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Overcoming Challenges Facing Advanced Therapies in the EU Market

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While advanced therapy medicinal products offer great clinical promise, most EU-approved products have not achieved satisfactory commercial performance. Here we highlight a number of issues that prevent current products from obtaining commercial success and pitfalls that developers must overcome in future product development.

Recent developments in therapeutic technologies have enabled a much-needed shift from classical "one size fits all" protocols to personalized medicine strategies. Advanced Therapy Medicinal Products (ATMPs), comprising cell-, gene-, and tissue-engineered therapies, remain at the forefront of this advancement, contributing substantially to global biotechnology market growth. Due to their highly personalized nature, ATMPs are usually associated with high development and manufacturing costs (Abou-El-Enein et al., 2016), stringent regulatory requirements (Abou-El-Enein et al., 2014a), reimbursement challenges (Abou-El-Enein et al., 2014b), and complex interventional procedures. Although many advanced therapies demonstrate remarkable clinical trial results (reviewed in Trounson and McDonald, 2015), achieving positive therapeutic outcomes is only one factor determining market success for such therapies.

Currently, seven ATMPs are granted marketing authorization that is valid throughout the European Union (EU) (Table 1 and Table S1). While these products represent a welcome addition to current therapeutic arsenals for unmet medical needs and rare diseases, those marketed now for 3–7 years have failed to meet their pre-launch sales expectations and, in some cases, are being discontinued by their manufacturers and removed from the market. For example, within 1 year of obtaining EU-wide marketing authorization, MACI was suspended and Provenge was withdrawn from the market, both for poor commercial performance. Glybera, a gene therapy with a high price tag, currently struggles with insurance reimbursements. ChondroCelect, the first approved ATMP, will also be withdrawn in November 2016 due to commercial reasons together with the lack of reimbursement in key European countries. Here we examine the factors that account for these failures and describe a variety of possible remedies. This analysis focuses on the EU perspective, though many findings are relevant to other global markets.

Small Target Populations and Commercial Markets for Orphan Drugs

In early development of therapeutic candidates, the expected number of target patients serves as a major predictor of future market success. Nevertheless, therapies that target rare medical conditions, also known as orphan diseases, are increasingly being developed by small biotech and select larger pharmaceutical companies. The European Medicines Agency (EMA) offers 10 years of market exclusivity and reduced regulatory fees as incentives to develop orphan-designated products. Moreover, assuming clinical efficacy, market adoption of orphan medicines is expected to be faster than for conventional drugs due to the scarcity of other treatment options. This assumption is often incorporated by developers into their business model to attract operating capital. Three ATMPs (Glybera, Holoclar, and Strimvelis) received EU marketing authorization using orphan status. To date, only one patient has received commercially available Glybera (September 2015, Charité University Hospital, Berlin, Germany). For this single patient, the developer obtained upfront payment from the health insurance following direct negotiations (https://www.technologyreview.com/s/601165/the-worlds-most-expensive-medicine-is-a-bust/). Such therapeutics targeting rare diseases place manufacturers into a pricing predicament. To generate sufficient revenue, these therapeutics are highly priced, as is the case of Glybera, fueling discontent with both patients and insurers (Abou-El-Enein et al., 2014b). To address this, governments and the European Commission could take action by drafting legislation and guidelines that provide streamlined reimbursement schemes across all European countries (see below), especially for products that are urgently needed but expected to yield low financial returns on investments. While Glybera therapy was well tolerated and effective in reducing increased blood lipid levels, more cases are required to collect sufficient evidence supporting therapeutic efficacy during the post-marketing surveillance phase.

