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ADaM Implementation for ADA Data

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ABSTRACT

ADA is the term which refers to Anti-drug antibodies generated by administration of Therapeutic Proteins (TP) as immunogenicity response. ADA can significantly influence drug exposure, bioavailability, safety and efficacy. ADA analysis is becoming more prevalent in drug development.

The CDISC ADaM team has created a sub team to investigate the implementation and standardization of ADA analysis dataset. This poster is to share **the proposal of** ADA analysis dataset ADaM implementation. It covers from overview of multi-tier immunogenicity assessments, key data points included in ADA analysis, to a new structure to be proposed with highlights about dataset metadata, analysis parameters, variable metadata, data examples and summary of reporting/analysis.

INTRODUCTION

An anti-drug antibody (ADA) is generated as an immune response to a drug (generally a biologic therapeutic). ADA data analysis is also referred to as "immunogenicity analysis." ADA analysis includes a summary of ADA incidence and magnitude (results from an ADA assay). When combined with additional relevant data, ADA may be used for analyzing clinical impact on pharmacokinetics (PK), pharmacodynamics (PD), and efficacy and safety.

ADA data are collected through multitier assessments:

- Tier 1 refers to ADA sample testing in an ADA screening assay that detects serum antibodies which bind to the drug.
- Tier 2 refers to when the screening result is positive or potentially positive; if so, a sample is tested in the confirmatory assay. When the sample has negative results in Tier1 and/or Tier 2, the drug concentration at the same sampling timepoint is compared with the assay drug tolerance level (DTL) to conclude whether the sample result is reliable (negative) or inconclusive. DTL is a critical attribute of an assay and is defined as the maximum concentration of drug that may be present in the sample and still be able to detect positive control ADA.
- Tier 3 tests confirm positive samples for magnitude in a semiquantitative manner. The magnitude is measured via dilution until the signal is near the cut point of the assay and is referred to as titer. There are no units for titer, as it is a dilution. In some labs, the magnitude is reported as the signal-to-noise ratio (SN) of the ADA screening assay.
- Tier 4 assessments include assays to characterize the ADA. One example is the neutralizing ADA assay, which is used to measure if the ADA in a sample blocks the binding site of the drug to its target. Neutralizing antibodies have the capacity to block pharmacological activity of the drug. Other possible characterization assays include determining the domain of the drug that the ADA binds to.

Thus, collected ADA data generally includes a screening result, a confirmatory result, a magnitude result (either as titer or SN), and a neutralizing antibody result. These are basic data points collected for ADA data analysis. In addition, ADA assay attributes and drug concentration levels are used in the immunogenicity reporting analysis.

In addition to sample-level data, ADA data are summarized at a subject level based on all ADA samples collected for the subject. Subject-level reporting enables evaluation of the effect of ADA on PK, PD, and efficacy and safety. Some key derived data points may include the following:

- Time to ADA onset
- Maximum posttreatment titer/SN for subjects with positive ADA

- Change of titer/SN before and after treatment
- Treatment-emergent ADA (boosted/induced)
- Duration of positive ADA, persistent/transient ADA

This paper includes the first draft of ADA analysis dataset ADaM implementation guidance developed by CDISC ADA ADaM sub team. This draft is still undergoing CDISC review and is not considered final.

ADAM METADATA

The ADADA dataset is designed to follow the Analysis Data Model Basic Data Structure (BDS). More information about BDS can be found in ADaMIG v1.3 (available at https://www.cdisc.org/standards/foundational/adam).

DATASET METADATA

Typically, the Analysis Dataset Metadata for an ADA dataset is specified as follows:

Table 1 is Data Structure. The Data Structure Name, Data Structure Description, and CDISC Notes are intended to provide information to assist developers in preparing their datasets and are not intended to be metadata submitted in define.xml.

Data Structure Name	Data Structure Description	Class of Dataset	SubClass of Dataset	CDISC Notes
ADADA	Basic Data Structure Anti-Drug Antibody Analysis	BASIC DATA STRUCTURE	ANTI-DRUG ANTIBODY ANALYSIS	Dataset designed to support ADA analysis. Primarily sourced from the SDTM Immunogenicity Specimen Assessments domain and supplemented by information from the Pharmacokinetics Concentrations, Exposure, or other relevant domains.

Table 1. Data Structure

Table 2 shows how dataset metadata are specified for ADA. This layout matches Define-XML v2.1 (available at https://www.cdisc.org/standards/data-exchange/define-xml), which includes a methodology for representing SubClass. ADA datasets are of the Class BASIC DATA STRUCTURE, SubClass ANTI-DRUG ANTIBODY ANALYSIS.

Some text in Table 2, including dataset name and description (label), can be modified. In this metadata example, "parameter qualifier" refers to the therapeutic drug name which generated the ADA, "parameter" refers to tiered ADA assessment, "analysis visit" refers to the ADA sampling event, and "analysis timepoint" refers to the sample.

Dataset	Description	Class - SubClass	Structure	Purpose	Keys	Documentation	Location
ADADA	Anti-Drug Antibody Analysis Dataset	BASIC DATA STRUCTURE • ANTI-DRUG ANTIBODY ANALYSIS	One record per subject per parameter qualifier per parameter per analysis visit per analysis timepoint	Analysis	STUDYID, USUBJID, PARQUAL, PARAMCD, AVISIT, ATPT	See program …	adada.xpt

Table 2. Define.xml Example Dataset Metadata

PARAMETERS

Anti-drug Antibody Analysis sub class follows BDS principle to populate parameter variables: PARCATx, PARAM, PARAMCD, etc. The examples in this section and this paper do not include all required ADaM variables.

