



NOVEMBER 27TH, 2018

[Listen to our Audio Podcast](#)



Featuring Dr. Laura Jaeger, Science Policy Analyst for CDER's Biomarker Development and Regulatory Science Team

Resources:

1. [Considerations for Discussion of a New Surrogate Endpoint\(s\) at a Type C PDUFA Meeting Request](#)
2. [PDUFA VI Commitment letter](#)
3. [Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products](#)
4. [Table of Surrogate Endpoints](#)
5. [21st Century Cures Act](#)

Upcoming Events:

1. [SBIA Webinar: FDA Study Data Technical Conformance Guide- Nov. 27 @ 1:30 PM EDT](#)
2. [SBIA Webinar: Final Guidance for Industry: Use of Electronic Health Record Data in Clinical Investigations – Dec. 6 @ 1:00 PM EDT](#)

Early Engagement with FDA to Discuss Novel Surrogate Endpoints

Sponsors planning to use novel surrogate endpoints (SEs) as primary efficacy endpoints can now consult FDA early in the drug development process by requesting Type C IND meetings.

As stated in the [PDUFA VI Commitment letter](#), such meetings will allow FDA to engage with sponsors who would like to employ a biomarker as an SE that has not been used previously as the primary basis for product approval in the proposed context of use. Sponsors who request these meetings will benefit from a discussion about whether the SE could support a traditional or accelerated approval. The meetings will also allow for early identification of any gaps in scientific knowledge and discussion of how they might be addressed.

Meeting Requests: As outlined in the FDA Draft Guidance: "[Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products](#)," the sponsor must include a background package when submitting a meeting request. The background package should include adequate information for the FDA to assess the potential utility of the meeting and to identify FDA staff necessary to discuss proposed agenda items. It should also include summaries of preliminary human data indicating there is an impact of the drug on the biomarker at a dose that appears to be generally tolerable.

The agency will accept or deny the Type C meeting request within 21 calendar days of the request. If accepted, the meeting will occur within 75 calendar days of the request.

Meeting Background Package: *Unlike other Type C meeting requests, a complete meeting background package is due at the time of the meeting request.*

The cover letter for the background package for the Type C meeting should clearly indicate that the purpose of the meeting is to discuss a new SE not previously used for accelerated or traditional approval for the proposed context of use. In the background package, the sponsor should consider including the following information:

- Relationship of the SE with the clinical outcome. For example:
 - *Rationale for using the SE as a primary endpoint:* What clinical outcome is the SE proposed to predict? What is the rationale for using an SE rather than the clinical outcome measure? What evidence exists to support the relationship between the SE and the clinical outcome?
 - *Relationship of the SE with the causal pathway(s):* What is known about the causal pathway(s) for the intended disease, and how does the SE relate to them?



CDER Small Business and Industry Assistance (SBIA)

Division of Drug Information | Office of Communications

10001 New Hampshire Avenue | Hillandale Bldg, 4th Floor | Silver Spring, MD 20993

(866) 405-5367 or (301) 796-6707

CDERSBIA@fda.hhs.gov

www.fda.gov/cdersbia

- *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 stable or does it only occur for a short time? If a minimum threshold for change has been selected (both size and duration), how was this value determined? Is there information about the sensitivity and specificity of any measurement tools used to create this value?
- *Consistency of SE response under various conditions:* How does the SE predict the clinical outcome across different subgroups of the targeted 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 tools supported by clinical evidence and recognized by experts 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 therapeutic product. For example:
 - *Predictive value of therapeutic-induced changes in the SE:* What is the evidence that a therapeutic-induced change in the SE will predict a change in the clinical outcome?
 - *Off-target effects of the therapeutic product:* Is there evidence to suggest that 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?
- Reliability of the measurement tool(s) used to detect the SE. For example:
 - *Operations manual:* Does the operations manual include a detailed process from specimen collection to results reporting?
 - *Performance characteristics of the measurement tool(s):* To what extent have the performance characteristics of the measurement tool 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?

Additional details and questions to consider can be found in the [Considerations for Discussion of a New Surrogate Endpoint\(s\) at a Type C PDUFA Meeting Request](#) document.

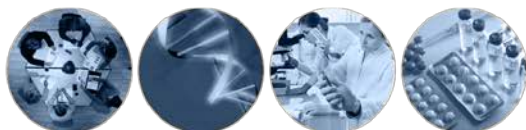
All required documents should be submitted together at the time of the meeting request. CDER strongly suggests that copies of meeting packages be provided in both electronic and paper format. The CDER project manager will advise on the number of desk copies needed for the meeting attendees.

These Type C meetings, in combination with [the Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure](#), described in our last issue, are highly valuable to companies that plan to use novel biomarkers. These two resources are part of FDA's commitment to the goal of expanding existing transparency initiatives, enhancing regulatory science and facilitating drug development, which fulfills [21st Century Cures](#) requirements.

Cheers,
Renu Lal, Pharm.D.
CDER Small Business and Industry Assistance

Issues of this newsletter are archived at <http://www.fda.gov/cdersbiachronicles>

This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.



CDER Small Business and Industry Assistance (SBIA)

Division of Drug Information | Office of Communications

10001 New Hampshire Avenue | Hillendale Bldg, 4th Floor | Silver Spring, MD 20993

(866) 405-5367 or (301) 796-6707

CDERSBIA@fda.hhs.gov

www.fda.gov/cdersbia