Chapter 11. Data Collection and Submission

Specifications for the Conduct of Toxicity Studies by the Division of Translational Toxicology at the National Institute of Environmental Health Sciences

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11. Data Collection and Submission

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11.1. Computer System for Data Input (NTP Provantis)

In accordance with National Institute of Environmental Health Sciences (NIEHS) policy, all data collected shall be returned to NIEHS via electronic files. Data management shall adhere to relevant National Institutes of Health (NIH) and NIEHS Data Management and Sharing plans. A copy of the data is permitted to reside at the testing laboratory.

For in vivo data from animal studies, NIEHS supplies licenses to NTP Provantis, which is a commercial, hosted product configured for use by NIEHS and the testing laboratories to collect data for studies. NTP Provantis permits access by multiple laboratories but prevents laboratory personnel from viewing the content of studies performed in other laboratories. NTP Provantis is a computerized real-time data collection system that includes:

- Customizable protocol input for unique study design
- The ability to track maternal animals and individual pups from specific litters
- A hierarchical security structure to control access to individual data files (e.g., technician clearance, study director clearance)
- Real-time dose calculation for gavage studies based on body weights and dosing volume
- Integration of measuring apparatus that allows input of values directly into the system without manual reentry
- The ability to create summary reports for all major study endpoints during the course of the study, including standard parametric and nonparametric analyses for monitoring study progress

In compliance with the Food and Drug Administration's Good Laboratory Practice (GLP) guidelines, NTP Provantis is validated for use in a GLP environment, and all changes are subject to a revalidation process before release to the laboratories. The testing laboratory shall be responsible for documenting their acceptance of the use of NTP Provantis in their GLP environment and the qualification/calibration of balances and other equipment interfaces used for input to the data management system.

With the approval of the contracting officer's representative (COR), the testing laboratory may use a data collection system similar to NTP Provantis and arrange for all data collected to be entered retrospectively by the laboratory into NTP Provantis or returned in an electronically readable format with full metadata attached.

Some data are not suited for direct collection in NTP Provantis. In this case, the testing laboratory shall return the data in electronically readable files with all appropriate metadata. The COR shall obtain agreement from NIEHS for the format of these files before submitting the data. This data submission shall include the original (raw) instrument data files. As applicable and required by the individual protocol outline, analysis results shall be submitted electronically following approval of the study report by the COR.

Data collection shall adhere to the Division of Translational Toxicology (DTT) Data Dictionary (DDD)[1] when possible. The testing laboratory shall work with DTT to register new terms in the DDD prior to using the terms in data submissions to DTT.

If required to perform analysis on human study samples, sensitive data and all patient agreements covering the data shall be submitted to DTT in accordance with NIH policy,[2] which is available to contractors and staff with government identification badges and NIEHS network accounts.

11.1.1. Hardware

The testing laboratory will be expected to provide electronic balances with cables to interface with the computer. Specifications for compatible balances can be provided. Wireless connections are discouraged.

11.1.2. NTP Provantis Users

Access to NTP Provantis is governed by guidance documents. Users are required to employ the following:

- Guidance for NTP Provantis Users
- Guidance for NTP Provantis Training
- Guidance for NTP Provantis System Changes
- Guidance for NTP Provantis Information Technology

These guidance documents can be found in the Chemical Effects in Biological Systems[3] (CEBS) bin for NTP Provantis guidance documents. These documents are available to contractors and staff with government identification badges and NIEHS network accounts.

NIEHS also produces documentation that includes expectations of use for users of NTP Provantis, as well as hints, guide sheets, and tips on use of tables.

These documents can be found in the CEBS bin.[4]

11.1.3. Study Protocol

When a study is initiated, the study protocol is created in NTP Provantis under the NTP Provantis support contract at the request of the testing laboratory with COR approval. The testing laboratory then adds the protocol information, including information about the test article (e.g.,

[1] https://cebs.niehs.nih.gov/cebs/paper/15466
[2] https://junction.niehs.nih.gov/divisions/director/osim/policy/human-research/index.htm
[3] https://connect.niehs.nih.gov/cebs3/cebsbin/index.cfm?action=main.showBin&bin_id=430
[4] https://connect.niehs.nih.gov/cebs3/cebsbin/index.cfm?action=main.showBin&bin_id=715

name, CASRN, treatment groups); the animals studied (e.g., species, strain, sex, supplier, number per treatment group, cage allocation to racks); and the scheduled activities (e.g., collection of body weights, feeder weights, clinical signs). The testing laboratory enters the information into the protocol a week before study initiation.

