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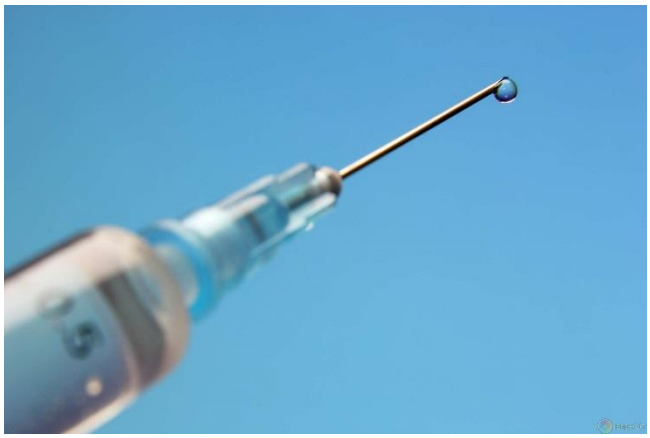
Regulating Advanced Therapies



Advanced Therapy Medicinal Products (ATMPs) are complex biological medicines which promise to transform the treatment of many diseases. There is debate as to how the development of ATMPs is affected by various factors including EU regulation and affordability. This POSTnote discusses ATMP development and regulation, and how this might change after Brexit.

Overview

- ATMPs are mainly regulated by EU law in which the UK's regulatory bodies currently have a strong voice.
- The UK has a strong ATMP sector, concentrated primarily in academia and small biotechnology firms.
- ATMPs are expensive to develop and administer but several countries use flexible reimbursement mechanisms to fund their use in patients.
- ATMPs offer potential cures for diseases that currently lack them or are expensive to treat long-term.
- Retaining harmonised ATMP regulation with the EU after Brexit is seen as key for patient access, clinical research, and for the UK to retain its lead in the field.

Background

Typically, medicines contain a single active ingredient and are made in large quantities to treat a specific condition in a large population. These medicines are regulated by efficacy, safety, and quality procedures, and monitored for their long-term safety after they have been licensed for use in patients.[1,2] Newer medicines can be more complex but are regulated on the same principles. Medicines involving modified cells, containing genetically modified material, or comprising engineered human or animal tissues are collectively known as Advanced Therapy Medicinal Products or ATMPs (Box 1).[3,4] One example is gene therapy, in which a working gene is delivered into patients with single gene disorders such as cystic fibrosis. Another is immuno-therapies[5,6] which have been some of the most promising recent developments in cancer therapy, particularly in the treatment of blood cancers. An ATMP developed by Novartis has recently been granted approval in the USA and is likely to soon be approved in the EU.[7] It works by genetically altering cells of the own patient's immune system and "re-programming" them to recognise cancerous cells. This specific group of ATMPs have attracted hundreds of millions of pounds in funding.

The Cell and Gene Therapy Catapult, a government funded platform designed to assist researchers and companies with commercialising ATMPs, regards the economic contribution of ATMPs to the UK as positive. There were approximately 50 ATMP developers and 22 licensed ATMP manufacturers in 2016.[8] It is speculated that the global ATMP market will be worth £9-14bn annually by 2025, with the UK comprising ~ 4%, higher than its market share of other medicines.[9] Cell, gene and tissue therapies present challenges to regulators as pre-existing regulations were initially designed around

Box 1. Advanced Therapy Medicinal Products

ATMPs are medicinal products that treat, prevent, or diagnose disease, which are comprised of genes, cells or tissues that have either been substantially manipulated or that are not intended to be used for the same essential function(s) in the recipient as in the donor.[4] They are classified as:

- Somatic Cell Therapy Medicinal Products, which contain cells or tissues that have been manipulated to change their biological characteristics, or cells or tissues not intended to be used for the same essential functions of the body.
- Gene Therapy Medicinal Products, which work by inserting genes into the body, for example to treat genetic disorders or chronic diseases.
- Tissue Engineered Products, which contain cells or tissues that have been modified in order to repair, regenerate or replace a tissue or an organ.
- Combined ATMPs, which contain one or more medical devices as an integral part of the medicine, such as cells embedded in a biodegradable matrix or scaffold.

less complex medicines. An EU Regulation implemented in 2008 attempted to address the regulatory challenges raised and created the medicinal category of ATMPs.[3] Since then, only nine ATMPs have been centrally licensed for use in the EU.[10,11,12]

Challenges include a perception amongst developers that there are many regulatory barriers to central licensing, circumvention of the ATMP Regulation via an exemption clause, and issues of affordability for healthcare providers.[13,14,15] This note explores these challenges and the potential impact of Brexit on ATMP regulation in the UK.

