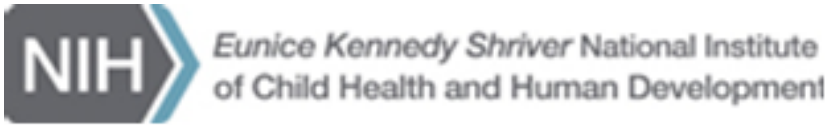
Roundtable #2
Biomarkers in Drug Development for Rare Diseases

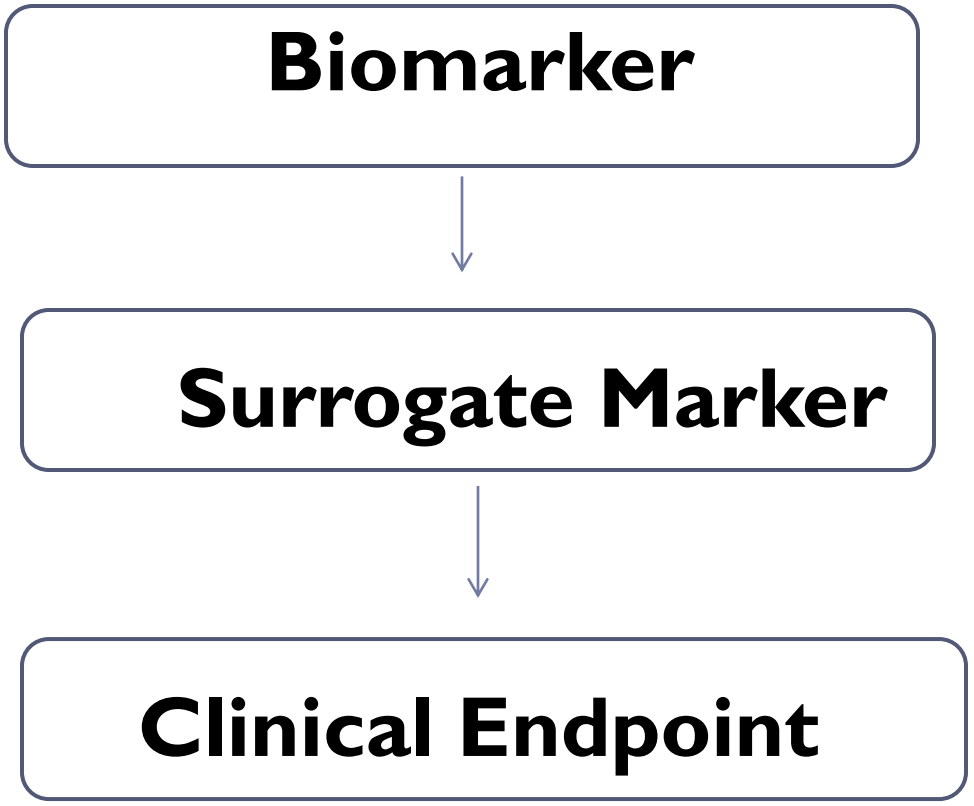
April 29, 2013



Guidance for Industry

Qualification Process for Drug Development Tools

Biomarker Progression Model



Definition of Biomarker

- Characteristic that is objectively measured and evaluated as an indicator of a:
  - Normal biologic process
  - Pathogenic process
  - Biological response to a therapeutic intervention
- Can define a physiologic, pathologic, or anatomic measurement that is thought to relate to biological function
- Changes in a biomarker following treatment predict/relate to pharmacologic activity which predict clinical outcome

Categories of Biomarkers

- Prognostic: baseline categorization by degree of risk for disease occurrence/progression
- Predictive: baseline characteristic that categorizes patient by likelihood for response
- Pharmacodynamic (activity): dynamic assessment that shows a biologic response has occurred after the intervention
  - BP, cholesterol, HbA1C, intraocular pressure, X-ray, CRP

Categories of Biomarkers

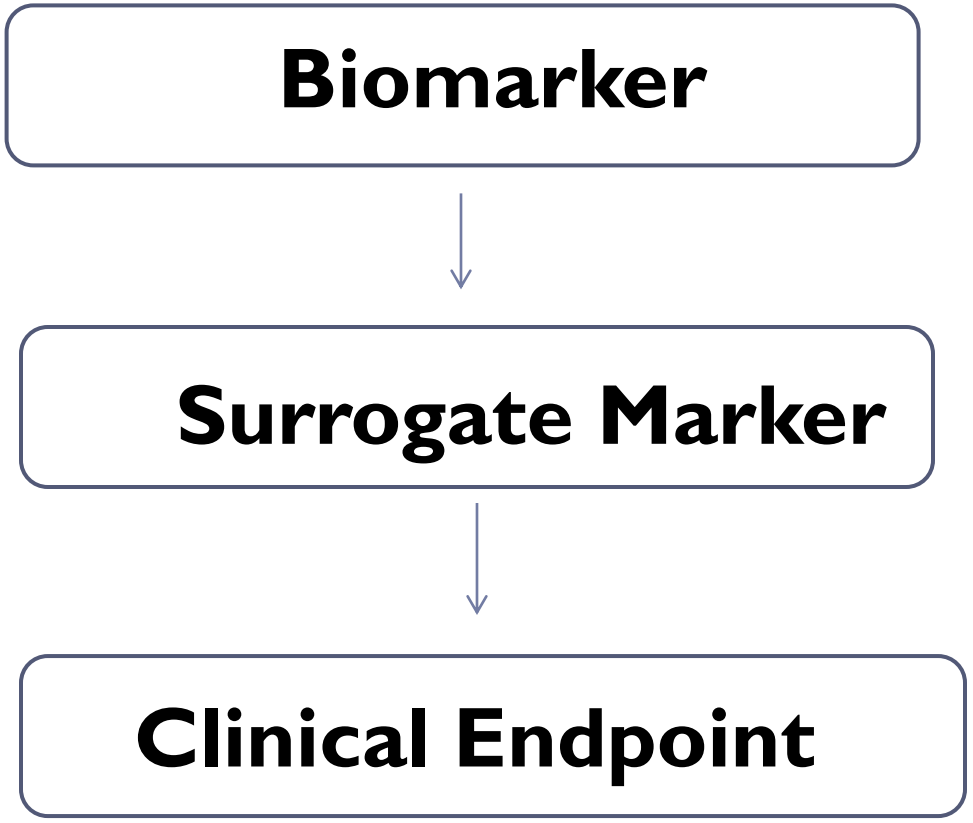
- **Surrogate endpoint: biomarker intended to substitute for a clinical efficacy endpoint**

