PQRI Stability Shelf-Life Working Group Glossary Ver 1 0.doc

Term	Definition	Reference
Accelerated testing	Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.	ICH Q1A
Acceptance criteria:	Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures	ICH Q6A
	"(20) Acceptance criteria means the product 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 (or any other convenient subgroups of manufactured units)."	CFR 21 Part 210.3
Batch	"(2) Batch means 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." See also 'Lot'	CFR 21 Part 210.3

Term	Definition	Reference
Boot Strap Technique	A sample of size n is selected with replacement from the original sample. This process is then repeated a large number of times, where each time the sample mean and standard deviation are calculated.	Kutner, Nachtsheim, and Neter. Applied Linear Regression Models. 4th ed. New York: McGraw-Hill Irwin, 2004. pg. 459.
Bracketing	The design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system	ICHQ1A
Broad Inference Space	The space to which inference is based on the entire population of batches, not just those batches observed. The observed batches are assumed to be representative of the entire population, including future batches.	Stroup, Walter W., et al. SAS for Mixed Models. 2nd ed. Cary, NC: SAS Institute Inc., 2006. pg. 211.
Calibration	(aka “Inverse Regression”) The process of obtaining predicted values of x based on the fitted line for values of y (i.e. y = a + bx); Using a new response (y) to predict x.	Draper, Norman R., and Harry Smith. Applied Regression Analysis. 3rd ed. New York: John Wiley & Sons, Inc., 1998. pg. 83.
	The use of known data on the observed relationship	Wikipedia. March 2007.

Term	Definition	Reference
	between a dependent variable and an independent variable to make estimates of other values of the independent variable from new observations of the dependent variable.	
Combination product:	A drug product which contains more than one drug substance.	ICH Q6A
Confidence Band	A confidence interval around the entire regression line for the population mean at each value of x.	Stroup, Walter W., et al. SAS for Linear Models. 4th ed. Cary, NC: SAS Institute Inc., 2002. pg. 11.
Confidence Bound(s)	Upper and/or lower confidence interval estimates (i.e. statistic ± multiplier*standard error).	"One-sided and Two-sided Confidence Bounds." www.weibull.com. ReliaSoft Corporation. 1998-2007.
Confidence Interval	An interval constructed from a random sample of the data in such a way that C% of all random samples will yield intervals that capture the true parameter value (where C is the confidence coefficient).	DeVeaux, Velleman, and Bock. Intro Stats. 2nd ed. Boston: Pearson Education, Inc., 2006. pg. 440.
Consumer Risk	Statistical probability of the "pass" decision from testing a batch that is at or below the "limiting quality". In hypothesis-based testing, when the null hypothesis is that the batch is at or below the limiting quality, consumer risk is the same as Type I error.	
Continuous Process Verification:	An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.	ICH Q8A

Term	Definition	Reference
Coverage	1) The proportion of the population within the target interval. 2) Coverage of the batch at the limiting quality. This "coverage" is then used in the name of the corresponding test and should not be confused with the coverage that the batch actually has.	
Coverage (Limiting Quality Standard)	Dave C	
Coverage (Statistical / Tolerance)	The percentage of the time similarly constructed intervals (i.e. confidence, prediction, tolerance) contain the true parameter/value of interest. The parameter of interest for a tolerance interval is a percentile of the distribution.	Parkhurst, Anne M. "Confidence Intervals, Prediction Intervals." STAT 870 Multiple Regression notes, 2001. Module 04.
Coverage Probability	The probability the parameter of interest lies within the estimated interval constructed for that parameter.	Casella, George and Roger L. Berger. Statistical Inference. 2nd Ed. Duxbury Thomson Learning, 2002. pg. 440.
Critical In Process Control	Critical In-Process Controls are checks (i.e. tests or measurements) performed during production to monitor and, if appropriate, to adjust the process and/or to ensure drug substance or drug product critical quality attributes are met.	
Critical Process Parameter	A process parameter that impacts a Critical Quality Attribute(s) and presents a significant risk to the process failing to produce the desired quality.	

