Study Data Reviewer's Guide

Nonclinical

(nSDRG)

13-Week Repeat Dose Toxicity Study on
PCDRUG1234 in Rats

(PC201904)

PCLS Pharmaceuticals

CONTENTS

Abbreviations

Acronym	Translation
nSDRG	Nonclinical Study Data Reviewer's Guide
SEND	Standard for Exchange of Nonclinical Data
LIMS	Laboratory Information Management System
CDISC	Clinical Data Interchange Standards Consortium

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PC201904

1. nSDRG Introduction

This document provides context for the SEND tabulation datasets and terminology for Study PC201904, in addition to what is provided in the Data definitions (define.xml) file, to facilitate the FDA reviewer's and Data manager's use of the datasets. It also includes a summary of SEND dataset conformance findings.

1.1 Study Protocol Title, Number, and Report Version

Study Title	13-Week Repeat Dose Toxicity Study on PCDRUG1234 in Rats
Study Number	PC201904
Study Version	1.0

1.2 Summary of SEND Dataset Creation Process

<<This section should be updated with SEND Dataset Creation Process>>

This section describes a high-level summary of the process by which the SEND dataset was created from study data.

Example: For the study PC1234, all in-life, clinical pathology, postmortem data were collected with LIMS 1 (Company 1). Bioanalytical data were collected using LIMS 2 (Company 2). Input (raw data extracts) from each of the LIMS via LIMS-specific adaptors was processed by SEND Solution XXX (Company X) to produce one integrated SEND dataset with a define.xml, a validation report and LIMS terms mapped to controlled terminology.

1.3 SEND Dataset Verification

<<This section should be updated with SEND dataset verification process>>

A positive statement needs to be included in this section.

Example: Data in the SEND datasets are an accurate representation of the data for Study No. PC1234. Any differences between the data sets and the report are described in section 6.2 . Verification procedures and documentation supporting this are available upon request.

2. Study Design

2.1 Study Design Summary

<<This section can be updated with textual description, if required >>

This section provides a brief textual description of the protocol design

Example: In study PC1234, MRA1234 was given to male and female rats by Intravenous route at doses of 0 (vehicle), 2, 10, and 50 mg/kg/day for one month followed by a four week recovery period for all groups .Control group consisted of 15 subjects per sex and Treatment groups consisted of 18 subjects per sex. Following 4 weeks of treatment, all but 5 subjects per sex were euthanized. The remaining subjects continued onto a 4 week treatment-free recovery period, and were euthanized.

Group	Treatment	Dose Level	Dose Concentration	Dose Volume	Number of Animals					
					Main				TK	
					NonRecovery		Recovery			
					F	M	F	M	F	M
Group 1	Vehicle	0 mg/kg	0mg/kg		10	10	5	5	0	0
Group 2	PCDRUG1234	2 mg/kg	2mg/kg		10	10	5	5	5	5
Group 3	PCDRUG1234	20 mg/kg	20mg/kg		10	10	5	5	5	5
Group 4	PCDRUG1234	200 mg/kg	200mg/kg		10	10	5	5	5	5

2.2 Trial Design Domain Overview

Study Group	Trial Arms		Element in each Epoch			Trial Set	
SPGRPCD	ARMCD	ARM	Prestudy	Treatment	Recovery	SETCD	SET
Group 1	1	Vehicle Control	Acclimation	Vehicle Control		1	Group 1, Control, nonrecovery
	1R	Vehicle Control with recovery	Acclimation	Vehicle Control	Recovery	1R	Group 1, Control, recovery
Group 2	2	2 mg/kg PCDRUG	Acclimation	2 mg/kg PCDRUG, once daily		2	Group 2,2 mg/kg PCDRUG, nonrecovery
	2R	2 mg/kg PCDRUG with recovery	Acclimation	2 mg/kg PCDRUG, once daily	Recovery	2R	Group 2,2 mg/kg PCDRUG, recovery
	2	2 mg/kg PCDRUG	Acclimation	2 mg/kg PCDRUG, once daily		2TK	Group 2,2 mg/kg PCDRUG, TK

