Study Data Reviewer's Guide
Nonclinical

Study Title	Characterization of Hepatitis B Vaccine T-Cell Dependent Antibody Response in Cynomolgus Monkeys
Study Number	8326556
Sponsor	Covance Laboratories Inc. 3301 Kinsman Boulevard Madison, Wisconsin 53704-2523 United States of America
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1. SDRG INTRODUCTION

This document provides context for the SEND tabulation datasets and terminology for Study 8326556, in addition to what is provided in the 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.

This study was meant to assess the feasibility of a method; it alone did not produce a validated method. It was paired with a sister study that will not be included in the donation. This is not indicative of current validation work by Covance.

This study was selected for the following reasons:

1. Vaccine compound
2. Immunology endpoints
3. Standard clinical pathology endpoints
4. Standard clinical observation endpoints

This study has the following limitations regarding the pilot program:

1. No control group for comparison
2. This characterization cannot stand alone and relies on results of another study
3. No biodistribution, toxicokinetics, respiratory, or mortality endpoints

1.1 Study Title, Number, and Version

Study Title	Characterization of Hepatitis B Vaccine T-Cell Dependent Antibody Response in Cynomolgus Monkeys
Study Number	8326556
Study Version	Final

1.2 Summary of SEND Dataset Creation Process

All inlife, clinical pathology, and post-mortem data were collected with Pristima by Covance Inc. Immunogenicity data were collected externally from Pristima by Covance Inc. The SEND module prepares a copy of the raw study data by using the Pristima Application Programming Interface (API) connector or CSV import functionality and produces an integrated SEND dataset with Controlled Terminology mapping applied and accompanying define.xml. The Immunogenicity data was integrated manually using R and the Visual Define Editor Tool.

The Immunogenicity domain and its supplemental qualifiers were manually tabulated and written as xpt files. Base R was used to label and encode the data. The SASxport package version 1.6.0 was used to import and write SAS files in R.

The Visual Define-XML Editor was used to modify the original define-xml output to include the IS metadata, as well as to address several system limitations.

1.3 SEND Dataset Verification

Data in the SEND datasets are an accurate representation of data in the study report for Study No. 8326556. This SEND dataset is to be used only for evaluation of SEND dataset review in general. While some data originated from a validated system, manual changes were not subject to a QC process. This dataset is not meant to be used for assessment of any treatment or compound but instead the viability of SEND as a review foundation. Any differences found by comparison between the datasets and the report are described in section 6.2.

2. STUDY DESIGN

2.1 Study Design Summary

Group	No. of Animals Female	Dose Level (µg/dose)	Dose Concentration (µg/mL)[a]
1	4	20	20

a The HBsAg formulation was administered at a volume of 1 mL/dose.

2.2 Trial Design Domain Overview

The following diagram illustrates the trial design.

Study Group	Trial Arms		Element in each Epoch		Trial Set	
SPGRPCD	ARMCD	ARM	PREDOSE	DOSING	SETCD	SET
1	1	Dose	Predose	G1 - Hepatitis B Vaccine: 20 ug/dose	1	Dose

3. STANDARDS, FORMATS, AND TERMINOLOGIES AND THEIR VERSIONS

3.1 Standards Used

Standard or Dictionary	Standard or Dictionary	Versions Used
Tabulation Datasets	CDISC SEND IG	3.1
Tabulation Datasets	Technical Conformance Guide	4.3
Controlled Terminology	CDISC SEND Controlled Terminology	2019-06-28
Data Definition file	CDISC DEFINE.XML	2.0.0

3.2 Rationale for Standards Selection

The versions of the standards used were the most current ones listed in FDA's Study Data Standards Catalog or the most recent CT package available in our SEND system at the time of dataset creation.

