

Chemistry Specifications for Chemistry Services Contractors  
National Toxicology Program  
Project Management  
Final  
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### *1. General Requirements*

1. The Contractor shall develop realistic schedules for assigned work and update the schedules when priorities change
2. Work performed by subcontractors to this contractor shall meet all of the requirements set forth in the contract including those requirements specific to the functional activity(s) governing each assignment.
3. Provide an estimate of costs for all assignments in the assignment memo.
4. Upside deviations of costs from estimated costs for any assignment shall be reported to the COR in a timely manner.
  1. Costs exceeding or expected to exceed their estimated costs shall be reported in the Monthly Status Report (Section 4. Reporting Requirements) for each assignment.
  2. The Principal Investigator shall note in the appropriate forum in the Information Management System when an assignment exceeds or is expected to exceed its estimated costs.
  3. If an assignment exceeds or is expected to exceed its estimated costs by more than 30% the Principal Investigator shall contact the COR to obtain permission to exceed the estimated costs, or to revise the scope of the task to bring the costs within the estimate.

### *5. Contract Start-up*

1. The Contractor shall provide for timely start-up of contract work after award.
2. It is expected that the Contractor shall ensure the following items are in order at the time of award:
  1. All management documents are in place.
  2. Adequate staff is on hand.
  3. Facilities are as proposed and ready.

### *6. Continuity of Services*

1. The Contractor shall provide for timely and cost-effective continuity of services in the event of contract termination or transfer, including but not limited to the following:

1. Provide for orderly transition in the event of award to a new follow-on contractor.
2. Provide for orderly transfer of work to the Government in the event of contract termination.

*7. Consultants*

1. Consultants may be used from time to time to advise the contractor on various aspects of assigned projects.

## 2. *Personnel*

The Principal Investigator, Task Leaders for Chemistry (Characterization, Formulation, Bioanalysis, and ADME/Toxicokinetics), Laboratory Animal Management, Health and Safety, Quality Assurance, as well as Study Directors, shall be employees of the Chemistry Contractor (e.g., not consultants or subcontractors). The interaction and coordination of efforts needed amongst these discipline areas makes it critical that they be physically and organizationally together.

### 1. Key Personnel

#### 1. *Principal Investigator*

1. The Principal Investigator, as key personnel, shall be considered essential to the contract and must be responsible for the daily management of the contract.
2. The Principal Investigator is the contractor's authorized point of contact with the COR and other contractors as appropriate. The Principal Investigator has responsibility for the performance of all Contractor-assigned work.
3. The Principal Investigator must be knowledgeable and up to date in all aspects of the Program/Contract, including the status of all assigned work, record keeping, reporting, and detailed analysis of cost for any or all functions which make up the total operation. General qualifications expected of a Principal Investigator include:
  1. A Doctorate, or the equivalent relevant experience in chemistry or a related field.
  2. Significant experience in managing analytical chemistry programs of this type.

#### 2. Task Leaders/Study Directors

##### 1. *Chemist – Bioanalytical Chemistry*

1. This individual is responsible for bioanalytical chemistry methods development and analysis of biological tissues and fluids for a specified chemical or test article and/or its metabolites. General qualifications for the Bioanalytical Chemist include:

2. A Bachelor of Science degree in chemistry or a related science, or any combination of years of experience in chemistry or bioanalytical chemistry and full time college-level study in the particular field totaling 4 years.
3. 2+ years of analytical chemistry experience with trace analysis of biological samples.

#### 2. *Chemist – Characterization*

1. This individual is responsible for methods development and subsequent analysis of a chemical or test article for identification and purity, including analyses for other bioactive substances, metals, and volatile organic compounds that may be present in a the material. General qualifications for the Characterization Chemist include:
  1. A Bachelor of Science degree in chemistry or a related science, or any combination of years of experience in chemistry and full time college-level study in the particular field totaling 4 years.
  2. 2+ years of analytical chemistry experience, which includes trace analysis.

#### 3. *Chemist – Formulations*

1. This individual is responsible for methods development and subsequent analysis of dosed vehicles for a specified chemical or test article. General qualifications for the Formulations Chemist include:
  1. A Bachelor of Science degree in chemistry or a related science or any combination of years of experience in chemistry and full time college-level study in the particular field totaling 4 years.
  2. 2+ years of analytical chemistry experience.

#### 4. *Toxicokineticist*

1. This individual is responsible for the execution of ADME and toxicokinetic studies similar to those described in the NTP Chemistry Specifications, Section 2.5. Animal Studies, for the

Preliminary Toxicokinetic Study and Toxicokinetic Study Functional Activities, and compartmental and non-compartmental modeling of the data arising from these studies. General qualifications for the Toxicokineticist include:

1. A Master's degree or a Bachelor of Science degree and any combination of additional years of experience and graduate level study in toxicokinetics or a related science totaling 2 years.
2. 5+ years of experience conducting toxicokinetic or pharmacokinetic studies.
3. Demonstrated experience (publication record) in analyzing and modeling toxicokinetic data.

5. *Materials Handling/Chemical Containment Facility Manager*

1. This individual is responsible for the reduction of the particle size of test articles as necessary to meet specific NTP requirements; homogenization of chemicals or test articles and repackaging into containers specified by the COTR; and shipment of chemicals, test articles, and biological or environmental samples to an NTP-designated laboratory or research facility. General qualifications for the Materials Handling/Chemical Containment Facility Manager include:
  1. A Bachelor's degree in chemistry, biology, materials science, or a related field, or any combination of years of experience in chemistry, biology, or materials science and full time college-level study in the particular field totaling 4 years.
  2. 2+ years of experience managing a sample-handling program or facility, sample handling, including sample shipments of biological materials and biohazards, and sample tracking; handling of hazardous chemicals.

6. *Quality Assurance Officer*

1. This individual shall be responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in

conformance with the regulations in Part 58, "Good Laboratory Practices for Non-clinical Laboratory Studies (Federal Register, Friday December 22, 1978, Part II and any later interpretations published by the FDA). The Quality Assurance Officer shall have management support and organizational independence from the personnel engaged in the direction and conduct of the study. General qualifications for the Quality Assurance Officer include:

1. A Bachelor's degree or any combination of years of experience in a related field and full time college-level study in the particular field totaling 4 years.
  2. The QA Officer shall also have 2+ years of experience managing QA, with specific relevant experience in conducting GLP work related to the chemistry services described in Section 2. Technical Requirements of these Specifications.
  3. Appropriate scientific experience to ensure understanding of the tasks or reports being inspected or audited in chemistry and toxicokinetics.
2. The QA Officer shall have supervisory experience when the Quality Assurance Unit consists of more than one person.

