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

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 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 European public assessment report (EPAR). 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

TABLE 2

Elements with variables scored per marketing approval type[a,b]

Element	Variable	SA (*N* = 5)	CA (*N* = 2)	UEC (*N* = 1)	NA (*N* = 6)
Product profile					
Product type	GTMP	2	0	1	3
	CTMP	1	1	0	1
	TEP	1	1	0	2
	Combined	1	0	0	0
Starting material	Autologous	4	1	0	2
	Allogeneic	0	1	0	1
	Not applicable	1	0	1	3
End product	Refrigerated	2	0	0	0
	Room temperature	2	1	0	0
	Nitrogen-cryopreserved	0	1	0	1
	Other-cryopreserved	1	0	1	1
	Unspecified	0	0	0	4
Previous approved in other jurisdictions	Yes	3	0	0	0
Indication area	Cancer	2	0	0	2
	Congenital, hereditary, neonatal diseases	1	0	1	2
	Eye diseases	0	1	0	1
	Immune system diseases	0	1	0	0
	Musculoskeletal diseases	2	0	0	1
Lack alternative treatment	Yes	1	2	1	2
Orphan drug designation	Yes	1	2	1	3
Scientific evidence					
Quality	Potency assay	5	2	1	6
	Release: sterility	5	1	0	4
	Release: purity	5	1	0	4
	Release: viability	5	2	0	2
	Release: activity	3	1	1	3
Preclinical	Toxicity	4	2	1	6
	Efficacy	5	1	1	6
	Dose	3	1	1	6
Pivotal trial design	RCT	4	0	0	2
	Clinical primary EP	5	1	0	4
	Clinical relevance primary EP	5	2	0	3
	Significant outcome	5	1	0	1
Clinical outcome	Significant primary EP	5	1	0	1
	Beneficial effect	1	2	1	0
Regulatory process					
	Scientific advice	5	2	1	4
	Restricted labeling	5	1	1	0

[a] Per element, variables are scored for each (non-)approval type of ATMP.
[b] Abbreviations: CA, conditional approved; CTMP, cell therapy medicinal product; EP, endpoint; GTMP, gene therapy medicinal product; NA, non-approved; RCT, randomized controlled trial; SA, standard approved; TEP, tissue engineering product.

trial design. Significant and clinically relevant efficacy of Provenge® combined with the acknowledged unmet medical need for the target indication (oncology), outweighed the risks and uncertainties related to the safety profile. Compelling efficacy outcomes for Strimvelis®, with the acknowledged unmet medical need, outweighed risks and uncertainties surrounding latent severe adverse events [14]. Despite these favorable regulatory opinions, divergent positions were submitted for two approved products (Imlygic®: *N* = 1; Provenge®: *N* = 13).

As a prerequisite for conditional approval pathways, the body of evidence was overall less robust and associated with more uncertainty compared with standard approved ATMPs (Table 4). Uncertainty about significant clinical benefits for Holoclar® was recognized because

TABLE 3

Major issues mentioned in the assessment reports for marketing authorization[a,b]

Drug category	Authorization	Quality	Preclinical	Clinical trial design	Clinical outcome
Approved (*N* = 8)	Standard (*N* = 5)	In process control (1)		Endpoint (1)	
		Release specification (1)			
		Specific release test (1)			
	Conditional (*N* = 2)	Specific release test (2)			
	UEC (*N* = 1)	Vector (1)	Toxicology (1)	Endpoint (1)	Efficacy (1)
		Specific release test (1)			Safety (1)
Non-approved (*N* = 6)		Vector (2)	Toxicology (4)	Design (5)	PD (2)
		GMP facility (3)	Animal model (1)	Endpoint (2)	GCP (3)
		In process control (2)	Efficacy (1)		Efficacy (6)
		GMO test (1)			Safety (5)
		Starting material (1)			
		Specific release test (1)			
		Specific release test (4)			

[a] Per category (quality, preclinical, clinical trial design, and clinical outcome) the major issues including the number of products for which that major objection was raised is mentioned: Green, resolved at time of final decision; orange, acceptable at time of final decision; red, unresolved at time of final decision.
[b] Abbreviations: GCP, good clinical practice; GMO, genetically modified organism; PD, pharmacodynamics.

of the retrospective, nonrandomized, uncontrolled observational study design. Yet, this was outweighed by the manageable risks and acknowledged unmet medical need. Unmet medical need outweighed nonconfirmatory clinical benefit and safety because of uncertainty in clinical trial design for Zalmoxis®. A divergent position was undersigned by three members of the Committee for medicinal products for human use (CHMP).

