

INTERVIEW

Government Initiatives Promoting Cell and Gene Therapy Manufacturing and its Associated Supply Chain in the UK



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Q In your recently published article on adaptation through collaboration, you provided a nice overview of how orchestrated collaboration amongst key stakeholders had accelerated ATMP adoption. Could you give us a few examples of government initiatives that have been particularly effective?

MP: In terms of the collaborations, models such as ‘public–private partnerships’ have gained significant popularity in Europe. The biggest one among these is the Innovative Medicines Initiative (IMI), a partnership between the European Union and the European pharmaceutical industry. IMI collaborates on projects addressing issues around stem cells, which are the starting materials for cell and gene therapy essentially. We’ve seen a lot of progress and significant articles coming out of these initiatives. A couple of examples are STEMBANCC and EBiSC, which brings together not only commercial developers but also academic innovators that are pioneering the understanding of the way stem cells work and behave, to enable the standardization of how to handle and bank them and in the long term, how to use them in a quality assured manner to produce cell and gene therapies.

These collaborations are a very efficient way to bring together actors that would otherwise be competitors and allow them to develop shared knowledge and best practices that in the end will allow everyone to optimize their performance, safety and quality characteristics of their products.

In the UK, we have such an initiative on stem cells for sharing preclinical, clinical and pharmacological work, called Human-Induced Pluripotent Stem Cells Initiative (HiPSi). The initiative helps to share knowledge with European academic and developer networks.

Q Could you provide an overview of the existing consortia, private–public partnerships and accelerated development pathways that currently exist in the UK?

MP: We are currently seeing a shift from collaborations on basic and translational research and discovery to more product development, production and commercially relevant collaborations as well as stages of policy making around medicines regulation and approvals, market access and reimbursement.

The Early Access to Medicine Scheme (EAMS), and the Accelerated Access Review pathway are two pioneering UK initiatives by the UK’s Medicines and Healthcare Products Regulatory Agency (MHRA) and the Department of Health and Social care (DHSC), respectively. Although they’re not bricks-and-mortar collaborations per se, they’ve so far requested and welcomed multi-stakeholder engagement, input and dialogue, with the MHRA and DHSC already reaching out to industry and academic innovators and developers to understand the key requirements to adapt existing pathways and launch new schemes that could accelerate the patient access to breakthrough or transformative therapies.

The EAMS scheme established in 2014 is more progressed and its main focus has been around regulatory acceleration to allow earlier assessment of promising new medicines that do not yet have a marketing authorization and making them available to patients with life-threatening diseases when

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there is a clear unmet medical need. Under the scheme, the MHRA will give a scientific opinion on the benefit/risk balance of the medicine, based on the data available when the EAMS submission was made.

The more recent Accelerated Access Review is still evolving, being part of the DHSC’s plan for a faster adoption of innovative therapies in the NHS and UK-wide clinical practice. By leveraging learnings from and the future thinking of EAMS, this approach aims to strengthen the Early Access to Medicines Scheme, further taking into account how this fits with the EU Adaptive Pathways Pilot, as well as the NICE Technology Appraisal, the NICE Implementation Collaborative and other UK reimbursement schemes.

Although the UK aims to stay ahead of the curve through adoption of these schemes, similar initiatives to accelerate regulatory approval and reimbursement are also underway in Europe and other member states. We also have examples from countries like France and Italy where they’ve recently revised or launched new ways to reimburse and assess the value of orphan indications, or in a couple of instances also regenerative medicine and ATMP assets.

Table 1 (reproduced from [1]) gives an overview of the relevant licensing pathways in EU, USA and UK that can impact the acceleration of ATMP development.

Q What are some of the similarities and differences in initiatives that we see across geographies (e.g., USA, Japan, EU)? Are there any in particular that are effective, which the UK may consider adopting?

MP: The health systems across Europe and, more importantly, globally are quite different, therefore I wouldn’t necessarily say the UK should directly adopt them, but can certainly benefit from their experience. Although we’re seeing significant developments globally so far, strategies or pathways being rolled out in countries like the USA are tailored very much to their local healthcare policy landscapes, hence to say the UK could adopt them as such would probably be impractical, if not an oversimplification.

Certainly, it's worth looking into and trying to identify factors that could be added, embedded or in some way influence the forward-looking pathways currently underway in the UK. In the past 30 years, since the HIV epidemic, the US FDA has launched several accelerated and fast track schemes such as the Fast Track Scheme, the Accelerated Approval process, and more recently the Priority Review System and Breakthrough Therapy Designation. These new regulatory approaches aim at giving patients better access to innovative drugs, including regenerative medicine products by providing developers with continuous regulatory and scientific support and dialogue from an early development stage.