3.3 Nonstandard Terminology

The following nonstandard terminology was used on this study:

Dataset Name	Variable(s)	Codelist(s)	Term(s) Used	Meaning
IS	ISTEST; ISTESTCD	ISTEST; ISTESTCD	HBsAg IgG; IGGHBA	Hepatitis B Vaccine (HBsAg) IgG Serum Analysis
IS	ISTEST; ISTESTCD	ISTEST; ISTESTCD	HBsAg IgM; IGMHBA	Hepatitis B Vaccine (HBsAg) IgM Serum Analysis
LB	LBTEST; LBTESTCD	LBTEST; LBTESTCD	Other Urine Microscopic Findings; OTHR	Sperm was observed as present during the microscopic examination of the urine sample

4. DESCRIPTION OF STUDY DATASETS

4.1 Dataset Summary

Dataset Name	Dataset Label	Supplemental Qualifiers?	Related Records?	Observation Class
TS	Trial Summary			Trial Design
TE	Trial Elements			Trial Design
TA	Trial Arms			Trial Design
TX	Trial Sets			Trial Design
CO	Comments			Special Purpose
DM	Demographics			Special Purpose
SE	Subject Elements			Special Purpose
EX	Exposure			Interventions
DS	Disposition	X		Events
BW	Body Weight	X		Findings
BG	Body Weight Gain	X		Findings
CL	Clinical Observations	X		Findings
IS	Immunogenicity Specimen Assessments	X		Findings
LB	Laboratory Test Results	X		Findings

4.2 Dataset Explanation

4.2.1 CL

Incidence tables for clinical observations in the report use the values in CLORRES and not CLSTRESC.

Observations observed in the pen of animals and cannot be attributed to a single individual are recorded under each animal in that given cage with a modifier of “group observation”. These records are presented against each USUBJID as they were collected and reported and do not contain a POOLID.

4.2.2 DS

The DSSTDTC is the date and time a death status is assigned to a subject, not necessarily the time of removal from study alive.

4.2.3 LB

LBMETHOD is populated with the instrument name concatenated with the parameter name recorded in the data collection system.

LBTPT is incorrectly populated with operational information of what type of collection is being done at that time. As the collections are not timed, and only occur once per day, both LBTPT and LBTPTNUM should not be populated.

Not all parameters included in the LB Domain require units of measurement to be associated with the result. This results in some LBORRESU values being null when there is a value in LBORRES or no LBSTRESU value when LBSTRESC is provided.

LB coded numbers are decoded in the LB Coded Numbers attachment.

4.2.4 IS

This domain does not exist in the SEND IG and was extended from the SDTMIG. This domain was modeled off of the SEND 3.1 LB domain but modified for presenting immunogenicity endpoints.

Controlled Terminology has general terms for IgG and IgM however no specific terms related to HBsAg. The codelist was extended to include these specific endpoints.

When results were below the limit of quantitation, they are represented per the Technical Conformance Guide 4.3. A SUPPIS domain was also supplied to detail the numeric replacement for summary statistics.

4.2.5 Define File

The domain sequence in the define file does not follow the sequence in the SENDIG, nor are the General Observation Class domains in alphabetical order.

Variables with a DataType of ‘float’ and ‘integer’ are represented with a ‘Length’ attribute representing the maximum allowable length in our data repository. This value is 3 for PHASEDAY variables and 8 for other variables. Floating point variables can be analyzed with the ‘SignificantDigits’ attribute.

Value-Level metadata is described in the TS and TX where it is necessary to define another codelist or describe a different ‘Length’ attribute. The ‘Length’ attribute for these variables contains the maximum allowable length in our data repository.

Certain codelists are combined across variables that use the same codelists.

The following variables should have “date” listed as their Type instead of “datetime” as there is only a date present for all values: RFSTDTC; RFENDTC; BRTHDTC; SESTDTC.

Due to the mix of systems used to generate the define file, the variable OIDs, IS and SUPPIS domain OIDs, and the method OIDs do not have semantic meaning.

