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Standard Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry[1]

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1. Scope

1.1 This terminology covers process analytical technology in the pharmaceutical industry. Terms are defined as they are used relative to the PAT framework in the pharmaceutical industry. Terms that are generally understood and in common usage or adequately defined in other readily available eferences are not included except where particular delineation to process analytical technology may be more clearly stated.

1.2 This terminology is therefore intended to be selective of terms used generally in process analytical technology as it is applied in the pharmaceutical industry and published in a number of documents, such as those listed in the succeeding sections. The listing is also intended to define terms that appear prominently within other related ASTM standards and do not appear elsewhere.

1.3 The definitions are substantially identical to those published by the U.S. Food and Drug Administration and other authoritative bodies, such as ISO, IEC, ITU, and national standards organizations.

1.4 This terminology supplements current documents on terminology that concentrate on process analytical technology as it is applied in the pharmaceutical industry.

1.5 An increasing number of product designations and designations for chemical, physical, mechanical, analytical, and statistical tests and standards are coming into common usage in the literature, regulatory environment, and commerce associated with process analytical technology in the pharmaceutical industry. Section 2 lists those documents referenced in this terminology.

1.6 The values stated in SI units are to be regarded as standard. No other units of measurement are included in this standard.

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E456 Terminology Relating to Quality and Statistics

E869 Test Method for Performance Evaluation of Fuel Ethanol Manufacturing Facilities

E1117 Practice for Design of Fuel-Alcohol Manufacturing Facilities

E1126 Terminology Relating to Biomass Fuels (Withdrawn 2003)[3]

E1285 Guide for Identification of Bacteriophage Lambda (λ) or Its DNA (Withdrawn 2014)[3]

E1286 Guide for Identification of Herpes Simplex Virus or Its DNA (Withdrawn 2014)[3]

E1287 Practice for Aseptic Sampling of Biological Materials (Withdrawn 2008)[3]

E1298 Guide for Determination of Purity, Impurities, and Contaminants in Biological Drug Products (Withdrawn 2014)[3]

E1342 Practice for Preservation by Freezing, Freeze-Drying, and Low Temperature Maintenance of Bacteria, Fungi, Protista, Viruses, Genetic Elements, and Animal and Plant Tissues (Withdrawn 2011)[3]

E1344 Guide for Evaluation of Fuel Ethanol Manufacturing Facilities

E1493 Guide for Identification of Bacteriophage M13 or Its DNA (Withdrawn 2014)[3]

E1531 Practice for Detection of Mycoplasma Contamination of Cell Cultures by Growth on Agarose Medium (Withdrawn 2014)[3]

E1532 Practice for Detection of Mycoplasma Contamination of Cell Cultures by Use of Bisbenzamide DNA-Binding Fluorochrome (Withdrawn 2014)[3]

E1533 Practice for Indirect Detection of Mycoplasma in Cell Culture by 4'-6-Diamidino-2-2 Phenylindole (DAPI) Staining (Withdrawn 2014)[3]

[1] This terminology is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical and Biopharmaceutical Products and is the direct responsibility of Subcommittee E55.91 on Terminology.

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

[3] The last approved version of this historical standard is referenced on www.astm.org.

E1536 Practice for Detection of Mycoplasma Contamination of Bovine Serum by Large Volume Method (Withdrawn 2014)[3]
E1564 Guide for Design and Maintenance of Low-Temperature Storage Facilities for Maintaining Cryopreserved Biological Materials
E1565 Guide for Inventory Control and Handling of Biological Material Maintained at Low Temperatures
E1566 Guide for Handling Hazardous Biological Materials in Liquid Nitrogen
E2500 Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment
E2629 Guide for Verification of Process Analytical Technology (PAT) Enabled Control Systems

2.2 *U.S. Government Publications:*[4]

21 CFR 210.3(b) Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General—Definitions
21 CFR 314.3(b) Applications for FDA Approval to Market a New Drug—General Provisions—Definitions

2.3 *ICH Publications:*[5]

