Modelling of Anti-Drug Antibodies in SENDIG 3.0

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Introduction

Formation of anti-drug antibodies (ADA) interfere with the intended pharmacokinetic profile of a treatment. Hence it is important information when interpreting data from many studies, both clinical and nonclinical. The modelling of ADA endpoints with use of controlled terminology have proven to be difficult.

CDISC is underway with an approach for modelling of ADA in the IS domain (in dialogue with the author group of this poster). This solution split the description of ADA endpoints into a combination of generic and non-generic components.

The IS domain is not part of SENDIG 3.0 (or 3.1). This poster presents ADA modelling in the SEND LB domain. This approach is an independent adaptation from the currently provisional IS domain ADA modelling, allowing for submission of ADA endpoints from nonclinical studies under SENDIG 3.0. As an adaptation of the IS ADA modelling, the presented approach is designed to facilitate transition to any customizations of SEND domains enabled by SENDIG 3.1 (expanded LB or full custom domain including but not limited to IS in SEND).

Table 1: Proposed modelling of 12 ADA endpoints in SENDIG v3.0 using the LB domain

ADA Endpoint description		ADA modelling in LB (SENDIG 3.0)			
		LBTEST	LBTESTCD	LBCAT	SUPPLB QVAL for = QNAM =ABBTAR / QLABEL = Antibody Binding Target indicating specificity of measured ADA*
Binding antibodies	**Screening** for binding antidrug antibodies	Binding ADA - Screening	ADA_BABS	Antidrug antibodies	Free text description of Antibody Binding Target - i e. specificity towards test article (including specific epitopes if relevant)
	Confirmation of detection of binding antidrug antibodies	Binding ADA - Confirmation	ADA_BABC	Antidrug antibodies	Free text description of Antibody Binding Target - i e. specificity towards test article (including specific epitopes if relevant)
	Quasi-quantification of binding antidrug antibodies	Binding ADA - Quasi-quantification	ADA_BABQ	Antidrug antibodies	Free text description of Antibody Binding Target - i e. specificity towards test article (including specific epitopes if relevant)
Neutralizing antibodies	**Screening** for neutralising antidrug antibodies	Neutralizing ADA - Screening	ADA_NABS	Antidrug antibodies	Free text description of Antibody Binding Target - i e. specificity towards test article (including specific epitopes if relevant)
	Confirmation of neutralising antidrug antibodies	Neutralizing ADA - Confirmation	ADA_NABC	Antidrug antibodies	Free text description of Antibody Binding Target - i e. specificity towards test article (including specific epitopes if relevant)
	Quasi-quantification of neutralising antidrug antibodies	Neutralizing ADA - Quasi-quantification	ADA_NABQ	Antidrug antibodies	Free text description of Antibody Binding Target - i e. specificity towards test article (including specific epitopes if relevant)
Cross reactive binding antibodies	**Screening** for crossreactive binding antidrug antibodies at screening	Cross-React Binding ADA - Screening	ADA_XS	Antidrug antibodies	Free text description of Antibody Binding Target(s) - i e. specificity towards test article and cross reactivity to specific endogenous structures resembling test article (e.g. coagulation factors, insulin, GLP-1,...)
	Confirmation of detection of crossreactive binding antidrug antibodies	Cross-React Binding ADA - Confirmation	ADA_XC	Antidrug antibodies	Free text description of Antibody Binding Target(s) - i e. specificity towards test article and cross reactivity to specific endogenous structures resembling test article (e.g. coagulation factors, insulin, GLP-1,...)
	Quasi-quantification of crossreactive binding antidrug antibodies	Cross-React Binding ADA - Quasi-quant	ADA_XQ	Antidrug antibodies	Free text description of Antibody Binding Target(s) - i e. specificity towards test article and cross reactivity to specific endogenous structures resembling test article (e.g. coagulation factors, insulin, GLP-1,...)
Cross reactive neutralizing antibodies	**Screening** for crossreactive neutralising antidrug antibodies	Cross-React Neutraliz ADA - Screening	ADA_XNS	Antidrug antibodies	Free text description of Antibody Binding Target(s) - i e. specificity towards test article and cross reactivity to specific endogenous structures resembling test article (e.g. coagulation factors, insulin, GLP-1,...)
	Confirmation of crossreactive neutralising antidrug antibodies	Cross-React Neutraliz ADA - Confirmation	ADA_XNC	Antidrug antibodies	Free text description of Antibody Binding Target(s) - i e. specificity towards test article and cross reactivity to specific endogenous structures resembling test article (e.g. coagulation factors, insulin, GLP-1,...)
	Quasi-quantification of crossreactive neutralising antidrug antibodies	Cross-React Neutraliz ADA - Quasi-quant	ADA_XNQ	Antidrug antibodies	Free text description of Antibody Binding Target(s) - i e. specificity towards test article and cross reactivity to specific endogenous structures resembling test article (e.g. coagulation factors, insulin, GLP-1,...)

