HealthAffairsBlog

Nearly One-Third Of New Drugs Are No Better Than Older Drugs, And Some Are Worse

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A Focus On Expediting Drug Development

Congress has instructed the Food and Drug Administration (FDA) to expedite the development and review of promising new drugs through the creation of four programs: accelerated approval, fast-track, breakthrough, and priority review. In a recent *Health Affairs* article, James D. Chambers and colleagues reported that drugs approved under one or more expedited programs were, on average, associated with larger health gains than those approved under conventional development and review programs. They concluded that the FDA has prioritized the review of drugs that offer the largest clinical advancements.

Chambers and his colleagues should be applauded for using as their metric net health benefit, which is the raison d'être of any pharmaceutical intervention. Although they focused on the FDA's expedited programs, their research also revealed important information about the benefits of new drugs that is highly patient-relevant, namely, that 20 percent of expedited drugs and 41 percent of non-expedited drugs offered zero or negative incremental health gains over older comparators.

Expedited Programs Benefit Higher-Value Drugs

Examining drugs approved between 1999 and 2012, the researchers found that drug-indication pairs (some drugs are approved for multiple indications, and each drug-indication pair may separately benefit from expedited development or review) in one expedited program averaged a benefit of 0.22 quality-adjusted life years (QALYs) vis-à-vis comparator treatments, versus a 0.06 QALY benefit for those drugs developed and approved without any program. Similarly, those in all

three programs (breakthrough was not included because it was instituted in 2012) averaged a 1.13 QALY benefit.

These findings provide reassurance that the government's expert pharmaceutical agency has, on average, correctly applied its various expedited programs to drugs that confer greater health benefits. The FDA has explained that the fast-track designation, which contemplates approval after phase 2 trials, was modeled after the approval of the HIV treatment zidovudine (AZT) and may therefore be appropriate in instances where phase 2 trials show "dramatic evidence of increased survival" early in a drug's development. The FDA's *Manual of Policies and Procedures* (section 6020.3) describes the priority review designation, under which the FDA aims to review completed applications in six months instead of 10 months, as "intended to direct [FDA] resources" to drugs that provide "significant improvements" in safety or effectiveness. Similarly, FDA regulations state that accelerated approval is for drugs that provide "meaningful therapeutic benefit over existing treatments." All three programs are intended to focus on drugs that address unmet medical needs.

Still, Chambers and his colleagues found average net QALY gains of only 0.22 for drugs that qualified for one expedited program. To place this figure in context, one QALY could represent either one additional year lived in perfect health, or some longer period of time lived with an illness or condition that makes health less than perfect (for example, living two additional years with a health-related quality-of-life weight of 0.5). In addition, actual QALY gains are likely smaller, as the researchers themselves appropriately acknowledged; this is due to publication bias that could lead to disproportionate reporting of favorable QALY values, as well as the fact that efficacy data based on surrogate measures can have a poor correlation with survival, which in some cases may mean that efficacy data are not borne out in higher-quality, confirmatory trials.

A more substantial 1.13 average QALY gain was identified for drugs in all three expedited programs, although this result was based upon only 10 drug-indication pairs, or just 7 percent of the 135 drug-indication pairs studied.

Many New Drugs Are Less Beneficial Than Older Ones

Another key finding emerging from Chambers and his colleagues' work is that 29 percent of new drug-indication pairs performed no better than existing treatment options, including some that performed more poorly. For non-expedited pathway drugs, this figure was 41 percent. Thirteen non-expedited drug-indication pairs directed to neuropsychiatric and neurological disease had a near-zero median QALY benefit (-0.002 QALYs) vis-à-vis the older comparators (see Chambers, et al., Appendix Exhibit 3). Eleven non-expedited drug-indication pairs directed to musculoskeletal and rheumatologic disease were associated with a mean 0.10 QALY loss vis-à-vis their comparators.

