Glossary of Terms

Specifications for the Conduct of Chemistry Activities for Toxicology Research Performed by the Division of Translational Toxicology at the National Institute of Environmental Health Sciences

Glossary of Terms

The following are definitions of terms used throughout the Division of Translational Toxicology (DTT) Chemistry Specifications and related documents.

Accuracy (Relative Error): Closeness of a measured value to the nominal value. Acceptable accuracy is typically demonstrated when measured values are ≤ ± 10% (formulation); ≤ ± 15% (bioanalysis) of the nominal value.

Actual (expected) concentration: The concentration that was prepared based on the amount of test article actually weighed out and the subsequent dilution(s).

"All laboratory work completed": The phrase "all laboratory work completed" is defined as the point at which ongoing bench work is complete, laboratory personnel have checked notebooks, and the data package has been assembled for review by quality control and the quality assurance unit (QAU).

Analytical measurement limits: Measurement limits consist of four parameters that define the ability of an analytical method or assay to measure a target analyte at a specified concentration. These parameters are the limit of detection (LOD), limit of quantitation (LOQ), experimental limit of quantitation (ELOQ), and lower limit of quantitation (LLOQ).

Batch: For pure substances or known chemical mixtures: a "batch" is a subset of a lot. There can be many "batches" in a single lot, but a single batch can contain only one lot. (e.g., a lot is the full quantity defined by the preparer, which may be separated into many batches). The "batch" should be traceable to a lot, and therefore has been made under the same criteria as the lot.

For *dose formulations*, a batch constitutes a single weighing of a chemical or test article for a single dose group, which is subsequently formulated on a single day. If a second (or third, etc.) weighing is done for the same dose group and is subsequently made into a formulation on the same day, each weighing constitutes a new batch for the same mix date. Weighings that occur on separate days constitute different mix dates. Dose analysis (when required) must be performed on all batches made on the same mix date. Determined concentrations of multiple batches of a formulation, prepared on a single mix date, must be within 5% of each other.

CASRN: A Chemical Abstracts Service (CAS) registry number® (also referred to informally as a CAS number) is a unique identification number assigned by CAS in the United States to every chemical substance described in the open scientific literature. It includes all substances described from 1957 to the present, plus some substances from the early 1800s (source: Wikipedia, accessed June 2023).

Certificate of Analysis (COA): Provided by a chemical supplier to document lot purity for a supplied chemical.

Data Sheet: A summary of a report containing specific information described in Chapter 7. Reporting Requirements of the DTT Chemistry Specifications.

Default DTT animal species: DTT typically uses the Hsd:Sprague Dawley® SD® rat, CD-1, or B6C3F1/N (toxicology/carcinogenicity studies) mouse in its studies.

Deliverable: A deliverable is the product of work conducted on a contract; the finished result of a step of work; or any unique and verifiable product, result, or capability to perform a service that must be produced to complete a process, phase, or project under a contract.

Determined (found) concentration: The reported concentration resulting from an analysis of the prepared formulation or sample.

Draft final report: A draft report in electronic format (PDF and MS Word) that describes the work performed for the assignment and details the results obtained. The draft final report shall be, in the contractor's estimation, a final report subject only to review and approval by the contracting officer's representative (COR). As such, the draft final report shall contain a description of the method(s) used; the results of the assignment, normally in tabular form; plots of appropriate analytical instrument outputs (chromatograms, spectra, thin-layer chromatography plates, etc.); and appendices specified by the COR, for example, an Analytical Method Standard Operating Procedure, when applicable (Chapter 7. Reporting Requirements). If a review of the draft final report by the COR results in changes to the report, the contractor shall submit a new version of the draft final report to the COR that reflects the required changes, prior to submission of the final report.

DTT Chemistry Specifications: The phrase "DTT Chemistry Specifications" refers to this document.

DTT Project Management System (DTT PMS, ORBIT): An electronic means of collection and management of information from one or more sources and the distribution of that information to one or more audiences. This sometimes involves those who have a stake in, or a right to the information. Currently, the DTT employs a customized Microsoft Dynamics 365 Project Service Automation application known as ORBIT for project management.

DTT Toxicology Specifications: The phrase "DTT Specifications" refers to the Specifications for the Conduct of Toxicity Studies by the Division of Translational Toxicology at the National Institute of Environmental Health Sciences.[1]

DTTID: A number assigned by DTT to concepts, proposals, and projects tracked in ORBIT.