#### 7. *Veterinarian*

1. This individual, with experience in laboratory animal medicine, is responsible for monitoring the health of experimental animals and interacting with the Principal Investigator and the NTP personnel concerning all phases of the animal experiments. General qualifications of the Veterinarian include:
  1. Graduate of Veterinary College recognized by the American Veterinary Medical Association.
  2. Diplomate of the American College of Laboratory Animal Medicine (preferred) or eligible by experience and education to take the examination.

3. Previous experience in managing laboratory animals, in particular rodents of all ages, including dams and their litters in a toxicology, or toxicokinetic setting.

8. *Health and Safety Officer*

1. A qualified Health and Safety Officer shall be designated to monitor worker health and safety conditions during all phases of the work. In his/her role as Health and Safety Officer, he/she shall be responsible to someone other than the Principal Investigator and the Principal Investigator's subordinates, and shall have the authority to bring unsafe conditions to the attention of higher management. The Health and Safety Officer may have other responsibilities within the Chemistry Contractor's organization; however, the amount of time devoted explicitly to health and safety is to be commensurate with the scale of the Chemistry Contractor's operations. General qualifications of the Health and Safety Officer include:
  1. Bachelor's degree (at a minimum) majoring in industrial hygiene, chemistry, biology, safety engineering, or a closely related science or engineering field.
  2. At least two years experience in occupational health and safety, along with completion of courses in general occupational health and hazard control indicating the acquisition of successively greater levels of knowledge regarding industrial hygiene. This experience shall have taken place within the last 4 years. A Master's degree in industrial hygiene, safety engineering or a Bachelor's degree in industrial hygiene, safety engineering, with one year of experience, is an acceptable substitute for this experience.
  3. Training shall have been completed within the last eighteen months, and will be refreshed with additional training at an interval not exceeding eighteen months.



4. Recent experience in working with specific requirements of local, state, and federal statutes relating to occupational health and safety, environmental protection, and chemical monitoring.
5. Demonstrated ability to deal effectively with the scientific and managerial staffs in responsibly implementing the health and safety program.

### 3. Support Staff

1. *Animal Care Staff*: Animal care technicians shall have training and experience in the administration of test articles via the required routes of exposure, in providing appropriate animal care, and in evaluating clinical signs of toxicity.
2. *Necropsy Staff*: Prosectors shall be trained and experienced in the anatomy and dissection of laboratory animals, particularly rodents.
4. *Quality Assurance Staff*  
QA staff shall be appropriately trained in the conduct of audits and inspections of assignment activities
5. *Data Management Staff*  
Data management staff shall have appropriate training in data entry for all systems used to collect and store data generating under for the NTP.

### 3. *Facilities*

#### 1. Floor Plans

1. Floor plans shall show locations where all program activities will be conducted. Floor plan requirements for specific program areas are given below:

##### 1. *Animal Facility*

1. Floor plan indicating quarantine rooms, animal rooms, showers/change areas and rest rooms; storage areas for feed, bedding and general storage; cage and rack washers; emergency power source and those areas in which emergency power operates. This floor plan is to indicate traffic flow for

personnel, animals, test article, feed/bedding, supplies, and equipment through the facility.

2. A separate floor plan of the animal facility is to indicate room airflow directionality and indicate the location of all safety equipment, such as eyewash stations, safety showers, fire control equipment, etc.
3. A floor plan indicating ventilation equipment and ductwork, including interior and exterior exhausts, shall be supplied. A floor plan for the roof(s) shall indicate the location of each of the building(s) general air intakes and exhausts and the location of the exhaust for each hood or vented enclosure.

## *2. Chemistry*

1. A floor plan of the chemical containment/dose formulation preparation area(s) for handling of neat chemicals and/or test articles, including storage areas, supporting equipment, and exhaust hoods.
2. Floor plans shall indicate storage areas for bulk chemical and dose formulations, bulk chemical and dose formulation analysis, dose formulation, and supporting equipment and exhaust hoods.
3. Floor plans for all areas used for chemical analysis, including instrument placement, ventilation, airflow, and traffic patterns.

## *3. Other Areas*

1. Indicate QA offices and filing space, data archives, waste storage, and special study facilities.

### *2. Emergency Facility Support*

1. Facilities shall have a tested back-up power source with automatic changeover equipment that is sufficient to preserve the integrity of ongoing animal studies, stored chemicals and biosamples.
2. Emergency power must handle those areas critical to the program such as animal rooms, HVAC, storage freezers/refrigerators, waste storage, etc.

3. Essential mechanical equipment must be guarded or alarmed. Provisions for prompt maintenance response must be provided. Alternative air handling systems for inhalation studies are required.

## 2. Animal Facilities

1. All animal facilities used for this program must be approved by the NTP and will be evaluated with respect to criteria outlined in the "Guidelines for Carcinogen Bioassay in Small Rodents" (DHHS Publication No. (NIH) 76-801), "Long Term Holding of Laboratory Rodents" (ILAR News, XIX, #4, 1976), the "Guide for the Care and Use of Laboratory Animals for Research Involving Chemical Carcinogens" (DHHS Publication No. (NIH) 76-900), the "Guide for the Care and Use of Laboratory Animals NRC) and any other additions and exceptions thereof.
2. Research is to be conducted in accordance with the Public Health Services Policy on Humane Care and Use of Laboratory Animals, Office of Laboratory Animal Welfare (OLAW). Accreditation of toxicology research and testing facilities by an external peer review organization such as AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care International) or CCAC (Canadian Council on Animal Care) is required.
3. It is the responsibility of the Chemistry Contractor to establish policy and procedures to address entry of approved staff and visitors into the animal facility. Entry shall be prohibited to those individuals that have been in another animal facility within the last 48 hours regardless of disease status of that facility.
4. The animal facilities shall be designed and managed to prevent contamination of animals with pathogenic organisms and to prevent contamination of personnel and the environment with test articles and also to prevent cross-contamination of animals with other test articles.

## 3. Chemistry, Dose Formulation and Biosample Analysis

1. The Chemistry Contractor must have the analytical instrumentation required for dose formulation, chemical characterization, and biosample method development and analysis. The specific types of equipment required include, but is not limited to, gas and/or liquid chromatographs, with a

variety of detectors, e.g., flame ionization, electron capture, mass spectrometry, ultraviolet/visible (UV/Vis), nitrogen phosphorous, charged aerosol, and/or evaporative light scattering. Other equipment includes instruments required for infrared spectrophotometry, proton- and carbon-nuclear magnetic resonance (COSY and ROSY) spectrometry, differential scanning calorimetry, thermogravometric analysis, and/or thin-layer chromatography and equipment required for determination of physical properties, e.g., boiling and/or melting point, density, optical rotation, etc.