- **Clinical endpoint: variable that reflects how a patient feels, functions, survives**

Biomarker to Predict

- Efficacy
  - Means to measure beneficial disease outcomes
  - Reduction in morbidity
    - Patient Reported Outcomes
    - Clinical trial outcome measurement tools
      - Clinician
      - Caregiver
  - Reduction in mortality
- Safety

Biomarker Progression Model

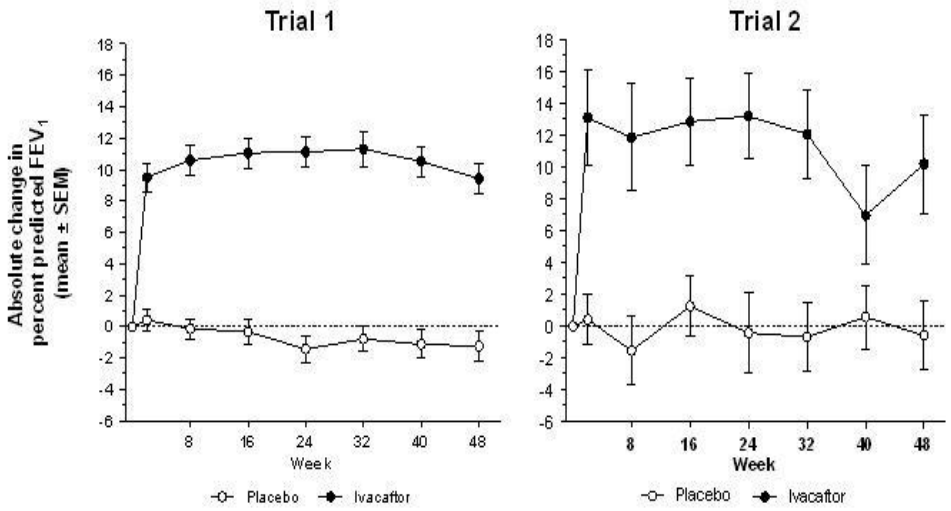


Cystic Fibrosis Biomarkers

- Lung MRI
- Lung Clearance Index

- Ivacaftor (Kalydeco), Vertex

Kalydeco Label: FEV1



Kalydeco Label: Efficacy

- Patients treated with KALYDECO demonstrated statistically significant improvements in risk of pulmonary exacerbations, CF symptoms (in Trial 1 only), and gain in body weight. Weight data, when expressed as body mass index normalized for age and sex in patients <20 years of age, was consistent with absolute change from baseline in weight.

Duchenne Muscular Dystrophy

- Molecular defect in Duchenne muscular dystrophy: genetic mutations causing *lack* of functional dystrophin muscle protein
- Mechanism of action of intervention: exon skipping to produce *partially* functional dystrophin
- Biomarker of effect: 6 minute walk test
- Surrogate biomarker: dystrophin concentration on muscle bx
- Clinical effect: decreased morbidity/ clinical improvement measured by ??

Urea Cycle Defects

- N-acetylglutamate synthase (NAGS) gene defect
- Biomarker/surrogate biomarker: NH_3

Hydroxyurea

- Used to treat sickle cell disease
- MOA: increase HbF, which is more resistant to sickling with low oxygen tension
- NHLBI has sponsored multiple pediatric clinical trials with HU to treat children with SS Disease

Baby HUG Trial

- Children 9-18 months of age
- Sickle cell ds: Hb SS or $S\beta^0$ thalassemia
- Intervention: HU 20 mg/kg/d x 2 years
- Primary outcomes
  - Renal function: DTPA GFR (serum cr, cystatin C)
  - Splenic function: sulfur colloid liver-spleen scan (ratio of nuclear decay counts in spleen and liver, proportion of RBC with pits and RBCs with Howell-Jolly bodies
- Secondary outcomes:
  - Pain
  - Dactylitis
  - Acute chest syndrome
  - Hospitalization
  - Transfusion

Summary Comments

- Need trail of evidence relating biomarker to clinical outcome
- Biomarker related to mechanism of action of drug/device/intervention for efficacy, safety