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Accelerated Approval

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Overview

- Accelerated approval - Evidence standards
- Confirmatory Trials

Standard for a drug or biological product to be approved

- Approval of a drug requires:
  - Substantial evidence of effectiveness
  - Demonstration that the benefit of the drug outweighs the risk for the intended use

- Substantial evidence of effectiveness is defined as:

  "evidence consisting of ***adequate and well-controlled investigations****, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved,* ***on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling*** *or proposed labeling thereof."*

FD&C Act section 505(d) (21 U.S.C. § 355(d)); draft Guidance for Industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019).

Food and Drug Administration Safety Innovations Act (FDASIA)

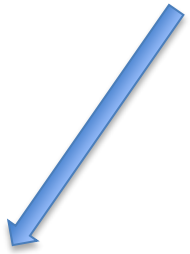
"The Secretary may approve an application for approval of a product for a **serious or life-threatening disease or condition**…upon a determination that the product has **an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit**, or on a **clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect** on irreversible morbidity or mortality or other clinical benefit, **taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments**."

Section 506 (c) of the Food Drug and Cosmetic Act (21 U.S.C. 356(c))

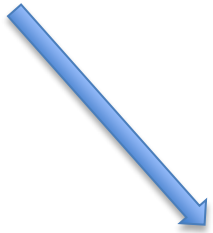
Meeting Patient's Needs by Streamlining Development

- A surrogate endpoint is often a laboratory measurement, radiographic image, physical sign, or other measure, that is not itself a direct measurement of clinical benefit, is expected to predict clinical benefit (or lack of benefit or harm)
  - Data supporting a conclusion that a surrogate endpoint is indeed able to predict a clinical endpoint may be based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence

Strength of Evidence Distinguishes Surrogates



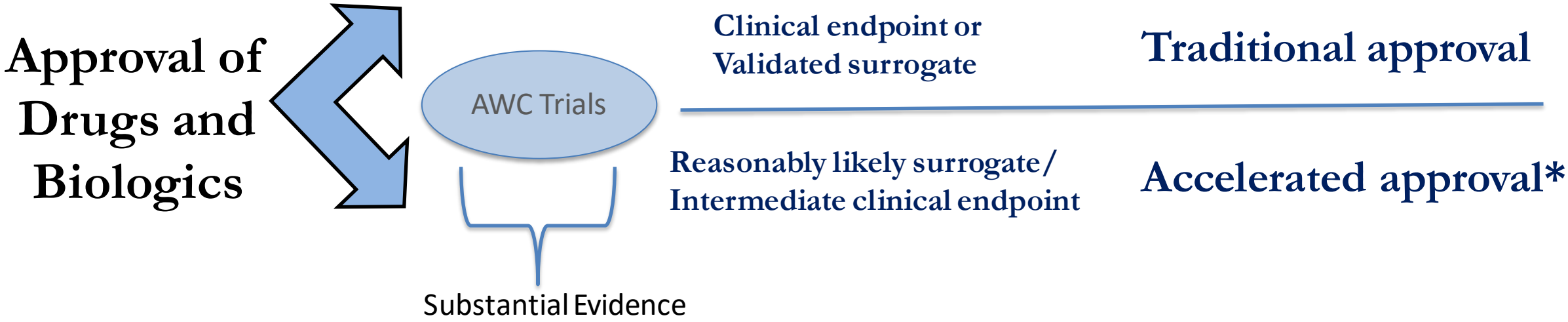
Validated Surrogate - marker that is *known to predict clinical benefit*, e.g., blood pressure and stroke, forced expiratory volume (FEV1) in certain pulmonary diseases



Reasonably Likely Surrogate - marker that is *reasonably likely to predict clinical benefit*, e.g., total kidney volume in polycystic kidney disease, clearance of amyloid plaque in Alzheimer's disease

https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

U.S. Drug and Biological Product Approval Pathways



AWC – Adequate and Well Controlled Trials
21 CFR 314.126

* 21 CFR Part 314, Subpart H (for drugs)
21 CFR Part 601, Subpart E (for biologics)
Food and Drug Administration Safety and Innovation Act 506(c)

Meeting Patient's Needs by Streamlining Development

- For **serious and life-threatening diseases without adequate therapies**, there is an urgency to get effective and safe therapeutics to patients
- In certain cases, we may have sufficient understanding of the disease to identify a **surrogate endpoint or intermediate clinical endpoint** that occurs earlier in the course of the disease and is predictive of a clinically meaningful outcome/endpoint
  - Creates an opportunity for a more streamlined development program by enabling trials that may be shorter and in certain cases smaller
  - Greater access as confirm the benefit
- There is a tradeoff between smaller, faster drug development to meet an unmet medical need for serious, life-threatening disease and the greater uncertainty as to whether the reasonably likely surrogate does indeed predict clinical benefit

Challenges with Accelerated Approval

- Main challenge is identification of a surrogate for which we have sufficient evidence that it is reasonably likely to predict clinical benefit
- Identification of a surrogate endpoints requires sufficient understanding of disease pathogenesis
- Many animal models of diseases do not fully recapitulate key aspects of the human disease and are not "translational"—meaning that apparent drug "benefit" observed in such models fails to predict drug benefit in clinical studies
- Epidemiologic data may demonstrate a relationship between a surrogate and disease outcome but need evidence that the change in the surrogate correlates with a change in clinical benefits

Confirmatory Trials

- Post-marketing trials are routinely be required to verify and describe the drug's clinical benefit.
- By assessing the drug's clinical benefit, the goal of the confirmatory trial is to address the remaining uncertainty of the surrogate endpoint's relation to clinical benefit
- Expectation is that some trials will not confirm clinical benefit
- Once a drug is on the market, if confirmatory trials are not ongoing at the time of approval there can be challenges in conducting the trials needed to confirm clinical benefit

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