The main characteristics and principles these schemes consider include the level of unmet medical need for a certain disease, as well as the degree of innovation of the product being assessed. The relevant gravity of these factors changes the level of risk aversion of the FDA regulators to allow products to enter clinical use earlier, upon the requirement to continue to gather evidence through the real world patient use of these therapies. Such iterative approaches allow the real-time update of the regulators' decision-making criteria, as well as continuously inform the effectiveness and safety profile of the assets they're looking into.

The launch of the Breakthrough Therapy Designation scheme in 2012 was a regulatory watershed, and we've since seen a number of new ATMPs going selectively through that route. This potentially means it's providing a level of flexibility that is much more tailored to cell and gene therapies.

Another example which is much more focused on regenerative medicine and ATMPs is Japan's Sakigake expedited approval initiative, which allows preferential or earlier access of promising regenerative medicines to the market and to the patients for about 7 years, while they bring additional evidence to build the safety and benefit profile of the drug. The scheme requires the first commercial launch in Japan, making it a localized approach. This is also important because the Japanese population is quite homogenous compared to the genetic makeup across Europe or the USA, making it more straight forward to launch certain accelerated pathways.

Q Where in ATMP manufacturing and supply chain do you think exists the greatest need(s) for collaboration and innovation?

MP: With the advent of ATMPs, it is the first time we're seeing such a level of cross-dependency across different stages of the drug development value chain. With traditional small molecule drugs or biologics, each stage of the development pathway is considered almost like a box with very defined boundaries. To the contrary, with the ATMPs

▶ **TABLE 1**

Key examples of the existing and emerging pathways of relevance to ATMPs covering regulatory, reimbursement, and access and new stakeholder dialog platforms in EU, US, and the UK..

Region	Existing tools	New and emerging schemes	Platforms to facilitate adoption
EU	<ul style="list-style-type: none"> • ATMP regulation • Emergency use, exceptional circumstances • Orphan designation • ATMP hospital exception • Scientific Advice, Protocol Assistance • Compassionate use for unlicensed drugs • Conditional Marketing Approval 	<ul style="list-style-type: none"> • Accelerated assessment • Adaptive pathways pilot (lifecycle approach) • EU PRIME scheme on priority medicines Reimbursement: <ul style="list-style-type: none"> • Managed entry/patient access agreements 	<ul style="list-style-type: none"> • European Medicines Agency (EMA) Innovation Taskforce: for academics and SMEs • STAMP from EC Expert Group • Parallel reviews: <ul style="list-style-type: none"> – EMA/HTA scientific advice – EMA/FDA review • Registries and other PHV tools; EMA Registries pilot
USA	<ul style="list-style-type: none"> • Fast Track • Accelerated approval (with surrogates) • Priority review Reimbursement: <ul style="list-style-type: none"> • Coverage with evidence development 	<ul style="list-style-type: none"> • Special Medical Use (SMU) for disease subsets • Breakthrough Therapy designation • Regenerative Medicine Advanced Therapy designation (RMAT) Reimbursement: <ul style="list-style-type: none"> • Managed access for private payers 	<ul style="list-style-type: none"> • FDA Critical Path Innovation Meeting • Parallel Scientific advice between EMA/FDA
UK	<ul style="list-style-type: none"> • Early Access to Medicines Scheme (EAMS) • UK Specials • NICE Scientific Advice mechanism 	<ul style="list-style-type: none"> • Accelerated Access Review (AAR) • NHS Commissioning through evaluation • NHS Executive Specialized Commissioning schemes 	<p>MHRA Innovation Office Regenerative Medicine one stop shop* Innovation Partnership: NHS, MHRA, NICE, NIHR NICE Office for Market Access NICE 'mock' technology appraisal on CD-19 CAR-T</p>

ATMP: Advanced Therapy Medicinal Products. The list is not exhaustive. ATMP regulation: (EC) No. 1394/2007.

*The UK's One Stop Shop: includes MHRA, the Human Tissue Authority, The Human Fertilisation and Embryology Authority (HFEA), and Health Research Authority (HRA). Table reproduced with permission from [1].

there need to be almost a continuance of decision-making and evidence gathering to be able to finally and confidently characterize the benefit:risk profile of a new cell or gene therapy.

To be more descriptive, these therapies are different from conventional pharmaceuticals as the majority of them are patient tailored and patient derived, thus they call for for a continuum of processes across development and production, whereby the starting material comes from a patient and the final product is manufactured in near patient-environments and not in a manufacturing plant somewhere far. After a number of laborious quality controls, these products need to go back into the clinical setting

to be administered to patients, where they need to be handled by a very different set of clinical personnel not used to doing stages of drug product manufacturing, and finally be administered by clinicians through invasive procedures back into the patient they were initially taken from.

