FDA Issues Guidance on Demonstrating Substantial Evidence of Effectiveness

The FDA released draft guidance Dec. 20 that complements and expands 21-year-old guidance on demonstrating substantial evidence of effectiveness for drug and biological products.

The 1998 guidance was issued in response to the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105–115), which, provided many examples of the types of evidence that could be considered confirmatory evidence, with a specific focus on adequate and well-controlled trials of the test agent in related populations or indications, as well as a number of illustrations of a single adequate and well-controlled trial supported by convincing evidence of the drug’s mechanism of action in treating a disease or condition.

The FDA noted that while FDAMA introduced a specific new area of flexibility in the evidence needed to support effectiveness, many other characteristics of the evidence support effectiveness that can vary (notably, trial designs, trial endpoints, statistical methodology) and evidence that varies in such ways potentially can provide substantial evidence of choosing for assessment symptoms that are expected to improve with the treatment. FDA encourages sponsors to first explore using existing PRO instruments for assessing subjects’ symptoms before developing a de novo PRO instrument.

- To minimize subject recall error and measurement error, sponsors should use instruments that are administered daily (e.g., 24-hour recall period) and that focus on capturing subjects’ symptoms. Patients should complete the PRO instruments at the same time each day. Improvement in, or resolution of, symptoms should be demonstrated for a meaningful, pre-specified duration of time (e.g., one week), and not based solely on a single day’s assessment.

- For newly developed instruments, or existing instruments that have not been tested in the target patient population, it may be useful for sponsors to test the appropriateness and clarity of any proposed PRO instruments’ instructions, recall period, items and response options by conducting cognitive interviews with a number of patients (e.g., 8 to 10 patients) matching the target population to decrease the possibility of introducing measurement error because of patients’ misunderstanding or incomplete understanding of the PRO instruments.

- When modifying an existing instrument or developing a new PRO, sponsors should consider that Phase 2 trials should help inform finalization of scoring algorithms and endpoint definitions. Piloting the proposed PRO instrument in Phase 2 trials can provide sponsors an opportunity to evaluate the instrument’s psychometric properties and performance (reliability, validity and ability to detect change) as well as provide guidelines for interpreting clinically meaningful within-patient change in scores and confirm the endpoint definition. Pilot results also can inform plans for implementing the proposed instruments in Phase 3 trials. The FDA also recommended sponsors analyze PRO endpoints as continuous or ordinal variables, with the choice’s justification based on the nature of the data, using baseline values as covariates. “The FDA does not recommend a responder analysis endpoint or a percentage change from baseline endpoint unless the targeted response is complete resolution of symptoms,” the guidance said.

- The statistical analysis plan should include prespecified alternative approaches for analysis if extreme outliers occur, such as analyses based on ranks.
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