Expedited approval programs and potential impact on drug postmarketing safety-related actions: A review of the literature

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Abstract (revised)

Background: The Center for Drug Evaluation and Research (CDER) within the U.S. Food and Drug Administration (FDA) utilizes several drug approval pathways, some of which fall under the broad category of expedited approval (EA) programs, which is further subcategorized as fast track, priority review, accelerated approval, and breakthrough therapy. While EA programs exist to advance public health by expanding the pool of available efficacious drug therapies, in recent years, a body of literature has emerged to assess their potential impact on postmarketing safety-related actions, including new therapeutic biologics (NTBs) and new molecular entities (NMEs).
Purpose: The purpose of this literature review was to determine whether CDER products approved under EA programs impact postmarketing safety-related actions with respect to significance of labeling (e.g., Boxed Warning versus a Warning), frequency, or time-to-event.
Methodology: We searched Embase and PubMed using key terms for each EA program in combination with terms like 'postmarketing surveillance' and 'drug safety'. Articles were included if they met two criteria: (1) measured at least one of three safety-related actions of interest (updates to safety-related sections of the drug label, withdrawal from the market due to safety concerns, or FDA issuance of safety communications); and (2) quantitatively compared EA with non-EA with respect to significance of labeling, frequency, or time-to-event.
Results: The search retrieved 156 articles, of which five were retained for review. The articles included drugs approved from January 1997 to December 2016. All five articles found a difference in postmarketing safety-related actions that suggest EA programs are associated with increased frequency of (n=4), shorter time to (n=2), or increased significance of (n=2) a labeling change.
Conclusion: Current data suggest an association between EA programs and increased postmarketing safety-related actions; however, because the data are observational and subject to bias, they remain inadequate to prove a causal link. The data suggest that pharmacovigilance groups who conduct surveillance under a risk-based model should consider prioritizing new drugs, including NTBs and NMEs, that are approved under expedited conditions for safety surveillance.

Introduction

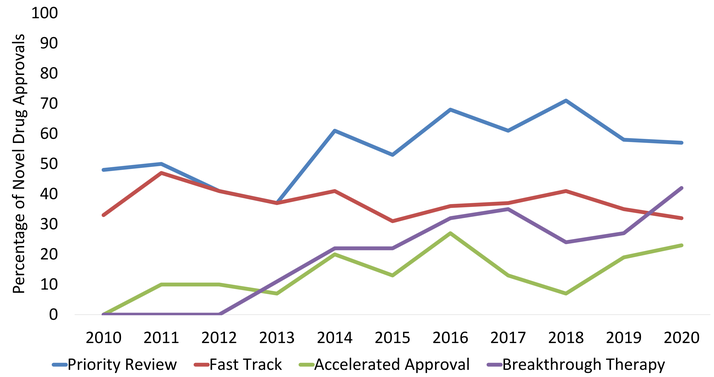
CDER performs an essential public health task by ensuring that safe and effective drugs are available to improve the health of people by thoroughly reviewing data it receives, such as randomized controlled trials that assess validated clinical outcomes.[1,2] Under standard review, FDA has a 10-month window to make its approval decision, which is sometimes scrutinized for delaying access to drugs for serious or life-threatening conditions.[2] In response, four programs (one pathway and three designations) that fall under the broad category of expedited approval (EA) were created to quicken the approval of promising new therapies. These include:

- **Fast Track (FT) designation:**[3] for drugs that treat a serious condition and fill an unmet medical need
- **Priority Review (PR) designation:**[4] for drugs that treat a serious condition and would provide a significant improvement in safety or effectiveness
- **Accelerated Approval (AA) pathway:**[5] for drugs that treat a serious condition, provide a meaningful advantage over available therapies, and demonstrate an effect on a surrogate/intermediate clinical endpoint
- **Breakthrough Therapy (BT) designation:**[6] for drugs that treat a serious condition and have preliminary clinical evidence of substantial improvement over available therapy on clinically significant endpoint(s)

Figure 1 shows trends in the percentage of novel drug approvals under each EA program from 2010 to 2020.

Introduction (cont.)

Figure 1. Percentage of Novel Drug Approvals Under EA Programs from 2010 to 2020[7,*]



*Drugs may be approved under more than one EA program

Methods

- Five searches of Embase and PubMed were conducted using the search terms in Table 1. Each EA program was searched in combination with terms like 'postmarketing surveillance' and 'drug safety'. Articles were included if they met two criteria:
  1. Measured at least one of three safety-related actions of interest: (A) updates to safety-related sections of the drug label, (B) withdrawal from the market due to safety concerns, or (C) FDA issuance of safety communications
  2. Quantitatively compared EA with non-EA with respect to significance of labeling, frequency, or time-to-event
- Safety-related actions were classified using the following terms:
  - Significance of labeling: comparisons made between rates of safety-related actions stratified by category (e.g., Boxed Warning [BW], Contraindications, Warnings and Precautions [WP], etc.)
  - Frequency: comparisons made between rates of safety-related actions (not stratified)
  - Time-to-event: comparisons made between time-to-event of overall or stratified safety-related actions
- Favorable safety-related actions were defined as follows:
  - For significance of labeling and frequency, a lower rate of events in the category or overall
  - For time-to-event, a longer time-to-event