2. The Contractor shall have access to (via subcontract or cooperative agreement) appropriate facilities required for characterization of nanomaterials.
3. The Contractor shall have appropriate facilities required for the conduct of dose formulation, chemical characterization, and biosample method development and analysis Functional Activities required by the SOW.

#### 4. Chemical, Biosample, and Hazardous Waste Storage

1. The Chemistry Contractor must have (a) controlled access chemical containment/dose preparation facility(ies) suitable for handling neat chemicals and/or test articles. The containment facility shall include:
  1. Secured, controlled access chemical/test article storage facilities must be available for retention of the test article at  $4 \pm 3^{\circ}\text{C}$  or at ambient temperature as specified by the NTP Test article storage includes storage of 55-gallon drums. Cold storage at  $-20 \pm 5^{\circ}\text{C}$  must be available for analytical reference standards and natural products used as test articles.
  2. Suitable V-shell blenders with intensifier bars, to be used for feed formulation preparation.
  3. Designated areas for hazardous waste storage prior to disposal.
  4. It is the responsibility of the Chemistry Contractor to establish policy and procedures to address entry of approved staff and visitors into the chemical containment/dose preparation facility. Policies and procedures shall include the following.
    1. Personal protective equipment (PPE) required while in the containment facility.

2. Appropriate monitoring of personnel entering and exiting the facility, including procedures to prevent contamination outside the containment facility by persons exiting the facility after handling neat chemicals or test articles.
5. It is the responsibility of the Chemistry Contractor to establish policy and procedures to appropriately monitor ventilation systems, including hoods, HVAC, and HEPA filtration units.
2. The Chemistry Contractor must have secured storage facilities for retention of biological samples at  $\leq -70^{\circ}\text{C}$ .

5. *Data and Quality Assurance Archives*

1. A secured, limited access area shall be provided for maintenance of all study records. In addition, Quality Assurance records must be stored in a secured, limited access area.

#### 4. *Quality Program*

Laboratory management and the Principal Investigator are responsible for the quality of work performed and products delivered under this contract. Quality Assurance (QA) activities provide information that allows management and the Principal Investigator to assess the quality of work performed under this contract and to rectify deficiencies as may be needed. Quality Control (QC) activities ensure that the records, results, and reports, i.e., all information generated by study-conduct staff, are accurate and complete.

##### 1. General Requirements

1. All work performed by the Contractor or any Subcontractor for any assignment that directly supports an NTP Toxicology study shall comply with Food and Drug Administration Good Laboratory Practices for Nonclinical Laboratory Studies (FDA GLP Regulations; Federal Register, 12/22/78, Part II et seq. <http://www.fda.gov/ohrms/dockets/98fr/980335s1.PDF>) unless specifically authorized by the COR. The requirement that work performed conform to FDA GLP requirements applies to all of the following functional activities, unless directed otherwise by the COR:

1. Protocol Development (PD)

2. Comprehensive Chemical Analysis (CCA)
  3. Chemical Reanalysis (CRA)
  4. Formulation Development and Validation (FDV)
  5. Formulation Analysis (FA) including referee analysis (when done in support of an NTP GLP study)
  6. Formulation Preparation (FP) (when done in support of an NTP GLP study)
  7. Formulation Preparation and Analysis (FPA) (when done in support of an NTP GLP study)
  8. Biosample Method Development and Validation (BMDV)
  9. Biological Sample Analysis (BSA) (when done in support of an NTP GLP study)
  10. Toxicokinetic Study (TKS)
  11. Special Chemical Analysis (SCA) (when done in support of an NTP GLP study)
2. The Contractor shall establish an effective quality program that meets the requirements set forth in this contract and complies with the requirements of the NTP Chemistry Specifications, which addresses the following objectives:
1. Establish a Quality Management Plan
  2. Establish an effective and independent Quality Assurance Unit, headed by a qualified Quality Assurance Officer
  3. Establish policies and procedures that ensure quality control at all levels, including development of a contract-wide quality control program.
  4. Develop and maintain Standard Operating Procedures for all contract operations, procedures, assignments, and tasks, which describe how each activity is to be performed.
  5. Ensure that work performed by subcontractors meets the same quality requirements as work performed by the prime contractor.

## 2. Quality Management Plan

### 1. Requirements

1. The contractor shall develop and implement a Quality Management Plan (QMP) that governs all work performed under this contract.
2. The QMP shall follow the requirements set forth in the U.S. Environmental Protection Agency (EPA) "Requirements for Quality Management Plans (EPA QAR-2) available from <http://www.epa.gov/quality/qs-docs/r2-final.pdf>. Specifically, the QMP must include, but is not limited to, the following:
  1. The QMP shall ensure that all work performed meets all applicable contractual requirements, including the requirement that the work be performed in compliance with Federal GLPs unless specifically approved by the COR.
  2. Policies governing the QC review of data generated by the contract.
  3. Policies for generation, use and maintenance of SOPs applicable to all contract activities, which describe how all operations, procedures, assignments, and tasks shall have SOPs that describe how each is to be performed (see Section 2.1.3.4. Standard Operating Procedures for detailed SOP requirements).
  4. Policies that describe the use of the QAU to inspect and review routine work and work in progress.
  5. Policies regarding the reporting and resolution of QA findings brought to the attention of management.
  6. Policies regarding the involvement of the QAU with respect to GLP compliance for all operations, procedures, assignments, and tasks performed under the contract.
  7. Policies governing the relationships between the QAU and the Principal Investigator, Task Leaders, and Contract Staff.
3. The QMP shall conform to the requirements found in Part 4. Reporting Requirements.

### 3. Quality Assurance Unit (QAU)

1. The QAU is independent of work managed by the Principal Investigator and therefore has no direct responsibility for its quality. The primary responsibility of the QAU is to provide information that enables management and the Principal Investigator to assess the quality of work performed under this contract and to rectify deficiencies as may be needed. Thus, QAU activities enable management and others to assign a proper level of confidence to the work performed and reported by study staff. Requirements for the organization and function of the QAU under this contract are specified in the FDA GLP regulations. Requirements of special interest to this contract are given below.

