



Regulatory Basis for U.S. Drug & Biologics Approval

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FDA Mission:

- FDA is responsible for:
 - Assurance of the Safety, Efficacy and Security of:
 - **Drug and Biological** products
 - **Medical Devices**
 - **Food** supply
 - **Cosmetics**
 - **Radiation products**
- FDA **does not** take into account cost or payment issues
- FDA **does not** regulate “practice of medicine”

Applicable FDA Centers for this Workshop:



Center for Drug Evaluation and Research (CDER)

- Drugs and Therapeutic Antibodies
- Office of Hematology and Oncology Products



Center for Biologics Evaluation and Research (CBER)

- Cellular and Gene Therapies, Vaccines



Center for Devices and Radiologic Health (CDRH)

- Devices, In Vitro Diagnostics, Diagnostic and Therapeutic Radiologics

Combination Products

- Some products require reviews across Centers:
 - Drug-Eluting Stents
 - CDRH-stent, CDER-drug
 - Office of Combination Products determines the center that will conduct the primary review
 - Usually based on which component of the combination is responsible for the primary therapeutic effect
 - Example: Heat-activated cytotoxic drug activated by high-intensity ultrasound would likely be primarily reviewed in CDER with collaboration by CDRH.

Safety and Efficacy Requirements:

Drugs (FD&C Act) and Biologics (PHS Act)

- FD&C Act “Safe and Effective”
 - Adequate and well-controlled investigations (typically 2 or more trials)
 - Experts qualified to evaluate the effectiveness of the drug
 - Reach a conclusion that the drug will have the effect it purports

- PHS Act “Safe Pure and Potent”
 - 1997 FDA Modernization Act – Minimize differences in review and approval between drugs and biologics

- For all intents and purposes, Safety and Efficacy of Drugs and Biologics use a similar evidentiary framework

FDA Historical Perspective on Oncology Efficacy Endpoints

- 1970s, there were limited available therapies and tumor shrinkage (response rate) was accepted as a primary endpoint for approval
- 1980s, a change in this interpretation occurred:
 - Asymptomatic radiographic tumor shrinkage may not translate into an improvement in overall outcome (particularly given the toxicity of the cytotoxic agents being evaluated)
- Efficacy should be based on Direct Clinical Benefit
 - How one “Feels, Functions or Survives”

Categories of Efficacy Endpoints

- Direct Measure of Clinical Benefit
 - Overall Survival
 - Measures of symptoms or function
 - Patient Reported Outcomes
 - Decrease in morbid complications (Skeletal Related Events)

- Established Surrogate of Clinical Benefit
 - Substantial existing data and regulatory precedence increasing the certainty that the surrogate is predicting true clinical benefit
 - Dependent on Clinical Situation: DFS (adjuvant breast)

- Unestablished Surrogate of Clinical Benefit
 - Limited existing data, lack of regulatory precedence
 - Response rate in most solid tumor settings

There are Two Approval Pathways for Drugs and Biologics in the U.S.

- Regular Approval
- Accelerated Approval

Regular Approval

- Regular approval requires
 - Substantial evidence of Safety and Efficacy
 - Well-controlled clinical trials (usually 2 or more)
 - based on **prolongation of life, a better life or an established surrogate for either of the above.**

- Therefore, efficacy endpoints for Regular Approval may include:
 - Overall Survival (“Prolongation of life”)
 - Patient Reported Outcomes or SRE delay (“A better life”)
 - DFS in Breast Cancer (“Established Surrogates”)

- There is no comparative efficacy requirement for Regular Approval
 - Drug or Biologic must be shown to be safe and effective
 - (as effective as an alternative therapy for the same disease and indication)
 - Allows for non-inferiority

Accelerated Approval

- Accelerated approval “Serious or life-threatening diseases”
 - “Provide meaningful therapeutic benefit... over existing therapies”
 - “*Surrogate endpoint... reasonably likely... to predict clinical benefit*”
 - “Subject to the requirement that the applicant study the drug further”
 - Post-Marketing Clinical Trials are Required
 - Would usually be underway at the time of accelerated approval
 - Applicant should carry out studies with due diligence

- There are benefits and risks to the Accelerated Approval Pathway
 - Benefits: Can use an unestablished surrogate endpoint
 - Usually provides for earlier events and smaller, quicker trials
 - Risks:
 - Must show it is better than existing therapy
 - Must complete post-marketing trials and confirm meaningful clinical benefit
 - 10% of accelerated approvals have been withdrawn for failure to confirm benefit

Life-Threatening Diseases: Regulatory Flexibility in Oncology

- **Safety:**
 - Historically, acceptance of higher degrees of toxicity

- **Efficacy:**
 - Acceptance of a Single Trial rather than 2 or More Trials
 - For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent, and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform.
 - Acceptance of alternative development strategies
 - Frequent use of the Accelerated Approval Pathway
 - Use of Surrogate Endpoints – Radiographic PFS, Response Rate

- **Overall Risk-Benefit Determination for NDA or BLA Review**
 - Takes into consideration more than just the safety and efficacy data
 - Available Therapy, Disease, Indication, Regulatory Precedence, State of Science

Other Aspects of Efficacy Endpoints: Susceptibility to Bias and Accuracy of Timing of the Event

- Overall Survival is the Gold Standard in Oncology
 - Interpretation of Event is not an issue (least prone to bias)
 - Event timing is known to the day

- Radiographic Time to Event (PFS, DFS, MFS)
 - Interpretation of the event requires investigator or independent review
 - Event timing is dependent on the frequency of radiographic assessments

- Time to Intervention (e.g. cystectomy) has not been used for approval in bladder cancer and is problematic
 - While delay or avoidance altogether of major surgery may be considered a direct clinical benefit, there are significant concerns regarding the potential for bias (Investigator and Patient Decision Determines the Endpoint)
 - Mitigation of possible bias may include blinding, placebo or sham procedure and pre-defined objective triggers for intervention; however these may or may not be feasible

Summary

- Many options for efficacy endpoints to describe clinical benefit, but uncertainty increases with the use of surrogate endpoints
- Increased uncertainty associated with surrogate endpoints requires additional evidence that the surrogate endpoint predicts true clinical benefit
- Even when attempting to measure direct clinical benefit, bias must be addressed and mitigated
- Approval decisions are based on a risk-benefit assessment using all available data to determine whether the drug or biologic provides clinically meaningful benefit to patients