ICH R2 (Q1) Validation of Analytical Procedures: Text and Methodology
ICH Q6A Guidance for Industry—Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
ICH Q6B Guidance for Industry—Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
ICH Q7 Guidance for Industry—Good Manufacturing Practice Guide For Active Pharmaceutical Ingredients
ICH Q8 (R2) Guidance for Industry—Pharmaceutical Development
ICH Q9 Guidance for Industry—Quality Risk Management
ICH Q10 Guidance for Industry—Pharmaceutical Quality System
ICH Q11 Guidance for Industry—Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)

2.4 *ISO Publications:*[6]

ISO 9000:2005 Quality Management Systems—Fundamentals and Vocabulary
ISO EN 14971:2012 Medical Devices—Application of Risk Management for Medical Devices
ISO/IEC Guide 51:2014 Safety Aspects—Guidelines for Their Inclusion in Standards
ISO Guide 73:2009 Risk Management—Vocabulary

2.5 *Other Publication:*

EU GMP Glossary

[4] Available from U.S. Government Printing Office Superintendent of Documents, 732 N. Capitol St., NW, Mail Stop: SDE, Washington, DC 20401, http://www.access.gpo.gov.

[5] Available from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Secretariat, c/o IFPMA, 15 ch. Louis-Dunant, P.O. Box 195, 1211 Geneva 20, Switzerland, http://www.ich.org.

[6] Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, http://www.ansi.org.

3. Terminology

3.1 *Definitions:*

acceptance criteria, *n*—numerical limits, ranges, or other suitable measures for acceptance of test results. **ICH Q7**

accuracy, *n*—the accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found. **ICH Q8 (R2)**

active pharmaceutical ingredient (API) (or drug substance), *n*—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. **ICH Q7**

analytical procedure, *n*—the analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc. **ICH Q8 (R2)**

analyzer, *n*—an instrument designed to measure and report a property of the process, material, or environmental condition.

API starting material, *n*—a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure. **ICH Q7**

at-line measurements, *n*—measurement where the sample is removed, isolated from, and analyzed in close proximity to the process stream.

attribute, *n*—a characteristic or inherent property or feature.

batch, *n*—a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture. **21 CFR 210.3(b)**

batch number, *n*—See **lot number**.

batch process, *n*—a noncontinuous operation in which discrete quantities of material are transformed using individual or sequential steps. **21 CFR 210.3(b)**

bioburden, *n*—the level and type (for example, objectionable or not) of micro-organisms 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. **ICH Q7**

calibration, *n*—the demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. **ICH Q7**

capability of a process, *n*—ability of a process to realize a product that will fulfil the requirements of that product. The concept of process capability can also be defined in statistical terms. **ISO 9000:2005, ICH Q10**

change management, *n*—a systematic approach to proposing, evaluating, approving, implementing, and reviewing changes. **ICH Q10**

chemical transformation step, *n*—for chemical entities, a step involved in the synthesis of the chemical structure of the drug substance from precursor molecular fragments. Typically it involves C-X or C-C bond formation or breaking. **ICH Q11**

computer system, *n*—a group of hardware components and associated software designed and assembled to perform a specific function or group of functions. **ICH Q7**

computerized system, *n*—a process or operation integrated with a computer system. **ICH Q7**

contaminants, *n*—any adventitiously introduced materials (for example, chemical, biochemical, or microbial species) not intended to be part of the manufacturing process of the drug substance or drug product. **ICH Q6B**

contamination, *n*—the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, API (active pharmaceutical ingredient), or dosage form during production, sampling, packaging, or repackaging, storage, or transport. **ICH Q7**

continual improvement, *n*—recurring activity to increase the ability to fulfil requirements. **ISO 9000:2005**

continuous process—a process in which material is added, processed, and removed in an uninterrupted manner.

continuous process verification, *n*—an alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated. **ICH Q8 (R2)**

contract manufacturer, *n*—a manufacturer who performs some aspect of manufacturing on behalf of another entity.

