

FDA-NIH Biomarker Working Group

BEST (Biomarkers, EndpointS, and other Tools) Resource

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Food and Drug Administration (US)
Silver Spring (MD)

National Institutes of Health (US)
Bethesda (MD)

Food and Drug Administration (US), Silver Spring (MD)
National Institutes of Health (US), Bethesda (MD)

The U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH) are joint sponsors of the BEST (Biomarkers, EndpointS, and other Tools) Resource.

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Effective, unambiguous communication is essential for efficient translation of promising scientific discoveries into approved medical products. Unclear definitions and inconsistent use of key terms can hinder the evaluation and interpretation of scientific evidence and may pose significant obstacles to medical product development programs. Lack of clarity and consistency is also problematic in other scientific areas where FDA oversees product safety (e.g., foods and tobacco) to promote public health interests.

In the spring of 2015 the FDA-NIH Joint Leadership Council identified the harmonization of terms used in translational science and medical product development as a priority need, with a focus on terms related to study endpoints and biomarkers. Working together with the goals of improving communication, aligning expectations, and improving scientific understanding, the two agencies developed the BEST (Biomarkers, EndpointS, and other Tools) Resource. The first phase of BEST comprises a glossary that clarifies important definitions and describes some of the hierarchical relationships, connections, and dependencies among the terms it contains.

The BEST glossary aims to capture distinctions between biomarkers and clinical assessments and to describe their distinct roles in biomedical research, clinical practice, and medical product development. Because the glossary is intended to be broadly applicable to multiple communities of users and stakeholders, its definitions address nuances of usage and interpretation for a wide variety of terms currently in use. Further, based on differing stakeholder needs, it has built in flexibility, when possible and appropriate, to accommodate those interests. NIH and FDA intend to use the definitions included in this glossary when communicating on topics related to its contents (e.g., biomarkers) to ensure a consistent use of the terms and therefore, a common understanding of the issues.

The BEST glossary is meant to be a “living” resource that will be periodically updated with additional terms and clarifying information. We welcome [feedback](#), including specific proposed edits with rationale, from all stakeholders, including the scientific and medical communities, patients, providers, industry, and regulators, so that as we refine and elaborate on these terms, they will remain relevant, thus fostering consistent usage and ultimately help to accelerate development and refinement of medical products which lead to improvements in health outcomes. Suggested revisions will be considered on a regular basis.

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Terms and Definitions

accelerated approval

Regulatory mechanism by which new drugs¹ meant to treat serious, life-threatening diseases and that provide meaningful therapeutic benefit to patients over existing treatments can be approved on the basis of adequate and well-controlled clinical trials establishing that the drug has an effect on a reasonably likely surrogate endpoint or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity (intermediate clinical endpoint). Postmarketing confirmatory trials have been required to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit.

Relevant Links:

[FDA/Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics](#)

analytical validation

Establishing that the performance characteristics of a test, tool, or instrument are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol (which may include specimen collection, handling and storage procedures). This is validation of the test's, tool's, or instrument's technical performance, but is not validation of the item's usefulness.

assay

An analytic procedure for detecting or measuring the presence, amount, state or functional activity of a biomarker. An assay is one component of a test, tool, or instrument.

Assessment

The interpretation or the evaluation of the measurement.

¹ References to drugs or drug products include both human drugs and biological drug products regulated by the Food and Drug Administration's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research unless otherwise specified.

biomarker

A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives. Categories of biomarkers include:

- susceptibility/risk biomarker
- diagnostic biomarker
- monitoring biomarker
- prognostic biomarker
- predictive biomarker
- pharmacodynamic/response biomarker
- safety biomarker

Relevant links:

[FDA/Center for Drug Evaluation and Research Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools](#)

[FDA/Center for Drug Evaluation and Research Biomarker Qualification Program Webpage](#)

[FDA/Center for Drug Evaluation and Research Drug Development Tools \(DDT\) Qualification Programs Webpage](#)