Regulating Advanced Therapies

Bringing a medicine to market, including an ATMP, has three main stages.[16] The first is scientific research and development leading to a candidate therapy. Secondly, this candidate therapy must be shown to be safe and effective in clinical trials and manufactured to agreed standards, before being licensed by a regulator. The Medicines & Healthcare Products Regulatory Agency (MHRA) regulates medicines in the UK and the European Medicines Agency (EMA) regulates medicines for the entire EU.[1,17] The EMA is responsible for the approval of ATMPs throughout the EU. Once licensed, the developer requires a market for the therapy. In the UK this is most likely to be the NHS, but only after the National Institute for Health and Care Excellence (NICE) has determined if a drug is cost-effective.[18]

Classification

Classifying a medicine as an ATMP is optional for a developer but enables access to advice from regulators and provides clarity on the development path to be followed.[19] Some exemptions can be applied and are discussed later. The classification is provided by the EMA's Committee of Advanced Therapies (CAT), a multidisciplinary body that assesses the quality, safety and efficacy of ATMPs and provides an advisory service to ATMP developers.[20] The CAT is comprised of nominated representatives from each member state; the MHRA represents the UK.[21] The CAT's classifications, such as "Tissue Engineered Products" are non-binding and the national regulatory authorities of Member States may classify products differently.[13,22] The classifications (Box 1) are broadly similar to those created by the Food and Drug Administration in the USA.[3] Apart from this classification process, ATMPs are regulated in much the same way as other medicinal products, requiring clinical trials and post-treatment surveillance.

European Law

ATMPs are regulated principally by European Regulation (1394/2007/EC), implemented in the UK in 2008. They can be subject to other EU laws, such as the EU Cell and Tissue Directives, depending on their composition and classification (Box 1).[3,23,24,25] The ATMP Regulation had three aims:

- to establish a unified framework to assess ATMPs and guarantee a high level of health protection for patients
- to ensure the free movement of ATMPs within the EU
- to foster the competitiveness in this sector in the EU.[3]

UK Regulations

The donation, procurement and testing of tissues, cells and starting materials for ATMPs are regulated by the Human Tissues Authority under EU legislation and the EU Cell and Tissue Directives.[26] The subsequent stages, including manufacture, storage, clinical trials and distribution, are regulated by the MHRA - also under EU legislation.[26] The Health Research Authority is responsible for assessment of governance and legal compliance of all project based research undertaken in England.[27] All the UK agencies involved in the regulation of ATMPs can be contacted through the MHRA's designated single point of contact, the 'One Stop Shop'.[28,29]

Exemptions from EU Central Licensing

Unlicensed medicines can be used outside of clinical trials such as in academic studies or in certain medical situations. In the UK, there are two exemptions through which ATMPs can be used to treat patients without going through the central licensing procedure:

- The **Hospital Exemption** within the EU ATMP Regulation enables 'non-routine' use of custom-made ATMPs to be prescribed to a patient by a physician to be used within hospitals in the same Member State.[4]
- The **'Specials' Exemption**, is the UK interpretation of Article 5.1 of the EU Pharmaceuticals Directive and allows an authorised healthcare professional to supply an ATMP for an individual patient under their responsibility to treat an unmet medical need (a condition for which no licensed treatment exists).[23,30]

There are three key differences between these exemptions in the context of ATMPs. The Hospital Exemption requires that the ATMP is prepared and used within the same EU Member State whereas the Specials allows for it to be imported from elsewhere.[4] The Hospital Exemption also stipulates that the ATMP is administered in a hospital whereas the Specials does not.[4] The final difference is that the Specials requires that no existing licensed product can treat the condition whereas the Hospital Exemption has no such requirements.[4] Outside of the central licensing procedure, the Specials Exemption is the favoured route in the UK for enabling patient access to ATMPs.

It has been suggested that the Hospital Exemption may deter developers from applying for central licensing which involves higher development costs and post-marketing obligations, such as long-term safety monitoring.[14,31] However, if an ATMP were not to be granted central licensing then its availability would be limited to the Member State in which it is produced.[4] It is important to note that under the exemptions it is not a requirement to collect long-term safety data, however many Member States' national healthcare agencies do collect this data.

ATMP Research and Development

ATMP development is undertaken by a wide range of organisations. Smaller ATMP developers concentrated in academia, hospitals, and small and medium sized

enterprises (SMEs) generally focus on rare conditions with smaller patient populations which lack any treatment or cure. Larger ATMPs developers, either existing pharmaceutical companies or large biotech companies, tend to focus on diseases with larger patient populations–such as cancers–which may already have treatments available.[13,32] For these reasons the challenges faced by ATMP developers are diverse. For smaller developers there are challenges in addressing the expense of development and the process of central licensing as they tend to lack specialised legal and regulatory knowledge.[13,33,34] Larger developers face challenges in delivering the therapies to patients, making them affordable for national healthcare agencies, and scaling up manufacture.[13,33,34]