control number, *n*—See **lot number**.

control model, *n*—procedure or mathematical expression (algorithm) that uses the outputs of the process model combined with any other data inputs required to calculate values for the critical control parameters for the process; it uses input data from the process to generate an actionable command or commands that are issued to the control system. **E2629**

control strategy, *n*—a planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The 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. **ICH Q10**

control system, *n*—system that responds to inputs signals from the process, its associated equipment, other programmable systems, or an operator, or combinations thereof, and generates output signals causing the process and its associated equipment to operate in the desired manner. **E2629**

corrective action, *n*—action to eliminate the cause of a detected non-conformity or other undesirable situation. **ISO 9000:2005**

DISCUSSION—Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence.

critical, *n*—describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification. **ICH Q7**

cross-contamination, *n*—contamination of a material or product with another material or product. **ICH Q7**

current good manufacturing practices (CGMP), *n*—current regulations published by the United States Food and Drug Administration (FDA) regarding manufacturing, processing, packaging and storing of drug and biological products. **E1287**

decision maker(s), *n*—person(s) with the competence and authority to make appropriate and timely quality risk management decisions. **ICH Q9**

detectability, *n*—the ability to discover or determine the existence, presence, or fact of a hazard. **ICH Q9**

detection limit, *n*—the detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value. **ICH R2 (Q1)**

Design of Experiments (DoE), *n*—the arrangement in which an experimental program is to be conducted, and the selection of the levels (versions) of one or more factors or factor combinations to be included in the experiment. **E456**

design reviews, *n*—planned and systematic reviews of specifications, design, and design development and continuous improvement changes performed as appropriate throughout the life-cycle of the manufacturing system. Design reviews evaluate deliverables against standards and requirements, identify problems, and propose required corrective actions. **E2500**

detectability, *n*—the ability to discover or determine the existence, presence, or fact of a hazard.

deviation, *n*—departure from an approved instruction or established standard. **ICH Q7**

drug product, *n*—a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo. **21 CFR 210.3(b)**

drug substance, *n*—See API. **ICH Q7**

enabler, *n*—a tool or process which provides the means to achieve an objective. **ICH Q10**

expiry date (or expiration date), *n*—the date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used. **ICH Q7**

feedback / feedforward, *n*—can be applied technically in process control strategies and conceptually in quality management. **ICH Q10**

DISCUSSION—*Feedback*: The modification or control of a process or system by its results or effects. *Feedforward*: The modification or control of a process using its anticipated results or effects.

formal experimental design, *n*—a structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as "design of experiments". **ICH Q8 (R2)**

harm, *n*—damage to health, including the damage that can occur from loss of product quality or availability. **ICH Q9**

hazard, *n*—the potential source of harm (ISO/IEC Guide 51:2014). **ICH Q9**

impurity, *n*—any component present in a raw material, intermediate, API, or dosage form that is not the desired entity.

impurity profile, *n*—a description of the identified and unidentified impurities present in a raw material, intermediate, API, or dosage form.

in-line measurements, *n*—measurement where the sample is not removed from the process stream, and can be invasive or non-invasive.

in-process control (or process control), *n*—checks performed during production in order to monitor and, if appropriate, to adjust the process or to ensure that the intermediate or API, or both, conforms to its specifications. **ICH Q7**

in-process material, *n*—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.

in-process tests, *n*—measurements performed during manufacturing and pertaining to the process or products within the process.

intermediate, *n*—material produced during manufacture that undergoes further change or purification. Intermediates may or may not be isolated.

intermediate precision, *n*—intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, etc. **ICH R2 (Q1)**

innovation, *n*—the introduction of new technologies or methodologies. **ICH Q10**

knowledge management, *n*—systematic approach to acquiring, analysing, storing, and disseminating information related to products, manufacturing processes, and components. **ICH Q10**

linearity, *n*—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. **ICH R2 (Q1)**

lot, *n*—a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits. **21 CFR 210.3(b)**

lot number, control number, or batch number, *n*—any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of drug product or other material can be determined. **21 CFR 210.3(b)**

manufacture, *n*—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. **ICH Q7**

manufacturing process, *n*—a set of activities or operations performed to deliver a desired output.