PARCAT1 examples:

- For primary ADA assay results or PK concentration, PARCAT1 = “Collection”
- For derivation based on sample ADA assay results at one time point, PARCAT1 = "Sample Interpretation".
- For derivation based on multiple samples for 1 subject at the end of study or derivation based on cumulative sample collections to the timepoint for the same subject, PARCAT1 = "Subject Summary"
- For ADA assay attributes which are usually a set of constant values for a specific assay used to assess anti-drug antibody in a study: These attributes include drug tolerance level and minimum required dilution.
    - If there is only one assay for a study, its attributes can be presented with PARCAT1 = "Assay Attributes".
    - If there are multiple types of assays due to either different analytes or different laboratories, the corresponding group of assay attributes must be presented as variables in accordance with the analyte and laboratory. See Figure 1, this approach allows relevant attributes listed in line with corresponding sample records tested by that assay. It also benefits programming in record-level calculation and derivation. For example, drug tolerance level is used to compare with drug concentration level at ADA sampling time to determine whether drug concentration exceeds the drug tolerance level.

PARQUAL	PARQTYPE	PARCAT1	PARAMCD	PARAM	DTL	MRD	ISNAM
Anti-Drug X	ADATARGET	Collection	SCRRSLT	Screening Result	2000	4	LABabc
Anti-Drug X	ADATARGET	Collection	CNRRSLT	Confirmatory Result	2000	4	LABabc
Anti-Drug X	ADATARGET	Collection	TITER	Titer	2000	4	LABabc
Anti-Drug X	ADATARGET	Sample Interpretation	ADASAMP	Sample ADA Status	2000	4	LABabc
Anti-Drug X	ADATARGET	Subject Summary	ADASUBJ	ADA Subject Status	2000	4	LABabc

Figure 1. Assay Attributes DTL, MRD and ISNAM are presented as variables.

PARQUAL and PARQTYPE (Planned for release in ADaM IG v3):

- ADaMIG v3 BDS variables PARQUAL and PARQTYPE are included for ADADA subclass. More details can be found in ADaMIG v3 to be published soon. In ADADA, PARQUAL is used as a qualifier to differentiate (1) ADAs generated by different therapeutic products or (2) therapeutic products and domain names. For example, drug name, endogenous protein, isotype, epitope, domain: IL-2, TNFR, IL-6R, IL-17A. When using SDTMIG v3.4 or a later version, PARQUAL can be derived from ISBDAGNT.
- PARQTYPE should be assigned the value from controlled terminology, PARQTYPE = “ABTARGET”.
- If using PARQUAL, then PARQTYPE must be used as well.

PARAM and PARAMCD:

Below are recommended values for common parameters and parameter codes.

- Further define multitier assessments when PARCAT1 = “Collection”
    - Sensitivity screening assay: PARAM = “Screening Result”, PARAMCD = “SCRRSLT”
    - Confirmative assay: PARAM = “Confirmatory Result”, PARAMCD = “CNRRSLT”
    - Titration assay: PARAM = “Titer”, PARAMCD = “TITER”
    - Signal to noise: PARAM = “Signal to Noise”, PARAMCD = “SN”
    - Neutralizing (NAb) screening assay: PARAM = “Neutralizing Screening Result”, PARAMCD = “NABSCR”
    - Neutralizing (NAb) confirmative assay: PARAM = “Neutralizing Confirmatory Result”, PARAMCD = “NABCNR”
    - Neutralizing (NAb) assay: PARAM = “Neutralizing Antibody Result”, PARAMCD = “NABRSLT”
    - Neutralizing (NAb) titration assay: PARAM = “Neutralizing Antibody Titer”, PARAMCD = “NABTTR”
    - Domain specificity ADA assessment: PARAM = “Domain ADA”, PARAMCD = “ADADRSLT”
    - Domain specificity NAb assessment: PARAM = “Domain NAB”, PARAMCD = “NABDRSLT”
    - Domain specificity ADA screening, confirmative, titer, SN:
        - PARAM = “Domain ADA Screening”, PARAMCD = “ADADSCR”
        - PARAM = “Domain ADA Confirmative”, PARAMCD = “ADADCNR”
        - PARAM = “Domain ADA Titer”, PARAMCD = “ADADTTR”
        - PARAM = “Domain ADA SN”, PARAMCD = “ADADSN”
        - PARAM = “Domain NAB Screening”, PARAMCD = “NABDSCR”
        - PARAM = “Domain NAB Confirmative”, PARAMCD = “NABDCNR”
        - PARAM = “Domain NAB Titer”, PARAMCD = “NABDTTR”
        - PARAM = “Domain NAB SN”, PARAMCD = “NABDSN”
    - When lab provided screening and confirmative assay results: PARAM = “Binding Antibody Result”, PARAMCD = “ADARSLT”
    - When lab provided neutralizing screening assay result and confirmative assay result: PARAM = “Neutralizing Antibody Result”, PARAMCD = “NABRSLT”
- Further organize sample interpretation when PARCAT1 = “Sample Interpretation”
    - PARAM = “Sample ADA Status”, PARAMCD = “ADASAMP”
    - PARAM = “Sample NAB Status”, PARAMCD = “NABSAMP”
    - PARAM = “Sample ADA and NAB status”, PARAMCD = “ADANABS”
    - PARAM = “Domain ADA Status”, PARAMCD = “ADADOMN”
    - PARAM = “Domain NAB Status”, PARAMCD = “NABDOMN”
    - PARAM = “Domain ADA and NAB Status”, PARAMCD = “ADANABD”
- Further organize subject level summary when PARCAT1 = “Subject Summary”
    - PARAM = “Treatment-induced ADA Positive”, PARAMCD = “ADATRI”
    - PARAM = “Treatment-boosted ADA Positive”, PARAMCD = “ADATRB”

