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Regulatory Policies

Comparison of regulatory pathways for the approval of advanced therapies in the European Union and the United States

Carolina Iglesias-Lopez[1], Mercè Obach[2], Antonio Vallano[1,2,*], Antonia Agustí[1,3]

[1] *Department of Pharmacology, Therapeutics and Toxicology. Universitat Autònoma de Barcelona, Bellaterra, Spain*
[2] *Medicines Department, Catalan Healthcare Service, Barcelona, Spain*
[3] *Clinical Pharmacology Service, Vall d'Hebron University Hospital, Barcelona, Spain*

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ABSTRACT

Background aims: Regulatory agencies in the European Union (EU) and in the United States of America (USA) have adapted and launched regulatory pathways to accelerate patient access to innovative therapies, such as advanced therapy medicinal products (ATMPs). The aim of this study is to analyze similarities and differences between regulatory pathways followed by the approved ATMPs in both regions.
Methods: A retrospective analysis of the ATMPs approved by EU and US regulatory agencies was carried out until May 31, 2020. Data were collected on the features and timing of orphan drug designation (ODD), scientific advice (SA), expedited program designation (EP), marketing authorization application (MAA) and marketing authorization (MA) for both regions.
Results: In the EU, a total of fifteen ATMPs were approved (eight gene therapies, three somatic cell therapies, three tissue-engineered products and one combined ATMP), whereas in the USA, a total of nine were approved (five gene therapies and four cell therapies); seven of these were authorized in both regions. No statistical differences were found in the mean time between having the ODD or EP granted and the start of the pivotal clinical trial or MAA in the EU and USA, although the USA required less time for MAA assessment than the EU (mean difference, 5.44, $P = 0.012$). The MAA assessment was shorter for those products with a PRIME or breakthrough designation.. No differences were found in the percentage of ATMPs with expedited MAA assessment between the EU and the USA (33.3% versus 55.5%, respectively, $P = 0.285$) or in the time required for the MAA expedited review (mean difference 4.41, $P = 0.105$). Approximately half of the products in both regions required an Advisory Committee during the MAA review, and 60% required an oral explanation in the EU. More than half of the approved ATMPs (67% and 55.55% in the EU and the USA, respectively) were granted an ODD, 70% by submitting preliminary clinical data in the EU. The mean number of SA and protocol assistance per product conducted by the European Medicines Agency was 1.71 and 3.75, respectively, and only 13% included parallel advice with health technology assessment bodies. A total of 53.33% of the products conducted the first SA after the pivotal clinical study had started, reporting more protocol amendments. Finally, of the seven ATMPs authorized in both regions, the type of MA differed for only two ATMPs (28.6%), and four out of eight products non-commercialized in the USA had a non-standard MA in the EU.
Conclusions: The current approved ATMPs mainly target orphan diseases. Although EU and US regulatory procedures may differ, the main regulatory milestones reached by the approved ATMPs are similar in both regions, with the exception of the time for MAA evaluation, the number of authorized products in the regions and the type of authorization for some products. More global regulatory convergence might further simplify and expedite current ATMP development in these regions.

Introduction

Advanced therapy medicinal products (ATMPs) feature cells, genes or tissues. In the last decade, the first advanced therapies have been launched into the market, and as a result of the recent increase in research and development, regulatory agencies have adapted and launched new regulatory pathways compatible with the novelty, complexity and technical specificity of these products. It has been recognized by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) that the evaluation of ATMPs requires specific expertise that goes beyond the traditional pharmaceutical field [1].

* Correspondence: Antonio Vallano, PhD, MD, Medicines Department, Catalan Healthcare Service, Travessera de les Corts 131-159, 08028, Barcelona, Spain.
E-mail address: avallano@catsalut.cat (A. Vallano).

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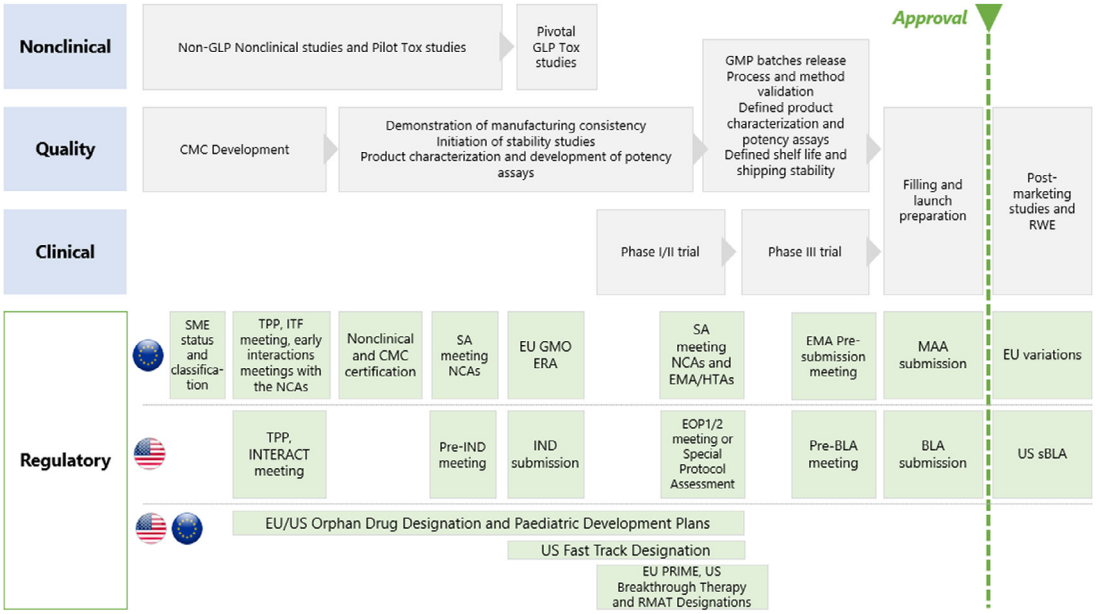

Figure 1. Overview of EU and US regulatory steps for advanced therapies during development. CMC: Controls Manufacturing Chemical; EOP1/2: End-of-Phase 1 or 2; EU: European Union; GLP: Good Laboratory Practices; GMO: Genetically Modified Organism; GMP: Good Manufacturing Practices; IND: Investigational New Drug; ITF: Innovative Task Force Meeting; INTERACT: Initial Targeted Engagement for Regulatory Advice; NCAs: National Competent Authorities; PD: Pharmacodynamic; SA: Scientific Advice; sBLA: Supplemental Biologics License Application; SME: Small and Medium Enterprise; Tox: toxicity; TPP: target product profile; RWE: Real World Evidence; US: United States of America.

In the USA, current Good Manufacturing Practice (cGMP) for phase 1 investigational drugs, which include biological drugs, is exempt from complying with 21 CFR part 211 (cGMP for finished pharmaceuticals) under 21 CFR 210.2(c) (referred to as phase 1 investigational drugs). However, this exemption does not apply to an investigational drug for use in a phase 1 study once the investigational drug has been made available for use by or for the sponsor in a phase 2 or 3 study, as described in §312.21(b) and (c), or the drug has been lawfully marketed. In the EU, cGMP requirements are detailed in 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*. (Color version of figure is available online).

There are several optional and mandatory regulatory procedures to be followed throughout drug development (Figure 1). No studies have been conducted thus far to analyze the regulatory steps taken in the European Union (EU) and the in the United States of America (USA) for the approved ATMPs; thus, the aim of this study is to analyze and compare the regulatory pathways followed by these therapies in both regions.

Methods

To perform the retrospective study of the approved ATMPs in the EU and USA, the following approach was used:

(i) Search strategy: data were primarily extracted from the EMA and FDA websites (www.ema.europa.eu, www.fda.gov). European data were gathered from European public assessment reports, orphan designation product reports and publicly available EMA agendas, minutes and highlights. US data were collected mainly from FDA drug summary reports and "Summary Basis of Regulatory Action" documents and other approval history-related documents published for the approved cellular and gene therapy products. The search was carried out until May 31, 2020. In addition, a search for the main clinical trials of the approved ATMPs was conducted using the ClinicalTrials.gov database.