material, *n*—a general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs, and packaging and labeling materials. **ICH Q7**

material specification, *n*—a set of criteria to which a material must conform to be considered acceptable for its intended use.

manufacturing systems, *n*—elements of pharmaceutical and biopharmaceutical manufacturing capability, including manufacturing systems, facility equipment, process equipment, supporting utilities, associated process monitoring and control systems, and automation systems, that have the potential to affect product quality and patient safety. **E2500**

measurement system, *n*—system of sensors, instruments, or analyzers, or combinations thereof, that collects signals generated by passive or active interaction with process material or process equipment and converts those signals into data. **E2629**

mother liquor, *n*—the residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API, or impurities, or combinations thereof. It may be used for further processing. **ICH Q7**

off-line measurements, *n*—measurement where the sample is removed, isolated from, and analyzed in an area remote from the manufacturing process.

on-line measurements, *n*—measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream.

outsourced activities, *n*—activities conducted by a contract acceptor under a written agreement with a contract giver. **ICH Q10**

packaging material, *n*—any material intended to protect an intermediate or API during storage and transport. **ICH Q7**

parameter, *n*—a measurable or quantifiable characteristic of a system or process.

parametric release, *n*—a system of release that gives assurance that the product is of the intended quality based on the information collected during the manufacturing process.

performance indicators, *n*—measurable values used to quantify quality objectives to reflect the performance of an organization, process or system, also known as "performance metrics" in some regions. **ICH Q10**

pharmaceutical quality system (PQS), *n*—management system to direct and control a pharmaceutical company with regard to quality. **ICH Q10**

platform manufacturing, *n*—the approach of developing a production strategy for a new drug starting from manufacturing processes similar to those used by the same applicant to manufacture other drugs of the same type (for example, as in the production of monoclonal antibodies using predefined host cell, cell culture, and purification processes, for which there already exists considerable experience). **ICH Q11**

precision, *n*—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 the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision, and reproducibility.

preventive action, *n*—action to eliminate the cause of a potential non-conformity or other undesirable potential situation. **ISO 9000:2005**

DISCUSSION—Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence.

procedure, *n*—a documented description of the operations to be performed, the precautions to be taken, and the measures to be applied directly or indirectly related to the manufacture of an intermediate, API, or drug product. **ICH Q7**

process aids, *n*—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 (for example, filter aid, activated carbon). **ICH Q7**

process analytical technology (PAT), *n*—system for designing, analyzing, and controlling manufacturing through timely measurements (that is, during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. **ICH Q8 (R2)**

process control, *n*—checks performed during manufacturing to measure critical attributes and, if appropriate, adjust the process to deliver the desired output(s). **ICH Q7**

process model, *n*—mathematical expression (algorithm) that uses data from the measurement system(s) (inputs to the process model) to calculate the value of one or more of the process material attributes (outputs from the process model) at the time the measurement was taken. **E2629**

process parameter, *n*—an attribute of the manufacturing system.

process robustness, *n*—ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality. **ICH Q8 (R2)**

production, *n*—all operations involved in the preparation of an API from receipt of materials through processing and packaging of the API. **ICH Q7**

product lifecycle, *n*—all phases in the life of the product from the initial development through marketing until the product's discontinuation. **ICH Q9**

product realization, *n*—achievement of a product with the quality attributes appropriate to meet the needs of patients, health care professionals, and regulatory authorities (including compliance with marketing authorization) and internal customer requirements. **ICH Q10**

qualification, *n*—action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation. **ICH Q7**

quantitation limit, *n*—the quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which 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, and is used particularly for the determination of impurities or degradation products, or both. **ICH Q8 (R2)**

quality, *n*—the degree to which a set of inherent properties of a product, system or process fulfills requirements (see ICH

