Advancing knowledge, awareness,
and education of gene and cell therapy

AMERICAN SOCIETY of GENE & CELL THERAPY

Surrogate Endpoints to Accelerate Gene Therapy Product Development

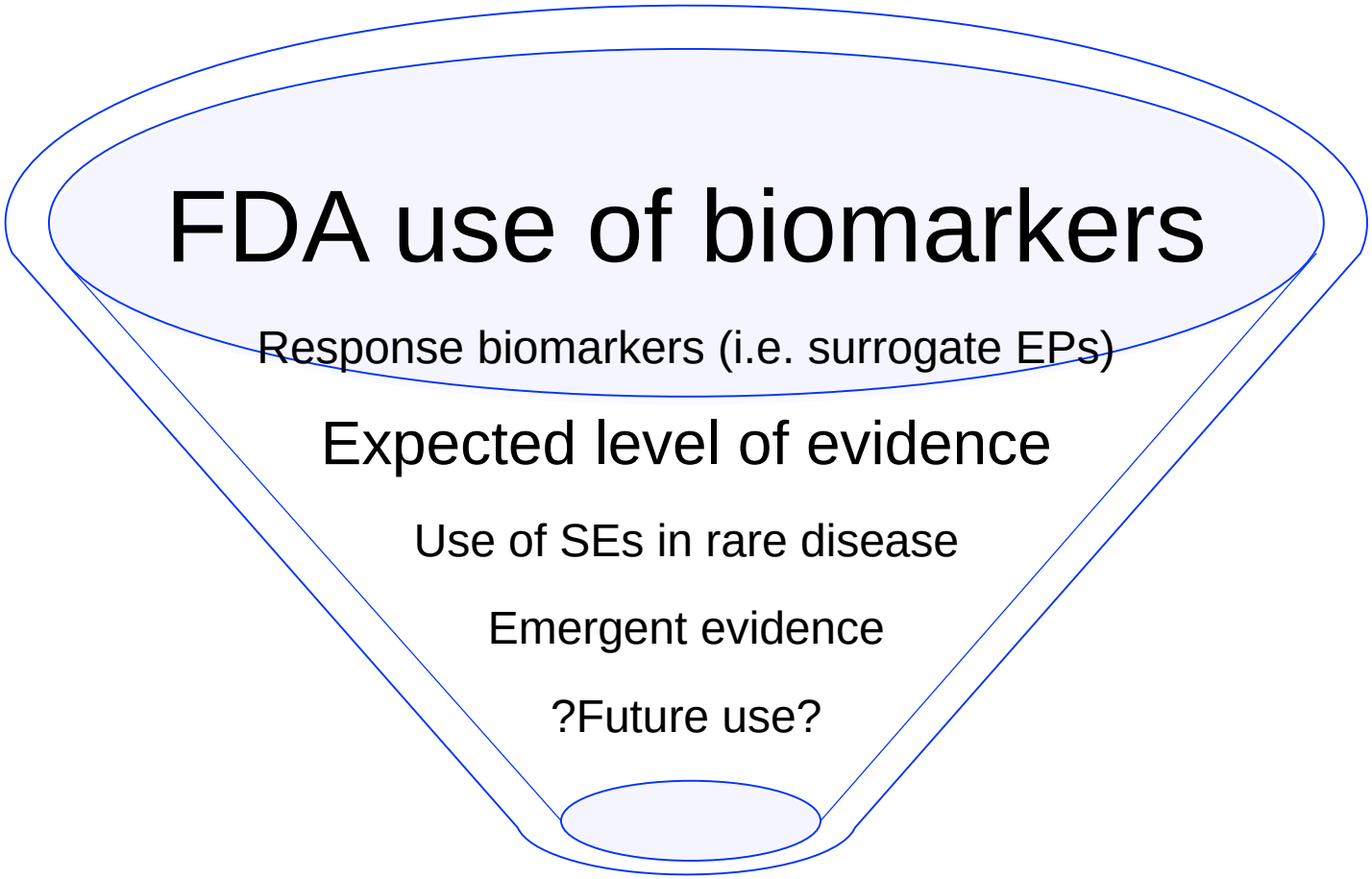
Dan Levy, MD-PhD

ASGCT-FDA Liaison Meeting, 18 November 2019

Disclosure:

