A Comparative Analysis of Regulatory Divergence in Expedited Oncology Approvals : Evidence, Pathways, and Timelines Across FDA, EMA, TGA, and PMDA

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BACKGROUND

- **Expedited approval pathways** allow earlier access to oncology therapies for life-threatening diseases, based on limited clinical evidence and surrogate endpoints.
- The **FDA**, since the introduction of the **AA** program in 1992, has been the earliest and most frequent user of expedited pathways. Comparable frameworks exist at the **EMA (CMA), TGA (Provisional), and PMDA (CEA).**
- Inherent uncertainties in clinical trials can lead to **divergent regulatory approaches**, creating cross-national gaps in approval timing and raising concerns for equitable patient access.

OBJECTIVE

- To evaluate how the **EMA, TGA,** and **PMDA** differed from the ***FDA-first expedited oncology approvals** (2019–2023), focusing on the concordance in **approval pathways, use of pivotal trial evidence, and procedural timelines**.

  * The earliest global authorization, where the FDA granted AA for a novel oncology drug before any other regulatory agency.

METHODS

Study design

- This study included oncology drug–indication pairs with FDA-first expedited approval (2019–2023). Subsequent regulatory actions by EMA, TGA, and PMDA were tracked through March 2025, and **pairwise comparisons were conducted between FDA and each agency for dual approvals**.

Data Sources

- FDA-first expedited approvals
  - from FDA's annual Novel Drug Approvals reports and publicly accessible drug approval databases
- Subsequent approvals by EMA, TGA, and PMDA
  - from official regulatory assessment reports and publicly accessible drug approval databases.

Data Extraction

Procedural metrics

- **Submission date:** Calendar day on which the marketing authorization application was filed with each agency
- **Approval date:** Calendar day of the official regulatory decision
- **Approval pathway:** expedited vs standard

Clinical evidence

- **Pivotal trial(s):** Clinical study forming the approval basis, identified by the corresponding ClinicalTrials.gov NCT number.

Analytical variables within the pivotal trial(s) identified and as interpreted in regulatory assessment reports

- **Target population:** Patient cohort forming the approved indication
- **Primary endpoint:** Efficacy endpoint used for regulatory judgment
- **Data cut-off date:** Latest data freeze date used in the analysis

Outcome Measures & Statistical Analysis

Overview

- Landscape of FDA-first expedited approvals (2019–2023) and subsequent EMA, TGA, and PMDA approvals, with comparative assessment of whether subsequent agencies relied on the same pivotal trial(s) as the FDA.

Concordance

- Among subsequent approvals based on the same pivotal trial(s) as the FDA, we compared three analytical variables** as defined in the pivotal trial(s) and interpreted in each agency's regulatory assessment report.

  **Each component (target population, primary endpoint, DCO) was evaluated against the FDA decision and classified as concordant or divergent.

Procedural timing

- EMA, TGA, and PMDA review time were compared against FDA using the Wilcoxon rank-sum test stratified by expedited vs. standard approvals.
  - Review time: days between submission and approval within each agency
- Associations between submission and approval intervals were assessed using Spearman's rank correlation coefficients (ρ), stratified by expedited vs. standard approvals.
  - Submission interval: days between FDA submission and submission to EMA, TGA, or PMDA
  - Approval interval: days between FDA approval and subsequent agency approval.

CONCLUSIONS

- Regulatory agencies differed in their use of expedited versus standard pathways for the same oncology drugs, leading to variations in approval timing and disparities in treatment opportunities.
- Even when reviewing the same evidence, agencies applied different analytical considerations on target population and data maturity
- Greater international collaboration and alignment in evidentiary standards are needed to reduce these disparities and strengthen the reliability of expedited approval frameworks.

RESULTS

Overview of FDA-first expedited approvals and subsequent EMA, TGA, PMDA approvals

