional medicine. It is often the case with rare disease indications, that ATMP clinical programs are compressed into one or two clinical studies, followed by conditional approval with post-marketing commitments. To this end, ATMPs often utilise Early Access Programs, which allow for supply to patients prior to marketing approval.

Furthermore, another barrier to the commercial viability for ATMPs is the supply chain, which contributes significantly to the overall cost of goods and is limited by infrastructure, temperature requirements and, of course, the time-frame for transportation taking into consideration cell viability. Poor co-ordination of supply and logistic conditions have the potential to negatively affect the quality of ATMPs.

Manufacturing, logistics and supply chain challenges

The manufacture of ATMPs is a specialist area. ATMPs require complex, critical starting materials compared to New Chemical Entities (NCEs) and standard biologics.

Manufacturing is one of the biggest challenges facing ATMP developers looking to in-license products as many of those projects originate from academia or hospital research and the method of manufacture used is can often be unsuitable for, or unable to support, later-stage development.

In addition, the supply of and continuity of quality raw materials can also have a significant impact on manufacture as well as the maturity of production technologies, GMP requirements, variability and process validation.

To make cell and gene therapies more accessible, manufacturers are increasingly looking to reduce costs by utilizing continuous manufacturing and digitization. For example, digital health could lead to better trial recruitment and help monitor medicines in patients, post-approval.

The total number of UK licenced facilities has remained at 26, of which 11 are commercially owned – including two with commercial production (MIA) licences – Oxford Biomedica which has four commercially licensed facilities all based in Oxford and the Cell and Gene Therapy Catapult in Stevenage. The network of 26 facilities in the UK, operated by 21 organisations, comprises 11 dedicated cell therapy sites, eight dedicated gene therapy sites, and seven multifunctional sites13.

Robust connected supply chains and near patient GMP is a pre-requisite for successful ATMP sector development. One of the barriers to the commercial viability for ATMPs is the supply chain logistics for the incoming apheresis units and the final product, which can be limited by infrastructure, temperature requirements, scale and, the period for transportation taking into consideration cell viability.

Key trends seen as improvements in supply chain logistics include, more therapies being devised as allogeneic products as they attract lower and simpler logistics, cryopreservation and ensure longer shelf life.

In 2019, the ThermoFisher Scientific CryoHub received its MHRA licence for the cryogenic storage of material and global logistics solutions, and a greater number of companies such as Glycostem, Cell Medica and TC Biopharm are building their own in-house facilities, as a long-term investment that can decrease expenses related to third-party services and technology transfer, while safeguarding production expertise.

13 Catapult: Cell and Gene Therapy Manufacturing in the UK: November 2020
The European landscape continued

The use of block chain technologies is used to digitally connect and integrate supply chain with manufacturing to address the security, scheduling, and communication issues between advanced treatment therapy centres and manufacturing facilities.

The systems adhere to the EU, UK and US Good Manufacturing (GMP) and Good Distribution Practices (GDP) and regulatory requirements. An integrated block chain solution to supply chain and manufacturing of ATMP’s would permit a safer and more secure therapy delivery process.

Pricing and Reimbursement

A critical feature of ATMPs is price. Tisagenlecleucel has a U.K. list price of £282,000 for a one-time infusion14 and Strimvelis® costs £594,000 per patient15.

Consequently, providers are faced with difficult decisions concerning their value for money, reimbursement, and budget impact implications.

Unlike typical pharmaceuticals, cell and gene therapies fall under various regulatory categories which impact pricing, reimbursement and market access.

Additionally depending on size of target population, funding routes may vary from individual funding requests at local hospital level (e.g. for cell and gene therapies targeting diseases with single digit incidence), to formal product evaluations at national and/or regional level (where larger patient populations are concerned).

In the United Kingdom, the National Institute for Health and Care Excellence (NICE) evaluates ATMPs through two different HTA processes: the STA (Single Technology Appraisal) or the HSTP (Highly Specialised Technologies Programme).

The STA is used for products targeting non-rare diseases and relies on cost-effectiveness analysis (CEA); the HSTP evaluates products for ultra-rare diseases, allowing a higher Incremental Cost-Effectiveness Ratio (ICER) threshold16.