Insufficient Evidence to Support Product Reimbursement and Variations in Reimbursement Standards

Studies that compare clinical effectiveness of one therapeutic approach against other available approaches are usually lacking for ATMPs targeting diseases with limited treatment options. The results of such studies are therefore unavailable for performing health technology assessments (HTAs) to determine appropriate pricing and reimbursement schemes. As a result, pricing strategies for ATMPs are mainly based on manufacturing costs, market size, and cost utility analyses that

Table 1. Market Features of EU-Authorized Advanced Therapy Medicinal Products

ATMP	ChondroCelect	Glybera	MACI	Provenge	Holoclar	Imlygic	Strimvelis
Product Class	tissue-engineered therapy (based on autologous cells)	AAV-mediated in vivo gene therapy	tissue-engineered therapy (based on autologous cells)	autologous somatic cell therapy	tissue-engineered therapy (based on autologous cells)	oncolytic HSV-mediated in vivo gene therapy	ex vivo autologous hematopoietic stem cell gene therapy
Price tag	€20.000	€1.1 million	not available	$93,000 (only in the US)	not available	$65,000 (only in the US)	€594,000
National reimbursement in the EU	only achieved in three EU countries (Spain, Belgium, and the Netherlands)	not achieved	not achieved	not achieved	not achieved	not achieved	not achieved
Authorization outside EU	N/A	N/A	N/A	authorized by US FDA on April 29, 2010	N/A	authorized by US FDA on October 27, 2015	N/A
Current status in EU	available (will be withdrawn on November 30, 2016)	available	suspended by EMA on November 19, 2014	withdrawn by EMA on May 6, 2015	available	available	available
Time from filling until obtaining EU marketing authorization	June 1, 2007 to October 5, 2009 (circa 29 months)	December 23, 2009 to October 25, 2012 (circa 34 months)	September 1, 2011 to June 27, 2013 (circa 23 months)	December 30, 2011 to September 6, 2013 (circa 21 months)	March 6, 2013 to February 17, 2015 (circa 24.5 months)	August 28, 2014 to December 16, 2015 (circa 16.5 months)	May 1, 2015 to May 26, 2016 (circa 13 months)
Special considerations	N/A	subject to additional monitoring[a]; has orphan designation[b]; authorized under exceptional circumstances[c]	subject to additional monitoring[a]	subject to additional monitoring[a]	subject to additional monitoring[a]; has orphan designation[b]; authorized under conditional approval[d]	subject to additional monitoring[a]	subject to additional monitoring[a]; has orphan designation[b]

ATMP, Advanced Therapy Medicinal Product; EMA, European Medicines Agency; FDA, Food and Drug Administration.

[a]A medicinal product is usually subject to additional monitoring when there is less information available on it than on other medicines, for example because it is new to the market or there is limited data on its long-term use. It does not mean that the medicine is unsafe.

[b]An orphan designation is granted to a product when the prevalence of the treated condition in the EU is not more than 5 in 10,000 or it is unlikely that marketing of the product would generate sufficient returns to justify the investment needed for its development.

[c]Authorization under exceptional circumstances is eligible when an applicant is unable to provide comprehensive data on the efficacy and safety of a product under normal conditions of use, for example when the indication for which the product is intended is encountered very rarely as in the case of Glybera.

[d]A conditional marketing authorization is granted when a product qualifies as meeting an unmet medical need and is in the interest of public health but with less complete data than is normally required. This may apply to medicinal products with orphan designation such as Holoclar and the authorization is subject to certain specific obligations to be reviewed annually.

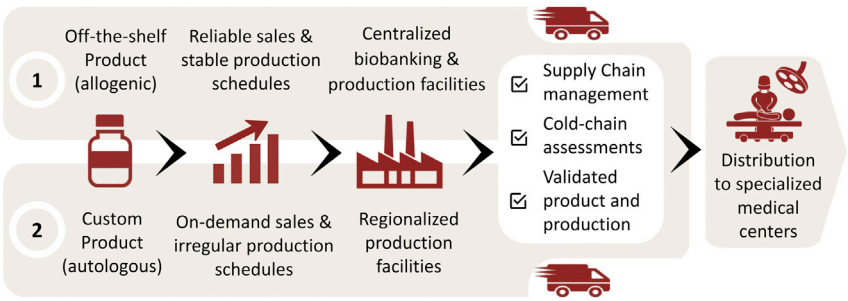

Figure 1. Assessing ATMP Product Supply Chain Strategies for Advanced Therapies in Post-marketing Settings