#### 2. Requirements

The points that follow are extracted from the FDA GLP regulations and are presented below because they are especially pertinent to the work performed under this contract. The QA activities and requirements shall include but not necessarily be limited to:

1. The primary responsibility of the QAU is to provide information that enables management and the Principal Investigator to assess the quality of work performed under this contract.
2. The Quality Assurance Officer must report to a level of management above the Principal Investigator.
3. The QAU may NOT approve or reject a procedure, datum, result, or report that is generated in the performance of this contract.
4. The QAU may NOT perform any work for which it has responsibility to monitor, or which may inhibit its authority to independently and objectively assess any work performed under this contract.
5. The QAU shall conduct inspections of work in progress and data audits that assess the extent to which work performed under this contract complies with protocols, SOPs, contractual requirements, and FDA GLP regulations.
6. The QAU shall maintain a system for tracking assignments made to the contractor. The NTP maintains a Computerized Project Management System (Section 2, Part 6. Information Management) that the QAU may elect to use as the master schedule.



7. The QAU shall audit the accuracy, completeness, and consistency of information in final reports compared to original (source) records, prior to submission to the NTP.
8. The QAU shall prepare assessment reports that enable management and study staff to understand the effectiveness of their overall operations and make decisions that may be needed to ensure or improve product quality.
9. Records generated by the QAU and resultant actions taken by management shall be made available for review by NTP staff during site visits and progress evaluations, but are otherwise proprietary documents not available for review by outside parties.

#### 4. Quality Control (QC)

1. 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. Accordingly, QC is an integral part of study conduct; however, it is applied after primary work has been performed, so its impact on quality is restricted to retrospective measures. Thus, study-conduct staff, managed by the Principal Investigator determines prospective aspects of product quality such as regular instrument maintenance, good use of laboratory notebooks, and proper sample preparation. Feedback from QC activities is a valuable management tool for use by the Principal Investigator, but the prospective activities performed by the study-conduct staff are the fundamental determinants of study quality.

#### 5. Requirements

1. The contractor shall implement policies and procedures that encourage quality performance from the assignment of a task to its conclusion.
2. Internal QC Program
  1. The contractor shall implement an internal quality control program that ensures complete and accurate documentation of all operations, procedures, assignments, and tasks performed under the contract. This includes, but is not limited to:

1. The use of appropriate calibration samples and system suitability standards.
2. Establishment of suitable calibration schedules for each instrument used by the program.
2. Procedures that are part of the internal quality control program shall be separate from and subject to periodic assessment by the QAU.
3. External QC Program
  1. The contractor shall participate in an external program to assess the quality of the contractor's performance. This program shall include, but is not limited to the following:
    1. On-site inspection, with prior notification, by the COR and/or his/her designee, of equipment, facilities, records and procedures; including those of the QAU.
    2. Periodic evaluation of standard reference materials provided from commercial or non-commercial sources.
6. Standard Operating Procedures (SOPs)
7. Objectives
  1. Develop standard operating procedures (SOPs) for all contract operations, procedures, and assignments.
  2. Maintenance of SOPs
  3. Compliance with SOPs
8. Requirements
  1. All laboratory operations, procedures, assignments, and tasks shall have SOPs that describe how each is to be performed.
  2. Types of SOPs:
    1. Laboratory operations or procedures of a general nature shall be conducted with SOPs that outline the essential parts of the procedure, including documentation. For example, under this requirement the Dose Formulation Development (DFD) functional activity will have an SOP that describes how a DFD is to be performed, the documentation to be used and the controls to be applied while performing the assignment.

2. Laboratory operations or procedures of a routine or repetitive nature shall be conducted with explicit SOPs that describe the operation to be performed.
  1. Assignments that are governed by a signed study protocol shall be conducted using explicit SOPs (e.g., Section 2, Part 5. Animal Studies).
  2. Analyses using validated methods shall be conducted using substance-specific SOPs.
  3. Assignments that are developmental in nature e.g., Section 2, Part 3.2. Formulation Development shall be conducted using SOPs that describe the procedure(s) that must be followed to meet the requirement of the assignment.
3. See Section 4. Reporting Requirements for additional SOP requirements.
4. The contractor shall implement a regular review process for all SOPs in accordance with the policies set forth in the QMP.
5. The contractor shall ensure compliance with all SOPs by contract staff.
6. Subcontractors
7. Objectives
  1. Ensure that all work performed by subcontractors conforms to the requirements of the prime contractor's Quality Management Plan.
8. Requirements
  1. Work performed by subcontractors for this contract shall meet all the requirements set forth in the contract.
  2. The Contracting Officer must be informed of all subcontracting efforts and must approve all subcontracts before they can be issued.
  3. The Contractor's QAU shall monitor work done by subcontractors and report results to management, so that management may be informed about the quality of work performed by subcontractors.
9. Additional Information
  1. Additional information about Quality Management Programs suitable for nonclinical laboratory work is available from the following sources:

1. The EPA Quality System Website: HYPERLINK  
"http://www.epa.gov/quality1/index.html"  
<http://www.epa.gov/quality1/index.html>
2. The FDA GLP regulations are available from the Code of Federal Regulations, 21 CFR Ch.1 (4/1/1999 Edition). Website: HYPERLINK  
"http://www.gpoaccess.gov/cfr/index.html"  
<http://www.gpoaccess.gov/cfr/index.html>
2. Additional information about FDA GLP regulations is available from the FDA/ORA Compliance Program Guidance: GLP Supporting Documents. Website: HYPERLINK  
"http://www.fda.gov/ora/compliance\_ref/bimo/GLP/default.htm"  
[http://www.fda.gov/ora/compliance\\_ref/bimo/GLP/default.htm](http://www.fda.gov/ora/compliance_ref/bimo/GLP/default.htm)

## 6. *Animal Care and Use Requirements*

### 1. General Requirements

1. The contract shall be conducted in compliance with the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals, the Animal Welfare Act Regulations, the current edition of the *Guide for the Care and Use of Laboratory Animals* (the *Guide*), and all local, state or federal regulations and policies; and all animal care policies described in the NTP Chemistry Specifications.
2. The Contractor shall have an approved animal welfare assurance statement on file with the NIH Office of Laboratory Animal Welfare (OLAW) prior to contract award (*Note: an offeror that does not have a PHS Assurance may be selected but the Contracting Officer will have to initiate the process of obtaining an assurance from OLAW, and contract funds may not be expended for animal work, until the assurance has been approved*).
3. The Contractor shall be accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC).
4. If animal species regulated by the USDA are involved in a contract, the contractor shall be registered with the Secretary of Agriculture of the United States in accordance with 7 U.S.C 2136 and 9 CFR sections 2.25 through 2.28.

