Study Data Reviewer's Guide

Nonclinical
(*nSDRG*)

Repeated dose toxicity study by intramuscular administration of vaccine in rabbits

Laboratory Study Number: RABBITV1

Sponsor Reference Number: RABBITV1

Revision History		
Date	**Version**	**Summary**
06-May-2019	1.0	Final
03-Jan-2020	2.0	Anonymized and adapted for CBER Pilot Submission

Sponsor

Vaccine Lab

Study Data Reviewer's Guide (Study RABBITV1)

CONTENTS

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. SDRG Introduction

This document provides context for the SEND tabulation datasets and terminology for study RABBITV1, in addition to the information provided in the Data definitions file (define.xml), to facilitate the FDA reviewer's and Data manager's use of the datasets.

1.1 Study Title, Number, and Report Version

Study Title	Repeated dose toxicity study by intramuscular administration of vaccine in rabbits
Study Number	RABBITV1
Study Version	Final Report. There have been no report amendments.

1.2 Summary of SEND Dataset Creation Process

Datasets were derived from 3 different LIMS systems, with one domain created manually. Trial Design datasets were collected from a LIMS. In-life data and clinical pathology data were collected using a different LIMS. Postmortem data were collected using another LIMS. The IS domain was created manually.

Input (raw data extracts) from each of the LIMS via LIMS-specific adaptors was processed by SEND Solution to produce one integrated SEND dataset with a define.xml and a Pinnacle21 Validator (Version: 2.2.0) to perform a double check in compliance with SEND. This package was provided by the CRO to the Sponsor.

After receipt of the original SEND 3.0 dataset from the CRO, the Sponsor updated the files for SEND version 3.1. Some domains were modified to conform to SEND IG 3.1, by adding the variables –NOMDY, --NOMLBL –USCHFL and –FOCID, where correct data could be determined.

An IS (Immunogenicity Specimen) domain was manually created by adapting from the SDTM model for customized use for this nonclinical study. Data was transcribed to Excel from the final report table for immunogenicity, then transformed to .xpt using SAS.

1.3 SEND Dataset Verification

Data in the SEND datasets are an accurate representation of the data in the study report for Study No. RABBITV1. Any differences between the datasets and the report are described in section 6.2 of this document.

Verification procedures and documentation supporting this are available upon request (from original CRO for original dataset).

2. Study Design

2.1 Study Design Summary

In study RABBITV1, the test items were given to male and female rabbits by the intramuscular route on three occasions at 2-weeks intervals (on Days 1, 15 and 29) according to the following table:

Group	Treatment	Nominal dose level of adjuvant (mg/dose)	Nominal dose level of hemagglutinin (µg HA/strain/dose) (1)	Number, sex and identity of animals
1	Control item (NaCl 0.9%)	0	0	10 males: N30641 to N30650 10 females: N30711 to N30720
2	SENDVACC10	12.5	15	10 males N30651 to N30660 10 females: N30721 to N30730
3	SENDVACC99	12.5	45	10 males N30661 to N30670 10 females: N30731 to N30740

At the end of the treatment period, the first five animals/sex (principal animals) were euthanized 2 days after the last injection (on Day 31), while the last five animals/sex (recovery animals) were euthanized after a 4-week observation period after the last injection (on Day 57).

2.2 Trial Design Domain Overview

All trial design domains described in the SEND Implementation Guide are included in the submission. The trial design was mapped according to the table below:

Study Group	Trial Arms		Element in each Epoch			Trial Set	
SPGRPCD	**ARMCD**	**ARM**	**Pre Treatment**	**Treatment**	**Recovery**	**SETCD**	**SET**
1	G1A1	Group 1, Control	PreDosing	Control	-	G1A1	Group 1, Control
	G1A2	Group 1, Control, Recovery	PreDosing	Control	Recovery	G1A2	Group 1, Control, Recovery
2	G2A1	Group 2, SENDVACC10	PreDosing	SENDVACC10	-	G2A1	Group 2, SENDVACC10
	G2A2	Group 2, SENDVACC10, Recovery	PreDosing	SENDVACC10	Recovery	G2A2	Group 2, SENDVACC10 Recovery
3	G3A1	Group 3, SENDVACC99	PreDosing	SENDVACC99	-	G3A1	Group 3, SENDVACC99
	G3A2	Group 3, SENDVACC99 Recovery	PreDosing	SENDVACC99	Recovery	G3A2	Group 3, SENDVACC99 Recovery

3. Standards, Formats, and Terminologies and their Versions

3.1 Standards Used

Component	Standard or Dictionary	Versions Used
Tabulation Datasets	CDISC SEND	Originals were SEND 3.0. Updated to SEND3.1 for CBER POC submission
Controlled Terminology (all domains except IS)	CDISC SEND Controlled Terminology	2018-12-21
Controlled Terminology for IS domain	CDISC SDTM Controlled Terminology	2019-09-27
Data Definition file (.xml)	CDISC DEFINE	2.0

3.2 Rationale for Standards Selection

The standards versions used were the most current ones listed in the FDA Catalogue of Study Data Standards when the time of datasets were originally created. The datasets were then updated to SEND IG 3.1 and anonymized so they could be shared openly within the SEND for CBER Team's Proof of Concept (POC) activities.