To date, patient access to ATMPs in England has been relatively good, with largely positively decisions from the NICE. Examples of U.K appraised ATMPs include, Kymriah® and Yescarta® which have been evaluated through STA, while Strimvelis® and Luxturna® by HSTP.

As many as 70 ATMPs could become available in the United Kingdom by 2024, although not all will progress to gaining marketing authorisation17.

In 2017, Strimvelis® was recommended, within its marketing authorisation, by NICE as an option for treating adenosine deaminase deficiency–severe combined immunodeficiency (ADA-SCID). It was the first gene therapy to be funded by the NHS.

Furthermore, both the NHS and the NICE have been hailed by industry for the quick acceptance and funding in particular of CAR-T cell therapy. NHS England’s commercial deal with the manufacturer Novartis was the first full access deal on breakthrough CAR-T therapy in Europe, and came less than 10 days after the treatment was granted its European marketing authorisation. It represented one of the fastest funding approvals in the 70 year history of the NHS. The viral vector used to transduce patient T-cells to produce Kymriah® is exclusively manufactured in the UK by Oxford Biomedica.

In the UK, Patient Access Schemes (PAS) are routinely used for ATMP pricing, and are one way in which pharmaceutical companies can lower the acquisition cost of a medicine for the NHS, enabling patients to gain access to high cost medicine treatments.

Essentially, PASs are confidential pricing agreements proposed by pharmaceutical companies to enable patients to gain access to drugs or other treatments that may not be considered to be cost-effective under normal circumstances. In some forms, they are known as ‘risk sharing’ or ‘rebate’ schemes. In effect, there are usually forms of simple price discounting, which enable companies to retain control of (undiscounted) list prices across countries but also, in principle, facilitate renegotiations of the discount should the need arise.

Challenges

Despite consideration to support and accelerate ATMP authorisation, patient access remains a challenge. Cell and gene therapies present particular difficulties for health technology assessment bodies (HTAs), such as NICE. Due to the personalised nature of cell and gene therapies, they are generally expensive to manufacture and administer and there may be a lack of data available to assess their cost and clinical effectiveness because of small patient populations.

In addition, cell and gene therapies tend to be one off treatments but they have the potential to deliver substantial long-term health gains, meaning large up-front costs for the NHS. This is very different to how the NHS currently pays for medicines18. As therapies continue to come to market, NHS England, NICE and the industry will need to continue to work together and remain flexible to ensure NHS patients can access treatments.

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17 Davis H. Specialist Pharmacy Services Horizon Scanning Lead. Personal communication, 14 February 2020
18 UK BioIndustry Association: Cell and Gene Therapy Explained
France

Similar to the UK, France has become one of the most influential countries on the CGT scene not only within Europe but also globally. France has a rich history of trailblazing in this area.

Notably, in the late 1990s, France conducted a gene therapy trial, treating immune-deficient babies whose life expectancy would have been three to four years. While some developments post-trial led to it eventually being shutdown, it was deemed a success because in the majority of children involved, it did suppress symptoms of immune deficiency\(^\text{19}\). But what has happened since then?

Back in May 2011, ATMPs were incorporated into national legislation in order to comply with the European Regulation of 13 November 2007, which had previously excluded it. Whilst the regulatory requirements for marketing authorisation under EU law still apply in France, there is a national workaround where by ATMPs can receive a national authorisation known as ATMP prepared on a non-routine basis (MTI-PP).

This allows the use of ATMPs that are made in France (by a pharmaceutical manufacturer or an authorised hospital by the French Medicine Agency (ANSM) and used only in French hospitals under the responsibility of a physician, and in accordance with a medical prescription for an individual patient. The ANSM grants the HE authorisation and in practice, some hospitals in France use this process to get authorisation.

Furthermore, in January 2020, the High Authority of Health (HAS) affirmed that between 2020 and 2021, more than 20 gene therapies will be available on the market.

Interestingly, some people have raised concerns that the national authorisation for ATMPs in France is a threat for pharmaceutical companies because its legal definition is not strict and its regime could be used for products that could be covered by marketing authorisation under EU law.

However, this authorisation is a good opportunity for hospitals in a financial context, as it could provide access to new financial resources.

In addition, hospitals benefit from a favourable opinion from the public authorities, and the risk of hospitals being sanctioned for their (wrong) application of the HE rules is low.