(ii) Eligibility criteria: medicine products classified as ATMPs according to EMA criteria and those classified as cellular and gene therapy products in the USA were included in the study [2,3]. To compare only those products that are considered ATMPs in both regions, the approved hematopoietic progenitor cell cord blood products in the USA were discarded from this analysis since they are not considered ATMP products in the EU but under transplantation laws. In addition, only products authorized under centralized procedures in the EU were considered, excluding those ATMPs approved under "hospital exemption" since these products are non-industrially manufactured and tailor-made for a single patient.

(iii) Data extraction and collected variables: the authors designed specific data extraction forms using Excel 2019 (Microsoft Corporation, Redmond, WA, USA) to collect information related to the approved ATMPs' regulatory development: scientific advice (SA) number and timing in EU and US pre-investigational new drug application (pre-IND) and pre-biological license application (pre-BLA) meetings, along with special protocol assessment procedure; timing and features of EU and US orphan drug designation (ODD), including significant benefit for the EU; and timing and features of expedited programs, marketing authorization application (MAA) and type of approval for the approved ATMPs in both regions. The expedited programs were classified as priority medicines (PRIME) designation in the EU and breakthrough designation, fast track and regenerative medicine advanced therapy (RMAT) in the USA. Information on expedited programs for other chemical and biological drugs was also collected. The types of marketing authorization (MA) were classified as standard approval, conditional approval and exceptional circumstances in the EU and standard approval and accelerated approval program in the USA. The date of EU approval was based on the positive Committee for Medicinal Products for Human Use (CHMP) opinion. Finally, the issues raised at the scientific advisory group meetings during the MAA evaluation were collected for both regions, and the categorization approach was sourced and adapted from Barkholt *et al.* [4]. ATMP classification and certification procedures were excluded from the analysis since they are European-specific. Environmental risk assessment procedures were also excluded, as they differ between the two regions [5].

(iv) Statistical analysis: analysis of categorical and continuous variables was performed by means of the distribution of frequencies, proportions, 95% confidence interval (CI), mean, standard deviation (SD), median, interquartile range (IQR) and range (minimum and maximum). Statistical differences were evaluated using the chi-square test for categorical variables and paired Student's *t*-test for continuous variables. Comparison of

temporal variables was made only for common ATMPs approved in both regions. A two-tailed significance was set at a level of 0.05. The statistical analysis was performed using SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

In the EU, a total of 15 ATMPs were approved for 16 different clinical indications, whereas in the USA, a total of nine therapies were approved for 10 clinical indications. The ATMPs approved in both regions, year of submission and approval and clinical indications authorized are shown in Table 1. A total of seven of these ATMPs were approved in both the EU and USA (five being gene therapy medicinal products [GTMPs]), eight therapies were approved only in the EU and two were approved only in the USA. In the EU, eight (53.33%) ATMPs were GTMPs, three (20%) were somatic cell therapy medicinal products, three were tissue-engineered products (20%) and one (6.66%) was a combined ATMP. In the USA, five (55.55%) were GTMPs and four (44.44%) were cell therapies.

Orphan drug designation

Ten out of 15 approved therapies in the EU (67%) were granted an ODD during development (seven GTMPs, two somatic cell therapy medicinal products and one tissue-engineered product), whereas in the USA, five GTMPs out of nine approved ATMPs (55.55%) obtained this designation. In the EU, Yescarta, Kymriah and Luxturna each received two ODDs, whereas in the USA, Yescarta received three ODDs and Kymriah received two (Table 2). Of the seven products that were developed in both the EU and the USA, four obtained an ODD in both regions (57.14%).

In the EU, significant benefit did not need to be demonstrated for five medicinal products at the time of designation, as they targeted rare conditions lacking any approved therapies in the EU (33.3% of all approved ATMPs and 50% of those with an ODD). Only three ATMPs approved (30% of the approved products with an ODD) obtained the designation supported only by pre-clinical data (Glybera, Luxturna and Zynteglo). With regard to Alofisel, this information was not known, and the rest submitted preliminary clinical data (70%) (Table 2).

The mean ± SD time between having the ODD granted and the start of the pivotal clinical trial was 3.16 ± 26.93 months in the EU (median, −2.50, IQR, −15.75 to 30.25, range, −34 to 41) and −7.57 ± 28.72 months in the USA (median, −15, IQR, −25 to 14, range, −49 to 36), meaning that the main clinical trial started prior to having the ODD granted (Figure 2). When analyzing the four ATMPs with an orphan designation in both regions, the mean ± SD time between having the ODD granted and the start of the pivotal clinical trial was 1.50 ± 16.37 months in the EU (median, −2.50, IQR, −11.25 to 15.25, range, −15 to 28) and −5 ± 30.57 months in the USA (median, −3, IQR, −31 to 19.50, range, −49 to 36). This difference was not statistically significant (mean difference, 6.5 months, 95% CI, −20.14 to 33.14, $P = 0.558$).

The mean ± SD time between having the ODD granted and MAA submission was 55.53 ± 35.13 months in the EU (median, 51, IQR, 22–72, range, 12–123) and 27.14 ± 16.73 months in the USA (median, 36, IQR, 11–40, range, 5–48) (Figure 2). When analyzing the four ATMPs with an orphan designation in both regions, the mean ± SD time between having the ODD granted and MAA was 32.83 ± 19.02 months in the EU (median, 30, IQR, 20–47.25, range, 12–63) and 28.3 ± 14.29 months in the USA (median, 30.50, IQR, 13.25–39, range, 11–48). This difference was not statistically significant (mean difference, 4.50 months, 95% CI, −15.21 to 24.21, $P = 0.583$).

Of those therapies that were granted an ODD, none of them lost the designation after their MA, and only Alofisel needed an oral explanation during the EU MAA procedure to maintain the designation. Finally, Kymriah and Zolgensma (13.33% of the approved products) required the submission of a critical report addressing the possible similarity to other authorized orphan medicinal products in the EU.

Scientific Advice procedures

In the EU, all authorized ATMPs followed a SA or protocol assistance procedure (in the case of an orphan medicinal product) with the EMA. The mean ± SD number of SA procedures per product was 1.71 ± 0.75 (median, 2, IQR, 1–2, range, 1–3), whereas the mean ± SD number of protocol assistance procedures was 3.75 ± 1.05 (median, 4, IQR, 3–4.75, range, 2–5). The questions for all products pertained to quality and non-clinical and clinical development. A total of six (40%) of the approved therapies had the first EMA SA prior to the start of the pivotal clinical study, whereas a total of eight products (53.33%) had it later (Figure 3A). The mean ± SD time from the first SA to the start of the pivotal study was −2.50 ± 41.34 months (median, 6, IQR, −35 to 15.5, range, −74 to 85). The mean ± SD number of reported protocol amendments to the pivotal study for those products that had the SA after starting the main study was 5.60 ± 1.67 (median, 6, IQR, 4–7, range, 3–7), whereas it was 3.75 ± 1.67 (median, 4, IQR, 2.25–5, range, 1–6) for those products that had the SA prior to starting the main study. The mean ± SD time from the first EMA SA to MAA was 55.86 ± 33.23 months (median, 46, IQR, 40–70, range, 10–129). Only Zynteglo underwent a parallel advice procedure with health technology assessment bodies, whereas Kymriah benefited from the pilot version of this program (13.33% of the approved ATMPs in the EU).

With regard to the USA, Kymriah, Yescarta, Luxturna and Zolgensma had pre-BLA meetings. The mean ± SD time from the pre-BLA meeting to MAA was 7.40 ± 5.68 months (median, 5, IQR, 2.5–13.5, range, 2–14). Kymriah, Luxturna and Zolgensma also had reported pre-IND meetings, with a mean ± SD time from these meetings to the start of the pivotal study of 47.50 ± 34.78 months (median, 46.50, IQR, 15.50–80.50, range, 13–84) and 74.75 ± 47.30 months (median, 63, IQR, 36.75–124.50, range, 34–139) from the meeting to MAA. The applicants of Kymriah and Imlygic applied for the special protocol assessment procedure 1 year before the start of the main trial (Figure 3B).

