HPR81

Breakthrough Therapy (BT) and Fast Track (FT) Designations in New Drug Applications and Biologic License Applications (NDAs/BLAs) to FDA's Center for Drug Evaluation and Research (CDER), 2013-2025

Sarah Ronnebaum, PhD | HEOR, Precision AQ
Bethesda, MD, USA
For further information, contact sarah.ronnebaum@precisionaq.com or visit us at https://www.precisionaq.com

INTRODUCTION

- The United States Food and Drug Administration (FDA) has several expedited programs to speed drug development and approval (**Table 1**).

Table 1: Summary of FDA expedited programs

	BT	FT	AA	Priority
Qualifying criteria	Treats serious condition **AND** preliminary clinical evidence indicates substantial improvement over available therapies	Treats serious condition **AND** preliminary non-clinical or clinical data suggests unmet medical needs are addressed, **OR** has been designated as a qualified infectious disease product	Treats serious condition, provides meaningful advantage over existing treatments, **AND** demonstrates effect on surrogate endpoint or intermediate clinical endpoint	Treats a serious condition **AND** would provide a significant improvement in safety or effectiveness **OR** has been designated as a qualified infectious disease product **OR** has been submitted with a priority review voucher
Submission request timing	With IND or after; ideally before end-of-phase II meeting	With IND or after; ideally before the pre-NDA/pre-BLA meeting	During development to support the use of a surrogate endpoint and plan confirmatory trials	With original NDA/BLA or efficacy supplement
Features	Guidance on drug development, organizational commitment, rolling review, and other actions to expedite review	Actions to expedite development and review; rolling review	Approval based on surrogate endpoint or intermediate clinical endpoint	Faster time to review NDA/BLA (6 vs 10 months)
Program initiated	2012	1997	1992	1992

Source: *FDA, 2014.*[1] ***Abbreviations:*** *AA, accelerated approval; BLA, biologic license application; BT, breakthrough therapy; FDA, United States Food and Drug Administration; FT, fast track; IND, investigational new drug; NDA, new drug application.*

- The objective of this study was to assess key factors associated with BT and FT designations, likelihood of priority review, and impact on the time required for FDA review of original NDAs/BLAs, and to compare trends for AA designations.

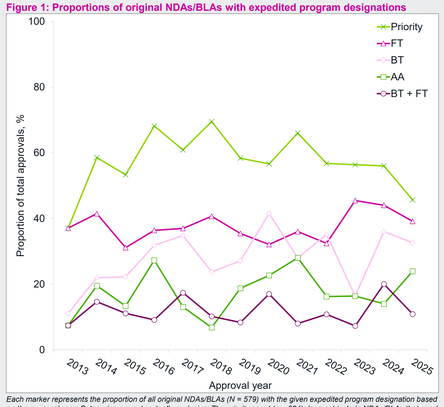
METHODS

- Trends in expedited program designations were examined among original NDAs/BLAs within CDER approved between 2013-2025 to capture the earliest year in which BT, FT, and AA were all available.[2] NDAs/BLAs with multiple indications were considered to have an expedited program designation if any indication had that designation. Each approval's indication was categorized by therapy area using International Classification of Diseases, 11th Revision (ICD-11) codes.
- Details on whether each NDA/BLA was approved in the first cycle of review and was identified as first-in-class by CDER were extracted from 2013-2025 annual approval reports.[3]
- Relative risks (RR) with 95% confidence intervals (CI) were calculated for comparisons of interest. The likelihood of receipt of priority review designation excluded NDAs/BLAs using priority review vouchers.

RESULTS

- Between 2013-2025, 579 NDAs/BLAs were approved by CDER. Among these, 28% (annual range, 11% to 42%) received BT, 38% (31% to 45%) received FT, and 12% (7% to 20%) received both designations. Priority review and accelerated approval were applied to 58% and 17% of all applications, respectively (**Figure 1**).

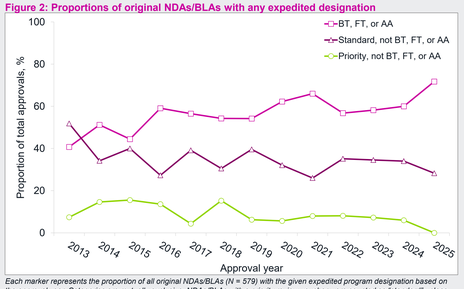
Figure 1: Proportions of original NDAs/BLAs with expedited program designations



Each marker represents the proportion of all original NDAs/BLAs (N = 579) with the given expedited program designation based on the approval year. Categories are not mutually exclusive. The priority count (n = 334) does not include NDAs/BLAs that used priority review vouchers (n = 19). ***Abbreviations:*** *AA, accelerated approval; BT, breakthrough therapy; FT, fast track.*

- The proportion of NDAs/BLAs with BT, FT, and/or AA increased from 41% in 2013 to 72% in 2025. Only 8% of all applications without BT, FT, or AA received priority review without the use of a voucher (**Figure 2**).

Figure 2: Proportions of original NDAs/BLAs with any expedited designation



Each marker represents the proportion of all original NDAs/BLAs (N = 579) with the given expedited program designation based on the approval year. Categories are mutually exclusive. NDAs/BLAs with a priority review voucher were counted as "standard" unless they also had BT, FT, or AA designation. ***Abbreviations:*** *AA, accelerated approval; BT, breakthrough therapy; FT, fast track.*

- NDAs/BLAs with orphan drug designation (48% of all NDAs/BLAs) were significantly more likely to receive BT, FT, or AA designation. NDAs/BLAs that were determined to be first-in-class drugs by CDER (41% of all NDAs/BLAs) were significantly more likely to also have BT or FT designation (**Table 2**).
- Applications indicated for neoplasms were significantly more likely to receive BT, FT, and AA designation. Applications indicated for infectious and parasitic diseases were also significantly more likely to receive FT designation. In contrast, indications with lower likelihood of expedited designations included nervous system (BT), skin (FT), and endocrine, nutritional, and metabolic diseases and infectious and parasitic diseases (AA; **Table 2**).