Dan Levy is an employee and stockholder of Pfizer, Inc., which is developing potential gene therapies for rare diseases

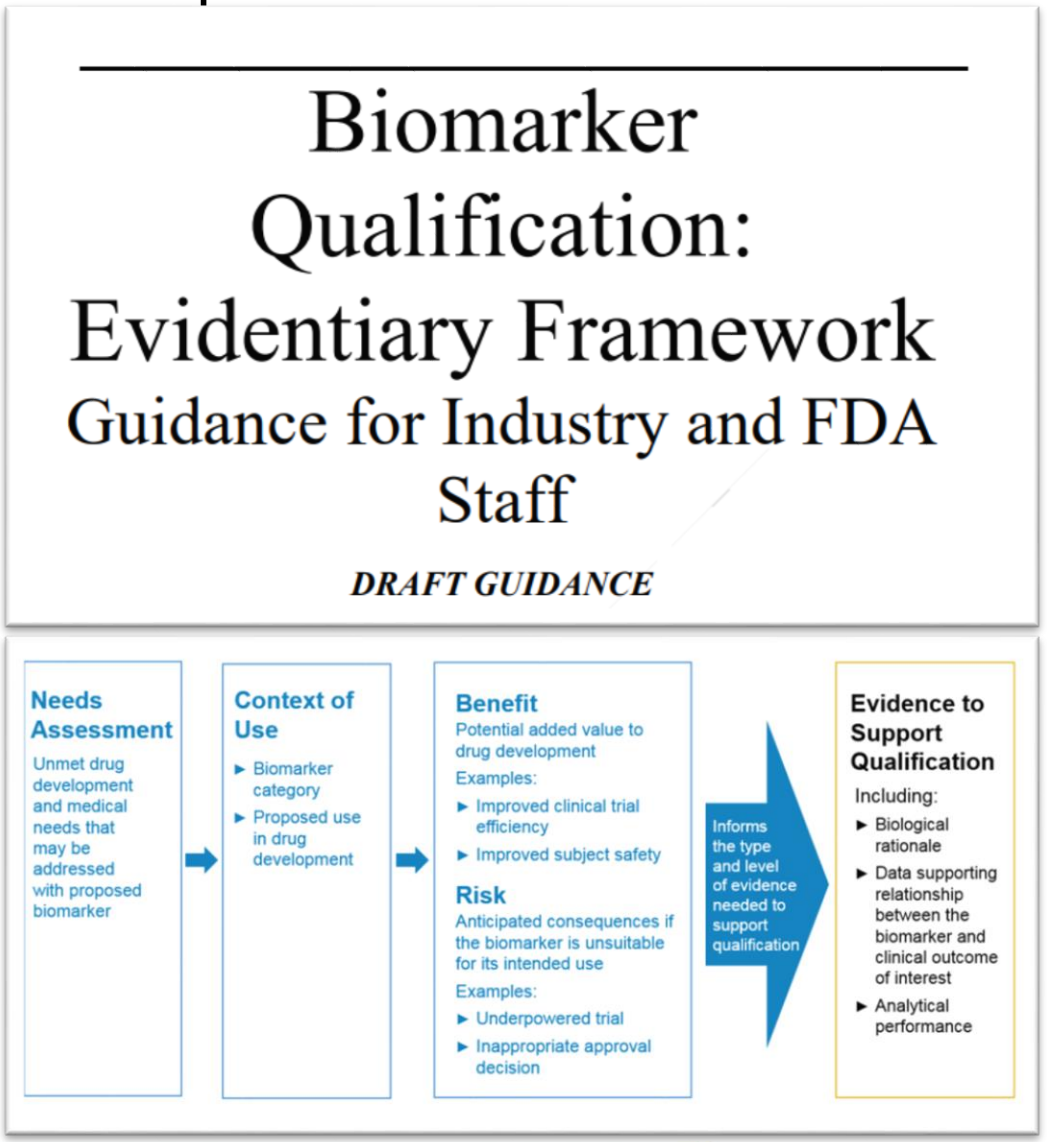
Focus of presentation



Existing guidance

FDA Draft Guidance on biomarker qualification

Despite the clear guidance, additional flexibility and/or clarity around utilization of biomarkers, particularly for use as surrogate endpoints for accelerated approval, is warranted



