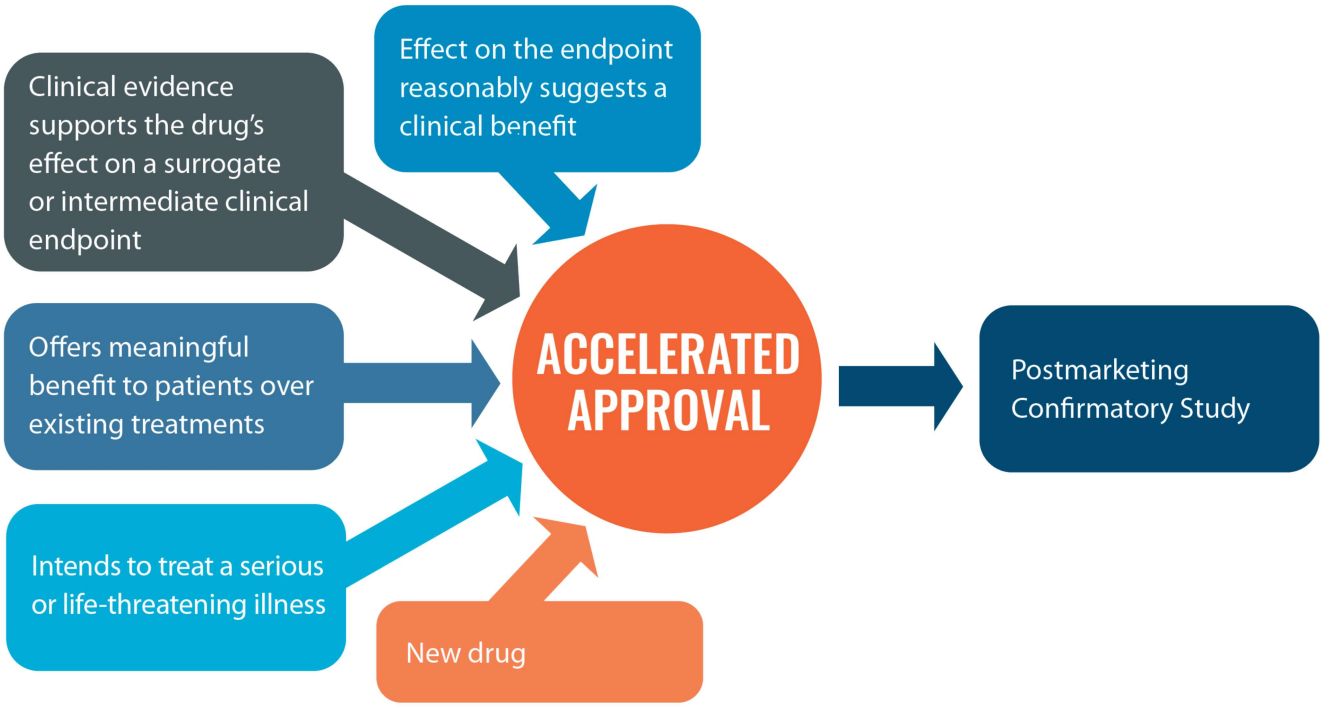

a drug's intended clinical benefit,[47] and agree to conduct a postmarketing confirmatory study or studies to verify and describe the relationship between the endpoint and the anticipated expected clinical benefit.[48] The difference between the two approval pathways is a question of evidence regarding the predictive ability of an endpoint, *i.e.*, how much direct clinical evidence there is regarding that particular endpoint.

For accelerated approvals, adequate and well-controlled studies will have shown that a drug has an effect on one of two types of endpoints: (1) a surrogate endpoint[49] that is "reasonably likely" to predict clinical benefit; or (2) an intermediate clinical endpoint[50] other than an effect on irreversible morbidity or mortality (IMM) that is "reasonably likely" to predict an effect on IMM or other clinical benefit.[51] In other words, accelerated approval is based on a drug's effect on a surrogate or intermediate clinical endpoint that is "reasonably likely" to impact clinical outcomes. However, the meaning of the approval—that the product is safe and effective for its intended uses—is the same.

47 21 U.S.C. § 356(c); Expedited Programs Guidance, supra note 31, at 19–22. FDA takes a comprehensive approach in its evaluation. FDA determines whether a particular endpoint is appropriate by considering all relevant evidence including the pathophysiologic or causal pathways of the disease, the drug's effect on the endpoint, and empirical and clinical evidence that supports a conclusion that the drug is reasonably likely to have an effect on the endpoint. Empirical evidence can include, among other things, epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers. *See* Expedited Programs Guidance, *supra* note 31, at 19–22.

48 *See* 21 U.S.C. § 356(c)(2); 21 C.F.R. §§ 314.510 & 601.41 (1993). Accelerated approval sponsors also are required to obtain preapproval of promotional materials prior to their use in marketing.

49 A "surrogate endpoint" can be a laboratory measurement, radiographic image, or physical sign that is reasonably likely to predict a drug's intended clinical benefit on overall survival (e.g., long-term suppression of HIV viral load in plasma; reduction in tumor size; progression-free survival (PFS) in advanced cancer patients; and sputum culture status and infection relapse rates in patients with pulmonary tuberculosis). Expedited Programs Guidance, supra note 31, at 17¬–19; ICER Report, *supra* note 35, at 12; Kelong Han et al., *Progression-free Survival as a Surrogate Endpoint for Overall Survival in Glioblastoma:* A Literature-based Meta-analysis From 91 Trials, 16 Neuro-Oncology 696, 696–97 (2014), available at https://academic.oup.com/neuro-oncology/article/16/5/696/1192459?login=true.

50 Intermediate clinical endpoints may include, for example, a short-term, significant decrease in the relapse rate of multiple sclerosis; or a demonstrated delay in delivery of early labor. Expedited Programs Guidance, *supra* note 31, at 18.

51 *See* 21 U.S.C. § 356(c)(1)(A); 21 C.F.R. §§ 314.500, 314.510, 601.40 & 601.41 (1993); 57 Fed. Reg. at 58958–59.