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Handling Anti-Drug Antibody (ADA) Data for Efficient Analysis

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ABSTRACT

Large molecules have revolutionized the pharmaceutical industry. The complex nature of these therapeutics can be mistaken by the human body as foreign substances and their interactions with various endogenous proteins in the human body may induce an immunogenicity effect to produce anti-drug antibodies (ADAs). Based on their interaction with antigen binding sites, ADAs are classified as non-neutralizing antibodies (non-NAbs) and neutralizing antibodies (NAbs). These could impair the functionality of the drug by interfering with PK performance, decrease drug efficacy, and trigger serious hypersensitivity reactions. Monitoring ADA is key to evaluating safety, post-marketing surveillance, and defining risk mitigation strategies. High-quality programming support with solid understanding of ADA data is critical for the programmers to map it to relevant CDISC standard tests that serves as a base to create efficient and impactful ADA analysis. This paper will illustrate the mapping of unique raw data such as ADA Screening, ADA Confirmation, NAbs data, titer results from various sources into the Immunogenicity Specimen Assessments (IS) SDTM domain, deriving relevant ADA variables at the ADaM level, and share highlights of standard ADA reporting. Moreover, a few unique scenarios like how to handle baseline positive and post baseline positive results in relation to their titer values in summary report with oncology example data will be demonstrated. Additionally, this paper briefly touches upon the foundational mechanics of ADA, its impact in clinical trials, and relevant regulatory guidelines.

INTRODUCTION

Biotherapeutics have revolutionized our ability to treat life-threatening diseases. These proteins, including monoclonal antibodies (mAbs), are widely used to make drugs that have been more successful at treating various diseases and some cancers because of their higher specificity and better-characterized mechanisms of action (Lu *et al*., 2020). Nevertheless, human systems are programmed to respond to or fight against any unrecognized foreign invaders, including some biologics. These may therefore result in induction of immune responses (shown as a black box in Figure 1 as this is a complex process) to the therapeutic molecule that leads to the generation of anti-drug antibodies (ADA) [Figure 1]. The consequences of the immune response to the biologics can range from no effect to serious adverse events, including life-threating complications such as anaphylaxis, neutralization of the effectiveness of lifesaving or highly effective therapies, or neutralization of endogenous proteins with nonredundant functions (FDA-2013-D-0092, 2013).

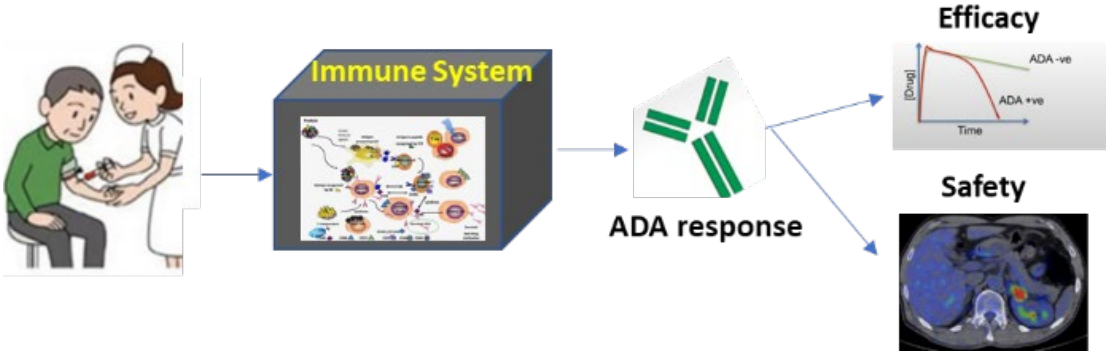

Figure 1: **Overview of Immunogenicity**

Pharmacokinetics (PK) is how the body responds to a drug which describes absorption, distribution, metabolism, and excretion (ADME) as a function of time. Pharmacodynamics (PD) is the impact of the drug on the body, and PD allows us to quantify the relationship between a drug and its pharmacologic or toxicologic effect it has on patients. ADA responses can affect the PK, PD, safety, and efficacy of a therapeutic candidate. The clinical effects of ADA formation can be highly variable and may cause adverse events that put the patient at risk. In this paper, we will discuss a multi-tiered ADA testing scheme, its raw data structure, its mapping into the SDTM IS domain, and deriving analysis dataset parameters for efficient analysis and reporting.