Q6A definition specifically for "quality" of drug substance and drug (medicinal) products.) **ICH Q9**

quality assurance (QA), *n*—the sum total of the organized arrangements made with the object of ensuring that all APIs or drug products are of the quality required for their intended use and that quality systems are maintained. **ICH Q7**

quality attribute, *n*—an attribute that affects product quality.

quality control (QC), *n*—checking or testing that specifications are met. **ICH Q7**

quality manual, *n*—document specifying the quality management system of an organization. **ISO 9000:2005**

quality objectives, *n*—a means to translate the quality policy and strategies into measurable activities. **ICH Q10**

quality planning, *n*—part of quality management focused on setting quality objectives and specifying necessary operational processes and related resources to fulfil the quality objectives. **ISO 9000:2005**

quality policy, *n*—overall intentions and direction of an organisation related to quality as formally expressed by senior management. **ISO 9000:2005**

quality risk management, *n*—a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. **ICH Q9**

quality system, *n*—the sum of all aspects of a system that implements quality policy and ensures that quality objectives are met. **ICH Q9**

quality target product profile (QTPP), *n*—a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. **ICH Q8 (R2)**

quality unit(s), *n*—an organizational unit independent of production which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization. **ICH Q7**

quarantine, *n*—the status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection. **ICH Q7**

range, *n*—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. **ICH R2 (Q1)**

raw material, *n*—a general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates, APIs, or products.

real time release testing (RTRT), *n*—the ability to evaluate and ensure the quality of in-process or final product, or both, based on process data, which typically include a valid combination of measured material attributes and process controls. **ICH Q8 (R2)**

reference standard, primary, *n*—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: (*1*) obtained from an officially recognized source, or (*2*) prepared by independent synthesis, or (*3*) obtained from existing production material of high purity, or (*4*) prepared by further purification of existing production material **ICH Q7**

reference standard, secondary, *n*—a substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis. **ICH Q7**

repeatability, *n*—repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision. **ICH R2 (Q1)**

reprocessing, *n*—introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (for example, distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process, and not reprocessing. **ICH Q7**

reproducibility, *n*—reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology). **ICH R2 (Q1)**

requirements, *n*—the explicit or implicit needs or expectations of the patients or their surrogates (for example, health care professionals, regulators and legislators). In this document, "requirements" refers not only to statutory, legislative, or regulatory requirements, but also to such needs and expectations. **ICH Q9**

retest date, *n*—the date when a material should be re-examined to ensure that it is still suitable for use. **ICH Q7**

reworking, *n*—subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (for example, recrystallizing with a different solvent). **ICH Q7**

risk, *n*—combination of the probability of occurrence of harm and the severity of that harm. **ISO EN 14971:2012**

risk acceptance, *n*—the decision to accept risk (ISO Guide 73:2009) **ICH Q9**

risk analysis, *n*—the estimation of the risk associated with the identified hazards. **ICH Q9**

risk assessment, *n*—a systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. **ICH Q9**

risk communication, *n*—the sharing of information about risk and risk management between the decision maker and other stakeholders. **ICH Q9**

risk control, *n*—actions implementing risk management decisions (ISO Guide 73:2009) **ICH Q9**

risk evaluation, *n*—a systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. **ICH Q9**

risk identification, *n*—the systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description. **ICH Q9**

risk management, *n*—the systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk. **ICH Q9**

risk reduction, *n*—actions taken to lessen the probability of occurrence of harm and the severity of that harm. **ICH Q9**

risk review, *n*—review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk. **ICH Q9**

robustness, *n*—the robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage. **ICH R2 (Q1)**

safety, *n*—freedom from unacceptable risk. **ISO EN 14971:2012**

sample, *n*—a portion, piece, or segment that is representative of a whole.