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ATMP manufacturing has a very different chain of events using techniques that have not been fully translated, scaled up or industrialized from the academic research setting. It's been difficult, as well as insufficient to just repurpose existing manufacturing techniques and

processes from small molecules and biologics, and tailor them to ATMPs. To truly commercialize this space, we also need to start developing new manufacturing and quality control processes; an area where we see a lot of collaboration. Both partnering and externalization of in-house operations are currently generating new manufacturing techniques and protocols that are being jointly developed by commercial developers, academics, suppliers and other service providers who know how to manage cost of goods, production timelines, quality controls and other product critical quality attributes (CQAs) that the regulators and health authorities need to see in order to be confident about the manufacturing quality of ATMPs.

Product supply is the second challenging element. The much bigger clinical and patient focus of these therapies requires that we gain the capacity to work in a different and more distributed way of manufacturing, rather than centrally in a manufacturing plant, as is the case with mainstream drugs. This requires increased capacity to spread the stages of production between the patient care settings and the quality controlled environments of cellular and genetic manipulation and production owned by the product developers or their external suppliers.

Engaging patients throughout the process also makes the clinical assessment more challenging. It's not easy to conduct the traditional randomized control trials (RCTs) involving hundreds or thousands of patients, given that each product comes from a single patient, creating a plateau on the capacity of a manufacturer to prepare materials for clinical trials. Moreover, the majority of cell and gene therapies currently being developed are for very rare or niche indications that require smaller clinical trials. Therefore, they require that regulators are open to accepting a more gradual build up of evidence, compared to what they're used to seeing with traditional small molecules and biologics.

This finally brings us to the later stages of the value chain, closer to the establishment and assessment of the reimbursable value of a product,

which is not easy to predict at the time of pricing and/or reimbursement negotiations. This is because of two reasons: as explained previously the size of clinical trials for ATMPs is smaller than conventional RCTs, at least in the majority of current indications under development. Secondly, the value of cell and gene therapies lies in their promise for long-term management or even the cure of a disease, which means that their effectiveness needs to be monitored in the actual real world setting after the patient has received the therapy, rather than predicted via clinical trials.

That makes the reimbursement assessment and negotiation schemes currently in place, which rely heavily on modeling and predicting product clinical and cost-effectiveness, of limited value calling for a shift towards new valuation frameworks. This has been the primary goal of the emerging iterative and accelerated pathways that allow the regulators, developers, as well as Health Technology Assessors (HTAs) and payers to engage in continuous interactions and monitoring of patient reactions to these therapies once they've received them. On that ground they can then retrospectively adapt or reassess their decision-making criteria, pricing arrangements or even the indication of the market authorization.

ATMPs are a fledgling therapeutic area, marking an unprecedented need to collaborate throughout the pathway of development of a new product, from discovery and early development to patient access and reimbursement.

Q Where do you see the biggest opportunity for government initiatives to impact the progress of cell and gene therapy commercialization?

MP: Various governments have initiated centers of excellence to accelerate the development of cell and gene therapies. Through Innovate UK, the UK government has launched a funding competition for up to £30 million to roll out the first network of three centers of excellence for cell and gene therapies in the UK, named Advanced Therapy Treatment Centres (ATTCs).

The goal of these centers is to provide an environment of collaboration between developers, manufacturing suppliers, tracking and transport/logistics systems providers, and the NHS clinical setting and infrastructure, to evolve manufacturing practices at the point of care, as well as the accompanying processes and manufacturing tools needed, and then try them in these environments. These networked environments will also allow the MHRA regulators to be included, as to understand and qualify these new tools and procedures earlier, as well as enable a more predictable enrolment of patient in clinical trials in these Centers, which can then be monitored continuously in real world settings. Additionally, these centers are required to establish

the IT infrastructure and databases to monitor and capture all the evidence throughout these collaborative processes, as well as pre- and post-treatment of the patient.

Another example of such a specialized collaboration is the GSK's partnership with Italy's San Raffaele-Telethon Institute for Gene Therapy, which is where GSK launched its first cell and gene therapy, Strimvelis, and is the only place where patients in Europe can get access to this medicine.

Looking at other countries, Germany with the Charite Institute is also putting in place a similar center of excellence. In Canada, CCRM is trying to do pretty much a very similar approach, bringing together developers with the Canadian health system and manufacturers around the establishment of novel supply and evaluation processes and infrastructure to accelerate the development and use of ATMPs in the country.

Alongside these collaborative initiatives and resulting policy outcomes, the UK needs to be fast in implementing the necessary infrastructure to understand not only how to discover ATMPs, but also make, test and deliver them to patients in this country, which is what the UK treatment centers are expected to spearhead.

FINANCIAL & COMPETING INTERESTS DISCLOSURE

M Papadaki is an employee of ABPI, the Association of the British Pharmaceutical Industry, the UK's trade body for branded medicine manufacturers.

This interview includes the authors personal views and not the formal positions or policies of her current or former employer organizations.

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