Poster HTA232

# Review of Real-World Evidence (RWE) in Marketing Authorization Applications (MAAs) Highlight Differences in Evidentiary Standards Among Regulatory and Health Technology Assessment (HTA) Bodies

**Shivani Aggarwal[1], David Goldfarb[2], Chiara Cantoni[3]**

[1]Landmark Science, Inc., Los Angeles, CA, USA, [2]Landmark Science, Inc., New York, NY, USA, [3]IQVIA, Paris, France

## Background and Rationale

- The growing use of real-world data (RWD) and real-world evidence (RWE) in drug development has driven the need for harmonization of guidelines and standards among regulatory authorities and Health Technology Assessment (HTA) bodies.
- Evidentiary standards for RWE vary across regulators and HTA bodies although differences are not well-characterized.
- Regulatory acceptance of MAAs with RWE is well-documented, but its acceptance by HTA bodies remains less clear.
- We compared regulatory and HTA decisions on six drug marketing applications, analyzing how different regulatory bodies and HTA bodies align or differ in their assessments.
- **Objective: to characterize acceptance by regulators and HTA bodies of RWE used as either supportive or substantial evidence in MAAs. Through six examples, we examined whether RWE submitted for regulatory decision-making was accepted across different regulators and HTAs.**

## Methods

### Data Collection

- We conducted a targeted literature review of regulatory and HTA feedback on drug approvals containing RWE as supportive or substantial evidence in MAAs from January 2021 - present.
- **Regulatory focus**: Food and Drug Administration (FDA) [US], European Medicines Agency (EMA) [Europe], Health Canada (HC) [Canada], & Medicines and Healthcare products Regulatory Agency (MHRA) [UK] due to their significant roles in the regulatory landscape.
- **HTA focus**: NICE [UK], G-BA and IQWIG [Germany], HAS [France], AEMPS [Spain], CAD (formerly CADTH) [Canada], SMC [Scotland], and TLV [Sweden] provide a comprehensive analysis of HTA reviews of the same RWE.

### Case Study Selection

- We selected **six medicines** for analysis based on RWE included in their MAA submissions:
  - Idecabtagene vicleucel (ide-cel)
  - Omburtamab
  - Sotorasib
  - Alpelisib
  - Palovarotene
  - Tacrolimus
- These were chosen to represent a range of therapeutic areas and evidence types.

### Data Extraction

- We collected publicly available regulatory reports from sources including the FDA, EMA, MHRA, and HC websites, HTA reports from individual HTA bodies, and summary HTA reports from IQVIA's Market Access Insights®, formerly known as HTA Accelerator.
- Two independent reviewers extracted information on the use and evaluation of RWE.
- We reviewed feedback from regulators & HTA bodies regarding the RWE.

### Categorization and Analysis

- RWE evidence in the MAA was categorized as:
  - **Substantial**: RWE provided the primary data & played a key role in decision-making
  - **Supportive**: RWE provided supplementary evidence in the MAA
- RWE acceptance was categorized as:
  - **Accepted**: RWE accepted based on review
  - **Partially accepted**: RWE accepted but limitations were noted
  - **Not Adequate**: RWE was reviewed and discussed but deemed insufficient and therefore not used/accepted
  - **Not Discussed**: RWE was not addressed or discussed by the reviewing body
- We compared findings across regulatory bodies & HTA bodies to identify patterns of concordance or divergence in RWE evaluation.
- We analyzed common concerns and themes related to the evaluation of RWE.

## Results

### Table 1. Overview of selected medicines and RWE contributing to MAAs

| Drug | Ide-cel | Omburtamab | Sotorasib | Alpelisib | Palovarotene | Tacrolimus |
|---|---|---|---|---|---|---|
| **Manufacturer** | Bristol-Myers Squibb | Y-mAbs | Amgen | Novartis | Ipsen | Astellas |
| **Indication** | Relapsed or refractory multiple myeloma | Neuroblastoma with CNS / leptomeningeal metastasis | KRAS G12C+ advanced NSCLC | PI3KCA-related overgrowth spectrum | Fibrodysplasia ossificans progressive | Rejection prevention in lung transplantation |
| **Orphan Drug Status?** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Adult or pediatric?** | Adult | Pediatric | Adult | Adult and Pediatric | Adult and Pediatric | Adult and Pediatric |
| **RWE Study Design** | ECA with pivotal Ph2, systematic literature review | ECA with pivotal Ph1 | Retrospective cohort studies, systematic literature review | Retrospective single-arm study | ECA with pivotal Ph3 | Retrospective arm and historical comparator from literature review |
| **Data Source** | EMR and Registry† | Registry‡ | EMR | Chart review | Chart Review | Registry¥ |
| **Filing Purpose** | First indication | First indication | First indication | Expanded indication* | First indication | Expanded indication* |
| **Application Type** | BLA | BLA | NDA | NDA | NDA | sNDA |