11.1.4. In-life Data Collection

Animal body weights, food and water consumption data, clinical observations, and animal removal information shall be collected and stored in NTP Provantis. Data are checked for completeness and validity each day. If needed, corrections are made using NTP Provantis and a reason for the change is entered into the audit trail.

11.1.5. Pathology

Weights and observations made at necropsy and at tissue trimming are recorded in NTP Provantis. A standard terminology, the NTP Provantis lexicon, is used to describe gross and microscopic lesions. Data are entered into the computer by choosing the organs, sites, morphologies, and qualifiers from a menu on the computer screen. The study pathologist can review and change diagnoses at any time during the evaluation of a study.

11.1.6. Data from Instruments

The testing laboratory may use instruments not connected to NTP Provantis to collect data (e.g., instruments used in neurological testing or clinical pathology). These data are imported into NTP Provantis using the data import feature. The testing laboratory works with NTP Provantis support contract personnel to design a form for data import that the testing laboratory uses to import the data.

11.1.7. Non-Provantis Data

Some data are too large to be captured in raw form into NTP Provantis (e.g., profiles from clinical pathology instruments, next generation sequencing files). These files shall be loaded into a CEBS collection portal or CEBS bin. Before files are submitted, the COR shall work with NIEHS program leads and the CEBS administrator to ensure that all data and metadata needed for FAIR (findable accessibility, interoperability, and reusability) data standards are included. In general, these are raw data, any transformed or normalized data, outliers, methods used for transformation, links between data files and animal ID in NTP Provantis, and any reporting about the method and results.

11.1.8. Locking

The testing laboratory is responsible for locking each animal after pathology data entry is complete. After the study is complete, the testing laboratory requests that the NTP Provantis support contractor lock the study.

After the study is locked, the testing laboratory will no longer have access to the study other than reading access. The testing laboratory is responsible for saving a copy of the data before locking if such data are needed by the testing laboratory.

11.1.9. Reports

The testing laboratory uses data summaries from NTP Provantis to make the laboratory report. Table templates have been set up in NTP Provantis for this purpose, but can be modified by the testing laboratory at the direction of the COR.

NIEHS staff should set up separate table templates in NTP Provantis (and not use table templates that the testing laboratory has set up when running its reports). If modifications are made in table templates within NTP Provantis, the testing laboratory will support staff in replicating results.

As predetermined for a test program and agreed upon by the contractor (including Quality Assurance Unit), pathology data may be exported from NTP Provantis to the Histopathology Slide Review Module (SRM) for review and reporting. The testing laboratory shall document acceptance of SRM after review of verification documentation. When the data are in SRM, DTT tables shall be used to present the data for the laboratory report.

11.2. Submission of Reports and Data

11.2.1. Content and Format of Reports

Reports shall be prepared according to the instructions provided in this document. The content and format of reports that are not described in these Specifications are to be discussed with the program COR.

11.2.2. Submission of Reports

Laboratory reports (including final study reports, prestart chemistry reports, prestart inhalation reports, and toxicokinetic reports) shall be submitted to the COR. Final accepted reports shall be provided in PDF format. Digital signatures are acceptable. If any element of a report needs to be scanned, they shall be scanned at 300 dpi (black and white) to a single searchable PDF file. Password protection shall not be used, nor will any document property restrictions. If the report requires an amendment, the entire amended report shall be submitted to the COR.

11.2.3. Submission of Data to the NTP Archives

All original source documentation is the property of NIEHS and shall be sent to the NTP Archives. Only that correspondence related to the technical conduct of a study shall be included. Site visit and Annual Program Review reports and responses to action items shall not be submitted to the NTP Archives.