Glybera® was approved under exceptional circumstances (EUC) after a long and extensive assessment procedure, involving many re-evaluations by the Committee of advanced therapies (CAT) and CHMP [15]. Many uncertainties about quality, efficacy, and safety led to unfavorable recommendations for approval twice. Before the final re-examination, a lack of robust efficacy outcomes was considered a major concern. Yet, a post-hoc analysis revealed a beneficial effect with

TABLE 4

Benefit–risk assessment per category[a,b]

Drug	Quality	Preclinical	Design	Efficacy	Safety	Unmet medical need	Benefit–Risk
Standard approval							
Chondrocelect®	++	+/−	_ _	+	++		++
Imlygic®			_	+	+		+
MACI®	++		++	++	++		++
Provenge®	_ _		+/−	++	_	▲	+
Strimvelis®			+/−	++	_	▲	++
Conditional approval							
Holoclar®	_		+/−	+	+	▲	++
Zalmoxis®			+/−	+/−	_	▲	+
Approval under exceptional circumstances							
Glybera®	_ _		+/−	+/−	+/−	▲	+
Nonapproval							
Advexin	_ _	_ _	_ _	_ _	_ _		_ _
CLG	_ _	_ _		_ _	_ _		_ _
Cerepro	+	+	_ _	_ _	_ _		_ _
Heparesc			_ _	_ _	+/−		_
Hyalograft	_ _	_ _	_ _	+/−	_ _		_ _
OraNera	_ _	_ _	_ _	_ _	_ _		_ _

[a] _ _, unsatisfactory, unresolved major objections; −, uncertainty, concerns, and risks, trend towards unsatisfactory; +/−, neutral, mentioned but no clear judgement; +, uncertainty, trend towards satisfactory; ++, satisfactory; empty box, not mentioned; ▲, unmet medical need considered in benefit/risk-assessment.
[b] Abbreviation: CLG, Contusugene Ladenovec Gendux.

Glybera® for a subgroup of patients ($N = 5$). The unmet medical need for this subgroup was crucial to reach approval from UEC, taking the ultra-orphan status into consideration. Consequently, the label was restricted to this patient group. The final CHMP opinion was not supported by 16 members, who undersigned a divergent position.

Nonapproval of ATMPs was associated with numerous scientific deficiencies (Table 4). Half of the nonapproved products had an unsatisfactory profile for all scientific evidence elements. For all nonapproved products, the clinical trial design was regarded as unsatisfactory, which hindered regulators from evaluating the clinical data. Positive results related to quality and preclinical studies were demonstrated for Cerepro. However, an unsatisfactory clinical trial design and clinical outcomes resulted in nonapproval. For Heparesc, the clinical safety profile was acceptable, but the clinical trial design and clinical efficacy were judged to be unsatisfactory. For Hyalograft only clinical efficacy was acceptable, but other aspects were unsatisfactory. For four (out of six) nonapproved products, unmet medical need was acknowledged, but did not outweigh scientific deficiencies. During the application procedure, five out of six nonapproved products were withdrawn by the company before a final decision was made by the regulators.

Pharmaceutical quality

The numerous scientific issues related to pharmaceutical quality demonstrate that this domain remains problematic in the ATMP field [6]. A main pharmaceutical quality issue in the submitted applications concerned the level of validation of release testing quality control (QC) for different clinical trial stages and for approval. EU GMP requirements appear to be more stringent compared with other jurisdictions (e.g., USA or Japan) and might impose development hurdles. In this context, both the revised first-in-human clinical trials EU Guideline and the EU GMP guideline for ATMPs give hints of quality aspects, such as potency testing and use of biomarkers, although the proof of that expectation will 'be in the eating' [16–18].

