PharmaSUG China 2025 - Paper DS-176

# Immunogenicity Analysis Data Model (ADIS) Design Strategy by Using Categorical Analysis Variables

Yiwei Jiang, Liqin Jin, Yingying Yan, Tao Zhang, Qilu Pharmaceutical Co. Ltd

## ABSTRACT

With the increasing application of bispecific antibodies (BsAbs) or multispecific antibodies compounds as anti-cancer agents in clinical trials, more stringent and complex immunogenicity analytical requirements are emerging. When designing an immunogenicity analysis data model (ADIS), programmers must account for multiple antibodies and their associated indicators within a single antibody. The complexity of this information makes it challenging to establish clear and straightforward mapping rules in ADIS, which is based on the Analysis Data Model (ADaM) basic data structure (BDS).

This paper uses anit-PD-1/anti-CTLA-4 bispecific antibody as an example to demonstrate flexible mapping strategies by appropriately leveraging PARCATy and AVALCATy, which enhances the intelligence of variable mapping in ADIS.

## INTRODUCTION

Anit-PD-1/anti-CTLA-4 bispecific antibody consists of two distinct antibodies - anti-PD-1 IgG4 (aPD-1) and anti-CTLA-4 IgG1 (aCTLA-4). The immunogenicity assessment follows the laboratory testing procedure outlined in Figure 1. The testing results include three indicators: anti-drug antibodies (ADAs, including BsAbs, aPD-1 and aCTLA-4 results), neutralizing antibodies (NAbs, including anti-PD-1 and anti-CTLA-4 NAb results), and titer value.

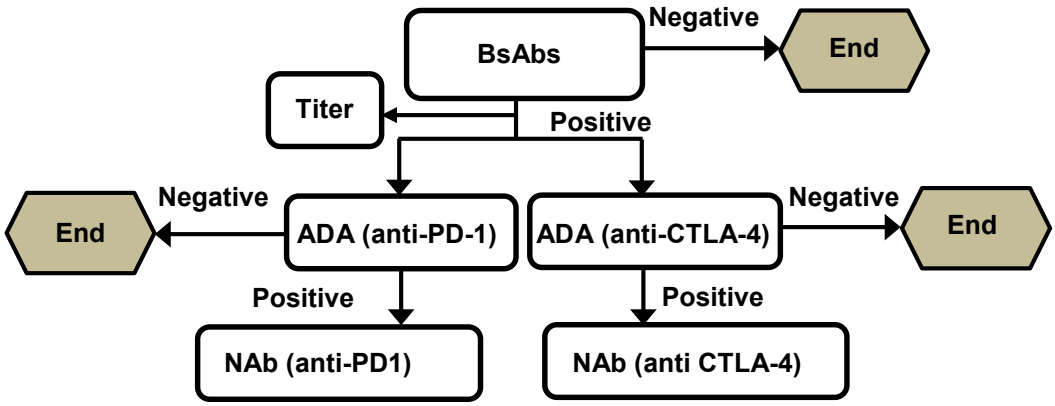



**Figure 1. Laboratory testing procedure for immunogenicity of bispecific antibodies**

The flowchart indicates that aPD-1/aCTLA-4 and their corresponding NAb results will only be tested when BsAbs result is positive. And only when aPD-1 or aCTLA-4 is tested as positive, their corresponding NAb result will be tested. Titer is also only tested when BsAbs result is positive.

## IMMUNOGENICITY ANALYSIS

ADIS should contain the testing results by presenting one record per subject per indicator per timepoint which can be directly inherited from SDTM IS. This could follow conventional way to mapping variables of BDS ADaM. Here is focusing on the specific analysis of immunogenicity. Part of potential analysis tables of bispecific antibody are shown in Table 1, Table 2 and Table 3 Please note that ADA/NAb status definitions and classifications are study-specific, as diagnostic criteria may differ among sponsors and analytical platforms.