DTXSID: Distributed structure-searchable toxicity (DSSTox) substance identifier (DTXSID) used in the Environmental Protection Agency CompTox Dashboard.**Error! Bookmark not defined.**

Executive Summary: A narrative summary inserted below the header and before the quality assurance statement, which summarizes the results of each analysis in the report and gives the conclusion of the report. For example, a report describing an assay to determine the identity and purity of a chemical would contain paragraphs describing the results of any spectrometric assays performed to confirm the identity, results of chromatographic assays to determine purity, any impurities identified, results of any compendial assays (e.g., water content), and a statement summarizing the conclusions of the study (e.g., the material was identified as methanol with a purity of >99%).

[1] https://ntp.niehs.nih.gov/go/DTT_toxicologyspecs

Experimental limit of quantitation (ELOQ): Defined as the concentration of the lowest standard that meets the acceptability criteria of the assay (normally ±10% relative error, with a relative standard deviation of ≤10%). Used in formulation analysis.

Final report: The final report consists of the approved draft final report, with a signed good laboratory practices (GLP) compliance page (as appropriate), and a signed quality assurance statement (Chapter 7. Reporting Requirements), which is uploaded to a designated folder in ORBIT as an electronic copy in MS Word or PDF format.

Gavage: Bolus oral dosing route in which a dose formulation is administered via intubation.

Good laboratory practices (GLP or GLPs): GLP embodies a set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported, and archived. These studies are undertaken to generate data by which the hazards and risks to users, consumers, and third parties, including the environment, can be assessed for pharmaceuticals (only preclinical studies), agrochemicals, cosmetics, food additives, feed additives and contaminants, novel foods, biocides, detergents, etc. GLP helps assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments. The U.S. Food and Drug Administration (FDA) has rules for GLP in 21 CFR 58. These are the rules used for preclinical trials in the United States on animals prior to clinical research in humans. Research in the United States that is not conducted under these restrictions or research done outside the United States that is not conducted according to the Organisation for Economic Co-operation and Development guidelines (or FDA rules) might be inadmissible in support of a new drug application in the United States.

Impurity: Any substance found in a test article that is not the test article or a known primary constituent of the test article, when the test article is a known mixture.

Interim Report: Preliminary results of an assignment in electronic format, usually as a data table. Interim Reports are to be posted to the DTT IMS under the applicable Task, as soon as the lab work that generated the data has been completed. See Appendix A.2. Data Submission Requirements for requirements for data submissions.

Limit of detection (LOD): Defined as three times the standard deviation of the blank or the lowest standard, expressed as concentration.

Limit of quantitation (LOQ): Defined as 10 times the standard deviation of the blank or lowest standard, expressed as concentration. Used in formulation analysis.

Lot: A "lot" is an item/product that is produced under preparer-defined criteria under certain conditions (e.g., controlled materials/ingredients, under a controlled temperature, for a controlled time frame, for a certain quantity, volume, or time period).

Lot number: Identification number assigned to a particular quantity or lot of material from a single manufacturer or preparer. To completely identify a chemical, you must include both the lot number and the batch number if multiple batches are produced or anticipated. Format of the completely qualified lot number shall be "lot number (batch number)." For example, batch 2 of lot 123ABC-2 would be written 123ABC-2(2). When a single lot of material is procured at two different times, each procurement constitutes a new batch.

Lower limit of quantitation (LLOQ): Defined as the concentration of the lowest standard that meets the acceptability criteria of the assay (normally ±20% relative error, with a relative standard deviation of ≤20%). Used in biosample analysis.

Matrix: Defined as the biological tissue or fluid that is the subject of an analysis, e.g., plasma, liver, or adipose.

Method verification: Demonstration of the ability of an analytical method to quantitate samples having concentrations above the analytical range of the method.

Nominal concentration: The concentration specified by the study protocol or study design document.

Nontargeted Analysis (NTA): NTA encompasses a rapidly evolving set of mass spectrometry, nuclear magnetic resonance, and other non-specific techniques aimed at characterizing the chemical composition of complex samples, identifying unknown compounds, and/or classifying samples, without prior knowledge regarding the chemical content of the samples.

Omics: NTA (e.g., exposomics, metabolomics, proteomics) in a variety of sample types using appropriate analytical systems (e.g., liquid chromatography coupled with high-resolution mass spectrometry).

ORBIT task (project task): A description of the work requested by a COR or other authorized staff that is entered into ORBIT. Tasks in ORBIT include the estimated lab start and completion dates and estimated report date along with a description of the scope of the assignment and the work required. The ORBIT task entry is reviewed and approved by the COR. As the work progresses, the contractor updates the corresponding ORBIT task as necessary. A unique number assigned by ORBIT (Project Task ID) identifies each task.