[FDA/Center for Devices and Radiological Health Draft Guidance for Industry, Tool Developers, and Food and Drug Administration Staff: Medical Device Development Tools](#)

[FDA/Center for Devices and Radiological Health Medical Device Development Tools \(MDDT\) Webpage](#)

candidate surrogate endpoint

An endpoint still under evaluation for its ability to predict clinical benefit.

clinician-reported outcome

A type of clinical outcome assessment. A measurement based on a report that comes from a trained health-care professional after observation of a patient's health condition. Most ClinRO measures involve a clinical judgment or interpretation of the observable signs, behaviors, or other manifestations related to a disease or condition. ClinRO measures cannot directly assess symptoms that are known only to the patient. ClinRO measures include:

- Reports of particular clinical findings (e.g., presence of a skin lesion or swollen lymph nodes) or clinical events (stroke, heart attack, death, hospitalization for a particular cause), which can be based on clinical observations together with

biomarker data, such as electrocardiogram (ECG) and creatine phosphokinase (CPK) results supporting a myocardial infarction

- Rating scales, such as:
 - Psoriasis Area and Severity Index (PASI) for measurement of severity and extent of a patient's psoriasis
 - Hamilton Depression Rating Scale (HAM-D) for assessment of depression

clinical benefit

A positive clinically meaningful effect of an intervention, i.e., a positive effect on how an individual feels, functions, or survives.

clinical outcome

An outcome that describes or reflects how an individual feels, functions or survives.

clinical outcome assessment

Assessment of a clinical outcome can be made through report by a clinician, a patient, a non-clinician observer or through a performance-based assessment. There are four types of COAs.

- clinician-reported outcome
- observer-reported outcome
- patient-reported outcome
- performance outcome

Relevant links:

[FDA/Center for Drug Evaluation and Research Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools](#)

[FDA/Center for Drug Evaluation and Research Clinical Outcome Assessment Qualification Program Webpage](#)

[FDA/Center for Drug Evaluation and Research Drug Development Tools \(DDT\) Qualification Programs Webpage](#)

[FDA/Center for Devices and Radiological Health Draft Guidance for Industry, Tool Developers, and Food and Drug Administration Staff: Medical Device Development Tools](#)

[FDA/Center for Devices and Radiological Health Medical Device Development Tools \(MDDT\) Webpage](#)

clinical utility

The conclusion that a given use of a medical product will lead to a net improvement in health outcome or provide useful information about diagnosis, treatment, management, or prevention of a disease. Clinical utility includes the range of possible benefits or risks to individuals and populations.

clinical validation

Establishing that the test, tool, or instrument acceptably identifies, measures, or predicts the concept of interest.

ClinRO

See clinician-reported outcome.

COA

See clinical outcome assessment.

COU

See context of use.

concept

In a regulatory context, the concept is the aspect of an individual's clinical, biological, physical, or functional state, or experience that the assessment is intended to capture (or reflect).

content validation

Establishing from qualitative research the extent to which the clinical outcome assessment instrument measures the concept of interest including evidence that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use.

context of use

A statement that fully and clearly describes the way the medical product development tool is to be used and the medical product development-related purpose of the use.

construct validation

Establishing, using quantitative methods, the extent to which the relationships among items, domains, and concepts of a clinical outcome assessment conform to *a priori* hypotheses concerning logical relationships that should exist with other measures or characteristics of patients and patient groups.

criterion validation

Establishing the extent to which the scores of a clinical outcome assessment instrument are related to a known gold standard measure of the same concept. For most COAs, criterion validity cannot be measured because there is no gold standard.

diagnostic biomarker

A biomarker used to identify individuals with the disease or condition of interest or to define a subset of the disease.