Expedited program designations

In the EU, four approved ATMPs obtained priority medicines (PRIME) designation (26.67%), three of them—Kymriah, Yescarta and Zynteglo—the same year the scheme was launched, with Zolgensma obtaining the designation the following year. All the therapies, except for Zolgensma, obtained PRIME designation after having started the main clinical trial that was the basis of the submission. The mean ± SD time from the start of the pivotal clinical trial to PRIME designation was 5.25 ± 10.56 months (median, 6.50, IQR, −5.50 to 14.75, range, −8 to 16) (Figure 4A). The mean ± SD time from obtaining PRIME designation to MAA submission was 18.66 ± 4.46 months (median, 20.28, IQR, 14.61–23.19, range, 14.04–24.24). Both Kymriah and Yescarta obtained the designation just over a year before MAA submission, whereas Zynteglo and Zolgensma obtained the designation approximately 2 years before submission (Figure 4B). Although chimeric antigen receptor T-cell products were approved for the same indication, i.e. relapsed or refractory diffuse large B-cell lymphoma in adults, Kymriah obtained PRIME designation for the treatment of pediatric patients with relapsed or refractory B-cell acute lymphoblastic leukemia, whereas Yescarta obtained the designation for the diffuse large B-cell lymphoma indication.

In the USA, four out of nine ATMPs approved were granted breakthrough designation (44.44%), (Kymriah, Yescarta, Luxturna and Zolgensma). With the exception of Zolgensma, all these therapies obtained breakthrough designation after having started the main clinical trial that was the basis of the submission. Kymriah obtained two

Table 1
Overview of approved ATMPs in the EU and USA (up to May 2020).

Product	Product description	EU indication and approval	US indication and approval
Axicabtagene ciloleucel (Yescarta; Kite Pharma)	Cell-based GTMP, autologous T cells transduced with gamma retroviral vector	• Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma • Treatment of primary mediastinal large B-cell lymphoma after two or more lines of systemic therapy Submitted: 29 Jul 2017 CHMP PO: 28 Jun 2018 Status: authorized	• Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma and diffuse large B-cell lymphoma arising from follicular lymphoma Submitted: 31 Mar 2017 Approved: 18 Oct 2017 Status: authorized
Tisagenlecleucel (Kymriah; Novartis Pharmaceuticals Corporation)	Cell-based GTMP, autologous T cells transduced with lentiviral vector	• Treatment of pediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukemia that is refractory, in relapse post-transplant or in second or later relapse • Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy Submitted: 02 Nov 2017 CHMP PO: 28 Jun 2018 Status: authorized	• Treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse • Treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma not otherwise specified, high grade B-cell lymphoma and diffuse large B-cell lymphoma arising from follicular lymphoma Submitted: 27 Oct 2017 Submitted: 02 Feb 2017 Approved: 01 May 2018 Approved: 30 Aug 2017 Status: Authorized
Voritegene neparvovec (Luxturna; Spark Therapeutics Inc. & Novartis Europharm Limited)	Non-cell-based GTMP, AAV-2	• Treatment of adult and pediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells Submitted: 29 July 2017 CHMP PO: 20 Sep 2018 Status: authorized	• Treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy; patients must have viable retinal cells Submitted: 16 May 2017 Approved: 19 Dec 2017 Status: authorized
Spheroids of human autologous matrix-associated chondrocytes (Spherox; CO.DON AG.)	TEP, spheroids of human autologous matrix-associated chondrocytes	• Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (ICRS grade III or IV) with defect sizes up to 10 cm^2 in adults Submitted 03 Dec 2012 CHMP PO: 18 May 2017 Status: authorized	*Not approved in the USA*

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Table 1 (*Continued*)

Product	Product description	EU indication and approval	US indication and approval
Darvadstrocel (Alofisel; Takeda Pharma A/S.)	SCTP. Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue	• Treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn disease when fistulas have shown an inadequate response to at least one conventional or biologic therapy Submitted: 2 Mar 2016 CHMP PO: 14 Dec 2017 Status: authorized	*Not approved in the USA*
Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human ΔLNGFR and HSV-TK Mut2 (Zalmoxis; MolMed S.p.A.)	Cell-based GTMP, allogeneic T cells genetically modified with retroviral vector	• Adjunctive treatment in hematopoietic cell transplantation Submitted: 05 Mar 2014 CHMP PO: 23 Jun 2016 Status: withdrawn	*Not approved in the USA*
Autologous CD34+ cell-enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence from human hematopoietic stem/progenitor (CD34+) cells (Strimvelis; Orchard Therapeutics BV)	Cell-based GTMP, autologous CD34+ cells transduced with retroviral vector	• Treatment of severe combined immunodeficiency due to ADA deficiency Submitted: 01 May 2015 CHMP PO: 01 Abr 2016 Status: authorized	*Not approved in the USA*
Talimogene laherparepvec (Imlygic; Amgen)	Non-cell-based GTMP, rHSV-1	• Treatment of adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease Submitted: 28 Aug 2014 CHMP PO: 22 Oct 2015 Status: authorized	• Indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery Submitted: 28 Jul 2014 Approved: 27 Oct 2015 Status: Authorized
Ex vivo-expanded autologous human corneal epithelial cells containing stem cells (Holoclar; Holostem Terapie Avanzate s.r.l.)	TEP, *ex vivo*-expanded autologous human corneal epithelial cells containing stem cells	• Treatment of adult patients with moderate to severe limbal stem cell deficiency, unilateral or bilateral, due to physical or chemical ocular burns Submitted: 06 Mar 2013 CHMP PO: 18 Dec 2014 Status: authorized	Not approved in the USA
Sipuleucel-T (Provenge; Dendreon Corporation)	SCTP, autologous peripheral blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor	• Treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate-resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated Submitted: 30 Dec 2011 CHMP PO: 27 Jun 2013 Status: withdrawn	• Treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer Submitted: 30 Oct 2009 Approved: 29 Apr 2010 Status: authorized
Autologous cultured chondrocytes on porcine collagen membrane (MACI; Vericel Corporation)	TEP, autologous chondrocytes expanded *ex vivo* expressing chondrocyte-specific marker genes, seeded onto a CE marked porcine-derived type I/III collagen membrane	• Repair of symptomatic, full-thickness cartilage defects of the knee (grade III and IV of the Modified Outerbridge Scale) of 3–20 cm^2 in skeletally mature adult patients Submitted: 01 Sep 2011 CHMP PO: 25 April 2013 Status: withdrawn	• Repair of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults Submitted: 04 Jan 2016 Approved: 13 Dec 2016 Status: authorized

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Table 1 (*Continued*)

