The Role of Real-World Evidence in Cell and Gene Therapy Regulatory and Health Technology Assessment Decisions

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Background & Objective

Randomized controlled trials (RCTs) remain the proverbial gold standard for demonstrating the efficacy and safety of medical products. Regulators and health technology assessment (HTA) bodies have become increasingly open to evaluating real-world evidence (RWE) to support their review and assessment of medical products. Systematic reviews have demonstrated that RWE has increasingly been submitted in Food and Drug Administration (FDA) and HTA applications in recent years.[1-3] These reviews have shown that RWE is typically best suited for medical products intended to treat rare diseases with unmet needs and severe outcomes.[1-3] This correlation is due to the fact that conducting an RCT in these situations may be impractical, unethical, or infeasible. Cell and gene therapies (C&GTs) challenge the traditional evidence generation paradigm as they (1) typically treat ultra rare diseases, (2) receive expedited approval, which often means there is a lack of mature clinical data, (3) offer potentially curative effects with unknown long-term outcomes[4-5], and (4) are often highly priced[6], raising concerns about affordability and cost-effectiveness. Accordingly, C&GTs are prime candidates for using RWE in lieu of a more traditional evidence generation approach. The objective of this study is to examine how RWE is used in C&GT regulatory and HTA applications and how it impacts regulatory and HTA decision-making processes.

Methods

FDA approval materials for C&GTs (excluding cord blood treatments) from 2016-2021 were screened to determine if RWE was included or planned, the type of RWE used, and the role of the RWE in the approval package. For two case studies (onasemnogene abeparvovec and idecabtagene vicleucel), approval documentation from the European Medicines Agency (EMA) and HTA agencies (i.e., the National Institute for Health and Care Excellence [NICE], the Institute for Clinical and Economic Research [ICER], and Haute Autorité de Santé [HAS]) were also reviewed. The use and impact of RWE in these two submissions were compared.

Table 1. FDA-Approved Cell and Gene Therapies, 2016-2021

Ten in-scope C&GT approvals since 2016 by FDA	Included or planned RWE?	Indication
ABECMA® (idecabtagene vicleucel)	✓	The treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy (4th Line+ treatment of RRMM)
BREYANZI® (lisocabtagene maraleucel)	✓	The treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy
KYMRIAH® (tisagenlecleucel)	✓	The 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
LUXTURNA® (voretigene neparvovec-rzyl)	✓	The treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy
MACI® (autologous cultured chondrocytes on a porcine collagen membrane)	X	The repair of single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement in adults
RETHYMIC® (allogeneic processed thymus tissue–agdc)	✓	Immune reconstitution in pediatric patients with congenital athymia
STRATAGRAFT® (allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat)	✓	The treatment of adults with thermal burns containing intact dermal elements for which surgical intervention is clinically indicated
TECARTUS® (brexucabtagene autoleucel)	✓	The treatment of adult patients with relapsed or refractory mantle cell lymphoma
YESCARTA® (axicabtagene ciloleucel)	✓	The treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy
ZOLGENSMA® (onasemnogene abeparvovec-xioi)	✓	The treatment of patients with spinal muscular atrophy (SMA)

Results

Ten C&GTs, nine of which included RWE in the application, were initially approved by the FDA during 2016-2021 (Table 1). The most common types of RWE submitted were external control arms (ECAs) (n=3), an analysis of data from an Expanded Access Program (EAP) (n=3), and RWE-based Literature (n=2)/Observational Studies (n=2; categories are not mutually exclusive) (Figure 1). Uses ranged from providing substantial (n=2) or supportive (n=5) evidence of effectiveness to providing real-world context around the therapy/indication (n=1) and planned fulfillment of post-marketing requirements (n=3; categories are not mutually exclusive) (Figure 2).

In their FDA applications, onasemnogene abeparvovec and idecabtagene vicleucel both utilized RWD-based ECAs. For onasemnogene abeparvovec, the same RWD sources were used to inform the ECA across most of the regulatory/HTA agencies; however, for onasemnogene abeparvovec, a clear trend was not apparent as most agencies relied on a mix of clinical sites, registries, and research databases to inform the ECA (data not shown). For onasemnogene abeparvovec, RWE influenced the decision for the FDA, EMA, and HAS submissions; however, NICE and ICER noted challenges with the RWE regarding variable natural history across patients and small patient numbers. For idecabtagene vicleucel, FDA, EMA, HAS, and ICER noted uncontrolled confounding, data loss, and inconsistent standard of care over time; despite these limitations, EMA found that the RWE helped to contextualize the trial results (Table 2).

