Recommendations for Anti-Drug Antibody (ADA) Modeling in SENDIG v3.0 and v3.1

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1. Overview: Purpose of this Document

The purpose of the PHUSE Investigating Endpoint Modeling project team (the IEM team) White Paper is to provide recommendations for the modeling of anti-drug antibody (ADA) data utilizing the existing domains and variables available in the CDISC SEND Implementation Guide (SENDIG v3.0), and the use of custom domains and nonstandard variables adapted from the SDTMIG to be used with SENDIG v3.1.

2. Scope

Immunogenicity data modeling for CDISC SENDIG v3.0 and SENDIG v3.1.

3. Definitions

ADA: Anti-Drug Antibody
bAb or BAB: Binding Antibody
CDISC: Clinical Data Interchange Standards Consortium
nAb or NAB: Neutralizing Antibody
nSDRG: Nonclinical Study Data Reviewer's Guide
SDTM: Standard Data Tabulation Model
SDTMIG: Standard Data Tabulation Model Implementation Guide
SEND: Standard for the Exchange of Nonclinical Data
SENDIG: Standard for the Exchange of Nonclinical Data Implementation Guide
IEM: Investigating Endpoint Modeling
IS domain: Immunogenicity Specimen

4. Problem Statement

As a follow-up to the IEM team's publication on Nonclinical Biomarker Modeling, a Working Group initiated discussions as to how best to model ADA data, given the current SENDIG (Versions 3.0 and 3.1) does not provide a clear methodology for reporting and tabulating the ADA data collected from nonclinical studies. This Working Group consisted of individuals from pharmaceutical companies, the U.S. Government, contract research organizations, the CDISC Microbiology Standards Subteam and software vendors. The participants in this Working Group recognized the challenges in implementing a standard approach given the evolving SEND data standard, the different ADA testing strategies across industry, and the varied therapeutic modalities currently in development. However, despite these challenges, the Working Group acknowledged the importance of developing a solution for the present in order to provide a framework to drive consistency and inform future ADA model development. Therefore, with the SDTM practices and recommendations in mind and knowledge of ongoing CDISC IS domain discussions, the Working Group developed a landscape of possible solutions for modeling nonclinical ADA data, which would be consistent with the approach to modeling of clinical ADA data as of January 2nd, 2020. The Working Group believes this model provides flexibility to present data from testing strategies where testing ends at a screen endpoint or when a combination of screen, confirmatory, and quasi-quantitation testing methodologies are employed.

5. Background

5.1.Investigation Phase

To provide reporting and tabulation solutions for nonclinical ADA data, the first challenge for the Working Group was to understand the different ADA testing strategies, and the different therapeutic modalities in development. Therefore, the participants gathered examples of both nonclinical and clinical ADA data from their respective organizations. A review of these example datasets allowed the Working Group to develop a common understanding of varied ADA endpoints, different collection methods, varied approaches to ADA data interpretation, and enabled the participants to understand the complexities associated with ADA reporting.

It became evident that in many cases, the standard use of the existing domain examples and associated controlled terminology in the current SENDIG would not support the tabulation and complete analysis of nonclinical ADA data as the tiered testing strategies (screening and confirmation), the quasi-quantitative nature of the endpoints, and various considerations related to drug specificity (e.g. from combination studies and epitope differentiation) pose additional challenges to modeling (see Figure 1). In addition, the different assay types (binding antibodies, neutralizing antibodies, cross-reactive binding antibodies, and non-cross-reactive antibodies) further challenged the ability to provide standardized modeling as often the aforementioned categories may be present in a single study.

Despite these challenges, the team was able to develop recommendations for SENDIG v3.0 modeling and provide recommendations for custom domains which can be utilized with SENDIG v3.1. Initial recommendations were provided via a poster at the *PHUSE Computational Science Symposium 2018*.

5.2. Decision Methodology

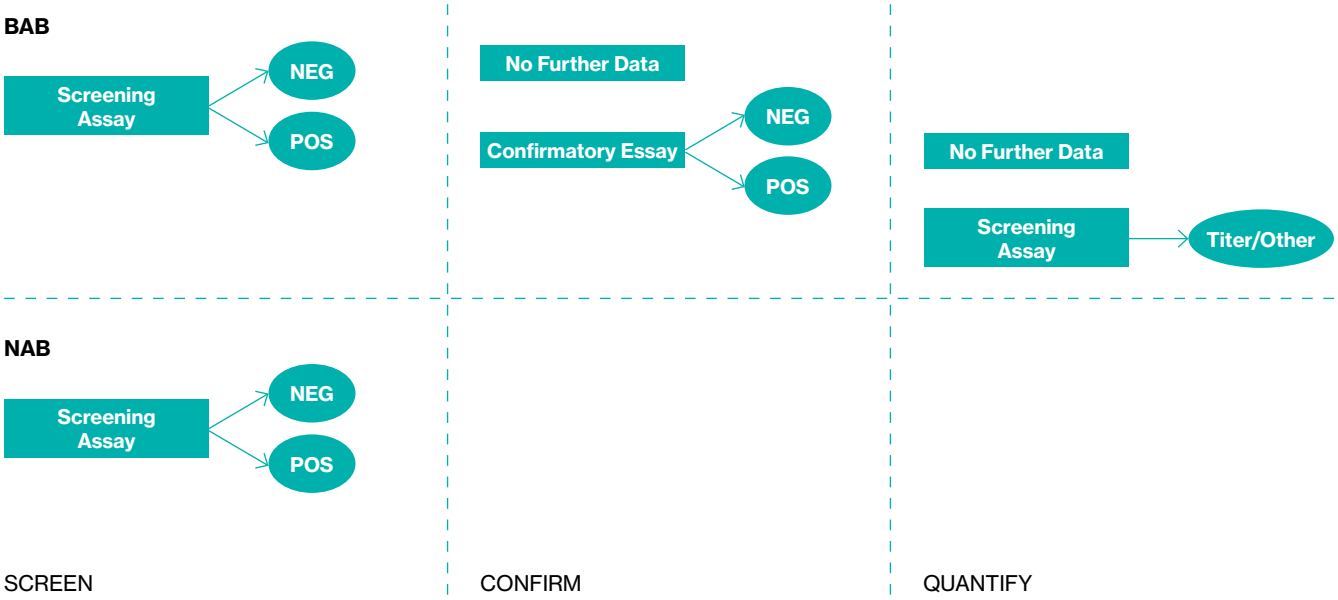
The immunogenicity testing scheme influences the combination of SEND IG variables to accurately reflect the collected data in a study. While most nonclinical study testing schematics only use screening ADA assays, tiered testing strategies may also be used, such as the example presented in Figure 1. Further, the complexity of the testing algorithm will increase when dosing multiple biologics in combination, when multiple confirmatory assays are used for complex molecules, and when additional binding characterization assays are anticipated. Additional examples for incorporating complexity are provided in the Appendices.

An additional point of consideration is that some companies will present the results for each sample as well as a final result (overall ADA status) for each subject, which is determined by a priori criteria established by the individual companies. Currently, these a priori criteria are determined by individual companies and therefore the algorithms may vary among companies. For example:

- Incidence of ADA is determined by counting at least 1 positive result at any timepoint.
- Incidence of ADA is determined by at least 1 positive result at any timepoint after initial dosing.

- Incidence of ADA induction (development of ADA) is determined using the following criteria: if both pre- and post-dose samples have positive titers, the animal is only considered positive for the induction of ADA when the post-dose titer is at least a threshold higher than the titer prior to initial dosing (e.g. 0.48).

Figure 1: Example ADA Tiered Testing Scheme for a Single Binding Target X



Companies may use all or some components of this testing strategy (e.g. screening and titer only versus screening, confirmatory and titer).

6. Recommendations

6.1. Recommendations for Modeling ADA Data

Recommendations for modeling ADA leverage the SDTM practices for the modeling of ADA data in clinical studies (i.e. Immunogenicity Specimen [IS] domain), the knowledge of ongoing CDISC discussions, and the limitations of many first generation SEND software systems which are incompatible with custom domains. The recommendations presented utilize either the existing Laboratory (LB) domain and variables available in SENDIG v3.0, or the use of a custom IS domain.

While the strategy for immunogenicity testing will vary across companies and will be dependent on the type of modality and dosing schedule (i.e. single or in combination), the general principles for the modeling of ADA data in both SEND v3.0 and SEND v3.1 are presented in Table 1 and Table 2, and specific examples are provided in the Appendix.

The recommendations for the modeling of nonclinical ADA data in SENDIG v3.0 is intended to be as consistent as possible with the modeling of ADA in the SDTM IS domain, while respecting the constraints of SENDIG v3.0. Unlike the SDTM IS domain, the LB domain lacks variables to describe the assay tier [i.e. screening, confirmatory, quasi-quantitation (relative magnitude)] and lacks variables to describe the specificity (towards the test article or cross-reactivity to specific endogenous structures).

Therefore, the recommendation from this Working Group is to use --TEST to define the ADA endpoint (type of antibodies and assay tier) and --SCAT to define the specificity for presentation of ADA data using SENDIG v3.0.

To unambiguously define a full ADA assay endpoint, ADA test codes should be combined with additional variables:

1) An assay tier/purpose "ISTSTOPO" (SENDIG v3.1 custom) or modified "LBTESTCD" and "LBTEST" (SENDIG v3.0)
   - screening
   - confirmation
   - quasi-quantitation

2) Description of the specificity of the ADA investigated by the assay "ISBDAGNT" (SENDIG v3.1 custom) or "LBSCAT" (SENDIG v3.0)
   - drug molecule
   - specific epitopes/moieties within a drug molecule
   - endogenous molecule (these are aligned into the ADA_X and ADA_NABX --TESTCD)

Note: Controlled terminology for the above variables are still in development at CDISC and may differ upon publication of terms for these purposes.