Product	Product description	EU indication and approval	US indication and approval
Alipogene tiparvovec (Glybera; uniQure biopharma B. V.)	Non-cell-based GTMP, AAV-1/2	• Indicated for adult patients diagnosed with familial lipoprotein lipase deficiency and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions; indication is restricted to patients with detectable levels of LPL protein Submitted: 23 Dec 2009 CHMP PO: 23 Jun 2011 Status: withdrawn	Not approved in *the* USA
Characterized viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins (ChondroCelect; TiGenix N.V.)	TEP, caracterized viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins	• Repair of single symptomatic cartilage defects of the femoral condyle of the knee (ICRS grade III or IV) in adults; concomitant asymptomatic cartilage lesions (ICRS grade I or II) might be present Submitted: 01 Jun 2007 CHMP PO: 25 June 2009 Status: withdrawn	*Not approved in USA*
Betibeglogene autotemcel (Zynteglo; bluebird bio B.V.)	Cell-based GTMP, genetically modified autologous CD34+ cell-enriched population that contains hematopoietic stem cells transduced with lentiviral vector	• Treatment of patients 12 years and older with transfusion-dependent β-thalassaemia who do not have a $\beta 0/\beta 0$ genotype, for whom hematopoietic stem cell transplantation is appropriate but an HLA-matched related hematopoietic stem cell donor is not available Submitted: 21 Aug 2018 CHMP PO: 26 Apr 2019 Status: authorized	*Not approved in the USA*
Azficel-T (laViv; Fibrocell Technologies, Inc.)	Autologous cellular product	*Not approved in the EU*	• Indicated for improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults Submitted: 22 Dec 2010 Approved: 21 June 2011 Status: authorized
Onasemnogene abeparvovec-xioi (Zolgensma; AveXis, Inc., & Novartis Gene Therapies EU Limited)	Non-cell-based GTMP, AAV-9	• Treatment of patients with 5q spinal muscular atrophy with a biallelic mutation in the *SMN1* gene and a clinical diagnosis of spinal muscular atrophy type 1 or patients with 5q spinal muscular atrophy with a biallelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene Submitted: 09 Oct 2018 CHMP PO: 26 Mar 2020 Status: authorized	• Treatment of pediatric patients less than 2 years of age with spinal muscular atrophy with biallelic mutations in the *SMN1* gene Submitted: 01 Oct 2018 Approved: 24 May 2019 Status: authorized
Allogeneic cultured keratinocytes and fibroblasts in bovine collagen (Gintuit; Organogenesis Incorporated)	Allogeneic cultured keratinocytes and fibroblasts in bovine collagen	*Not approved in the EU*	• Indicated for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults Submitted: 13 Mar 2011 Approved: 09 Mar 2002 Status: authorized

Indications according to labeling of each region. Date of EU marketing authorization application submission corresponds to the date when the application was received by the EMA.
ADA, adenosine deaminase; AAV, adeno-associated viral vector; cDNA, complementary DNA; HSV-TK Mut2, herpes simplex I virus thymidine kinase; ICRS , International Cartilage Regeneration & Joint Preservation Society; ΔLNGFR, low-affinity nerve growth factor receptor; PO, positive opinion; SCTP, somatic cell therapy medicinal product; TEP, tissue-engineered product.

Table 2
Summary of ODDs granted in the EU and USA for approved advanced therapies.

Product	Orphan indication		ODD at MA		EU prevalence to support the ODD	Data available to support the ODD	Significant benefit criterion in the EU	
	EU	US	EU	US			No satisfactory treatment was authorized in the EU	Designated with the need to justify significant benefit
Yescarta	Treatment of diffuse large B-cell lymphoma	Treatment of diffuse large B-cell lymphoma	Yes; COMP adopted an LoQ and required an OE	Yes	2.4 in 10 000	Preliminary clinical data showing a favorable response in patients with progressive disease who are refractory to previous treatments.	NA	Yes
	Treatment of primary mediastinal large B-cell lymphoma	Treatment of primary mediastinal large B-cell lymphoma	Yes; COMP adopted an LoQ and required an OE		0.3 in 10 000	Preliminary clinical data in patients affected by the condition who responded to treatment with the product as assessed by imaging	NA	Yes
	NA	Treatment of follicular lymphoma	NA		NA	NA	NA	NA
Kymriah	Treatment of diffuse large B-cell lymphoma	Treatment of diffuse large B-cell lymphoma	Yes	Yes	4.5 in 10 000	Pre-clinical data and preliminary clinical data showing antitumor activity of the proposed product	NA	Yes
	Treatment of B-cell lymphoblastic leukemia/ lymphoma	Treatment of acute lymphoblastic leukemia	Yes	Yes	1 in 10 000	Preliminary clinical data in patients	NA	Yes
Luxturna	Treatment of Leber congenital amaurosis	Treatment of inherited retinal dystrophy due to biallelic *RPE65* gene mutations	Yes; COMP adopted an LoQ and required an OE	Yes	1 in 10 000	Pre-clinical data supporting improvements in visual function	Yes	NA
	Treatment of retinitis pigmentosa			Yes	3.7 in 10 000			
Alofisel	Treatment of anal fistula	NA	Positive COMP opinion after appealing a negative opinion	NA	2.3 in 10 000	Not known	Yes	NA
Zalmoxis	Adjunctive treatment in hematopoietic cell transplantation	NA	Yes	NA	0.32 in 10,000	Clinical trials in patients were ongoing	NA	Yes
Strimvelis	Treatment of severe combined immunodeficiency due to adenosine deaminase deficiency	NA	Yes	NA	0.02 in 10 000	Clinical trials in patients were ongoing	Yes	NA
Imlygic	Not orphan drug in the EU	Treatment of stage IIb-IV melanoma	NA	Yes	NA	NA	NA	NA
Holoclar	Treatment of corneal lesions with associated corneal (limbal) stem cell deficiency due to ocular burns	NA	Yes	NA	0.3 in 10 000	Clinical trials in patients were ongoing	NA	Yes

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Table 2 (*Continued*)

Product	Orphan indication		ODD at MA		EU prevalence to support the ODD	Data available to support the ODD	Significant benefit criterion in the EU	
	EU	US	EU	US			No satisfactory treatment was authorized in the EU	Designated with the need to justify significant benefit
Glybera	Treatment of lipoprotein lipase deficiency	NA	Yes	NA	0.02 in 10 000	Evaluation of the effects of adeno-associated viral vector expressing LPL in experimental models was ongoing. At the time of submission of the application for orphan designation, no clinical trials in patients with LPL deficiency were initiated.	Yes	NA
Zynteglo	Treatment of ß-thalassemia intermedia and major	NA	Yes	NA	1 in 10 000	Pre-clinical results in a model of β-thalassemia intermedia	NA	Yes
Zolgensma	Treatment of spinal muscular atrophy	Treatment of spinal muscular atrophy	Yes	Yes	0.4 in 10 000	Clinical trials with the medicine in patients with spinal muscular atrophy were ongoing	Yes	NA

COMP, Committee for Orphan Medicinal Products; LoQ, list of questions; LPL, lipoprotein lipase; NA, not applicable; OE, oral explanation.

breakthrough designations, one for the B-cell precursor acute lymphoblastic leukemia indication and the other for diffuse large B-cell lymphoma indication. The mean ± SD time from the start of the main clinical trial to obtaining breakthrough designation was 10 ± 15.13 months (median, 11, IQR, −2.50 to 22, range, −15 to 23) (Figure 4A). The mean ± SD time from obtaining breakthrough designation to MAA submission was 20.2 ± 8.14 months (median, 19.56, IQR, 13.02–28.50, range, 11.04–30.96). Similar to the EU, both Kymriah and Yescarta obtained the designation just over a year before MAA submission, whereas Luxturna and Zolgensma obtained the designation over 2 years before MAA submission (Figure 4B). Three approved products (33.33%) received fast track designation (Provenge, Imlygic and Zolgensma). Zolgensma obtained fast track and breakthrough designations consecutively. The mean ± SD time from the start of the main clinical trial to obtaining fast track designation was −8.33 ± 35.64 months (median, 2, range, −48 to 21). The mean ± SD time from obtaining fast track designation to MAA submission was 58.96 ± 15.57 months (median, 60.12, range, 42.84–73.92). None of the approved ATMPs have been granted RMAT designation, and no product with this designation has yet been launched in the US market.

When analyzing the three most common ATMPs approved in the EU and USA, the mean ± SD time between having the expedited designation granted and starting the pivotal clinical trial in the EU was 6.33 ± 12.66 months (median, 11, range, −15 to 28) and 5.66 ± 18.58 months in the USA (median, 11, range, −15 to 21). This difference was not statistically significant (mean difference, −0.66 months, 95% CI, −23.75 to 22.42, $P = 0.912$). The mean ± SD time between having the expedited designation granted and MAA in the EU was 16.80 ± 3.02 months (median, 18, range, 14.04–20.04) and 19.68 ± 5.70 months in the USA (median, 18, range, 15–26.04). This difference was not statistically significant (mean difference, 0.24 months, 95% CI, −0.32 to 0.80, $P = 0.209$).

