"Hitchhiker's Guide" to Bioprocess Design

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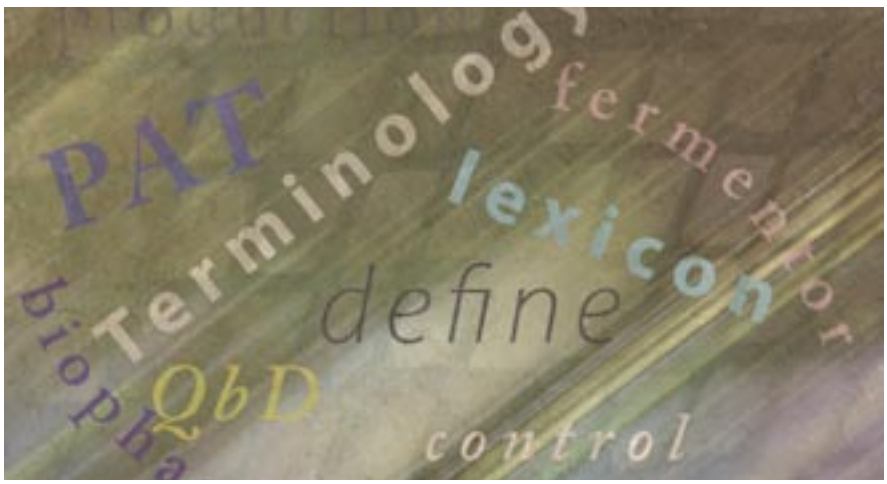

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Acceptance criteria Numerical limits, ranges, or other suitable measures for acceptance of results from analytical procedures that a drug substance, drug product, or materials at other stages of their manufacture should meet (**1**).

Numerical limits, ranges, process signatures, or other suitable measures that are necessary for making a decision to accept or reject the result of a process, in-process variable, a product, or any other convenient subgroups of manufactured units (**2**).

Numerical limits, ranges, or other suitable measures for acceptance of test results (**3**).

Accuracy The accuracy of an analytical procedure expresses the closeness of agreement between the value that is accepted either as a conventional true value or an accepted reference value and the value found (**4**).

Active pharmaceutical ingredient (API) See *drug substance*.

Analytical procedure Refers to the way of performing an analysis. It should describe, in detail, the steps necessary to perform each analytical test. This may include but is not limited to a sample, a reference standard and reagent preparations, use of the apparatus, generation of the calibration curve, and use of the formula for calculation (**4**).

Analyzer An instrument designed to measure and report a property of the process, material, or environmental condition (**2**).

At-line measurements Measurement in which a sample is removed, isolated from, and analyzed in close proximity to the process stream (**2**).

Attribute A characteristic and inherent property or feature (**2**).

Batch A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity of by the amount produced in a fixed time interval (**3**).

Batch process A noncontinuous operation in which discrete quantities of material are transformed using individual or sequential steps (**2**).

A process that leads to the production of finite quantities of material by subjecting quantities of input materials to an ordered set of processing activities over a finite period using one or more pieces of equipment (**5**).

Bioburden The level and type (e.g., objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates, or APIs. Bioburden should not be considered contamination unless the levels have been exceeded, or defined objectionable organisms have been detected (**3**).

Biological activity The specific ability or capacity of a product to achieve a defined biological effect. Potency is the quantitative measure of biological activity (**1**).

Bulk material See *drug substance*.

Cause and effect diagram Cause and effect diagram: A tool for analyzing process dispersion. It is also referred to as "root cause analysis", the "Ishikawa diagram" (because Kaoru Ishikawa developed it), and the "fishbone diagram," (because it

resembles a fish skeleton). It illustrates the main causes and subcauses (of process variation) leading to an effect (symptom) (**6**).

Characteristic Factors, elements or measures that define and differentiate a process, function, product, service, or other entity (**6**).

Characterization study A late-stage study that evaluates a process to increase process knowledge and examines proposed operational ranges and their individual and/or combined impact on target protein quality (**7**).