Safety, efficacy, and PK/PD can be affected by the development of anti-drug antibodies. The ADA generated by the immune response interacts with the therapeutic antibody binding at the non-binding site (figure 2a) or the binding region (figure 2b). Non-neutralizing ADA does not affect binding of a therapeutic antibody to target, and it may by itself have altering effects on the half-life of a therapeutic. On the other hand, neutralizing ADA (**NAbs**) may interact directly with pharmacologically relevant sites of action, eventually obscuring the interactions between a therapeutic and its target (Chirmule *et al*., 2012).

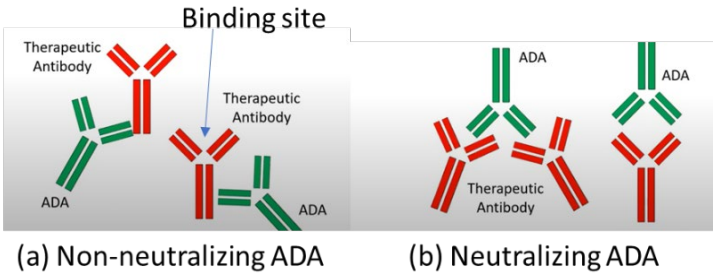

Figure 2: **Illustration of the interaction of Therapeutic (red) with ADA (green).**

ADA TESTING SCHEME

Once study drug is administered to a patient, ADA levels will be measured and capture in data structures typically described in a study-specific data transfer plan (DTP). The Food and Drug Administration (FDA) and experts in immunogenicity testing have published guidelines (FDA-2009-D-0539, 2019) for the immunoassays used to detect antibodies against biologic drugs. For each scheduled timepoint, blood samples will be analyzed for ADA levels. As shown in the schematic representation in Figure 3, based on the outcome of the ADA screening, a series of hierarchical follow-up steps will be performed to finetune the results. These include ADA screening and testing for ADA confirmatory and neutralizing antibodies (NAb).

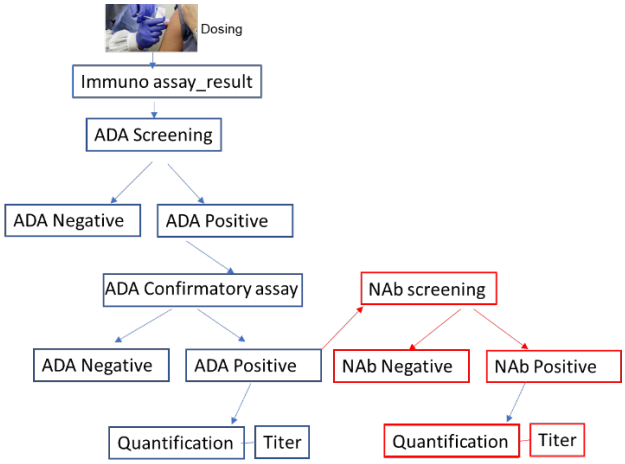

Figure 3:

Understanding the basics behind ADA data structures is important to statistical programmers for efficient mapping and further analysis.

ADA screening results can be either negative (no further confirmation required) or positive. If the ADA result is positive, then the data should be validated through a confirmatory assay, which can be negative (no further assay required) or positive. If positive, additional quantification of the data and its titer value which corresponds to the highest dilution factor that still yields a positive reading is important for interpretation of the data. In addition, for positive ADA confirmatory assays, an NAb assay including quantification of the data and its titer value will be performed as shown in Figure 3.

MAPPING RAW ADA DATA INTO SDTM IS DOMAIN

The sample DTP in Table 1 illustrates the list of ADA-related Immunogenicity specimen assessments along with their description, expected results and units. For simplicity, only Binding ADA (BAb) and Neutralizing ADA (NAb) result categories are shown in this demonstration.