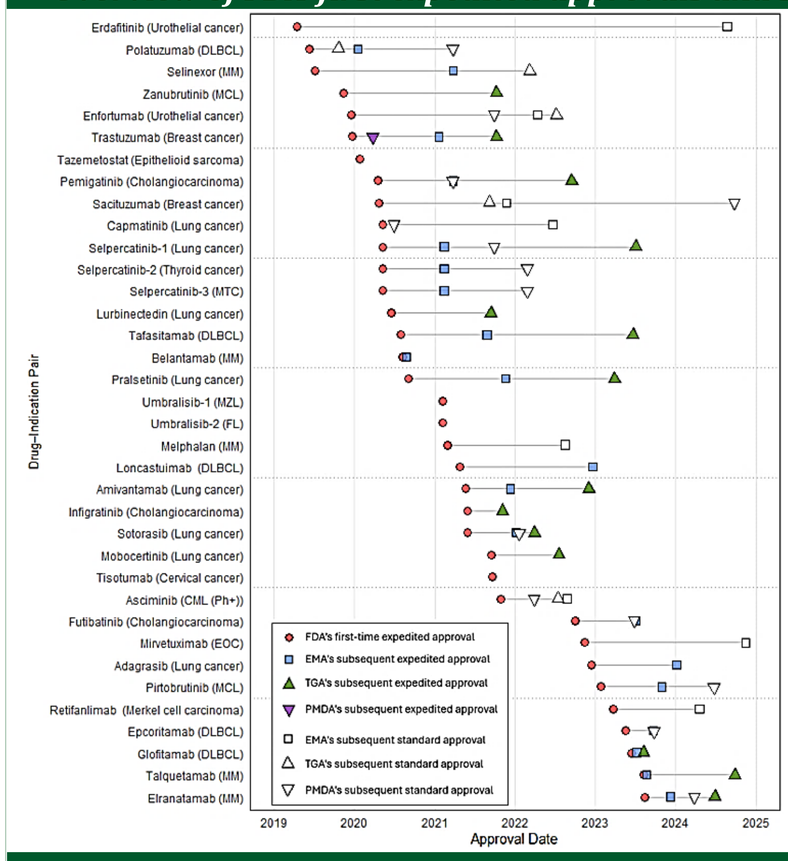


Figure 1. FDA-first expedited oncology approvals and subsequent regulatory decisions by EMA, TGA, and PMDA (2019–2023)

- Between 2019 and 2023, the FDA was the earliest to grant expedited approval for 36 oncology drug–indication pairs.
- **Figure 1** illustrates the chronological sequence of subsequent regulatory approvals by the EMA (n=28), TGA (n=20), and PMDA (n=15).

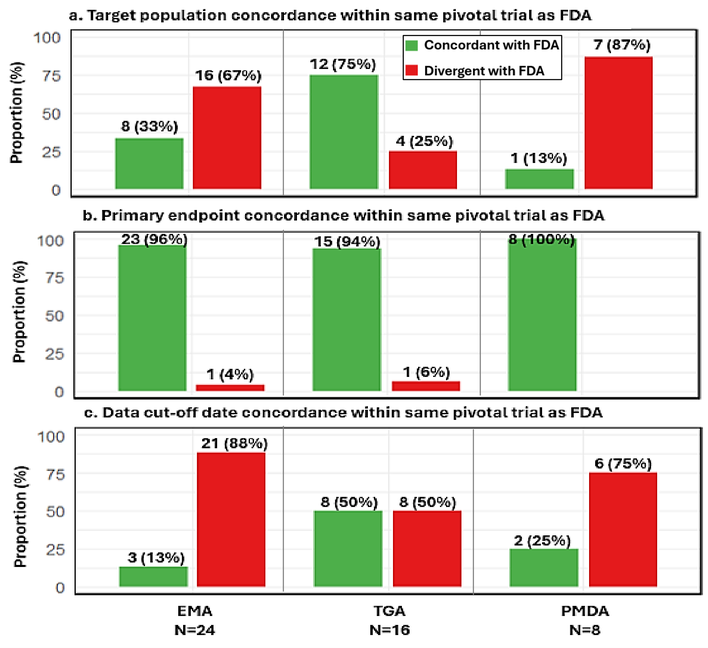
Table 1. Classification of subsequent approvals by approval pathway and pivotal trial concordance relative to the FDA-first expedited approvals.

Classification	EMA	TGA	PMDA
Subsequent expedited approval	20 (72)	13 (72)	1 (8)
Based on **same** pivotal trial(s) as the FDA	20 (72)	13 (72)	1 (8)
Based on **different** pivotal trial(s) as the FDA	0 (0)	0 (0)	0 (0)
Subsequent standard approval	8 (28)	5 (28)	11 (91)
Based on **same** pivotal trial(s) as the FDA	4 (14)	3 (17)	7 (58)
Based on **different** pivotal trial(s) as the FDA	4 (14)	2 (11)	4 (33)
Total	28 (100)	18 (100)	12 (100)

NOTE: Values are presented as n(%), percentages indicate the proportion of each agency's total subsequent approvals of FDA-led cases. Sums may not total to 100% because of rounding; Three PMDA cases and two TGA cases were excluded from the classification due to the lack of publicly available regulatory review documents, which prevented the assessment of pivotal trial and analytical concordance.