- PARAM = “Treatment-emergent ADA Positive”, PARAMCD = “ADATRE”
- PARAM = “Transient ADA Positive”, PARAMCD = “ADATSP”
- PARAM = “Persistent ADA Positive”, PARAMCD = “ADAPSP”
- PARAM = “Baseline ADA Status”, PARAMCD = “ADABL”
- PARAM = “Post Baseline ADA Status”, PARAMCD = “ADAPB”
- PARAM = “ADA Subject Status”, PARAMCD = “ADASUBJ”
- PARAM = “Maximum Change in Titer”, PARAMCD = “MTTCHG”
- PARAM = “NAB Subject Status”, PARAMCD = “NABSUBJ”
- PARAM = “Overall Subject Status Summary”, PARAMCD = “ADAOVAL”
- PARAM = “Time to onset ADA (day)”, PARAMCD = “TIMOSADA”
- PARAM = “Duration of Positive ADA (day)”, PARAMCD = “ADADUR”

Risk-based characterization testing can include cross-reactivity to other proteins: endogenous proteins; Isotype assessment; and Epitope specificity (e.g., domain specificity for multi-domain products)

VARIABLE METADATA

This section describes variables that may be used to represent ADA data. ADA assay attributes may include drug tolerance level (DTL), minimum required dilution (MRD), minimum reportable titer (MRT), assay lab identification (ISNAM) and PK concentration at ADA sampling time. ADA datasets should also include subject-level flags (indicating whether a subject is evaluable), sample-level flags (e.g., indicator for last valid ADA), the indicator to tell whether an ADA sample has corresponding PK data, and whether PK concentration exceeds DTL. ADA data also requires nominal and actual relative time variables to the first dose and to the relative dose.

Standard BDS and subject-level (ADSL) variables are commonly used in ADA besides of additional SDTM variables to ensure traceability and integrity. See CDISC wiki for commonly used BDS and ADSL variables. In addition, ADA data also includes nominal and actual relative time variables following standard ADNCA variable naming conventions in the ADaMIG for Non-compartmental Analysis Input Data (ADNCA; available at https://www.cdisc.org/standards/foundational/adam/)).

Here we only focus on new proposed variables and variables with specific usage in ADA. See Table 3 for standard dataset variables with specific use for ADA. These variables are described in tabular format. The 2 rightmost columns, Core and CDISC Notes, provide information about the variables to assist developers in preparing their datasets. These columns are not meant to be metadata submitted in define.xml. The Core column describes whether a variable is required, conditionally required, or permissible. The CDISC Notes column provides more information about how variable should be derived. In addition, the Type column specifies whether the variable being described is character or numeric. A richer set of data types (e.g., text, integer, float), described in the Define-XML Specification (available at https://www.cdisc.org/standards/data-exchange/define-xml), should be provided in the metadata by the developer.

Variable Name	Variable Label	Type	Codelist / Controlled Term	Core	CDISC Notes
ADAEVFL	ADA Evaluable Subject Flag	Char	Y	Req	Flag to indicate evaluable subject for ADA analysis (Y = evaluable, Null = unevaluable). When a subject does not have a post-treatment ADA sample, it is unevaluable for ADA analysis.
ADAEVFN	ADA Evaluable Subject Flag (N)	Num	1	Perm	Numeric flag for evaluable subject indicator (1 = evaluable, Null = unevaluable). ADAEVFN can only be included if ADAEVFL is also included
ADAXFL	ADA Sample Exclusion Flag	Char	Y	Perm	Flag for exclusion of a sample into ADA analysis (Y = exclusion, Null = inclusion).
ADAXFN	ADA Sample Exclusion Flag (N)	Num	1	Perm	Numeric flag for exclusion of a record into ADA analysis (1 = exclusion, Null = inclusion). ADAXFN can only be included if ADAXFL is also included.
ADAwXRS	Reason w for ADA Exclusion	Char		Perm	This variable is used to explain why the record is not included in the ADA; it is sponsor defined (e.g., lab disability). One record can be excluded for multiple reasons.
ADAwXRSN	Reason for ADA Exclusion of w (N)	Num		Perm	Numeric representation of ADAwXRS. Useful for ordering of values of ADAwXRS or for other purposes. There must be a one-to-one relationship between ADAwXRSN and ADAwXRS. ADAwXRSN cannot be present unless ADAwXRS is also present. When ADAwXRS and ADAwXRSN are present, then on a given record, either both must be populated or both must be null.
ACYCLE	Analysis Cycle	Num		Perm	This is a record-level identifier that reflects cycle and may be of particular importance for studies that examine ADA in cancer patients. There must be a one-to-one mapping between ACYCLE and ACYCLEC. When ACYCLE and ACYCLEC are present, then on a given record, either both must be populated or both must be null.

Variable Name	Variable Label	Type	Codelist / Controlled Term	Core	CDISC Notes
ACYCLEC	Analysis Cycle (C)	Char		Perm	Character representation of the ACYCLE variable. Text characterizing to which analysis cycle the record belongs. This is a record-level identifier that reflects cycle and may be of particular importance for studies that examine ADA in cancer patients. There must be a one-to-one mapping between ACYCLE and ACYCLEC. When ACYCLE and ACYCLEC are present, then, on a given record, either both must be populated or both must be null.
NFRLT	Nom. Rel. Time from Analyte First Dose	Num		Perm	This is the planned elapsed time from first exposure to treatment associated with PARAM.
AFRLT	Act. Rel. Time from Analyte First Dose	Num		Perm	This is the actual elapsed time from first exposure to treatment associated with PARAM.
FRLTU	Rel. Time from First Dose Unit	Char	(PKUNIT)	Perm	This is the unit for all elapsed times from first dose.
RFTDTM	Datetime of Ref. Dose	Num		Perm	Reference exposure to study treatment
NRRLT	Nominal Rel. Time from Ref. Dose	Num		Req	This is the planned elapsed time for sample point from reference exposure to study treatment.
ARRLT	Actual Rel. Time from Ref. Dose	Num		Req	This is the actual elapsed time for sample point from reference exposure to study treatment.
RRLTU	Rel. Time from Ref. Dose Unit	Char	(PKUNIT)	Req	This is the unit for all elapsed times from reference dose.
AVALCATy	Analysis Value Category y	Char		Perm	A categorization of AVAL or AVALC within a parameter. Not necessarily a one-to-one mapping to AVAL and/or AVALC. For example, if PARAM is "Headache Severity" and AVAL has values 0, 1, 2, or 3, AVALCAT1 can categorize AVAL into "None or Mild" (for AVAL 0 or 1) and "Moderate or Severe" (for AVAL 2 or 3). AVALCATy is parameter variant. Consider for reporting Titer range, as needed.