5. The Contractor and all contract facilities shall have a functional Institutional Animal Care and Use Committee (IACUC). All proposals for use of animals must be described in Animal Study Protocols that have been approved by the IACUC.
6. Animal experimental protocols, approved by the contractor's institutional animal care and use committee (IACUC), shall be deliverables to the NIEHS COR prior to the commencement of work. These contractor-approved protocols shall also be available to the NIEHS ACUC.
7. The Contractor shall utilize a Laboratory Animal Veterinarian to supervise the care and health of the animals.
8. Animals shall be anesthetized to alleviate pain in procedures that may cause more than momentary or slight pain. Animals with the following conditions shall be euthanized immediately to avoid further pain and distress:
  1. conditions interfering with their normal postural movements, eating, or drinking,
  2. debilitating conditions or other conditions indicating pain or distress as judged by an experienced laboratory animal specialist, or
  3. other conditions including moribundity (described below).
9. All protocols involving animals shall clearly identify blood collection procedures. Blood collection sites, collection volume, procedures, and anesthetics used shall be defined for interim as well as terminal sampling. For IV studies the site and volume of dosing shall be specified. When interim blood samples from rats and mice are collected from the retro-orbital sinus or other sites (e.g., tail vein), animals shall be anesthetized using ~70:30 carbon dioxide:oxygen. Whenever practical, or at the direction of the COR, to reduce the numbers of animals used in each study, cannulated animals shall be used in GLP toxicokinetic studies. Animals shall not be fasted prior to sample collection. Methods for harvesting serum and plasma shall be described. Overnight urine collection procedures must be clearly explained. Total blood sample volume taken at interim bleeds shall not exceed 2.0% of body weight for rats and 2.5% of body weight for mice. At terminal bleeds, death of the animals will be assured immediately following the bleeding procedure and if necessary, the animal shall be euthanized with CO<sub>2</sub>.

## 2. Moribund Sacrifice of Rodents

1. Moribund animals and animals scheduled for interim and final necropsies shall be euthanized, preferably by asphyxiation via CO<sub>2</sub>, by appropriately trained personnel using methods and techniques established by the American Veterinary Medical Association (AVMA) panel of euthanasia and approved by the Contractor's IACUC and the COR.
2. For euthanasia of moribund animals during the course of a study, the following criteria should be supplemented with professional judgment. The final decision for euthanasia of moribund animals shall be made by the responsible scientist or the Principal Investigator and shall not be left to the discretion of the technicians. Major reasons for euthanasia of animals during the course of a study include:
  1. large masses and other conditions preventing eating and drinking;
  2. major injuries and lesions such as non-healing ulcers related to husbandry and treatment;
  3. diseases and conditions indicating severe pain; and
  4. adequate indication that the animal may not survive until the next observation as judged by an experienced laboratory animal specialist.
3. Other conditions for euthanasia of rodents are listed below. (Adapted from Rao, G.N. and Huff, J. [1990]. Refinement of long-term toxicity and carcinogenesis studies. *Fundamental and Applied Toxicology* 15:33-43.)
  1. Loss of 20–25% body weight in < 1 week
  2. Gradual but sustained decline in body weight, indicating partial and sustained anorexia
  3. Prolonged unhealthy appearance such as rough coat, hunched posture, and distended abdomen
  4. Prolonged diarrhea leading to emaciation
  5. Prolonged or intense diuresis leading to emaciation
  6. Persistent coughing, wheezing, and respiratory distress
  7. Paralysis and other nervous disorders leading to anorexia and continuous decline in body weight

8. Bleeding from natural orifices not due to minor injuries
9. Persistent self-induced trauma complicating minor injuries
10. Microbial infections interfering with toxic responses

### *3. Quarantine Requirements*

1. Animals shall be quarantined for a minimum of 14 days prior to dosing unless COR approval is obtained for a shorter duration.
2. At the end of the quarantine/acclimation period, the animals shall be examined and released from quarantine for study (if healthy), by a Laboratory Animal Veterinarian.

## *7. Information Management*

The NTP Program Operations Branch (POB) at the National Institute of Environmental Health Sciences (NIEHS) will employ two electronic databases to track activity under this contract: ChemTask and NTP IMS. ChemTask is used to assign and track the work under the chemistry contracts; NTP IMS is used to capture all communications related to a project and to provide a multi-user collaboration environment for the POB and its chemistry contractors.

### *1. General Requirements*

1. The Contractor must establish procedures and policies which promote effective communication with the COR relating to the status of all on-going work, including schedule and costs performed under this contract. As part of this effort the Contractor shall establish a comprehensive information management system to monitor all on-going work, establish schedules and track costs. This system may serve as the Contractor's Master Schedule for work performed under FDA GLPs.
2. The Contractor shall be responsible for entering a description of the work requested by the COR into the NTP's ChemTask database whenever new work is assigned, and shall update ChemTask whenever an assignment is modified, a milestone is reached, or the assignment is completed. The descriptions entered into the ChemTask database shall 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, as the Contractor understands it. The first time an assignment is entered, the

estimated report date may be estimated by adding the number of weeks allowed from laboratory work complete to draft final report due specified in this SOW for each report type (Section 4. Reporting Requirements). Whenever the estimated laboratory work completed date changes, the Contractor update it with the new estimated date and also update the estimated report date. When the actual laboratory work complete date is known, the estimated report date shall be updated with a more realistic deadline. The ChemTask entry shall be reviewed by the COR, who subsequently will approve the entry prior to commencement of work by the contractor. As the work progresses the Contractor shall update the corresponding ChemTask entry with estimated and actual lab start, lab complete and report dates as necessary.

3. For each new request from the COR, the contractor shall update the NTP IMS by creating Task with a description of the scope of the work requested and a milestone schedule for each assignment. The milestone schedule shall include dates for some or all of the following at the direction of the COR:
  1. Commencement of lab work
  2. Completion of lab work
  3. Completion of Draft Final report
  4. Commencement of QC review
  5. Commencement of QA review
  6. Submission of Draft Final report
4. Subsequent communication between the contractor and the COR regarding the assignment shall take place in the NTP IMS. This includes, but is not limited to, discussions of problems encountered in the course of completing the assignment, interim results, draft final reports, and articles from the literature related to the assignment.
  1. Interim results reports shall be posted to the NTP IMS as attachments to the relevant Task.
  2. Draft final reports shall be posted to the NTP IMS as review documents attached to the relevant Task.
5. The Contractor shall have an Internet connection that will provide standard broadband Internet, e-mail, and FTP capabilities.



