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Scientific Evidence Supporting Benefits of Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015–2017

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Introduction:
The US Food and Drug Administration (FDA) exercises flexibility in the requirement that new drugs provide substantial evidence of benefit under the Food, Drug and Cosmetic Act. Provisions in law and policy provide numerous exceptions to the historical scientific standard of 2 or more controlled clinical trials demonstrating statistically significant evidence of benefit.

Objectives:
To examine implementation of the FDA requirement for "substantial evidence" of benefit among a large group of recently approved new molecular entities (NMEs). We used FDA annual drug approval reports to derive a list of approved NMEs between 2015 and 2017 and their approval pathways (e.g. breakthrough, accelerated approval). The scientific standards of interest were: (1) reproducible results—defined as 2 or more clinical trials providing evidence of benefit; (2) randomized design-a trial with patients randomized to treatment, active drug or placebo comparison groups; (3) clinical scale or benefit-a measurable effect on the patient's health rather than a biomarker or surrogate endpoint; and (4) 100 or more patients treated with active drug-to assess biological variability and identify adverse effects.

Results:
We identified 225 pivotal trials cited as evidence of benefit for the FDA approval of 101 new therapeutic agents from 2015 to 2017. Expedited pathways and incentives were common. Overall, 36 of 101 products (36%) met all 4 standards, and 3 drugs meet none of them. We identified 14 drugs (14%) approved on the basis of a single, uncontrolled trial, including 5 drugs with fewer than 100 patients treated. Extent of scientific evidence also varied by therapeutic area: all 4 standards were met by all the dermatological products (n = 9), respiratory products (n = 3) and 2 of 3 ophthalmological drugs. Oncology drugs (n = 29) varied the most, with 2 agents meeting all 4 standards but 8 meeting only 1 standard. Drugs approved under the orphan drug incentive (n = 43) included all 3 drugs meeting none of the standards and 16 of 20 drugs (80%) without a controlled trial.

Conclusion:
FDA approval of new molecular entities now reflects a body of scientific evidence of benefit that varies from an uncontrolled trial in a few patients to randomized comparative trials enrolling thousands. Without randomized controls, the scientific evidence of benefit is without protection against conscious or unconscious bias, atypical patient selection, and unmeasured confounding.