Table 2: Likelihood of expedited program designation by orphan status, first-in-class status, and therapy area

RR (95% CI)	BT	FT	AA
Orphan indication, n = 283	3.01 (2.21-4.11)	1.68 (1.35-2.09)	3.93 (2.5-6.19)
First-in-class, n = 236	2.14 (1.64-2.78)	1.41 (1.15-1.74)	1.19 (0.83-1.70)
By therapy area:			
Neoplasms, n = 160	2.52 (1.97-3.23)	1.28 (1.03-1.59)	9.28 (6.00-14.37)
Endocrine, nutritional and metabolic diseases, n = 71	1.30 (0.92-1.83)	1.05 (0.77-1.43)	0.15 (0.04-0.58)
Certain infectious and parasitic diseases, n = 61	0.86 (0.54-1.36)	1.96 (1.58-2.42)	0.17 (0.04-0.69)
Nervous system, n = 52	0.52 (0.27-1.00)	1.02 (0.71-1.46)	0.76 (0.37-1.56)
Skin, n = 35	0.59 (0.28-1.25)	0.36 (0.16-0.82)	NE
Circulatory system, n = 27	0.65 (0.29-1.44)	0.78 (0.43-1.40)	0.21 (0.03-1.43)
Blood or blood-forming organs, n = 26	1.24 (0.72-2.14)	0.81 (0.45-1.45)	0.21 (0.03-1.48)

Values represent the RR (95% CI) of receiving the indicated expedited program designation. The review of associations by therapy area was limited to indications with >25 NDAs/BLAs. Green font indicates a significantly higher likelihood of association, and purple indicates a significantly lower likelihood of association. ***Abbreviations:*** *AA, accelerated approval; BT, breakthrough therapy; CI, confidence interval; FT, fast track; NE, not estimable; RR, relative risk.*

- Applications with BT, FT, BT + FT, or AA were more likely to receive priority review designation than applications without these designations (**Table 3**).
- Furthermore, applications with BT or AA designations had a small but significantly higher likelihood of approval in their first review cycle compared to applications without these designations (**Table 3**).

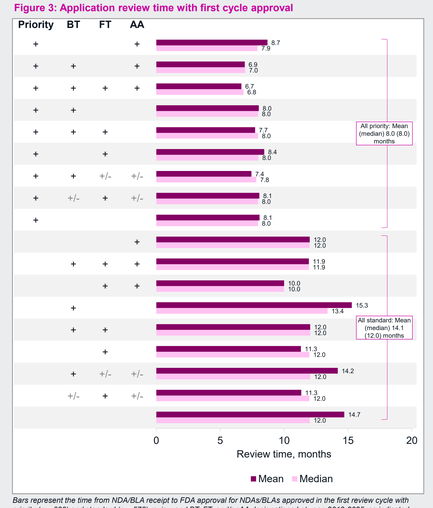
Table 3: Likelihood of priority review and of first cycle approval by expedited program designation

RR (95% CI)	Priority review	First cycle approval
BT vs not BT	2.08 (1.86-2.34)	1.12 (1.06-1.19)
FT vs not FT	1.99 (1.74-2.28)	1.06 (0.99-1.13)
BT + FT vs neither designation	3.80 (3.04-4.74)	1.13 (1.02-1.25)
AA vs not AA	1.92 (1.74-2.11)	1.13 (1.07-1.20)

Values represent the RR (95% CI) of receiving priority review (excluding NDAs/BLAs using priority review vouchers) or of being approved in the first review cycle. Green font indicates a significantly higher likelihood of association. ***Abbreviations:*** *AA, accelerated approval; BT, breakthrough therapy; CI, confidence interval; FT, fast track; RR, relative risk.*

- Among all 579 approvals, 497 (86%) were approved in the first review cycle. Within first-cycle approvals, applications with priority review received FDA approval in mean (median) 8.0 (8.0) months, while standard review approval required 14.1 (12.0) months. The fastest approval pathway was associated with BT, FT, and AA combined (**Figure 3**).
- Applications that were not approved in the first review cycle required a mean (median) 35.3 (26.7) months for approval.

Figure 3: Application review time with first cycle approval



Bars represent the time from NDA/BLA receipt to FDA approval for NDAs/BLAs approved in the first review cycle with priority (n = 630) and standard (n = 578) review and BT, FT, and/or AA designations between 2013-2025, as indicated. ***Abbreviations:*** *+/-, with or without designation; AA, accelerated approval; BT, breakthrough therapy; FT, fast track.*

CONCLUSIONS

- BT and FT are more likely to be granted to NDAs/BLAs for orphan indications, first-in-class therapies, and therapies targeting neoplasms; FT is also more likely for indications related to infectious and parasitic disease, per its original intent. An NDA/BLA with BT, FT, or both is more likely to be granted priority review, and an NDA/BLA with BT alone or in combination with FT is more likely to be approved in the first cycle of review. BT or FT designations did not substantially affect NDA/BLA review time compared to priority-only designation. However, these designations may indirectly reduce overall review time by increasing the likelihood of priority review, which provides a meaningful reduction in application review time versus standard review.
- Overall, expedited programs have been shown to substantially reduce the time required for clinical development.[4,5] However, issues specific to a given therapeutic area, such as patient recruitment challenges in rare diseases and indications with lengthy time-to-event outcomes, must be considered in comparing trends across NDAs/BLAs and examining outcomes associated with expedited program designations.

References
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