The recommendations for the modeling of nonclinical ADA data in SENDIG v3.1 is based on the CDISC Microbiology Standards Subteam and CDISC Microbiology IS modeling team recommendations as of January 2nd, 2020 for usage of two domain variables, --BDAGNT (Binding Agent) and --TSTOPO (Test Operational Objective). Leveraging these domain specific variables, where SENDIG v3.1 enables the use of the IS domain

as a custom domain, enables the use of --TSTOPO to describe the assay tier and --BDAGNT to describe the specificity.

In cases where a company has defined an a priori approach in assessing overall ADA status of the animal, the recommendation is to depict this using the derived flag (--DRVFL). The nSDRG and Define file should describe the algorithm (i.e. a priori approach) to determining overall ADA status. If using the IS domain with a derived value, --TSTOPO and all sample identifying fields will be empty. An example of using the derived flag (--DRVFL) with the IS domain is provided in Table 3, using the third animal status definition from Section 5.2 and an incremental difference of 0.48.

Table 1: Modeling of Nonclinical ADA Data

	Modeling of Nonclinical ADA Data in the IS Domain (SEND v3.1)						Modeling of Nonclinical ADA Data in the IS Domain (SEND v3.1)			
	Endpoint description	**ISTESTCD**	**ISTEST**	**ISBDAGNT**[a]	**ISCAT**	**ISTSTOPO**[b]	**LBTESTCD**	**LBTEST**[c]	**LBCAT**	**LBSCAT (or other variable or SUPPLB)**
Binding antibodies	Screening for binding ADA	ADA_BAB	Binding Antidrug Antibody	CT or Extensible text description of specificity towards test article (including specific epitopes if relevant)	Antidrug antibodies	SCREEN	ADA_BABS	Binding ADA SCREENING	Antidrug antibodies	Free text description of specificity towards test article (including specific epitopes if relevant)
	Confirmation of detection of binding ADA	ADA_BAB	Binding Antidrug Antibody	CT or Extensible text description of specificity towards test article (including specific epitopes if relevant)	Antidrug antibodies	CONFIRM	ADA_BABC	Binding ADA CONFIRM	Antidrug antibodies	Free text description of specificity towards test article (including specific epitopes if relevant)
	Quasi-quantification of binding ADA	ADA_BAB	Binding Antidrug Antibody	CT or Extensible text description of specificity towards test article (including specific epitopes if relevant)	Antidrug antibodies	QUANTIFY	ADA_BABQ	Binding ADA QUASI-QUANT	Antidrug antibodies	Free text description of specificity towards test article (including specific epitopes if relevant)
Neutralizing antibodies	Screening for neutralizing ADA	ADA_NAB	Neutralizing Binding Antidrug Antibody	CT or Extensible text description of specificity towards test article (including specific epitopes if relevant)	Antidrug antibodies	SCREEN	ADA_NABS	Neutralizing ADA SCREENING	Antidrug antibodies	Free text description of specificity towards test article (including specific epitopes if relevant)
	Confirmation of neutralizing ADA	ADA_NAB	Neutralizing Binding Antidrug Antibody	CT or Extensible text description of specificity towards test article (including specific epitopes if relevant)	Antidrug antibodies	CONFIRM	ADA_NABC	Neutralizing ADA CONFIRM	Antidrug antibodies	Free text description of specificity towards test article (including specific epitopes if relevant)
	Quasi-quantification of neutralizing ADA	ADA_NAB	Neutralizing Binding Antidrug Antibody	CT or Extensible text description of specificity towards test article (including specific epitopes if relevant)	Antidrug antibodies	QUANTIFY	ADA_NABQ	Neutralizing ADA QUASI QUANT	Antidrug antibodies	Free text description of specificity towards test article (including specific epitopes if relevant)

Notes: Modeling in the IS domain uses two variables (-TESTCD and -TSTOPO) to define the ADA endpoint. Modeling in the LB domain uses only one variable (-TEST) to define the ADA endpoint. ISCAT and LBCAT variables are used in the same manner in both the IS and LB domains. Use of LBSCAT is used here to identify applicable specificity.
ADA = Antidrug antibodies; Coagulation factors = CFS; X-reactive = Cross-reactive or Cross-reactivity.
a. ISBDAGNT is a domain-specific variable to qualify the ISTEST variable/describe the specificity. Utilize Controlled Terminology from SDTM-BAISTEST and SDTM-MICROORG.
b. ISTSTOPO is used to describe the assay tier.
c. LBTEST was constructed as a concatenation of ISTEST + ISTSTOPO.

Table 2: Modeling of Nonclinical ADA Data, Cross-reactive

	Modeling of Nonclinical ADA Data in the IS Domain (SEND v3.1)						Modeling of Nonclinical ADA Data in the LB Domain (SEND v3.0)			
	Endpoint description	**ISTESTCD**	**ISTEST**	**ISBDAGNT**[a]	**ISCAT**	**ISTSTOPO**[b]	**LBTESTCD**	**LBTEST**[c]	**LBCAT**	**LBSCAT (or other variable or SUPPLB)**
Cross-reactive binding antibodies	Screening for X reactive binding ADA	ADA_X	Cross-Reactive Binding Antidrug Antibody	CT or Extensible text description of specificity towards test article and X-reactivity to specific endogenous structures resembling test article (CFS, insulin, GLP-1)	Antidrug antibodies	SCREEN	ADA_XS	X-reactive Binding ADA SCREENING	Antidrug antibodies	Free text description of specificity towards test article and X-reactivity to specific endogenous structures resembling test article (CFS, insulin, GLP-1)
	Confirmation of detection of X reactive binding ADA	ADA_X	Cross-Reactive Binding Antidrug Antibody	CT or Extensible text description of specificity towards test article and X-reactivity to specific endogenous structures resembling test article (CFS, insulin, GLP-1)	Antidrug antibodies	CONFIRM	ADA_XC	X-reactive Binding ADA CONFIRM	Antidrug antibodies	Free text description of specificity towards test article and X-reactivity to specific endogenous structures resembling test article (CFS, insulin, GLP-1)
	Quasi-quantification of X reactive binding ADA	ADA_X	Cross-Reactive Binding Antidrug Antibody	CT or Extensible text description of specificity towards test article and X-reactivity to specific endogenous structures resembling test article (CFS, insulin, GLP-1)	Antidrug antibodies	QUANTIFY	ADA_XQ	X-reactive Binding ADA QUASI-QUANT	Antidrug antibodies	Free text description of specificity towards test article and X-reactivity to specific endogenous structures resembling test article (CFS, insulin, GLP-1)
Cross-reactive neutralizing antibodies	Screening for X reactive neutralizing ADA	ADA_NX	Neutraliz Cross-React Bind Antidrug AB; Neutralizing Cross-Reactive Binding Antidrug Antibody[d]	CT or Extensible text description of specificity towards test article and X-reactivity to specific endogenous structures resembling test article (CFS, insulin, GLP-1)	Antidrug antibodies	SCREEN	ADA_NXS	Neutralizing X-reactive ADA SCREENING	Antidrug antibodies	Free text description of specificity towards test article and X-reactivity to specific endogenous structures resembling test article (CFS, insulin, GLP-1)
	Confirmation of X reactive neutralizing ADA	ADA_NX	Neutraliz Cross-React Bind Antidrug AB; Neutralizing Cross-Reactive Binding Antidrug Antibody[d]	CT or Extensible text description of specificity towards test article and X-reactivity to specific endogenous structures resembling test article (CFS, insulin, GLP-1)	Antidrug antibodies	CONFIRM	ADA_NXC	Neutralizing X-reactive ADA CONFIRM	Antidrug antibodies	Free text description of specificity towards test article and X-reactivity to specific endogenous structures resembling test article (CFS, insulin, GLP-1)
	Quasi-quantification of X reactive neutralizing ADA	ADA_NX	Neutraliz Cross-React Bind Antidrug AB; Neutralizing Cross-Reactive Binding Antidrug Antibody[d]	CT or Extensible text description of specificity towards test article and X-reactivity to specific endogenous structures resembling test article (CFS, insulin, GLP-1)	Antidrug antibodies	QUANTIFY	ADA_NXQ	Neutralizing X-reactive ADA QUASI-QUANT	Antidrug antibodies	Free text description of specificity towards test article and X-reactivity to specific endogenous structures resembling test article (CFS, insulin, GLP-1)

Notes: Modeling in the IS domain uses two variables (-TESTCD and -TSTOPO) to define the ADA endpoint. Modeling in the LB domain uses only one variable (-TEST) to define the ADA endpoint. ISCAT and LBCAT variables are used in the same manner in both the IS and LB domains. Use of LBSCAT to communicate specificity.
ADA = Antidrug antibodies; Coagulation factors = CFS; X-reactive = Cross-reactive or Cross-reactivity.
a. ISBDAGNT is a domain-specific variable to qualify the ISTEST variable/describe the specificity. Utilize Controlled Terminology from SDTM-BAISTEST and SDTM-MICROORG.
b. ISTSTOPO is used to describe the assay tier.
c. LBTEST was constructed as a concatenation of ISTEST + ISTSTOPO.
d. Abbreviations used due to character limit for ISTEST.