ATMPs have unusual production, marketing, distribution, and utilization requirements compared to other conventional medical products. These products must reach clinical provider sites intact with validated sterility, safety, and potency. Importantly, requisite economically viable and reliable production, preservation (cold chain assessment), and clinical batch distribution must be carefully developed and maintained. Typically, two possible scenarios govern the basic flow of ATMPs from manufacturer (developer) to distributor (specialized centers) to customer (patients). Substantial sales expected for allogeneic cells can be accommodated using large-scale manufacturing facilities with integrated biobank and cryopreservation protocols. Custom autologous cell-based and personalized products targeting rare diseases are limited and produced on demand, requiring multiple smaller regional manufacturing facilities directed at potential markets. The common supply chain objective is to eventually deliver these products, considering their shelf life and handling requirements, to specialized medical centers that have the necessary capabilities and infrastructure to provide the therapeutic products to patients in a controlled, safe environment.

consider valuations of potential benefits. Prices for such therapies are estimated in the high range considering the high costs associated with ATMP manufacturing, the small market size (especially for orphan products), and the potentially high utility of providing lifelong clinical benefits from a single application (e.g., as with Glybera). The insufficient evidence available on comparative clinical effectiveness of these new products may discourage healthcare payers from negotiating reimbursement strategies with developers. For instance, Provenge only exhibits an average 4-month mean survival prolongation in treated patients. This low clinical benefit does not justify its high cost, as indicated by the UK National Institute for Health and Care Excellence (NICE). The now-defunct developer of Provenge (Dendreon, USA) has been acquired by another pharma company aiming to cut costs and improve their marketing strategy to ensure better return on investment (Ledford, 2015). To overcome insufficient available evidence at time of assessment, developers should be engaged early in dialog with health insurers and consider other tools to maximize the reimbursement potential of cell and gene therapies (Abou-El-Enein et al., 2014b).

The HTA methodologies required to negotiate appropriate reimbursement strategies for orphan medications vary widely across different European member states, adding more complexity. For instance, the Swedish HTA is based on cost effectiveness, human value, and solidarity, while in Germany, HTA assessment relies solely on cost effectiveness analysis (Gammie et al., 2015). This extends further to pricing procedures; in the UK, for example, the incremental cost-effectiveness ratio is the basis for pricing, while in Germany, clinical benefit, budget impact, and international price potential are the basis for this determination. Moreover, payment models for gene therapies targeting rare diseases have also been debated (Abou-El-Enein et al., 2014b). Typically, reimbursement for most drugs is a lump sum, upfront payment during treatment. Due to the cost-density burden of cell and gene therapies on payers, upfront payments appear unfavorable. Several alternative approaches have been proposed such as annuity payments with risk sharing, which spread costs over several years contingent on the product's clinical efficacy (also known as pay-for-performance), and annuity payments without risk sharing (Carr and Bradshaw, 2016). These proposals, however, face several challenges for implementation, especially the pay-for-performance models due to a lack of accessible endpoints, among other reasons (Abou-El-Enein et al., 2014b; Carr and Bradshaw, 2016). Although risk-sharing may seem advantageous to payers, changes to current payment approaches may still encounter resistance, as exemplified by the single Glybera-treated case, which settled for upfront payment.