The Study Data Technical Conformance Guide (version 4.2) was used as a reference.

3.3 Nonstandard Terminology

Dataset Name	Variable	Codelist	Term Used	Meaning
CL	CLSTRESC	Within Normal Limits Results	No clinical signs	Same as standard = NORMAL Note : use of the nonstandard term was probably due to an oversight by the Test Facility in transforming terminology. This was not corrected for the POC.
IS	ISTEST	Immunogenicity Specimen Assessments Test Name	H1 Specific IgG Antibody Titer	A measurement of the H1 specific IgG antibody concentration in a biological specimen, as determined by titration.

4. Description of Study Datasets

4.1 Dataset Summary

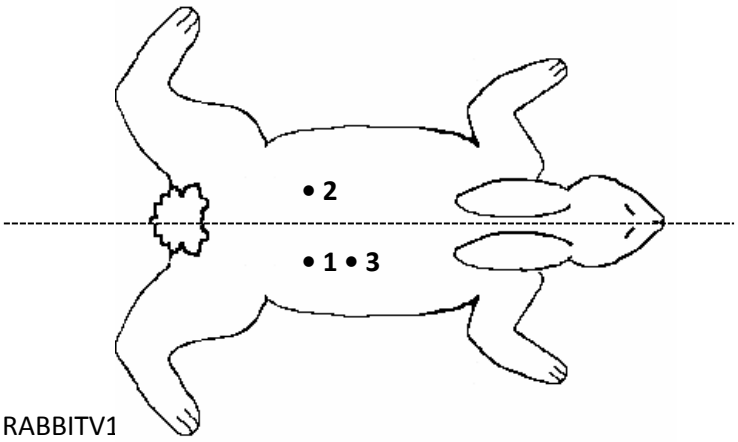
Dataset Name	Dataset Label	Supplemental Qualifiers?	Related Records?	Observation Class
TA	Trial Arms			Special Purpose
TE	Trial Elements			Special Purpose
TS	Trial Summary			Special Purpose
TX	Trial Sets			Special Purpose
CO	Comments			Special Purpose
DM	Demographics			Special Purpose
SE	Subject Elements			Special Purpose
EX	Exposure			Interventions
DS	Disposition			Events
BG	Body Weight Gains			Findings
BW	Body Weight			Findings
CL	Clinical Observations	X	X	Findings
FW	Food and Water Consumption			Findings
LB	Laboratory	X		Findings
MA	Macroscopic Findings	X	X	Findings
MI	Microscopic Findings	X	X	Findings
OM	Organ Measurements			Findings
VS	Vital Signs			Findings
POOLDEF	Pooled Definition			Relationship Datasets
IS	Immunogenicity Specimens			Custom Findings

4.2 Dataset Explanation

4.2.1 CL-Clinical Signs

Injection Sites (applies to findings in CL, MA and MI) :

Injection Site 1, 2 or 3 refer to three injection sites used for dose administration. Each injection was



performed in the dorsal muscles on the back of the subject.

Timepoints :

Explanation of timepoints in CL domain

CLTPTNUM	CLTPT	Explanation
1	Before treatment	Timepoint of observation recorded on dosing days only, prior to treatment.
2	After treatment	Timepoint of observation recorded on dosing days only, after treatment.
3	24h	Apparent error in data collection, by choosing a timepoint within the LIMS that was not relevant for the observation. Timpoint of observation recorded only for seven subjects on Day 30.
4	3 hours after treatment	Timepoint recorded for DERMAL Local Reaction observations on dosing days only. **Only non-normal observations included in CL domain.**
No value	No value	No timepoint recorded or expected for observations on non-treatment days.

4.2.2 EX-Exposure

Specific injection sites (1, 2 or 3) per dose are not included in the EX domain.

4.2.3 FW-Food Consumption

The Food consumption individual values table is listed by Subject ID. Records in the FW domain are represented by POOLID rather than USUBJID, even though there is only one USUBJID per POOLID. Sponsor assumes this is a result of the LIMS or SEND conversion system used at the CRO.

4.2.4 MA-Macroscopic Findings

SEND 3.1 new variable --FOCID was not added to this domain. For observations specific to injection sites, see MASPEC = SITE, INJECTION and MAANTREG = SITE 1 or 2 or 3. For Pilot, Sponsor is interested to understand if the –ANTREG approach is sufficient or if –FOCID is preferred or needed by reviewers

For most subjects, the specific injection site is not present in MAANTREG, only subjects N30641 and N30643 have specific injection sites ID listes in MAANTREG.

4.2.5 MI-Macroscopic Findings

MIANTREG includes numbered injection site for most subjects' observations for MISPEC « SITE, INJECTION », but is missing for injection site observations on subjects : N30641 and N30642.

4.2.5 IS-Immunogenicity Specimens

A custom domain was created by transcribing titers for antigen-specific antibodies from the study report

(Table 2 of the Final Immungenicity Phase Report) to Excel, then converting to .xpt format.