Ireland

Ireland is fast becoming one to watch when it comes to ATMP development in Europe. Over the last few years, there has been a significant effort to position itself as a key market for the life sciences sector, particularly for CGT.

Current landscape

Nine of the top 10 pharmaceutical companies are present in Ireland and in a recent report by IDA Ireland, they stated that Ireland is ‘becoming a hub for investment into cell and gene therapy development and manufacture’.

With the Irish government and the Health Products Regulatory Authority (HPRA) working closely with the industry to provide solutions for every area of ATMP development from research, to manufacturing and logistics, we’re bound to see increased investment and activity.

For instance, in February 2021, Japanese multinational pharmaceutical and biopharmaceutical company, Takeda, announced it was investing $36 million in a cell therapy facility in Dublin.

In Ireland, three ATMP products have been withdrawn from the market and one marketing authorisation application for an ATMP product expired and was not renewed.

The Health Products Regulatory Authority (the HPRA) is the regulatory body with responsibility for ATMPs and is also the regulatory body responsible for authorising clinical trials in Ireland. Clinical trials involving human medicinal products containing or consisting of genetically modified organisms also require authorisation from the Environmental Protection Agency (EPA).

The National University of Ireland, Galway (NUIG) has established the Centre for Cell Manufacturing Ireland (CCMI) as part of NUIG’s Regenerative Medicine Institute’s translational mission to manufacture human Mesenchymal Stem Cells (hMSCs) for use in clinical trials.

This facility was the first of its kind to receive regulatory authorisation from the HPRA to manufacture ATMPs in Ireland. The CCMI was granted a manufacturing authorisation in 2013 and was funded by the Health Research Board and Science Foundation Ireland. Linked to the CCMI, NUIG offers a postgraduate course in Cellular Manufacturing and Therapy.

EU funding has provided assistance to research and development of ATMPs in Ireland, through FP7 funding, including Merlin, which is aimed at new opportunities in stomal cell therapy R&D, and REDDSTAR, which develops and tests stomal cell therapy to treat for diabetes mellitus.

The Irish Research Council, associate agency of the Department of Education and Skills, under the aegis of the Higher Education Authority, has provided funding for postgraduate education research of ATMPs in Ireland.

Commercial development

The ATMP field is rapidly moving from a pure science focus, led by small industry and universities, to a focus on how to commercialise such therapies.

The high cost of ATMPs is predominantly driven by the small scale of manufacturing, the high degree of scientific testing required for the products and the need for ongoing patient monitoring testing which combined requires significant capital investment. Reimbursement of ATMPs is frequently mentioned as a major hurdle, both from a developer and health technology assessment (HTA) body point of view, as the manufacturing of ATMPs is considered more expensive by nature and is expected to impose pressure on healthcare budgets.

Combining the active ATMP pipelines with the prospect of healthcare budget constraints, sustainable ATMP reimbursement has become the next major challenge in this field.

Manufacturing, logistics and supply chain challenges

The main challenge for the import and export of human tissues and cells is the supply chain issue, which has a significant impact on the costs of the goods. Temperature requirements for transportation and storage is also a barrier and the mode of transport for ATMPs must have tailored temperature conditions, preservation techniques, and quality-control solutions.

Tracing requirements as per the Medicinal Products Regulations 2007 and 2009 mean that a system must be established so that both the raw materials and the ATMP itself can be adequately traced from sourcing to delivery of the product to the user. Adequate records relating to this must be kept to ensure full traceability and compliance with the Regulations.

The labelling requirements of the ATMP must be clearly displayed during transportation of the product to ensure it is adequately stored throughout the process and that it is delivered to the correct end user within the specified time period, as most living cells have a short shelf life of just a number of days.

Manufacturing constraints and the short shelf life of the product require the implementation of tight controls on logistical arrangements, which adhere to Good Manufacturing Practice (GMP), Good Distribution Practice (GDP) and ICH Q10 to ensure that patients receive these products safely at the correct time and within the shelf life.
The European landscape continued

Italy

Surprisingly, even though there is no uniform legislation on CGT in Italy, of the 11 ATMPs that have been approved in Europe, three of them were developed in Italy\(^{21}\).

The general authority on ATMPs in Italy is the Italian Medicines Agency (AIFA) and with their authorisation for production and use, it is possible to access ATMPs not yet authorised or not subject to specific clinical trials in Italy, in the absence of a valid therapeutic alternative, when the patient is in danger of loss of life or significant damage to health.