Inventory of the records sent shall be recorded on the NTP Archives Inventory/Index lists as shown on succeeding pages of this chapter. The Inventory/Index lists shall be prepared by the testing laboratory and shall accompany the records to the NTP Archives. Each section in the NTP Archives Inventory/Index and subpart thereof shall be separated by a stiff paper or cardboard divider or shall be contained in a file folder. A tab affixed to the divider or a label on the file folder shall identify the section and subpart. The testing laboratory shall provide the folders or dividers and boxes for the records they submit.

The records pertaining to a study shall be sent after the pathology materials are sent to the NTP Archives. If records from a study are shipped in parts at different times, Inventory/Index lists

shall accompany each shipment. The NTP Archives clerk will prepare and maintain a master copy of the Inventory/Index for this study to show all receipts of records from the testing laboratory, computer data forms, or other sources.

Pathology materials (slides, blocks, and tissues) shall be sent to the NTP Archives as specified in Chapter 8, Section 8.13 and in study specific SOWs under Milestones and Deliverables. Pathology materials shall not be placed in the same box with original study documents.

A copy of all final reports reviewed by the testing laboratory's Quality Assurance Unit for a study shall be submitted to the NTP Archives. A copy of each standard operating procedure (including revisions) in effect and used during the conduct of each study shall be submitted. Electronic copies, rather than hard copies, are acceptable if the laboratory prefers.

Archival materials shall be appropriately boxed and shipped prepaid to the NTP Archives. The following Inventory/Index organization scheme shall be used:

NTP Archive Inventory/Index – Archive Records for Each Study

- Section I. General
- Section II. Test Article Records
- Section III. Study Type (to be indicated on each set of forms; e.g., Repeated Dose, Subchronic, Chronic, Transgenic Study, Toxicokinetic Study, Separate Special Study)

The full archival inventory list is provided in Appendix A.

11.2.4. Electronic Submission of Data

All original study documentation and reports shall be organized and submitted to the NTP Archives using a secure file transfer service to transfer irreplaceable data from DTT-sponsored studies securely and reliably.

The data shall be organized according to the Archive Inventory/Index forms. Files shall be prepared as follows:

- Files shall be organized in folders according to the Archive Inventory/Index and presented in order. Each file name shall include sufficient information to identify the specific section of the NTP Archive Inventory/Index Form to which the data refer.
- The entire NTP Archive Inventory/Index shall be included as a separate file. The inventory file shall include experiment number, date, laboratory name, test article, study type and duration, species, CASRN, and Provantis study number or NIEHS study ID.
- It is not necessary to send data already deposited in CEBS or loaded into NTP Provantis.
- Data are to be sent in electronic formats such as JSON, Excel, or XML with sufficient metadata to permit reuse. Raw data, normalized data, and the results of statistical analysis shall be provided. Analysis methods shall be described in sufficient detail to permit replication, or the software shall be provided.

- Summary data tables may also be converted to PDF or scanned at 300 dpi (black and white) to searchable PDF files. The files are to contain document restrictions except for printing and content copying.
- All frames of data shall be positioned in either portrait or landscape orientation (whichever is appropriate for that page). Oversized pages shall be reduced or photographed to allow the data to fit on a single page. Chart recorded data shall be scrolled left to right or top to bottom, depending on how the script runs on the tracings.
- When data are missing, a file shall be submitted in the location of the missing data that explains why the data are missing. If study data records are of such quality that they cannot be scanned, a cross-reference shall be included in the file index that gives the location of the raw data or records.
- The electronic archival package shall be examined by the study laboratory for completeness, accuracy, and quality before submission to the NTP Archives.

11.3. Peer Review

The Division of Translational Toxicology (DTT) conducted a peer review of chapters 1, 2, 3, 4, 11, and 12 within the draft *Specifications for the Conduct of Toxicity Studies by the Division of Translational Toxicology at the National Institute of Environmental Health Sciences* by letter in February 2022 by the expert listed below. Reviewer selection and document review followed established DTT practices. The reviewer was charged to:

1. Peer review the following chapters within the draft Specifications for the Conduct of Toxicity Studies by the Division of Translational Toxicology at the National Institute of Environmental Health Sciences.
    - Chapter 1: General Personnel Requirements
    - Chapter 2: Facilities
    - Chapter 3: Health and Safety
    - Chapter 4: Quality Program
    - Chapter 11: Data Collection and Submission
    - Chapter 12: Report Formats and Guidance
2. Comment on the completeness of each chapter.