## 2. Database Requirements

1. The Contractor shall employ an appropriate Internet browser to access the NTP IMS. Currently FireFox, Chrome and Safari are supported.
2. The COR will make available to the contractor, 5 license seats, to allow access to the NTP IMS. If additional licenses are needed, it shall be the responsibility of the Contractor to supply sufficient licenses to its employees to allow access to the NTP IMS system.
3. The Contractor shall design and implement an internal computerized project management system to provide for task scheduling, and shall report the status of all tasks required under this contract as follows:
  1. The project management system shall be an interactive-type database management program with a user interface to the computer that can be easily accessed and queried and shall display and print reports requested by the COR.
  2. The project management system shall provide the capability to allow the electronic transfer of the results of analyses to the COR as specified for each task.
  3. The project management system shall provide the following information for each task: assignment date, work started date, current status of on-going work, work completion date, draft final report completion date, commencement of QC review date, commencement of QA review date, report submission date (estimated and actual), NTP report–approved date, final report date, and a description of the assigned work. For assignments in Section 2. Part 5. Animal Studies, the information shall include the expected completion dates for each phase of the work (e.g., literature review, in-life, draft final report).
  4. The project management system may be used to fulfill the functions of a Master Schedule.

## 3. Compound Inventory

1. The Contractor shall maintain an electronic inventory of all chemicals received as test articles, which are stored at the Contractor's facility. The Contractor shall maintain a separate inventory for high throughput screen (HTS) chemicals stored at its facility.

2. The chemical/test article inventory shall include, at minimum:
  1. The amount on-hand, updated monthly
  2. Identifying information including, but not limited to, chemical name, CAS registry number (CASRN), lot number, source, receipt date
  3. The inventory system shall be fully searchable by at minimum, chemical name, CASRN, lot number, source, and/or receipt date.
3. The HTS chemical inventory shall meet all of the requirements for the chemical/test article and in addition, shall include identifying information related to the HTS program, e.g., Tox21 Chemical Identification Number (CID), NTP CID, Tox21 Substance Identification Number (SID), PubChem CID and/or SID, etc.

#### 4. Records Retention

1. The Contractor shall maintain hard copies of all chemistry reports and data sheets, along with all supporting data and instrument output (raw data) in accordance with their corporate records retention policy or a period of 5 years after the end of the contract, whichever is longer.
2. The Contractor shall maintain microfiche copies of all chemistry report and data sheets, including the supporting raw data in accordance with their corporate records retention policy or a period of 10 years following completion of the contract, whichever is longer.
3. In the event of a change in the Contractor's status, the Contractor shall arrange to transfer the raw data to a third party designated by the COR.

#### 5. IT Systems Security

1. The Contractor shall provide a finalized System Security Plan (SSP) for approval by the COR and NTP Contracting Officer within 60 days of Contract award.
2. The SSP shall address security procedures, maintenance, and monitoring required for all systems used to store and/or transmit, modify, or otherwise interact with NTP data. As well as system-level security procedures, maintenance, and monitoring for the Contractor's corporate IT.

## ***5. Health and Safety Program***

### **1. Objectives:**

1. Ensure that all work under this contract is performed in a safe and healthful manner.
2. Establish procedures at the contract facility which, when implemented, will protect the contract staff.
3. Safely dispose of waste from the contract.

### **2. Requirements:**

1. The Contractor shall comply with the applicable requirements set forth in Section 3. Health and Safety Minimum Requirements for Chemistry Services Contractors.
2. The Contractor shall comply with all federal, state, and local regulations for receipt, storage, handling, and shipping of hazardous chemicals, and with the National Cancer Institute (NCI) Safety Standards for Research Involving Chemical Carcinogens, DHEW Publication no (NIH) 77-900 (1975), and subsequent revisions; and the NIH Guidelines for the Laboratory Use of Chemical Carcinogens, NIH Publication no 81-2385 (May 1981), and subsequent revisions. All shipments must comply with DOT regulations and Section III of the NTP Specifications requirements for chemical shipments. To ensure compliance, the Contractor must be aware of all applicable existing or pending legislation.
3. It is estimated that the Contractor shall procure, receive, handle, and ship several controlled substances per year. The Contractor shall obtain and maintain full Drug Enforcement Agency (DEA) licensing (Schedules 1-5). Storage and shipment of controlled substances by the Contractor shall comply with all DEA regulations.
4. The Contractor shall develop and implement a detailed health and safety plan (HASP) that demonstrates compliance with the Occupation Safety and Health Act and applicable state and local safety and health codes, standards, and regulations, and also meets the requirements set forth in the NTP Specifications.

1. The plan shall include details for protection of property and the avoidance of work interruptions pursuant to the performance of this contract.
2. Reporting requirements relating to the HASP can be found in Section 4. Reporting Requirements.
5. The contractor shall safely dispose of toxic wastes, including excess chemicals and biological or biologically contaminated, fluids and tissues generated by the contractor in support of sponsor assignments and studies, in accordance with all applicable federal, state, and local laws and regulations See Section III of the NTP Specifications for additional requirements.
  1. The contractor shall report disposal of hazardous waste as part of the Monthly Status Report (Section 4. Reporting Requirements)

### *Appendix 1.1. Definitions of Terms*

The following are definitions of terms used throughout this Statement of Work

1. *Information Management System (NTP IMS, ChemTask)*: 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 that information. Currently, the National Toxicology Program employs several electronic databases in this capacity. Two electronic databases apply to this contract: ChemTask and the NTP IMS (currently Innotas). ChemTask is used to assign and track the work under the chemistry contracts; NTP IMS is used to capture all communications related to a project and to provide a multi-user collaboration environment for the POB and its chemistry contractors.
2. *ChemTask Memo*: A description of the work requested by the Contracting Officer's Representative (COR) that is entered into the ChemTask database. ChemTask memos 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 ChemTask entry is reviewed and approved by the COR. As the work progresses the Contractor updates the corresponding ChemTask memo as necessary. A unique number (ChemTask number) assigned by the ChemTask database identifies each ChemTask memo.
3. *Interim Report*: Preliminary results of an assignment in electronic format, usually as a data table. Interim Reports are to be posted to the NTP IMS under the applicable Task, as soon as the lab work that generated the data has been completed. See Appendix 4.2 for requirements for data submissions.
4. *Draft Final Report*: A draft report in electronic format (PDF) 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 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, TLC plates, etc.); and appendices including a Data Summary and Analytical Method Standard Operating Procedure (AM), when applicable (Section 4. 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.