- 72% of EMA (20/28) and TGA (13/18) decisions were expedited and all relied on the same pivotal trial(s) as the FDA **(Table 1).**
- By contrast, PMDA granted 92% of approvals through standard pathways—58% used the same pivotal trial(s) as the FDA and 33% relied on different trial(s)—with only 8% granted through expedited approval **(Table 1).**

Analytical concordance on the same pivotal-trial basis, compared with the FDA



- For subsequent approvals based on the same pivotal trial(s) as the FDA, EMA had 24 cases, TGA had 16 cases, and PMDA had 8 cases **(Table 1).**

a. Target population **(Figure 2)**
   - PMDA: Divergence in 87% (7/8) of cases, due to requirements to include Japanese population analyses.
   - EMA: Divergence in 67% (16/24), often by approving broader target population criteria than the FDA.
   - TGA: Divergence in 25% (4/16), showing greater consistency with the FDA.

b. Primary endpoints were highly consistent across agencies, with >94% concordance for all three agencies relative to the FDA **(Figure 2)**.

c. Data cut-off date **(Figure 2)**
   - EMA: Divergence in 88% (21/24) of cases, with a median extension of 193 days (IQR 105–459).
   - PMDA: Divergence in 75% (6/8), with a median extension of 53 days (IQR –23–105).
   - TGA: Divergence in 50% (8/16), with a median extension of 87 days (IQR 0–500).

Figure 2. Comparison of key clinical characteristics across agencies for subsequent approvals based on the same pivotal trial as the FDA-first expedited approval

Procedural timing differences in subsequent approvals after FDA-first expedited approvals

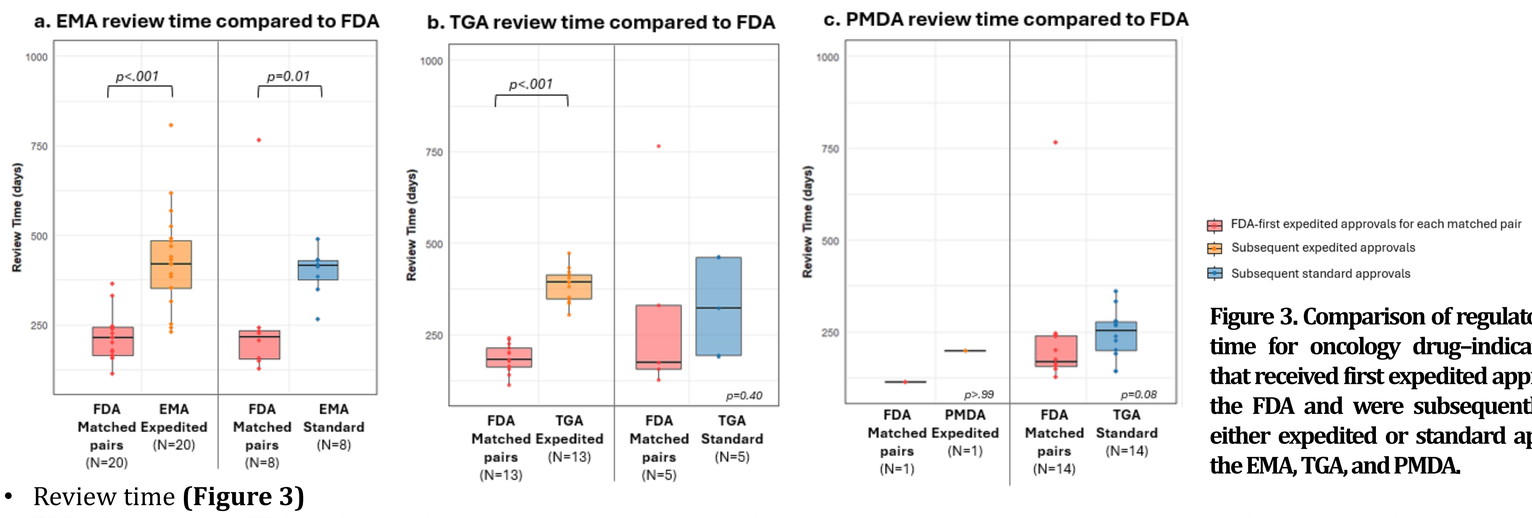


Figure 3. Comparison of regulatory review time for oncology drug–indication pairs that received first expedited approval from the FDA and were subsequently granted either expedited or standard approval by the EMA, TGA, and PMDA.