Categories of Biomarkers

Many types of potential biomarkers

This presentation will focus on pharmacodynamic/response biomarkers

Types of Biomarkers*
diagnostic biomarker
monitoring biomarker
pharmacodynamic/response biomarker (e.g., clinical trial endpoints, including surrogate endpoints)
predictive biomarker
prognostic biomarker
safety biomarker
susceptibility/risk biomarker

https://www.fda.gov/media/122319/download

Biomarkers as Surrogate Endpoints

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.
  - Validated biomarkers should be applicable to gene therapy clinical trials to support traditional approval
- *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.
  - Greater cooperation and discussion is needed to determine the level of evidence to support reasonably likely SEs
- *Candidate SEs* are still under evaluation for their ability to predict clinical benefit.

"FDA Facilitates the Use of Surrogate Endpoints in Drug Development" November 5, 2018 Issue

Download (PDF - 181KB)
Listen to Podcast (MP3) and Transcript

Listen to our Audio Podcast!

Featuring Abena Agyeman, Ph.D.
Staff Fellow and Science Policy Analyst for CDER's Biomarker Development and Regulatory Science Team

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:

Resources:

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

Upcoming Events:

https://www.fda.gov/drugs/fda-facilitates-use-surrogate-endpoints-drug-development-november-5-2018-issue

FDA Commissioner Scott Gottlieb comments:

World Economic Forum Davos, Switzerland Jan 2018

With gene therapy "you're often able to observe the efficacy very early in clinical trials... so the issues that the agency's going to confront are going to be less about determining [efficacy]…and more focused on long term durability and safety and product issues … We're really at an inflection point right now where we are defining the modern rules about how these technologies are going to be regulated. We're going to be looking at accelerated approval endpoints for earlier approval on questions of efficacy with more vigorous long term follow up."

As the majority of gene therapies are intended to treat rare diseases, utilization of accelerated pathways critical

RMAT Designation Opportunities

Language from FDA Guidance document on RMAT program

- Section 506(g) of the FD&C Act, as added by the Cures Act, explains that FDA may grant accelerated approval to products that have received RMAT designation. Under this provision, as appropriate, RMATs may be eligible for accelerated approval based upon previously agreed-upon surrogate or intermediate endpoints that are reasonably likely to predict long-term clinical benefit,
- As further specified in section 506(g)(7) of the FD&C Act, sponsors of products that have been granted RMAT designation and which receive accelerated approval may be able to fulfill the post-approval requirements from clinical evidence obtained from sources other than the traditional confirmatory clinical trials. Under this provision, as appropriate, the post-approval requirements for RMATs receiving accelerated approval may be satisfied by the following….

Greater opportunity to discuss and implement these provisions would benefit the field

https://www.fda.gov/media/120267/download

Potential for Use of Biomarkers in Rare Diseases

Reasonably likely SE may greatly enhance development of drugs for rare diseases

- Approximately 80% of rare diseases are caused by genetic defects
- 75% of RDs affect children
  - the signs and symptoms of many RDs can be observed at birth or during childhood because of genetic nature
- 6–8% of the global population has a rare disease
- 7000 distinct RDs
  - only about 4000 genes have been identified for the 7000 RDs described in the OMIM database

Gene replacement provides unique opportunity for biomarker use, particularly in the setting of rare disease

https://www.intechopen.com/books/role-of-biomarkers-in-medicine/biomarkers-in-rare-genetic-diseases

Past Experience:
Established biomarkers

Diseases & Surrogate EPs used for approval
(small sample)