- Example: Sweat chloride levels may be used as a diagnostic biomarker to confirm cystic fibrosis.
- Example: Galactomannan may be used as a diagnostic biomarker to classify patients as having probable invasive aspergillosis for enrollment into clinical trials of antifungal agents for treatment of invasive aspergillosis.
- Example: Blood sugar or hemoglobin A1c (HbA1c) may be used as a diagnostic biomarker when evaluating patients to identify diabetes mellitus.
- Example: Blood pressure may be used as a diagnostic biomarker when evaluating patients to identify hypertension.
- Example: Serum creatinine or glomerular filtration rate (GFR) may be used as a diagnostic biomarker when evaluating patients to identify patients with kidney failure.
- Example: Ejection fraction may be used as a diagnostic biomarker in patients with heart failure to identify patients with a subset of disease.

endpoint

A precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined.

expedited access

A voluntary program for certain medical devices that demonstrate the potential to address unmet medical needs for life threatening or irreversibly debilitating diseases or conditions. Under the Expedited Access Pathway (EAP) Program, the FDA works with device sponsors to try to reduce the time and cost from development to marketing decision without changing the FDA's standards.

Relevant Links:

[FDA/ Center for Devices and Radiological Health Guidance for Industry and Food and Drug Administration Staff: Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions](#)

[FDA/ Center for Devices and Radiological Health Expedited Access Pathway Program Webpage](#)

fit-for-purpose — A conclusion that the level of validation associated with a medical product development tool is sufficient to support its context of use.

intended use

The specific clinical circumstance or purpose for which a medical product or test is being developed. In the regulatory context, “intended use” refers to the objective intent of the persons legally responsible for the labeling of medical products.²

intermediate clinical endpoint

In a regulatory context, an endpoint measuring a clinical outcome that can be measured earlier than an effect on irreversible morbidity or mortality (IMM) and that is considered reasonably likely to predict the medical product’s effect on IMM or other clinical benefit. The intermediate clinical endpoint may be a basis for full approval if the effect on the endpoint is considered clinically meaningful. It may also be a basis for accelerated approval if the IMM effect is considered critical for use of the drug or for expedited access for medical devices intended for unmet medical need for life threatening or irreversibly debilitating diseases or conditions.

- Example: Exercise tolerance has been used as an intermediate clinical endpoint in trials of device treatments for heart failure.
- Example: A treatment for preterm labor was approved based on a demonstration of delay in delivery. Under accelerated approval, the sponsor was required to conduct postmarketing studies to demonstrate improved long-term postnatal outcomes.

Relevant Links:

[FDA/Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics](#)

[FDA/Center for Devices and Radiological Health Guidance for Industry and Food and Drug Administration Staff: Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions](#)

[FDA/ Center for Devices and Radiological Health Expedited Access Pathway Program Webpage](#)

measurement

The obtained value using a test, tool, or instrument.

medical product development tool

Methods, materials, or measurements used to assess the effectiveness, safety, or performance of a medical product. In a regulatory context, examples of MPDTs are

² 21 CFR 201.128

clinical outcome assessments, assessments of biomarkers, and non-clinical assessment methods or models.

Relevant links:

[FDA/Center for Drug Evaluation and Research Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools](#)

[FDA/ Center for Drug Evaluation and Research Animal Model Qualification Program Webpage](#)

[FDA/Center for Drug Evaluation and Research Biomarker Qualification Program Webpage](#)

[FDA/Center for Drug Evaluation and Research Clinical Outcome Assessment Qualification Program Webpage](#)

[FDA/Center for Drug Evaluation and Research Drug Development Tools \(DDT\) Qualification Programs Webpage](#)

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[FDA/Center for Devices and Radiological Health Medical Device Development Tools \(MDDT\) Webpage](#)

MPDT

See medical product development tool.

monitoring biomarker

A biomarker measured serially and used to detect a change in the degree or extent of disease. Monitoring biomarkers may also be used to indicate toxicity or assess safety, or to provide evidence of exposure, including exposures to medical products.

