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Advanced therapies push regulatory boundaries

Novel therapeutic approaches require more regulatory flexibility and transparency

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The regulation of new medical applications has always been lagging behind the science that enabled these therapies in the first place, but emerging therapeutic approaches are pushing the boundaries harder than ever. Although fundamental principles around safety, efficacy and quality are cast in stone, new interpretations and greater flexibility are required for the clinical use of advanced medicines and treatments without introducing unacceptable risks. There are also ethical considerations that, although not new, are amplified by the potential of emerging therapies to address previously untreatable conditions.

All major regulatory bodies, such as the US Food and Drug Administration (FDA) and the European Medical Agency (EMA), have for some years been aware of the challenges posed in particular by Advanced Therapy Medicinal Products (ATMPs). These roughly include three categories: gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (SCTMPs) and tissue-engineered products (TEPs), many of which have emerged from the "omics" revolution and stem cell research.

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Advanced Therapy Medicinal Products

Both GTMPs and SCTMPs involve *ex vivo* manipulation of cells, but with a crucial difference in terms of manufacture and function. GTMPs deliver recombinant DNA to specific target cells in the body, whereas SCTMPs are whole cells or tissues genetically manipulated to change their biological characteristics or functions for preventing, diagnosing or treating disease. These cells can be autologous, coming from the patient, allogeneic from another human being or xenogeneic from animals. One recent example of GMTP is recombinant viral vaccines against cancer engineered from an immunogenic virus particle to express tumour antigens, cytokines or both [1].

SCTMPs were the first AMPs to be tested clinically in 1997 for corneal epithelial stem cell transplantation. Since then, the technique has been extended to include treatment of autoimmune diseases and cancer immunotherapy by manipulating tumour cells or the patient's own T cells. Yet, despite successful clinical trials, there are little data on the potential health risks associated with production processes and transplantation techniques, according to a recent paper [2]. The authors argue that culturing cells requires animal and/or human-derived products, which could introduce toxic or infectious agents through contamination.

TEPs, the third category of ATMP, involve larger-scale tissue engineering to replace damaged or diseased tissues or whole organs. The technique has already been applied to replace or regenerate bone, cartilage, blood vessels, muscle tissue and skin. It often uses scaffolds or matrices to provide structural support and chemical cues to encourage cells to migrate and differentiate to ensure the resulting tissue or organ works properly. These scaffolds are made from natural materials such as collagen or from synthetic polymers, while the cellular components can be of human or animal origin, with or without genetic modification. One example is the recent replacement of a bladder, where the scaffold was essential during the growth and embedding process after incorporation into the patient to handle the mechanical forces [3]. It also highlights some of the regulatory challenges in assessing the safety and efficacy of TEPs, because the scaffold must be strong enough for implantation of the tissue but must also be non-toxic and ideally of such a material and construction that it degenerates once it is no longer needed.

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There are also treatments that do not fall under the definition of ATMP, such as phage therapy to treat pathogenic bacterial infections, or gene editing. The latter has another dimension in that the technique is not confined to medicine but also extends to

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agriculture and the environment, raising regulatory challenges that may not be entirely unrelated. In fact, the FDA through its various departments is responsible for all these sectors and has been formulating a common strategy for regulating gene editing in each case, while taking account of the different applications and circumstances (https://blogs.fda.gov/fdavoice/index.php/2017/01/fdas-science-based-approach-to-genome-edited-products/). The main reason for this common approach is that, at the molecular level, similar risks of off-target mutations occur irrespective of the target genome. Furthermore, an edited gene may involve multiple pathways, creating potential for unintended consequences even where there are no off-target changes.

In the case of biomedical applications, the era of gene editing is just beginning, but the potential of the technique to be applied to any gene and not just those implicated in inherited disorders raises obvious ethical concerns [4]. Normally, consideration of medical products involves balancing risk and efficacy or patient benefit with a focus on curing disease rather than say cognitive benefits. However, there are bound to be some borderline cases, especially if it targets genes that play crucial roles in mental health or performance.

Hospital exemption and compassionate use

Meanwhile, there are some common themes arising from new therapies in general. Many of these use biological material and involve new protocols. This means that safety needs to be assessed carefully and that it may take many years to match the level of established therapies, as in the case of the corneal epithelial stem cell transplantation. Many advanced therapies have therefore been designated for last resort treatments when the bar for both safety and efficacy can be lowered. "The UK has a 'Specials' regime for products that are not licensed, that is not in clinical trials and not holding a marketing authorisation (MA)", noted Ian Rees, Unit Manager for Inspectorate Strategy and Innovation at the Medicines and Healthcare Products Regulatory Agency (MHRA) in London. "However, these products do have to be manufactured on a licensed premise which ensures that it and the products comply with GMP (Good Manufacturing Practice) for medicines. Products manufactured at these sites are made against a prescription to meet the special clinical needs of individual patients".