Complex Supply Chains and Lack of Standardization in Procedures

Unlike conventional therapies, supply chain management and lack of standardization in manufacturing procedures are critical factors that influence ATMP success rates (Figure 1). Cell therapies often have short shelf lives and are particularly sensitive to damage by inappropriate shipping conditions. For example, patient biopsies required for Holoclar manufacturing must be received by the manufacturer within 24 hr after procurement. Most importantly, this product has only a 36 hr shelf life; therefore, time transporting this personalized product from manufacturing sites to the site of patient administration must be direct and reliable; this may set severe limitations for worldwide application. Provenge has even more challenging conditions, where product shelf life is 18 hr in a cooled insulated container that must be infused within 3 hr once opened. Establishing regional manufacturing sites represents a possible solution and is a more suitable model for rare diseases or personalized autologous cell products (Figure 1). However, a de-centralized approach should be planned with care since having multiple manufacturing facilities may not be financially feasible, especially in markets with low or fluctuating sales. On the other hand, the use of central high-throughput manufacturing sites to prepare and cryopreserve allogeneic cell therapies and in vivo gene therapy products at lower cost, while maintaining product quality and minimizing batch-to-batch variation, is now considered by some biotechs and big pharma as the model of choice, particularly for meeting the demand for the clinically advanced chimeric antigen receptors (CAR)-T cell research programs to treat cancer (Walker and Johnson, 2016). Moreover, the manufacturers of ChondroCelect (Tigenix, Belgium) decided to withdraw their autologous product from the EU market and focus on its allogeneic stem cell platforms

as a more commercially viable pipeline. Therefore, developers must adapt their production capabilities to meet projected numbers of treated patients and avoid financial losses associated with operating manufacturing facilities.

Complicated Administration Techniques and Reluctance of Physicians to Use Advanced Therapies

ATMPs often require different formulations and relatively complicated methods of administration compared to conventional drug products. For instance, autologous cellular products such as ChondroCelect and MACI are administered via costly two-stage surgical procedures; one for tissue harvest and another for implanting resulting cell products. Patients receiving these procedures must understand both risks and compliance with a specific outpatient follow-up plan. Clinical success of any such product relies greatly on the skill of the surgical team performing the associated surgical procedures. Therefore, highly specialized technical training of the healthcare providers applying these novel therapies becomes critical to treatment success (Abou-El-Enein et al., 2014a). The novelty and uncertainties associated with ATMPs also render many physicians reluctant to use them on their patients, as the ATMP treatment risks would fall primarily on treating physicians. Market adoption of advanced therapies, therefore, cannot follow conventional models of company-physician relationships. Specialized medical centers associated with university hospitals, for instance, possessing the appropriate infrastructure and highly trained medical personnel could assume responsibility for integrating these new treatments into routine clinical practices and advertise them in an ethical fashion, so that wider patient populations are reached and treated successfully. Primary care physicians should then refer patients to these centers for ATMP treatments. This clinical implementation model might address intrinsic high production and shipping costs and shelf life issues (Figures 1 and S1) commonly associated with centralized manufacturing facilities (especially if establishing regionalized facilities is not justified) while avoiding liabilities from unauthorized product use and inadequately prepared clinical practices. These centers might more easily assume the functions of negotiating suitable reimbursement schemes with healthcare providers and payers. Legislation should consider these factors and grant market authorization for these products only if they are used in specialized centers with additional post-marketing surveillance. This model would also support the physician decision-making process while improving credibility for these products among patients and providing reliable and sustainable resources for follow-up, product traceability, and data collection on patient outcomes.

Potential Risks Associated with Administration of Gene Therapies

A major challenge for effective treatment using gene therapies remains their potential for stimulating an immune reaction and many such treatments thus require immunosuppression (e.g., Glybera), which adds to overall therapeutic risks for the product. Moreover, some gene therapies rely on the use of modified infectious virus (e.g., Imlygic) and given this formulation, the products carry risks of life-threatening viral infection in immunocompromised individuals. This risk also extends to healthcare providers and individuals accidentally exposed to the virus during preparation or product administration or those in close contact to treated patients. Therefore, a holistic approach to education, awareness, and support is needed for patients, their families, and their physicians to address potential benefits as well as possible risks associated with the therapeutic administration (Abou-El-Enein et al., 2015). Effective public outreach programs are required to identify the target audience and inform them of the potential risks associated with such therapies. Time and financial requirements for outreach activities, however, may limit contributions from the scientific and academic communities. Therefore, it is essential that such outreach programs receive support from governments with sufficient financial and human resources.

