SAME EVIDENCE, DIFFERENT DECISIONS: HOW REGULATORY STANDARDS SHAPE ORPHAN DRUG APPROVALS

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APPERTURE FOCUSED VALUE

HTA 320

BACKGROUND

- Orphan drug development is supported through regulatory incentives and expedited review pathways intended to improve treatment availability for rare diseases
- Regulatory agencies including the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and Health Canada (HC) independently evaluate orphan therapies using distinct evidentiary frameworks for regulatory approval
- As such, regulatory decisions may differ across agencies evaluating the same therapy despite review of similar submitted evidence
- Understanding differences in regulatory decision-making across agencies may help inform evidence generation strategies, regulatory planning, and patient access for orphan therapies

OBJECTIVE

- **This study examines how cross-agency differences in the evaluation of manufacturer-submitted evidence shapes regulatory evaluations across three selected orphan drug cases reviewed by the FDA, EMA, and HC**

METHODS

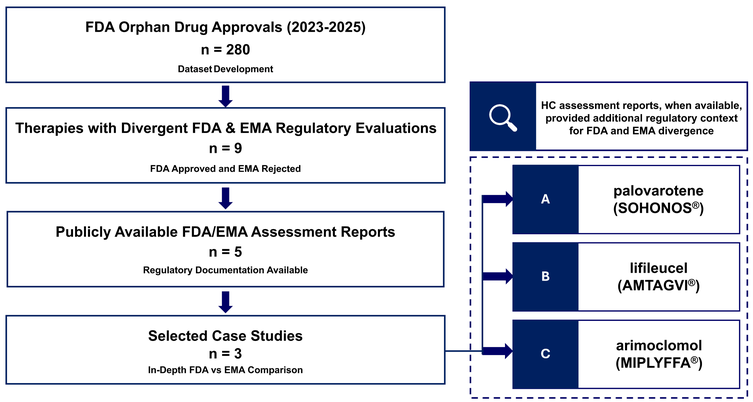
Data Source and Case Selection

- **FDA orphan drug approvals** from **2023-2025** were used as the **starting point for identifying therapies** with **divergent FDA and EMA regulatory evaluations**, as orphan therapies are frequently first reviewed in the US **(Fig 1)**
- **Three case studies** with publicly available FDA and EMA assessment reports **were selected** from five eligible therapies to represent **distinct patterns of evidentiary uncertainties** and **regulatory interpretation**: **palovarotene (SOHONOS®), lifileucel (AMTAGVI®), and arimoclomol (MIPLYFFA®)**
- **HC assessment reports** were included, **when available**, **to provide broader regulatory context** surrounding FDA and EMA divergence

Comparative Regulatory Review

- **FDA, EMA, and HC assessment reports** were reviewed **to evaluate evidentiary uncertainties** and **agency-specific regulatory concerns** across case studies
- **Findings were grouped** into domains related to **trial design, endpoint validity, results interpretability, and safety considerations (Fig 2-4)**
- Agency-specific evaluations of identified evidence gaps were reviewed **to assess how remaining uncertainties informed final regulatory decisions (Fig 2-4)**

Figure 1. Case Selection for Comparative Regulatory Review



Abbreviations: EMA: European Medical Agency; FDA: US Food and Drug Administration; HC: Health Canada

