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**RARE DISEASE WORKSHOP SERIES**  
Improving the *Clinical Development Process*

# Brief Review of Day 1

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# Review of Surrogate and Biomarkers Considerations for their use

- Clinical endpoints are preferable when they can be used
- Surrogate endpoints have challenges
- Use in Accelerated Approval requires sufficient data to show; “reasonably likely to predict clinical benefit”
- Requires significant data, but what?



# Many examples of surrogates use: The good, the bad and the ugly

- Multiple products approved in inborn errors of metabolism
  - Cysteamine, BH4, Ceredase, Urea Cycle Dz
- History of problems
  - Common disease issues
  - Rare disease examples: bad assays, poor compartment relevance, lack of synthesis of effects, missed off target effects
- Off target adverse effects



# Reviewed surrogate examples Organized by categories

- Blood levels of neurotoxic small molecule
- Urinary substrate excretion
- Imaging or special modalities
- Inflammatory or disease injury biomarkers
- CSF fluid markers for CNS disease
- Assessment of protein expression in Duchenne



## Key Findings from examples

- Good assays are important : some new assays of old analytes may be far improved for use as surrogates
- Direct relevance is easy but knowing all the pathways of pathophysiology is hard
- Assure the measured result is relevant to the disease compartment
- “Calibration” Need clarity on the how the magnitude off surrogate change relates to clinical effect
- If using surrogates, the study must be large enough to assure sufficient safety data
- Use of tissue expression assays are very challenging and need careful consideration
- Imaging is exciting but is still uncertain



## Review of today

- Two talks on “intermediate” endpoints
  - Physiologic measures of physical function
  - Not as removed as surrogates from a clinical measure
  - Discussion on how these measures should be viewed for uses in ultra-rare disease studies
- Discussion on questions
  - Interpretation of examples
  - Qualification criteria
  - Verification of clinical benefit



# Proposed Disease Criteria

## 1) Disease Criteria

### **Cause of disease clearly understood**

The genetic or pathophysiologic basis of the disease should be distinct and understood. This is critical to understanding the relevance of the biomarker to the disease process.

### **Pathophysiology mechanisms reasonably understood**

The process of the disease should be understood well enough to ascertain that what major pathways of disease are relevant to the clinical outcome. This is essential to understanding drug mechanism and biomarker relevance.



# Drug Criteria

## 2) Drug Criteria

### **Drug mechanism of action is direct and known**

- In order to reduce the risk of a drug mechanism that is on a parallel but clinically irrelevant pathway, the mechanism for how the drug is acting on the disease should be clear and direct to the disease process. This avoids situations in which the drug increases the marker through an irrelevant pathway that is not related to the disease process.
- The drug mechanism on the surrogate should be direct and known

### **Drug pharmacokinetics, pharmacodynamics and metabolism are relevant to the disease process being treated**

- The drug needs to be shown to exist in the sites of required action after administration in concentrations expected to be therapeutic, and demonstrate action in models that support a pharmacodynamic effect



# BioMarker Criteria

## 3) Biomarker Criteria

### **Biomarker has direct relationship to disease process**

- The biomarker should be directly traceable to the disease process and is best closely related to the block in activity or abnormality of the disease

### **Biomarker assay is sensitive and specific with a sufficient dynamic range**

- The assay should be able to distinguish abnormal from normal with sufficient precision and accuracy to be a reliable tool in the clinical setting.
- The dynamic range must be sufficient to assure that variation between patients or methodology could overshadow the relevant changes in the marker.
- The change in the marker must be calibrated to a change in relevant pathology by assessing a range of doses subtherapeutic to therapeutic in an animal model

### **Sampling compartment predicts disease compartment**

- The site of sampling whether it is blood, urine, CSF, an X-ray/image or a biopsy, must reflect the relevant disease compartment.
- If the disease process occurs in multiple relevant compartments, it should be shown that the sampling compartment is correlated with the other compartments
- The reflected compartment



# Preclinical Data

## 4) Preclinical Model Data Criteria

### **Preclinical studies show dynamic dose-response relationship on pathophysiology**

- Studies in preclinical models show that incremental changes in the biomarker do correlate with incremental changes in pathophysiological change.
- The degrees of change required to achieve meaningful changes in pathophysiology should be understood best by conducting experiments with subtherapeutic to supraherapeutic dosing

### **Preclinical studies should evaluate show a clinical effect if plausible**

- If a clinical impact on the diseases is readily measurable in the model, and correlates with the marker, this can help contribute to the qualification.

### **Survey of human disease shows a relationship to biomarker**

- Clinical disease severity or progression is shown to be generally correlated to the biomarker concentration in cross-sectional study of human patients. This is supportive of relevance but may not always be possible ahead of use of a biomarker.



## **Discussion: Interpretation of data from Day 1: Biomarkers in Rare Diseases and what have we learned**

Are biomarkers in rare genetic diseases more likely to be predictive of clinical disease given their closer and more direct relationship to the disease and mechanisms?

Identify key points regarding what works for predictive biomarkers.

What does not work and what can we use to filter/test proposed biomarkers?

What checks should be established?



## **Discussion: Establish qualification criteria for biomarkers**

Do the proposed criteria help drive scientifically sound qualifiable surrogates?

How do the proposed criteria work and what is missing or not adequate?

Is there a way to incorporate our experiences into credible starting place for a guidance?



## **Discussion: Verification of clinical benefit post approval**

How do we finish the development and obtain the right confirmatory data to establish clinical efficacy?

What are the best approaches to study design and conduct in the post-marketing environment?

What are the best practices needed in pre-approval development to allow effective post-approval confirmation?



# Post-Marketing Confirmation

- RDBPC study early post approval, perhaps in territories not approved
- Open label long-term study using objective endpoint or blinding of reading
- Natural history-controlled study
- Registry type large program focusing on major indisputable endpoint
- Other designs?