Variable Name	Variable Label	Type	Codelist / Controlled Term	Core	CDISC Notes
AVALCAyN	Analysis Value Category y (N)	Num		Perm	Numeric representation of AVALCATy. Useful for ordering of values of AVALCATy or for other purposes. There must be a one-to-one relationship between AVALCAyN and AVALCATy within a parameter. AVALCAyN cannot be present unless AVALCATy is also present. When AVALCATy and AVALCAyN are present, then on a given record, either both must be populated or both must be null. Consider for reporting Titer range, as needed.
MRD	Minimum Required Dilution	Num		Req	Indicates the MRD for an assay (assay sensitivity)
MRT	Minimum Reportable Titer	Num		Perm	MRT (assay variability; similar to MRD)
DTL	Drug Tolerance Level	Num		Req	Indicates the DTL for an assay. DTL is a critical assay attribute and is defined as the maximum concentration of drug that may be present in the sample and still be able to detect positive control ADA.
PKCONC	PK Concentration	Num		Req	PK concentration of drug analyte at ADA sampling.
PKCONCU	PK Concentration Units	Char	(PKUNIT)	Cond	Unit for PKCONC and DTL; PKCONCU is used to hold unit for PKCONC and DTL. Producer should maintain the same unit for both PKCONC and DTL at the same record.
EXDTLFL	PK Concentration Exceeds DTL Flag	Char	Y	Perm	Flag to indicate PK concentration exceeds (greater than) DTL (Y = exceed, Null = not exceed), sample-level flag.
EXDTLFN	PK Concentration Exceeds DTL Flag (N)	Num	1	Perm	Numeric flag to indicate PK concentration exceeds (greater than) DTL. EXDTLFN can only be included if EXDTLFL is also included.
ADAPKFL	ADA with Corresponding PK Flag	Char	Y, N	Perm	Flag to indicate whether ADA sample has matching PK (Y = has, N = does not have); sample-level flag.

Variable Name	Variable Label	Type	Codelist / Controlled Term	Core	CDISC Notes
ADAPKFN	ADA with Corresponding PK Flag (N)	Num	1, 0	Perm	Numeric flag to indicate whether ADA sample has matching PK. ADAPKFN can only be included if ADAPKFL is present.
LADAFL	Flag for Last Analyzed ADA Sample	Char	Y	Perm	Flag to indicate if it is last valid ADA sample; sample-level flag.
LADAFN	Flag for Last Analyzed ADA Sample (N)	Num	1	Perm	Flag to indicate if it is last valid ADA sample. LADAFN can only be included if LADAFL is present.
LXDTLFL	Last PK Conc. Exceeds DTL Flag	Char	Y	Perm	Flag to indicate PK concentration at last valid ADA sampling time exceeds (Greater than) DTL (Y = exceed, Null = not exceed); subject level flag
LXDTLFN	Last PK Conc. Exceeds DTL Flag (N)	Num	1	Perm	Numeric flag to indicate PK concentration at last valid ADA sampling time exceeds (greater than) DTL (Y = exceed, Null = not exceed). LXDTLFN can only be included if LXDTLFL is present.
BLPOFL	ADA Baseline Positive Flag	Char	Y, N	Perm	Flag to indicate if subject has baseline ADA positive.
BLPOFN	ADA Baseline Positive Flag (N)	Num	1, 0	Perm	Numeric flag to indicate if subject has baseline ADA positive; BLPOFN can only be included if BLPOFL is present.
PBPOFL	ADA Post-baseline Positive Flag	Char	Y, N	Perm	Flag to indicate if subject has post-baseline ADA positive
PBPOFN	ADA Post-baseline Positive Flag (N)	Num	1, 9	Perm	Numeric flag to indicate if subject has post-baseline ADA positive; PBPOFN can only be include in PBPOFL is present.

Table 3. Anti-drug Antibody Analysis Variables

For multi-period studies that ADA can be summarized by period in additional to overall ADA subject-level summary. There are alternate ways to present data in analysis dataset to allow reporting both period-level subject summary and overall subject-level summary. For example see Figure 6. Subject Baseline ADA and Post Baseline ADA data presented as parameter in conjunction use of APERIOFigure 6, for a two periods study, period-level variables ADEV01FL, ADEV02FL, LXDT01FL, LXDT02FL, BLPO01BL, BLPO02FL, PBPO01FL, PBPO02FL can be used for ADA subject evaluable, last PK conc exceeds DTL, baseline ADA positive, and post-baseline ADA positive. Another option is to use parameter Baseline ADA Status (ADABL), Post baseline ADA Status (ADAPB) to summarize baseline positive and post-baseline positive status at each period (APERIOD), see Figure 7.

Table 4 includes variables that are described in the ADaMIG but are not required for general BDS use. However, for ADA use, they are required. The only difference between these variables and what is in the ADaMIG is the value for Core.

Variable Name	Variable Label	Type	Codelist /Controlled Term	Core	CDISC Notes
DOSEA	Actual Treatment Dose	Num		Req	DOSEA represents the actual treatment dosage associated with the record.
DOSEU	Treatment Dose Units	Char	(UNIT)	Req	The units for DOSEP and DOSEA. It is permissible to use suffixes such as “P” and “A” to record different units for DOSEP and DOSEA, with labels modified accordingly.