Study Group	Trial Arms		Element in each Epoch			Trial Set	
SPGRPCD	ARMCD	ARM	Prestudy	Treatment	Recovery	SETCD	SET
Group 3	3	20 mg/kg PCDRUG	Acclimation	20 mg/kg PCDRUG, once daily		3	Group 3,20 mg/kg PCDRUG, nonrecovery
	3R	20 mg/kg PCDRUG with recovery	Acclimation	20 mg/kg PCDRUG, once daily	Recovery	3R	Group 3,20 mg/kg PCDRUG, recovery
	3	20 mg/kg PCDRUG	Acclimation	20 mg/kg PCDRUG, once daily		3TK	Group 3,20 mg/kg PCDRUG, TK
Group 4	4	200 mg/kg PCDRUG	Acclimation	200 mg/kg PCDRUG, once daily		4	Group 4,200 mg/kg PCDRUG, nonrecovery
	4R	200 mg/kg PCDRUG with recovery	Acclimation	200 mg/kg PCDRUG, once daily	Recovery	4R	Group 4,200 mg/kg PCDRUG, recovery
	4	200 mg/kg PCDRUG	Acclimation	200 mg/kg PCDRUG, once daily		4TK	Group 4,200 mg/kg PCDRUG, TK

3. Standards, Formats, and Terminologies and their Versions

3.1. Standards Used

Dataset Component	Standard or Dictionary	Versions Used
Tabulation Datasets	CDISC SEND Implementation Guide	SEND IMPLEMENTATION GUIDE VERSION 3.0
Controlled Terminology	CDISC SEND Controlled Terminology	SEND Terminology 2018-12-21
Data Definition file	CDISC DEFINE	2.0
Validation Rules	FDA Business Rules	FDA Business Rules v1.3
Validation Rules	FDA Specific SEND Validation Rules	FDA Validator Rules v1.2

3.2 Rationale for Standards Selection

<<This section should be updated with rationale for standard selection>>

The standards versions used were the most current at the time of dataset creation

Example: The standards and versions selected were the most current ones listed in FDA's Study Data Standards Catalog at the time of dataset creation.

3.3 Nonstandard Terminology

The following nonstandard terminology was used:

Dataset Name	Variable	Codelist	Term Used	Meaning
TS	TSPARMCD	SEND Trial Summary Parameter Test Code	LOT	
TS	TSPARMCD	SEND Trial Summary Parameter Test Code	QATYPE	
TS	TSPARMCD	SEND Trial Summary Parameter Test Code	TRTPUR	
TS	TSPARM	SEND Trial Summary Parameter Test Name	Lot Number	
TS	TSPARM	SEND Trial Summary Parameter Test Name	Quality Assurance type	
TS	TSPARM	SEND Trial Summary Parameter Test Name	Percent Purity of Compound	

4. Description of Study Datasets

<< This section should be updated with Description of Study Datasets >>

This section provides additional context for SEND domains that is not adequately addressed in define.xml or SENDIG. Answers to the following questions may be helpful:

- Are the submitted data taken from an ongoing study? If so, what was the cutpoint(s)? What will be coming?
- Were the SEND datasets used as sources for the analysis?
- Were any domains planned but not submitted because no data were collected?
- Are the submitted data a subset of collected data? (The answer will be "yes" if data were collected but not included in the submission.) Explanation can be provided in Section 6.2 .
- If an extension study is being documented, include description(s) of any data that have been copied from or are located in another study in the submission, such as the use of one control group for multiple studies.

Example: The submitted SEND datasets represent a completed study. LIMS reports and not SEND datasets were used for data analysis. All data in the study report are included In the SEND dataset.

4.1 Dataset Summary

Dataset Name	Dataset Label	Supplemental Qualifiers?	Related Records?	Observation Class
DS	Disposition			Events
BG	Body Weight Gains			Findings
BW	Body Weights			Findings
CL	Clinical Observations			Findings
DD	Death Diagnosis			Findings
EG	ECG Test Results			Findings
FW	Food and Water Consumption			Findings
LB	Laboratory Tests Results			Findings
MA	Macroscopic Findings	X	X	Findings
MI	Microscopic Findings	X	X	Findings
OM	Organ Measurements			Findings
PC	Pharmacokinetics Concentrations			Findings
PM	Palpable Masses			Findings
PP	Pharmacokinetics Parameters			Findings
SC	Subject Characteristics			Findings
TF	Tumor Findings			Findings
VS	Vital Signs			Findings
EX	Exposure			Interventions
RELREC	Related Records			Relationship
CO	Comments			Special Purpose
DM	Demographics			Special Purpose
SE	Subject Elements			Special Purpose
TA	Trial Arms			Trial Design
TE	Trial Elements			Trial Design
TS	Trial Summary			Trial Design
TX	Trial Sets			Trial Design