Chemometrics The science of relating measurements made on a chemical system or process to the state of that system by application of mathematical or statistical methods (**8**).

Common cause variability Random error or bias in a performance measure due to endemic deviation from the expected value in the process of its measurement. This type of variability is inherent in a system as it exists, and it is both predictable (probabilistically) and definable.

Causes of variation that are inherent in a process over time. They affect every outcome of the process and everyone working in the process (**6**).

Comparable A conclusion that products have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on safety or efficacy, including immunogenicity, of a drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical data might contribute to the conclusion (**9**).

Conformance lots A predetermined number of production lots, typically three, that represent the licensed process and evaluated to demonstrate consistency (**7**).

Consistency lots See *conformance lots*.

Contaminants Any adventitiously introduced materials (e.g., chemical, biochemical, or microbial species) not intended to be part of the manufacturing process of a drug substance or product (**1**).

Contamination The undesired introduction of impurities of a chemical or microbiological nature; of foreign matter into or onto a raw material, intermediate, or API during production, sampling, packaging, or repackaging, storage, or transport (**3**).

Continual improvement Ongoing activities to evaluate and positively change products, processes, and quality system to increase effectiveness (**10**).

Continuous improvement An ongoing effort to improve products, services, and processes. These efforts can seek incremental improvement over time or breakthrough improvement all at once (**11**).

Optimizing the characteristics and parameters to a target value and reducing variation around that value (**12**).

Continuous process An uninterrupted process of adding, processing, and removing material (**2**).

Continuous process verification An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated (**13**).

Control module Typically a collection of sensors, actuators, other control modules, and associated process equipment that, from the point of view of control, is operated as a single entity (**5**).

Control strategy A planned set of controls derived from current product and process understanding that assures process performance and product quality. These controls can include parameters and attributes related to drug substance and drug product, materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (**14**).

Corrective action Action taken to eliminate the causes of an existing discrepancy or other undesirable situation to prevent recurrence (**10**).

Corrective and preventive action (CAPA) A systematic approach that includes actions needed to correct (correction), prevent recurrence (corrective action), and eliminate the cause of potential nonconforming product and other quality problems (preventive action) (**10**).

Systematic approach to correct, prevent, and eliminate the cause of potential nonconforming product and other quality problems. *Corrective* refers to a reaction or an activity meant to correct a nonconformance that has already occurred. *Preventive* refers to an action or activity meant to prevent recurrence of a nonconformance.

C_p The ratio of tolerance to 6 sigma, or the upper specification limit (USL) minus the lower specification limit (LSL) divided by six sigma. It is sometimes referred to as the engineering tolerance divided by the natural tolerance and is only a measure of dispersion (**6, 15**).

C_{pk} index Equals the lesser of the upper specification limit (USL) minus the mean divided by three sigma (or the mean) minus the lower specification limit (LSL) divided by three sigma. The greater the C_{pk} value, the better (**6, 15**).

Critical Refers to a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that a drug substance meets its specification (**3**).

Critical process parameter (CPP) A process parameter the variability of which has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure that a process produces the desired quality (**16**).

An input process parameter that should be controlled within a meaningful, narrow operating range to ensure that drug substance quality attributes meet their specifications. Although, parameters with wide operating ranges may also affect product quality, they are generally easily controlled and not as likely to result in excursions that affect quality and are therefore low risk (**7**).

Critical quality attribute (CQA) A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure desired product quality (**16**).

Data integration The process of combining data from different sources and providing users with a unified view of those data (**17**).

Degradation products Molecular variants resulting from changes in a

desired product or product-related substances brought about over time and/or by the action of light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Such changes may occur as a result of manufacture and/or storage (e.g., deamidation, oxidation, aggregation, and proteolysis). Degradation products may be product-related substances or product-related impurities (**1**).

