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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 For example, within 1 year of obtaining EU-wide marketing authorization, MACI was suspended and Provenge was withdrawn from the market, both for poor commercial performance.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 ChondroCelect, the first approved ATMP, will also be withdrawn in November 2016 due to commercial reasons together with the lack of reimbursement in key European countries.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.