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Clinical Benefits of Accelerated Approval

Summary: This study found that the FDA's Accelerated Approval Program is critical for early access to valuable therapies for serious or life-threatening diseases, thereby improving clinical outcomes.

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Background

The Accelerated Approval Program (AAP) was formally established by the U.S. Food and Drug Administration (FDA) regulations in 1992 during the HIV epidemic and later codified in statute in 1997. The program allows for earlier approval of drugs that treat serious conditions while preserving FDA's high standards for safety and effectiveness. By allowing approval based upon a surrogate endpoint—a marker such as a laboratory measurement, radiographic image, physical sign or other measure instead of a direct measure of clinical benefit, or certain intermediate endpoints—the AAP has led to more than 250 new therapies being made available to patients earlier than they otherwise would have been under traditional approval processes. Accelerated approval (AA) allows patient access roughly 3.2 years earlier than traditional approval. The AAP is widely considered a success and only a handful of therapies to date have been failed to confirm their clinical benefit and removed from the market as a result.[1–3]

In this study, we looked at real world utilization of five drugs (Table 1) that were granted AA, and projected the total clinical benefits for those who had access sooner due to the AAP.

Table 1: Drugs included in analysis[4]

Drug	Condition	AA Date	Conversion to Traditional Approval Date
Alecensa (alectinib)	NSCLC	12/11/2015	11/6/2017
Alimta (pemetrexed for injection)	NSCLC	8/19/2004	7/2/2009
DepoCyt (cytarabine)	Lymphomatous meningitis	4/1/1999	4/19/2007
Norvir (ritonavir)	HIV	3/1/1996	5/26/1999
Remicade (infliximab)	Crohn's Disease	8/24/1998	4/1/2003

Findings

We found that AA has resulted in thousands or even millions of patients gaining earlier access to each of the five drugs sampled for this analysis (Table 2).

- Alecensa and Alimta were awarded AA for treatment of patients with non-small cell lung cancer (NSCLC) that had progressed or did not respond to prior therapy. Earlier access to these two medicines due to AA resulted in nearly 200,000 additional years lived for these patients compared with their expected survival had the drugs not been available.

- DepoCyt, also a cancer treatment, was granted AA for the treatment of lymphomatous meningitis, a condition in which cancer has spread to the lining around the brain, with poor prognosis and limited treatment options. Earlier access to DepoCyt resulted in a total of more than 1,800 additional years of life for patients with this hard-to-treat cancer.

- In the case of Norvir to treat HIV, more patients lived longer and with improved quality of life—defined as the number of patients that lived for six months or more without an occurrence of AIDS-defining illness or death—than would have if Norvir had not been granted AA. More than 100,000 additional HIV patients survived six months or more without complications due to the AA of Norvir.

- AA of Remicade meant that patients with Crohn's Disease collectively experienced nearly 4 million additional years with reduced or no symptoms from their condition, a chronic illness associated with severe and sometimes life-threatening complications. The earlier access to Remicade improved patients' quality of life while reducing the need for additional healthcare resource utilization.

While these findings highlight the value to patients of the earlier access to medicines that AA provides, it is important to note that the existence of the AAP can also significantly affect a company's expected return on investment for a pipeline drug candidate—particularly for conditions where the clinical endpoints can take many years to manifest—which these findings do not address. In some cases, the possibility of an AA can affect whether or not a company makes the investment to develop a new drug at all.

Table 2: Patient Impact of Accelerated Approval

Drug	Condition	Years of Earlier Access due to AA	No. of Patients Receiving Earlier Access*	Measure of Benefit	Cumulative Benefits to Patients Receiving Earlier Access**
Alecensa	Lung Cancer	1.9	29,227	Life years gained	58,941
Alimta	Lung Cancer	4.9	558,290	Life years gained	130,268
DepoCyt	Brain Cancer	8.1	24,120	Life years gained	1,809
Norvir	HIV	3.2	684,372	Patients living without AIDS-associated complication	106,762
Remicade	Crohn's Disease	4.6	7,796,808	Years of symptom control	3,941,719

*'Patients Receiving Earlier Access' refers to the number of patients receiving each medicine earlier than they would have if AA had not been granted. For those medicines that extend life, this includes some patients who would not have received the medicine without AA because they would have died before the standard approval date.