Design of experiment(s) (DOE) A branch of applied statistics dealing with planning, conducting, analyzing, and interpreting controlled tests to evaluate factors that control the value of a parameter or group of parameters (**6**).

Design space The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to assure quality. Working within the design space is not considered a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval (**13**).

Desired product A protein that has the expected structure (or that is expected from the DNA sequence and anticipated posttranslational modification — including glycoforms) and the intended downstream modification to produce an active biological molecule (**1**).

Desired state of a process All sources of variation are defined and controlled, and end product variation is minimal (**18**).

Detectability The ability to discover or determine the existence, presence, or fact of a hazard (**19**).

Detection limit The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample that can be detected (but not necessarily quantitated) as an exact value (**4**).

Development study See *characterization study*.

Deviation Departure from an approved instruction or established standard (**3**).

Discrepancy Data or result outside of an expected range; an unfulfilled requirement; may be called nonconformity, defect, deviation, out-of-specification, out-of-limit, or out-of-trend (**10**).

Dosage form See *drug product*.

Drug product Dosage form in the final immediate packaging intended for marketing (**3**).

A pharmaceutical product type that contains a drug substance, generally, in association with excipients (**1**).

Drug substance Material that is subsequently formulated with excipients to produce a drug product. It can be composed of the desired product, product-related substances, product-related impurities, and process-related impurities. It may also contain excipients including other components such as buffers (**1**).

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body (**3**).

Edge of failure The boundary to a variable or parameter, beyond which the relevant quality attributes or specifications cannot be met (**16**).

Engineering or evaluation study See *characterization study.*

Excipient An ingredient added intentionally to a formulation that should not have pharmacological properties in the quantity used (**1**).

Experimental design See *design of experiment(s)*.

Failure mode analysis (FMA) A procedure to determine which malfunction symptoms appear immediately before or after failure of a critical parameter in a system. After all possible causes are listed for each symptom, the process is designed to eliminate problems (**6**).

Failure mode effects analysis (FMEA) A systematized group of activities to recognize and evaluate the potential failure and its effects of a product or process, identify actions that could eliminate or reduce the occurrence of that potential failure, and document the process (**6**).

Failure mode effects and criticality analysis (FMECA) A procedure performed after a failure mode effects analysis to classify each potential failure effect according to its severity and probability of occurrence (**6**).

Finished product See *drug product.*

Fishbone diagram See *cause and effect diagram*.

Harm Damage to health, including the damage that can occur from the loss of product quality or availability (**10, 19**).

Hazard A potential source of harm (**19**).

Hazard analysis and critical control point (HACCP) A quality management system for effectively and efficiently ensuring farm-to-table food safety in the United States. HACCP regulations for various sectors are established by the Department of Agriculture and the Food and Drug Administration (**6**).

Impurity Any component present in a drug substance or drug product that is not the desired product, a product-related substance, or an excipient including buffer components. It may be either process- or product-related (**1**).

Any component present in an intermediate or API that is not the desired entity (**3**).

Any component present in a raw material, intermediate, API, or dosage form that is not the desired entity (**2**).

Impurity profile A description of identified and unidentified impurities present in the API (**3**).

A description of identified and unidentified impurities present in a raw material, intermediate, API, or dosage form (**2**).

Inherent variability See *common cause variability.*

In-line measurements Measurement where the product is not removed from the process stream; can be invasive or noninvasive (**2**).

In-process control Checks performed during production to monitor and, if appropriate, adjust a process and/or ensure that an intermediate or API conforms to its specifications (**3**).

Checks performed during manufacturing to measure critical attributes and, if appropriate, adjust a process to deliver the desired output(s) (2).

In-process material Any material(s) fabricated, compounded, blended, or synthesized using a chemical, physical, or biological process that is produced for and being used in the preparation of an intermediate, drug substance, or drug product (2).

In-process tests Measurements performed during manufacturing and pertaining to the process or products within that process (2).

Intermediate Material produced during manufacture that undergoes further change or purification. Intermediates may or may not be isolated (2).

