Validation and Calibration

Definitions and Terminology

ACCEPTANCE CRITERIA: The specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan that are necessary for making a decision to accept or reject a lot or batch of raw material, intermediate, packaging material, or active pharmaceutical ingredient. This term can also be applied to validation.
(FDA Guidance, part 7. Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients. Draft).

ACCURACY - The degree of agreement between a measured value and the accepted reference value.
(National Institute for Occupational Safety and Health, U. S. NIOSH Manual of Analytical Methods. 2003).

Options:

ACCURACY - The degree of correlation with the value achieved by the previous method *(WHO Polio Manual 2 (3.2), 2005).*

ACCURACY - The degree of closeness of the determined value to the nominal or known true value under prescribed conditions. This is sometimes termed *trueness*. *(FDA. Guidance for industry. Bioanalytical Method Validation, 2001).*

ACCURACY OF MEASUREMENT- Closeness of the agreement between the result of a measurement and a true value of the measurement. *(ISO 15189:2007, Medical laboratories - Particular requirements for quality and competence)*

ACTION LIMITS - The range limits which include 99.7 % of the results (±3 standard deviations). Any results laying outside these limits requires an immediate corrective action.
(ISRAC Policy and evaluation of control Testing Performed by Accredited Testing & Calibrations Laboratories, 1-681001, version 03, 2008)

ALERT LIMITS - CONTROL LIMITS - The range limits that include all 95% of the results (±2 standard deviations). These limits are also named the warning limits.
(ISRAC Policy and evaluation of control Testing Performed by Accredited Testing & Calibrations Laboratories, 1-681001, version 03, 2008)

BATCH (or LOT) - A defined quantity of starting material, or product processed in a single process or series of processes so that it is expected to be homogeneous.
(WHO. Quality assurance of pharmaceuticals: a compendium of guidelines, v.2 (GMP), 2004).

BIAS - The difference between the expectation of the test results and an accepted reference value. Bias is the total systematic error as contrasted to random error. There may be one or more systematic error components contributing to the bias. A larger systematic difference from the accepted reference value is reflected by a larger bias value.
(ISO 3534-1: 2006 Statistics -- Vocabulary and symbols)

BIOLOGICAL MATRIX - A discrete material of biological origin that can be sampled and processed in a reproducible manner. Examples are blood, serum, plasma, urine, feces, saliva, sputum, and various discrete tissues.
(FDA. Guidance for industry. Bioanalytical Method Validation, 2001).

BLANK - A sample of a biological matrix to which no analytes have been added that is used to assess the specificity of the bioanalytical method.
(FDA. Guidance for industry. Bioanalytical Method Validation, 2001).

CALIBRATION - The set of operations that establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by material measure and the corresponding values of the measurand.
(National Conference of Standards Laboratories, NCSL RP-1, 1996).

Options:

CALIBRATION - An operation that, under specified conditions, in **a first step** establishes a relation between the quantity values with "*measurement uncertainties*" provided by measurement standards and corresponding indications with associated "*measurement uncertainties*" and, in **a second step**, uses this information to establish a relation for obtaining a measurement result from an indication. *(Analytical Methods and reference Materials program, AMRM Glossary, NIH, USA, 2009)*

CALIBRATION - The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a traceable standard over an appropriate range of measurements. *(FDA Guidance, part 7. Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients. Draft).*

CALIBRATION INTERNAL - Calibration of the laboratory equipment is performed by the laboratory according to its requirements. A laboratory accredited to Internal Calibration is not accredited for selling calibration services to outside customers.
(ISRAC Policy on - Traceability and Uncertainty of Measurement, 1-661002, version 07, 2009)

CALIBRATION STANDARD - A biological matrix to which a known amount of analyte has been added or *spiked*. Calibration standards are used to construct calibration curves from which the concentrations of analytes in QCs and in unknown study samples are determined.
(FDA. Guidance for industry. Bioanalytical Method Validation, 2001).

CALIBRATION GRAPH - Plot of analytical response vs. known mass or concentration of analyte.
*(National Institute for Occupational Safety and Health, U. S. NIOSH Manual of Analytical Methods. 2003)***.**

Options:
CALIBRATION (standard) CURVE - The relationship between instrument response and known concentrations of the analyte.
(FDA. Guidance for industry. Bioanalytical Method Validation, 2001).

CRITICAL OPERATION - An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.
(WHO. Quality assurance of pharmaceuticals: a compendium of guidelines, v.2 (GMP), 2004).

CROSS-VALIDATION - A comparison of validation parameters when two or more bioanalytical methods are used to generate data within the same study or across different studies. An example of cross-validation would be a situation where an original validated bioanalytical method serves as the *reference* and the revised bioanalytical method is the *comparator.*
(FDA. Guidance for industry. Bioanalytical Method Validation, 2001).

