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EU decision-making for marketing authorization of advanced therapy medicinal products: a case study

Q1 Sofieke de Wilde[1,‡], Delphi G.M. Coppens[2,‡], Jarno Hoekman[2,3], Marie L. de Bruin[2,4], Hubert G.M. Leufkens[2], Henk-Jan Guchelaar[1] and Pauline Meij[1], p.meij@lumc.nl

A comparative analysis of assessment procedures for authorization of all European Union (EU) applications for advanced therapy medicinal products (ATMPs) shows that negative opinions were associated with a lack of clinical efficacy and identified severe safety risks. Unmet medical need was often considered in positive opinions and outweighed scientific uncertainties. Numerous quality issues illustrate the difficulties in this domain for ATMP development. Altogether, it suggests that setting appropriate standards for ATMP authorization in Europe, similar to elsewhere, is a learning experience. The experimental characteristics of authorized ATMPs urge regulators, industry, and clinical practice to pay accurate attention to post-marketing risk management to limit patient risk. Methodologies for ATMP development and regulatory evaluations need to be continuously evaluated for the field to flourish.

Introduction

Over the past decade, there has been increased interest in the development of ATMPs towards marketing authorization. In 2009, Regulation EC No.1394/2007 came into force as the first specific regulatory framework for approval of this potentially new class of medicinal products in the EU [1,2]. By August 2017, the number of ATMP regulatory procedures for marketing authorization was 16, a number that has been coined as relatively low given the recent impressive advances in basic molecular and clinical Q2 science in the field of ATMPs [3–5].

It is well known that ATMP developers face various scientific and technological challenges, from manufacturing and quality issues [6] to preclinical and clinical efficacy and safety issues [1]. Moreover, additional hurdles in the trajectory towards approval are experienced by academic developers, such as a lack of regulatory knowledge, insufficient financial support, and clinical trial-related problems, such as recruitment [7]. Although Regulation EC No. 1394/2007 includes high-level requirements for approval, because the field is rapidly evolving, standardization of regulatory requirements for approval is difficult and perhaps undesirable. Consequently, during the decision-making process, regulators need to deal with novel issues that have not been previously discussed in other regulatory procedures [8]. Given these developmental and regulatory complexities, scientific uncertainties during benefit–risk assessments are prevalent.

In this study, we provide insight into decision-making for approval of ATMPs in Europe between 1 January 2009 and 1 July 2017 by characterizing regulatory assessment procedures for marketing authorization, and analyzing identified major issues and considerations for benefit–risk outcomes (see Appendix 1 in the supplemental information online [9–13]).

Cohort analysis of assessment procedures

From the 14 ATMPs included in our study, five were standard approvals, three were approved via an expedited pathway (defined as conditional approval or approval under exceptional

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TABLE 1

Products used in the analysis[a]

Product	ATMP subtype	Starting material	Approval type	Date of final outcome
Chondrocelect®	TEP	Autologous	Standard approval	October 2009
Imlygic®	GTMP – *in vivo*	N/A	Standard approval	October 2015
MACI®	TEP	Autologous	Standard approval	April 2013
Provenge®	CTMP	Autologous	Standard approval	June 2013
Strimvelis®	GTMP – *ex vivo*	Autologous	Standard approval	April 2016
Holoclar®	TEP	Autologous	Conditional approval	December 2014
Zalmoxis®	CTMP	Allogeneic	Conditional approval	June 2016
Glybera®	GTMP – *in vivo*	N/A	Under exceptional circumstances	October 2012
Advexin	GTMP – *in vivo*	N/A	Nonapproval (withdrawn)	December 2008
CLG	GTMP – *in vivo*	N/A	Nonapproval (withdrawn)	June 2009
Cerepro	GTMP – *in vivo*	N/A	Nonapproval (withdrawn)	April 2007
Heparesc	CTMP	Allogeneic	Nonapproval	October 2015
Hyalograft	TEP	Autologous	Nonapproval (withdrawn)	January 2013
OraNera	TEP	Autologous	Nonapproval (withdrawn)	March 2013