senior management, *n*—person(s) who direct and control a company or site at the highest levels with the authority and responsibility to mobilize resources within the company or site. **ICH Q10**

severity, *n*—a measure of the possible consequences of a hazard. **ICH Q9**

signed (signature), *n*—the record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature. **ICH Q7**

solvent, *n*—an inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API. **ICH Q7**

specification, *n*—a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. "Conformance to specification" means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. **ICH Q7**

specificity, *n*—specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc. **ICH R2 (Q1)**

stakeholder, *n*—any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. Decision makers might also be stakeholders. For the purposes of this guideline, the primary stakeholders are the patient, healthcare professional, regulatory authority, and industry. **ICH Q9**

state of control, *n*—a condition in which the set of controls consistently provides assurance of continued process performance and product quality. **ICH Q10**

starting material, *n*—any substance used in the production of a medicinal product, but excluding packaging materials. **EU GMP Glossary**

subject matter experts (SMEs), *n*—individuals with specific expertise and responsibility in a particular area or field (for example, quality unit, engineering, automation, development, operations, and so forth). **E2500**

trend, *n*—a statistical term referring to the direction or rate of change of a variable(s). **ICH Q9**

validation, *n*—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. **ICH Q7**

validation protocol, *n*—a written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results. **ICH Q7**

verification, *n*—a systematic approach to verify that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly. This is an umbrella term that encompasses all types of approaches to assuring systems are fit for use such as qualification, commissioning and qualification, verification, system validation, or other. **E2500**

yield, expected, *n*—the quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data. **ICH Q7**

yield, theoretical, *n*—the quantity that would be produced at any appropriate phase of production based upon the quantity of material to be used, in the absence of any loss or error in actual production. **ICH Q7**

3.2 *Bioprocess Definitions:*

accessible, *adj*—permitting close approach or contact that could include requiring removal or opening of an access panel or door. **E1117**

aerobic, *adj*—able to live, grow, or take place only where free oxygen is present. **E1126**

aerobic fermentation, *n*—fermentation processes that require the presence of oxygen. **E1126**

alpha complementation, *n*—the ability of a short aminoterminal fragment (alpha fragment) of β-galactosidase to form a functional complex with the carboxyl terminal fragment (omega fragment). **E1493**

anaerobic, *adj*—living or active in an oxygenless environment. **E1126**

anaerobic bacteria, *n*—microbes whose metabolisms require the absence of free oxygen. **E1126**

anaerobic fermentation, *n*—fermentation processes conducted in the absence of oxygen. The following anaerobic fermentation processes are significant in obtaining useful forms of energy from biomass: (*1*) alcoholic fermentation, fermentation processes whereby certain microorganisms convert glucose and other substrates with alcohol as an end product, (*2*) methane fermentation, generally termed anaerobic digestion. (See also **anaerobic digestion**). **E1126**

anhydrous, *adj*—a material that does not contain water either absorbed on its surface or as water of crystallization; a water-free product. **E1126**

aseptic sampling, *n*—sampling process in which no extraneous microorganisms or substances are introduced into the sample or its original bulk material as a result of the sampling system and activity. **E1287**

azeotrope, *n*—constant boiling mixture; for ethanol-water, the azeotrope of 95.6 % ethanol and 4.4 % water (both percentages by volume) boils at one atmosphere pressure. **E1344**

azeotropic distillation, *n*—the use of an organic solvent to create a new constant boiling point mixture, a method used to produce anhydrous ethanol from the ethanol water azeotrope. **E1344**

backset, *n*—the liquid portion of the thin stillage that is recycled as part of the process liquid in mash preparation. **E1344**

bacteriophage, *n*—a virus that infects bacteria. **E1285**

basic hydrolysis, *n*—the chemical addition of water to a compound. **E1344**

batch fermentation, *n*—batch of nutrient mixture and microorganisms mixed in a vessel and allowed to ferment. **E1344**

bioconversion, *n*—a general term describing the use of biological systems to transform one compound into another. Examples are digestion of organic wastes or sewage by microorganisms to produce methane. **E1126**

biomass, *n*—biomass—total weight of living matter in a given volume. **E1126**

capsomere, *n*—a structural subunit of the outer protein shell (capsid) of a virus consisting of protein monomers. **E1286**