Figure 2: Comparative Regulatory Assessment - palovarotene

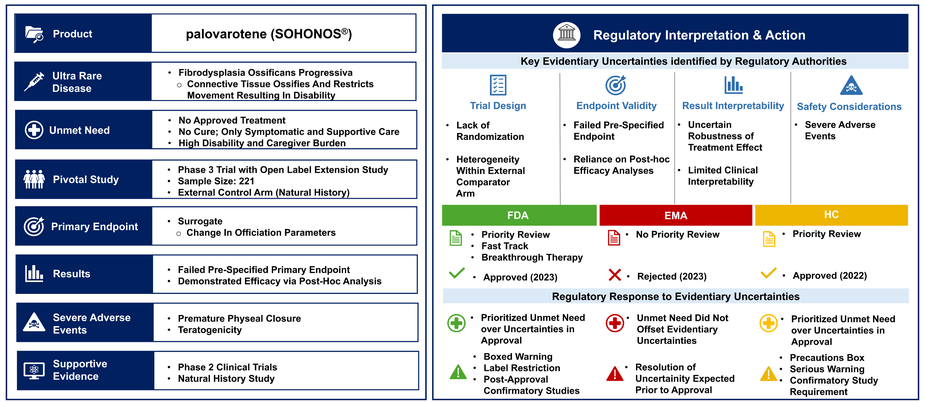


Figure 3: Comparative Regulatory Assessment - lifileucel

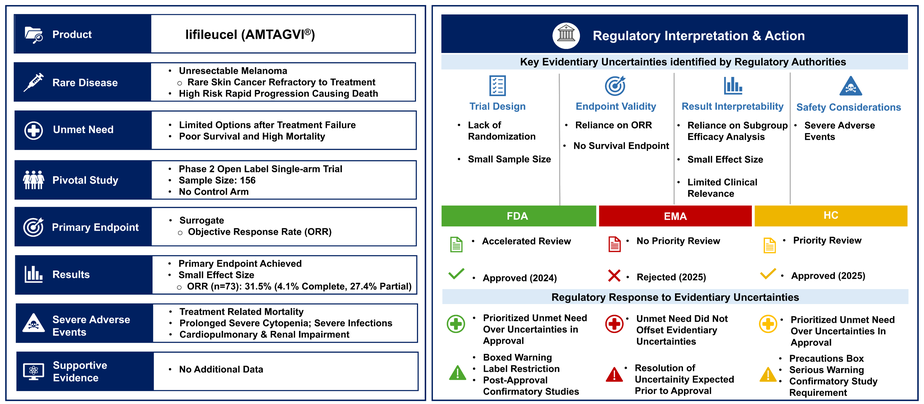
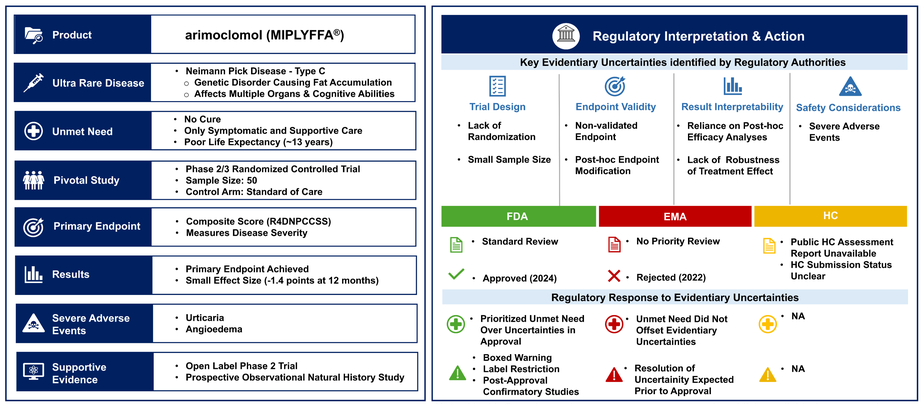


Figure 4: Comparative Regulatory Assessment - arimoclomol



Note: Health Canada regulatory assessments were only publicly available for approved therapies, as review reports are not routinely published for rejected submissions

Review | Approved | Not Approved | Unmet Need | Management of Uncertainties

RESULTS

- Across the three case studies, **FDA, EMA, and HC** identified **similar evidentiary uncertainties related to trial design, endpoint validity, results interpretability, and safety considerations as following:**
  - **Lack of randomization,**
  - **Heterogenous external comparators,**
  - **Limited sample sizes,**
  - **Reliance on surrogate endpoints,**
  - **Post-hoc analyses,**
  - **Uncertainty regarding the robustness of treatment effect,**
  - **Clinical interpretability of treatment effect,**
  - **Severe adverse events**
- **FDA** managed **evidence uncertainty** by **incorporated labeling restrictions**, **boxed warning, post-marketing requirements**, and **confirmatory study obligations**
- **EMA required** major **evidence gaps to be resolved prior to authorization** rather than through post-approval commitments
- **HC managed remaining evidence in the following ways:**
  - **HC** incorporated **labeling restrictions, boxed warnings, risk management measures, and confirmatory study requirements** for **palovarotene**
  - **HC** applied **conditional approval**, **serious warnings and precautions, and confirmatory study requirements to manage evidence gaps** for **lifileucel**

LIMITATIONS

- Case selection started with FDA-approved therapies, which may underrepresent orphan drugs reviewed first through non-US regulatory pathways
- Publicly available regulatory reports may not fully reflect internal regulatory deliberations and/or all factors influencing final agency decisions

CONCLUSIONS

- **FDA, EMA, and HC** often identified **similar evidentiary uncertainties** yet **reached different regulatory decisions** for the same **orphan therapies**
- Regulatory divergence **reflected differences** in agency willingness **to accept uncertainty at the time of approval** and reliance on post-approval evidence generation
- These findings highlight the importance of **proactively aligning clinical trial design, endpoint selection, and evidence generation strategies** with the **expectations of individual regulatory agencies** during orphan drug development

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