ORBIT: The DTT project management application. ORBIT, which stands for organizational resource and business information tool, is based on Microsoft's Dynamics 365 Project Operations and tracks information related to DTT concepts, proposals, projects, and project tasks. ORBIT is used to assign and track the work under the chemistry contracts, to capture all communications related to a project, and to provide a multi-user collaboration environment for DTT and its contractors.

Precision (Relative Standard Deviation, RSD): Closeness of the measured values of replicates to each other. Acceptable precision is typically demonstrated when the RSD is ≤ ± 5% (formulation) ≤ ± 15% (bioanalysis) of the mean found value.

Primary matrix: Primary matrix refers to the biological matrix (e.g., plasma) that is the focus of an analytical method development, qualification, and/or validation. The default primary matrix for biosample method development and validation is male Sprague Dawley (SD) rat plasma. Note: The SD rat strain is different from the Hsd:Sprague Dawley$^{\dot{O}}$SD$^{\dot{O}}$ rat described above.

Quality assurance (QA): QA refers to planned and systematic processes that provide confidence in a product's suitability for its intended purpose. QA provides information that enables management and the principal investigator to assess the quality of work performed under this contract and to rectify deficiencies as needed. Thus, QA activities enable management and others to assign a proper level of confidence to the work performed and reported by study staff.

Quality Assurance Unit (QAU): The QAU is a group of people who are responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls conform with the requirements of a study, functional activity, or chemistry support activity as set forth in this contract and/or a study protocol or standard operating procedure (SOP). The QAU is entirely separate from and independent of the personnel engaged in the direction and conduct of the study, functional activity, or chemistry support activity.

Quality control (QC): QC is one of many resources managed by the principal investigator, which along with the study-conduct staff are the primary determinants of quality. The purpose of QC is to ensure that the records, results, and reports, i.e., all information generated by study-conduct staff, are accurate and complete.

Quality Management Plan (QMP): The QMP provides guidance on how quality will be ensured on the project through design reviews, documentation, and other protocols. It gives management and the customer a clear understanding of how quality will be maintained and what documentation they can expect (addressing quality) during the life of the project. The plan is generated by the project team and is used as a cross-reference for other documentation and as a guide for responsibility on the quality aspects of the project. Team members refer to it to find documents (either in whole or as a reference) that they need to examine regarding quality standards for their deliverables. Managers refer to it to clarify what practices are considered essential for quality performance and to affirm who is responsible for those practices. The customer may refer to the QMP for assurance that quality practices are in place for their deliverables (and to identify any specific practices for which they are responsible). Much of the content in QMPs is often in the form of references. There may be references to performance standard guides, quality standards (such as FDA GLPs), and internal support documents. The QMP is normally limited to a single project and is specific in terms of outlining responsibilities and ownership (https://www.projectmanager.com/blog/quality-management-plan).

Recovery: Comparison of the found concentration of a vehicle standard to the found concentration of a corresponding solvent standard.

Report addenda: In addition to the body of the report, each report may contain one or more addenda summarizing the report in various ways.

Rounding and the use of "significant figures": When performing calculations using measurements, the values should be used as received from the measuring instrument. Measurements for intermediate calculations should not be rounded; rounding should occur only when reporting the final result of a calculation. "Significant figures" primarily refers to a type of rounding and is arguably appropriate when roundoff of the final answer is the dominant contribution to the uncertainty. However, there are many important situations in which roundoff of the final answer is not the dominant contribution to the uncertainty. The uncertainty should be explicitly stated when it is known (e.g., 1.23 ± 0.06 or 1.23 [4.9%]). Tabled values should be reported with values that reflect the precision of the underlying measurements. All values in a table should be reported with the same precision if they arise from the same measurements. When there are differences in the precision of measurements used to produce a result, tabled values may be rounded to the precision of the least precise measurement. Rounding rules applied to the values in the table shall be stated in a footnote to the table.

Safety Data Sheet (SDS): A safety data sheet (or material safety data sheet) provided by chemical suppliers includes information such as the properties of each chemical; the physical, health, and environmental health hazards; protective measures; and safety precautions for handling, storing, and transporting the chemical. It also provides guidance for each specific chemical on things such as personal protective equipment, first aid, and spill cleanup procedures.

Secondary matrix: A secondary matrix is defined as a matrix that differs from the primary matrix because it is a different matrix from the same species (e.g., SD rat brain) or the same matrix (e.g., plasma) from a different species, strain, sex, or aged animal; a different anticoagulant has been used for blood collection (e.g., K_3EDTA versus heparin).

Selectivity: The ability of an analytical method to distinguish the analyte of interest from the background.