Intermediate precision Expressed within laboratory variations: different days, different analysts, different equipment (4).

Intra-assay precision See *repeatability*.

Ishikawa diagram See *cause and effect diagram*.

Key operational parameter See *key process parameter*.

Key performance indicator (KPI) Metrics used to quantify quality

Acronyms

AAPS American Association of Pharmaceutical Scientists
API Active pharmaceutical ingredient
ASTM American Society of Testing and Materials
AUC Analytical ultracentrifugation
CAPA Corrective and preventive action
CASSS California Separations Science Society
CD Circular dichroism
CER Carbon dioxide evolution rate
CMC Chemistry, manufacturing, and controls
COD Critical operating data
CPA Critical product attribute
CPP Critical process parameter
CQA Critical quality attribute
CQP Critical quality parameter
CQV Continuous quality verification
CPV Continuous process verification
CZE Capillary zone electrophoresis
DAE Differential and algebraic equations
DCS Distributed control system
DFSS Design for Six Sigma
DOE Design of experiment(s)
DO Dissolved oxygen
DSP Downstream processing
EBR Electronic batch record
EDMS Enterprise document management system
ELISA Enzyme-linked immunosorbent assay
EMS Enterprise manufacturing system
FDA United States Food and Drug Administration
FFF Field flow fractionation
FMEA Failure mode, effects analysis
FMECA Failure mode, effects and criticality analysis
FTA Fault tree analysis
FT-IR Fourier transform infrared spectroscopy
GAMP Good automated manufacturing practice
GCP Good clinical practice
GEP Good engineering practice
GLP Good laboratory practice
GMP Good manufacturing practice
HACCP Hazard analysis and critical control points
HAZOP Hazard operability analysis
HCP Host cell protein
HIC Hydrophobic interaction chromatography
HPLC High performance liquid chromatography
ICH International Conference on Harmonisation
IEC Ion exchange chromatography
IEF Isoelectric focusing
IFPAC International Forum on Process Analysis and Control
ISA Instrument Society of America
ISPE International Society for Pharmaceutical Engineering
IVC Integral viable cells
KQI Key quality indicator
KPI Key performance indicator
KPP Key process parameter
LAL *Limulus* amebocyte lysate
LT Laboratory testing
LSL Lower specification limit
MA Membrane absorber
MALS Multi-angle light scattering
MES Manufacturing execution system
MF Micro filtration
MPC Model predictive control
MS Mass spectrometry
MSX Methionine sulphoxamine
NFF Normal flow filtration
NIR Near infrared
NMR Nuclear magnetic resonance
OEE Overall equipment effectiveness
OOS Out-of-specification
Op Ex Operational excellence
OUR Oxygen uptake rate
PAC Process analytical chemistry
PAI Preapproval inspection or productivity improvement appraisal
PAR Proven acceptable range
PAT Process analytical technology
PCA Principal components analysis
PCR Polymerase chain reaction
PDA Parenteral Drug Association
PFD Process flow diagram
PHA Preliminary hazard analysis
PLS Partial least squares or projection to latent structures
PTM Posttranslational modifications
PV Process validation
QA Quality assurance
QbD Quality by design
QC Quality control
q-PCR Quantitative polymerase chain reaction
QRM Quality risk management
RC Respiration coefficient
ROI Return on investment
RPC Reverse-phase chromatography
RT Real-time
RTR Real-time release
SB Systems biology
SDS-PAGE Sodium-dodecyl sulfate polyacrylamide gel electrophoresis
SEC Size-exclusion chromatography
SOP Standard operating procedure
SPC Statistical process control
TFF Tangential flow filtration
UF Ultra filtration
USL Upper specification limit
USP United States Pharmacopeia
UV Ultraviolet
VIS Visible

Symbols

C_p Process capability
C_{PK} Process capability index
Q_p Specific production rate
s Standard deviation

objectives to reflect the performance of an organization, process, or system (**14**).