Figure 1. Type of RWE Included in FDA Application

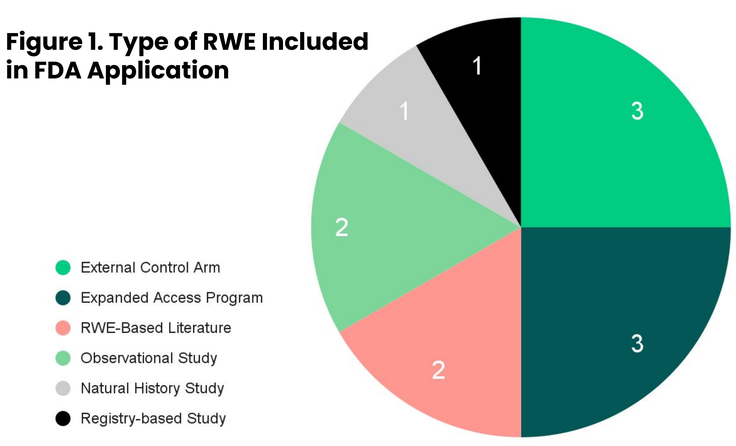
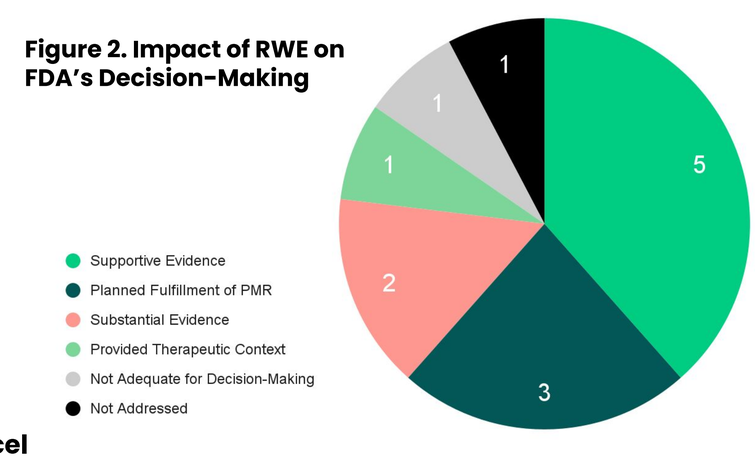


Figure 2. Impact of RWE on FDA's Decision-Making



Conclusions

RWE was included in almost all C&GT applications submitted to FDA from 2016 to 2021. This evidence often played a strong role in the application package, either through providing evidence of efficacy and safety or addressing post-marketing requirements. However, the RWE did not always contribute to FDA's decision-making.

In the two case studies examined, there was variability among the regulators and HTA agencies in the level of support that RWE contributed to their decisions. These use cases thus provide important learnings for sponsors and agencies seeking to navigate the evolving field of using RWD to support regulatory/HTA decision-making.

Table 2. Regulatory and HTA review of RWE included in applications for onasemnogene abeparvovec and idecabtagene vicleucel

Product		FDA Review	EMA Review	ICER Review	NICE Review	HAS Review
Onasemnogene abeparvovec to treat SMA	*Decision*	Approved	Conditionally approved	Value-based price benchmark at 1.1-1.9M in May 2019	Recommended with restrictions	ASMR III (moderate added benefit) for SMA Type 1 or 2; ASMR V (no added benefit) for SMA Type 3
	Feedback	Single-arm trial data compared favorably to natural history data for survival and motor function	EMA noted that single-arm trial data compared favorably to natural history data for survival	Results showed prolonged survival and improved motor function; uncertainty in low patient numbers, long-term efficacy	Uncertainty in low patient numbers, limited long-term efficacy evidence, generalizability with National Health Service population	Patients in the ECA were older, had less severe disease than those in the clinical studies; uncertainty in the comparative efficacy due to unadjusted comparison to the ECA
	Impact	ECA provided substantial evidence and Expanded Access provided supportive evidence	ECA provided substantial evidence; Expanded Access and post-marketing data provided supportive evidence	Rated evidence as high certainty of effect	NICE required a managed access agreement to further data collection (including RWE)	HAS requested reassessment & noted need for registry and pharmacovigilance data to better understand long-term effects and safety
Idecabtagene vicleucel for 4th Line+ treatment of RRMM	*Decision*	Approved	Conditionally approved	50% reduction off list price needed to meet cost-effectiveness thresholds; panelists deemed it "low" long-term value for money	Not applicable, NICE assessment still in development	ASMR V (no added benefit)
	Feedback	Methodological issues such as missing data, differences in follow-up, response assessment, population heterogeneity, and bias in endpoint assessment	Long time period allowed for baseline data collection, overlapping recruitment periods between the single-arm trial and ECA at the same study centers, large amount of missing data	Inconsistent standard of care over time	Not applicable	Missing data for baseline prognostic factors & uncontrolled confounding likely biased ECA results
	Impact	ECA found to be inconclusive	ECA contextualized single-arm trial findings	ECA primary source for both clinical- and cost-effectiveness comparisons	Not applicable	ECA not considered in decision-making

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