4.3 Use of Supplemental Qualifiers

Dataset Name	Associated Dataset	Qualifiers Used
SUPPMA	Macroscopic Observations	Modifiers that are part of MAORRES for which SEND variables have not yet been developed.
SUPPMI	Microscopic Observations	Modifiers that are part of MIORRES for which SEND variables have not yet been developed.
SUPPCL	Clinical Observations	Modifiers that are part of CLORRES for which SEND variables have not yet been developed.
SUPPLB	Laboratory	The record that contains non-numeric values were part of LBORRES equal to the values used by the sponsor for calculations

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

5.1 Validation Outcome Summary

5.2 FDA SEND Validation Rules Version

The study dataset, except for the custom IS domain, was checked against Version 2.1 of the FDA's validation rules for SEND formatted nonclinical studies.

5.3 Issues

The following issues were reported by the Pinnacle 21 validator:

FDA Rule	Message	Domain(s)	Explanation	Occurrences in Pinnacle21 Validator
DD0073	Invalid Origin Type value	Define	This error is caused because the Origin values (COLLECTED, DERIVED & OTHER) in the Define file are not consistent with the values ('CRF', 'Derived', 'Assigned', 'Protocol', 'eDT', or 'Predecessor') that Pinnacle 21 ID-DD0073, is expecting. This inconsistency is caused because the Define file has been populated with values described in the SENDIG 3.0	410

			whereas the Pinnacle 21 rules have been designed based on the Define-XML v2.0 specification.	
FDAN232	No result modifier qualifier for MI domain	MI	Severity is not a modifier. Severity is populated in the MISEV variable.	52
FDAN232	No result modifier qualifier for MA domain	MA	Not an issue: no modifier is intended from MAORRES..	2
FDAN212	Duplicate records	MA	The warning description states that No Finding Result with the same Test Short Name (--TESTCD) for the same Subject (USUBJID) and the same Collection Date (--DTC) are expected. However, this is not sufficient to describe a unique MA row (--ORRES and --ANTREG must also be considered). There are a	15
FDAN212	Duplicate records	MI	The warning description states that No Finding Result with the same Test Short Name (--TESTCD) for the same Subject (USUBJID) and the same Collection Date (--DTC) are expected. However, this is not sufficient to describe a unique MI row (--ORRES and -ANTREG must also be considered) We therefore do not consider these warnings to be applicable.	888
DD0059	Define.xml/CDISC dataset Description mismatch	Define	The define file is populated with the descriptions based on what's available in the SENDIG in the domain section headers. Whereas what Pinnacle 21 is expecting is based on their interpretation which appears to come from page 12 of the SENDIG 3.0.	20
FDAN031	Model permissible variable added into standard domain	CO	Not an issue: additional variable COVAL1 added to the dataset in order to accommodate value longer than 200 characters.	1

6. Sponsor Decisions Related to Data Standard Implementations

6.1 Sponsor Defined Standardization Descriptions

1. The SEND Datasets do not include Permissible Variables for cases where all values for variables are null. The SEND Implementation Guide section 4.1.3 indicates that this is a Sponsor decision.

2. Regarding the –DTC variables, only the dates (without times) are reported for the following domains: BG, BW, CL, CO, DD, DM, DS, FW, LB, MA, MI, OM, and SE. The date and time are reported for the following domains: EX, VS, because information about time is helpful for interpreting study data.

3. The EX domain contains details regarding each theoretical dose administered.

6.2 Differences between SEND Datasets and Study Report

Data in the SEND datasets are an accurate representation of data in the study report for Study No. RABBITV1. The following differences have been noted:

1. Body weight and body weight gain raw data were recorded with decimals in the study raw data and in the body weight dataset, but they are presented with no decimal in the study report.

2. Body weight gain is the difference between two body weight measurements collected successively over time. So, all the individual measurements for each time-interval are given in the SEND dataset, including predose values; the measurements for the following time-intervals are also presented in Study report: 1/30, 30/56, 1/56.

3. Non-rounded Organ to Body Weight Ratio and Organ to Brain Weight Ratio are generated by PathData data export. A rounded calculation (which is different from the one used to generate study report data) is used to generate an OM dataset. In consequence, in a few rare cases, differences (that are not significant) due to rounding can exist between SEND and the study report.

4. Terminology recorded during data collection is presented in the study report. This terminology was converted into SEND Controlled Terminology during creation of the SEND datasets. Details concerning this conversion are included in the Define file.

5. In the MI domain (--ORRES), of the SEND dataset, severity is reported as MINIMAL, SLIGHT, MODERATE, MARKED or SEVERE, while it is presented as grade 1, 2, 3, 4 or 5, respectively, in the study report.

6. Local reactions were evaluated daily and reported in the study report but only local reactions observed were presented in the SEND dataset.

During the anonymization of the study report, any pages that were signed/scanned images (such as phase report title pages) were simply deleted , because they could not be edited to remove identifying information.

6.3 Nonstandard Electronic Data Submitted

No nonstandard electronic data are included in this submission.