Key process parameter (KPP) An input process parameter that should be carefully controlled within a narrow range that is essential for process performance. A key process parameter does not affect critical (product) quality attributes (CQAs). If the acceptable range is exceeded it may affect the process (e.g., yield, duration) but not product quality (**7**).

Key quality indicator (KQI) Metrics used to quantify product quality objectives to reflect the performance of a quality control strategy.

Knowledge management Systematic approach to collecting, analyzing, storing, and disseminating information related to products, processes, and components (**14**).

Knowledge space The sum of existing information composed of prior knowledge, the body of scientific information and data about the product and process (**20**).

Life-cycle All phases in the life of a product from its initial development through marketing until discontinuation (**13**).

Linearity The linearity of an analytical procedure is its ability (within a given range) to obtain test results that are directly proportional to the concentration (amount) of analyte in the sample (**4**).

Lot See *batch*.

Manufacture All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and related controls (**3**).

All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs or drug products and related controls (**2**).

Manufacturing process A set of activities or operations performed to deliver the desired output (**2**).

Manufacturing space The multidimensional combination and interaction of output variables (e.g., product and process-based performance indicators or KQIs and KPIs) that promises to further enhance product knowledge and process understanding and ultimately allow a correlation of product and process performance to their respective design elements.

Material A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs, and packaging and labeling materials (**3**).

Microheterogeneity Slight differences in large, complex macromolecules that result in a population of closely related but unidentical structures. Protein microheterogeneity can arise from many sources; (e.g., genetic variants, cellular proteolysis, translational and posttranslational modifications) and during commercial production.

Nonconformity A deficiency in a characteristic, product specification, process parameter, record, or procedure that renders the quality of a product unacceptable, indeterminate, or noncompliant with specified requirements (**10**).

Noncritical operational parameter See *noncritical process parameter*.

Noncritical process parameter All input process parameters that fall outside the definition for critical process parameters (CPPs) are noncritical. These are divided into key and nonkey process parameters (**7**).

Nonkey operational parameter See *nonkey process parameter*.

Nonkey process parameter An input process parameter that has been demonstrated to be easily controlled or that has a wide acceptable limit. Nonkey process parameters may have an impact on drug substance quality or process performance if acceptable limits are exceeded (**7**).

Off-line measurements Measurement in which a sample is removed, isolated from, and analyzed in an area remote from the manufacturing process (**2**).

On-line measurements Measurement in which a sample is diverted from the manufacturing process, and may be returned to the process stream (**2**).

Operational parameter See *process parameter*.

Out-of-control process A process in which the statistical measure being evaluated is not in a state of statistical control (**6**).

Parameter A measurable or quantifiable characteristic of a system or process (**2**).

Parametric release A system of release that gives assurance that the product is of intended quality based on information collected during the manufacturing process (**2**).

Performance attribute See *performance parameter*.

Performance parameter An output variable or outcome that cannot be directly controlled but is an indicator that the process performed as expected (**7**).

Potency A measure of biological activity using a suitably quantitative biological assay (also called *potency assay* or *bioassay*) based on a product attribute that is linked to the relevant biological properties (**1**).

Precision The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision, and reproducibility. The precision of an analytical procedure is usually expressed by variance, standard deviation, or coefficient of variation of a series of measurements (**4**).

Preventive action Action taken to eliminate the cause of a potential discrepancy or other undesirable situation to prevent such an occurrence (**10**).

Procedure A documented description of operations to be performed, precautions to be taken, and measures to be applied directly or indirectly related to the manufacture of an intermediate or API (**3**).

A documented description of operations to be performed, precautions to be taken, and measures to be applied directly or indirectly related to the manufacture of an intermediate, API, or drug product (**2**).

Process aids Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves

participate in a chemical or biological reaction (e.g., filter aid, activated carbon) (**3**).

Process analytical technology (PAT) A system for designing, analyzing, and controlling manufacturing through timely measurements (e.g., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality (**13**).