The EMA has a similar category called "hospital exemption" for ATMPs. Therapeutic products for which there are not yet enough data to gain full market authorisation (MA) may be granted permission for use in hospitals on a case-by-case basis for individual patients, when fully approved treatments have failed. But this can still be a cause for concern, according to Eve Hanna, pharmacist and analyst at Creativ-Ceutical, a consulting firm serving health authorities in France. "Even if there are good reasons explaining why these exemptions are needed, these products are used without concrete requirements on demonstrated quality, efficacy and safety", she said. "So this may be an issue to be addressed".

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As Rees pointed out, there is a wide range of medicines that have been granted exemptions and not always because they have unproven efficacy or safety—it can be a formulation that is tolerated better by specific individuals or groups. "There are a very wide range of products from the reasonably conventional, such as tablets or capsules, which have been modified for people who either can't take these as solids or with certain additives removed due to intolerance, through to a range of ATMPs for example skin cells, corneal stem cells and encapsulated liver cells", he explained. In some cases, ATMPs proceed to full MA status, as was the case with the nine therapies approved so far in the EU, which include treatments for prostate cancer, cartilage defects and metastatic defects of the knee (https://www.ehc.eu/european-commission-report-on-the-atmp-regulation/).

Most regulators are convinced that advanced new medicines do not call for radical changes of the underlying principles of evaluation. "Although technologies for gene editing are new for application in human medicines, the standard elements of medicines development and fundamental aspects of scientific evaluation still apply in order to assure the quality, safety and efficacy of the resulting medicinal products and to ensure that they are appropriately authorised, whether for mass market or individual treatments. They do not need to be changed", Rees commented. "A key part of the current healthcare regulatory regimes is to ensure that the correct product is given to the correct patient based on full scientific understanding". Even personalised medicines could be covered by the existing framework, since many treatments are already geared to the individual patient. "An example of current healthcare treatments that are clearly beneficial but can be dangerous in an unintended recipient is seen in blood transfusions, which MHRA also regulates, where cross-matching of blood groups is essential to avoid harm", Rees explained.

Ethical and legal challenges

Advanced medicines can also raise ethical and legal questions for compassionate use of unproven therapies. Such issues surfaced in the most infamous case so far, where an Italian group called the Stamina Foundation claimed it could transform mesenchymal stem cells from bone marrow into neural stem cells to treat various neurodegenerative diseases including Parkinson's disease or muscular dystrophy. Although these claims were dismissed as scientifically implausible and unsupported by any published data [5], Italian courts allowed compassionate use after patients clamoured for access to it. The saga eventually came to a close when criminal charges including fraud against the founder of the Stamina Foundation were resolved through a plea bargain. The case was an example of unsubstantiated hype about regenerative medicine, but it also exposed the tension between patients desperately seeking access to experimental medicines and the demand for evidence of efficacy and safety. In the Stamina case, a number of courts gave in to public pressure in granting access to the treatment, whereas the Italian medicine agency denied compassionate use given the total lack of published data [6].

US regulators have also come under pressure to accelerate access to investigational new drugs, as the FDA calls them. The FDA was heavily criticised in 2014 by the Goldwater Institute, which accused the agency of imposing a lengthy exemption process, by

which time it was often too late (https://goldwater-media.s3.amazonaws.com/cms_page_media/2015/1/28/Right%20To%20Try.pdf). That institute is known as a conservative and libertarian think tank with its own political agenda, and the FDA has been partly exonerated by a more recent report from the US Government Accountability Office, which pointed out that the FDA approved almost 99 per cent of the 5,800 requests it had received under its expanded access programme 2012 through 2015 and that nearly 96 per cent of these requests were for single patients (https://www.gao.gov/assets/690/685729.pdf). In the case of emergency cases, the FDA typically responded within hours and non-emergency cases within the allotted 30 days.

Nonetheless, this report called on the FDA to better communicate how it will use the data from such cases, which often involve seriously ill patients who would not subsequently participate in clinical trials. This addresses a more general issue, namely concerns among drug manufacturers and investors that adverse results from early access could prejudice later clinical trials and delay commercialisation. As a result, some smaller pharmaceutical or biotech companies have been denying expanded access for their own experimental drugs.