- Review time **(Figure 3)**
  - EMA: Longer than FDA for both subsequent expedited approvals(419 vs 214 days, p<0.001) and subsequent standard approvals(414 vs 216 days, p=0.014).
  - TGA: Longer than FDA for subsequent expedited approvals(394 vs 182 days, p<0.001) and for subsequent standard approvals(not statistically significant).
  - PMDA: Longer than FDA for subsequent standard approvals (not statistically significant)

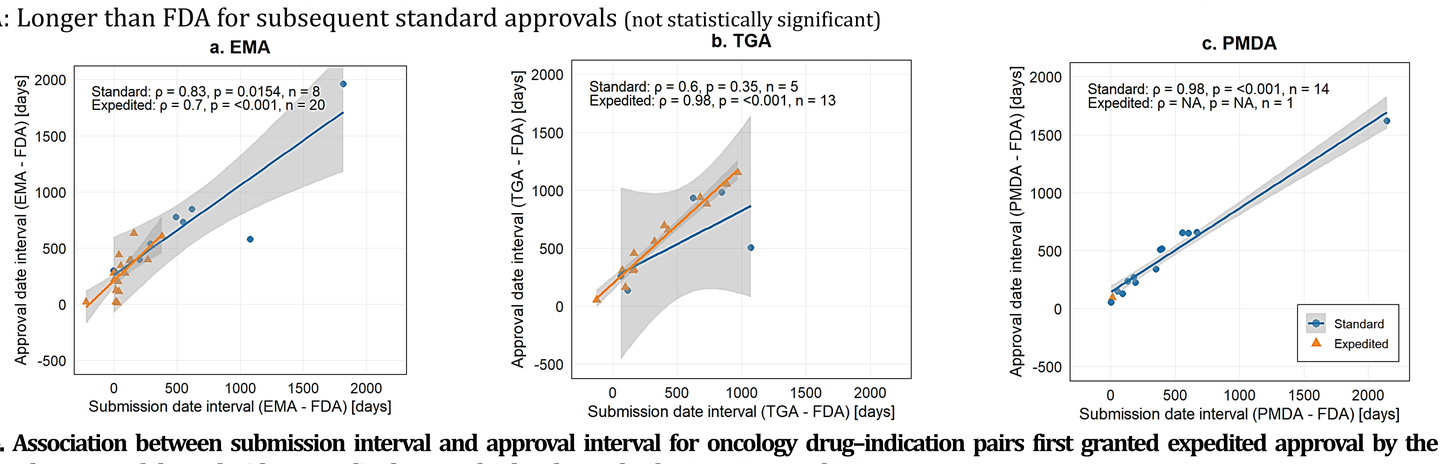


Figure 4. Association between submission interval and approval interval for oncology drug–indication pairs first granted expedited approval by the FDA, and subsequently approved through either expedited or standard pathways by the EMA, TGA, and PMDA.

NOTE: ρ(rho) correlation interpretation: 0.90-1.00: very strong; 0.70-0.89: strong; 0.40-0.69: moderate; 0.10-0.39: weak; 0.00-0.10: negligible

- Submission and approval delays **(Figure 4)**
  - EMA: Subsequently expedited cases were submitted soon after FDA(IQR 0–35 days), while standard cases showed long delays(IQR 248–713 days) both strong correlations with approval delays(ρ=0.70, ρ=0.83).
  - TGA: Longer submission intervals for subsequently expedited cases(IQR 135–540 days) and very strong correlations with approval delays(ρ=0.98).
  - PMDA: Most subsequent standard approvals had submission delays(IQR 135–615 days) and very strong correlations with approval delays(ρ=0.98).

Abbreviation FDA, Food and Drug Administration; EMA, European Medicines Agency; TGA, Therapeutic Goods Administration (Australia); PMDA, Pharmaceuticals and Medical Devices Agency (Japan); CMA, Conditional Marketing Authorisation; Provisional, Provisional Approval Pathway; CEA, Conditional Early Approval; DCO, Data Cut-off date; IQR, Interquartile Range

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