5. *Final Report*: The Final report consists of the approved Draft Final report, with a signed GLP compliance page (as appropriate), and a signed Quality Assurance statement (Section 4. Reporting Requirements), which is uploaded to the Drop-box folder on the POB server (currently: <https://forum.niehs.nih.gov/sitescape/ext/dispatch.cgi/megavolt>) as an electronic copy in PDF format.
6. *Report Addenda*: In addition to the body of the report, each report may contain 1 or more addenda summarizing the report in various ways.
7. *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%).
8. *Data Summary*: An appendix to the report that contains a summary of the method(s) developed and/or used in the report along with a table or tables summarizing the results of the analysis. Figures containing instrument output and reference spectra and/or chromatograms are attached to the appendix. For the purposes of this contract, a data summary is a Data Sheet (see Attachment 3.6. Data Sheet) when it is included as an appendix to a Chemistry Report (see Section 2.3.5. Chemistry Reports).
9. *Analytical Measurement Limits*: Measurement limits consist of three parameters that define the ability of an analytical method or assay to measure a target analyte at a specified concentration. Limit of Detection (LOD), Limit of Quantitation (LOQ), and Experimental Limit of Quantitation (ELOQ) are defined below:
  - LOD shall be defined as 3 times the standard deviation of the blank or the lowest standard, expressed as concentration.
  - LOQ shall be defined as 10 times the standard deviation of the blank or lowest standard, expressed as concentration.

- ELOQ shall be defined as the concentration of the lowest standard that meets acceptability criteria of the assay (normally  $\pm 10\%$  relative error, with a relative standard deviation of  $\leq 10\%$ ).

10. Definitions of Concentration Terms

- Nominal concentration: The concentration specified by the study protocol or study design document.
  - Theoretical (Target) concentration: The prepared concentration, if done according to the standard operating procedure for dose preparation. Often the same as the target concentration.
  - Actual (Expected) concentration: The concentration that was prepared based on the amount of test article actually weighed out and the subsequent dilution(s).
  - Found (Determined) concentration: The reported concentration resulting from an analysis of the prepared formulation or sample.
11. "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 QAU.
12. 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).
13. 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)" e.g., 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.
14. 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 a mix date. Found concentrations of multiple batches of a formulation, prepared on a single mix date, must be within 5% of each other.

15. Standard Operating Procedure (SOP): A standard operating procedure is a set of instructions having 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 improving organizational results. Every good quality system is based on its standard operating procedures (SOPs).  
In clinical research, the International Conference on Harmonisation (ICH) 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 SOPs 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.
16. Test Article: A test article is any substance that the NTP has agreed to test. NTP test articles come from a wide variety of organic and inorganic substances, including synthetic industrial chemicals, pesticides, various pharmaceuticals, metals, 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.
17. 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 mixture.
18. FDA Good Laboratory Practices (GLP or GLPs): Good Laboratory Practice (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 US FDA has rules for GLP in 21CFR58. These are the rules used for preclinical trials in US on animals prior to clinical research in humans. Research in US that is not conducted under these restrictions or research done outside US that is not conducted according to the OECD Guidelines (or FDA rules) might be inadmissible in support of a New Drug Application in the US.

19. Quality Assurance: Quality Assurance (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 assess the quality of work performed under this contract and to rectify deficiencies as may be needed. Thus, QA activities enable management and others to assign a proper level of confidence to the work performed and reported by study staff.
20. Quality Assurance Unit (QAU): The quality assurance unit (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 are in conformance with the requirements of a study, functional activity or chemistry support activity as set forth in this contract and/or a study protocol or 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.
21. Quality Control: Quality Control (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.
22. Quality Management Plan: The quality management plan 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 both 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 be 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 quality management plan 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 quality management plans is often reference. There may be references to performance standard guides, quality standards (like FDA GLPs), and internal support documents. The quality management plan is normally limited to a single project and is specific in terms of outlining responsibilities and ownership. (Ref. <http://e-articles.info>)

23. *Cremophor®*: Cremophor EL® (CASRN: 61791-12-6) is the registered trademark of BASF Corp. for its version of polyethoxylated castor oil. It is prepared by reacting 35 moles of ethylene oxide with each mole of castor oil. The resulting product is a mixture: the major component is the material in which the hydroxyl groups of the castor oil triglyceride have ethoxylated with ethylene oxide to form polyethylene glycol ethers. Minor components are the polyethylene glycol esters of ricinoleic acid, polyethylene glycols and polyethylene glycol ethers of glycerol. Cremophor EL is a synthetic, nonionic surfactant; its utility comes from its ability to stabilize emulsions of nonpolar materials in aqueous systems. It is an effective nonionic solubilizer for aqueous-alcoholic solutions of lipophilic actives such as vitamins and essential oils, and also finds application as a co-emulsifier. Like most esters, it is stable under mildly acidic, neutral pH, and mildly alkaline conditions. See also Alkamuls EL-620®, which is the registered trademark of Rhodia Corp. for its version of polyethoxylated castor oil and shares the same CASN.
24. *Default NTP Animal Species*: The NTP typically uses the Harlan Sprague Dawley (HSD) rat (Envigo Hsd:Sprague Dawley® SD®) and/or the CD-1 (reproductive studies) or B6C3F1/N (toxicology/carcinogenicity studies) mouse in its studies.
25. *Primary Matrix*: Primary matrix refers to the target tissue or biological fluid that is the focus of an analytical method; e.g., plasma. The default primary matrix for biosample method development and validation is male Sprague-Dawley (SD) rat plasma. Note: The SD rat strain is not the same as the Envigo Hsd:Sprague-Dawley rat described above.
26. *Secondary Matrix*: A secondary matrix is defined as a matrix which differs from the primary matrix because: it is from a different species, strain, sex, or aged animal; a different matrix modifier has been used e.g., K3EDTA vs. Heparin; or it is a different tissue type.

27. Rounding and the use of "Significant Figures": When performing calculations using measurements, use the values as received from the measuring instrument. Do not round measurements for intermediate calculations; 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 where 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.,  $1.23 \pm 0.06$  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.
28. Pharmacodynamics: Pharmacodynamics refers to the study of the physiological effects of drugs on the body or on microorganisms or parasites within or on the body and the mechanisms of drug action and the relationship between drug concentration and effect. Pharmacodynamics is often summarized as the study of what a drug does to the body, whereas pharmacokinetics is the study of what the body does to a drug. In this context, pharmacodynamics is taken to include receptor and/or DNA binding, omics, physiological measurements, etc.
29. Glossary of Toxicokinetic Terms

Parameter	Non-Compartmental Analysis	Compartmental Analysis	Definition
C <sub>0min_pred</sub>	C <sub>0</sub>	—	Fitted plasma concentration at time zero (IV only).
C <sub>max</sub>	C <sub>max_obs</sub>	C <sub>max_predicted</sub>	Observed or Predicted maximum plasma (or tissue) concentration.
T <sub>max</sub>	T <sub>max_obs</sub>	T <sub>max_predicted</sub>	Time at which C <sub>max</sub> predicted or observed occurs.
Lambda <sub>z</sub>	Lambda <sub>z</sub>	—	Non-compartmental analysis (NCA) terminal elimination rate constant, NCA ke or kelim.