The number of cumulative PRIME designations granted for ATMPs from May 2016 to May 2020 was 32 out of 76 (42.10%) requested,

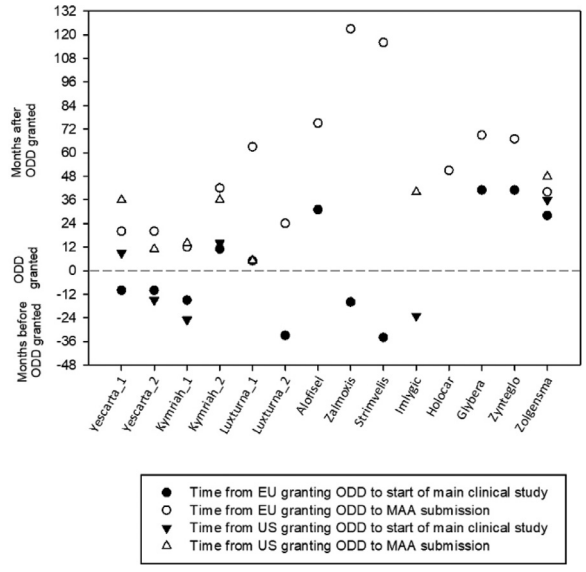

Figure 2. Relationship between date of granted ODD and start of main clinical study and MAA submission. No prospective clinical trials were conducted in support of Holoclar MAA. Yescarta_1 and Kymriah_1: treatment of diffuse large B-cell lymphoma indication in the EU and the USA. Yescarta_2: treatment of primary mediastinal large B-cell lymphoma indication in the EU and the USA. Kymriah_2: treatment of B-lymphoblastic leukemia/lymphoma in the EU and the USA. Luxturna_1: treatment of Leber congenital amaurosis in the EU and treatment of inherited retinal dystrophy due to biallelic *RPE65* gene mutations in the USA. Luxturna_2: treatment of retinitis pigmentosa in the EU. Yescarta received three ODDs in the USA: (i) treatment of diffuse large B-cell lymphoma, (ii) treatment of primary mediastinal B-cell lymphoma and (iii) treatment of follicular lymphoma. The two latest indications have been clustered (Yescarta_2) since they were granted almost at the same time.

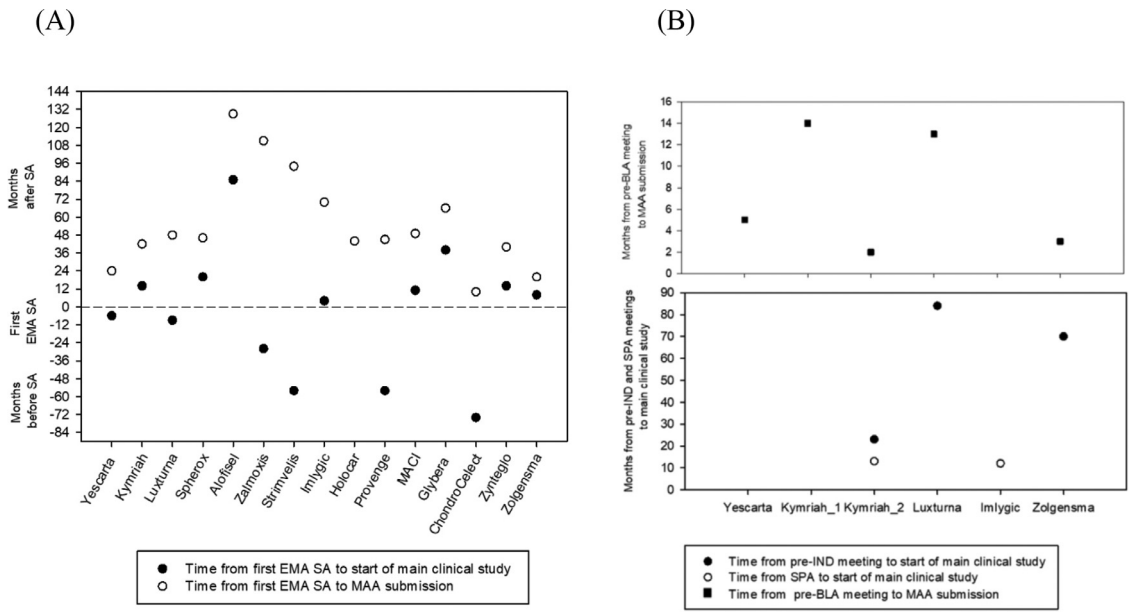

Figure 3. (A) Relationship between date of first EMA SA and start of main clinical study and MAA submission. (B) Relationship between reported meetings with the FDA and start of main clinical study and MAA submission. No prospective clinical trials were conducted in support of Holoclar MAA. Kymriah_1: treatment of diffuse large B cell lymphoma indication. Kymriah_2: treatment of B-lymphoblastic leukemia/lymphoma. pre-IND, pre-investigational new drug; SPA, Special Protocol Assessment procedure.

whereas it was 36 out of 199 (18.09%) requested for other chemical and biological drugs ($P< 0.0001$) (Figure 5). No cumulative data are reported for the breakthrough designation. The reported cumulative RMAT requests received from December 2016 until May 2020 add up to a total of 139; of these, 48 were granted (34.5%), 76 were declined (54.67%) and six were withdrawn (4.3%). Both RMAT and PRIME were launched in 2016, and the cumulative data indicate that slightly more PRIME designations are granted for ATMPs than RMAT designations (42.1% versus 34.5%, respectively).

Marketing authorization application

The mean ± SD time required from submission of the MAA to its final approval in the EU was 17.96 ± 10.97 months (median, 17.55, IQR, 10.78–21.42, range, 7.69–53.49) and 10.96 ± 4.62 months for those therapies with a PRIME designation (median, 9.30, IQR, 7.72–15.86, range, 7.69–17.55). The mean ± SD time of the first clock stop for all approved ATMPs was 6.56 ± 9.81 months (median, 3.65, IQR, 2.16–6.19, range, 0.85–43.70), whereas it was 1.59 ± 0.63 months for therapies with the PRIME designation (median, 1.66, IQR, 0.95–2.16, range, 0.85–2.20) and 9.03 ± 11.35 months for those without the PRIME designation (median, 5.55, IQR, 3.65–8.23, range, 2.86–43.70). The mean ± SD time of the second clock stop for all approved ATMPs was 2.03 ± 2.22 months (median, 1.05, IQR, 0.64–2.38, range, 0.03–7.75). After this second clock stop, there were second rounds of outstanding issues for nine of the approved ATMPs analyzed (60%), and even third and fourth rounds for ChondroCelect and Zalmoxis, respectively (13.33% of the approved products). For Zynteglo, there were no outstanding issues, although the European Commission requested clarifications on the label after the

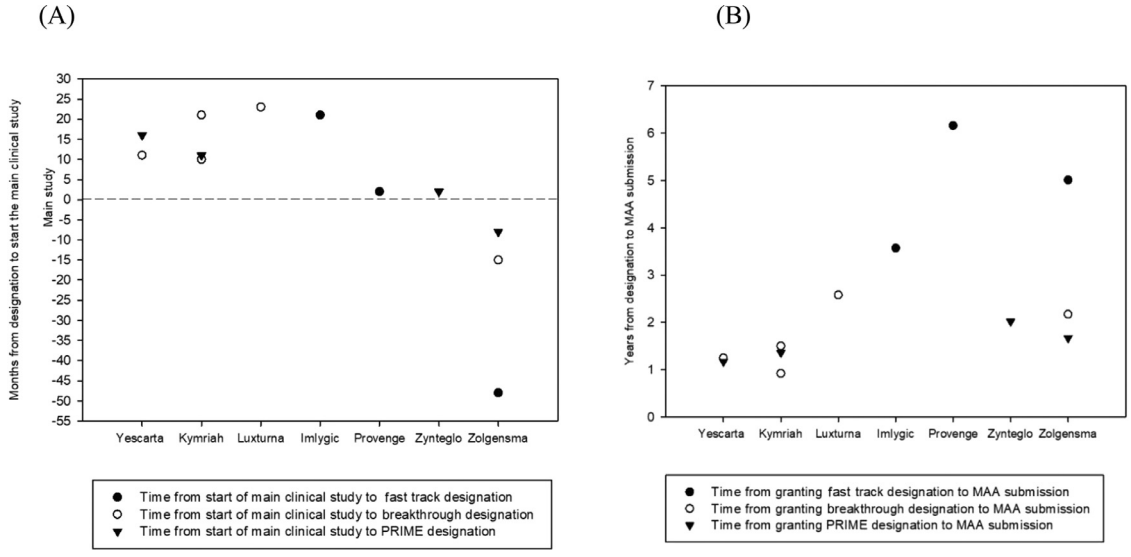

Figure 4. (A) Relationship between date of granting expedited programs and start of main clinical study. (B) Relationship between date of granting expedited programs and MAA submission. Kymriah obtained breakthrough designation for the following indications: treatment of adult patients with diffuse large B-cell lymphoma and treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.