The FDA has responded by specifying that wherever possible, investigational medical products should be used as part of a clinical trial because the data would make subsequent approval more likely. More significantly, the FDA has also stated that its approval of an investigational product for use in a specific case will not "interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval" (https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm).

Cancer vaccines are one class of such advanced drugs that can be made available to patients as a last resort before undergoing full clinical trials. Unlike vaccines against infectious diseases, cancer vaccines are therapeutic and designed to stimulate the patient's immune response to tumour antigens. These present a major challenge to regulators, according to Raj Puri, director of the Division of Cellular & Gene Therapies within the FDA's Centre for Biologics Evaluation and Research (CBER). "Cancer vaccines, as well as cellular and gene therapy products, are extraordinarily complex, multifaceted, and subject to rapid change as the technology progresses", he said. This itself has triggered research to help revise regulations. "To facilitate the development of cancer vaccines and immunotherapy products, labs within CBER are engaged in regulatory science-related research in this area", Puri commented. "Scientists within CBER are studying aspects of manufacturing, product characteristics, and safety of cancer vaccines, as well as immunotherapy products in animal models. Researchers are also developing assays for lot release specifications. This research is fundamental to FDA's ability to provide effective regulatory review of biological products, including biological immunotherapies".

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This has already accelerated approval of some cancer vaccines, Puri contended. "For example, FDA's recent approval of Kymriah, the first gene therapy in the United States, marks a new frontier in the treatment of acute lymphoblastic leukaemia. Kymriah is a customized treatment created using an individual patient's own T-cells, which are genetically modified to include a new gene that directs the patients T-cells to target and kill their leukaemia cells. This approval represents an exciting advancement for the research community, health care providers, and most importantly, patients", he explained.

Phage therapy

Another area that is pushing the boundaries of regulatory practice is phage therapy for treating bacterial infections that are resistant to traditional antibiotics. It is really a category of its own: a product that replicates on site within the target pathogen. The use of phages to combat bacteria was first explored in the early 20th century by Félix d'Hérelle and Frederick Twort but interest waned in most of the world after the discovery of penicillin. But research on phage therapy has resurged in the past few years with the rise of antibiotic resistance and growing evidence of the efficacy, although there are still questions over commercial feasibility and safety.

First, there are concerns that, since phages cause lysis of the bacterial cells, release of debris could trigger potentially severe reactions, especially toxic shock. During Phase II and III studies, further complications can arise in trying to recruit a statistically relevant homogenous population. In the case of diabetic foot ulcers for instance, where phage therapy shows considerable promise, phages need to be effective against a number of different bacteria. This requires a cocktail of multiple phages since these are highly specific, often confined to a given bacterial strain. As a result, it could take time and multi-site studies to establish safety and efficacy for all components of such cocktails. "Correct diagnosis of the infecting organism at strain level will be a must in order to select the right phage cocktail for treatment", commented Eric Pelfrene, from the EMA's Anti-Infectives and Vaccines office.

In the EU, the introduction of the Clinical Trial Regulation in 2019 will enable the coordination of trials by specialist phage therapy centres, making best use of specialist knowledge and products. But, as Pelfrene pointed out, phage therapy is unlikely to be used widely until such large-scale clinical trials have been conducted. "The study typically would include a comparator arm, that is best standard of care, with an investigational arm adding phage therapy in surplus", he said. Pelfrene cited the ongoing "Phagoburn trial" in several centres as the biggest European study so far (http://www.phagoburn.eu/). It is a combined Phase I/II multicentric clinical trial currently running in three European countries (France, Belgium and Switzerland), at various hospital burn units to assess the safety, effectiveness and pharmacodynamics of two therapeutic phage cocktails to treat either *Escherichia coli* or *Pseudomonas aeruginosa* burn wound infections. The hope is to replace conventional antibiotics for reducing risk of sepsis, which causes more than 50% of deaths from burn trauma.

It remains to be seen if Phagoburn will be enough to gain full marketing authorisation for phage therapy without any changes to the regulatory framework. The underlying problem is that compared with antibiotics, there are currently no phage products that have satisfied established regulatory framework in Europe or the United States. This issue has been acknowledged by the EMA, which called for more clinical trials before

contemplating any adaptation of the regulatory framework [7]. To some extent, this is a challenge for most if not all emerging therapies, for even if the broad framework is adequate, research is advancing rapidly. It will take more regulatory diligence to ensure that the rules keep up with the science.

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