centrifuge, *n*—machine that separates a mixture of solids and liquids by centrifugal force. **E1344**

continuous fermentation, *n*—nonstop flow of nutrients into a fermenting vessel, with the simultaneous outflow of products, organisms, and by-products. **E1344**

cryogenic temperatures, *n*—temperatures below or equal to −100°C. **E1564, E1565, E1566**

cryoprotectant, *n*—a chemical substance used to protect cells during freezing and rewarming. **E1342**

deleterious impurities, *n*—impurities that are a health or safety concern, particularly with respect to toxicity, carcinogenicity, or immunogenicity. Deleterious impurities must be controlled and their levels determined using suitable analytical methods. **E1298**

direct detection of mycoplasma, *n*—detection of mycoplasma by cultivation in culture media. **E1531, E1532, E1533, E1536**

DNA fluorochrome stain, *n*—staining of DNA specifically by the use of bisbenzamide fluorochrome stain or other DNA fluorochromes of comparable quality and performance, such as DAPI (4′,6-diamidine-2-phenyl-indole-2HCl)-Serva 18860. **E1532**

dry basis moisture content, *n*—of biomass, cells, or product fuels, the ratio of the weight of the water in a sample to the weight of the dry material. It is expressed as a percent. **E1126**

durability, *n*—the quality of a component to perform as designed for its design life. **E1117**

envelope, *n*—a layer of cell membrane-derived lipoprotein that surrounds the protein coat (capsid) of some viruses. **E1286**

enzyme, *n*—biological catalyst that is protein in nature. **E1344**

eutectic temperature, *n*—the temperature below which all liquid portions of an aqueous suspension have entered the solid phase. **E1342**

extreme weather conditions, *n*—environmental conditions that have occurred only once during the past 30 years. **E1117**

fermentation, *n*—the biochemical reaction process where microorganisms in a nutrient medium 56 convert a feedstock to a product. **E1344**

F factor, *n*—an episome of *E. coli*. Encoded on it are the functions necessary to produce an F pilus. **E1493**

flash point, *n*—the temperature at which a combustible liquid ignites. E1344

F pilus, *n*—protrusion on *E. coli* that is necessary for mating. The F pilus also contains the receptor for phage M13. E1493

freeze-drying, *n*—also known as lyophilization, sublimation of water from a frozen aqueous suspension. E1342

freezing, *adj*—lowering the temperature of an aqueous suspension to a point at or below the temperature of ice crystal formation. E1342

genome (of a virus), *n*—the genetic material consisting of nucleic acid (RNA or DNA). E1286

glucose, *n*—the most prominent simple sugar (6-membered $C_6H_{12}O_6$) produced from starches and cellulose material by hydrolysis. E1344

good engineering practices, *n*—include design practices and criteria accepted in professional societies (ASTM, AIChE, ASME, ACS, etc.), proved by experience, verified by actual data, etc., that will meet the process, safety, and environmental requirements of the system. E1117

hazardous biological materials, *n*—biological materials, and products derived therefrom, that pose a potential threat to human health. E1566

hydrolysis, *n*—the act of cleaving or splitting of complex molecules by the chemical addition of a water molecule. Acid hydrolysis is defined as the chemical addition of water to a compound. E1344

indirect detection of mycoplasma, *n*—detection of mycoplasma by DNA staining or any method other than cultivation. E1531, E1532, E1533, E1536

induction, *n*—the relief of repression of transcription of lysogenic phage genes encoding the functions for lytic growth, so that the phage will grow lytically. E1285

innocuous impurities, *n*—impurities that are not a health or safety concern in the product. The route of administration of the drug may be a significant criterion in the determination of whether an impurity is innocuous. E1298

liquid nitrogen freezers, *n*—freezers that operate by a refrigeration system in which cooling is provided by a refrigerant such as liquid nitrogen. E1565

liquid nitrogen storage, *n*—storage directly in liquid nitrogen or in the vapor phase above liquid nitrogen. E1566