Half-life	HL_Lambda_z	—	Lambda z half-life, $t_{1/2}$ , the terminal elimination half-life based on non-compartmental 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, also $k_e$ or $k_{elim}$ .
k10_Half-life	—	K10_HL	Half-life for the elimination process from the central compartment.
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 non-compartmental 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.
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 <http://www.summitpk.com/equations/equations.htm#S4> for equations used to calculate these parameters.

30. *NTP Specifications*: The phrase “NTP Specifications” refers to the Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program, January 2011.  
[http://ntp.niehs.nih.gov/ntp/Test\\_Info/FinalNTP\\_ToxCarSpecsJan2011.pdf](http://ntp.niehs.nih.gov/ntp/Test_Info/FinalNTP_ToxCarSpecsJan2011.pdf)
31. *NTP Reproductive Specifications*: The phrase “NTP Reproductive Specifications” refers to the Specifications for the conduct of studies to evaluate the reproductive and developmental toxicity of chemical, biological, and physical agents in laboratory animals for the National Toxicology Program (NTP), May 10, 2011 and all

subsequent revisions.

[http://ntp.niehs.nih.gov/ntp/Test\\_Info/FinalNTP\\_ReproSpecsMay2011\\_508.pdf](http://ntp.niehs.nih.gov/ntp/Test_Info/FinalNTP_ReproSpecsMay2011_508.pdf)

32. *NTP Chemistry Specifications*: The phrase “NTP Chemistry Specifications” refers to this document.

### *Appendix 1.2. Definitions of Acronyms*

The following are definitions for acronyms used throughout the NTP Chemistry Specifications and related documents.

#### *1. Analytical Techniques and Terminology*

AES:	Atomic Emission Spectroscopy
COA:	Certificate of Analysis
COSY:	Correlation Spectroscopy
HPLC:	High Performance Liquid Chromatography
FTIR:	Fourier-Transform Infrared Spectrophotometry
GC:	Gas Chromatography
GC-MS:	Gas Chromatography - Mass Spectrometry
GPC:	Gel-Permeation Chromatography
IC:	Ion Chromatography
ICP:	Inductively Coupled Plasma
ICP-OES:	Inductively Coupled Plasma Optical Emission Spectroscopy
ICP-MS:	Inductively Coupled Plasma Mass Spectrometry
IR:	Infrared Spectrophotometry
MS:	Mass Spectrometry
MS/MS:	2-Dimensional (2-D) Mass Spectrometry
NMR:	Nuclear Magnetic Resonance Spectroscopy
PCA:	Principal Component Analysis
PPB (ppb):	Parts Per Billion (ng/kg)
PPM (ppm):	Parts Per Million (mg/kg)
ROSEY:	Rotating-frame Overhauser Effect Spectroscopy
SEM:	Scanning Electron Microscopy
SIMS:	Secondary Ion Mass Spectrometry
TEM:	Transmission Electron Microscopy
TLC:	Thin-layer Chromatography
UPLC:	Ultra-high Performance Liquid Chromatography
UV/VIS:	Ultraviolet/Visible Spectroscopy or Detection
XRD:	X-ray Diffraction

XRF: X-ray Fluorescence

## 2. Contract Terms

CO: Contracting Officer

COR Contracting Officer's Technical Representative (COR)

FA: Functional Activity

PDF: Portable Document Format

PM: Program Manager

PO: Project Officer (pre-award), COR (post-award)

RFP: Request for Procurement

SOW: Statement of Work

## 3. Government Departments and Agencies

DEA: United States Drug Enforcement Agency

DHHS: United States Department of Health and Human Services

DOJ: Department of Justice

DOT: United States Department of Transportation

EPA: United States Environmental Protection Agency (U.S. EPA)

FDA: United States Food and Drug Administration

NIEHS: National Institute of Environmental Health Sciences

NIH: National Institutes of Health

NIOSH: National Institute of Occupational Safety and Health

NRC: Nuclear Regulatory Commission

NTP: National Toxicology Program

OSHA: Occupational Safety and Health Agency

## 4. Health and Safety

ACGIH: American Conference of Governmental Industrial Hygienists

CHO: Chemical Hygiene Officer

HASP: Health and Safety Plan

HSO: Health and Safety Officer

MSDS: Material Safety Data Sheet

PELS: Permissible Exposure Limits



STEL:	Short Term Exposure Limit
TLV:	Threshold Limit Value
TWA:	Time Weighted Average
WEEL:	Workplace Environmental Exposure Levels

#### 5. Quality Assurance

QA:	Quality Assurance
QAU:	Quality Assurance Unit
QC:	Quality Control
QMP:	Quality Management Plan
SOP:	Standard Operating Protocol
SSAP:	Substance-Specific Analysis Protocol

#### 6. Societies

ALAAC	Assessment and Accreditation of Laboratory Animal Care
AHPA	American Herbal Products Association
ASTM:	American Society for Testing and Materials (now ASTM International)
ACS:	American Chemical Society
SOT:	Society of Toxicology
USP:	United States Pharmacopeia

#### 7. Functional Activities

ADMES	Absorption, Distribution, Metabolism, and Excretion Study
BCM	Biochemical Measurement
BMDA	Biosample Method Development and Analysis
BMDV	Biosample Method Development and Validation
BSA	Biological Sample Analysis
CH	Chemical Handling
CIPS	Chemical Identity and Purity Screen
CP	Chemical Procurement
CRA	Chemical Reanalysis
CS	Chemical Storage

CCA	Comprehensive Chemical Analysis
EXS	Extended Stability Study
FA	Formulation Analysis
FD	Formulation Development
FDV	Formulation Development and Validation
FP	Formulation Preparation
FPA	Formulation Preparation and Analysis
FPAS	Formulation Preparation, Analysis, and Shipment
IVS	In vitro Study
LLID	Low-Level Impurity Determination
MIPS	Multiple Chemical Identity and Purity Screen
PAL	Palatability Study
PCD	Partition Coefficient Determination
PFS	Preliminary Formulation Studies
PTKS	Preliminary Toxicokinetic Study
PD	Protocols Development
RA	Referee Analysis
SHIP	Shipping
SCA	Special Chemical Activity
SIS	Special Inhalation Studies
TKS	Toxicokinetic Study
VA	Vehicle Analysis

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OPTIONAL

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HCP	High Throughput Chemical Procurement
HCH	High Throughput Chemical Handling
HIPS	High Throughput Identity and Purity Screen