The time required for the release of the authorisation for clinical trials is still a critical issue in Italy: this can vary from a minimum of 95 days up to a time that is difficult to quantify in a clear and defined manner, with a possible delay in the activation of the trial.

Current Industry landscape

Over the past ten years, the pharmaceutical industry has been the leading sector for increasing employment, production, and exports in Italy. Therefore, the commitment by pharmaceutical companies to operate in Italy is very beneficial.

Moreover, Italy is a leading player in Europe for production and innovation due to investments that have grown more than the European average in the last five years.

For example, Strimvelis was the first ex-vivo stem cell gene therapy to treat patients with a very rare disease called ADA-SCID (Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency). MolMed S.p.A. a clinical stage biotech company focused on research, development, manufacturing and clinical validation of innovative therapies was founded in 1996 in Milan.

MolMed became the first company in Europe to have obtained the GMP manufacturing authorisation for cell & gene therapies ex vivo for its proprietary products as well as for third parties and/ or in partnership (Strimvelis\(^ {\circledR} \), an Orchard gene therapy for ADA-SCID).

Companies specialising in advanced therapies have played a decisive role by increasing their investments and forming partnerships with public structures. The collaboration of the public system with the company becomes indispensable in ensuring that research innovation reaches the patient.

Advanced therapies are part of the innovative medicines that two separate funds economically support in Italy, one for innovative oncological medicines and the other for innovative medicines. The Funds were established for the first time in the 2017 Budget Law, with an endowment of €500 million each and in the process of refinancing in 2021.

The European landscape continued

Commercial development

Italy boasts, among others, numerous centres of excellence in the field of ATMPs. Italy has 15 production sites and 27 development projects in seven different therapeutic areas.

Besides this, the national biotech drug sector has a turnover of €7.9 billion.

Based on this data, Italy has all the key elements to have the opportunity to play a leadership role at an international level. However, some issues are still on the ground in advanced therapies, there is no adequate regulatory path and effective public-private interaction.

Logistics and supply chain challenges

The decree of the Ministry of Health of 12 April 2012 provides rules for the import/export of human blood and its products. This decree does not envisage the involvement of subjects other than tissue banks and user centres, such as owners of advanced therapy products and the pharmaceutical workshops where production takes place.

Only biobanks, hospitals, and affiliated institutions can do this. In other words, companies could encounter some problems in receiving the raw material which will negatively impact the development of the therapies.

Regarding the need for complete traceability of the product along the entire distribution chain, as clinical studies of advanced therapy products are increasingly multicentric - involving more countries on different continents - the biological material used as starting material could be subject to international transport. However, the current regulatory framework would not allow the realisation of effectively rapid deliveries.

Pricing, reimbursement and market access

National market access requirements for ATMPs can be a potential obstacle to the availability of ATMP in national markets once centralized European authorisation is obtained. This is because the requirements and evidence required for the products’ innovative nature may go beyond the data available at the time of the marketing authorisation, consequently causing delays in getting the product to market.

We know that a crucial factor relating to market access requirements is the price, and these therapies can be costly. In this regard, the institutional bodies responsible for setting the prices of drugs and the companies that are entering the market are developing different payment systems.

In particular, the Italian Regulatory Authority is inclined to use ‘pay for performance’ formulas that can only be applied if combined with real world evidence based on reliable monitoring records. This approach somewhat works in Italy, as active and functioning registers are highly integrated within the Italian national health system.

In Italy, five therapies have already obtained reimbursement by the National Health System. Four of them were inserted in class H (drugs for exclusive hospital use and not sold in public pharmacies), the other was inserted in class C (the patient pays for it). AIFA recently used an example of the application of the “pay for performance” formula for the first gene therapy based on CAR-T cells.
Spain

As in any other Member State, in Spain ATMPs can only be marketed if a marketing authorisation has been centrally granted by the European Commission or a national license is given in the context of the so-called hospital exemption.

In this regard, similar to France, it must be noted that the hospital exemption has materialised in Spain as an authorisation for hospital use, which can be granted exclusively to hospitals, even though manufacturing can take place out of their facilities.

This authorisation may only be granted after submitting enough evidence on the quality, safety and efficacy of the medicinal product, which limits the scope of the hospital exemption in Spain to ATMPs with a consolidated use in the country or ATMPs that have already undergone the necessary clinical trials to obtain such data.