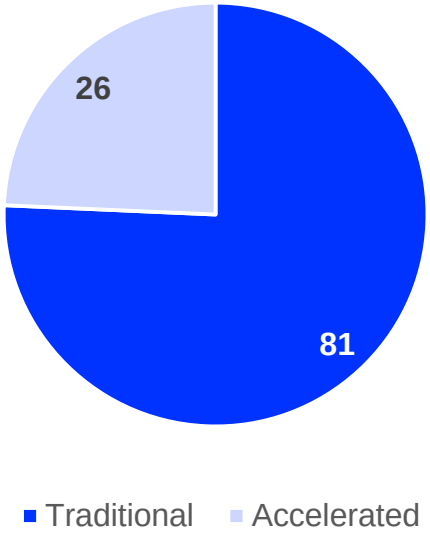
Disease or Use	Patient Population	Surrogate endpoint	Type of approval appropriate for
Alpha-1-antitrypsin deficiency	Patients with congenital alpha-1 antitrypsin deficiency	Plasma alpha-1 proteinase inhibitor	Traditional
Anticoagulation reversal (needed due to life-threatening or uncontrolled bleeding)	Patients treated with a direct or indirect FXa inhibitor when reversal of anticoagulation is needed	Percent change in anti-FXa activity, from baseline to nadir	Traditional
Acetylglutamate Synthase deficiency	Patients with hyperammonemia due to N-acetylglutamate synthase deficiency	Plasma ammonia	Traditional
Acromegaly	Patients with acromegaly who don't respond to or cannot undergo other standard therapies	Serum Insulin-like growth factor-I (IGF-1)	Traditional
Acromegaly	Patients with acromegaly who don't respond to or cannot undergo other standard therapies	Serum growth hormone and serum insulin-like growth factor-I (IGF-1)	Traditional
Acute Bronchospasm	Patients with acute bronchospasm associated with reversible obstructive airway disease or exercise	Forced expiratory volume in 1 second (FEV1)	Traditional
Anthrax vaccine	Persons at high risk of exposure to anthrax	Anti-protective antigen antibody response	Traditional
Asthma	Patients with asthma	Forced expiratory volume in 1 second (FEV1)	Traditional
Cystic fibrosis	Patients with cystic fibrosis	Forced expiratory volume in 1 second (FEV1)	Traditional
Cystinuria	Patients with cystinuria	Urinary/urine cystine	Traditional
Cytomegalovirus (CMV)	CMV seropositive and hemotopoietic transplant recipients requiring prophylaxis	Plasma CMV-DNA exceeding threshold for starting treatment	Traditional
Diphtheria vaccine (in combination vaccines)	Persons to be immunized against diphtheria	Anti-diphtheria toxoid antibody	Traditional
Duchenne muscular dystrophy (DMD)	Patients with DMD who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping	Skeletal muscle dystrophin	Accelerated
Exocrine pancreatic insufficiency	Patients with exocrine pancreatic insufficiency due to cystic fibrosis	Fecal coefficient of fat absorption	Traditional
Fabry disease	Patients with Fabry disease	GL-3 inclusion score in renal interstitial capillary endothelial cells and/or plasma GL-3 levels	Accelerated

https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

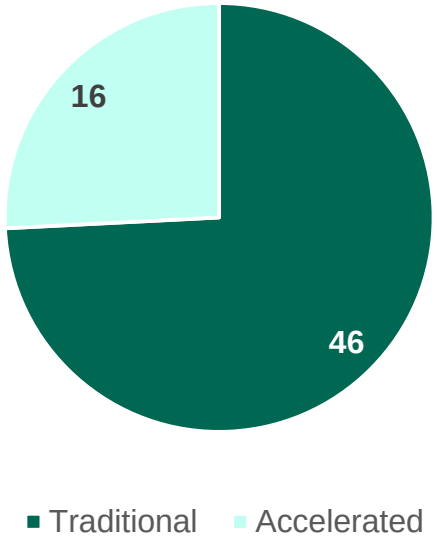
Surrogate EPs Used to Support Approvals

Non-cancer indications

Approvals Using Surrogate Endpoints



Pediatric Approvals Using Surrogate Endpoints



Majority of SE-based approvals have been with validated SEs for traditional approval, and a much smaller fraction of have been with reasonably likely SEs for accelerated approval