Table 1 shows the summary analysis of immunogenicity incidence. Definitions can be found in the footnote of the table.

| | Results | BsAbs (N=xx) n(%) | PD-1 (N=xx) n(%) | CTLA-4 (N=xx) n(%) |
|---|---|---|---|---|
| Baseline | Evaluable | xx | xx | xx |
| | Baseline ADA Negative | xx (xx.x) | x (xx.x) | x (xx.x) |
| | Baseline ADA Positive | xx (xx.x) | x (xx.x) | x (xx.x) |
| Post-baseline | Evaluable | xx | xx | xx |
| | ADA Positive[1] | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| | Treatment-induced [2] | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| | Treatment-boosted [3] | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| | ADA Negative[4] | xx (xx.x) | xx (xx.x) | xx (xx.x) |

[1] ADA Positive: subjects with treatment-induced or treatment-boosted.
[2] Treatment-induced: subjects with ADA negative at baseline and ADA positive after first administration.
[3] Treatment-boosted: subjects with ADA positive both at baseline and after first administration and the post-baseline titer increases to a higher level (9-fold or higher).
[4] ADA Negative: subjects with no treatment-induced and no treatment-boosted ADA response.

**Table 1. Summary of immunogenicity results**

Exploratory analyses of safety and efficacy influenced by immunogenicity are often necessary. Table 2 presents an approach to analyzing safety (or efficacy) within populations across different ADA/NAb statuses. The definitions of 'ADA Positive' population and 'ADA Negative' population are the same as those in Table 1.

| System Organ Class Preferred Term | ADA Positive (N=xx) n (%) | ADA Negative (N=xx) n(%) | NAb Positive[1] (N=xx) n(%) | NAb Negative[2] (N=xx) n(%) | ADA Negative + NAb Negative (N=xx) n(%) |
|---|---|---|---|---|---|
| TEAE | xx (xx.x) | xx (xx.x) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| <SOC #1> | xx (xx.x) | xx (xx.x) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| <PT #1-1> | xx (xx.x) | xx (xx.x) | xx (xx.x) | xx (xx.x) | xx (xx.x) |

[1] NAb Positive: ADA positive subjects with post-baseline NAb positive results.
[2] NAb Negative: ADA positive subjects with no post-baseline NAb positive results.

**Table 2. Analysis of safety (efficacy is similar) results influenced by immunogenicity**

Sometimes, time-to-event analysis is also required for immunogenicity. Table 3 shows the analysis of time from first ADA-positive testing result to negative-conversion testing results.

| Status of ADA | Statistics | BsAbs (N=xx) n(%) | PD-1 (N=xx) n(%) | CTLA-4 (N=xx) n(%) |
|---|---|---|---|---|
| ADA Positive | Duration of ADA Positive (Week) [1] | xx | xx | xx |
| | Median (95%CI) | xx (xx.x) | xx (xx.x) | xx (xx.x) |

[1] Median of duration of ADA positive is estimated by Kaplan-Meier Method.

**Table 3. Analysis of duration of ADA-positive**

## PARAMETER DESIGN OF ADA/NAB STATUS

As per table types mentioned above, parameter settings in ADIS should distinguish the information among 1) different antibodies, 2) and the information regarding various ADA or NAb statuses. Please note that categorizing ADA or NAb positive/negative must also be considered.

Complicated information poses challenges in designing ADIS mapping rules. Table 4 demonstrates a conventional approach to storing all information – by adding multiple PARAM/PARAMCD values to distinguish antibody types, ADA/NAb indicator types, and various statuses displayed in AVALC – this method presents limitations. Specially, 1) Filtering ADA/NAb POSITIVE/NEGATIVE conditions directly from AVALC in table programming code is suboptimal. 2) PARAMCD becomes difficult to constrain within 8 bytes due to excessive information in PARAM.