Inadequate Regulatory Knowledge

Lack of sufficient knowledge regarding regulatory requirements for ATMP approval in the EU by developers, particularly academic parties, may also contribute to small numbers of products reaching the market. Current complex regulatory approval pathways may inflict significant financial pressure on small biotech companies. For instance, Glybera approval took 3 years and four rounds of review by the Committee for Medicinal Products for Human Use (CHMP). Frequent reapplications of the marketing authorization request required for this process are costly and time-consuming, discourage investors, and hinder development processes. While EMA's Committee for Advanced Therapies (CAT) is very proactive in raising awareness about regulatory tools and incentives available for developers of advanced therapies, mechanisms to improve licensing pathways for these products while maintaining current rigorous, robust review processes as for other medicines appear critical. Initiatives such as the Breakthrough designation (US Food and Drug Administration), adaptive licensing, and EMA's PRIority MEdicines (PRIME) scheme have, therefore, been introduced to encourage innovative products addressing unmet medical needs and serious or life-threatening conditions, especially for ATMPs and orphan indications. Developers need to enlist support of regulatory experts at early stages to utilize these tools that facilitate their product development.

Looking Ahead

ATMPs promise curative treatment for many diseases, ranging from cancer to orphan genetic disorders. While market success for the EU authorized products has yet to be achieved, a growing number of gene-therapy clinical trials are reporting remarkable evidence for safety and efficacy in treating various severe inherited diseases. Some recent successes involve the use of adeno-associated virus-derived vectors for X-linked bleeding disorder and hemophilia B (factor IX deficiency) or transducing bone marrow hematopoietic stem cells with lentiviral vectors for targeting Metachromatic leukodystrophy (MLD), X-Linked Severe Combined Immunodeficiency (SCID), and adenosine deaminase deficiency (ADA)-SCID. Strimvelis, the first EU-approved ex vivo gene therapy for treating ADA-SCID, is an example of tremendous academic

efforts attracting interests from a pharma partner, GlaxoSmithKline (GSK, Ireland). Although Strimvelis' centralized authorization pathway will allow EU-wide product introduction, initially, all patients must be treated in Milan (where the product is manufactured) due to the drug's short shelf life until a cryopreserved product is developed that can then be shipped to different specialized medical centers. GSK priced Strimvelis at EUR 594,000 following negotiations with the Italian Medicines Agency (http://www.economist.com/blogs/economist-explains/2016/08/economist-explains-2), which is nearly half the price of Glybera, in order to facilitate patient's access to the therapy. It is however expected that high prices for advanced therapies will be reduced when manufacturing technologies reach a greater level of maturity, among other factors influencing market sustainability. With the intent of using Strimvelis as a catalyst for other possible ultra-rare indications, increased investment and market growth for cell and gene therapies in the coming decade is expected.

Notably, several limiting factors exist that block ATMPs from commercial viability and universal adoption by providers. Vigilance in abiding by our proposed stepwise approach (Figure S1) will enhance the process of translating these novel therapies into clinical applications that are sustainable on the market while involving all stakeholders at the most appropriate points early in the process. Probably most of these "best practice" approaches are already known to commercial developers, but they are often not mirrored in small biotech companies and academic research centers. Other procedural recommendations provided here could possibly contribute to stabilizing current volatile market activity (Brindley et al., 2011), ensuring survival of novel ATMPs in the healthcare marketplace and, therefore, limiting exploitation of vulnerable patient populations using unauthorized treatments.

SUPPLEMENTAL INFORMATION

Supplemental Information for this article includes one table and one figure and can be found with this article online at http://dx.doi.org/10.1016/j.stem.2016.08.012.

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