Variable Name	Variable Label	Type	Codelist /Controlled Term	Core	CDISC Notes
AVISIT	Analysis Visit	Char		Req	The analysis visit description; required if an analysis is done by nominal, assigned or analysis visit. AVISIT may contain the visit names as observed (i.e., from SDTM VISIT), derived visit names, time window names, conceptual descriptions (e.g., average, endpoint), or a combination of any of these. AVISIT is a derived field and does not have to map to VISIT from the SDTM. AVISIT represents the analysis visit of the record, but it does not mean that the record was analyzed. There are often multiple records for the same subject and parameter that have the same value of AVISIT. ANLzzFL and other variables may be needed to identify the records selected for any given analysis. See ADaMIG v1.3, Section 3.3.8, for information about flag variables. AVISIT should be unique for a given analysis visit window. In the event a record does not fall within any predefined analysis timepoint window, AVISIT can be populated in any way that the producer chooses to indicate this fact (e.g., blank or “Not Windowed”). The way that AVISIT is calculated, including the variables used in its derivation, should be indicated in the variable metadata for AVISIT. The values and the rules for deriving AVISIT may be different for different parameters within the same dataset. Values of AVISIT are producer defined and are often directly usable in clinical study report (CSR) displays.

Variable Name	Variable Label	Type	Codelist /Controlled Term	Core	CDISC Notes
AVALC	Analysis Value (C)	Char		Req	Character-valued response from ADA analysis/evaluation. AVAL is to be populated for ordering purpose for parameters except for PARAMCD = “TITER” or PARAMCD = “SN”. One-to-one mapping have to be maintained on the rows within a parameter when both AVAL and AVALC are populated.

Table 4. Standard BDS Variables with Stronger Core for ADA analysis

DATA EXAMPLES

Data example for a complete subject with one drug, two visits can be found in CDISC wiki for ADA. Examples included in this section focus on explaining the new concepts and new ideas.

Examples of analyzing ADA against one drug and ADA for multiple drugs/domains:

PARQUAL and PARQTYPE are introduced in BDS ANTI-DRUG ANTIBODY SubClass. These two variables are used as needed when there are multiple drug ADAs, or drug and domain-level ADAs involved. The goal is to describe the analysis value along with PARAM. They are permissible variables. PARQTYPE must have value of “ABTARGET” while PARQUAL is the name of drug, endogenous protein, isotype, epitope, or domain the antibody is target to. See below for some data examples.

Figure 2 shows how these two variables are applied to a study with one anti-drug antibody. It includes possible records for One drug study when PARCAT1 = “Collection”, “Sample Interpretation” or “Subject Summary”. In Figure 3, Figure 4 and Figure 5Figure 5, only records relevant to PARCAT1=”Collection” are included to save space. The concept of using PARQUAL and PARQTYPE applies to data for all parameter categories.

	USUBJID	PARQUAL	PARQTYPE	PARCAT1	PARAMCD	PARAM	AVISIT	AVAL	AVALC	DTYPE	ISSTRESC
1	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	SCRRSLT	Screening Result	SCREENING	-1	NEGATIVE		Negative
2	xxxx-xxx1	Anti-Drug X	ABTARGET	Sample Interpretation	ADASAMP	Sample ADA Status	SCREENING	-1	NEGATIVE		
3	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	SCRRSLT	Screening Result	CYCLE1	1	POSITIVE		Positive
4	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	CNRRSLT	Confirmatory Result	CYCLE 1	1	POSITIVE		Positive
5	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	TITER	Titer	CYCLE 1	0.5		HALFLLOQ	<1
6	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	SN	Signal to Noise	CYCLE 1	4.56789			4.56789
7	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	NABRSLT	Neutralizing Antibody	CYCLE 1	-1	NEGATIVE		Negative
8	xxxx-xxx1	Anti-Drug X	ABTARGET	Sample Interpretation	ADASAMP	Sample ADA Status	CYCLE 1	1	POSITIVE		
9	xxxx-xxx1	Anti-Drug X	ABTARGET	Sample Interpretation	NABSAMP	Sample NAB Status	CYCLE 1	-1	NEGATIVE		
10	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADATRI	Treatment-induced ADA Positive		0	Y		
11	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADATRB	Treatment-boosted ADA Positive		1	N		
12	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADATRE	Treatment-emergent ADA Positive		1	Y		
13	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADATSP	Transient ADA Response Positive		1	Y		
14	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADAPSP	Persistent ADA Response Positive		0	N		
15	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADABL	Baseline ADA Sample Status		-1	NEGATIVE		
16	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADAPSBL	Post Baseline ADA Sample Status		1	POSITIVE		
17	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADASUBJ	ADA Subject Status		5	TI Positive		
18	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	MTTCHG	Maximum Change in Titer		20			
19	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	NABSUBJ	NAb Subject Status		-1	NEGATIVE		
20	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADAOVAL	Overall Subject Status Summary		8	TI Positive NAB Negative		
21	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	TIMOSADA	Time to Onset ADA (day)		1			
22	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADADUR	Duration of Positive ADA (day)		10			

Figure 2. One drug: drug X.