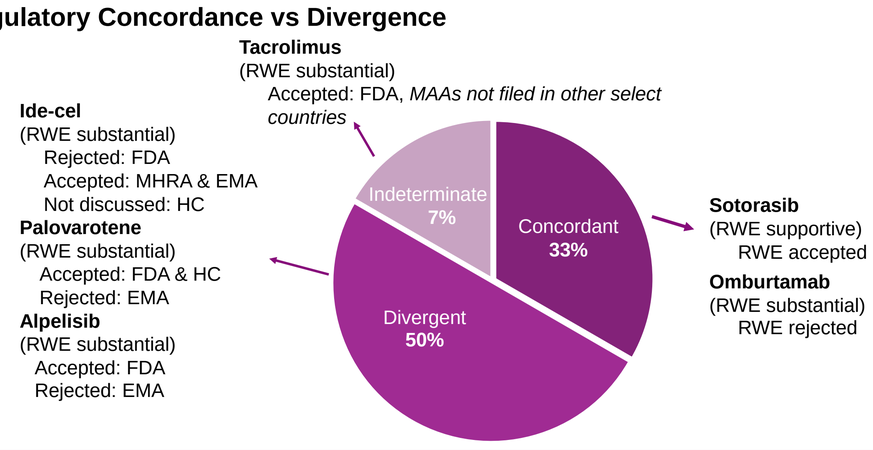
† Data sources used included clinical sites, Connect® MM Registry, Flatiron, GRN, M2Gen, and COTA. ‡ Central German Childhood Cancer Registry. ¥ Scientific Registry of Transplant Recipients. *Alpelisib and tacrolimus received expanded indications in the U.S. only. BLA=Biologics license agreement; CNS = Central nervous system; ECA = External control arm; EMR = Electronic medical record; NDA = New drug application; NSCLC = non-small cell lung cancer; sNDA = Supplemental new drug application.

### Table 2. RWE Acceptance for Six Medicines Among Four Regulatory Agencies

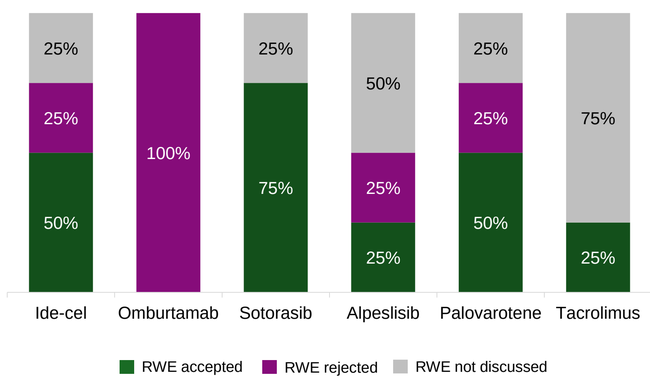
| Drug | Ide-cel | | Omburtamab | | Sotorasib | | Alpelisib | | Palovarotene | | Tacrolimus | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Evidence Type** | Substantial | | Substantial | | Supportive | | Substantial | | Substantial | | Substantial | |
| **Acceptance** | Drug | RWE | Drug | RWE | Drug | RWE | Drug | RWE | Drug | RWE | Drug | RWE |
| **FDA (US)** | ✓ | × | × | × | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **EMA (Europe)** | ✓ | ✓ | × | × | ✓ | ✓ | × | × | × | × | -- | -- |
| **HC (Canada)** | ✓ | -- | -- | -- | ✓ | -- | -- | -- | ✓ | ✓ | -- | -- |
| **MHRA (UK)** | ✓ | ✓ | -- | -- | ✓ | ✓ | -- | -- | -- | -- | -- | -- |

FDA = Food & Drug Administration (USA); HC = Health Canada (Canada); EMA = European Medicines Agency (Europe); MHRA = Medicines and Healthcare products Regulatory Agency (UK).