LBTEST	Description	ISCAT	ISTESTCD	ISTEST	ISORRES	ISORRESU
ADA_Screening	Screening for binding ADA	Binding ADA	ADASCRN	ADA Screening	Positive/Negative	
ADA_Confirm	Confirmation of Binding ADA detection	Binding ADA	ADACONFM	ADA Confirmation	Positive/Negative	
ADA_Quantitative	Quantification of Binding ADA	Binding ADA	ADAQUAN	ADA Quantity	23	RLU
ADA_Titer	Titer ADA	Binding ADA	ADATITER	ADA Titer	<1	dilution
NAB_Screening	Screening for neutralizing ADA	NEUTRALIZING ADA	NABSCRN	NAB ADA Screening	Positive/Negative	
NAB_Confirm	Confirmation of neutralizing ADA detection	NEUTRALIZING ADA	NABCONFM	NAB ADA Confirmation	Positive/Negative	
NAB_Quantitative	Quantification of neutralizing ADA	NEUTRALIZING ADA	NABQUAN	NAB ADA Quantity	23	RLU
NAB_Titer	NAB Titer	NEUTRALIZING ADA	NABTITER	NAB ADA Titer	3	dilution

Table 1: Sample ADA DTP Template

The sample raw assay results in the example below (Table 2) contain a total of 3 subjects with one record per subject per binding ADA per timepoint, and additional records as per the multi- tiered ADA testing scheme. For simplicity, this discussion focuses on one visit for each subject with different result scenarios.

USUBJID	VISIT	LBTPT	LBCAT	LBSCAT	SCRQL	SCRQN	SCRQNU	CONFQL	CONFQN	TITER	TiterU
XXXX-1000-100	CIDI	Predose	immunogenic	ATA	Negative	xxx.x	RLU				
XXXX-1000-100	CIDI	8 hrs post dose	immunogenic	ATA	Negative	xxx.x	RLU				
XXXX-1000-101	CIDI	Predose	immunogenic	ATA	Negative	xxx.x	RLU				
XXXX-1000-101	CIDI	8 hrs post dose	immunogenic	ATA	potential Positive	xxx.x	RLU	Negative			
XXXX-1000-102	CIDI	Predose	immunogenic	ATA	Positive	xxx.x	RLU				
XXXX-1000-102	CIDI	8 hrs post dose	immunogenic	ATA	potential Positive	xxx.x	RLU	Postive	xxx.x	1	dilution

Table 2: Sample External Raw Lab Data Containing ADA Results

After mapping the raw dataset to the SDTM IS dataset (Table 3), subject 100 contains only two records as the outcome of the assay is negative at both baseline and post-baseline. Subject 101 contains a total of 3 records, where the initial assay outcome is negative at baseline (ISSEQ 1) and subsequently positive at post-baseline (ISSEQ 2) and upon further confirmatory assay yielded negative (ISSEQ 3). This subject therefore does not require subsequent analysis. Subject 102 contains a total of 9 records, where the initial assay outcome is positive at baseline (ISSEQ 1) and subsequently positive at post-baseline (ISSEQ 2) and upon further confirmatory assay also yielded positive (ISSEQ 3) along with ADA quantification (ISSEQ 4) and titer value of 4 (ISSEQ 5). In addition, this subject necessitates further NAb assays which are displayed in rows 6 to 9: positive at screening (ISSEQ 6), positive at confirmatory assay (ISSEQ 7), NAb quantification (ISSEQ 8) and its titer value of 2 (ISSEQ 9).

DOMAIN	USUBJID	ISSEQ	ISCAT	ISTESTCD	ISTEST	ISORRES	VISIT	ISTPT	ISDTC
IS	XXXX-1000-100	1	Binding ADA	ADASCRN	ADA Screening	Negative	Cycle 1 Day 1	Predose	2019-07-08T00:53
IS	XXXX-1000-100	2	Binding ADA	ADASCRN	ADA Screening	Negative	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
IS	XXXX-1000-101	1	Binding ADA	ADASCRN	ADA Screening	Negative	Cycle 1 Day 1	Predose	2019-04-30T04:39
IS	XXXX-1000-101	2	Binding ADA	ADASCRN	ADA Screening	Positive	Cycle 1 Day 1	8 hrs post dose	2019-04-30T12:40
IS	XXXX-1000-101	3	Binding ADA	ADACONFM	ADA Confirm	Negative	Cycle 1 Day 1	8 hrs post dose	2019-04-30T12:40
IS	XXXX-1000-102	1	Binding ADA	ADASCRN	ADA Screening	Positive	Cycle 1 Day 1	Predose	2019-07-08T00:54
IS	XXXX-1000-102	2	Binding ADA	ADASCRN	ADA Screening	Positive	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
IS	XXXX-1000-102	3	Binding ADA	ADACONFM	ADA Confirm	Positive	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
IS	XXXX-1000-102	4	Binding ADA	ADAQUAN	ADA Quantity	234	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
IS	XXXX-1000-102	5	Binding ADA	ADATITER	ADA Titer	4	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
IS	XXXX-1000-102	6	Neutraizing ADA	NABSCRN	NAb ADA Screening	Positive	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
IS	XXXX-1000-102	7	Neutraizing ADA	NABCONFM	NAb Confirm	Positive	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
IS	XXXX-1000-102	8	Neutraizing ADA	NABQUAN	NAb Quantity	100	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
IS	XXXX-1000-102	9	Neutraizing ADA	NABTITER	NAb Titer	2	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54