	USUBJID	PARQUAL	PARQTYPE	PARCAT1	PARAMCD	PARAM	AVISIT	AVAL	AVALC	DTYPE	ISSTRESC
1	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	SCRRSLT	Screening Result	CYCLE 1	1	POSITIVE		Positive
2	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	CNRRSLT	Confirmatory Result	CYCLE 1	1	POSITIVE		Positive
3	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	TITER	Titer	CYCLE 1	0.5		HALFLLOQ	<1
4	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	SN	Signal to Noise	CYCLE 1	4.56789			4.56789
5	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	NABRSLT	Neutralizing Antibody	CYCLE 1	-1	NEGATIVE		Negative
6	xxxx-xxx1	Anti-Drug Y	ABTARGET	Collection	SCRRSLT	Screening Result	CYCLE 1	1	POSITIVE		Positive
7	xxxx-xxx1	Anti-Drug Y	ABTARGET	Collection	CNRRSLT	Confirmatory Result	CYCLE 1	1	POSITIVE		Positive
8	xxxx-xxx1	Anti-Drug Y	ABTARGET	Collection	TITER	Titer	CYCLE 1	1			1
9	xxxx-xxx1	Anti-Drug Y	ABTARGET	Collection	SN	Signal to Noise	CYCLE 1	10.2222			10.2222
10	xxxx-xxx1	Anti-Drug Y	ABTARGET	Collection	NABRSLT	Neutralizing Antibody	CYCLE 1	-1	NEGATIVE		Negative

Figure 3. Two drugs: drug X, drug Y

	USUBJID	PARQUAL	PARQTYPE	PARCAT1	PARAMCD	PARAM	AVISIT	AVAL	AVALC	DTYPE	ISSTRESC
1	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	SCRRSLT	Screening Result	CYCLE 1	1	POSITIVE		
2	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	CNRRSLT	Confirmatory Result	CYCLE 1	1	POSITIVE		
3	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	TITER	Titer	CYCLE 1	0.5		HALFLLOQ	<1
4	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	SN	Signal to Noise	CYCLE 1	4.56789			
5	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	NABRSLT	Neutralizing Antibody	CYCLE 1	-1	NEGATIVE		
6	xxxx-xxx1	Anti-Drug X Domain A	ABTARGET	Collection	SCRRSLT	Screening Result	CYCLE 1	1	POSITIVE		
7	xxxx-xxx1	Anti-Drug X Domain A	ABTARGET	Collection	CNRRSLT	Confirmatory Result	CYCLE 1	1	POSITIVE		
8	xxxx-xxx1	Anti-Drug X Domain A	ABTARGET	Collection	TITER	Titer	CYCLE 1	1			1
9	xxxx-xxx1	Anti-Drug X Domain A	ABTARGET	Collection	SN	Signal to Noise	CYCLE 1	4.56789			
10	xxxx-xxx1	Anti-Drug X Domain A	ABTARGET	Collection	NABRSLT	Neutralizing Antibody	CYCLE 1	-1	NEGATIVE		
11	xxxx-xxx1	Anti-Drug X Domain B	ABTARGET	Collection	SCRRSLT	Screening Result	CYCLE 1	1	POSITIVE		
12	xxxx-xxx1	Anti-Drug X Domain B	ABTARGET	Collection	CNRRSLT	Confirmatory Result	CYCLE 1	1	POSITIVE		
13	xxxx-xxx1	Anti-Drug X Domain B	ABTARGET	Collection	TITER	Titer	CYCLE 1	1		HALFLLOQ	<2
14	xxxx-xxx1	Anti-Drug X Domain B	ABTARGET	Collection	SN	Signal to Noise	CYCLE 1	4.56789			
15	xxxx-xxx1	Anti-Drug X Domain B	ABTARGET	Collection	NABRSLT	Neutralizing Antibody	CYCLE 1	-1	NEGATIVE		

Figure 4. One drug, two domains

	USUBJID	PARQUAL	PARQTYPE	PARCAT1	PARAMCD	PARAM	AVISIT	AVAL	AVALC	MRD	DTYPE	ISSTRESC
1	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	SCRRSLT	Screening Result	CYCLE 1	1	POSITIVE			
2	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	CNRRSLT	Confirmatory Result	CYCLE 1	1	POSITIVE			
3	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	TITER	Titer	CYCLE 1	0.5		1	HALFLLOQ	<1
4	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	SN	Signal to Noise	CYCLE 1	4.56789				
5	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	NABRSLT	Neutralizing Antibody	CYCLE 1	-1	NEGATIVE			
6	xxxx-xxx1	Anti-Drug Y	ABTARGET	Collection	SCRRSLT	Screening Result	CYCLE 1	1	POSITIVE			
7	xxxx-xxx1	Anti-Drug Y	ABTARGET	Collection	CNRRSLT	Confirmatory Result	CYCLE 1	1	POSITIVE			
8	xxxx-xxx1	Anti-Drug Y	ABTARGET	Collection	TITER	Titer	CYCLE 1	1		1		1
9	xxxx-xxx1	Anti-Drug Y	ABTARGET	Collection	SN	Signal to Noise	CYCLE 1	4.56789				
10	xxxx-xxx1	Anti-Drug Y	ABTARGET	Collection	NABRSLT	Neutralizing Antibody	CYCLE 1	-1	NEGATIVE			
11	xxxx-xxx1	Anti-Drug X Domain A	ABTARGET	Collection	SCRRSLT	Screening Result	CYCLE 1	1	POSITIVE			
12	xxxx-xxx1	Anti-Drug X Domain A	ABTARGET	Collection	CNRRSLT	Confirmatory Result	CYCLE 1	1	POSITIVE			
13	xxxx-xxx1	Anti-Drug X Domain A	ABTARGET	Collection	TITER	Titer	CYCLE 1	1		2	HALFLLOQ	<2
14	xxxx-xxx1	Anti-Drug X Domain A	ABTARGET	Collection	SN	Signal to Noise	CYCLE 1	4.56789				
15	xxxx-xxx1	Anti-Drug X Domain A	ABTARGET	Collection	NABRSLT	Neutralizing Antibody	CYCLE 1	-1	NEGATIVE			
16	xxxx-xxx1	Anti-Drug Y Domain A	ABTARGET	Collection	SCRRSLT	Screening Result	CYCLE 1	1	POSITIVE			
17	xxxx-xxx1	Anti-Drug Y Domain A	ABTARGET	Collection	CNRRSLT	Confirmatory Result	CYCLE 1	1	POSITIVE			
18	xxxx-xxx1	Anti-Drug Y Domain A	ABTARGET	Collection	TITER	Titer	CYCLE 1	4		4	LLOQ	<4
19	xxxx-xxx1	Anti-Drug Y Domain A	ABTARGET	Collection	SN	Signal to Noise	CYCLE 1	4.56789				
20	xxxx-xxx1	Anti-Drug Y Domain A	ABTARGET	Collection	NABRSLT	Neutralizing Antibody	CYCLE 1	-1	NEGATIVE			

Figure 5. Two drugs, one domain

When ADA is collected in a multi-period study or when ADA needs to be summarized at segments of study course in addition to over ADA status summary, below examples provide two alternative solutions with their own pros and cons. The developer has the flexibility to follow one or the other as needed. Figure 6Figure 6 shows that dataset could expand vertically when study segment increases. Figure 7

shows that dataset could instead expand horizontally. This concept applies to other subject level flag variables alike.

