Study examines quality of evidence for drugs granted accelerated FDA approval

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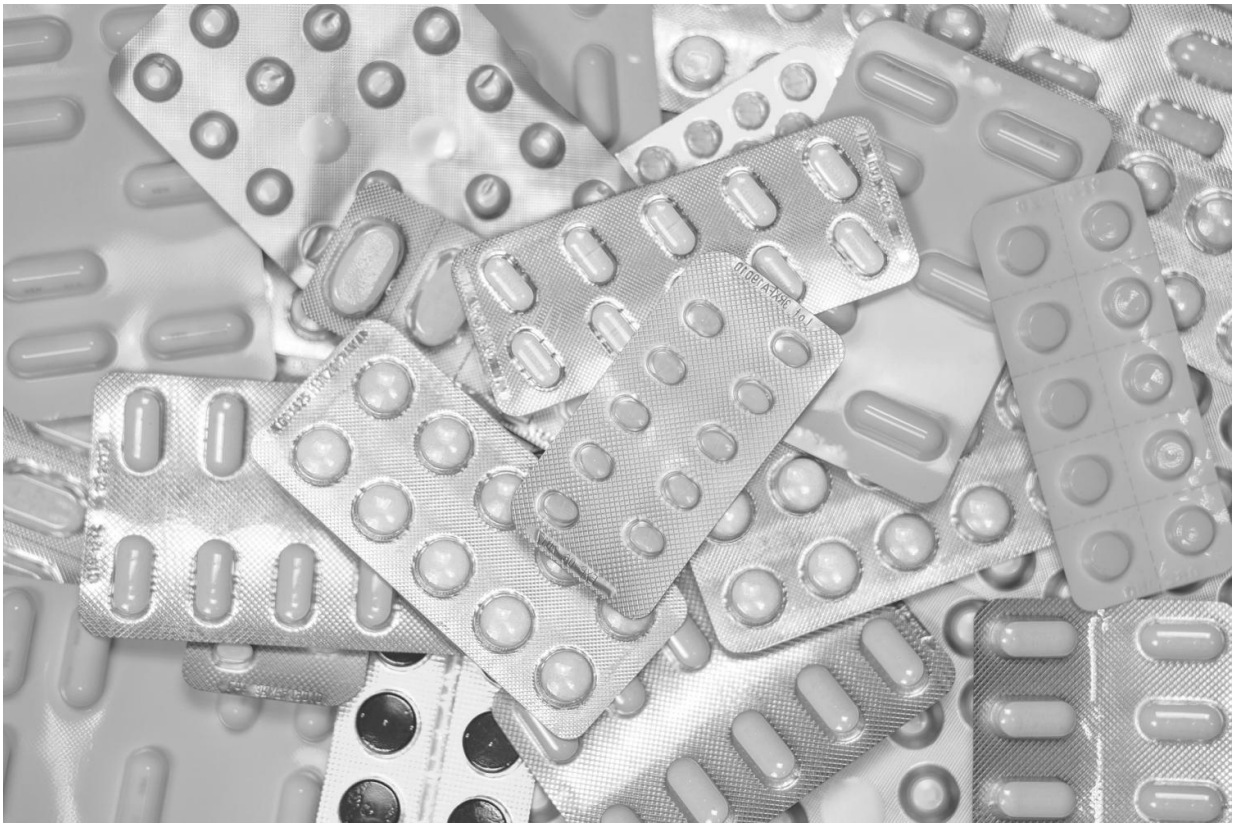

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Among drugs granted accelerated approval by the FDA in 2009-2013, efficacy was often confirmed in subsequent trials a minimum of 3 years after approval, and the use of nonrandomized studies and surrogate

measures, instead of clinical outcomes, was common, according to a study published by *JAMA*.

Drugs treating serious or life-threatening conditions can receive U.S. Food and Drug Administration (FDA) accelerated approval based on showing an effect in surrogate measures, such as biomarkers, laboratory values, or other physical measures, that are only reasonably likely to predict clinical benefit. Confirmatory trials are then required to determine whether these effects translate to clinical improvements.

Huseyin Naci, Ph.D., M.H.S., of the London School of Economics and Political Science, London, and colleagues compared the evidence on qualifying drugs before and after receiving accelerated approval, including the extent to which confirmatory studies were completed and determined whether the drugs demonstrated clinically meaningful benefits. Characteristics of preapproval and confirmatory studies were compared in terms of study design features (randomization, blinding, comparator, primary end point).

The FDA granted accelerated approval to 22 drugs for 24 indications between 2009 and 2013; 14 of the 24 indications for these drugs entered the market on the basis of single-intervention-group studies that enrolled a median of 132 patients, which some investigators would consider a small number. Half of required confirmatory studies were completed a minimum of three years after the approved drug was on the market.

The quality and quantity of postmarketing studies required by the FDA to confirm clinical benefit varied widely across indications. There were few statistically detectable differences in the key design features of trials conducted before and after approval. Nonrandomized studies were common in the accelerated approval pathway both before (60 percent) and after (44 percent) market entry. Even though the majority of completed studies showed positive results in the postmarketing period,

all completed confirmatory studies demonstrating drug benefit evaluated surrogate measures of disease activity rather than clinical outcomes. Clinical benefit had not yet been confirmed for eight indications that had been initially approved five or more years prior.

The study notes some limitations, including that the adequacy of the confirmatory studies in addressing questions about the drugs that the FDA considered to be unresolved was not examined because such insights are not available from the FDA documents.

More information: *JAMA* (2017). jamanetwork.com/journals/jama/… .1001/jama.2017.9415

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