Table 3: **Sample SDTM IS Domain Dataset**

ANALYSIS STRATEGY OF ADA RESULTS

The ADaM ADIS dataset will contain one record per subject per analysis parameter per timepoint (Table 4). Besides the records from the SDTM IS dataset, the ADIS dataset includes additional records for the following new derived parameters based on the ADA results that support the analysis.

1) **Treatment-induced ADA**: Incidence of ADA induction is determined if both baseline and post-baseline samples have positive titers, and the subject is only considered positive for the induction of ADA when the post-baseline titer is at least 4-fold greater than the titer prior to initial dosing.
2) **No Treatment-related ADA**: Subjects with negative post-baseline ADA results
3) **Post-baseline Positive ADA**: Incidence of ADA is determined by counting at least 1 positive result at any timepoint after initial dosing.
4) **Time to Onset of First ADA**: Select the analysis day of the first record with ADA-positive result after dosing.
5) **Last Visit ADA**: The latest visit on which a subject had a positive ADA result after dosing.
6) **Persistently Positive ADA**: Defined as ATA positive at 2 or more post-baseline assessments (with ≥ 16 weeks between first and last positive) or ATA positive at the last post-baseline assessment.
7) **Transiently Positive ADA:** Defined as having at least one post-baseline ATA positive assessment and not fulfilling the conditions of ATA persistently positive.
8) **NAb Negative**: NAb negative at baseline includes patients who are ADA-negative.
9) **NAb Incidence**: defined as having at least one positive NAb result at any time, including baseline and/or post baseline.

In addition, at the subject-level ADSL analysis dataset, the following two flag variables shall be included to support the summarization of ADA data. The ADA-evaluable flag (ADAFL) is set to Y if subjects have at least one baseline and one post-baseline record in the ADIS dataset. Similarly, the NAb evaluable flag (NABFL) is set to Y if subjects have at least one NAb result. Table 5 shows one way of summarizing ADA incidence.

USUBJID	ASEQ	PARCAT	PARAMCD	PARAM	AVALC	AVISIT	ATPT	ADT
XXXX-1000-100	1	Binding ADA	ADASCRN	ADA Screening	Negative	Cycle 1 Day 1	predose	2019-07-08T00:54
XXXX-1000-100	2	Binding ADA	ADASCRN	ADA Screening	Negative	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-101	1	Binding ADA	ADASCRN	ADA Screening	Negative	Cycle 1 Day 1	predose	2019-04-30T04:40
XXXX-1000-101	2	Binding ADA	ADASCRN	ADA Screening	Positive	Cycle 1 Day 1	8 hrs post dose	2019-04-30T12:40
XXXX-1000-101	3	Binding ADA	ADACONFM	ADA Confirm	Negative	Cycle 1 Day 1	8 hrs post dose	2019-04-30T12:40
XXXX-1000-102	1	Binding ADA	ADASCRN	ADA Screening	Positive	Cycle 1 Day 1	Predose	2019-07-08T00:54
XXXX-1000-102	2	Binding ADA	ADASCRN	ADA Screening	Positive	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-102	3	Binding ADA	ADACONFM	ADA Confirm	Positive	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-102	4	Binding ADA	ADAQUAN	ADA Quantity (RLU)	234	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-102	5	Binding ADA	ADATITER	ADA Titer	4	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-102	6	Neutraizing ADA	ADASCRN	NAb ADA Screening	Positive	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-102	7	Neutraizing ADA	ADACONFM	NAb Confirm	Positive	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-102	8	Neutraizing ADA	NABQUAN	NAb Quantity (RLU)	100	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-102	9	Neutraizing ADA	NABTITER	NAb Titer	2	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-102	10	Binding ADA	INDUCADA	Treatment induced A	N			
XXXX-1000-102	11	Binding ADA	NOTRTREL	No Treatment relate	N			
XXXX-1000-102	12	Binding ADA	TIMEADA	Time to onset of Firs	42			
XXXX-1000-102	13	Binding ADA	POSTADA	Post baseline ADA	Y			
XXXX-1000-102	14	Binding ADA	LVADA	Last visit ADA	Cycle 3			