	USUBJID	PARQUAL	PARQTYPE	PARCAT1	PARAMCD	PARAM	AVISIT	AVALC	APERIOD
1	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADABL	Baseline ADA Status		Negative	1
2	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADAPB	Post Baseline ADA Status		Positive	1
3	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADABL	Baseline ADA Status		Positive	2
4	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADAPB	Post Baseline ADA Status		Positive	2
5	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADABL	Baseline ADA Status		Positive	3
6	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADAPB	Post Baseline ADA Status		Positive	3
7	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADABL	Baseline ADA Status		Negative	
8	xxxx-xxx1	Anti-Drug X	ABTARGET	Subject Summary	ADAPB	Post Baseline ADA Status		Positive	

Figure 6. Subject Baseline ADA and Post Baseline ADA data presented as parameter in conjunction use of APERIOD.

	USUBJID	PARQUAL	PARQTYPE	PARCAT1	PARAMCD	PARAM	AVISIT	AVAL	BLPO01FL	BLPO02FL	PBPO01FL	PBPO02FL	ADEV01FL	ADEV02FL	BLPOFL	PBPOFL	ADAEVFL
1	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	SCRRSLT	Screening Result	CYCLE 1		N	Y	Y	Y	Y	Y	N	Y	Y
2	xxxx-xxx1	Anti-Drug X	ABTARGET	Collection	SCRRSLT	Neutralizing Antibody	CYCLE 9		N	Y	Y	Y	Y	Y	N	Y	Y

Figure 7. Subject Baseline ADA and Post Baseline ADA data presented as flag variable.

The analysis dataset can assign AVAL to corresponding AVALC when PARAMCD is not Titer or SN. The value of AVAL can be used to determine the order of display on analysis report. As see Figure 8, for Overall Subject Status Summary, PARAMCD=ADAOVAL, AVAL can be assigned in the order as desired according to severity of ADA responses.

PARAMCD=ADAOVAL	AVALC	AVAL
	Negative	-1
	Inconclusive	0
	Positive	1
	ADA Positive NAB Negative	1.1
	ADA Positive NAB Positive	1.2
	Non-TE ADA Positive	2
	Non-TE ADA Positive NAB Negative	2.1
	Non-TE ADA Positive NAB Positive	2.2
	TI ADA Positive	3
	TI ADA Positive NAB Negative	3.1
	TI ADA Positive NAB Negative	3.2
	TB ADA Positive	4
	TB ADA Positive NAB Negative	4.1
	TB ADA Positive NAB Positive	4.2

Figure 8. AVAL/AVALC can be populated when PARAMCD = ADAOVAL

EXAMPLES OF ADA REPORTING AND ANALYSIS

ADA analysis report usually consists of ADA summary tables, ADA listing tables and various figures. Examples of these TFLs can be found in CDISC wiki page.

ADA summary table

The key data points included in ADA summary table can be following.

- ADA subject-level status: ADA only, neutralizing ADA (NAb) only, combined

- Persistent/transient ADA (ADA duration)
- Time to ADA onset, boosted/induced/emergent positive.
- Summarized on all samples or summarized at planned visit/timepoint, or at baseline or on treatment.
    - Subject with positive ADA
    - NAb subject-level status
    - Maximum posttreatment titer/SN (usually in figure)
    - ADA sample level status (ADA/SN level)
    - ADA sampling condition: summary of PK concentration vs DTL
    - Others
    - Population: exclusion, evaluable, treated
    - By study, by indication, by dosage level

ADA Listing Table

Listing table usually contains raw collected data at each timepoint. Sometimes these data can be presented by subject level summary variables. Data points included in listing table can be following.

- Raw assay result, sample status: dose, drug concentration
- Treatment, Subject identifier, visit, study day, nominal / actual time relative to reference dose or to the first dose
- Subject level status (ADA only, NAB only, or combined), Maximum titer/SN for ADA positive ADA

ADA Impact summary on PK

Usually, ADA impact on PK is presented in plots to easily visualize data by ADA subject status. Some examples are below.

- Individual PK profile by ADA subject status
- Mean of post-BL C-trough by ADA subject status
- C-trough by ADA & SN
- Stat. summary of C-trough
- Other PK parameters: AUC, CL, C-max, Post hoc estimate
- Covariates in PopPK analysis

ADA Impact summary on Efficacy

ADA subject status is used as by category to compare efficacy end points.

ADA Impact summary on Safety

ADA subject status is used as by category to compare AE of interest.

TERMINOLOGY

The following abbreviations and terms are commonly used terminology in ADA analysis. Additional definitions in the CDISC Glossary (available at https://www.cdisc.org/standards/glossary) At the study level, some definitions may be adjusted for study-specific needs. This should be clearly defined in the dataset define file.

Note that the terms "positive" and "negative" may be used when referring to either sample or subject. In addition, there are certain terms that refer specifically to either samples or subjects.