Potency also frequently raised major objections for both approved and nonapproved ATMPs. ATMP developers experience difficulties in proper potency testing because of the lack of suitable animal models, with little or even no knowledge about the mechanism of action, and, therefore, also lack validated biomarkers. Developers could prevent failure during late-stage development through early investment in potency evaluation [19]. Vector-related problems belong to the fundamental development aspects of such products and should have been resolved before submission for approval. This also accounts for nondefined end-product storage conditions and shelf-life, which are all associated with negative opinions for approval.

In contrast to the early days of ATMP regulation, it is now possible to conditionally release a product by using a rapid-release test. Our findings demonstrate that a lack of a final release test was often resolved by the development of a rapid-release test for approved ATMPs. In this study, we analyzed the quality aspects that were mentioned and, thus, discussed in the EPARs. Although we compare the different approvals, we do not think that the quality requirements depend on the approval pathway. However, the objections that were discussed in the EPARs could have influenced the approval type. Furthermore, incomparability of the commercial product and clinical trial product raised major objections. This should and could be avoided by considering future aspects of development and proper clinical trial design during the early stages of ATMP development [7,20] to prevent withdrawals at Day 120 for those developers who might not have the resources to tackle resolvable major issues.

Clinical development

The observed suboptimal clinical trial designs that create uncertainty around clinical outcomes are in line with earlier reports of development hurdles experienced in the field [5,21]. However, half of currently approved ATMPs target orphan diseases, for which robust clinical trial design is not always possible as a result of small patient populations or a lack of alternative treatment [5,22,23]. Therefore, our observations of suboptimal study designs under expedited approval of ATMPs, such as lower numbers of recruited patients, should be interpreted within the context of orphan drugs. Yet, observations of suboptimal study design, such as nonrandomized trial design without a comparator, are in line with findings for conditionally approved non-orphan drugs in the EU [13].

Some major concerns related to clinical trial design, such as a change of primary endpoint, were also raised for standard approved ATMPs. Yet, regulators evaluated scientific evidence as sufficient for standard approval. In addition, unmet medical need was acknowledged and taken into account for decision-making. By contrast, a robust clinical trial design and clinical outcomes are mandatory for standard approval of conventional products [12]. This suggests that EU regulators are exploring an appropriate regulatory standard for ATMPs, where conventional products could be used as a useful reference.

Considerations for benefit–risk analysis

Here, orphan designation among the approved ATMPs skewed the level of scientific evidence to a nonconfirmatory nature. There is ample concern that, in the field of not only orphan drugs, but also targeted oncology products, the nature of evidence becomes less confirmatory with the use of nonrandomized data and surrogate endpoints [24]. The relatively high number of orphan designations in the field of ATMPs will impact the regulatory considerations for marketing approval in the future [25]. Unmet medical need has an important role in decision-making for the approval of orphan ATMPs, provided that the data should at least show some beneficial trends of efficacy or a favorable safety profile to receive approval. This feature is also seen in the field of regulating orphan drugs [11]. Yet, considerations of unmet medical need did not lead to a higher rate of positive opinions on orphan drug approval compared with treatments without unmet medical need [12]. This apparent dissimilarity between orphan ATMPs and orphan new entities needs to be explored further. Surprisingly, conditional approval and approval UEC for orphan ATMPs are not primarily initiated by the developers, but by the regulators. In line with previous work, these findings suggest that conditional approval is frequently used as a rescue option for approval [13]. For (ultra-)orphan indications, developers should take conditional approval and approval UEC into their strategic considerations for marketing authorization instead of leaving this to the regulators to propose.