Process capability Ability of a process to realize a product that will fulfill the requirements necessary. The concept can also be defined statistically (**14**).

A statistical measure of the inherent process variability of a given characteristic. The most widely accepted formula for process capability is six sigma (**6**).

Process capability index The value of a tolerance specified for a characteristic divided by the process capability. The several types of process capability indexes include the widely used C_p and C_{pk} (**6**).

Process control See *in-process control*.

Process justification study See *characterization study*.

Process parameter An attribute of the manufacturing system (**2**).

An input variable or condition of the manufacturing process that can be directly controlled in the process (**7**).

Process-related impurities Impurities that are derived from the manufacturing process. They may be derived from cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g., inducers, antibiotics, or media components), or downstream processing (e.g., processing reagents or column leachables) (**1**).

Process robustness The ability of a process to tolerate variability of materials and changes of the process and equipment without negatively affecting quality (**13**).

Process step See *unit operation*.

Process validation Documented evidence that a process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes (**3**).

Product The intended results of activities or processes; products can be tangible or intangible (**10**).

Product life-cycle All phases in the life of a product from the initial development through marketing until discontinuation (**19**).

Product-related impurities Molecular variants of the desired product (e.g., precursors, certain degradation products arising during manufacture and/or storage) that do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety (**1**).

Product-related substances Molecular variants of a desired product formed during manufacture and/or storage that are active and have no deleterious effect on the safety and efficacy of the drug product. These variants possess properties comparable to the desired product and are not considered impurities (**1**).

Proven acceptable range (PAR) A characteristic range of a process parameter for which operation within this range, while keeping other parameters constant, will produce a material meeting relevant quality criteria (**16**).

Qualification Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation (**3**).

Qualification lots See *conformance lots*.

Quality The suitability of either a drug substance or drug product for its intended use (**13**). This term includes such attributes as the identity, strength, and purity (**1**).

The degree to which a set of inherent properties of a product, system, or process fulfills requirements (**14, 19**).

Quality attribute A molecular or product characteristic that is selected for its ability to help indicate the quality of the product. Collectively, those attributes define identity, purity, potency, and stability of the product, as well as safety with respect to adventitious agents. Specifications measure a selected subset of the quality attributes (**9**).

Quality by design A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (**16**).

Quality control Checking or testing that specifications are met (**3**).

Quality risk management (QRM) A systematic process for assessment, control, communication, and review of risks to the quality of a drug product across the product life-cycle (**19**).

Quality system The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met (**19**).

Formalized business practices that define management responsibilities for organizational structure, processes, procedures, and resources needed to fulfill product and/or service requirements, customer satisfaction, and continual improvement.

Quantitation limit The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample that can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, used particularly for determination of impurities and/or degradation products (**4**).

Range The range of an analytical procedure is 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 (**4**).

Raw material A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates, APIs or products (**2**).

Real-time release (RTR) The ability to evaluate and ensure acceptable quality of in-process and/or final product based on process data, which typically include a valid combination of assessed material attributes and process controls (**16**).

Recipe The necessary set of information that uniquely identifies the production requirements for a specific product (**5**).

Reference standard, primary A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be obtained from an officially recognized source, prepared by independent synthesis, obtained from existing production material of high purity, or prepared by further purification of existing production material (**3**).

Reference standard, secondary A substance of established quality and purity, as shown by comparison with a primary reference standard, used as a reference standard for routine laboratory analysis (**3**).

Repeatability Precision under the same operating conditions over a short interval of time. Repeatability is also termed *intraassay precision* (**4**).

The variation in measurements obtained when one device is used several times by the same person to measure the same characteristic on the same product (**6**).

Reproducibility Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology) (**4**).

The variation in measurements made by different people using the same measuring device to measure the same characteristic on the same product (**6**).

Risk A combination of the probability of occurrence of harm and the severity of that harm (**10, 19**).

Risk acceptance The decision to accept risk (**19**).

Risk analysis Estimation of the risk associated with identified hazards (**19**).

