Racing to Market: What Happens After FDA Expedited Approval in Orphan Drugs?

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Background

- FDA expedited review pathways allow approval of therapies for serious or life-threatening rare diseases based on limited pre-approval evidence, with postmarketing requirements to verify clinical benefit.[1,2]
- The goal of this study was to understand the frequency and status of postmarketing requirements in orphan drugs.

Methodology

- We searched FDA databases to identify orphan drug indications approved via an expedited pathway (Priority Review, Fast Track, Breakthrough Therapy, or Accelerated Approval) between January 1, 2015, and December 31, 2024.[1-5]
- We then assessed postmarketing evidence by reviewing FDA indication approval letters and the Postmarketing Requirements and Commitments database to capture the presence, type, and status of postmarketing requirements, including confirmatory trials, along with approval characteristics (drug type, therapeutic area, and pathway used).
- Descriptive analyses were conducted.

Results

- A total of 180 orphan indications were approved via an expedited pathway during the study period (16.7%, 30/180 were approved via 1 pathway and 83.3%, 150/180 were approved via >1 pathway). (Fig. 1)
- Of all expedited indications, 80.4% (144/180) had postmarketing requirements, with 54.9% (79/144) requiring a confirmatory trial and 45.1% (65/144) requiring a non-confirmatory trial. (Fig. 2)
- Among indications requiring a confirmatory trial, 34.2% (27/79) verified clinical benefit, 50.6% (40/79) had trials ongoing or pending, 7.6% (6/79) had a negative trial (benefit not confirmed), and 7.6% (6/79) withdrew or did not conduct the trial. (Fig. 2)
- Among indications approved via 1 pathway that had postmarketing requirements (70.0%; 21/30), the most common pathway was Priority Review (52.4%; 11/21), followed by Accelerated Approval (23.8%; 5/21), Breakthrough Therapy (19.0%; 4/21), and Fast Track (4.8%; 1/21). (Fig. 3)
- Among indications approved via more than 1 pathway that had postmarketing requirements (123/150), the most common pathway was Priority Review (98.4%; 121/123), Breakthrough Therapy (61.8%; 76/123), Accelerated Approval (60.2%; 74/123), and Fast Track (54.5%; 67/123).

Conclusions

- The vast majority of orphan indications approved through FDA expedited pathways carry postmarketing requirements, yet few confirmatory trials have been completed and verified clinical benefit to date.
- Future research should explore the timing of postmarketing study completion to ensure clinical value for patients with rare diseases.

References

1. U.S. Food and Drug Administration. Fast track, breakthrough therapy, accelerated approval, priority review. Updated June 12, 2023. Accessed April 28, 2026. https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review
2. U.S. Food and Drug Administration. Priority NDA and BLA approvals. Updated March 2, 2026. Accessed April 28, 2026. https://www.fda.gov/drugs/nda-and-bla-approvals/priority-nda-and-bla-approvals
3. U.S. Food and Drug Administration. Fast track approvals. Updated January 13, 2025. Accessed April 28, 2026. https://www.fda.gov/drugs/nda-and-bla-approvals/fast-track-approvals
4. U.S. Food and Drug Administration. Breakthrough therapy approvals. Updated February 27, 2026. Accessed April 28, 2026. https://www.fda.gov/drugs/nda-and-bla-approvals/breakthrough-therapy-approvals
5. U.S. Food and Drug Administration. Accelerated approvals. Updated August 29, 2025. Accessed April 28, 2026. https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approvals

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Most orphan drugs approved via FDA expedited pathways require postmarketing evidence, yet confirmatory trials are often incomplete and verify benefit in only one-third of cases.

Stakeholders can use postmarketing evidence tracking to improve accountability and ensure timely confirmation of clinical benefit for rare disease therapies.

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Figure 1:
Expedited Pathway Use in Orphan Indications (n=180)

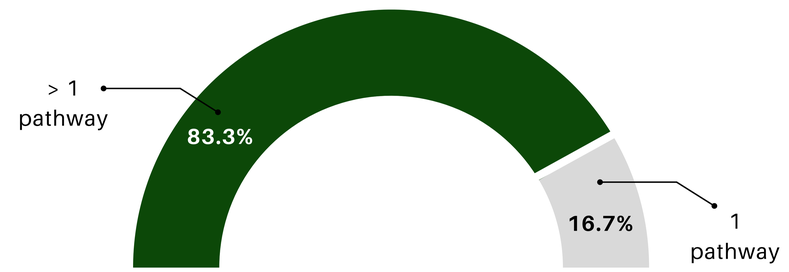

Figure 2:
Postmarketing Requirements for Expedited Orphan Indications

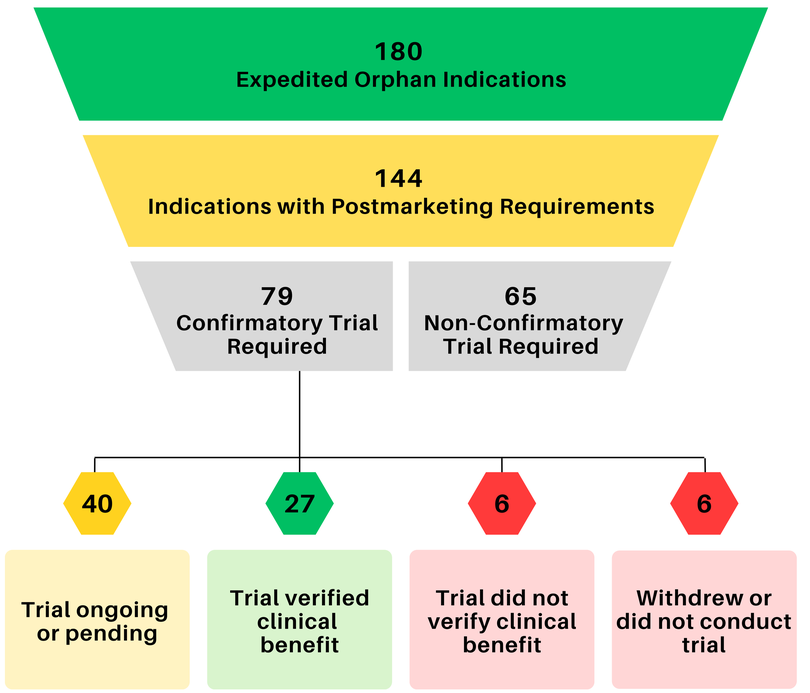

Figure 3:
Expedited Pathways Among Single Pathway Approvals (n=21)