*Specificity for antibodies is currently being considered by CDISC for a standard or non-standard variable. This poster only considers it as a non-standard variable for SEND.
The descriptions included in this poster is intended to resemble the proposals considered in CDISC at the time of poster submission.

Why is ADA modelling difficult?

The difficulty arise from the observation that the antibodies measured and reported as ADA endpoints are inherently drug specific. The modelling are further complicated as the overall status of an animal or trial subject is the result of a tiered application of assays (Figure 1) The strategy for the cascaded approach may differ from company to company, but the full picture of the general principle spans at least 12 generic endpoints laid out as 2x2x3 (Table 1):

- Binding ADA versus Neutralizing ADA
- Cross-Reactive ADA versus non-Cross-reactive ADA
- Different assays for Screening, Confirmation, and Quasi-quantification

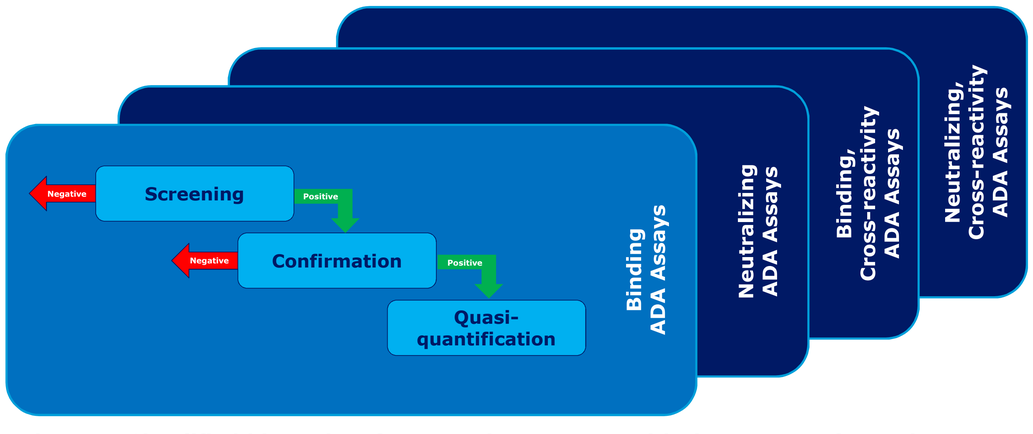

Figure 1: Simplified hierarchy of ADA testing strategy with three assays for each of four categories of ADAs. Although Assay strategies will differ between companies, all can be reported under the scheme laid out in this poster

Purpose of non-standard variable for ADA specificity?

Why could ADA not be described with the generic TEST/TESTCD component and rely on the study context for the specificity – without the non-standard variable for ADA specificity?

First of all, endpoint relying only on the generic component would have different meaning from compound to compound and study to study – but that was the overall idea with the question. Further, some studies contain combination therapies, some studies investigate different epitopes of a single compound and lastly, some studies may addressed cross-reactivity for more than one endogenous substance. As ADA specificity may be subject to such variation, it should be recognised as a separate modelling entity requiring support for standardised modelling. Currently this must be via a non-standard variable – similarly to how --RESMOD and –CALCN is currently used in SEND.

Going forward

As laid out in the introduction, SENDIG 3.1 allows for a broader range of options including custom domains. However the specific scenarios depend on how IT vendors move forward from the current widely implemented hard coding of domains and table structures. However, standardization in modelling would benefit not only reviewers, but also Sponsors, CROs and IT vendors.

Another discussion pending, is whether the overall ADA Induction Status of the subject should be represented in SEND. This topic requires further discussion and investigation.

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