Critically, observations of a lack of clinical efficacy for nonapproval of ATMPs are in line with argumentation for negative benefit–risk opinions on conventional medicinal products. Earlier research on conventional medicinal products showed that beneficial, clinically relevant efficacy outcomes are determinants for approval [11]. Furthermore, our findings indicate that the process of decision-making leading to nonapproval is similar between ATMPs and conventional medicinal products. Earlier research showed that major issues that were unresolved at the time of the final decision often led to withdrawal by the applicant [21]. Strikingly, the unresolved major issues of nonapproved ATMPs underline the challenges to the development of ATMPs [6,19,26]. Glybera® is the only approved product that appears to be an exception to the rule to be approved despite its uncertain benefit–risk profile; it was approved after a long regulatory process with a restricted label and many uncertainties [27]. Currently, the marketing authorization holder has decided not to extend the marketing authorization of the product.

Future implications

The current centralized system for ATMPs, including CAT experts and a range of advantages for ATMP developers, creates opportunity to learn and gain experience with these innovative products as well as the underlying science and technology [28]. As the field develops, it is important that regulatory standards (incrementally) coevolve to tailor procedures and decision-making for these ATMPs. Our observations indicate that EU regulators are inclined to be adaptive [29] and to endorse ATMPs for approval, without compromising necessary evidentiary support for positive benefit/risk opinions. There are also numerous regulatory adaptations that are to be implemented soon (e.g. the new Clinical Trial Regulation) in the EU. These will also affect ATMP development [30]. Others have been recently implemented, such as the new regulatory pathway for priority medicines (PRIME). Many of the investigational medicines that were included in the PRIME scheme are ATMPs [31]. Development efforts are also rapidly evolving. The ATMPs discussed here reflect a start of a huge clinical development pipeline [3–5,30], for which applications for approval will be filed in due course. Thus, the current analysis reflects decision-making for a small sample of first-generation ATMPs, making it difficult to draw generalizable conclusions for the future. It is possible that some observations are driven by product specificity and/or disease characteristics instead of by regulatory approval pathways. Therefore, it is crucial to continue to monitor regulatory outcomes and evaluate the ATMP regulatory framework.

Concluding remarks

EU regulators are making important steps in the field of ATMPs by balancing evidentiary support and medical needs with critical scientific uncertainties that could hamper marketing approval. The development, regulation, and clinical use of most ATMPs are still coevolving. In this context, defining appropriate regulatory standards taking into account the complexities inherit to these products is critical. Our observations concur not only with current defined standards for ATMPs, but also with the available space that regulations allow for facilitated pathways. As long as the risks are acceptable, this appears to be the way forward. Yet, because of the novelty and lack of clinical experience in this field, regulators, and those in industry and clinical practice need to pay accurate attention to postmarketing surveillance and risk-minimization measures, in particular for those products with a high degree of scientific uncertainty upon point of approval. For the field to flourish, developers and regulators need to collaborate to continuously monitor and evolve methodologies and regulations for ATMPs.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drudis.2018.03.008.