Table 3: Example of ADA Data Modeled in the IS domain, with Derived Overall Status

USUBJID	ISTESTCD	ISTEST	ISBDAGNT	ISCAT	ISTSTOPO	ISORRES	ISORRESU	ISSTRESC	ISSTRESN	ISSTRESU	ISDRVFL	VISITDY
ABC-1001	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				1
ABC-1001	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				22
ABC-1001	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				36
ABC-1001	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				50
ABC-1001	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		NEGATIVE		NEGATIVE			Y	
ABC-1002	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				1
ABC-1002	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				22
ABC-1002	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	2.01	titer		2.01	titer		22
ABC-1002	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				36
ABC-1002	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	2.51	titer		2.51	titer		36
ABC-1002	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				50
ABC-1002	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	1.82	titer		1.82	titer		50
ABC-1002	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		POSITIVE		POSITIVE			Y	
ABC-1003	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				1
ABC-1003	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				22
ABC-1003	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				36
ABC-1003	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	3.23	titer		3.23	titer		36
ABC-1003	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				50
ABC-1003	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		POSITIVE		POSITIVE			Y	
ABC-1004	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				1
ABC-1004	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	2.58	titer		2.58	titer		1
ABC-1004	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				22
ABC-1004	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				36
ABC-1004	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				50
ABC-1004	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		POSITIVE		POSITIVE			Y	
ABC-1005	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				1
ABC-1005	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	2.47	titer		2.47	titer		1
ABC-1005	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				22
ABC-1005	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	2.04	titer		2.04	titer		22
ABC-1005	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				36
ABC-1005	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	2.05	titer		2.05	titer		36
ABC-1005	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				50
ABC-1005	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	2.09	titer		2.09	titer		50
ABC-1005	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		NEGATIVE		NEGATIVE			Y	
ABC-1006	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				1
ABC-1006	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	1.61	titer		1.61	titer		1
ABC-1006	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				22
ABC-1006	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	2.22	titer		2.22	titer		22
ABC-1006	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				36
ABC-1006	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				50
ABC-1006	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		POSITIVE		POSITIVE			Y	

6.2. Data Modeling Using Contributing Report from Toxicology Report as Data Source

Best practices for preparing the data model is collaboration between the bioanalytical scientist and data modeler to proactively coordinate the data format from the lab. It is acknowledged, however, that this is not always feasible; this section addresses how to create the SEND format using the bioanalytical contributing report as the source data, as illustrated in Figure 2.

To map content into SEND format, different sections of the bioanalytical report will be referenced based on answering questions in the flow chart. First, the assay specificity should be determined based on the method description as the assay reagent (often the test article). If more than one assay specificity is used, then repeat as needed following the mock examples provided in the Appendices. Numeric values will be obvious from the results table, including differentiation by multiple plus signs. Units for numeric values may be determined from the table headers or method description, which may be in the report body or an appendix. The use of a confirmatory step is also determined from the method description. Derived ADA status per animal may be tabulated or only described in the toxicology report body or bioanalytical contributing report body. An example is shown in Table 4, resulting in the Table 5 data model.

Figure 2: Mapping to SEND from a Bioanalytical Contributing Report

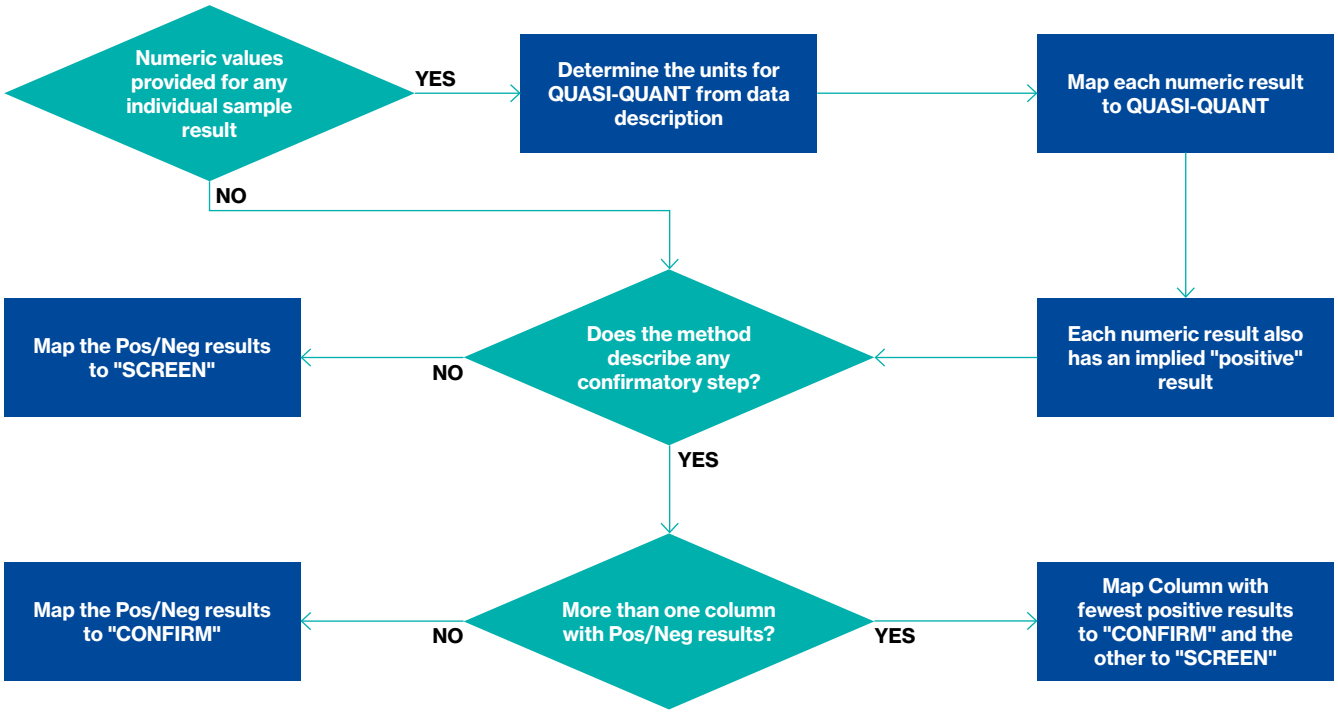


Table 4: Example ADA Result Table from a Nonclinical Report

Dose (mg/kg/week)	Animal Number	ADA Results (Log Titer) by Day						ADA Induction Status of Animal	% Incidence of an ADA Induction
		Day 1 Predose	Day 8 Predose	Day 15 Predose	Day 22 Predose	Day 29 Predose	Day 36 Predose		
15 (IV)	004M	Neg	Neg	Neg	Neg	2.15	3.33	Positive	50
	005M	Neg	Neg	Neg	1.57	2.01	2.89	Positive	
	006M	Neg	Neg	Neg	Neg	Neg	Neg	Negative	
	016F	1.45	Neg	Neg	Neg	Neg	Neg	Negative	
	017F	1.65	1.78	1.84	1.79	1.81	1.66	Negative	
	018F	1.50	2.13	2.25	2.75	2.56	1.99	Positive	
	Prevalence (%)	50	33.3	33.3	50	66.7	66.7		

% Incidence of ADA Induction = (Number of animals with induced ADA/number of evaluable animals) x 100; ADA = Anti-drug antibodies; F = Female; IV = Intravenous; M = Male; Neg = Negative (<1.30 log titer); Prevalence = Number of animals positive for ADA at a specific time point/number of animals at that time point.

There are clearly numeric results in Table 4, and the unit is "log titer" from the table header rows. For argument's sake, we assume that the method description makes no mention of a confirmatory step, discussing only titration; therefore, we follow the second question to the left and map the POS/NEG to screening, resulting in Table 5. Please note that if there was a discussion of confirmatory in the bioanalytical report, since there is only one pos/neg result, then we would map to confirm and Table 5 would have "Confirm" instead of "Screen" in the relevant rows. In the Appendices, this corresponds to Figure A3b.

Table 5: ADA Data Modeled from Nonclinical Report Example in Table 4

USUBJID	ISTESTCD	ISTEST	ISBDAGNT	ISCAT	ISTSTOPO	ISORRES	ISORRESU	ISSTRESC	ISSTRESN	ISSTRESU	ISDRVFL	VISITDY
15-004M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				1
15-004M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				8
15-004M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				15
15-004M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				22
15-004M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				29
15-004M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	2.15	titer		2.15	titer		29
15-004M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				36
15-004M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	3.33	titer		3.33	titer		36
15-004M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		POSITIVE		POSITIVE			Y	
15-005M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				1
15-005M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				8
15-005M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				15
15-005M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				22
15-005M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	1.57	titer		1.57	titer		22
15-005M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		POSITIVE				29
15-005M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	2.01	titer		2.01	titer		29
15-005M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				36
15-005M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	2.89	titer		2.89	titer		36
15-005M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		POSITIVE		POSITIVE			Y	
15-006M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				1
15-006M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				8
15-006M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				15
15-006M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				22
15-006M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				29
15-006M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				36
15-006M	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		NEGATIVE		NEGATIVE			Y	
15-016F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN							1
15-016F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	1.45	titer	1.45	titer			1
15-016F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				8
15-016F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				15
15-016F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				22
15-016F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				29
15-016F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				36
15-016F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		NEGATIVE		NEGATIVE			Y	

USUBJID	ISTESTCD	ISTEST	ISBDAGNT	ISCAT	ISTSTOPO	ISORRES	ISORRESU	ISSTRESC	ISSTRESN	ISSTRESU	ISDRVFL	VISITDY
15-017F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				1
15-017F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	1.65	titer		1.65	titer		1
15-017F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				8
15-017F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	1.78	titer		1.78	titer		8
15-017F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				15
15-017F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	1.84	titer		1.84	titer		15
15-017F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				22
15-017F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	1.79	titer		1.79	titer		22
15-017F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				29
15-017F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	1.81	titer		1.81	titer		29
15-017F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				36
15-017F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	1.66	titer		1.66	titer		36
15-017F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		NEGATIVE		NEGATIVE			Y	
15-018F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				1
15-018F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	1.50	titer		1.50	titer		1
15-018F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				8
15-018F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	2.13	titer		2.13	titer		8
15-018F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				15
15-018F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	2.25	titer		2.25	titer		15
15-018F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				22
15-018F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	2.75	titer		2.75	titer		22
15-018F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				29
15-018F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	2.56	titer		2.56	titer		29
15-018F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				36
15-018F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	1.99	titer		1.99	titer		36
15-018F	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		POSITIVE		POSITIVE			Y	

7. Conclusion

This paper recommends several options for modeling nonclinical ADA data in a SEND-consistent format that are proposed for use until there are CDISC published standards for this data type. The recommendations take into consideration the CDISC Standards SENDIG v3.0 and v3.1. As published, these Implementation Guides do not directly address ADA data for nonclinical, but do provide concepts that can support ADA modeling.