4.2 Dataset Explanation

<<This section is required to be updated for datasets for which hyperlinks have been provided in Section 4.1>>

Note: Provide a numeric subheading for each dataset and ensure that is appears in the table of content, e.g. 4.2.1, 4.2.2, 4.2.3, etc.

4.3 Use of Supplemental Qualifiers

Dataset Name	Associated Dataset	Qualifiers Used
SUPPMA	Macroscopic Findings	Result Modifiers<<Additional text to be updated>>
SUPPMI	Microscopic Findings	Result Modifiers<<Additional text to be updated>>

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5. Data Standards Validation Rules, Versions, and Conformance Issues

5.1 Validation Outcome Summary

A total of 9787 issues were identified by the FDA Validator Rules 1.3.

5.2 FDA SEND Validation Rules Version

Rule conformance to SEND 3.0 was evaluated using FDA Validator Rules v1.3 which are associated with FDA Business Rules v1.4

5.3 Validation Issues

The following rules were reported by the MySEND Validator:

FDA Rule ID	Publishers Rule ID	FDA Business Rule Description	Validator Rule Description	Domain(s)	Count	Explanation
SD0006	FDAB013	No baseline flag record in Domain for subject	Baseline flags for Laboratory results, Vital Signs, ECG, Pharmacokinetic Concentrations, and Microbiology results should be submitted if the data was collected or can be derived.	EG, LB, PC, VS	386	Baseline flags are not provided in study hence can be considered invalid

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FDA Rule ID	Publishers Rule ID	FDA Business Rule Description	Validator Rule Description	Domain(s)	Count	Explanation
CT2002	CG0021	Conformance with the SDTMIG Domain Models is minimally indicated by following SDTM-specified controlled terminology and format guidelines for variables, when provided When the CRF includes a list of values for a qualifier field that includes "Other" and the "Other" is supplemented with a "Specify" free text field,	Variable should be populated with terms from its CDISC controlled terminology codelist. New terms can be added as long as they are not duplicates, synonyms or subsets of existing standard terms.	TS	6	Additional parameters such as Lot Number, Quality Assurance Type and Percent Purity of Compound are available as per the study report hence included to the domain
SD1087	FDAB034	Study Start and End Dates must be submitted and complete.	Study Day of Start (--STDY) variable should be included into dataset, when Start Study Date/Time (--STDTC) variable is present	SE	1	The SE domain does not contain the variables Study Day of Start or Start Study Date/Time, thus this is a false positive
SD1083	FDAB016	Collection Study Day should be populated when Date/Time of Collection is available.	Collection Study Day (--DY) variable should be included into dataset, when Collection Study Date/Time (--DTC) variable is present.	CO	1	No data is available for CODTC
SD0026	FDAB012	Assessment results must include units whenever a unit of measure is available.	Original Units (--ORRESU) should not be NULL, when Result or Finding in Original Units (--ORRES) is provided	LB	120	Albumin/Globulin is measured in Ratio.

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FDA Rule ID	Publishers Rule ID	FDA Business Rule Description	Validator Rule Description	Domain(s)	Count	Explanation
SD0029	CG0425	--STRESU: Standardized units used for --STRESC and --STRESN.	Standard Units (--STRESU) should not be NULL, when Character Result/Finding in Std Units (--STRESC) is provided.	LB	120	Albumin/Globulin is measured in Ratio.
SD1091	FDAB034	Study Start and End Dates must be submitted and complete.	Study Day of End (--ENDY) variable should be included into dataset, when End Study Date/Time (--ENDTC) variable is present.	SE	1	The SE domain does not contain the variables Study Day of End or End Study Date/Time, thus this is a false positive
SD1092	CG0222	The permissible Study Day variables (--DY, --STDY, and --ENDY) describe the relative day of the observation starting with the reference date as Day 1. They are determined by comparing the date portion of the respective date/time variables (--DTC, --STDTC, and --ENDTC) to the date portion of the Subject Reference Start Date (RFSTDTC from the Demographics domain).	Study Day of End (--ENDY) variable value should be populated, when End Study Date/Time (--ENDTC) and Subject Reference Start Date/Time (RFSTDTC) variables values are provided, and both of them include complete date part.	SE	340	The SE domain does not contain the variables Study Day of End or End Study Date/Time, thus this is a false positive