In addition, 20 percent of expedited drug-indication pairs were associated with either a QALY loss or an absence of gain. Eight drug-indication pairs directed to circulatory diseases benefiting from at least one expedited program were, on average, associated with a 0.13 QALY loss vis-à-vis their older comparators. Some proportion of drugs benefiting from two or even all three expedited programs may have underperformed their older comparators, as reflected in standard deviations, all of which extend well below the zero QALY threshold (see Exhibit 1 below and Chambers, et al., Exhibit 3). Unfortunately, because the data appear to be right-skewed, and because Chambers, et al., reported inter-quartile widths without reporting values for quartiles 1 or 3 and did not report the underlying data, the number of drugs in multiple expedited programs that underperformed their competitors cannot be determined. However, in Appendix Exhibits 4–6, Chambers, et al., indicate that some drugs in each of the three expedited programs resulted in QALY losses of 0.3 or greater magnitude.

Interestingly, drug-indication pairs benefiting from either zero or one program had the least negative values for mean minus standard deviation, as well as the least positive values for mean QALY gain. These relatively narrow data dispersions suggest that drugs benefiting from zero or one expedited program, which constitute 82 percent of new drugs approved between 1999 and 2012, may have

little difference from existing medicines, such as additions to a therapeutic class that have similar molecular structures and similar mechanisms of action.

Exhibit 1: QALY Data For Drug-Indication Pairs

	No Program	At Least 1 Program	Multiple Programs	1 Program	2 Programs	3 Programs
Number Of Pairs	59	76	30	46	20	10
Mean QALY Gain	0.059	0.388	0.654	0.215	0.415	1.132
Std Dev	0.275	1.302	1.982	0.466	2.136	1.627
Mean minus Std Dev	-0.216	-0.914	-1.328	-0.251	-1.721	-0.495

Source: Exhibit 3, "Drugs Cleared Through The FDA's Expedited Review Offer Greater Gains Than Drugs Approved By Conventional Process," James D. Chambers and coauthors, Health Affairs*, August 2017.*

A Greater Focus On Efficacy Is Needed

There is keen interest from multiple stakeholders in expediting the approval of new drugs, particularly those drugs that appear most promising in early testing. This interest is driven by patients whose suffering is not sufficiently alleviated by existing medicines; by their caregivers, who seek new options to treat disease; by the pharmaceutical industry, which benefits financially when drugs are approved more quickly; and by Congress and the FDA, which are viewed more favorably when government is perceived as promoting the efficient development and approval of important new medicines. Pressure arising out of this political and social context to approve new drugs quickly is augmented by the ease and transparency with which speed can be measured and reported.

Speed matters little, however, for drugs that offer little or no advantage over existing therapies. Unfortunately, the measurement of efficacy is challenging, comprehension of quality-adjusted life years is low, and awareness of regulatory approval standards is poor. Many people mistakenly assume that the FDA and other gatekeepers sufficiently screen drugs for meaningful benefit. With efficacy assumed, efforts by patient groups are directed at promoting faster availability and lower cost. Policy makers have responded by repeatedly focusing on expediting the availability of new drugs, most recently seen in the push for pre-approval expanded access. A commensurate focus on the efficacy of new drugs is needed.

Summing Up

Expedited programs help direct regulatory resources toward the most promising new drugs, and Chambers and his coauthors demonstrate one metric on which the FDA has apparently distinguished more beneficial drugs from less beneficial ones. However, another important contribution of their study is to quantify the benefit of new drugs, showing the extent to which many new drugs, including many expedited drugs, are no better than existing alternatives. Among other things, their data show that many drugs, even those benefiting from expedited programs, may result in QALY losses vis-à-vis their comparators.

These findings suggest that some of the focus on development and approval speed should be redirected to promoting, measuring, and reporting drug efficacy. They also suggest that efforts to promote access to new drugs make little sense without careful consideration of drug efficacy levels, absent which substantial health care expenditures may be directed to drugs that do not outperform the prior standard of care.

Authors' Note

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DRUGS AND MEDICAL INNOVATION

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