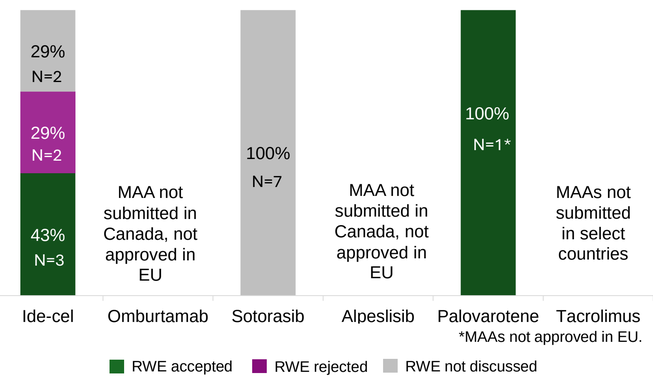
### Figure 1. Regulatory Concordance vs Divergence




### Figure 2. Regulatory Acceptance of RWE by Drug




### Figure 3. HTA Acceptance of RWE by Drug

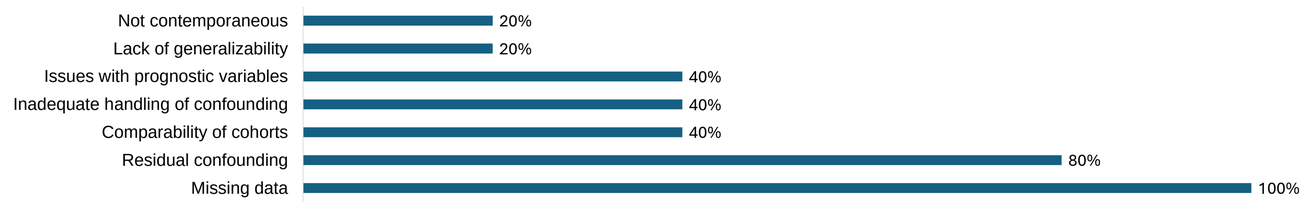



### Table 3. RWE Acceptance for Medicines Reviewed by HTA Bodies

| Drug | Ide-cel | | | Sotorasib | | | Palovarotene | | |
|---|---|---|---|---|---|---|---|---|---|
| **Acceptance** | Drug Reimbursed? | RWE Reviewed? | RWE Accepted? | Drug Reimbursed? | RWE Reviewed? | RWE Accepted? | Drug Reimbursed? | RWE Reviewed? | RWE Accepted? |
| **CAD (Canada)** | × | ✓ | ✓ | × | × | -- | ✓ | ✓ | ✓ |
| **NICE (UK)** | Review terminated | -- | -- | ✓ | × | -- | | | |
| **HAS (France)** | ✓ | × | × | ✓ | × | -- | | | |
| **G-BA (Germany)** | ✓ | × | × | ✓ | × | -- | | | |
| **AEMPS (Spain)** | ✓ | ✓ | ✓ | Indeterminate | × | -- | | | |
| **TLV (Sweden)** | × | ✓ | ✓ | ✓ | × | -- | | | |
| **SMC (Scotland** | -- | -- | -- | ✓ | × | -- | | | |

*Omburtamab, alpeslisib, and tacrolimus are not presented due to MAAs not being filed and/or submitted in select countries presented here.

### Figure 4. Common Biases and Limitations Expressed by HTA Bodies for Ide-cel Review




Proportions are based on a denominator of N=5, representing the HTAs that reviewed Ide-cel (CAD, HAS, G-BA, AEMPS, and TLV).

- HTA evaluation of RWE for ide-cel was concordant for G-BA and HAS (RWE not adequate), and AEMPS and TLV (RWE supportive), while CAD partially accepted RWE as supportive.
- Supportive RWE in sotorasib's MAA was not discussed by HTA bodies, though other RWE such as from registries and MAIC were submitted with varied acceptance.
- CAD accepted RWE for palovarotene as supportive.
- Common concerns from regulators and HTA bodies included biases from incomplete data, study arm comparability, and residual confounding.

## Conclusion

- For the evaluated cases, RWE providing supportive or substantial evidence in MAAs was accepted more frequently by FDA than EMA.
- HTA reviews highlighted differing standards of RWE acceptability. Common types of biases and limitations highlighted by HTA bodies included handling of confounders and prognostic variables, handling of missing data, and residual confounding.
- Consideration should be given to these differences when generating RWE for regulatory decision-making and appraisals.
- Select drugs submitted to the FDA were used as case studies and therefore may not be representative of all MAAs, such as MAAs using RWE for EMA only.

## Plain Language Summary

- This project looks at how different regulatory and health authorities evaluate RWE when approving new drugs. We found that these agencies often have different standards for accepting RWE.
- Sponsors should account for these differences when preparing their RWE submissions, tailoring their studies such as by addressing common biases to meet the specific requirements of each body to improve their chances of use and acceptance of the RWE in the submission.

References are available upon request to the corresponding author:
Shivani@landmarkscience.com
This study was funded by Landmark Science, Inc.

LANDMARK SCIENCE