Under the EU ATMP Regulation, as with all medicines, developers must obey stringent quality standards for manufacture and in clinical trials, known as Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) respectively.[35,36] These regulations apply equally to smaller and larger developers and are regarded as essential for patient safety, despite the high costs. However, after the implementation of the ATMP Regulation, a reduction in the number of both ATMP developers and the number of treatments offered was reported (Box 2).[14]

The EMA is developing guidelines for developers to promote ATMP development and patient access to ATMPs.[37] However, a stakeholder workshop convened in 2016 concerning these guidelines highlighted that it was not clear how the guidelines fit into the existing regulations.[38] One of the biggest challenges is to minimise the barriers for developers whilst still fulfilling the overarching requirement for patient safety. The finalised EMA guidance is expected to be published by the end of 2017.

Post-treatment Surveillance

As with all medicines, ensuring that data pertaining to the traceability of patient, product, and starting materials are stored and shared safely, is a key consideration. Under the EU Cell and Tissue Directives, all cell and tissue products must be traceable from donor to patient, and this information held for 30 years post-transplantation.[23,24,25] Following administration to a patient, data must be collected over a long period of time to understand the safety and effectiveness of a therapy, and to record side-effects and potential adverse events.[39] The Regenerative Medicine Expert Group regard the NHS as being in a unique position to address this and support ATMP development as a single, national healthcare provider, enabling effective monitoring of patient data.[40] However, this is not only a national issue and following Brexit sharing of such data with the EU may be problematic. This was explored in POSTnote 561.

Box 2. Case Study - Cells in the Treatment of Burns

Since the 1980s, Belgian cell banks had supplied human skin cells to treat burns to over 1,000 severe burn patients.[14] After the 2008 ATMP Regulation cell banks were notified by the Belgian regulators that their products were now seen as ATMPs, no longer permitting their use in patients, despite that inspections by the authorities had not revealed significant quality or safety issues.[14] Since this time further investment has enabled the use of human skin cells for burns therapy.

Infrastructure

The UK is regarded in the EU as a leader of ATMP research with a strong academic base and a particular focus on early stage clinical research. However, while the UK leads the EU in terms of ATMP manufacturing capacity, with 44% of the EU's GMP accredited facilities and projected free manufacturing capacity of 34% for 2017, none of the therapies licensed in the EU are manufactured in the UK.

The government has recognised the importance of the broader research area by establishing the Office for Life Sciences, supported an agenda for Regenerative Medicine, and invested in supporting infrastructure such as the Cell and Gene Therapy Catapult manufacturing centre in Stevenage.[41,42,43] The creation of the manufacturing centre in Stevenage will further expand the UK's manufacturing capacity but it has received mixed responses from some stakeholders, with worries that it could reduce demand for existing ATMP manufacturers and reduce private investment in such facilities.

Post-Brexit, UK-based ATMP developers want to ensure that the UK remains an attractive place for academics and industry, as the complexity of developing these medicines requires a high level of expertise, often at the post-doctoral level. The number of people qualified for the quality control and clinical delivery of ATMPs is also limited, as is the training pipeline for these roles. Several reports propose that in order to address these difficulties, the UK should establish specialist centres of excellence to concentrate expertise on treating patients with cell and gene therapies.[44]

ATMP Affordability

ATMPs are expensive to develop and manufacture. Of the ATMPs licensed in the EU, there are very few agreements by national healthcare authorities to pay for them, largely due to a lack of evidence on their cost-effectiveness.[45] Four of the nine centrally licensed ATMPs in the EU are unavailable for commercial reasons, such as a lack of manufacturing facilities and profitability.[46,47,48,49] For example, GSK expects to make less than 1% of its revenue for pharmaceuticals from its recently approved ATMP, Strimvelis. However this drug provides the only cure for a rare disease and represents a good example of how flexible payment enables ATMP usage in patients (Box 3).[50,51] A key aspect of these therapies is their potential to offer outright cures for diseases which are otherwise very expensive or impossible to treat. ATMPs generally have a higher cost per treatment, but many are administered only once, potentially reducing their long-term cost (Box 3).[52,53] However, given their initial expense, it is important to assess the longevity of the therapy outcomes as they will only be cost-effective if their effects are robust and long-term. NICE and NHS England have worked on adapting the existing framework to assess these therapies but it remains a challenge for the

Box 3. Strimvelis & Italy - Pay per Performance
GSK's Strimvelis is a gene therapy to treat ADA-SCID, an enzyme deficiency that leads to complete immunodeficiency, commonly known as "bubble-boy disease".[54,55] It affects approximately 12 children a year in Europe.50 The cost of treating these patients with the current gold-standard treatment of enzyme replacement therapy is hundreds of thousands of dollars a year.50 The Italian Medicines Agency will only pay the €594,000 price-tag for Strimvelis if the therapy works in a patient.50