The authors propose that ADA data can be modeled in the LB domain, according to SENDIG v3.0 concepts by using extended terminology for LBTEST and LBTESTCD, and using LBSCAT to describe the specificity towards the test article or cross-reactivity to specific endogenous structures, as shown in Table 1. This approach is suggested only for data providers desiring to use SENDIG v3.0, which does not allow the use of any domain not published in that version.

The authors propose ADA data can also be modeled through use of an IS domain, by adding it as a "custom" domain according to SENDIG v3.1 concepts that do allow use of domains not published within that version. The IS domain recommendation is based on the principles that are published in SDTMIG v1.5, plus some new domain variables being developed and implemented by CDISC for clinical data. The IS domain approach for nonclinical ADA provides more robust structure to the data model by using the ISBDAGNT and ISTSTOPO variables described in Table 1.

Using either proposal, both the individual animal timepoint results and the overall subject ADA status can be modeled within the same domain, by differentiating the overall status using the --DRVFL variable to indicate the derived record. The use of –DRVFL requires supporting information in the nSDRG and the Define file.

While some companies may postpone inclusion of ADA data from their SEND datasets in v3.0 or v3.1, it is recommended to work on an implementation plan quickly, as health authorities and research organizations have expressed interest in receiving this data electronically.

8. Disclaimer

The authors expect that CDISC concepts for the IS domain published for clinical data in SDTMIG will be developed for formal implementation in future evolutions of the SENDIG. In the meantime, the authors of this paper, who are members of both the CDISC SEND Team and the PHUSE Nonclinical Topics Working Group, propose ways data providers can use existing SEND LB domain and SDTM IS domain concepts to enable modeling of ADA data that may support e-data provision to regulatory authorities.

9. Appendices

9.1. References (last accessed January 2nd, 2020):

FDA website: FDA Data Standards Catalog
https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources

FDA website: Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection (January 2019)
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/immunogenicity-testing-therapeutic-protein-products-developing-and-validating-assays-anti-drug

EMA website: Guideline on Immunogenicity assessment of therapeutic proteins
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-immunogenicity-assessment-therapeutic-proteins-revision-1_en.pdf

Wiki page (PHUSE ADA Modeling team): Modeling Endpoints: How to Model Anti-Drug Antibody Data in Nonclinical Studies
https://www.phusewiki.org/wiki/index.php?title=Modeling_Endpoints:_How_to_Model_Anti-Drug_Antibody_Data_in_Nonclinical_Studies

Wiki page (CDISC Microbiology IS Modeling team)
https://wiki.cdisc.org/display/CT/IS+Examples+in+SDTMIG+V3.4

Standards: CDISC Standard Exchange of Nonclinical Data (SEND) Implementation Guide version 3.0 (account required)
https://www.cdisc.org/system/files/members/standard/foundational/send/sendigv3.zip

CDISC Standard Exchange of Nonclinical Data (SEND) Implementation Guide version 3.1 (account required)
https://www.cdisc.org/system/files/members/standard/foundational/send/SENDIG_v_3_1.zip

CSS 2018 Poster on ADA Modeling in SEND
http://www.phusewiki.org/wiki/images/1/11/PP_-_Modelling_of_ADA_in_SEND_-_PhUSE_CSS_18_final.pdf

9.2. Mock Examples for Mapping of Testing Schemes

Figure A1a: SEND v3.0 Example ADA Tiered Testing Scheme for a Single Binding Target X

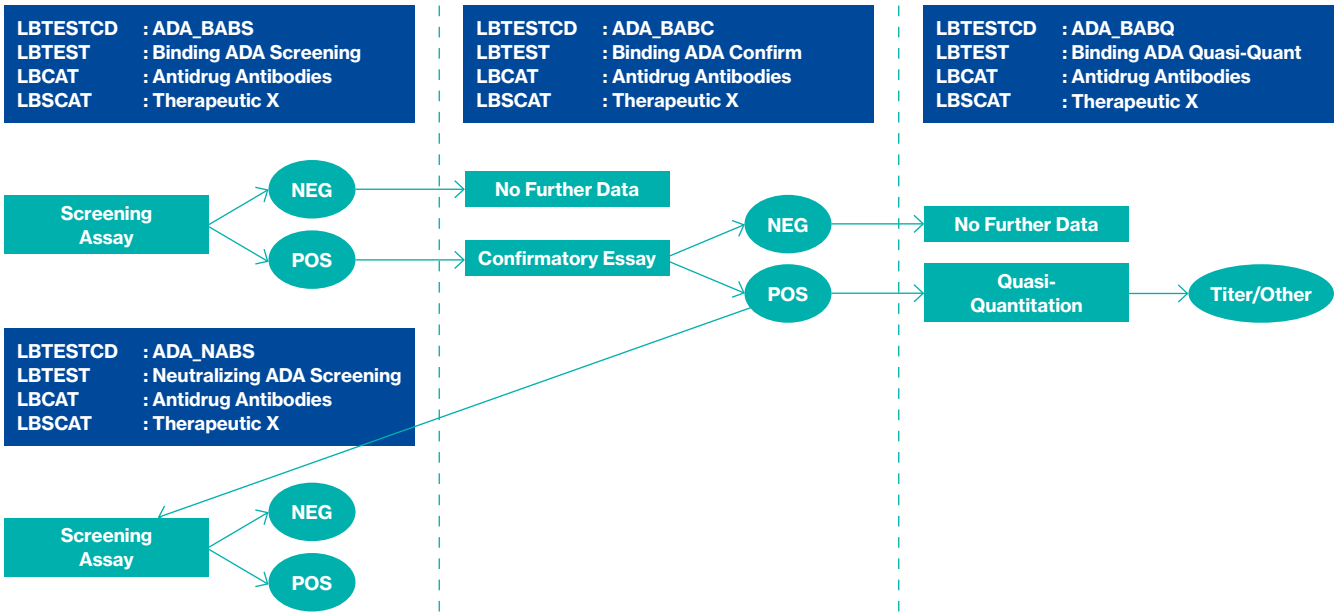
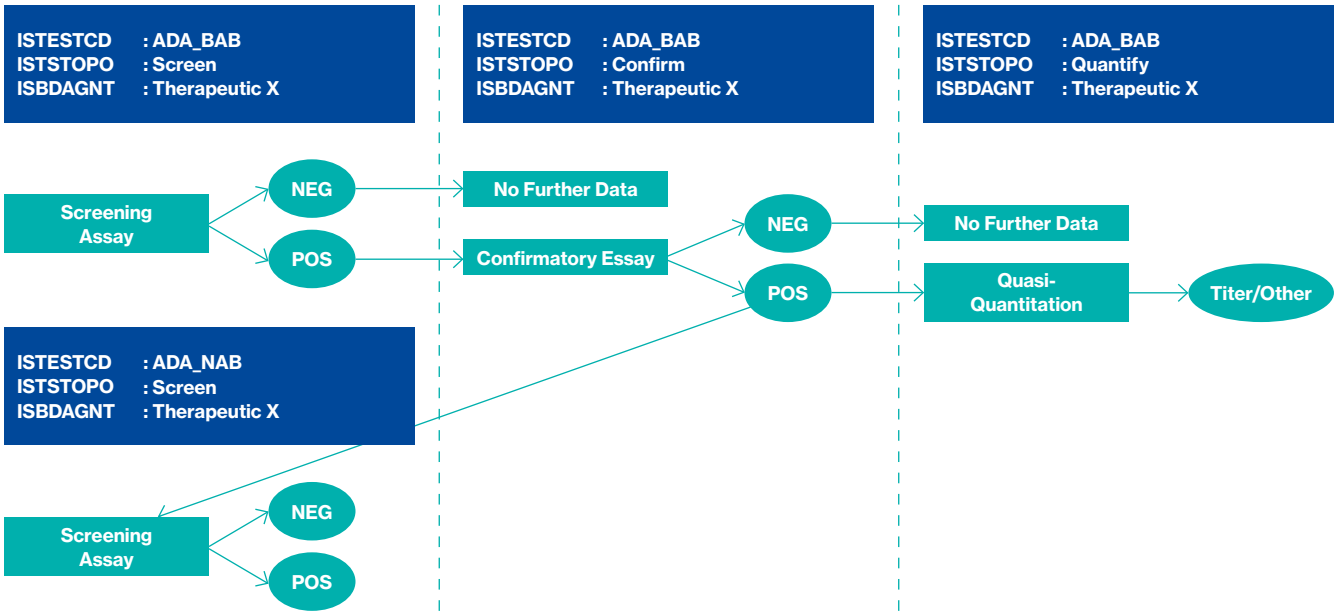


Figure A1b SEND v3.1 Example ADA Tiered Testing Scheme for a Single Binding Target X



Note: Therapeutic X is the agent that is being used for treatment (e.g. test article or vaccine).