https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

Recent Evidence with Biomarkers in Gene Therapy Development Programs

Clotting Factor Activity Accepted by FDA as SE

Draft guidance shows that agency thinking evolved with emergent data

- Several programs have shown correlative evidence
- July 2018 Draft Guidance was first time FDA documented acceptance of factor activity as a viable surrogate endpoint:
  - "Factor activity may be considered as a surrogate endpoint for primary efficacy assessment under the accelerated approval pathway. However, to support the use of this surrogate endpoint, we recommend that you:
    - Resolve discrepancies in factor assay results from various assay methods prior to considering a target factor activity as a surrogate endpoint for primary efficacy assessment.
    - Determine a target factor activity level within the range of factor activity of normal population."

Implication for the development of additional surrogate endpoints:

Additional surrogate endpoints for approval may similarly be based on biomarkers that reflect the activity of the gene that is transferred (e.g., enzyme activity). It would be helpful for sponsors to understand quality and quantity of correlative evidence that led FDA to accept factor activity as a surrogate endpoint.

https://www.fda.gov/media/113799/download

Emergent Evidence on Biomarkers in Gene Therapies:

Can ongoing development programs provide sufficient evidence to support a “reasonably likely” SE?

Ongoing studies of gene therapy may support connectivity between SE and clinical outcome

Several INDs have shared early data that suggests alignment/relationship between biomarker expression and “hard” clinical EP

Implication for the development of additional surrogate endpoints:

Each disease may require specific FDA guidance on the value of the SE, the expectations of the degree of correlation between SE and clinical outcome, and the strength of the clinical outcome, *per se*. However, sponsors will benefit from a general guidance on the considerations for planning a nonclinical/clinical package to support such an relationship that could possibly result in an accelerated or traditional approval.

Recommendation to CBER:

Acknowledgement of established biomarkers (per FDA's SE table) and discussion/guidance regarding pathway for opportunities with emerging data

Established biomarkers
A1AT Deficiency (α1-proteinase inhibitor) Gaucher Disease (platelet count, spleen/liver volume) PKU (Phe)

"Reasonably Likely" biomarkers
DMD (full-length dystrophin) Fabry (GL3) – *the recently issued guidance is helpful*

Emerging Data – opportunities for FDA guidance
XLMTM Beta thalassemia Sickle Cell Disease Dystrophinopathies

Closing Queries

Some Questions:

- Data accumulated from multiple hemophilia GTx studies helped to support an accelerated approval pathway. But what opportunities could exist for an even rarer disease, with only 1-2 investigational programs?
- How can data from prior (non-GTx) ERT programs be used to support an accelerated approval pathway for a gene therapy program?
  - Gene product provides replacement of wild-type enzyme (as with clotting factors etc.)
  - Gene product enzymatically removes harmful metabolites (Pompe, Fabry, etc.)
- How can precedent from full approval using validated surrogates will also apply to gene therapy (e.g. as with ERTs for PKU, A1AT deficiency)?
- What is the level of data needed to transition "reasonably likely" surrogates to validated surrogates for full approval? (ASGCT encourages a totality of evidence approach)
- Can Ph1b/2 data be used to establish SE relationship with outcome, such that registrational trial and BLA filing be based on surrogate?
  - ASGCT supports a consideration of gathering required confirmatory "post-market" data be derived from those very same trial subjects (i.e. can same study/subjects be used to first achieve accelerated approval via the biomarker and then transition to full approval upon subsequent acquisition of confirmatory clinical outcomes from the same trial population
    - This approach may require a specific blinding plan to ensure that review of the patient-level surrogate data remains firewalled from the active study team