DTT carefully considered reviewer comments in finalizing this document.

Peer Reviewer

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Appendix A NTP Archive Inventory/Index

Test Article: _____ CASRN:_____

Laboratory: _____ Study No. (e.g., C #): _____

Address: _____ Provantis No. (e.g., C12345-01): _____

Contract No.: _____ Laboratory Study No.: _____

Table A-1. Section 1–General[a]

	Box # or Date Sent[b]	Other Location or Comment[c]	Archive Location[d]
A. Personnel (indicate time interval and job)			
1. List of key/critical personnel who participated in the study			
2. Identify consultants (by name and full address; specify work performed)			
B. List of subcontractors (by name and full address; specify work performed)			

[a]Records that pertain to multiple areas within one section or to multiple sections and cannot be separated conveniently to fit into the filing scheme are to be filed in one section and referenced in the other section(s) to which they pertain.
[b]Include the box number for the current shipment in which the listed data/materials are included. If the data/materials listed were submitted in a prior shipment, indicate the date of that prior shipment.
[c]If data/materials listed have been included in another location, the other location is to be identified here. This space is also included for additional explanatory comments.
[d]This column will be completed by NTP Archival staff when storing the listed data/materials.

Test Article: _____ CASRN:_____

Laboratory: _____ Study No. (e.g., C #): _____

Address: _____ Provantis No. (e.g., C12345-01): _____

Contract No.: _____ Laboratory Study No.: _____

Study Type(s): _____

Table A-2. Section 2–Test Substance Records

	Box # or Date Sent[a]	Other Location or Comment[b]	Archive Location[c]
A. Identity (Manufacturer, Lot[s], Date)			
B. Characterization			
C. Bulk Stability			
D. Shipment (from Analytical Contractor or Manufacturer)			
E. Receipt			
F. Storage			
G. Bulk Analyses (Identity and Purity Analyses)			
H. Vehicle Analyses			
I. Test Article/Vehicle Method Validation			
J. Test Article/Vehicle			
1. Dose preparation records			
2. Dose preparation and room dose analyses			
3. Homogeneity study			
4. Animal room dose analyses			
K. Inventory/Use Records for Bulk Test Article			
L. Shipment of Test Article Aliquot(s) to Analytical Contractor			
M. Related Correspondence			

[a]Include the box number for the current shipment in which the listed data/materials are included. If the data/materials listed were submitted in a prior shipment, indicate the date of that prior shipment.
[b]If data/materials listed have been included in another location, the other location is to be identified here. This space is also included for additional explanatory comments.
[c]This column will be completed by NTP Archival staff when storing the listed data/materials.

Test Article: _____ CASRN:_____

Laboratory: _____ Study No. (e.g., C #): _____

Address: _____ Provantis No. (e.g., C12345-01): _____

Contract No.: _____ Laboratory Study No.: _____

Study Type(s): _____ Route: _____

Date Dosing Initiated: _____ Date Necropsy Completed: _____

Table A-3. Section 3–Records by Study Type[a]

	Box # or Date Sent[b]	Other Location or Comment[c]	Archive Location[d]
A. Study assignment (including modifications pertaining to the technical aspects of each study); laboratory-approved protocol with amendments and deviations			
B. Vehicle Records (brand, source, dates purchased, lot no(s)., dates of use, and test article(s) for which used; for corn oil, peroxide analysis with indication of lot no(s). and dates of analysis)			
C. Dosing Records			
1. Dose preparation procedure(s)			
2. Dose preparation log			
3. Dose analysis			
4. Stability study			
D. Diet Analysis			
E. Water Analysis			
F. Water Treatment (commercial and in-house)			
G. Animal Records (prestudy)			
1. Species, strain, source, age			
2. Receipt			
3. Conditions of quarantine (caging, food, water)			
4. Health examination/clinical signs in quarantine			
5. Release for study			
6. Disposal of extra animals			
H. Animal Records (in-life) (for studies supported by Provantis)[e]			
1. Provantis in-life and pathology protocol validation reports			