Figure A2a SEND v3.0 Example ADA Screening Only Scheme

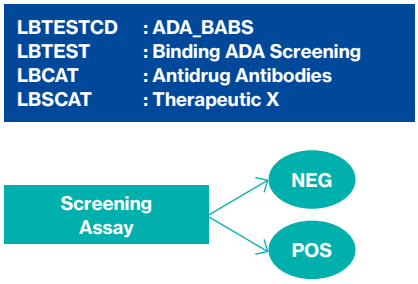
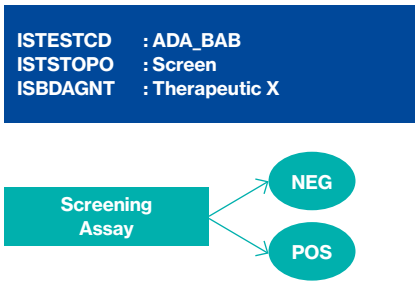


Figure A2b SEND v3.1 Example ADA Screening Only Scheme



Note: Screening only is a popular schematic for nonclinical studies where a binary readout for potential exposure impact is all that is needed to interpret results.

Figure A3a SEND v3.0 Example ADA Two-Tiered Scheme

Figure A3b SEND v3.1 Example ADA Two-Tiered Scheme

Note: Screening and titration is a popular schematic for nonclinical studies where pre-existing antibodies are suspected to differentiate changes within a subject.

Figure A3a SEND v3.0 Example ADA Two-Tiered Scheme

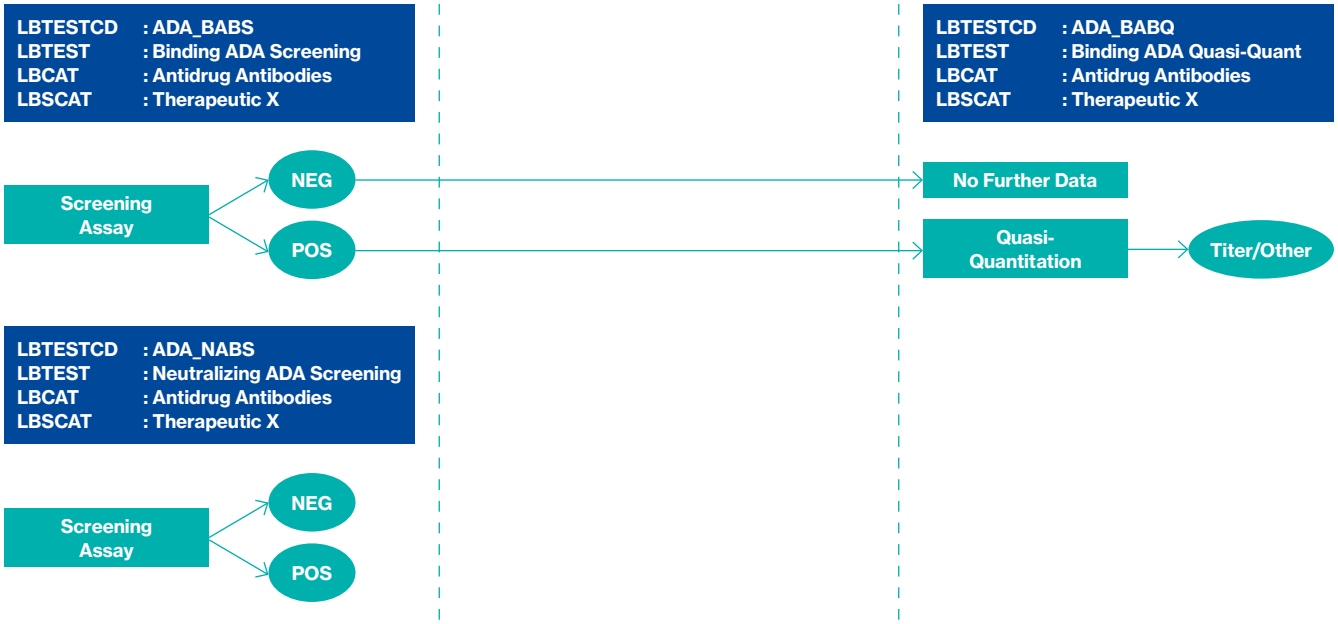
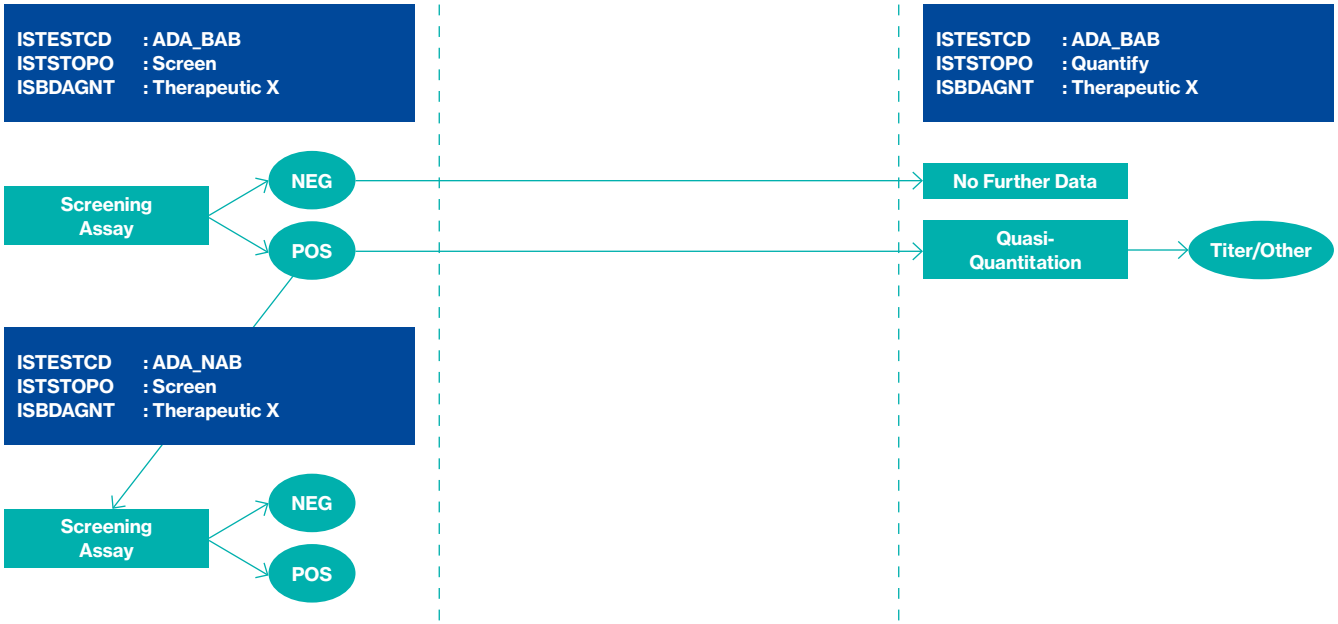


Figure A5b SEND v3.1 Example ADA Two-Tiered Scheme Plus Neutralizing



Note: Screening, titration, and neutralizing are frequently used for high-risk molecules where the decrease in effective exposure can give false negative results for potential on-target toxicology.