Table 4: Sample ADaM ADIS Domain Dataset

	Total (N=xx) n (%)
Subjects with a baseline and at least one post-baseline sample	n
Baseline Negative	n
Negative post-baseline[2]	m (%)
Positive post-baseline[3]	m (%)
Baseline Positive	n
Negative post-baseline[2]	m (%)
Treatment induced ADA[1]	m (%)
NAb negative[8] at baseline	n
NAb incidence[9]	m (%)
Total positive post-baseline	m (%)

The percentage denominators are the first row counts of evaluable subjects, not the analysis set population. Superscript numbers refer to the derived parameters explained in the above section.

Table 5: Sample Summary of Anti-Drug Antibody (ADA) Incidence

CONCLUSION

Development of ADA in subjects can impact the data interpretation of a therapeutic. Hence, understanding and accurate analysis of ADA data is necessary. Profiling the clinical impact of ADA formation refines the immunogenicity risk assessment and defines appropriate risk mitigation strategies (Lotz *et al*., 2022). This in turn helps in answering a few important clinical development-stage questions in early-stage and late-stage studies as shown in Table 6.

Early-stage Development	Late-stage Development
▪ Do any pre-existing x-reactive antibodies increase after dosing ▪ Is ADA observed increase or decrease after repeated dosing ▪ Can any mitigation strategies likely decrease or increase risk profile	▪ Will a dosing regimen, change in manufacturing or Patient population change in immunogenicity profile

Table 6: Few Important Clinical Development-Stage Questions

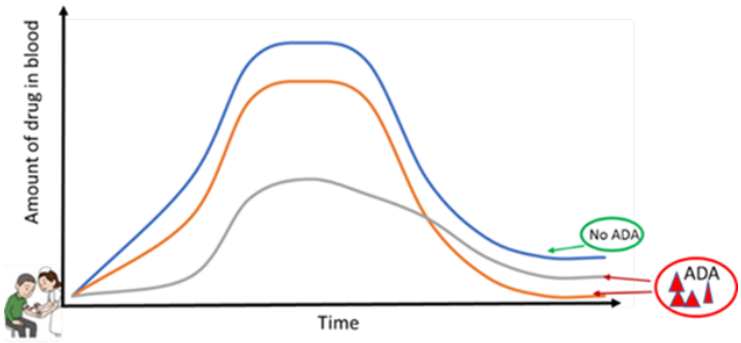

Figure 4: Drug concentration by time. Model showing the effect of ADA on PK plot.

The general concentration-time curve explains how the drug moves throughout the body (PK) and its PD effect. The presence of ADA will impair the ADME processes. Figure 4 illustrates how the ADA concentration affects pharmacokinetic parameters including maximum plasma concentration (Cmax) and area under the curve (AUC). The blue line refers to the normal ADME process with the highest Cmax. The presence of ADA in a subject when it binds with the active site increases the elimination of the study drug as shown in the grey line where the Cmax is lowered significantly. On the other hand, if the ADA binds with the non-active regions it will not alter the Cmax very much, as shown in the orange line. This has also been demonstrated by Bartelds *et al*., (2011) that the clinical trial data for patients without anti-adalimumab antibodies had significantly higher adalimumab concentrations compared with patients having both antibody titers. Thus, understanding ADA and its analysis is required for statistical programmers to properly map this type of data, as this significantly benefits the PK/PD analysis.

REFERENCE

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