Term	Definition	Reference
Critical Quality Attribute	A physical, chemical, biological or microbiological property or characteristic that needs to be controlled (directly or indirectly) to ensure product quality.	ICH Q8 (R1) Draft 7.0
Degradation product:	A molecule resulting from a chemical change in the drug molecule brought about over time and/or by the action of e.g., light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Also called decomposition product.	ICH Q6A
Design Space	The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.	ICH Q8A
Dosage form	A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.	ICHQ1A
Drug product	The dosage form in the final immediate packaging intended for marketing.	ICHQ1A
Drug substance	The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.	ICHQ1A

Term	Definition	Reference
Expiration date	The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification if stored under defined conditions, and after which it must not be used.	ICHQ1A
Fixed Batch Effects	An effect in which the levels in the study represent all possible levels of the factor, or at least all levels about which inference is to be made.	Stroup, Walter W., et al. SAS for Mixed Models. 2nd ed. Cary, NC: SAS Institute Inc., 2006. pg. 4.
Formal Experimental Design:	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 Q8A
Formal stability studies	Long term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of a drug substance or the shelf life of a drug product.	ICHQ1A
Identified impurity:	An impurity for which a structural characterization has been achieved.	ICH Q6A
Impurity:	1) Any component of the new drug substance which is not the chemical entity defined as the new drug substance. (2) Any component of the drug product which is not the chemical entity defined as the drug substance or an excipient in the drug product	ICH Q6A

Term	Definition	Reference
Intermediate testing	Studies conducted at 30°C/65% RH and designed to moderately increase the rate of chemical degradation or physical changes for a drug substance or drug product intended to be stored long term at 25°C.	ICHQ1A
Limiting quality	The quality of the batch considered "unacceptable". The quantitative expression of the limiting quality depends on the metric used for "quality" (e.g., coverage). The quantitative definition of limiting quality should be used when designing tests and acceptance criteria.	
Long term testing	Stability studies under the recommended storage condition for the re-test period or shelf life proposed (or approved) for labeling.	ICHQ1A
Lot	"(10) Lot means 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." See also 'Batch'	CFR 21 Part 210.3

Term	Definition	Reference
Matrixing sort	The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.	ICH Q1A
Narrow Inference Space	The space to which inference is based on specific batches (i.e. those batches used in the analysis). Uncertainty in the estimation is removed because inference is not being made to the entire population of batches.	Stroup, Walter W., et al. SAS for Mixed Models. 2nd ed. Cary, NC: SAS Institute Inc., 2006. pg. 211.
New drug product:	A pharmaceutical product type, for example, tablet, capsule, solution, cream, etc., which has not previously been registered in a region or Member State, and which contains a drug ingredient generally, but not necessarily, in association with excipients.	ICH Q6A
Normal Operating Range (NOR)	The range of acceptable performance around a target value for parameters associated with the product's control space.	
One-Sided Interval	A (1-α)% interval constructed in such a way that (1-α)% of the population lies above the lower bound (for a one-sided lower interval) or (1-α)% lies below the upper	"One-sided and Two-sided Confidence Bounds." www.weibull.com. ReliaSoft

Term	Definition	Reference
	bound (for a one-sided upper interval).	Corporation. 1998-2007.
Pooling	The process of combining data from two or more populations to estimate a statistic when we are willing to assume that the estimated value is the same in both populations.	DeVeaux, Velleman, and Bock. Intro Stats. 2nd ed. Boston: Pearson Education, Inc., 2006. pg. 561.
Prediction Band	A prediction interval around the entire regression line for future values of y at each value of x.	Stroup, Walter W., et al. SAS for Linear Models. 4th ed. Cary, NC: SAS Institute Inc., 2002. pg. 11.
Prediction Interval	A confidence interval for a new observation.	Draper, Norman R., and Harry Smith. Applied Regression Analysis. 3rd ed. New York: John Wiley & Sons, Inc., 1998. pg. 82.
Process Analytical Technology (PAT):	A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., 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 Q8A
Process Capability	"Process capability is a statistical measure of the inherent process variability for a given characteristic." Typically characterized by process capability indices: Cp, Cpk, Cpm, Ct	Specifications for the Chemical and Process Industries, ASQC Quality Press, 1996, Pg 98.