Figure A5a SEND v3.0 Example ADA Tiered Testing Scheme for Combination Therapy

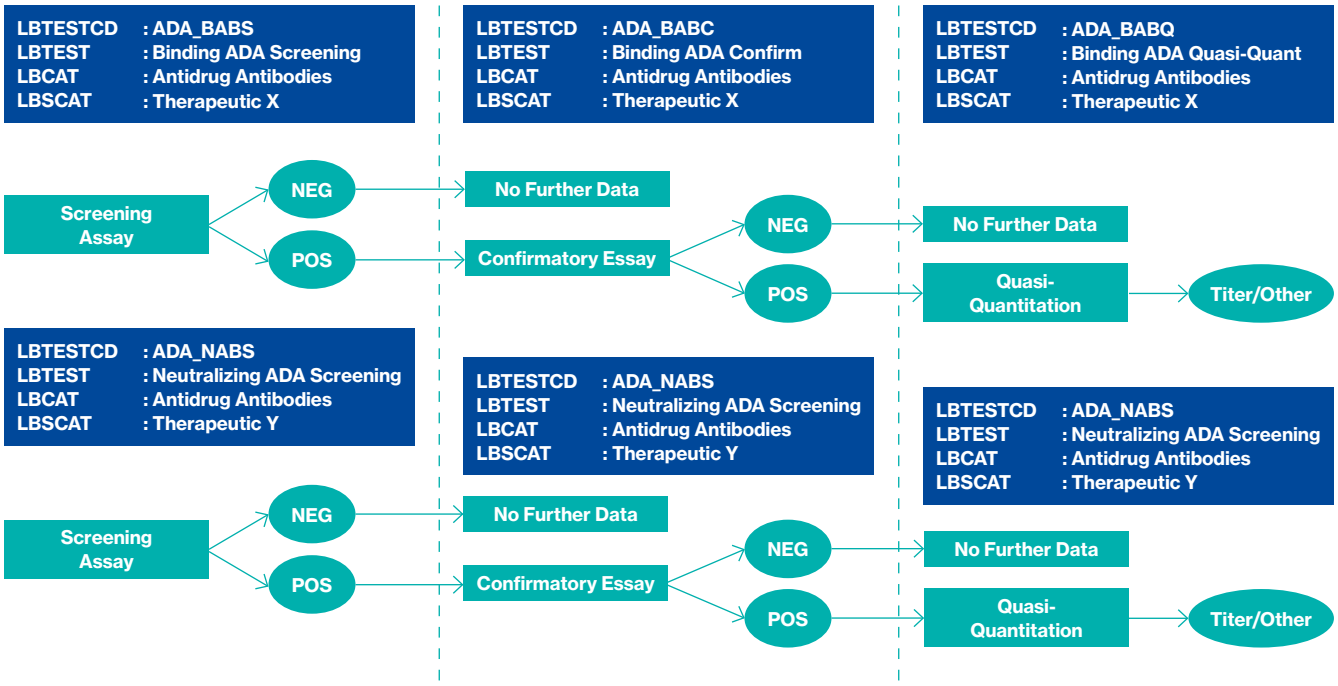
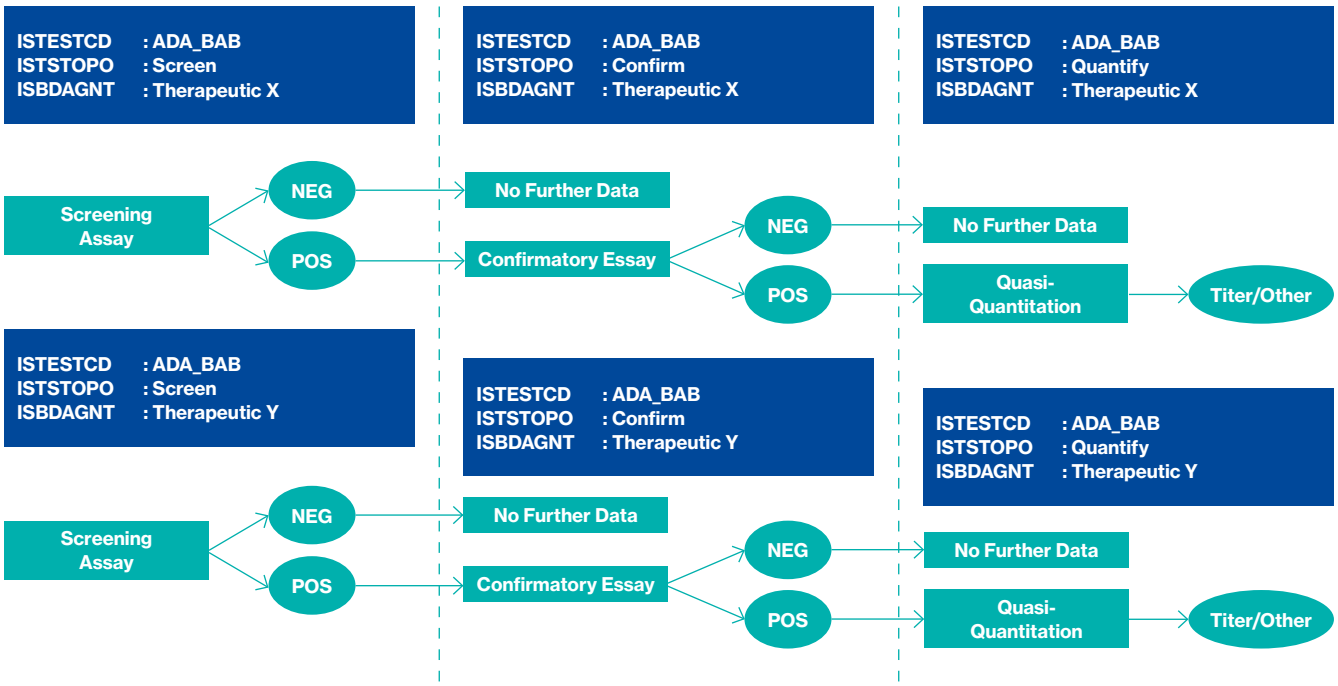


Figure A5a SEND v3.0 Example ADA Tiered Testing Scheme for Combination Therapy



Note: As for monotherapy, many testing schematics for nonclinical studies only include screening assays.

Figure A6a SEND v3.0 Example ADA Tiered Testing Scheme for Vaccine Testing

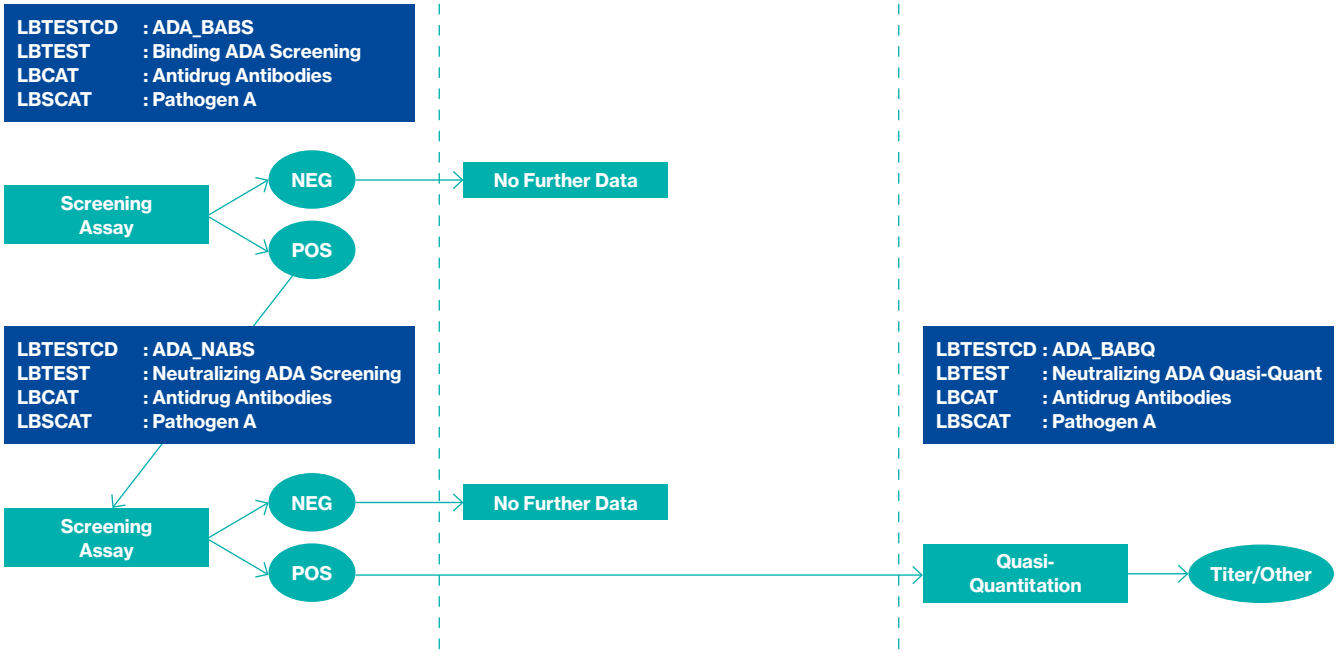
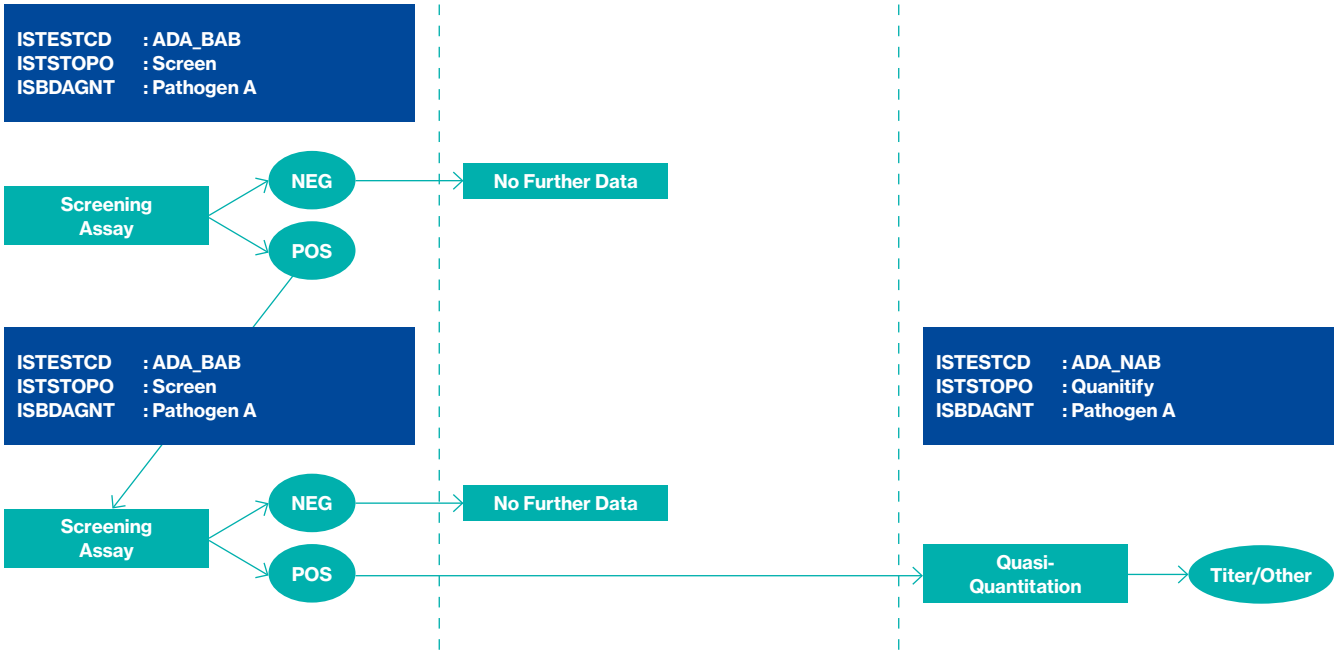


Figure A6b SEND v3.1 Example ADA Tiered Testing Scheme for Vaccine Testing



Note: For vaccines, neutralization is the efficacy endpoint, so there is frequently less emphasis on the binding antibody assays and titration of the neutralizing response to examine correlation with protection endpoint.