EXAMINATION - Set of operations having the object of determining the value or characteristics of a property. In some disciplines (e.g. microbiology) an examination is the total activity of a number of tests, observations or measurements. *(ISO 15189:2007, Medical laboratories - Particular requirements for quality and competence).*

GMP (Good Manufacturing Practice) - All elements in the established practice that will collectively lead to final products or services that consistently meet appropriate specifications and compliance with national and international regulations.
(PIC/S GMP Guide for blood establishments, PE 005-2, 2004)

IN-PROCESS CONTROL - Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specification.
(WHO. Quality assurance of pharmaceuticals: a compendium of guidelines, v.2 (GMP), 2004).

INSTALATION QUALIFICATION - Establishing confidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerances.
(FDA, "Guidelines on General Principles of Process Validation." Rockville, MD, May 1993, updated 2009.).

LINEARITY - The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.
(FDA. Guideline for Industry. Text on Validation of Analytical Procedures, ICH-Q2A, 1995).

LOD - Limit of detection - Smallest amount of analyte which can be distinguished from background.
(National Institute for Occupational Safety and Health, U. S. NIOSH Manual of Analytical Methods. 2003).

Options:
LOD - The lowest concentration of an analyte that the bioanalytical procedure can reliably differentiate from background noise. *(FDA. Guidance for industry. Bioanalytical Method Validation, 2001).*

LOQ - Limit of quantification - The lowest (**LLOQ - Lower Limit)** or highest **(ULOQ - Upper Limit)** amount of an analyte in a sample that can be quantitatively determined with suitable precision and accuracy.
(FDA. Guidance for industry. Bioanalytical Method Validation, 2001).

MATRIX EFFECT - The direct or indirect alteration or interference in response due to the presence of unintended analytes (for analysis) or other interfering substances in the sample.
(FDA. Guidance for industry. Bioanalytical Method Validation, 2001).

MEASUREMENT- Set of operations having the object of determining a value of a quantity. *(ISO 15189:2007, Medical laboratories - Particular requirements for quality and competence).*

MEDIA BLANK - An unexposed sampler, not taken to the field or shipped, used for background correction of sample readings or for recovery studies.
(National Institute for Occupational Safety and Health, U. S. NIOSH Manual of Analytical Methods. 2003).

METHOD - A comprehensive description of all procedures used in sample analysis.
(FDA. Guidance for industry. Bioanalytical Method Validation, 2001).

PACKAGING MATERIAL - Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.
(WHO. Quality assurance of pharmaceuticals: a compendium of guidelines, v.2 (GMP), 2004)

PRECISION - The repeatability or reproducibility of individual measurements expressed as standard deviation (SD), or relative standard deviation (CV).
*(National Institute for Occupational Safety and Health, U. S. NIOSH Manual of Analytical Methods. 2003)***.**

Options:
PRECISION - The variation of the results as represented by the standard deviation or the coefficient of variation. *(WHO Polio Manual 2 (3.2), 2005).*

PRECISION - The closeness of agreement (*degree of scatter*) between a series of measurements obtained from multiple sampling of the same homogenous sample under the prescribed conditions. *(FDA. Guidance for industry. Bioanalytical Method Validation, 2001).*

PROFICIENCY TESTING - Any interlaboratory testing program where stable specimens are sent to participating laboratories for analysis. Results from all participating laboratories are compared, pooled, and tabulated by the testing program operator with the purpose of improving laboratory performance.
(National Institute for Occupational Safety and Health, U. S. NIOSH Manual of Analytical Methods. 2003)**.**

QUALIFICATION - The action of proving that any equipment or process works correctly and consistently and produces the expected results. Qualification is part of, but not limited to, a validation process, i.e., installation qualification (IQ), operation qualification (OQ), and performance qualification (PQ).
(FDA Guidance, part 7. Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients. Draft).

QUALITY ASSURANCE - The sum total of the organized activities performed with the intent to ensure that all APIs are of the quality required for their intended use.
(FDA Guidance, part 7. Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients. Draft).

Options:
QUALITY ASSURANCE - All planned and systematic activities implemented within the quality system and demonstrated as needed to provide adequate confidence that an entity will fulfil requirements for quality.
(PIC/S GMP Guide for blood establishments, PE 005-2, 2004)

QUALITY CONTROL - Operational techniques and activities that are used to fulfill the requirements for quality in compliance with the specification.
(PIC/S GMP Guide for blood establishments, PE 005-2, 2004)

QUALITY CONTROL UNIT - Any person or organizational element designated by the firm to be responsible for the duties relating to quality control.
(FDA Guidance, part 7. Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients. Draft).

QUALITY MONITORING - That part of a quality assurance program concerned with maintenance and improvement of quality which deals with the identification and use of indicators to detect variations from standards or specifications.
(PIC/S GMP Guide for blood establishments, PE 005-2, 2004)

QUARANTINE - The status of materials isolated physically or by other effective means pending a decision on their subsequent use.
(FDA Guidance, part 7. Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients. Draft).

RANGE - The interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.
(FDA. Guideline for Industry. Text on Validation of Analytical Procedures, ICH-Q2A, 1995).

RAW MATERIAL - Any ingredient intended for use in the production of APIs. These may include starting materials, process aids, solvents, and reagents.
(FDA Guidance, part 7. Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients. Draft).