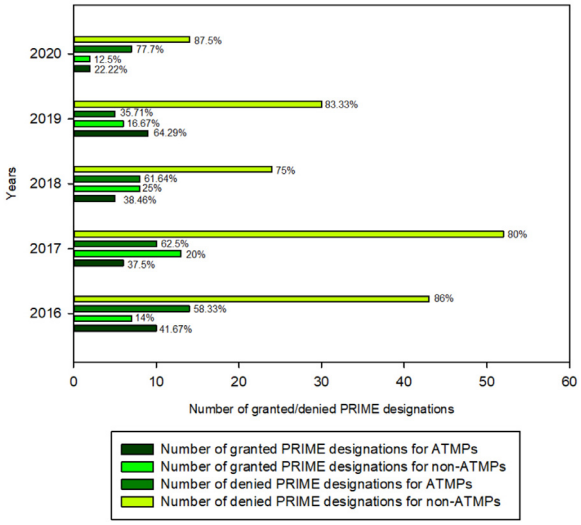

Figure 5. Number of PRIME designations granted and denied for ATMPs versus non-ATMPs (from May 2016 to May 2020). (Color version of figure is available online).

positive Committee for Advanced Therapies/CHMP opinion. Finally, nine of the approved products required an oral explanation (60%) to obtain the approval.

In the USA, the mean ± SD time required from submission of the MAA to its final approval was 8.16 ± 3.05 months (median, 6.98, IQR, 5.95–10.31, range, 5.13–14.98) and 6.85 ± 1.10 months for those products with breakthrough designation (median, 6.63, IQR, 5.49–7.56, range, 5.13–7.72). It took 7 months for Yescarta and Luxturna to obtain approval through a rolling submission.

The mean ± SD time required from submission of the MAA to its final approval among approved ATMPs in both regions was 13.64 ± 4.58 months in the EU (median, 13.76, IQR, 8.56–17.81, range, 7.82–19.78) and 8.20 ± 3.29 months in the USA (median, 6.98, IQR, 6.11–10.40, range, 5.13–14.98). The difference was statistically significant (mean difference, 5.44 months, 95% CI, 1.63–9.25, $P = 0.012$).

A total of seven products (46.67%) in the EU and six products (66.66%) in the USA required an advisory committee during the MAA. The issues raised to the advisory committees were different in the EU and the USA, and the most common questions were related to target population, evidence of clinical efficacy and clinical pharmacology (including dose and route of administration) (Table 3).

Expedited Marketing authorisation applications assessments

The MAAs of Strimvelis, Yescarta, Kymriah, Zynteglo and Zolgensma were reviewed under an accelerated assessment (AA) (33.33% of the approved products), being the mean ± SD time from submission to final approval 10.96 months in the EU (median, 10.78, IQR, 7.75–14.29, range, 7.69–17.55). Only Zynteglo could keep the AA until the end of the procedure.

A total of five (55.55%) of the approved products obtained a priority review in the USA, including all of the approved therapies that were granted breakthrough designation (Yescarta, Kymriah, Luxturna and Zolgensma). Provenge was granted fast track designation and also obtained a priority review since at the time of its development the breakthrough designation was not available. The mean ± SD time for approval under priority review was 6.56 ± 0.91 months (median, 6.73, IQR, 5.74–7.25, range, 5.13–7.72).

There was no difference in the percentage of ATMPs with an expedited MAA assessment between the EU (33.3%, 95% CI, 15–58.5%) and the USA (55.5%, 95% CI, 26.6–81.2%) ($P = 0.285$).

Kymriah, Yescarta and Zolgensma obtained expedited MAA review in both regions (42.86% of ATMPs authorized in both regions). The mean ± SD time from submission to final approval of these products was 10.99 ± 4.58 months in the EU (median, 9.3, IQR, 7.82–15.85, range, 7.82–17.55) and 6.58 ± 1.07 months in the USA (median, 6.73, IQR, 5.49–7.50, range, 5.13–7.72). The difference was not statistically significant (mean difference, 4.41, 95% CI, −1.70 to 10.53, $P = 0.105$).

Table 3
Comparison of the issues discussed in scientific advisory group meetings during the MAA for approved advanced therapies in the EU and USA.

	Kymriah		Luxturna		Imlygic		Provenge	
	EU	US	EU	US	EU	US	EU	US
Product potency								①
Pharmacology (including dosing and route of administration)						①		①
Pharmacokinetics (biodistribution)			①					
Target population and indication	②		③		②	①	①	
Choice of endpoints				①	①			
Sufficient clinical package to support the MA						①		
Clinical efficacy results	④				①		①	①
Clinical benefit	①		②					
Clinical safety							①	
Safety with regard to product administration		①		①				
Limited S&E follow-up, RM and post-marketing	①			①			①	
Risk-benefit assessment		①		①		①		
Regulatory pathway for approval						①		
Total	⑧	②	⑥	④	④	⑤	④	③

Categorization approach was sourced and adapted from Barkholt *et al.* [4]. LaViv and Gintuit were only approved in the USA. Issues discussed in scientific advisory group meeting during MA procedure for laViv were pharmacology (one issue), clinical safety (five issues), limited S&E follow-up and RM and post marketing (one issue). Issues discussed in scientific advisory group meeting during MA procedure for Gintuit were validation process and assays (one issue), impurities, microbiological contamination (two issues) and comparability and consistency issues (one issue). Glybera was approved only in the EU. Issues discussed in the scientific advisory group meeting during the MA procedure for Glybera were choice of endpoints (one issue), pharmacodynamics and drug interactions (one issue), target population and indication (one issue). Zolgensma required a scientific advisory group meeting in the EU. Issues discussed included pharmacology (including dosing and route of administration) (one issue), target population and indication (one issue) and clinical benefit (one issue). For Zolgensma, no advisory committee meeting was held in the USA because initial review of information submitted did not raise concerns or controversial issues that would have benefited from an advisory committee discussion. RM, risk management; S&E, safety and efficacy.

Types of Marketing Authorizations

In the EU, 10 (66.7%) ATMPs have been authorized under standard approval, four (26.7%) under conditional approval and one (6.7%) under exceptional circumstances. In the USA, six (66.7%) have been authorized under standard approval and three (33.3%) under an accelerated approval program. Of the seven ATMPs authorized in both regions, the type of MA differed for only two ATMPs (28.6%); Yescarta and Kymriah were authorized under standard approval in the EU but under an accelerated approval program in the USA. Four out of eight products non-commercialized in the USA had a non-standard MA in the EU. Five therapies were withdrawn in the EU, whereas two of those are still authorized in the USA (Table 1).