- Example: Hepatitis C virus ribonucleic acid (HCV-RNA) may be used as a monitoring biomarker when assessing patients with chronic hepatitis C to evaluate disease status or burden.
- Example: International normalized ratio (INR) or prothrombin time (PT) may be used as a monitoring biomarker for patients on warfarin.
- Example: Prostate-specific antigen (PSA) may be used as a monitoring biomarker when assessing patients with prostate cancer to evaluate disease status or burden.
- Example: Cancer antigen 125 (CA 125) may be used as a monitoring biomarker when assessing patients with ovarian cancer to evaluate disease status or burden.
- Example: B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP) may be used as a monitoring biomarker during follow-up to supplement clinical decision making in pediatric patients with pulmonary hypertension.

observer-reported outcome

A type of clinical outcome assessment. A measurement based on a report of observable signs, events or behaviors related to a patient's health condition by someone other than the patient or a health professional. Generally, ObsROs are reported by a parent, caregiver, or someone who observes the patient in daily life and are particularly useful for patients who cannot report for themselves (e.g., infants or individuals who are cognitively impaired). An ObsRO measure does not include medical judgment or interpretation. ObsRO measures include:

- Rating scales, such as:
 - Acute Otitis Media Severity of Symptoms scale (AOM-SOS), a measure used to assess signs and behaviors related to acute otitis media in infants
 - Face, Legs, Activity, Cry, Consolability scale (FLACC), a measure used to assess signs and behaviors related to pain
- Counts of events (e.g., observer-completed log of seizure episodes)

ObsRO

See observer-reported outcome.

outcome

The measurable characteristic (clinical outcome assessment, biomarker) that is influenced or affected by an individual's baseline state or an intervention as in a clinical trial or other exposure.

outcome assessment

An assessment of an outcome that results in recorded data point(s) (e.g., for a biomarker or clinical outcome assessment).

patient-reported outcome

A type of clinical outcome assessment. A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's response. Symptoms or other unobservable concepts known only to the patient can only be measured by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also be observable by others. PRO measures include:

- Rating scales (e.g., numeric rating scale of pain intensity or Minnesota Living with Heart Failure Questionnaire for assessing heart failure)
- Counts of events (e.g., patient-completed log of emesis episodes or micturition episodes)

PerfO

See performance outcome.

performance outcome

A type of clinical outcome assessment. A measurement based on a task(s) performed by a patient according to instructions that is administered by a health care professional. PerfOs require patient cooperation and motivation. PerfO measures include:

- Measures of gait speed (e.g., timed 25 foot walk test)
- Measures of memory (e.g., word recall test)

pharmacodynamic/response biomarker

A biomarker used to show that a biological response has occurred in an individual who has received an intervention or exposure.

- Example: Circulating CD20-positive B lymphocytes may be used as a pharmacodynamic/response biomarker when evaluating patients with systemic lupus erythematosus to assess response to a B-lymphocyte stimulator inhibitor.
- Example: Blood pressure may be used as a pharmacodynamic/response biomarker when evaluating patients with hypertension to assess response to an antihypertensive agent or sodium restrictions.
- Example: Cholesterol may be used as a pharmacodynamic/response biomarker when evaluating patients with hypercholesterolemia to assess response to a lipid-lowering agent or dietary changes.
- Example: Hemoglobin A1c (HbA1c) may be used as a pharmacodynamic/response biomarker when evaluating patients with diabetes to assess response to antihyperglycemic agents or lifestyle changes.
- Example: Sweat chloride may be used as a pharmacodynamic/response biomarker when evaluating patients with cystic fibrosis to assess response to antihyperglycemic agents.
- Examples: International normalized ratio (INR) may be used as a pharmacodynamic/response biomarker when evaluating a patient's response to warfarin treatment.
- Examples: Viral load may be used as a pharmacodynamic/response biomarker when evaluating response to antiretroviral treatment.

predictive biomarker

A biomarker used to identify individuals who are more likely than similar patients without the biomarker to experience a favorable or unfavorable effect from a specific intervention or exposure.

- Example: Epidermal Growth Factor Receptor (EGFR) mutations may be used as a predictive biomarker when evaluating non-small cell lung cancer patients to select patients for anti-EGFR drug therapy.