4.3 Use of Supplemental Qualifiers

Dataset Name	Variable Name (QNAM)	Variable Label (QLABEL)	Description
SUPPDS	PHSENAME	Phase name	The phase in which records were collected in for traceability to raw data.
SUPPDS	PHASEDAY	Day of Phase	The day records were collected on for traceability to raw data.
SUPPBW	PHSENAME	Phase name	The phase in which records were collected in for traceability to raw data.
SUPPBW	PHASEDAY	Day of Phase	The day records were collected on for traceability to raw data.
SUPPBG	PHSNAME1	Start Phase name	The phase in which records began collected for traceability to raw data.
SUPPBG	PHSNAME2	End Phase name	The phase in which records ended collected for traceability to raw data.
SUPPBG	PHSEDAY1	Start Day of Phase	The first day of a record's collection interval for traceability to raw data.
SUPPBG	PHSEDAY2	End Day of Phase	The last day of a record's collection interval for traceability to raw data.
SUPPCL	PHSENAME	Phase name	The phase in which records were collected in for traceability to raw data.
SUPPCL	PHASEDAY	Day of Phase	The day records were collected on for traceability to raw data.
SUPPLB	PHSENAME	Phase name	The phase in which records were collected in for traceability to raw data.
SUPPLB	PHASEDAY	Day of Phase	The day records were collected on for traceability to raw data.
SUPPIS	ISCALCN	Numeric Replacement	The numeric result used for summary statistics

5. DATA STANDARDS VALIDATION RULES, VERSIONS, AND CONFORMANCE ISSUES

5.1 Validation Outcome Summary

205 warnings were identified and are further explained in the following section.

5.2 FDA SEND Validation Rules Version

Rule conformance to SEND 3.1 was evaluated using Pinnacle 21 Community, version 3.0.1, which includes checks for conformance against the FDA Specific SEND Validation Rules Version 1.3, and Business Rules Version 1.4.

5.3 Errors

No errors were found during validation.

5.4 Warnings

The following warnings were reported:

Rule	Message	Domain	Count	Explanation
CG0168	CODTC is populated, when comment is a child record of another domain	CO	1	CODTC is populated for records with an IDVARVAL of MIREFID as these comments are not for a specific record in the MI domain. The validator tool is incorrectly identifying these as child records.
CG0168	Inappropriate usage of variables in CO domain	CO	1	The variable MIREFID is populated as an IDVARVAL value for comments made against the same specimen. These comments are not attributed to a single record in the MI domain, therefore MISEQ cannot be populated as IDVARVAL.
FDAB013	No baseline flag record in LB for subject	DM	4	LBBLFL is an expected variable. However, all records are null as Covance did not collect or report baseline flag data for this study.
CG0021	DOMAIN value not found in 'SEND Domain Abbreviation' extensible codelist	IS	80	A user defined domain was used for parameters not included in the CT package. The codelist is extensible, therefore, this is acceptable.
CG0303	SEND/dataset variable label mismatch	IS	9	These variables were extended from the STDMIG, therefor there isn't a SEND label to match to.
CG0021	LBTEST value not found in 'Laboratory Test Name' extensible codelist	LB	8	User defined test names have been used for parameters not included in the CT package. The codelist is extensible, therefore, this is acceptable.
CG0021	LBTESTCD value not found in 'Laboratory Test Code' extensible codelist	LB	8	User defined test codes have been used for parameters not included in the CT package. The codelist is extensible, therefore this is acceptable.
FDAB012	Missing value for LBORRESU, when LBORRES is provided	LB	24	Not all parameters included in the LB Domain require units of measurement to be associated with the result.
FDAB012, CG0425	Missing value for LBSTRESU, when LBSTRESC is provided	LB	32	Not all parameters included in the LB Domain require units of measurement to be associated with the result.
FDAB031	Missing value for LBSTRESN	LB	8	When LBCAT is URINALYSIS and LBORRES is collected as a coded number, LBSTRESN may be NULL.
CG0021	RDOMAIN value not found in 'SEND Domain Abbreviation' extensible codelist	SUPPIS	29	A user defined domain was used for parameters not included in the CT package. The codelist is extensible, therefore, this is acceptable.
FDAB046	Missing TCNTRL Trial Sets Parameter	TX	1	The study design does not include a control group. Therefore, we have not included a TCNTRL TXPARMCD or TXVAL in the dataset.