Discussion

The major finding of the current study is that the main regulatory milestones are similar between regions, although some differences

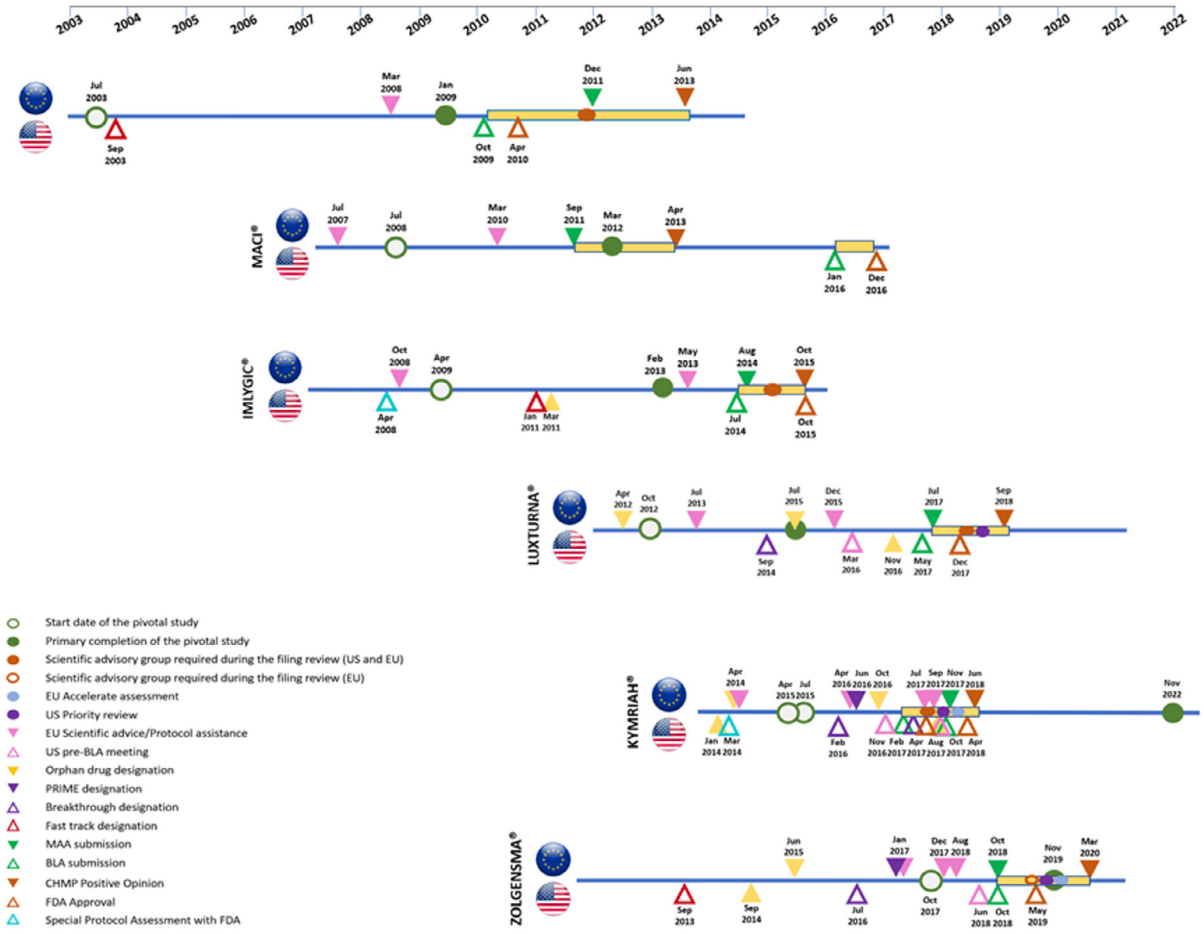

Figure 6. Comparison of regulatory pathways followed by ATMPs that were authorized in both regions. (Color version of figure is available online).

have become apparent (Figure 6). Over the last several years, a constant effort has been made to develop ATMPs focused mainly on orphan conditions. Almost 2100 clinical trials studying ATMPs were initiated between January 2014 and June 2019 worldwide, most of them cell and gene therapies in phase 1 or 2 of clinical development [6]. Interestingly, three times more of these interventional clinical trials were located in North America than in Europe. However, only 15 ATMPs in the EU and nine ATMPs in the USA had achieved MA by May 2020, representing 1.6% of overall approved products in Europe from 2009. These data reveal the necessity of understanding the gap between the large number of investigational products and the approved ATMPs and whether specific regulatory procedures were used to achieve their current status in the EU and the USA.

When analyzing all the steps involved in the procedure to achieve MA, the authors observed that more than half of the approved ATMPs obtained orphan status. With regard to the ODD programs in the EU and USA, medical plausibility and the prevalence of the disease need to be demonstrated. However, unlike in the EU, in the US there is no need to prove significant benefit over standard of care [7,8]. The authors' study indicates that in the EU, half of the approved ATMPs with an ODD targeted unmet medical needs, avoiding significant benefit demonstration and in part contributing to an open-label clinical designs. Moreover, the time analysis related to achieving orphan designation showed that there is no representative mean time to apply for the ODD; it is mainly product-specific and dependent on the duration of clinical development. Most of the approved therapies applied to the ODD once preliminary patient clinical data were available, possibly due to the fact that conventional non-clinical toxicological packages are not applicable to these therapies because of their patient specificity and lack of pre-clinical models [9]. By contrast, the therapies with a short period between granted ODD status and MAA submission might be in part due to the abbreviated clinical development, common in the case of advanced therapies, whereas those products with prolonged periods were probably attributable to recruitment issues, which are common in the case of rare diseases.

SA is a non-binding regulatory procedure offered to the sponsors at any stage of the ATMP development program. Although SA is not mandatory, it has been previously shown that products following SA recommendations at early stages of clinical development are more likely to achieve MA [10]. In the EU, advice can be provided by the EMA or the national competent authorities (NCAs). NCA SA is related to the suitability of early clinical development, whereas EMA SA will usually focus on the pivotal clinical trials that will support the MAA. Interestingly, half of the approved products did not seek advice from the EMA before starting the main study. This did not imply an impact on approval success, but a mean of two additional amendments to the protocol of the main study was observed. The fact that these therapies target unmet medical needs and the lack of clinical regulatory guidelines for specific medical conditions at that time might increase the need for this procedure. In 2020, the EMA has promoted a new pilot program to facilitate multiple SA procedures with the NCAs [11]. It should be noted that the review will be independent among the NCAs, and diverging opinions may still occur. Other options prior to a formal SA procedure include informal meetings with the NCAs in the EU focused on innovative therapies [12–14] or the so-called Innovation Task Force (ITF) and INitial Targeted Engagement for Regulatory Advice on CBER ProducTs (INTERACT) meetings with the EMA and FDA, respectively [15,16].

By contrast, the early development strategy should include discussions with the authorities regarding evidence generation. The abbreviated clinical development and non-controlled trials that accompany most ATMPs result in uncertainty about long-term efficacy and safety, which are the main constraints for obtaining product reimbursement [17]. Although approved through a standard authorization, Provenge, MACI and ChondroCelect were withdrawn because of poor commercial performance and/or lack of reimbursement in EU countries [18–20]. Despite the importance of this point, only 13% of the products conducted a parallel advice procedure with the EMA and European Network for Health Technology Assessment bodies [21].

In the USA, limited information with regards to meetings conducted with the FDA is available. Interestingly, in the case of ATMPs, special protocol assessment procedures were also reported, where the sponsors might reach an agreement with the FDA on the design and size of a single clinical trial to support the MA [22]. End-of-phase 2 meetings with the FDA are aimed at obtaining advice on pivotal study design and are similar to the EMA SA procedure when conducted with the same purpose. No comparisons between the two regions can be done for these SA procedures since there is no public information regarding when end-of-phase meetings were conducted with the FDA for the approved ATMP products.

Another milestone in the regulatory pathway in the EU and USA is the possibility of applying for an expedited program (see supplementary Table 1). These programs offer continuous support and guidance from the agencies during clinical development so as to optimize and speed up drug development plans and evaluation. Expedited programs are mainly aimed at those products that target unmet medical needs or serious conditions or bring a major therapeutic advantage to patients without treatment options. The FDA has created three types of expedited programs: the fast track designation in 1997, breakthrough therapy designation in 2012 and RMAT in 2016, whereas the EMA launched the PRIME designation scheme in 2016 [23–25].