FDA Rule ID	Publishers Rule ID	FDA Business Rule Description	Validator Rule Description	Domain(s)	Count	Explanation
SD1212	FDAB031	Standardized Result in Numeric Format must be populated whenever it is applicable.	Standardized Result in Numeric Format (--STRESN) variable value should be equal Standardized Result in Character Format (--STRESC) variable value, when Standardized Result in Character Format (--STRESC) variable value represents a numeric value.	OM,PP	281	STRESN value have the significant digits as per the study report
SE2315	FDAB048	Result modifier should be included in MA, MI and TF domains unless all findings are normal for nonclinical data.	A result modifier should be included in MA, MI and TF domains unless all findings are normal for nonclinical data.	MI,MA	99	Not all Findings in MA, MI have modifiers in the original results, such as those listed as a single word or all text incorporated into the Standardized Result.

6. Sponsor Decisions Related to Data Standard Implementations

6.1 Sponsor-Defined Standardization Descriptions

<< Section to be updated>>

This section describes sponsor-defined decisions related to data standardization that are important for review and interpretation of the data sets. There may be instances in which current implementation guides (e.g., SDTMIG, SENDIG) do not provide specific instruction as to how certain study data should be represented. In these instances, sponsors should discuss their proposed solution with the review division and submit supporting documentation that describes these decisions or solutions in the SDRG at the time of submission. In some instances, it may not be possible to represent a collected data element as a standardized data element. In these cases, there should be an explanation in the SDRG as to why certain data elements could not be fully standardized or were otherwise not included in the standardized data submission. The following are example topics for this section:

- Description of any custom domains
- Comment as to whether a dataset contains derived values in addition to raw data values. (Derived values are linked to raw data values within the same dataset.)
- If you are documenting an extension study, include description(s) of any data that have been copied from or are located in another study in the submission. One such example is the use of one control group for multiple studies.

6.2 Differences between SEND Datasets and Study Report

<< Section to be updated>>

This section describes differences that are present between the SEND datasets and the Final Study Report (the .pdf report.)It is recommended to include a table mapping study days in report to SEND study days, if/where they appear different. The following are examples topics for this section:

- Explain multiple study numbers, if existing in study data sets
- Include justification of why reference start date is different from first day of dosing, including any differences in the definition across subjects and description of the calculation of study days.

Example: The first day of dosing in the report and protocol is Day 0. The first day of dosing in the SEND datasets is Day 1 compliance with SEND. Accordingly, all study days in the SEND dataset are 1 day later than the corresponding day in the protocol and study report.

6.3 Nonstandard Electronic Data Submitted

<< Section to be updated>>

This section is for recording significant data issues, clarifications, explanations of traceability, and adjudications in the SDRG.

For example, data were not collected or were collected using different/incompatible terminologies, or were collected but will not fit into the format.

6.4 Legacy Data Conversion

<< Section to be updated>>

This section contains the Legacy Data Conversion Plan, and results Report, if a conversion was performed. Sponsors should evaluate the decision involved in converting previously collected non-standardized data (i.e., legacy study data) to standardized data (i.e. SEND). Sponsors should provide the explanation and rationale for the study data conversion in the SDRG. To mitigate traceability issues when converting legacy data, FDA recommends to prepare and submit a Legacy Data Conversion Plan and Report.

- The plan should describe the legacy data and the process intended for the conversion.
- The report should present the results of the conversions, issues encountered and resolved, and outstanding issues.
- Legacy data (i.e. legacy tabulation data) may be needed in addition to the converted data.