Term	Definition	Reference
Process Performance	"Process performance represents the actual distribution of product and measurement variability over a long period of time, such as weeks or months." Typically characterized by process performance indices: Pp, Ppk, Ppm, Pt	Specifications for the Chemical and Process Industries, ASQC Quality Press, 1996, Pg 101.
Process Robustness:	Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.	ICH Q8A
Producer Risk	Statistical probability of the "reject" decision from testing a batch whose quality is better than the "limiting quality". In hypothesis-based testing, when the null hypothesis is that the batch is at or below the limiting quality, producer risk is the same as Type II error.	
Protecting (Stat – alpha level)	The threshold that determines when we reject a null hypothesis; the probability of rejecting the null hypothesis when in fact it is true; (1-α)% of all random samples will yield interval estimates that capture (i.e. protect) the true parameter value; (1-α)% is the level of confidence for an interval estimate.	DeVeaux, Velleman, and Bock. Intro Stats. 2nd Ed. Boston: Pearson Education, Inc., 2006. pg. 441.
Proven Acceptance Range (PAR)	The range of acceptable performance around a target value for parameters associated with the product's design space.	
Quality by Design	A systematic process by which product quality and performance is achieved and assured by design of an	M. Nasr at the PQRI Workshop on Setting Specifications in the 21st

Term	Definition	Reference
	effective/robust manufacturing process and formulation.	Century. March 16, 2005
Quality Systems	Dave T	
Quality:	The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity.	ICH Q6A
	Terry – alternative definitions 3.1.1 quality degree to which a set of inherent characteristics (3.5.1) fulfils requirements (3.1.2)	ISO 9000
	"Quality means those features of products which meet customer needs and thereby provide customer satisfaction"	Juran's Quality Handbook Joseph Juran
	"Quality means freedom from deficiencies"	
Quantile	The pth quantile is the value of the response below which p proportion of the population values lie.	Hao, Lingxin and Daniel Q. Naiman. Quantile Regression. SAGE Publications, Inc., 2007. pg. 3.
Quantile Regression	An extension of Ordinary Least Squares Regression that models the relationship between one or more covariates X and the conditional quantile of the response variable Y given X=x.	SAS/STAT QUANTREG Documentation, pg. 3.

Term	Definition	Reference
Random Batch Effects	An effect in which the levels in the study plausibly represent a larger population with a probability distribution. Here the analysis focuses on estimating the variance among the entire population of batches.	Stroup, Walter W., et al. SAS for Mixed Models. 2nd ed. Cary, NC: SAS Institute Inc., 2006. pg. 5.
Regression Analysis	The statistical methodology that utilizes the relation between two or more quantitative variables so that a response or outcome variable can be predicted from the other, or others.	Kutner, Nachtsheim, and Neter. Applied Linear Regression Models. 4th ed. New York: McGraw-Hill Irwin, 2004. pg. 2.
Re-test date	The date after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given drug product	ICHQ1A
Re-test period	The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be re-tested for compliance with the specification and then used immediately. A batch of drug substance can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a re-test period. The same may be true for certain antibiotics.	ICHQ1A

Term	Definition	Reference
Shelf life (also referred to as expiration dating period)	The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.	ICHQ1A
Simultaneous Tolerance Interval	An approximate statistical tolerance interval that contains at least p proportion of the population.	PROC CAPABILITIES/Interval Statement/METHODS=3. SAS Help and Documentation. SAS Institute, Inc. 2003.
Specification – Release	The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release	ICHQ1A
Specification - Shelf life	The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its re-test period, or that a drug product should meet throughout its shelf life..	ICHQ1A