The present data indicate that more breakthrough designations have been granted than PRIME designations for the approved ATMPs (44.4% versus 26.7%). Although a low number of approved ATMPs obtained PRIME designation, almost all of the approved ATMPs that were under development when these programs were launched benefited from them, except for Luxturna in the EU. The authors' results also demonstrate that the mean time from the start of the main clinical trial to obtaining PRIME or breakthrough designation and the mean time from obtaining these designations to MAA submission were similar for both regions. However, the time for obtaining PRIME designation might not be representative since, if this program was available at the time, it might have been granted earlier for these therapies based on exploratory clinical data. Further analysis is required to conclude the mean time for applying to this program, although, with regard to the current approved therapies, it was requested after the main clinical trial started. The fact that the breakthrough designation was available but obtained later during development might be attributed to the qualifying criteria of this program, where clinical evidence that demonstrates substantial improvement over available therapies is required.

With respect to Kymriah, Yescarta and Zolgensma, PRIME and breakthrough designations were obtained consecutively. Although the breakthrough therapy and PRIME designations are equivalent in the two regions, the development requirements and regulatory guidance may differ. However, the authors' data demonstrate that the access of ATMPs to expedited programs is approved or rejected similarly in both agencies.

In the USA, the RMAT designation includes all the benefits of the fast track and breakthrough therapy programs and does not require evidence to indicate that the drug may offer improvement over available therapies. Therefore, RMAT designation would have been an attractive option for these approved products, but it is assumed that development was already too far advanced at the time the RMAT designation was put in place by the FDA.

In the EU, there is a notable difference in the number of PRIME designations that have been granted for ATMPs in comparison with other products, including chemicals and other biological drugs. This fact emphasizes again the type of disease the current ATMPs target. Even if the clinical design for ATMPs is typically non-controlled, this does not seem to be an obstacle to getting the expedited designations.

The final step to achieving MA is the MAA. The standard timelines for a BLA review comprise 10 months of the 60-day filing date and around 11 months for the CHMP opinion in the EU (taking into consideration 210 days for the assessment and approximately 4 months for the clock stops). For priority reviews in the USA or AA in the EU, these standard timelines can be reduced to approximately 6 months (including a clock stop of 1 month in the EU) [26,27].

For the approved ATMPs, the time required from submission of the application to approval is shorter for the USA, requiring a mean of approximately 10 months less in comparison with the EU. In the EU, the median time required for the MAA evaluation under standard or accelerated review exceeds the theoretical standard timelines by approximately 7 and 5 months, respectively. In the USA, the median time of a priority review exceeds the theoretical timelines by only 0.56 months. It should be noted that all the products with PRIME and breakthrough designation obtained AA and priority review for the MAA, respectivetly.

The duration of the first clock stop in the EU MAA usually has an average of 3–6 months, and in the case of approved therapies, this tends to be toward the upper limit. Spherox is considered an outlier since it spent almost 4 years in clock stop, likely due to major issues related to quality. A similar case occurred with Holoclar, which had a clock stop of 13 months. The four therapies with PRIME designation had a considerably shorter clock stop compared with other therapies without these designations. Continuous guidance from the agencies during development might reduce the number of major objections during evaluation and help applicants anticipate the potential questions. In the case of the approved ATMPs, there were second rounds of outstanding issues after the second clock stop for half of the approved ATMPs and even third and fourth rounds for some products. This fact might reflect the immaturity of the data initially submitted. With the exception of Zolgensma, which had a second round of outstanding issues, none of the products with a PRIME designation had second rounds of questions after the second clock stop.

In the USA, those products with a breakthrough designation had shorter MAA review time, associated to a priority review. By contrast, the rolling review offers the possibility of submitting completed sections of the BLA, rather than waiting until the whole dossier required for the application is available [25]. Yescarta and Luxturna agreed on a rolling submission with the FDA, the latter also being eligible for priority review once the BLA was filed. The fact of having submitted this way did not shorten the BLA review timeline in comparison with other drugs that were submitted in a conventional manner.

In exceptional cases, during the EU or US MAA review there is the need for an ad hoc expert group consultation to clarify issues raised by the reviewers [28,29]. The fact that in both regions approximately half of the assessed products required this additional expert consultation indicates the complexity and specificity of these therapies, including the types of target diseases and clinical programs with alternatives designs. Interestingly, although the main development milestones are similar between the two regions, the issues raised to the external committees during the MAA for the approved ATMP differ between the agencies.

Regarding the milestone of obtainging an expedited MAA assessment, in the EU, an AA allows a reduction in the timeframe for the MAA if the product is of major interest to public health and therapeutic innovation. Under this procedure, a first 30-day clock stop is expected (compared with a standard 3- to 6-month clock stop), and a second clock stop should not occur [30]. Although four out of five products with a granted AA had the shortest review time compared with other approved ATMPs, with the exception of Zynteglo, the

timelines for approval did not meet the expectations of an AA, and there was a shift to the standard timelines. For Yescarta and Kymriah, the AA was no longer compatible because of major objections in the first and second clock stops, whereas Zolgensma presented deficiencies in many quality and clinical aspects of the dossier. Therefore, it would be advisable for the developers to present a mature dossier when requesting an AA and to anticipate potential questions that may arise during the clarification phase to shorten it as much as possible; otherwise, the AA loses its purpose.

The equivalent program in the USA is the priority review designation. Although the expedited review designations do not guarantee a priority review, most breakthrough therapy designation products are assigned priority status. The priority review involved a shorter review time in comparison with other approved therapies without this designation (i.e. Yescarta, Kymirah, Luxturna and Zolgensma vs laViv, Imlygic, MACI and Gintuit). For those products with an expedited MAA review in both regions, the time required from submission of the application to approval is shorter for the USA, requiring a mean of 4.4 months less in comparison with the EU, although this difference is not statistically significant.

Finally, with regards to the type of authorisation, a MA via the centralized procedure for an ATMP in the EU may be granted in three ways: standard, conditional or MA under exceptional circumstances [31,32]. In the USA, there are two types of MAs: the standard and the accelerated approval [33] (see supplementary Table 2). Although for most of the therapies approved in both regions the type of MA granted was equivalent, it might differ, as was the case with Yescarta and Kymriah. Half of the products commercialized not in the US but in the EU obtained a non-standard EU approval. Consequently, all of them required post-authorization studies to provide comprehensive and conclusive clinical data, which may sometimes also result in a negative benefit-risk balance. This was the case with Zalmoxis, which failed to show benefit on the primary endpoint, and the application had to be withdrawn [34].

The limitations of this study include the small sample size, above all for those ATMPs approved both in the EU and the USA, and further analysis is required to delineate differences between the two regions. In addition, this study was limited to approved ATMPs and did not include ATMPs under current development. The public information available is also not the same for the two regions, which hampered the analysis. Nevertheless, this is an exhaustive study that evaluates and compares, when possible, the regulatory steps taken for the ATMPs approved thus far, and no similar analysis was found in the literature by the authors.

Conclusions

The first ATMPs launched in the last decade mainly target orphan diseases. From a regulatory standpoint, there are multiple procedures available to facilitate and foster the development of these therapies, allowing an earlier MA. Although the EMA and FDA have their own regulatory recommendations with regard to pre-clinical and clinical development, the authors have demonstrated that the main regulatory milestones reached by the approved ATMPs are similar. Nevertheless, the number of authorized products and time for MAA evaluation, as well as type of MA for some products, differ between the two regions. Increased global regulatory convergence among the main regulatory agencies is a current topic of debate and might be one of the key factors in simplifying and expediting the approval of ATMPs.

Declaration of Competing Interest

The authors have no commercial, proprietary or financial interest in the products or companies described in this article. The findings and conclusions in this article should not be construed to represent any agency determination or policy.

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Author Contributions

Conception and design of the study: CIL, AV, AA and MO. Acquisition of data: CIL. Analysis and interpretation of data: CIL, AV, AA and MO. Drafting or revising the manuscript: CIL. All authors have approved the final article.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcyt.2020.11.008.

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