| PARAM | AVALC |
|---|---|
| BSABS ADA STATUS | Treatment-induced ADA |

| PARAM | AVALC |
|---|---|
| | /Treatment-boosted ADA<br>/ADA Negative |
| BSABS NAB STATUS | NAb Positive with ADA Positive<br>/NAb Negative with ADA Positive<br>/ADA Negative |
| PD-1 ADA STATUS | Treatment-induced ADA<br>/Treatment-boosted ADA<br>/ADA Negative |
| PD-1 NAB STATUS | NAb Positive with ADA Positive<br>/NAb Negative with ADA Positive<br>/ADA Negative |
| CTLA-4 ADA STATUS | Treatment-induced ADA<br>/Treatment-boosted ADA<br>/ADA Negative |
| CTLA-4 NAB STATUS | NAb Positive with ADA Positive<br>/NAb Negative with ADA Positive<br>/ADA Negative |

**Table 4. Parameter name presents both antibody category and ADA/NAb category. And status of 'POSITIVE' or 'NEGATIVE' is not so clear by using AVALC only.**

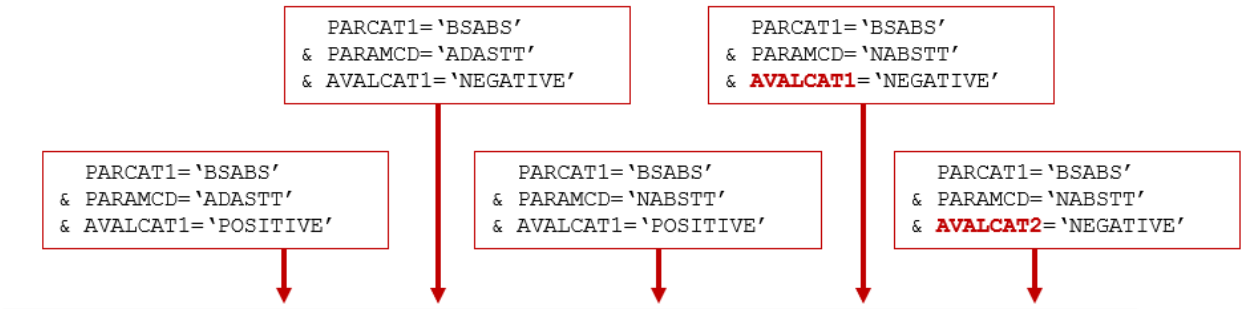
If ADIS in Table 4 is used to derive the populations of 'ADA Positive', 'ADA Negative', NAb Positive', 'NAb Negative' and 'ADA Negative+NAb Negative', the 'where' condition might be overly complex and prone to mistaking, as both PARAM and AVALC contain extensive information. This is particularly true for 'ADA Positive' and 'ADA Negative + NAB Negative' populations, where the code must account for two different AVALC values.

Because of the drawbacks, it's preferable to import categorical variables defined in ADaM Implementation Guide (ADaM IG) – PARCATy and AVALCATy (Jack Shostak, 2017). PARCATy categorizes the antibodies described in PARAM, while AVALCATy categorizes the 'POSITIVE' and 'NEGATIVE' groups of AVALC. Table 5 illustrates the use of these categorical variables. Additionally, the approach facilitates limiting the length of PARAMCD to 8 bytes (Karl Miller et al., 2013).