REPRODUCIBILITY - The precision of the procedure when it is performed under different conditions.
(WHO Polio Manual 2 (3.2), 2005).

Options:
REPRODUCIBILITY - The precision between two laboratories. It also represents precision of the method under the same operating conditions over a short period of time. *(FDA. Guidance for industry. Bioanalytical Method Validation, 2001).*

REFERENCE MATERIAL - A generic term that refers to a material or substance whose property values are sufficiently homogeneous and stable with respect to one or more specified properties, and whose fitness is well established for its intended use in a measurement process (e.g., calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials).
(*Analytical Methods and reference Materials program, AMRM Glossary, NIH, USA, 2009).*

REFERENCE VALUE - ASSIGNED VALUE - The quantitative or qualitative value that is assigned (accepted by convention as being the true value with known and acceptable uncertainty) to a Control Test Sample or primary standards.
(ISRAC Policy and evaluation of control Testing Performed by Accredited Testing & Calibrations Laboratories, 1-681001, version 03, 2008).
ACCEPTED REFERENCE VALUE - A value that serves as an agreed-upon reference for comparison, and which is derived as:
a) a theoretical or established value, based on scientific principles;
b) an assigned or certified value, based on experimental work of some national or international organization
c) a consensus or certified value, based on collaborative experimental work under the auspices of a scientific or engineering group
d) when a), b) and c) are not available, the expectation of the (measurable) quantity, i.e. the mean of a specified population of measurements
(ISO 3534-1: 2006 Statistics -- Vocabulary and symbols)

ROBUSTNESS - ability to provide accurate and precise results under a variety of conditions.
(WHO Polio Manual 2 (3.2), 2005).

RUGGEDNESS - Partial or complete analysis of variance using experiments in which operational parameters of a sampling and measurement method are varied within a small range to determine their effect on overall variance.
(National Institute for Occupational Safety and Health, U. S. NIOSH Manual of Analytical Methods. 2003).

SAMPLE - One or more parts taken from a system and intended to provide information on the system, often to serve as a basis for decision on the system or its production. *(ISO 15189:2007, Medical laboratories - Particular requirements for quality and competence).*

SELECTIVITY - The ability of the bioanalytical method to measure and differentiate the analytes in the presence of components that may be expected to be present. These could include metabolites, impurities, degradants, or matrix components.
(FDA. Guidance for industry. Bioanalytical Method Validation, 2001).

SENSITIVITY - capacity of the test procedure to record small variations between concentrations.
(WHO Polio Manual 2 (3.2), 2005)

SPECIFICATION - A list of detailed requirements with which the products or material used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.
(WHO. Quality assurance of pharmaceuticals: a compendium of guidelines, v.2 (GMP), 2004)

SPECIFICITY - the degree of uniformity of the response to the substance in question.
(WHO Polio Manual 2 (3.2), 2005).

SPIKE - A known mass of analyte added to a sampler for the purpose of determining recovery (analyst spikes), or for quality control (blind spikes).
(National Institute for Occupational Safety and Health, U. S. NIOSH Manual of Analytical Methods. 2003).

STABILITY - The chemical stability of an analyte in a given matrix under specific conditions for given time intervals.
(FDA. Guidance for industry. Bioanalytical Method Validation, 2001).

TRUENESS - The closeness of agreement between the average value obtained from a large series of test results and an accepted reference value.
NOTE: The measure of trueness is usually expressed in terms of bias. Trueness must not be confused with the term 'accuracy'.
(ISO 3534-1: 2006 Statistics -- Vocabulary and symbols)

UNCERTAINTY OF MEASUREMENT - Parameter, associated with the result of a measurement, that characterizes the dispersion of the values that could reasonably be attributed to the measurement. *(ISO 15189:2007, Medical laboratories - Particular requirements for quality and competence).*

VALIDATION - Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

Analytical Methods Validation - The process by which it is established, by laboratory studies, that the performance characteristics of the method meet the requirements for the intended analytical applications. *(FDA Guidance, part 7. Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients. Draft).*

On going validation - Control activities of the method characterize that taken during on going testing to approve the method control and that the validation results are valid. *(ISRAC Validation policy, 1-661004, version 04, 2007.)*

Prospective validation - Validation conducted prior to the distribution of either a new product, or product made under a revised manufacturing process, where the revisions may affect the product's characteristics.

Retrospective validation - Validation of a process for a product already in distribution based upon accumulated production, testing and control data. *(FDA, "Guidelines on General Principles of Process Validation." Rockville, MD, May 1993, updated 2009.).*

Re-validation - Repeating validation for method that already had validation. *(ISRAC Validation policy, 1-661004, version 04, 2007)*

VALIDATION PROTOCOL - A written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment, and decision points on what constitutes acceptable test results. *(FDA, "Guidelines on General Principles of Process Validation." Rockville, MD, May 1993, updated 2009.).*

WORST CASE - A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, which pose the greatest chance of process or product failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure. meeting its predetermined specifications and quality attributes.

(FDA, "Guidelines on General Principles of Process Validation." Rockville, MD, May 1993, updated 2009).