- Example: BReast CAncer genes 1 and 2 (BRCA1/2) mutations may be used as a predictive biomarker when evaluating women with ovarian cancer to assess the likelihood of response to Poly (ADP-ribose) polymerase (PARP) inhibitors.
- Example: Potassium channel, inwardly rectifying subfamily J, member 11 (KCNJ11) mutations may be used as predictive biomarkers when evaluating children with diabetes to identify a genetic etiology that is amenable to sulfonylurea treatment.
- Example: Human leukocyte antigen allele (HLA)-B*5701 genotype may be used as a predictive biomarker when evaluating human immunodeficiency virus (HIV) patients before abacavir treatment to identify the risk for severe skin reactions.
- Example: Certain Cystic fibrosis transmembrane conductance regulator (CFTR) mutations may be used as predictive biomarkers when evaluating patients with cystic fibrosis to select patients for treatment with ivacaftor.
- Example: Thiopurine methyltransferase (TPMT) genotype or activity may be used as predictive biomarkers when evaluating patients who may be treated with 6-mercaptopurine or azathioprine to identify those at risk for severe toxicity because of high drug concentrations.

PRO

See patient-reported outcome.

prognostic biomarker

A biomarker used to identify likelihood of a clinical event, disease recurrence or progression.

- Example: BReast CAncer genes 1 and 2 (BRCA1/2) mutations may be used as a prognostic biomarker when evaluating women with breast cancer to assess the likelihood of a second breast cancer.
- Example: Chromosome 17p deletions may be used as a prognostic biomarker when evaluating patients with chronic lymphocytic leukemia to assess the likelihood of death.
- Example: Prostate-specific antigen (PSA) may be used as a prognostic biomarker when evaluating patients with prostate cancer at diagnosis to assess the likelihood of cancer progression.
- Example: Plasma fibrinogen may be used as a prognostic biomarker to select patients with chronic obstructive pulmonary disease at high risk for exacerbation and/or all-cause mortality for inclusion in interventional clinical trials.
- Example: C-reactive protein (CRP) levels may be used as a prognostic biomarker to identify adult patients with a greater likelihood of coronary artery disease events.
- Example: Gleason score may be used as a prognostic biomarker when evaluating patients with prostate cancer to assess the likelihood of cancer progression.
- Example: Total kidney volume may be used as a prognostic biomarker to select patients with autosomal dominant polycystic kidney disease at high risk for progressive decline in renal function for inclusion in interventional clinical trials.

- Example: Peak VO₂ <15 ml/kg/min and pulmonary vascular resistance/systemic vascular resistance > 1.0 may be used as prognostic biomarkers when evaluating severity of pulmonary hypertension in pediatric patients.

qualification

A conclusion, based on a formal regulatory process, that within the stated context of use, a medical product development tool can be relied upon to have a specific interpretation and application in medical product development and regulatory review.

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[FDA/Center for Drug Evaluation and Research Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools](#)

[FDA/ Center for Drug Evaluation and Research Animal Model Qualification Program Webpage](#)

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[FDA/Center for Devices and Radiological Health Medical Device Development Tools \(MDDT\) Webpage](#)

reasonably likely surrogate endpoint

An endpoint supported by clear mechanistic and/or epidemiologic rationale but insufficient clinical data to show that it is a validated surrogate endpoint. Such endpoints can be used for accelerated approval for drugs or expedited access for medical devices. In the case of accelerated approval for drugs, additional trial data, assessing the effect of the intervention on the clinical benefit endpoint of interest will be collected in the post-marketing setting to verify whether an effect on the reasonably likely surrogate actually predicts clinical benefit in the specific context under study.

- Example: Outcomes of 6-month follow-up treatment (i.e., sputum culture status and infection relapse rate) have been considered reasonably likely to predict the resolution of pulmonary tuberculosis and have supported accelerated approval of drugs to treat tuberculosis.