	Box # or Date Sent[b]	Other Location or Comment[c]	Archive Location[d]
2. Room location			
3. Cage type and number per cage			
4. Randomization			
5. Identity code and confirmation records			
6. Bedding type, manufacturer, contaminants			
7. Cage filter type and source			
8. Feed type, source, lot no(s)., dates used, contaminants			
9. Type of water system and treatment			
10. Cage rotation			
11. Rack rotation			
12. Mortality checks			
13. Provantis in-life data			
a. Data collection forms			
b. Error corrections (when applicable) and exceptions reports			
c. Dosing records for gavage and dermal studies			
d. Perinatal exposure studies: dam, litter, and pup data			
I. Animal Records (in-life) (for studies not supported by Provantis)[f] Supply the records referred to in H.			
J. Records Unique to Inhalation Studies			
1. Chamber design and maintenance information			
2. Exposure system generation and monitoring description, operating procedures, and validation data			
3. Generator degradation results			
4. Chamber concentration versus time plots			
5. Chamber degradation results (without and with animals)			
a. Prestudy developmental data and results			
b. In-life study data and results			
6. Chamber atmosphere homogeneity results (without and with animals)			
a. Prestudy developmental data and results			

	Box # or Date Sent[b]	Other Location or Comment[c]	Archive Location[d]
b. In-life study data and results			
7. Particle/aerosol measurements (without and with animals)			
a. Prestudy developmental data and results			
b. In-life study data and results			
8. Generation and monitoring equipment maintenance and calibration records			
9. Chamber residual concentration/ overnight monitoring results			
10. Daily chamber exposure concentration data			
11. The prestudy developmental data and in-life study data are to be organized and indexed separately			
K. Animal Records (pathology)[e]			
1. IANRs			
2. Provantis slide, block inventory			
3. Necropsy log			
4. Organ weight records			
5. Histology processing records and associated records			
L. Animal Room Records			
1. Temperature raw data			
2. Humidity raw data			
3. Light cycle/intensity measurements			
4. Air changes/air flow			
5. Cleaning agents used			
M. Virology Screening Program Data			
N. Microbiological Testing Reports			
O. Genetic Monitoring Data			
P. Special Studies			
1. Clinical lab studies			
2. Other special studies			
Q. Final Report			
1. Introduction			
2. Materials and methods			
3. Results			
4. Discussion			
5. Appendices			

	Box # or Date Sent[b]	Other Location or Comment[c]	Archive Location[d]
R. SOPs in Effect for This Study Period Including Provantis SOPs			
S. Provantis			
1. Software version in use at time of study			
2. All administrative records relevant to study data processing			
3. Software receipt and maintenance records			
T. Internal Computer-generated Forms/Tables			
1. Toxicology			
2. Clinical chemistry			
3. Analytical chemistry			
4. Other			
U. Photographs Taken During the Study			
1. Gross observation documentation			
2. Microscopic observation documentation			
3. Other			
V. Incident (Experimental Impact) Reports			
W. Correspondence			

[a]Ancillary records may be kept by the study laboratory, but duplicate records should not be shipped to the NTP Archives.
[b]Include the box number for the current shipment in which the listed data/materials are included. If the data/materials listed were submitted in a prior shipment, indicate the date of that prior shipment.
[c]If data/materials listed have been included in another location, the other location is to be identified here. This space is also included for additional explanatory comments.
[d]This column will be completed by NTP Archival staff when storing the listed data/materials.
[e]The expectation is that in vivo studies shall be supported using NTP Provantis and that all in-life data and pathology records will be directly entered into NTP Provantis. The only records that shall be submitted with the archive file are those not directly captured or recorded in NTP Provantis. If paper records are utilized during the study (e.g., gavage dosing records, IANRs), planned or as a contingency, they shall be entered retrospectively into NTP Provantis and the original paper records submitted with the archive file.
[f]For in vivo studies that are not supported by NTP Provantis, the expectation is that all in-life data shall be submitted in a machine readable electronic format (non-PDF) to CEBS. If paper records are utilized during the study (e.g., gavage dosing records, IANRs), planned or as a contingency, they shall be entered retrospectively into an acceptable electronic format and the original paper records submitted with the archive file.