Standard operating procedure (SOP): An SOP is a set of instructions with the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness. Standard Operating Policies and Procedures can be effective catalysts to drive performance improvement and improve organizational results. Every good quality system is based on its SOPs. In clinical research, the International Conference on Harmonization defines SOPs as "detailed, written instructions to achieve uniformity of the performance of a specific function." SOPs are necessary to achieve maximum safety and efficiency of the performed research operations. The information technology industry uses the terms "Standard Operating Procedure" and SOP interchangeably to describe a best-practice approach to executing tasks related to the production and maintenance of hardware and software, as well as incident and change management.

Target (theoretical) concentration: The prepared concentration, if generated according to the SOP for dose preparation. Often the same as the theoretical concentration.

Test article: A test article is any substance for which DTT has selected to perform research. DTT test articles come from a wide variety of organic and inorganic substances, including synthetic industrial chemicals, pesticides, various pharmaceuticals, metals, botanicals, nutraceuticals, and food additives. These substances may be nanomaterials or contained within a biological or environmental matrix. A test article also includes active metabolites of the tested substance.

Upper Limit of Quantitation (ULOQ): Defined as the concentration of the highest standard that meets the acceptability criteria of the assay (normally ±20% relative error, with a relative standard deviation of ≤20%). Used in biosample analysis.

Toxicokinetic Terms

Parameter	Noncompartmental Analysis	Compartmental Analysis	Definition
C_0min_pred	C0	—	Fitted plasma concentration at time zero (IV only).

Parameter	Noncompartmental Analysis	Compartmental Analysis	Definition
Cmax	Cmax_obs	Cmax_predicted	Observed or predicted maximum plasma (or tissue) concentration.
Tmax	Tmax_obs	Tmax_predicted	Time at which observed or predicted Cmax occurs.
Lambda_z	Lambda_z	—	Noncompartmental analysis (NCA) terminal elimination rate constant (NCA K_e or K_{elim}).
Half-life	HL_Lambda_z	—	Lambda z half-life, t½, the terminal elimination half-life based on noncompartmental analysis.
Alpha	—	Alpha	Hybrid rate constant of the alpha phase.
Alpha_Half-life	—	Alpha_HL	Half-life for the alpha phase.
Beta	—	Beta	Hybrid rate constant of the beta phase.
Beta_Half-life	—	Beta_HL	Half-life for the beta phase.
k01	—	K01	Absorption rate constant (K_a).
k01_Half-life	—	K01-HL	Half-life for the absorption process to the central compartment.
k10	—	K10	Elimination rate constant from the central compartment (K_e or K_{elim}).
k10_Half-life	—	K10_HL	Half-life for the elimination process from the central compartment.

Parameter	Noncompartmental Analysis	Compartmental Analysis	Definition
k12 (k13, etc.)	—	K12	Distribution rate constant from the first to the second compartment, etc.
k21 (k31, etc.)	—	K21	Distribution rate constant from the second to the first compartment, etc.
Cl	Cl_obs, Cl_F_obs	—	Clearance, includes total clearance.
Cl1	—	CL	Clearance from the central compartment, Clapp or apparent clearance for IV groups.
Cl2	—	CLD2	Clearance from the secondary compartment.
Cl1_F	Cl_F (gavage)	CL_F	Apparent clearance of the central compartment, also Cl_F for gavage groups in noncompartmental models.
Cl2_F	—	CLD2_F	Apparent clearance from the secondary compartment.
V1	Vz_obs	V1	Volume of distribution for the central compartment, includes Vd and V, volume of distribution; Vz, apparent volume of distribution for NCA; and Vapp, apparent volume of distribution for IV studies.
V2	—	V2	Volume of distribution for the peripheral compartment.
Vss	Vss_obs, Vss_pred	Vss	Volume of distribution at steady state.

Parameter	Noncompartmental Analysis	Compartmental Analysis	Definition
V1_F	Vz_F_obs	V1_F	Apparent volume of distribution for the central compartment, includes Vd_F, V_F (for oral groups), and Vc_F.
V2_F	—	V2_F	Apparent volume of distribution for the peripheral compartment.
MRT	MRTINF_obs, MRTINF_pred	MRT	Mean residence time.
AUC_0-T	AUCall, AUClast	—	Area under the plasma concentration versus time curve (AUC) from time ti (initial) to tf (final).
AUCinf_pred	AUCINF_pred	AUCINF_pred	Area under the plasma concentration versus time curve (AUC) extrapolated to time equals infinity.

See https://www.ncbi.nlm.nih.gov/books/NBK557744/ for equations used to calculate these parameters.