Considerations for Discussion of a New Surrogate Endpoint(s) at a Type C PDUFA Meeting Request

Background

As stated in the PDUFA VI commitment letter:

FDA and industry believe that early consultation between review teams and sponsors is important for development programs where the sponsor intends to use a biomarker as a new surrogate endpoint that has never been previously used as the primary basis for product approval in the proposed context of use. Early consultation in the drug development program allows the review team to consult with FDA senior management to evaluate the sponsor's proposal before providing advice regarding the proposed biomarker as a new surrogate endpoint to support accelerated or traditional approval. Requests to engage with FDA on this topic will be considered a Type C meeting request. The purpose of this meeting is to discuss the feasibility of the surrogate as a primary endpoint, and identify any gaps in knowledge and how they might be addressed. The outcome of this meeting may require further investigation by the sponsor and discussion and agreement with the agency before the surrogate endpoint could be used as the primary basis for product approval. To qualify for this consultation, these Type C meeting requests must be accompanied by the complete meeting background package at the time the request is made that includes preliminary human data indicating impact of the drug on the biomarker at a dose that appears to be generally tolerable. The remaining meeting procedures as described in Section I.H of this document [for formal PDUFA meetings between sponsors and FDA] will apply.[1]

Unlike other Type C meetings, sponsors that wish to qualify for a Type C meeting under this commitment will submit a complete meeting background package at the time of their meeting request, which includes preliminary human data indicating impact of the drug on the biomarker at a dose that appears to be generally tolerable.[2] In addition, the cover letter for the background package for this Type C meeting should clearly state that the purpose of the meeting is to discuss a new surrogate endpoint not previously used for accelerated or traditional approval for the proposed context of use.

Procedural information for Type C meetings (e.g., where to submit the meeting background package, timelines for FDA's response, etc.) is discussed in the FDA Draft Guidance: "*Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*." The content and format for the background package for Type C SE meetings must follow these guidelines. In addition, below are some questions for sponsors to consider in preparing their complete meeting background packages. This is not a form but should be used as a guide and incorporated into a comprehensive background package.

[1] PDUFA VI Commitment Letter, Page 22.
[2] PDUFA VI Commitment Letter, Pages 18 and 22.

Relationship of the SE with the Clinical Outcome

Rationale for Using the SE as a Primary Endpoint
• What is the clinical outcome the SE is proposed to predict? • What is the rationale for using an SE rather than the clinical outcome measure (e.g., feasibility, study duration, sample size, etc.)? • What evidence exists to support the relationship between the SE and the clinical outcome of interest (e.g., epidemiologic studies, randomized controlled trials, data generated from therapeutic products from the same class)? • If the SE is proposed based upon prior publications and general scientific community acceptance, discuss the current body of evidence and the use of the SE in clinical studies. • If the disease course is typically acute, what are the expected long-term sequelae and could a change in the SE also reflect these clinical outcomes (e.g., reduction in viral shedding with influenza and reduced incidence of hospitalization due to complications from illness)?
Relationship of the SE with the Causal Pathway(s)
• What is known about the causal pathway(s) for the intended disease? What is the relationship of the SE to this pathway(s)? • Does the intended disease or use have multiple causal pathways? If so, what is the evidence that the specific pathway the SE monitors is the primary pathway leading to the outcome being assessed? • If the SE is on a single causal pathway, what is the evidence that this pathway is the predominant mechanism for pathogenesis? • If the SE is not on the causal pathway, what is the rationale, the evidence, and the strength of evidence that leads to the conclusion that a change in the SE will be predictive of a change in the clinical outcome of interest?
Threshold for Change Required to Demonstrate Clinical Relevance
• How much do changes in the SE reflect changes in the clinical outcome or the probability of the clinical outcome occurring? • What is the extent and timing of change in the SE that would predict the outcome of interest? • Is the change in the SE table or does it only occur for a short time? Would timing of sample collection be feasible? • If a minimum threshold for change has been selected (both size and duration), how was this value determined (include studies conducted and data generated)? If available, is there information about the sensitivity and specificity of any measurement tools used to include?
Consistency of SE Response under Various Conditions
• How does the SE predict the clinical outcome across different subgroups of the targeted population (e.g., demographic, disease severity, co-existing conditions, concomitant medications typical of the population)? • Is there data showing that the SE predicts the clinical response similarly across relevant subgroups?
Reliably Quantifying Changes in the Clinical Outcome Before and After Treatment
• Are there scoring systems or measurement tools commonly used in clinical practice, supported by high grade clinical evidence, and recognized by clinical expert groups to assess baseline disease status and/or the effect of treatment on the clinical outcome? • How specific and sensitive is the current standard to measure the clinical endpoint that the SE is intended to predict?

Relationship of the SE with the Therapeutic Product

Predictive Value of Therapeutic-Induced Changes in the SE
• What is the evidence that a therapeutic-induced change in the SE will be predictive of a change in the clinical outcome (e.g., the SE is a correlate vs. the SE has actual predictive value)?
Off-Target Effects of the Therapeutic Product
• Is there evidence (identified in human or animal studies) to suggest the therapeutic product could affect off-target causal pathways, resulting in harm that may or may not be reflected by changes in the SE? • Are there any pharmacologic effects that could influence the SE but that are unrelated to modifying the disease process (e.g., renal blood flow and creatinine)?

Reliability of the Measurement Tool(s) Used to Detect the SE

Operations Manual
• Does the operations manual include a detailed process from specimen collection to results reporting (e.g., information on sample collection and handling, sample processing, testing, results gathering, and interpretation)?
Performance Characteristics of the Measurement Tool(s)
• To what extent have the performance characteristics of the measurement tool (e.g., sensitivity, specificity, within laboratory precision and between laboratory reproducibility, and sample stability under expected handling conditions) been studied? • Is there a description of the sample type(s) that were used to generate the data for these studies included in the briefing package (e.g., prospective or retrospectively collected patient samples, left-over banked samples, samples spiked with defined levels of analyte)?