Reasonably Likely Surrogate Endpoint

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**Definition**

An endpoint supported by strong mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint is expected to be correlated with an endpoint intended to assess clinical benefit in clinical trials, but without sufficient clinical data to show that it is a validated surrogate endpoint. Such endpoints may be used for accelerated approval for drugs and potentially also for approval or clearance of medical devices. In the case of accelerated approval for drugs, postmarketing confirmatory trials have been required to verify and describe the anticipated effect on the irreversible morbidity or mortality or other clinical benefit.¹

**Examples**

- Outcomes of 6-month follow-up treatment (i.e., sputum culture status and infection relapse rate) have been considered reasonably likely to predict the resolution of pulmonary tuberculosis and have supported accelerated approval of drugs to treat tuberculosis.
- Decrease in iron stores for patients with iron overload caused by thalassemia has been considered reasonably likely to predict a decrease in transfusion-related adverse events caused by iron overload in the body and has supported accelerated approval of drugs to treat non-transfusion-dependent thalassemia (NTDT).
- Radiographic evidence of tumor shrinkage (response rate) and progression free survival in certain cancer types have been considered reasonably likely to predict an improvement in overall survival with certain therapies and have supported accelerated approval of drugs to treat these cancer types.
- Biochemical evidence of a clinically significant degree of improvement in alkaline phosphatase (ALP) at 12 months demonstrated in adequate and well controlled studies has been considered reasonably likely to predict decreased risk of liver transplant or death and has supported/ been the basis for evaluating the efficacy for an accelerated approval of a drug to treat adults with primary biliary cirrhosis and an inadequate response to ursodeoxycholic acid (UDCA), or as monotherapy in adults with primary biliary cirrhosis unable to tolerate UDCA.

¹ 21 CFR 314.510
Explanation

This glossary makes a distinction among three categories of endpoints under consideration to serve as surrogate endpoints (i.e., validated surrogate endpoint, reasonably likely surrogate endpoint, and candidate surrogate endpoint). The categories describe use of the endpoints for regulatory decision making in the U.S., based on the level of clinical validation. This discussion considers the use of “reasonably likely surrogate endpoints” in this context.

Randomized clinical trials testing the efficacy of new medical interventions that use as a primary endpoint a measure of clinical benefit provide the highest level of evidence for a clinical benefit, but the time and resources to demonstrate benefit on the endpoint directly are often substantial. Usually effects on surrogate endpoints are appealing because they can be detected far more rapidly or easily, or potentially less invasively, than the effect on a clinical outcome and often with far fewer patients. In situations where there is no effective treatment for a serious illness, use of surrogate endpoints can bring new therapeutics more quickly to those who need them. Effects on surrogate endpoints do not provide direct evidence of a clinical benefit of a therapy. Reasonably likely surrogate endpoints sometimes fail to predict an actual benefit. This limitation underscores the importance of the post-market study to confirm the clinical benefit of the drug.

The accelerated approval of drug and biologic products is governed by the regulations stated in 21 CFR part 314 subpart H, 21 CFR part 601 subpart E and section 506 (c) of the Food, Drug and Cosmetic Act as amended by section 901 of the Food and Drug Administration Safety and Innovation Act of 2012. The qualifying criteria for a drug (or biologic) to be considered under accelerated approval pathway for marketing in the US are that the drug is intended to treat a serious or life-threatening condition and provides a meaningful therapeutic benefit over available therapies. Approval can then be based on demonstration of an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on an intermediate clinical endpoint that can be measured earlier than irreversible morbidity or mortality and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit. It is expected that there will be empirical evidence that the observed change in the biomarker after the administration of a drug is likely to predict clinical benefit. This empirical evidence is disease specific and depends on the natural history of the disease. The adequacy of the empirical evidence to support the use of a reasonably likely surrogate endpoint is based on the biologic plausibility of the relationship between the disease and the biomarker and the magnitude of observed change in the biomarker that supports the relationship.