NHS to fund these therapies with the resources available. Examples of how the challenges in balancing patient access, company reimbursement, and affordability have been addressed by other national healthcare systems include:

- **Exemptions**: The German healthcare authority has granted "unlimited" Hospital Exemption at full price for Northwest Biotherapeutics' brain cancer ATMP, DCVax-L.[56] This demonstrates how different Member States regulators interpret the Regulation, in particular the 'non-routine' clause of the Hospital Exemption.
- **Conditional approval**: In Japan, a few ATMPs have been granted a seven year conditional licence after only 2-3 years of development.[57] This allows for early profits, while clinical data are collected (Box 4).[57] A similar EU scheme exists with a less generous time provision of a one year rolling conditional licence.[58]
- **Adaptive pricing**: Approaches include flexible pricing, in which healthcare providers pay the full price over a number of years and pay per performance, in which companies are reimbursed only if their product works (Box 3).[50,53]

Box 4. Case Study - Japan's Regenerative Medicines Legislation
Under Japan's 2014 legislation, ATMP developers are now required only to have a single clinical trial to obtain safety data before they are granted a licence.[57] These laws enable a seven year conditional approval to be granted for an ATMP, allowing for profits while trials to assess the dosing and effectiveness of the therapy are underway.[57] During these seven years companies must continue to collect data on the therapy and, at the end, must apply for final licensing or withdraw the product.[57] This has resulted in several therapies being brought to market. All the cell therapies currently approved in Japan, though few, are entitled to reimbursement. In contrast, the EU has approved nine therapies, only a few of which have ever been paid for by Member States healthcare agencies.

ATMP developers regard a lack of integration with the NHS and NICE as a problem. Unless the NHS is willing to pay for the therapies, there is little motivation to market a product in the UK before other countries which are more willing to pay for them, such as Italy (Box 3). To address this, it is seen by ATMP developers as key for the NHS to fund these therapies and train the staff required to deliver them, which is difficult given the pressure on NHS resources. This will be a heightened issue post-Brexit as it is unlikely that pharmaceutical companies will seek a separate licence in the UK before the EU, leading to delays in access to medicines, including ATMPs.

ATMPs after Brexit

While there is uncertainty about the terms of Brexit, the EMA is working on the assumption that as of 30 March 2019, the UK will become a "third country" in relation to the EU (i.e. with an economic agreement outside that of the EU).[59] Licence holders of centrally authorised medicinal products such as ATMPs are required by EU law to be located within the EU or European Economic Area (EEA).[60] This means that any company wishing to market an ATMP in the EU must have a presence in an EEA or EU country which holds the licence. Many scientists are concerned that Brexit will negatively affect pharmaceutical research in the UK.[61] However, in an open letter, Ministers have stated that the UK wants the closest possible deal for working with the EU in the field of pharmaceuticals and science post-Brexit.[62] This statement was received positively by the pharmaceutical industry, for whom long-term stability is seen as vital for continued patient access to medicines.[63]

EU Harmonisation

Remaining harmonised with EU regulations and retaining the close relationship between the MHRA and the EMA is regarded by most stakeholders as highly advantageous to the future success of ATMP development in the UK. Remaining harmonised with the EU also offers advantages in conducting clinical trials and marketing which require larger numbers of patients than the UK alone can provide. This is of particular importance for those ATMPs which have tended to focus on rare diseases.

The MHRA is internationally respected and works closely with the EMA in developing its regulations and focussing on regulating with a pragmatic, risk-based approach. [64,65,66,67] The MHRA is also proactive in its engagement with ATMP developers. Given that MHRA supplies a significant amount of the lead scientific expertise to the EMA during the medicines approval process, and an even higher proportion in the field of ATMPs, there is uncertainty about how this collaboration will change after Brexit.[68,69,70] This is compounded by the fact that the EMA will relocate from London to Amsterdam by March 2019.[71,72,73]

Future Directions

Despite the uncertainty surrounding Brexit, it is suggested that it provides the UK with an opportunity to review ATMP regulation and adapt it to reflect national perspectives.[74] Recent industry, government and independent reports make several suggestions. For example:

- The Government has proposed the establishment of a 'Transformative Designation' for medicines which offer the potential for significant patient benefits and ATMPs would be prime candidates. This would streamline the approval process and allow faster patient access.[75]
- Industry stakeholders have suggested that the government develop a long-term regulatory strategy and plan for the MHRA to lead in global standards. [44] The government has acknowledged this as evidenced by its recent response to the House of Commons Inquiry into Regenerative Medicine.[74]

POST is an office of both Houses of Parliament, charged with providing independent and balanced analysis of policy issues that have a basis in science and technology. POST is grateful to James Cameron for researching this briefing, to the Medical Research Council for funding his parliamentary fellowship, and to all contributors and reviewers. For further information on this subject, please contact the co-author, Dr Sarah Bunn.

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