low temperature preservation, *n*—stabilizing viable or biologically active material by freezing or freeze-drying. E1342

lysogen, *n*—a bacterial strain that has a phage stably maintained. In the case of lambda, the phage is integrated into the host genome. The integrated phage is called a prophage. E1285

moisture content, *n*—the amount of water contained in product, expressed as either a percentage of the mass of the oven-dry biomass or of the wet biomass, moisture content, dry basis. E1126

multiplicity of infection, *n*—the ratio of infecting phage to host bacteria. E1285

mycoplasma, *n*—the smallest prokaryotes capable of living freely, lacking a cell wall, having a circular double stranded DNA relatively rich in adenine and thymine, and containing 16s and 23s ribosomal RNAs. They can be found as contaminants in cell cultures. E1531, E1532, E1533, E1536

nucleocapsid, *n*—the outer protein coat or shell (capsid) of a virus plus its inner core of nucleic acid and proteins. E1286

normal operating conditions, *n*—the usual range of physical operating conditions (flow, pressure, temperature, etc.) for component or system. E1117

passive refrigeration, *n*—a refrigeration system in which cooling is provided by a refrigerant such as liquid nitrogen. E1564

pathogenic, *adj*—disease causing. E1287

plaque, *n*—a round, clear area in a layer of host cells caused by virus growth and resultant killing or lysis of the cells. E1286

press, *n*—mechanical device that removes liquids from solids by mechanically pressing the solids against a porous surface. E1344

production cycle, *n*—the series of operations required to process through the facility a quantity of feedstock mixed with water having a volume equal to the typical volume of the fermentation system and return the facility to the configuration at the start of the cycle. The quantity of water mixed with the feedstock shall be as per specification for normal operation. This volume is equal to the sum of the working volumes of all fermenters in a batch fermentation process. This volume is equal to the sum of the working volumes of each stage of fermentation in a continuous fermentation process E869

proximate analysis, *n*—the determination, by prescribed methods, of moisture, volatile matter, fixed carbon (by difference), and ash. The term proximate analysis does not include determinations of chemical elements or determinations other than those named. E1126

purity, of a biological drug product, *n*—the measure of the biologically active drug in relation to the total substances (not including additives) present in the drug product, usually expressed on a percentage basis. E1298

restriction endonuclease, *n*—a bacterial enzyme that cuts double-stranded DNA at positions consisting of specific short sequences of nucleotides. E1286

sterile, *adj*—free of any living organism. E1287

sugars, *n*—molecules of carbohydrate, namely monosaccharides and disaccharides such as glucose, galactose, mannase, sucrose or fructose, etc. E1344

supernatant, *n*—that liquid remaining after separation of a liquid/solid mixture. **E1344**

temperate bacteriophage, *n*—a bacteriophage that can grow lytically, killing the host, or can exist stably in the host. **E1285**

total weight basis moisture content, *n—of drug product, drug substance, or intermediate,* the ratio of the weight of the water in a sample to the weight of the wet material. It is expressed as a percent (also called wet basis moisture content). **E1126**

vacuum distillation, *n*—to affect separation of two or more liquids under reduced pressure operation of a distillation column. Vacuum reduces the boiling points of the liquids being separated.

vector, *n*—a fragment of DNA usually containing an origin of replication that is engineered to accept a foreign piece of DNA. **E1285**

vitrification, *n*—solidification of an aqueous suspension at low temperatures without the formation of ice crystals. **E1342**

volatile matter, *n*—those products, exclusive of moisture, given off by a material as gas or vapor, determined by definite prescribed methods that may vary according to the nature of the material. **E1126**

wet-basis moisture content, *n*—the moisture content expressed as the ratio of the weight of water in the drug product, drug substance or intermediate to the total weight of the fuel. **E1126**

wild type, *n*—the naturally occurring, original isolate. **E1285**

yeast, *n*—eukaryotic microorganisms (fungi) that produce alcohol and CO_2 under normal fermentation conditions. **E1344**