Use of Biomarkers in Clinical Trials

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Overview of Biomarker Uses

• Biomarker Definition

• Biomarkers in clinical practice

• Biomarkers in clinical research
Definition

- A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

- Different sources
  - Serum or plasma
  - Radiographic
  - Tissue

- Can be endogenous or exogenous
Biomarkers in Clinical Practice

• Aid in establishment of diagnosis of condition
  – Sweat chloride test for cystic fibrosis
  – Glucocerebrosidase enzyme level for Gaucher disease

• Establishment of severity of disease
  – Blood pressure and risk of stroke
  – Serum creatinine and degree of renal insufficiency
  – Serum bilirubin and degree of cholestasis

• Monitoring disease or effect of treatment
  – Hemoglobin A1C for glucose control in diabetes mellitus
  – Cancer antigen-125 (CA-125) for ovarian cancer
Biomarkers in Clinical Research

• Identify a target population for study
  – Human Epidermal Receptor-2 (HER-2) positive breast cancer for HER-2 receptor antagonist therapy (e.g., trastuzumab)
  – Anaplastic Lymphoma Kinase (ALK) positive non-small cell lung cancer for tyrosine kinase inhibitors (e.g., crizotinib)

• Population is more likely to respond to treatment based on the disease and the mechanism of action of the drug

• Does not mean that these biomarkers are acceptable clinical endpoints
Biomarkers in Clinical Research

• **Refine dose and/or dosing interval in phase 2 trials**
  – Improvement in urinary excretion of glycosaminoglycans (uGAG) in mucopolysaccharidoses (MPS)

• **Changes in pharmacodynamic markers are helpful in determining optimal dose for later phase trials**

• **Does not mean that these biomarkers are acceptable clinical endpoints**
Biomarkers as Endpoints

- Clinically meaningful endpoint
  - A direct measure of how a patient feels, functions or survives

- Surrogate Endpoint
  - An endpoint which utilizes a biomarker that is intended to substitute for a clinically meaningful endpoint
  - Change in a surrogate endpoint results in, or is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence
  - A subset of biomarkers may be suitable for use as surrogate endpoints

- Not all biomarkers, even clinically useful biomarkers, are suitable for use as surrogate endpoints
Surrogate endpoints

- **Validated Surrogate Endpoint**
  - An endpoint based on a biomarker for which evidence has established that a drug-induced effect on the surrogate predicts (results in) the desired effect on the clinical outcome
  - Can be used to support regular approval
  - Example: Blood pressure for antihypertensive agents

- **Unvalidated Surrogate Endpoint**
  - An endpoint based on a biomarker for which it is reasonably likely based on epidemiologic, therapeutic, pathophysiologic or other evidence to predict clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity
  - Cannot be used to support regular approval
  - Can be used to support “accelerated approval” under 21 CFR314.500
  - Example: Tumor regression in certain types of refractory tumors
Considerations for use of biomarkers as endpoints

• This evidence should include that the biomarker must be
  – reproducible within patients
  – responsive to clinically meaningful changes in disease activity
  – defined with respect to its temporal relationship with disease activity
  – change in expected direction with known effective treatments
  – that the biomarker of interest lies in the causal pathway of the disease.

• Identification of a potential biomarker that could be used as a surrogate marker in phase 3 trials requires
  – Careful and early planning
  – Discussion and concurrence of plans with the review division
Summary

• Biomarkers are used extensively to guide clinical practice

• Biomarkers in clinical research
  – Identify a target population
  – Evaluate dose response in phase 2 trials
  – Some may be used as clinical endpoints

• Not all biomarkers that are used in clinical practice are acceptable for use as clinical endpoints
  – Rigorous evaluation of a potential biomarker must be performed during clinical development to establish the justification for use as a clinically meaningful endpoint or surrogate endpoint before phase 3 trials begin
Thank you
Accelerated approval

• FDA may grant approval of a drug or biological product based on adequate and well-controlled trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit
  – Must treat serious or life-threatening disease for which there is no available therapy or provide benefit over available therapy

• Approval is subject to the requirement to verify and describe its clinical benefit in additional adequate and well-controlled trials that may be performed postmarketing
  – 21 CFR 314.500-560 (Subpart H) and 21 CFR 601.40-46 (Subpart E)