6. SPONSOR DECISIONS RELATED TO DATA STANDARD IMPLEMENTATIONS

6.1 Sponsor-Defined Standardization Descriptions

An IS and SUPPIS domain were included in this package. The creation of these domains is described in section 1.2.

6.2 Differences between SEND Datasets and Study Report

Data in the SEND datasets are an accurate representation of the data in the study report for Study 8326556, with the following differences noted:

- Dose administration data are included in the EX domain and not in the study report.
- Data collected in the predose phase are included in the dataset but may not all be included in the study report.
- Predose data in the study report are reported by phase days which differs from the VISITDY and the --DY in the datasets which are presented as study days. The phase days are provided in the supplemental domains.
- Age of the subjects is presented in the DM and TS domains.
    - DM: Each subject's actual age is presented in the DM domain, derived as Age = Subject Reference Start Date – Subject Date of Birth, rounded up to the nearest integer and presented in the age unit to match the age unit in the study report. The age range computed from the SEND dataset may differ from the age range presented in the study report, which is rounded down to the nearest whole number. Date of Birth is not presented in the study report.
    - TS: The planned age range of the test subjects [as a group] is presented using the Age Text and Age Unit Trial Summary Parameters (TSPARM) and matches the Age at Initiation of Dosing presented in the study protocol.
- Hepatitis B Vaccine (HBsg) Enzyme-Linked Immunospot (ELIspot) Sample Collection and Handling was not included in the SEND dataset. Only figures are present in the report for this endpoint.
- Body Weight change is presented in the SEND dataset but not in the report.
- Various models of calculators, computers, and computer programs were used to collect data in this study. Because different models round or truncate numbers differently, values in some report tables (e.g., means, standard deviations, or individual values) may differ slightly from those in SEND. Neither the integrity nor the interpretation of the data was affected by these differences.

6.3 Nonstandard Electronic Data Submitted

Nonstandard electronic data are not part of this submission.

6.4 Legacy Data Conversion

Legacy data are not part of this submission.

ATTACHMENTS

LB Coded Numbers

Color	**Abbreviation**
Pale/Colorless	CO
Straw	STRAW; S
Yellow	YELLOW
Dark Yellow	DK YELLOW
Amber	AMBER
Brown	BROWN
Red/Reddish-Brown ; Red	RED
Green	GREEN
Orange	ORANGE

Clarity	**Abbreviation**
Clear	CLEAR
Hazy/Slight Cloudy	SL CLOUDY
Cloudy	CLOUDY
Turbid	TURBID

Glucose	
Result	**Pristima Abbreviation**
Negative	NEGATIVE
100 mg/dL	TRACE
250 mg/dL	1+
500 mg/dL	2+
>/= 1000 mg/dL	3+

Bilirubin	
Result	**Pristima Abbreviation**
Negative	NEGATIVE
Small	1+
Moderate	2+
Large	3+

Ketones	
Result	**Pristima Abbreviation**
Negative	NEGATIVE
Trace	TRACE
15 mg/dL	1+
40 mg/dL	2+
>/= 80 mg/dL	3+

Blood	
Result	**Pristima Abbreviation**
Negative	NEGATIVE
Trace	TRACE
Small	1+
Moderate	2+
Large	3+

Protein	
Result	**Pristima Abbreviation**
Negative	NEGATIVE
Trace	TRACE
30 mg/dL	1+
100 mg/dL	2+
>/= 300 mg/dL	3+

Leukocyte Esterase	
Result	**Pristima Abbreviation**
Negative	NEGATIVE
Trace	TRACE
Small	1+
Moderate	2+
Large	3+

Grade		**0**	**1**	**2**	**3**	**4**
Abnormal Crystal Casts	Per Low Powered Field	Not Present	1-5	6-10	11-20	>20
Epithelial Cells RBC WBC	Per High Powered Field	Not Present	1-5	6-10	11-20	>20
Bacteria	Per High Powered Field	Not Present	Occasional, not seen in every field	Few in all fields	Moderate in all fields	Many in all fields, may obscure other elements