Figure A7a SEND v3.0 Example ADA Tiered Testing Scheme for Therapeutic with Endogenous Counterpart

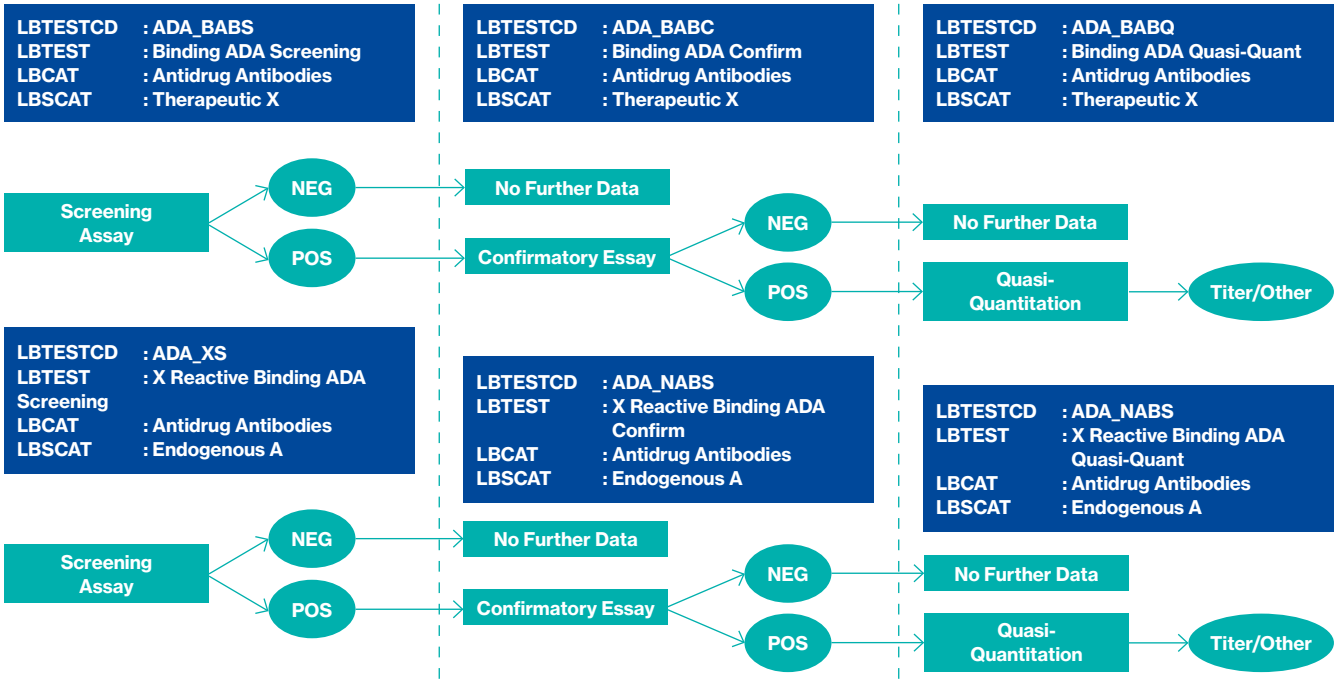
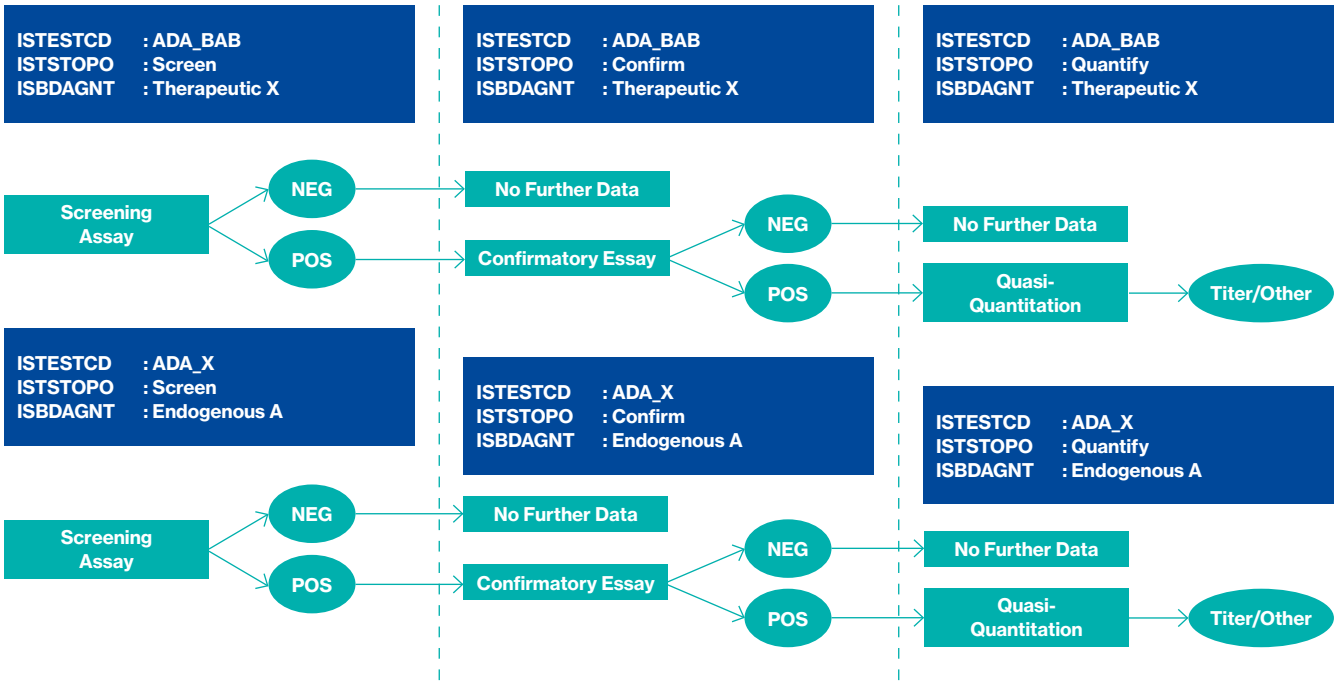


Figure A7b SEND v3.1 Example ADA Tiered Testing Scheme for Therapeutic with Endogenous Counterpart



Note: Evaluating immunogenicity against endogenous counterparts likely also includes neutralizing assays for both Therapeutic X and Endogenous A to further characterize potential safety risks if highly homologous to the human counterpart.

Figure A5a SEND v3.0 Example ADA Tiered Testing Scheme for Therapeutic with Multiple Domains When Differentiation of Response is Required

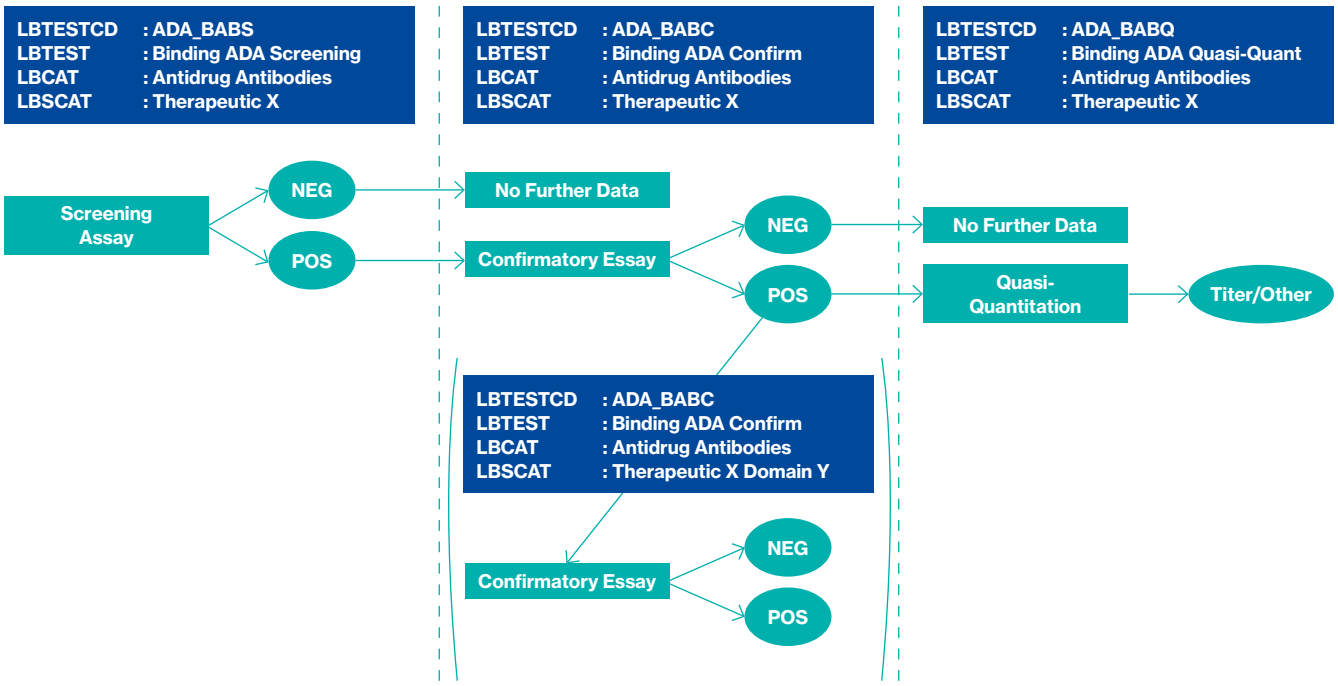
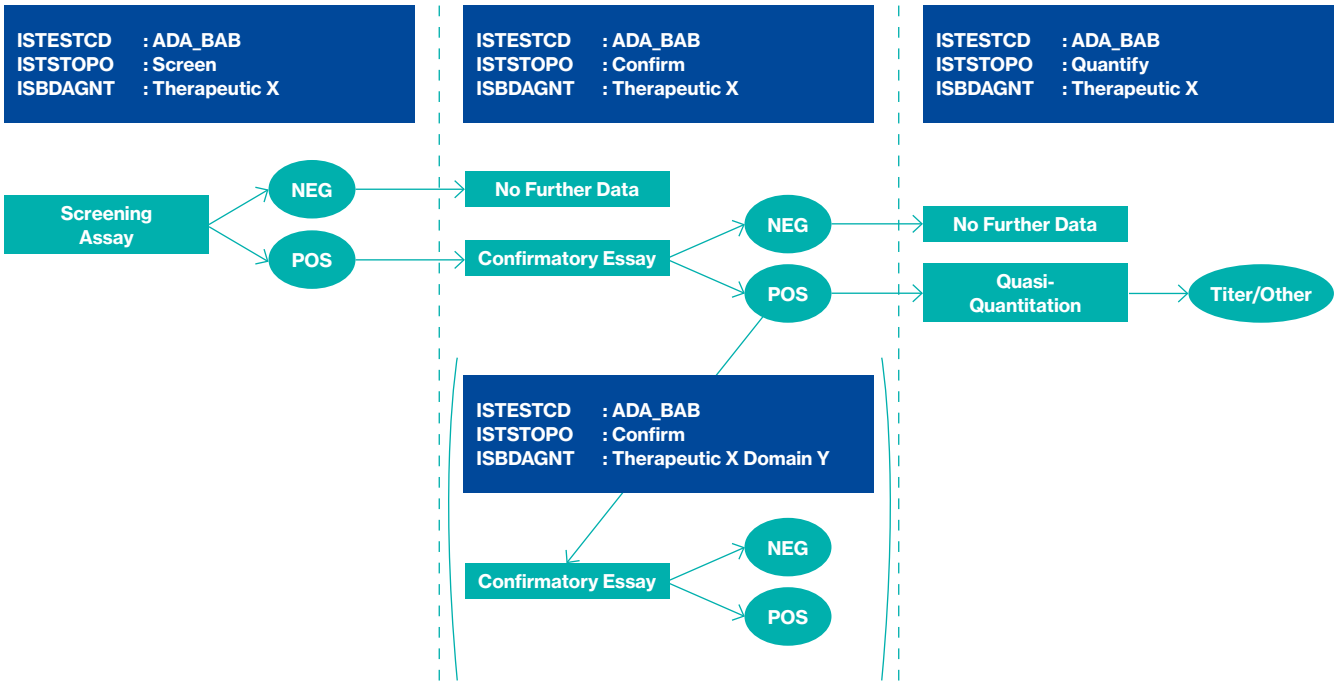