| Dataset | PARCAT1 | PARAM | PARAMCD | AVALC | AVALCAT1 | AVALCAT2 |
|---|---|---|---|---|---|---|
| ADIS | BSABS | ADA STATUS | ADASTT | Treatment-induced ADA<br>/Treatment-boosted ADA | POSITIVE | POSITIVE |
| ADIS | BSABS | ADA STATUS | ADASTT | ADA Negative | NEGATIVE | NEGATIVE |
| ADIS | BSABS | NAB STATUS | NABSTT | NAb Positive with ADA Positive | POSITIVE | POSITIVE |
| ADIS | BSABS | NAB STATUS | NABSTT | NAb Negative with ADA Positive | NEGATIVE | NEGATIVE |
| ADIS | BSABS | NAB STATUS | NABSTT | ADA Negative | | NEGATIVE |
| ADIS | PD-1 | ADA STATUS | ADASTT | Treatment-induced ADA<br>/Treatment-boosted ADA | POSITIVE | POSITIVE |
| ADIS | PD-1 | ADA STATUS | ADASTT | ADA Negative | NEGATIVE | NEGATIVE |
| ADIS | PD-1 | NAB STATUS | NABSTT | NAb Positive with ADA Positive | POSITIVE | POSITIVE |
| ADIS | PD-1 | NAB STATUS | NABSTT | NAb Negative with ADA Positive | NEGATIVE | NEGATIVE |
| ADIS | PD-1 | NAB STATUS | NABSTT | ADA Negative | | NEGATIVE |
| ADIS | CTLA-4 | ADA STATUS | ADASTT | Treatment-induced ADA<br>/Treatment-boosted ADA | POSITIVE | POSITIVE |
| ADIS | CTLA-4 | ADA STATUS | ADASTT | ADA Negative | NEGATIVE | NEGATIVE |
| ADIS | CTLA-4 | NAB STATUS | NABSTT | NAb Positive with ADA Positive | POSITIVE | POSITIVE |
| ADIS | CTLA-4 | NAB STATUS | NABSTT | NAb Negative with ADA Positive | NEGATIVE | NEGATIVE |
| ADIS | CTLA-4 | NAB STATUS | NABSTT | ADA Negative | | NEGATIVE |

**Table 5. PARCATy can categorize the antibodies and AVALCATy can categorize 'POSITIVE' and 'NEGATIVE' values. The AVALCAT2 differs from the AVALCAT1 in the categorization of NAb-negative population. The AVALCAT1 includes only NAb-negative subjects who are ADA-positive, while the AVALCAT2 also encompasses those who are ADA-negative.**

Taking Table 2 as an example and based on the ADIS design in Table 5, each variable carries specific information, making it easier and clearer to filter the conditions, which are listed in the Figure 2. Antibody is filtered using PARCAT1 while ADA or NAb status can be selected by filtering on PARAM/PARAMCD. Additionally, the 'POSITIVE' or 'NEGATIVE' status can be simply selected via AVALCATy. Note that AVALCAT1 does not include 'ADA Negative' in the NAb status because Group 4 only considers NAb status within the ADA positive population. Meanwhile, since the ADA negative population should still be included in Group 5, the AVALCAT2 is specially designed for conveniently selecting the 'ADA Negative+NAb Negative' population.




| System Organ Class<br>Preferred Term | ADA Positive<br>(N=xx)<br>n (%) | ADA Negative<br>(N=xx)<br>n(%) | NAb Positive[1]<br>(N=xx)<br>n(%) | NAb Negative[2]<br>(N=xx)<br>n(%) | ADA Negative +<br>NAb Negative<br>(N=xx)<br>n(%) |
|---|---|---|---|---|---|
| TEAE | xx (xx.x) | xx (xx.x) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| <SOC #1> | xx (xx.x) | xx (xx.x) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| <PT #1-1> | xx (xx.x) | xx (xx.x) | xx (xx.x) | xx (xx.x) | xx (xx.x) |

**Figure 2. Conditions to filter different analysis populations.**

Additionally, this approach provides greater flexibility in handling varying ADA/NAb status definitions across different study designs. The AVALC values can be easily adapted to accommodate study-specific criteria, while the ADA/NAb POSITIVE/NEGATIVE status remains straightforward to distinguish by filtering on AVALCATy. Introducing different AVALCATy allows for more flexible grouping based on AVALC. Moreover, adding indicators in PARAM for single antibodies defined in PARCATy further clarifies the analysis and simplifies table/figure programming.

