Study Data Reviewer's Guide

*Nonclinical*

*(nSDRG)*

13-Week Repeat Dose Toxicity Study on PCDRUG in Rats

(PC201708)

PCLS Pharmaceuticals

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# Abbreviations

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

# 1. nSDRG Introduction

This document provides context for the SEND tabulation datasets and terminology for Study PC201708, 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 PCDRUG in Rats |
| **Study Number** | PC201708 |
| **Study Version** | 1.0 |

## 1.2 Summary of SEND Dataset Creation Process

This is a synthetic dataset created based on published ranges for rat parameters, randomized data from public sources, and artificially adjusted to show signals as listed in Section 6.1. . Data was checked for SEND compliancy. Data were also validated against the FDA Specific SEND Validation Rules.

Domains from the SEND Submission template were converted to .csv files and uploaded into DSIMS, our commercial software solution that generates xpt files and define xml files. The standardized data were reviewed in ToxVision to ensure the datasets fit the needs of FDA nonclinical reviewers. SEND.xpt files were generated using an output function within DSIMS.

## 1.3 SEND Dataset Verification

Data in the SEND datasets are an accurate representation of the data for Study No. PC201708. 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

In study PC201708, PCDRUG was given to male and female rats by oral gavage at doses of 0 (vehicle), 2, 20, and 200 mg/kg/day for 13 weeks followed by a two week recovery period for all groups .Control group consisted of 15 subjects per sex and Treatment groups consisted of 15 subjects per sex. Following 13 weeks of treatment, all but 5 subjects per sex were euthanized. The remaining subjects continued onto a 2 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 | PCDRUG | 2 mg/kg | 2mg/kg |  | 10 | 10 | 5 | 5 | 5 | 5 |
| Group 3 | PCDRUG | 20 mg/kg | 20mg/kg |  | 10 | 10 | 5 | 5 | 5 | 5 |
| Group 4 | PCDRUG | 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 |
| 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 2017-03-31 |
| Data Definition file | CDISC DEFINE | 2.0 |
| Validation Rules | FDA Specific SEND Validation Rules | 2.1 |

## 3.2 Rationale for Standards Selection

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 | TSPARM | STSPRM | Quality Assurance type | Type of quality assurance used in the study |
| TS | TSPARM | STSPRM | Lot Number | Lot number of the test article |
| TS | TSPARM | STSPRM | Percent Purity of Compound | Percent purity of the test article |

# 4. Description of Study Datasets

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 Test 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

## 4.3 Use of Supplemental Qualifiers

|  |  |  |
| --- | --- | --- |
| **Dataset Name** | **Associated Dataset** | **Qualifiers Used** |
| SUPPMA | Macroscopic Findings | Result Modifiers that were part of MAORRES |
| SUPPMI | Microscopic Findings | Result Modifiers that were part of MIORRES |

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

## 5.1 Validation Outcome Summary

No errors in the standardized dataset were identified. A total of 942 warnings were identified by the Pinnacle 21 Community 2.2.1 Validator (formerly OpenCDISC). A total of 367 errors and 5 warnings were identified by the Pinnacle 21 Community 2.2.1 Validator against define file rules.

A total of 2436 warnings were identified by the FDA Nonclinical Validator Specifications version 2.1.

## 5.2 FDA SEND Validation Rules Version

Rule conformance to SEND 3.0 was evaluated using FDA Specific SEND Validation Rules, Version 2.1

## 5.3 Errors

### 5.3.1 Pinnacle21 Validator

The following errors were reported by the Pinnacle 21 Validator for the define file.

| **Rule** | **Message** | **Domain(s)** | **Count** | **Explanation** |
| --- | --- | --- | --- | --- |
| DD0038  (Define.xml) | Missing Value Level metadata for QVAL in Dataset 'SUPPMA'  Missing Value Level metadata for QVAL in Dataset 'SUPPMI' | SUPPMA, SUPPMI | 2 | Pinnacle rule based on the PMDA published define rules for clinical studies. We therefore do not consider these errors to be applicable |
| DD0034  (Define.xml) | Unknown NCI Code value for Term in Codelist 'Specimen'  Unknown NCI Code value for Term in Codelist 'SEND Trial Summary Parameter Test Name' | MA/MI/OM/TS | 95 | The NCI Code value present in the define file for each specimen or TSPARM are correct according to the Controlled Terminology list used in the study. |
| DD0073  (Define.xml) | Invalid Origin Type value | All | 247 | Pinnacle validator is using the PMDA defined rules that are not applicable for SEND. As per SEND IG 3.0, the allowed Origin values are “COLLECTED”, “DERIVED”, “OTHER” and “NOT AVAILABLE” (Section 3.2.2.1, page 19). |

## Warnings

### 5.4.1 Pinnacle21 Validator

The following warnings were reported by the Pinnacle 21 Validator:

| **Rule** | **Message** | **Domain(s)** | **Count** | **Explanation** |
| --- | --- | --- | --- | --- |
| FDAN212 | Duplicate Records | FW, MA, MI | 242 | This Rule does not include a sufficient number of variables to determine uniqueness. For example, neither –ORRES nor –DY, nor other timing variables other than --DTC were included. We therefore do not consider these warnings to be applicable. |
| FDAN341 | TSPARMCD value not found in 'SEND Trial Summary Parameter Test Code' extensible codelist  TSPARM value not found in 'SEND Trial Summary Parameter Test Name' extensible codelist | TS | 6 | TSPARM and TSPARMCD are extensible variables, and in order to capture study information not included in the codelist, the parameter test names Lot Number, Percent Purity of Compound, Quality Assurance type, LOT, QATYPE, TRTPUR |
| FDAN341 | EGSTRESC value not found in 'ECG Result' extensible codelist | EG | 354 | The values flagged are all numeric values which would not be included in a codelist. This is a bug in the Pinnacle 21 validator. |
| FDAN154 | Missing value for LBORRESU, when LBORRES is provided | LB | 120 | Certain LB parameters had qualitative results (Clarity, Color, etc.) or do not have associated units (pH, etc.). Thus, no unit was populated in ORRESU for these measurements. |
| FDAN169 | Missing value for LBSTRESU, when LBSTRESC is provided | LB | 120 | Certain LB parameters had qualitative results (Clarity, Color, etc.) or do not have associated units (pH, etc.). Thus, no unit was populated in STRESU for these measurements. |
| FDAN232 | No result modifier (--RESMOD) qualifier for MA domain  No result modifier (--RESMOD) qualifier for MI domain | MA, MI | 99 | Not all Findings in MA or MI have modifiers in the original results, such as those listed as a single word or all text incorporated into the Standardized Result. |
| FDAN035 | Variable is in wrong order within domain | EG | 1 | Pinnacle is expecting EGMETHOD before EGLEAD; but SEND IG 3.0 has EGLEAD before EGMETHOD. This order is wrong in SENDIG 3.0, but corrected in SENDIG 3.1. This does not affect reviewability of the EG data. |
| DD0059 (Define.xml) | Define.xml/CDISC dataset Description mismatch | PP, PC, MA | 3 | Issue with Pinnacle 21 validator where domain description is wrong. We therefore do not consider these warnings to be applicable |
| DD0024  (Define.xml) | Invalid Term in Codelist 'No Yes Response' | N/A | 1 | ‘N’ is a correct term in Codelist 'No Yes Response', therefore this is a false positive |
| DD0039  (Define.xml) | Variable is in wrong order within Dataset 'EG' | EG | 1 | Pinnacle is expecting EGMETHOD before EGLEAD; but SEND IG 3.0 has EGLEAD before EGMETHOD. This order is wrong in SENDIG 3.0, but corrected in SENDIG 3.1. This does not affect reviewability of the EG data. |

The following warnings were reported by the FDA Nonclinical rules Validator:

| **Rule** | **Message** | **Domain(s)** | **Count** | **Explanation** |
| --- | --- | --- | --- | --- |
| FDAN154 | Missing value for LBORRESU, when LBORRES is provided | LB | 1099 | Certain LB parameters had qualitative results (Clarity, Color, etc.) or do not have associated units (pH, etc.). Thus, no unit was populated in ORRESU for these measurements. |
| FDAN169 | Missing value for LBSTRESU, when LBSTRESC is provided | LB | 1099 | Certain LB parameters had qualitative results (Clarity, Color, etc.) or do not have associated units (pH, etc.). Thus, no unit was populated in STRESU for these measurements. |
| FDAN232 | No result modifier (MARESMOD) qualifier for domain | MA | 72 | Not all Findings in MA have modifiers in the original results, such as those listed as a single word or all text incorporated into the Standardized Result. |
| FDAN232 | No result modifier (MIRESMOD) qualifier for domain | MI | 27 | Not all Findings in MI have modifiers in the original results, such as those listed as a single word or all text incorporated into the Standardized Result. |
| FDAN212 | Duplicate records | PC | 120 | This Rule does not include a sufficient number of variables to determine uniqueness. For example, neither –ORRES nor –DY, nor other timing variables other than --DTC were included. We therefore do not consider these warnings to be applicable. |
| FDAN154 | Missing value for PMORRESU, when PMORRES is provided | PM | 3 | The PMORRES values were qualitative and did not have associated units. |
| FDAN169 | Missing value for PMSTRESU, when PMSTRESC is provided | PM | 3 | The PMSTRESC values were qualitative and did not have associated units. |
| FDAN341 | Value for TSPARM not found in 'SEND Trial Summary Parameter Test Name' CT codelist | TS | 3 | TSPARM is an extensible variable, and in order to capture study information not included in the codelist, the parameter test names Lot Number, Percent Purity of Compound, Quality Assurance type. |
| FDAN341 | Value for TSPARMCD not found in 'SEND Trial Summary Parameter Test Name' CT codelist | TS | 3 | TSPARMCD is an extensible variable, and in order to capture study information not included in the codelist, the parameter test codes, LOT, QATYPE, TRTPUR. |

# 6. Sponsor Decisions Related to Data Standard Implementations

## 6.1 Sponsor-Defined Standardization Descriptions

## 6.2 Differences between SEND Datasets and Study Report

1. In the Body Weight domain, body weights were adjusted to show decreased weights in Groups 3 and 4.
2. In the Body Weight Gain domain, the values were calculated from the adjusted body weights, so Groups 3 and 4 show decreased body weight gain.
3. In the Laboratory Test Results domain, values for AST, ALT, and ALP were adjusted to show an increase in Group 4, RBC, HGB, and HCT were adjusted to show a decrease in Group 4.
4. In the Organ Measurements domain, liver weights were adjusted to show an increase in Group 4.
5. In the Macroscopic and Microscopic Findings domains, liver findings were added to Group 3 and 4 to show increased liver effects. These were linked in the Related Records domain.
6. Tumor findings for liver were added to show increased liver effects in Group 4.
7. Premature deaths due to hepatocellular carcinoma were added to Group 4 and listed in the Death Diagnosis and Tumor Findings domains.