Referring to samples,

- an ADA-positive sample is any biological sample, tested for ADA, that shows a measurable amount of antibody.
- an ADA-negative sample is any biological sample, tested for ADA, that shows no measurable amount of antibody and also shows no measurable amount of drug (target) or an amount of drug deemed not to interfere with the detection of ADA.
- an inconclusive sample is any biological sample, tested for ADA, that shows no measurable amount of ADA, but also contains drug concentrations determined during ADA assay validation to interfere with the ADA detection.

Referring to subjects,

- ADA-evaluable subjects are those with at least 1 ADA assay result after treatment with drug.
- ADA-unevaluable subjects are those without at least 1 ADA assay result after treatment with drug. Would include those treated with placebo or those with only baseline ADA results (no post-dose results)
- ADA-positive subjects have at least 1 treatment-induced or treatment-boosted ADA-positive sample during the treatment or follow-up period, ADA response post-drug administration
- ADA-negative subjects are those without a treatment-induced or treatment-boosted ADA positive sample during the treatment or follow-up period related to drug administration; may include 1 or more of the following:
    - subjects when the last sample is below DTL.
    - non-treatment-emergent subjects
- ADA-inconclusive subjects do not have ADA positive samples (including after the follow-up period) but had drug levels above the ADA assay drug tolerance level in the last sample and hence drug levels could have interfered with the ADA assay. Some sponsors may include "ADA-inconclusive subjects" in category of "ADA-negative subjects". In this case, it needs to be clearly defined in dataset derivation note.

Abbreviations and terms	**Definition**
ADA	Anti-drug antibody; a biologic drug-reactive antibody, which includes pre-existing host antibodies that are cross-reactive with the administered biologic drug. ADA is synonymous with anti-therapeutic antibody (ATA), anti-product antibody (APA), anti-biologic antibody (ABA), and binding ADA.
ADA incidence	Proportion of the study population found to have seroconverted or boosted preexisting ADA during a study period; describes subjects who had a positive ADA response to the drug that was dosed in the trial (see treatment-emergent ADA)

Abbreviations and terms	Definition
ADA prevalence	Proportion of all individuals having drug-reactive antibodies (including pre-existing) at any point in time; describes all subjects with positive samples in the ADA assay (distinct from ADA incidence)
ADaM	Analysis Data Model
ADaMIG	ADaM Implementation Guide
ADSL	(ADaM) Subject-Level Analysis Dataset
BDS	(ADaM) Basic Data Structure
Binding ADA	Any biologic drug-reactive antibody that binds to the drug product (regardless of clinical outcome)
CDISC	Clinical Data Interchange Standards Consortium
Dataset	A collection of structured data in a single file
DTL	Drug tolerance level: the maximum concentration of drug that may be present in the sample and still be able to detect positive control ADA. Note that ADA samples with drug concentrations above the drug tolerance level may show false negative results due to interference.
MRD	Minimum required dilution
MRT	Minimum reportable titer
NAb	Neutralizing ADA; a biologic drug-reactive antibody that binds to the drug product in such a way as to diminish or prevent its pharmacologic activity (e.g., blocking the active binding site)
Non-neutralizing ADA	A biologic drug-reactive antibody that binds to the drug product but does not reduce or interfere with the drug activity
PD	Pharmacodynamics
PK	Pharmacokinetics
Pre-existing ADA	A drug-reactive antibody that is present prior to treatment (also referred to as "baseline ADA")
SN	Signal to noise (ratio)
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide
TFLs	Tables, figures, and listings
Titer	The numeric quantification of ADA present in a sample; typically expressed as the reciprocal of the highest dilution of the sample (e.g., 1:1000 being a titer of 1000), or alternatively derived through interpolation of the cut-point value from the assay dilution curve
Treatment-boosted ADA	A biologic drug-reactive antibody, present in the patient prior to drug administration, that was increased to a higher measurable level after initial drug administration (i.e., any time after the initial drug administration the ADA titer is greater than the baseline titer by a scientifically reasonable/defined margin such as a 4- or 9-fold increase)
Treatment-emergent ADA	Biologic drug-reactive antibody grouping that includes both treatment-induced and treatment-boosted ADA
Treatment-induced ADA	A biologic drug-reactive antibody that is produced (sero-conversion) any time following initial drug administration in a subject with no detectable pre-existing ADA

Table 5. Abbreviations and Terms

CONCLUSION

This proposal to implement ADaM BDS structure for ADA analysis dataset is to standardize ADA analysis dataset structure across the industry. The science behind the analysis of ADA data is considered when this implementation guide is developed. While following the BDS concept and principles, we introduced new variables in order to allow data traceability and data interpretation of ADA evaluation, satisfy the need for sample and subject level summary, as well as meet the analysis and reporting objectives. We realize that ADA is unique, and we have considered the general principles of BDS structure while creating this ADaM subclass of Anti-drug Antibody Analysis being proposed for ADA data.

In Anti-drug Antibody subclass, some permissible variables are consider required. PARQUAL and PARQTYP are also brought in from ADaMIG v3. The values to populate in PARAM and PARAMCD are recommended. However, those values are recommended only. The developer can follow the recommendation or define them in a reasonable way as needed. Our expectation is to help the developer to build this dataset in a consistent format regardless of studies, anti-drug antibody or sponsors' requirements. This should set the foundation for macro development and dataset validation, so as to improve the efficiency in analysis and reporting. Ultimately, it can boost submission preparation for the developer and assist the package review process for the agency reviewer.

This proposal is currently in review by the CDISC ADaM team. Please refer to CDISC wiki for most current version.

REFERENCES

- FDA Guidance January 2019: Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection Guidance for Industry
- EMU Guideline May 2017: Guideline on Immunogenicity assessment of therapeutic Proteins
- White Paper: Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides—Harmonized Terminology and Tactical Recommendations, Shankar et al 2014
- How Close Are We to Profiling Immunogenicity Risk Using In Silico Algorithms and In Vitro Methods?: an Industry Perspective, Gokemeijer et al 2017

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Please refer to the CDISC wiki for more information about ADA ADaM.

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