- Example: Decrease in iron stores for patients with iron overload caused by thalassemia has been considered reasonably likely to predict a decrease in transfusion-related adverse events caused by iron overload in the body and have supported accelerated approval of drugs to treat non-transfusion-dependent thalassemia (NTDT).
- Example: Radiographic evidence of tumor shrinkage (response rate) and progression free survival in certain cancer types have been considered reasonably likely to predict an improvement in overall survival with certain therapies and have supported accelerated approval of drugs to treat these cancer types.

safety biomarker

A biomarker used to indicate the presence or extent of toxicity related to an intervention or exposure.

- Example: Hepatic aminotransferases may be used as safety biomarkers when evaluating potential hepatotoxicity.
- Example: Serum creatinine may be used as a safety biomarker when evaluating patients on drugs that affect kidney function to monitor for nephrotoxicity.
- Example: Urinary kidney biomarkers (Kim-1, Albumin, Total Protein, β 2 Microglobulin, Urinary Clusterin, Urinary Trefoil Factor 3 and Urinary Cystatin C) may be used as safety biomarkers in animal studies for the detection of acute drug-induced nephrotoxicity, either tubular or glomerular with associated tubular involvement.
- Example: Corrected QT interval (QTc) may be used as a safety biomarker to assess the potential for drugs to induce Torsades de Pointes.

surrogate endpoint

An endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

From a U.S. regulatory standpoint, surrogate endpoints and potential surrogate endpoints can be characterized by the level of clinical validation:

- validated surrogate endpoint
- reasonably likely surrogate endpoint
- candidate surrogate endpoint

Relevant Links:

[FDA/Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics](#)

FDA/ Center for Devices and Radiological Health Guidance for Industry and Food and Drug Administration Staff: Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions

FDA/ Center for Devices and Radiological Health Expedited Access Pathway Program Webpage

susceptibility/risk biomarker

A biomarker that indicates the potential for developing a disease or medical condition or sensitivity to an exposure in an individual without clinically apparent disease or medical condition.

- Example: BReast CANcer genes 1 and 2 (BRCA1/2) mutations may be used as a susceptibility/risk biomarker to identify individuals with a predisposition to develop breast cancer.
- Example: Factor V Leiden may be used as a susceptibility/risk biomarker to identify individuals with a predisposition to develop deep vein thrombosis (DVT).
- Example: Apolipoprotein E (APOE) gene variations may be used as a susceptibility/risk biomarker to identify individuals with a predisposition to develop earlier onset of Alzheimer's disease.
- Example: Infection with certain human papillomavirus (HPV) subtypes may be used as a susceptibility/risk biomarker to identify individuals with a higher likelihood to develop cervical cancer.

test, tool, or instrument — An assessment system comprising three essential components: 1) materials for measurement; 2) an assay for obtaining the measurement; and 3) method and/or criteria for interpreting those measurements.

validated surrogate endpoint

An endpoint supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a clinical benefit. Therefore, it can be used to support traditional approval without the need for additional efficacy information.

- Example: Hemoglobin A1c (HbA1c) reduction is a validated surrogate endpoint for reduction of microvascular complications associated with diabetes mellitus and has been used for the basis for approval of drugs intended to treat diabetes mellitus.
- Example: HIV-RNA reduction is a validated surrogate endpoint for human immunodeficiency virus (HIV) clinical disease control and has been used for the basis for approval of drugs intended to treat HIV.
- Example: Low-density lipoprotein (LDL) cholesterol reduction is a validated surrogate endpoint for reduction of cardiovascular events and has been used for the basis for approval of statins.

- Example: Blood pressure reduction is a validated surrogate endpoint for reduction in rates of stroke, myocardial infarction, and mortality and has been used for the basis for the approval of drugs intended to treat hypertension.

validation

Establishing that the performance of a test, tool, or instrument is acceptable for its intended purpose. Elements of validation include but are not limited to the following:

- analytical validation
- clinical validation

The following apply to clinical outcome assessments:

- construct validation
- content validation
- criterion validation