Risk assessment A systematic process for organizing information to support a risk decision that is made within a risk management process. This process consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (**10**).

A systematic process of organizing information to support a risk decision made within a risk management process. It consists of identification of hazards and analysis and evaluation of risks associated with exposure to those hazards (**19**).

Risk communication The sharing of information about risk and risk management between the decision maker and other stakeholders (**19**).

Risk control Actions implementing risk management decisions (**19**).

Risk evaluation A comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk (**19**).

Risk identification Systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description (**19**).

Risk management Systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risk (**10, 19**).

Risk reduction Actions taken to lessen the probability of occurrance of harm and the severity of that harm (**19**).

Risk review Review or monitoring of output and/or results of the risk management process considering (if appropriate) new knowledge and experience about the risk (**19**).

Robustness Of an analytical procedure, the measure of its capacity to remain unaffected by small but deliberate variations in method parameters. This indicates its reliability during normal use (**4**).

The condition of a product or process design that remains relatively stable, with a minimum of variation, even though factors that influence operations or use, such as environment and wear, are constantly changing (**6**).

Robustness study See *characterization study*.

Sample A portion, piece or segment that is representative of a whole (**2**).

Set point The target value for a process parameter. The range around the set point is commonly stated in the manufacturing procedures or batch records (**7**).

Severity A measure of the possible consequences of hazard (**19**).

Six Sigma As a measure: Statistical definition of how far a process deviates from perfection.

As a target: Level of process performance equivalent to producing only 3.4 parts per million defects or has a yield of 99.9997%.

As a philosophy: Long-term business strategy focused on the reduction of cost through driving down variation in product and process.

A method that provides organizations tools to improve the capability of their business processes. This increase in performance and decrease in process variation leads to defect reduction and improvement in profits, employee morale, and quality of products or services. Six Sigma quality is a term generally used to indicate that a process is well controlled (±6 σ from the centerline in a control chart) (**6**).

Special cause ariability Nonrandom variability, which is transient and often assignable in nature. By definition, this type of variability is not inherent, predictable (probabilistically), or definable.

Causes of variation that arise because of special circumstances. They are not an inherent part of a process. Special causes are also referred to as *assignable causes* (**6**).

Specification A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product, or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. Conformance to specification means that a drug substance and drug product, when tested according to a listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval (**1**).

A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. Establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. Conformance to specifications means that the material, when tested according

to the listed analytical procedures, will meet the listed acceptance criteria (**3**).

Specificity The ability to assess unequivocally an analyte in the presence of components that may be expected to be present. Typically these might include impurities, degradants, and matrix (**4**).

State of control A condition in which a set of controls consistently provides assurance of continued process performance and product quality (**14**).

Statistical process control (SPC) The application of statistical techniques to control a process; often used interchangeably with the term "statistical quality control" (**6**).

Structural variation Variation caused by regular, systematic changes in output, such as seasonal patterns and long-term trends (**6**).

Systems biology Addresses the analysis of entire biological systems. It is an interdisciplinary approach to the investigation of all the components and networks contributing to a biological system (**21**).

Tampering Action taken to compensate for variation within the control limits of a stable system; tampering increases rather than decreases variation, as evidenced in the funnel experiment (**6**).

Trueness See *accuracy*.

Unit operation A discrete step or manipulation in a manufacturing process where process and operating parameters are defined to achieve a specific process objective (**7**).

Unit processing operation See *unit operation*.

Validation A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria (**3**).

Validation lots See *conformance lots*.

Validation protocol A written plan showing how validation will be conducted that defines acceptance criteria (**3**).

Variability Potential or propensity to vary.

Variation A change in data, characteristic, or function caused by one of four factors: special causes, common causes, tampering, or structural variation (**6**).

Waste Any activity that consumes resources and produces no added value to the product or service a customer receives (**6**).

Well-characterized products Chemical entities whose identity, purity, impurities, potency, and quantity can be determined and controlled.

References

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