Thus, the hospital exemption is considered as an alternative to the marketing authorisation for non-industrially manufactured ATMPs, which are not intended to be regularly marketed, but not as an alternative to clinical trials with ATMPs, which are subject to general requirements.

In any case, it must also be noted that a single authorisation is needed for every hospital, which will be initially granted for three years, and then for five years in successive renewals.

Despite the limited scope of the hospital exemption in Spain, the Ministry of Health has shown a particular interest in ATMPs. Spain is currently developing a comprehensive plan for these sort of medicinal products, which already applies to ATMPs, such as Kymriah® and Yescarta®.

Pricing, reimbursement and market access

In this context, the most pertinent issue ATMPs have faced in Spain has been their reimbursement, given the high prices at which these products are usually financed.

Due to recent efforts by the Ministry of Health to lower the prices of medicinal products, the reimbursement of ATMPs has been limited to certain therapeutic indications, and conditioned on strict compliance with newly approved pharma-clinical protocols and on effective clinical results.

However, results-based pricing in Spain is rare, as the highly decentralised Spanish healthcare system makes it extremely challenging to collect comprehensive data in this regard.

This is why the Ministry of Health has recently launched Valtermed, a new information application, still in a preliminary phase, but already applying to ATMPs. Valtermed allows hospitals to communicate to the Ministry all administrative, clinical and therapeutic data relevant to the reimbursement of the said products, and upon which their price conditions will be reviewed.
While there are many bumps on the road, it is very clear that CGT is the future of medicine.

Yes, there are issues over regulations, manufacturing, protecting intellectual property, R&D, and supply chain logistics, but if at the final stages, companies face the roadblock of recompense then the determination to streamline the other issues diminishes greatly.

Uncertainty around reimbursement has led to questions over whether healthcare systems across Europe are compatible with the high price tag that comes with this treatment, which can run into the millions per patient.

Furthermore, as mentioned the US leads by a large margin for ATMPs and this is perhaps largely due to the insurance based healthcare model in the US that allows easier reimbursement for ATMPs.

Is it really about the money?

While the price tag attached to these treatments seems staggering, the reality is that when ATMP treatment is proved to be effective, it can potentially provide significant cost savings in comparison with alternative treatments that only help manage illnesses. The issue of Health Economics is a key influence on decision makers and healthcare systems across Europe.

For example, in FT Health’s special report Regenerative Medicine, it stated that gene therapy Zolgensma®, for spinal muscular atrophy (SMA), is priced at $2.1 million but the existing non-ATMP treatment for SMA costs around $4 million over the space of 10 years.
Can European healthcare systems accommodate CGT costs? continued

Post-Covid world and CGT

Initially, the COVID-19 pandemic had a negative impact on CGT as research, manufacturing and supply chains were disrupted and many companies saw themselves having to shift focus to COVID-19 vaccine efforts. However, the newfound reality is that the receptiveness from various governments, regulators and investors to the life sciences industry throughout the pandemic will herald in a new era for CGT production moving forward.

The COVID-19 pandemic highlights the importance of the biomanufacturing and bioprocessing sectors. The demonstrated flexibility and agility of parallel teams of UK scientists and regulators to speedily develop, manufacture and distribute COVID-19 vaccines and other therapeutics has provided evidence that the tried-and-true approach on speed-to-market for ATMPs needs to be revisited.

The ATMP sector is now more than ever seeking guidance on ways to expedite the development and approval of safe and effective treatments while maintaining its high standards of quality, safety and efficacy.

CGT is attracting a flurry of positive attention from large pharmaceuticals and biotechs through to smaller dedicated ATMPs producers, manufacturing specialists, investors and healthcare regulators.

Businesses that continue to draw their attention to ATMP efforts will be setting themselves up to be ahead of positive change and benefit from inherent opportunities.

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About **Pharmaceutical & Healthcare Sciences Society (PHSS)**

PHSS is an independent not-for-profit society that provides industry leading guidance on regulation and GxP best practice in the international pharmaceutical and healthcare sector. We are often considered a bridge between industry and regulatory bodies, offering impartial advice and best guidance through technical documents and special interest group collaboration. We are voice for all stakeholders in the industry, suppliers and customers.

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