**Cumulative benefits reflect the added benefits when comparing the drug of interest with the best alternative treatment at the time of launch.

Methods

For this analysis, we sampled 5 drugs, chosen for the ability to identify clinical trial-relevant outcomes in utilization data, from among the over 250 drugs that have received AA. The selected drugs represent a variety of conditions and span the three decades since the AAP was introduced.

To estimate the number of patients who gained access to each drug early due to the AAP, we relied on real world utilization using claims data for each medicine from IQVIA for the period beginning on the date of AA and ending on the date of conversion to traditional approval.[5] The number of individuals receiving each drug was estimated based on total prescription fills and the defined daily dose (i.e., the average maintenance dose per day for a drug used for its main indication) for each drug. We assumed all utilization between the date of AA and date of conversion to traditional approval could be attributed to AA. We then assumed that in the one-year period post-conversion, the difference between the utilization observed during that period and the utilization observed in the first 12 months following AA were attributable to the AA process causing a utilization ramp-up period to occur earlier.

To estimate the clinical benefits associated with utilization of each drug, we used estimates from the literature reflecting the added clinical benefits associated with use of the drug that gained AA compared with the standard of care at the time of launch.[6–10]

The population-level benefits of the AAP were calculated by multiplying the estimated number of patients receiving earlier access to the medicine by the per-patient clinical benefits.

Limitations

While we strived to use the best data available, results of this study should be considered in light of the limitations. We limited the expected ramp-up period for each drug to one year, such that it was assumed that after the first year post-conversion, utilization would have been the same with or without AA. To the extent that uptake is more gradual, our results would be an underestimate of the benefits associated with AA. The utilization data relied upon to estimate the number of patients gaining earlier access was based on total prescription fills regardless of indication. However, all drugs considered in this study were assessed after their first indication, so there is no reason to believe that off label use would have been occurring. Finally, we used the conversion date as a proxy for when the drug would have become available if the AAP did not exist. It is not possible to know the precise timing of approval if the AAP was not in place, or if the medicine would have been approved at all.

Conclusions

Continuation of this program will encourage development of beneficial novel therapies and drive further gains in life expectancy and improved clinical outcomes.

1. Center for Drug Evaluation and Research. Accelerated Approval Program. *FDA*. Published online October 26, 2020. Accessed November 11, 2021. https://www.fda.gov/drugs/information-health-care-professionals-drugs/accelerated-approval-program

2. Sharp M. CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint. Published online December 31, 2020:19.

3. Kaltenboeck A, Mehlman A, Pearson SD. Strengthening the Accelerated Approval Pathway: An Analysis of Potential Policy Reforms and Their Impact on Uncertainty, Access, Innovation, and Costs. Published online April 26, 2021:41.

4. U.S. Food and Drug Administration. Approval Date(s) and History, Letters, Labels, Reviews. Drugs@FDA: FDA-Approved Drugs. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

5. PhRMA. Analysis of IQVIA drug utilization data. Estimates as of 3/31/2022 [Data on File].

6. Wilkinson S, Gupta A, Scheuer N, et al. Assessment of Alectinib vs Ceritinib in *ALK* - Positive Non–Small Cell Lung Cancer in Phase 2 Trials and in Real-world Data. *JAMA Netw Open*. 2021;4(10):e2126306. doi:10.1001/jamanetworkopen.2021.26306

7. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *The Lancet*. 2009;374(9699):1432-1440. doi:10.1016/S0140-6736(09)61497-5

8. Glantz MJ, Jaeckle KA, Chamberlain MC, et al. A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. *Clin Cancer Res Off J Am Assoc Cancer Res*. 1999;5(11):3394-3402.

9. Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. *The Lancet*. 1998;351(9102):543-549. doi:10.1016/S0140-6736(97)04161-5

10. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab Maintenance Therapy for Fistulizing Crohn's Disease. *N Engl J Med*. 2004;350(9):876-885. doi:10.1056/NEJMoa030815