## PARAMETER DESIGN OF TIME-TO-EVENT ANALYSIS

If time-to-event analysis in Table 3 or other specialized analysis is needed, we can also directly add new PARAM in ADIS (Table 6) or create TTE analysis datasets (Table 7) to satisfy the need.

| Dataset | PARCAT1 | PARAM | PARAMCD | AVALC |
|---|---|---|---|---|
| ADIS | BSABS | START DATE OF POST-BASELINE ADA POSITIVE | FSTAPDT | DDMMMYYYY |
| ADIS | BSABS | POST-BASELINE ADA POSITIVE END FLAG | APNEGFL | N/Y |
| ADIS | BSABS | POST-BASELINE ADA POSITIVE END DATE | APNEGDT | DDMMMYYYY |

**Table 6. Directly add new PARAM in ADIS.**

| Dataset | PARCAT1 | PARAM | PARAMCD | AVAL | STARTDT | ADT | CNSR |
|---|---|---|---|---|---|---|---|
| ADTTE | BSABS | DURATION OF ADA POSITIVE | DOAPW | ADT-STARTDT+1 | <Start date of post-baseline ADA positive> | < Post-baseline ADA Positive End date > | 0 |
| ADTTE | BSABS | DURATION OF ADA POSITIVE | DOAPW | ADT-STARTDT+1 | <Start date of post-baseline ADA positive> | <Last sample collecting date> | 1 |

**Table 7.Create TTE analysis dataset to meet the time-to-event analysis request.**

## CONSIDERATION OF COMPLIANCE WITH STANDARD

According to ADaM IG requirements, the relationship between PARAM and PARCATy must follow a many-to-one mapping structure. This rule is also validated by Pinnacle 21 (P21).

The variable design proposed in Table 5 may trigger a P21 error note: “Inconsistent value for PARCATy within a unique PARAMCD”. This occurs because P21 employs a straightforward text matching algorithm to verify many-to-one relationships (illustrated in Figure 3). To address this, we can give an explanation in Analysis Data Reviewer’s Guide (ADRG). Since the design really offers a convenient way for programmers, it worth weighing the pros and cons between strictly following standard and convenience of analysis TLF coding.

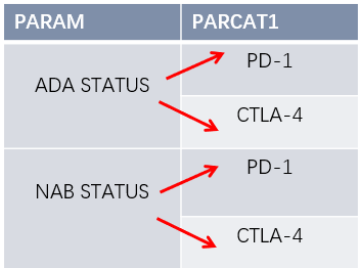



**Figure 3. P21 checks many-to-one mapping structure**

## CONCLUSION

Importing categorical variables in immunogenicity analysis dataset (ADIS) helps programmers to store the complicated information in a clever way when handling intricate immunogenicity analysis requirements and also solve the PARAMCD design when considering 8 bytes limitation. PARCATy can help categorize different antibody ingredients of bispecific antibodies or multispecific antibodies. And AVALCATy can categorize different definitions of ADA/NAb status. The combination of PARCATy, PARAM, AVALCATy, and AVALC makes TF coding easier and reduce the possibility of mistaking the information. Although the strategy mentioned in this paper may not fully comply with current ADaM IG specifications, it offers a more user-friendly design for the analysis dataset. The author believes it’s worth a careful cost-benefit analysis to select the strategy that best facilitates data analysis.

## REFERENCES

Karl Miller et al., (2013) Implementation Considerations for PARAM/PARAMCD Using ADaM BDS. PharmaSUG 2013 (DS04)

Jack Shostak. (2017) ADaM Grouping: Groups, Categories, and Criteria. Which Way should I Go? PharmaSUG 2017 (DS17)

Sabarinath Sundaram et al., (2023) Handling Anti-Drug Antibody (ADA) Data for Efficient Analysis. PharmaSUG 2023 (DS161)

## RECOMMENDED READING

- *Analysis Data Model Implementation Guide Version 1.3*

## CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Yiwei Jiang

Qilu Pharmaceutical
No.199 Kaibin Road, Xuhui District, Shanghai
yiwei.jiang@qilu-pharma.com

Liqin Jin
Qilu Pharmaceutical
No.199 Kaibin Road, Xuhui District, Shanghai
liqin.jin@qilu-pharma.com

Yingying Yan
Qilu Pharmaceutical
No.199 Kaibin Road, Xuhui District, Shanghai
yingying.yan@qilu-pharma.com

Tao Zhang
Qilu Pharmaceutical
No.199 Kaibin Road, Xuhui District, Shanghai
Tao26.zhang@qilu-pharma.com