Summary

- In cases of high unmet need, use of surrogate endpoints is critically important to align drug development strategies and approval pathways with patient expectations
- Many rare diseases qualify as serious diseases with unmet need. For some of these, SEs could be supported by strong natural history registries, even in cases of relatively small patient populations
- Challenges to use in setting of gene therapies:
  - Urgency to deliver life-impacting treatments to general population
  - Rapidly emerging science/technology (lack of prior data)
  - Replacement of faulty gene product may be entirely novel (lack of prior data)
  - Gene product may not be identical to the wild-type protein (lack of prior data)
- ASGCT believes that – in spite of these challenges – that there may still be reasonable and efficient pathways to achieve either accelerated or traditional approval via SEs
- **Request to FDA** – 1) Provide clarity regarding the recommended meeting forums where novel pathways may be discussed for a program 2) Issue guidance for Industry on the use of SEs in gene therapy programs for rare/ultra-rare conditions

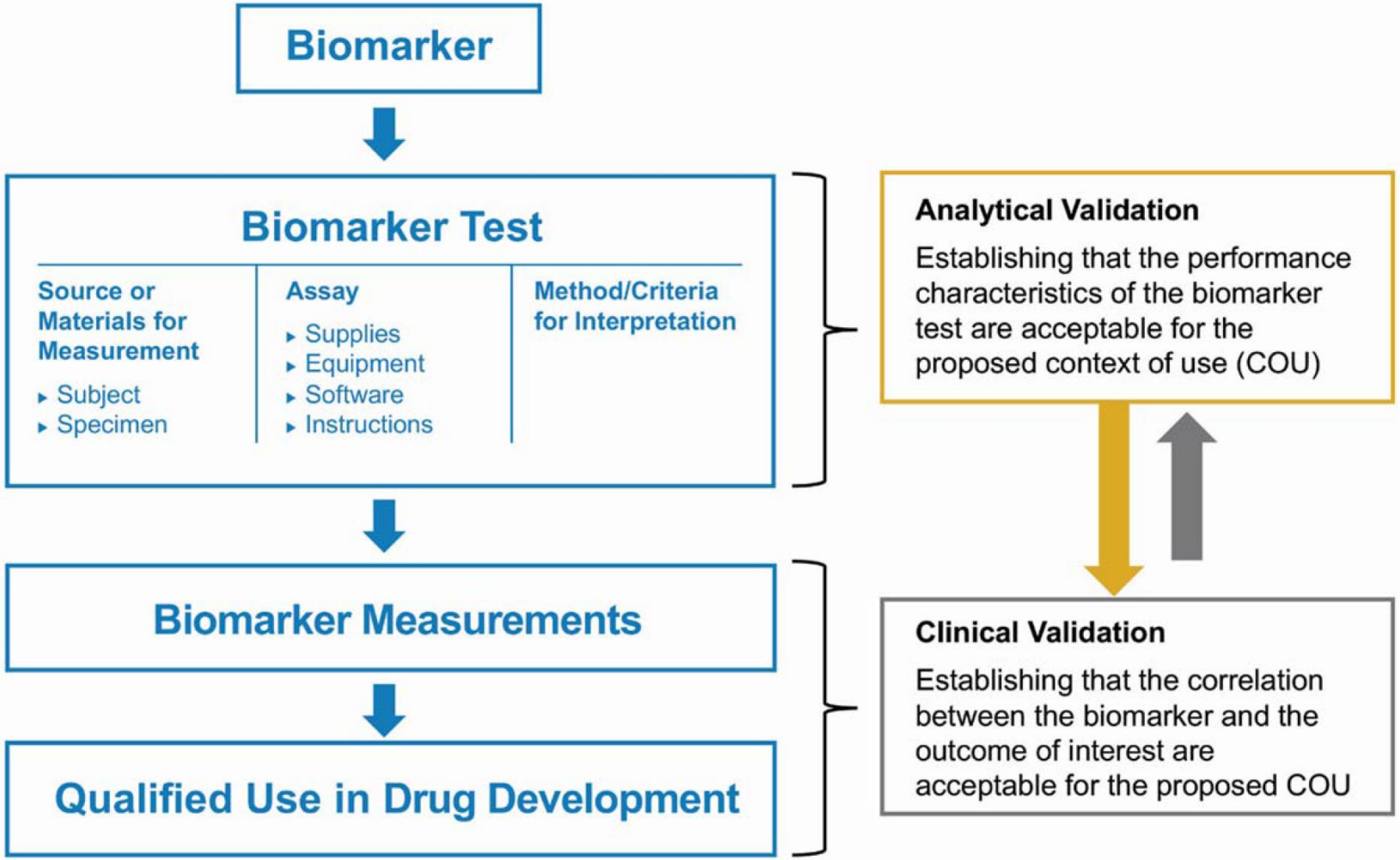
AMERICAN SOCIETY of
GENE & CELL
THERAPY

Advancing knowledge, awareness, and education of gene and cell therapy

Backup Slides

Biomarker Validation Approach

FDA draft guidance



https://www.fda.gov/media/122319/download

Proposed Use

FDA draft guidance

- Purpose of use in drug development (e.g., a prognostic biomarker *to support enrichment of Alzheimer's Disease clinical study/trial populations*, a safety biomarker *to evaluate drug-induced liver injury*)
- Proposed stage of drug development (e.g., phase 1 clinical trials, nonclinical safety studies)
- Clinical trial population or model system (e.g., healthy adult subjects, patients with COPD, rats, cultured mouse fibroblasts)
- Therapeutic mechanism of action (MOA) for which the biomarker is intended to have value, provided that the MOA is relevant to the biomarker's biology and intended utility (e.g., both the MOA and the biomarker are within the same biologic pathway or process)

Workshops convened to discuss the science to support biomarker qualification

- Institute of Medicine Workshop on Biomarker Qualification (2009),
- FDA co-sponsored Biomarkers Workshop with Howard Hughes Medical Institute (2013),
- FDA co-sponsored Brookings meeting on Advancing the Use of Biomarkers and Pharmacogenomics (2014),
- FDA co-sponsored workshop with M-CERSI and the Critical Path Institute on Evidentiary Considerations for Integration of Biomarkers in Drug Development (2015),
