CDER
SBIA CHRONICLES

NOVEMBER 5TH, 2018

FDA Facilitates the Use of Surrogate Endpoints in Drug Development

Listen to our Audio Podcast

Featuring Abena Agyemanm, PhD, Staff Fellow and Science Policy Analyst for CDER's Biomarker Development and Regulatory Science Team

To enhance the use of surrogate endpoints (SEs) in drug development, expand existing transparency initiatives, and facilitate the development of new and innovative products for patients**,** the FDA has made available additional resources for drug development programs intending to use SEs. One such resource is the Table of Surrogate Endpoints (SEs) That Were the Basis of Drug Approval or Licensure for both traditional and accelerated approval. This table lists SEs the FDA has accepted or could accept as primary efficacy endpoints in drug development programs. In addition, the FDA is also accepting Type C IND meeting requests focused on potential novel SEs that may be used in drug development programs.

What are SEs? An SE is a substitute for measuring an outcome being studied in a clinical trial. It can be a biomarker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is not itself a direct measurement of clinical benefit but is known to predict clinical benefit. Before an SE can be accepted in place of a clinical outcome, there must be extensive evidence showing that it can be relied upon to predict, or correlate with clinical benefit. From a regulatory standpoint, SEs can be characterized by the level of clinical validation:

- *Validated SEs* can reliably predict a clinical outcome, are accepted by FDA as evidence of benefit, and can be used to support traditional approval. They are supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the SE has a specific clinical benefit.
- *Reasonably likely SEs* are, as the name suggests, reasonably likely to predict a clinical benefit. These SEs are supported by strong mechanistic and/or epidemiologic rationale, but the amount of clinical data available is not sufficient to show that they are validated. They can be used to support accelerated approval, but post-approval clinical trials are needed to show that these SEs can be relied upon to predict, or correlate with, clinical benefit.
- *Candidate SEs* are still under evaluation for their ability to predict clinical benefit.

SEs may be used when testing new therapies and new indications for existing therapies. When an SE shows a beneficial effect through appropriate studies, its use may allow clinical trials to be conducted in smaller numbers of patients over shorter periods of time, thereby speeding up drug development.

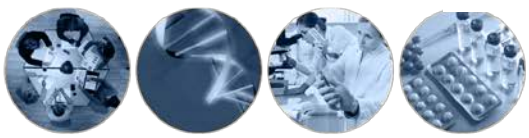
Whereas clinical outcomes directly measure efficacy, SEs involve measuring a substitute that predicts the clinical outcome. SEs may be a good alternative to use in cases where it may take a very long time to see an effect in treatment for a particular disease, or where the clinical benefit of improving the SE is well understood. They may also be used when conducting a clinical endpoint study would be unethical.

Resources:

1. Table of Surrogate Endpoints
2. Type C IND meetings requests
3. Biomarker Qualification Program
4. Public Docket on Publication of SE Table – Comments due by 12/31/18.

Upcoming Events:

1. Clinical Investigator Training Course - November 13-15, 2018
2. TBA - SBIA Webinar: FDA Study Data Technical Conformance Guide- Nov. 27 @ 1:30 EDT



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

Some SEs are a small subclass of biomarkers. In general, a biomarker is a defined characteristic that is objectively measured as an indicator of normal biological processes, pathologic processes, or responses to an exposure or intervention, including therapeutic interventions. In a drug development context, biomarkers may be used for several different purposes, such as identifying patients for clinical trial enrollment, monitoring the safety of a therapy, or finding out if a treatment is having the desired effect on the body. The Biomarker Qualification Program allows drug developers to request regulatory qualification of a biomarker for a particular context of use (e.g., surrogate endpoint for efficacy determination in a clinical trial) in drug development.

Table of Surrogate Endpoints: The Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure lists SEs that sponsors have used as primary efficacy clinical trial endpoints for approval of new drug applications (NDAs) or biologics license applications (BLAs). It also includes SEs that FDA anticipates could be appropriate for use as a primary efficacy clinical trial endpoint for drug or biologic approval, although they have not yet been used to support an approved NDA or licensed BLA.

This is the first time that FDA has publicly compiled SEs into a single resource, thereby providing easily-accessible information about how SEs might be used in clinical trials. The information is intended to provide greater clarity for drug developers on SEs that may be considered and discussed with FDA for individual development programs. It will also help facilitate discussions of potential SEs with FDA review divisions. The table will be updated by CBER and CDER every six months.

Some key considerations and limitations of the SE table include:

- The SE table is intended to facilitate but not replace discussions of individual drug development programs between the sponsor and the appropriate review division.
- The acceptability of the SEs for use in a particular drug or biologic development program will be determined on a case-by-case basis and is context-dependent. In part, it will rely on the disease, patient population, therapeutic mechanism of action, and availability of current treatments.
- An SE should not be assumed to be appropriate for use in a different program in a different clinical setting.
- If an SE was previously used to support accelerated approval of a drug or biologic but subsequent confirmatory trials failed to demonstrate the expected clinical benefit, it would no longer be accepted for this use and is not included on the table.
- The table does not include SEs that may have been accepted for past programs but are no longer acceptable as an endpoint to support registration.
- The table does not include composite endpoints that are a combination of biomarker SEs and clinical endpoints or clinical outcome assessments. If a composite endpoint was composed of multiple biomarker SEs, that information is included on the table.
- The list does not contain product names since an SE is not tied to a specific drug. Because an SE measures what happens in the body, it could be used in the development of multiple drugs for which that measurement is relevant.
- Separate adult and pediatric sections are provided. Pharmacokinetic endpoints that have supported extrapolation from adults to children are not included in the pediatric section.

When an SE clearly predicts a beneficial effect through appropriate studies, its use generally allows for more efficient drug development programs. The use of SEs for certain clinical studies has helped to expedite drug development. As science and technology advance, increased use of biomarkers and SEs will hopefully facilitate the more efficient development of safe and effective medical products.

FDA has established a public docket to receive suggestions and comments on the publication of the SE Table. Please submit comments by December 31. 2018.

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

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

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