Term	Definition	Reference
Specification:	A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities	ICH Q6A
	"Specification: A document that states the requirements to which a given product or service must conform."	ASQ/ANSI
	3.7.3 specification document (3.7.2) stating requirements (3.1.2) NOTE A specification can be related to activities (e.g. procedure document, process specification and test specification), or products (3.4.2) (e.g. product specification, performance specification and drawing).	ISO 9000

Term	Definition	Reference
Specified impurity:	An identified or unidentified impurity that is selected for inclusion in the new drug substance or new drug product specification and is individually listed and limited in order to assure the quality of the new drug substance or new drug product.	ICH Q6A
Statistical Process Control	The conversion of data to information using statistical techniques to document, correct, and improve process performance Use of statistical techniques such as control charts to analyze a process or its output so as to take appropriate actions to achieve and maintain a state of statistical control	NIST/SEMATECH e-Handbook of Statistical Methods Measurement System Analysis Reference Manual, Automotive Industry Action Group (AIAG)
Target Interval	The interval of some relevant product attribute (e.g., dose content) considered to be appropriate from the safety and efficacy perspectives. Ideally, it should be established based on clinical considerations. Target intervals published in guidance documents are often based on historical convention (e.g., 75%-125% label claim). A specific target interval is needed to define a parametric tolerance interval test.	
Tolerance Interval	An interval that protects a percentile of a distribution. An interval that protects a fixed proportion of the population with stated confidence.	"7.2.6.3 Tolerance intervals for a normal distribution." Engineering Statistics Handbook. National

Term	Definition	Reference
		Institute of Standards and Technology. 7/18/2006.
	An interval which can be claimed to contain at least a specified proportion p of the population with a high degree of confidence.	Hahn, Gerald J. "Statistical Intervals for a Normal Population Part I. Tables, Examples and Applications." Journal of Quality Technology. Vol 2. No. 3. July 1970.
	The tolerance limits are required to be such that the probability is equal to a preassigned value β that the tolerance limits include at least a given proportion γ of the population.	Wolfowitz, J. and A. Wald. "Tolerance Limits for a Normal Distribution." The Annuals of Mathematical Statistics. 1946.
Two-Sided Interval	A (1-α)% interval with an upper and lower bound constructed in such a way that α/2% of the population lies below the lower bound and α/2 lies above the upper bound.	"One-sided and Two-sided Confidence Bounds." www.weibull.com. ReliaSoft Corporation. 1998-2007.

Term	Definition	Reference
Type I error (also designated by alpha)	The probability to reject the null hypothesis when it is true. See also "consumer risk".	
Type II error (also designated by beta)	The probability of rejecting the alternative hypothesis (or failing to reject the null hypothesis) when the alternative hypothesis is true. See also "producer risk".	
Unidentified impurity:	An impurity which is defined solely by qualitative analytical properties, (e.g., chromatographic retention time).	ICH Q6A
Upper and/or Lower Bound	Upper bound: interval estimate constructed by statistic + multiplier*standard error. Lower bound: interval estimate constructed by statistic - multiplier*standard error.	"One-sided and Two-sided Confidence Bounds." www.weibull.com. ReliaSoft Corporation. 1998-2007.
β-content tolerance interval	A tolerance interval constructed in such a way that the probability the β-expectation tolerance interval captures at least β*100% of the population is γ, where γ is the level of confidence.	Mee, Robert W. "β-Expectation and β-Content Tolerance Limits for Balanced One-Way ANOVA Random Model." TECHNOMETRICS. Vol. 26. No. 3. 1984.

Term	Definition	Reference
β-expectation tolerance interval	A tolerance interval constructed in such a way that the expected proportion of the population falling within the interval is β, where $\beta \in [0,1]$.	Mee, Robert W. "β-Expectation and β-Content Tolerance Limits for Balanced One-Way ANOVA Random Model." TECHNOMETRICS. Vol 26. No. 3. 1984.