Results and Discussion

Table 1. Literature Search Results

Search Terms	Embase (n)	PubMed (n)	Total (n)
'fast track designation'	4	3	7
'breakthrough therapy designation'	2	1	3
'accelerated approval'	40	29	69
'priority review pathway'	25	3	28
'expedited approval'	28	21	49
Grand Total	**99**	**57**	**156**

Results and Discussion (cont.)

Key Findings:

- The time period for the articles included drugs that were approved between the dates of January 1997 to December 2016. The time frames surveyed in all articles overlapped.
- All five articles reported a difference in postmarketing safety-related actions that suggest EA programs are associated with increased frequency of (n=4), shorter time to (n=2), or increased significance of (n=2) a labeling change.
- One article found differences in postmarketing safety-related actions that favored EA for NTBs.
- Safety-related actions were heterogenous among the articles. The most frequent actions used to compare EA with non-EA were composites of different safety-related labeling changes and market withdrawals.
- Only one article included FDA issuance of safety communications as a safety-related action.

Figure 2. Characteristics of Articles Retained for Review

Comparisons between EA and non-EA from each of the five articles are summarized. Each category of safety-related action (significance of labeling, frequency, or time-to-event) is coded with a letter indicating the specific action and by color to indicate whether a statistically significant result was obtained, and whether EA or non-EA was favored. Each article may have more than one action in a single category and each box may represent one or more actions. Significant safety-related actions are summarized below.

	Postmarketing Safety-Related Actions					
	Significance of Labeling		Frequency		Time-to-Event	
Downing 2017[8]			A, B, C			
Mostaghim 2017[9]	A		A			
Pinnow 2018[10,*]	A, B		A, B	A, B	A, B	
Kim 2020[11,†]	A	A, B				
Bulatao 2020[12,§]	A, B	A, B	A, B	A	A, B	A, B

Legend
A = update to safety-related section of label
B = withdrawal from market due to safety concerns
C = FDA issuance of safety communication

*NMEs only
†Oncologic drugs only
§NTBs only

- Favors non-EA programs
- Favors EA programs
- No significant differences
- Not measured

Summary of Significant Safety-Related Actions by Category

Significance of Labeling

- Compared with non-EA drugs, EA drugs had a 1.48 (95% CI, 1.07-2.06) higher rate of changes to BW and Contraindications[9]
- Seven of 23 (30.4%) drugs approved under AA added new WP compared to 1 of 32 (3.1%) drugs approved under regular approval (*P*=0.024)[11]
- NTBs approved under PR had fewer BW, WP, and market withdrawals than those that were not (OR 0.11; 95% CI, 0.01-0.92)[12]

Frequency

- Postmarket safety-related actions were more frequent among therapeutics receiving AA (incidence rate ratio 2.20; *P*=0.02) compared to non-accelerated[8]
- Drugs under EA were characterized by a rate of 0.94 safety label changes for each drug per year compared with 0.68 safety label changes per year for standard approval drugs (rate ratio 1.38; 95% CI, 1.25-1.52)[9]
- FT was significantly associated with an increased occurrence of postmarket safety-related actions (OR 3.21; 95% CI, 1.23-8.40)[10]

Frequency (cont.)

- NTBs approved under AA had more label updates (median 7.0 vs. 2.0; *P*=0.005) and issues added (median 33.0 vs. 7.0; *P*=0.002) compared with those that were not[12]
- NTBs approved under PR had fewer label updates (2.0 vs. 3.0; *P*<0.05) compared with those under standard approval[12]

Time-to-Event

- Time to first safety-related action was shorter for drugs under AA (*P*=0.03) and FT (*P*=0.02) compared with those under standard approval pathways[10]
- Both NTBs and NMEs under AA had a significantly shorter time to first safety-related regulatory action compared to those that were not[12]

Limitations

- All five articles were observational, retrospective cohort studies which are subject to bias.
- The heterogeneity between methods and safety-related actions across the articles prevented a combined quantitative analysis.
- The majority of NMEs and NTBs included in the articles were approved under PR, limiting the generalizability of the results to the entire category of EA.
- Additionally, two articles analyzed all four EA programs and one article only looked at AA.

Conclusion

EA programs are increasingly used to approve therapeutic products. Current published data suggest an association between EA programs and increased postmarketing safety-related actions; however, because the data are observational and subject to bias, they remain inadequate to prove a causal link. The data suggest that pharmacovigilance groups who conduct surveillance under a risk-based model should consider prioritizing new drugs and therapeutic biologics that are approved under expedited conditions for safety surveillance.

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