[a] Abbreviations: CLG, Contusugene Ladenovec Gendux; CTMP, cell therapy medicinal product; GTMP, gene therapy medicinal product; TEP, tissue engineering product.

circumstances for this study), and six were nonapproved (Table 1). The product profiles of all assessed ATMPs are shown in Table 2. Characteristics, such as ATMP subtype, starting material, administration route, and storage conditions, were diverse for the different submitted products. Orphan drug designation was assigned to all expedited approved products, whereas only one (out of five) standard approved products and half (three out of six) of the nonapproved products were designated orphan drugs. For the expedited approved products, no alternative treatment was available, whereas this applied only to one out of five standard approved products and two (out of six) nonapproved products.

All standard approvals were tested according to standards on sterility, purity, and viability upon release. However, for the expedited approvals and nonapprovals, these release tests were not always discussed in the EPARs. Remarkable was the unspecified shelf-life and storage conditions for nonapproved products (four out of six).

The design of pivotal clinical trials was more robust for standard versus expedited approved and nonapproved products. For most (four out of five) of the standard approvals, a randomized controlled Phase 3 clinical trial was performed. By contrast, this was the case for only two (out of six) nonapproved and for none of the expedited approved products. The number of patients recruited was higher for the standard approved products (mean: 244 patients, range: 12–341) compared with nonapproved products (mean: 120 patients, range: 26–241) and expedited approved products (mean: 57 patients, range: 14–106). The defined primary endpoints were considered clinically relevant for all standard approved products, for some expedited approved ATMPs (two out of three) and for half (three out of six) of the nonapproved products.

A significant effect on the primary endpoint was demonstrated for all standard approved products. By contrast, significant effects were not demonstrated in two (out of three) expedited approved products and in five (out of six) nonapproved products. No added clinical benefit was demonstrated for most of the standard approved (four out of five) and for all the nonapproved products. Added clinical benefit was demonstrated for all expedited approved products because of the lack of alternative therapies.

Analysis of major issues

Major issues were evaluated across assessment procedures, regardless of final regulatory opinion (Table 3; for detailed descriptions see Table S1 in Appendix 2 in the supplemental information online).

For quality, major issues were noted for all products; for example, the vector (expedited approval one out of three, nonapproved: two out of six) and specific release tests (standard approved: one out of five, expedited approved: three out of three, nonapproved: five out of six). Whereas developers of the approved products were able to resolve the objections before final regulatory decision-making, developers of the nonapproved products were unable to resolve these major issues, which were mostly raised early during the assessment procedure, and decided to withdraw their product.

Most of the major issues related to preclinical studies were raised for nonapproved products, concerning animal models (one out of six), toxicology (four out of six) and efficacy studies (one out of six). By contrast, no major issues were noted for the approved products, except for one (out of three) expedited approved product, which concerned toxicology and was unresolved upon final decision-making. In addition, major issues indicated for nonapproved products were still unresolved at the time of final decision-making.

For clinical trial design, most major issues were also raised for nonapproved products. These issues concerned methodological issues or invalid clinical trial design (five out of six) and change of endpoints or uncertain clinical relevance of an endpoint (two out of six). A change of endpoints was also noted as a major issue for one standard and one expedited approved product. For the approved products, the major concerns were considered resolved, whereas all major issues around clinical trial design for the nonapproved products were unresolved upon final decision-making.

Major issues related to clinical outcomes were raised for all nonapproved products and for Glybera®, one of the approved products. A lack of favorable clinical outcomes for nonapproved products related to both efficacy (six out of six) and safety (five out of six). Furthermore, good clinical practice (GCP) was an issue in three (out of six) dossiers and pharmacodynamics data were too limited in two (out of six) nonapproved products.

Analysis of benefit–risk assessment

For standard approved ATMPs, benefit–risk balances were mainly based on clinical efficacy results (Table 4). The beneficial efficacy outcomes and a favorable safety profile resulted in a positive opinion for MACI®. The beneficial efficacy trend for Chondrocelect® and Imlygic® combined with satisfactory safety profiles resulted in standard approval, despite ample regulatory discussion about the clinical trial

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