References

1 Schneider, C.K. *et al.* (2010) Challenges with advanced therapy medicinal products and how to meet them. *Nat. Rev. Drug Discov.* 9, 195–201
2 EU (2004) Regulation EC. 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83. EC and Regulation (EC) No /726. *Off. J. EU* 324, 121–137
3 Maciulaitis, R. *et al.* (2012) Clinical development of advanced therapy medicinal products in Europe: evidence that regulators must be proactive. *Mol. Ther.* 20, 479–482
4 de Wilde, S. *et al.* (2016) Clinical development of gene- and cell-based therapies: overview of the European landscape. *Mol. Ther.* 3, 16073
5 Hanna, E. *et al.* (2016) Advanced therapy medicinal products: current and future perspectives. *J. Mark. Access Health Policy* 4, 31036
6 Salmikangas, P. *et al.* (2015) Manufacturing, characterization and control of cell-based medicinal products: challenging paradigms toward commercial use. *Regen. Med.* 10, 65–78
7 de Wilde, S. *et al.* (2016) Hurdles in clinical implementation of academic advanced therapy medicinal products: a national evaluation. *Cytotherapy* 18, 797–805
8 Coppens, D.G.M. *et al.* (2017) Global regulatory differences for gene and cell based therapies: consequences and implications for patient access and therapeutic innovation. *Clin. Pharmacol. Ther.* 103, 120–127
9 EMA (2018) *European Public Assessment Reports.* EMA
[10] EMA Inspections, Human Medicines Pharmacovigilanceand Committees Division (2017) *CAT Monthly Report of Application Procedures, Guidelines and Related Documents on Advanced Therapies — July 2017.* EMA
11 Putzeist, M. *et al.* (2012) Determinants for successful marketing authorisation of orphan medicinal products in the EU. *Drug Discov. Today* 17, 352–358
12 Putzeist, M. *et al.* (2013) EU marketing authorization review of orphan and non-orphan drugs does not differ. *Drug Discov. Today* 18, 1001–1006
13 Hoekman, J. *et al.* (2015) Use of the conditional marketing authorization pathway for oncology medicines in Europe. *Clin. Pharmacol. Ther.* 98, 534–541
14 Monaco, L. and Faccio, L. (2017) Patient-driven search for rare disease therapies: the Fondazione Telethon success story and the strategy leading to Strimvelis. *EMBO Mol. Med.* 9, 289–292
15 Melchiorri, D. *et al.* (2013) Regulatory evaluation of Glybera in Europe — two committees, one mission. *Nat. Rev. Drug Discov.* 12, 719
16 US Department of Health and Human Services *et al.* (2011) *Guidance for Industry Potency Tests for Cellular and Gene Therapy Products.* OCOD
17 EMA (2017) *Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products.* EMA
18 EC (2017) *EudraLex The Rules Governing Medicinal Products in the European Union Volume 4 Good Manufacturing Practice — Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products.* EC
19 Bravery, C.A. *et al.* (2013) Potency assay development for cellular therapy products: an ISCT review of the requirements and experiences in the industry. *Cytotherapy* 15, 9–19
20 de Wilde, S. *et al.* (2017) Understanding clinical development of chimeric antigen receptor T cell therapies. *Cytotherapy* 19, 703–709
21 Pignatti, F. *et al.* (2002) The review of drug applications submitted to the European Medicines Evaluation Agency: frequently raised objections, and outcome. *Eur. J. Clin. Pharmacol.* 58, 573–580
22 Fischbach, M.A. *et al.* (2013) Cell-based therapeutics: the next pillar of medicine. *Sci. Transl. Med.* 5 179ps7
23 Wirth, T. *et al.* (2013) History of gene therapy. *Gene* 525, 162–169
24 Kesselheim, A.S. *et al.* (2011) Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. *JAMA* 305, 2320–2326
25 Farkas, A.M. *et al.* (2017) Advanced therapy medicinal products for rare diseases: state of play of incentives supporting development in Europe. *Front. Med.* 4, 53
26 Committee for Advanced Therapies *et al.* (2010) Challenges with advanced therapy medicinal products and how to meet them. *Nat. Rev. Drug Discov.* 9, 195–201
27 Watanabe, N. *et al.* (2015) Re-examination of regulatory opinions in Europe: possible contribution for the approval of the first gene therapy product Glybera. *Mol. Ther.* 2, 14066
28 Salmikangas, P. *et al.* (2015) Marketing regulatory oversight of advanced therapy medicinal products (ATMPs) in Europe: the EMA/CAT perspective. *Adv. Exp. Med. Biol.* 871, 103
29 Liberti, L. *et al.* (2015) Adaptive licensing and facilitated regulatory pathways: a survey of stakeholder perceptions. *Clin. Pharmacol. Ther.* 98, 477–479
30 Borán, T. *et al.* (2017) Clinical development and commercialization of advanced therapy medicinal products in the European Union: how are the product pipeline and regulatory framework evolving? *Human Gene Ther. Clin. Dev.* 28, 126–135
31 EMA (2018) *PRIME: Priority Medicines.* EMA

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]
Pauline Meij[1,*]

[1]*Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, The Netherlands*
[2]*Utrecht Institute for Pharmaceutical Sciences Utrecht University, Utrecht, The Netherlands*
[3]*Innovation Studies Group, Faculty of Geosciences, Utrecht University, Utrecht, The Netherlands*
[4]*Copenhagen Centre for Regulatory Science, University of Copenhagen, Copenhagen, Denmark*

**Corresponding author.*

[‡]These authors contributed equally to this work.