- NIH-FDA Workshop on Biomarker Glossary of Terms (2015),
- the National Biomarker Development Alliance's Workshop on Collaboratively Building a Foundation for FDA Biomarker Qualification (2015), and
- Foundation for the NIH-FDA Workshop on Developing an Evidentiary Criteria Framework for Safety Biomarkers Qualification (2016).

https://www.fda.gov/media/122319/download

Other Resources

- BEST (Biomarker, Endpoints, and other Tools)
  - https://www.ncbi.nlm.nih.gov/books/NBK326791/
- Biomarkers Consortium Evidentiary Standards Writing Group: Framework for Defining Evidentiary Criteria for Biomarker Qualification. Final version 10/20/2016. Available at:
  - https://fnih.org/sites/default/files/final/pdf/Evidentiary%20Criteria%20Framework%20Final%20Version%20Oct%2020%202016.pdf
- The PDUFA VI goals letter is available at:
  - https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf

https://www.fda.gov/media/122319/download

Determining Evidence That Is Scientifically Sufficient To Support COU

From FDA draft guidance

- "The evidence sufficient to qualify a biomarker depends on its Context of Use (COU) and the potential benefits and risks associated with its use. The benefits and risks associated with a biomarker's COU drives expectations for the reliability of the biomarker to predict the outcome of interest. If the potential benefits far outweigh the potential risks and/or there are acceptable risk mitigation approaches, there could be increased tolerance for uncertainty. In such a case, the strength of evidence expected to support qualification could be lower. If the potential benefits minimally outweigh the risks of relying on the biomarker, the strength of evidence expected to support qualification should be higher."

- "Ultimately, whether there is sufficient evidence to support qualification of a biomarker for use in drug development depends on the selection of the appropriate biomarker for the proposed COU, the quality of the biomarker measurement, and the correlation of the biomarker with the outcome of interest. Evidence to support qualification consists of data to support clinical validation and analytical validation."

- "The requestor should provide data supporting the relationship between the biomarker and a clinical outcome that reflects how an individual feels, functions, or survives. This relationship should be supported by statistical analyses (see section V.) and should come from multiple independent data sources. Together this information can establish the clinical validity of a biomarker for a specified COU."

https://www.fda.gov/media/122319/download