Figure A5b SEND v3.1 Example ADA Tiered Testing Scheme for Therapeutic with Multiple Domains When Differentiation of Response is Required



Note: As previously described, many testing schematics for nonclinical studies only include screening assays. In these cases, the only confirmatory tests may be for individual domains, skipping titration and whole molecule confirmatory.

9.3. Mock Examples from a Nonclinical Report

Table A1a: Example ADA Result Table from a Nonclinical Report

Dose (mg/kg/week)	Animal Number	ADA Results					
		Day 1 Predose	Day 15 Predose	Day 29 Predose	Day 57 Predose	Day 85 Predose	Day 169 Predose
5	007	–	++	+++	+++	+++	+++
	008	–	+	+	++	+	–
	009	–	–	–	–	–	–
15	017 (replaced by 044)	–	++	NA	NA	NA	NA
	018	–	–	–	–	–	–
	019	+	+	+	+	+	+
	044	–	–	+	++	++	+

In Table A1a, the plus signs are an indicator of quasi-quantitation. So, in Figure 2, we take the right path at the first question. These plusses feel arbitrary, and you may be able to use "Arbitrary U" or something else depending on how detailed the method is. To illustrate the flexibility of this ADA model, however, we are going to use the plusses as categorical variables for High, Mid, and Low. At the second question, assume that the method description discusses a confirmatory step, so we move downward. With no additional data tables to differentiate screening and confirmation, we move left from the 3rd question, resulting in Table A1b. For categorizing subjects, we read the rest of the report and see that 5 of 7 are considered positive, so the rule applied was either positive at any timepoint OR positive at any timepoint post Day 1. This matches the testing schematic in Figure A1b except without the nAb testing and without the ability to map the screening data.

Table A1b: ADA Data Modeled from Nonclinical Report Example in Table A1a

USUBJID	ISTESTCD	ISTEST	ISBDAGNT	ISCAT	ISTSTOPO	ISORRES	ISORRESU	ISSTRESC	ISSTRESN	ISSTRESU	ISDRVFL	VISITDY
5-007	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				1
5-007	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				15
5-007	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	++		MID				15
5-007	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				29
5-007	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	+++		HIGH				29
5-007	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				57
5-007	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	+++		HIGH				57
5-007	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				85
5-007	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	+++		HIGH				85
5-007	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				169
5-007	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	+++		HIGH				169
5-007	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		POSITIVE		POSITIVE			Y	
5-008	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				1
5-008	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				15
5-008	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		+		LOW				15
5-008	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				29
5-008	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		+		LOW				29
5-008	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				27
5-008	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		++		MID				27
5-008	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				85
5-008	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		+		LOW				85
5-008	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				169
5-008	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		POSITIVE		POSITIVE			Y	
5-009	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				1
5-009	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				15
5-009	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				29
5-009	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				57
5-009	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				85
5-009	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				169
5-009	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		NEGATIVE		NEGATIVE			Y	
15-017	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				1
15-017	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				15
15-017	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	++		MID				1
15-017	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		POSITIVE		POSITIVE			Y	

USUBJID	ISTESTCD	ISTEST	ISBDAGNT	ISCAT	ISTSTOPO	ISORRES	ISORRESU	ISSTRESC	ISSTRESN	ISSTRESU	ISDRVFL	VISITDY
15-018	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				1
15-018	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				15
15-018	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				29
15-018	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				57
15-018	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				85
15-018	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				169
15-018	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		NEGATIVE		NEGATIVE			Y	
15-019	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				1
15-019	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	+		LOW				1
15-019	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				15
15-019	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	+		LOW				15
15-019	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				29
15-019	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	+		LOW				29
15-019	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				57
15-019	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	+		LOW				57
15-019	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				85
15-019	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	+		LOW				85
15-019	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				169
15-019	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	+		LOW				169
15-019	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		POSITIVE		POSITIVE			Y	
15-044	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				1
15-044	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				15
15-044	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				29
15-044	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	+		LOW				29
15-044	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				57
15-044	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	++		MID				57
15-044	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				85
15-044	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	++		MID				85
15-044	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				169
15-044	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	+		LOW				169
15-044	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		POSITIVE		POSITIVE			Y	

Table A2a: Example ADA Result Table from a Nonclinical Report

Animal Number	Day	Result A	Result B	Result C
101	1	NEG		NEG
101	15	POS		NEG
101	29	NEG		NEG
102	1	POS		NEG
102	15	POS		NEG
102	29	POS	1.05	POS
103	1	NEG		NEG
103	15	NEG		NEG
103	29	NEG		NEG
104	1	NEG		NEG
104	15	POS	1.19	POS
104	29	POS	1.42	POS

In Table A2a, there are numbers in column “Result B”. So, in Figure 2, we take the right path at the first question. Upon reading the method, these are ratios to the negative control. At the second question, assume that the method description discusses a confirmatory reagent, so we move downward. Now we see that there are two columns with POS/NEG, we move right from the third question. Since “Result A” has six positive results and “Result C” has three positive results, the former is the screening result and the latter is the confirmatory result. This corresponds to Figure A1b without the nAb. For categorizing subjects, we read the rest of the report and see that the a priori rule was negative at day 1 and positive at any timepoint post Day 1, leading to Table A2b. Please note that animal 101 does not have a confirmed positive result, so overall status is negative, and that animal 102 does not have a confirmed positive at Day 1, so overall status is Positive. Since negative screening implies negative confirmatory, “Result C” is only included if “Result A” is positive in Table A2b; however, you could map the entire column as well.

Table A2b: ADA Data Modeled from Nonclinical Report Example in Table A2a

USUBJID	ISTESTCD	ISTEST	ISBDAGNT	ISCAT	ISTSTOPO	ISORRES	ISORRESU	ISSTRESC	ISSTRESN	ISSTRESU	ISDRVFL	VISITDY
101	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				1
101	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				15
101	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				15
101	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				29
101	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		NEGATIVE		NEGATIVE			Y	
102	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				1
102	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				1
102	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				15
102	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	NEGATIVE		NEGATIVE				15
102	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				29
102	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				29
102	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	1.05	titer		1.05	titer		29
102	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		POSITIVE		POSITIVE			Y	
103	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				1
103	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				15
103	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				29
103	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		NEGATIVE		NEGATIVE			Y	
104	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	NEGATIVE		NEGATIVE				1
104	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				15
104	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				15
104	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	1.19	titer		1.19	titer		15
104	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	SCREEN	POSITIVE		POSITIVE				29
104	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	CONFIRM	POSITIVE		POSITIVE				29
104	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies	QUANTIFY	1.19	titer		1.19	titer		29
104	ADA-BAB	Binding Antidrug Antibody	Agent X	Antidrugantibodies		POSITIVE		POSITIVE			Y	

10. Project Contact Information

https://www.phusewiki.org/wiki/index.php?title=Modeling_Endpoints:_How_to_Model_Anti-Drug_Antibody_Data_in_Nonclinical_Studies

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