

How to deal with Immunogenicity Data in the clinical trail?

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What is Immunogenicity?

Immunogenicity is the ability of a foreign substance, such as an antigen, to provoke an immune response in the body of a human or other animal.

- Wanted: Vaccines
- Unwanted: anti-drug-antibodies (ADAs)

Why Immunogenicity information is important in the clinical trail?

Key to a successful and safe biopharmaceutical drug development program

Therapeutic Antibodies, enzyme therapies, peptides and combination products can elicit an immune response that may impact their **safety** and **efficacy**.

Why Immunogenicity information is important in the clinical trail?

Key to a successful and safe biopharmaceutical drug development program

Unwanted:

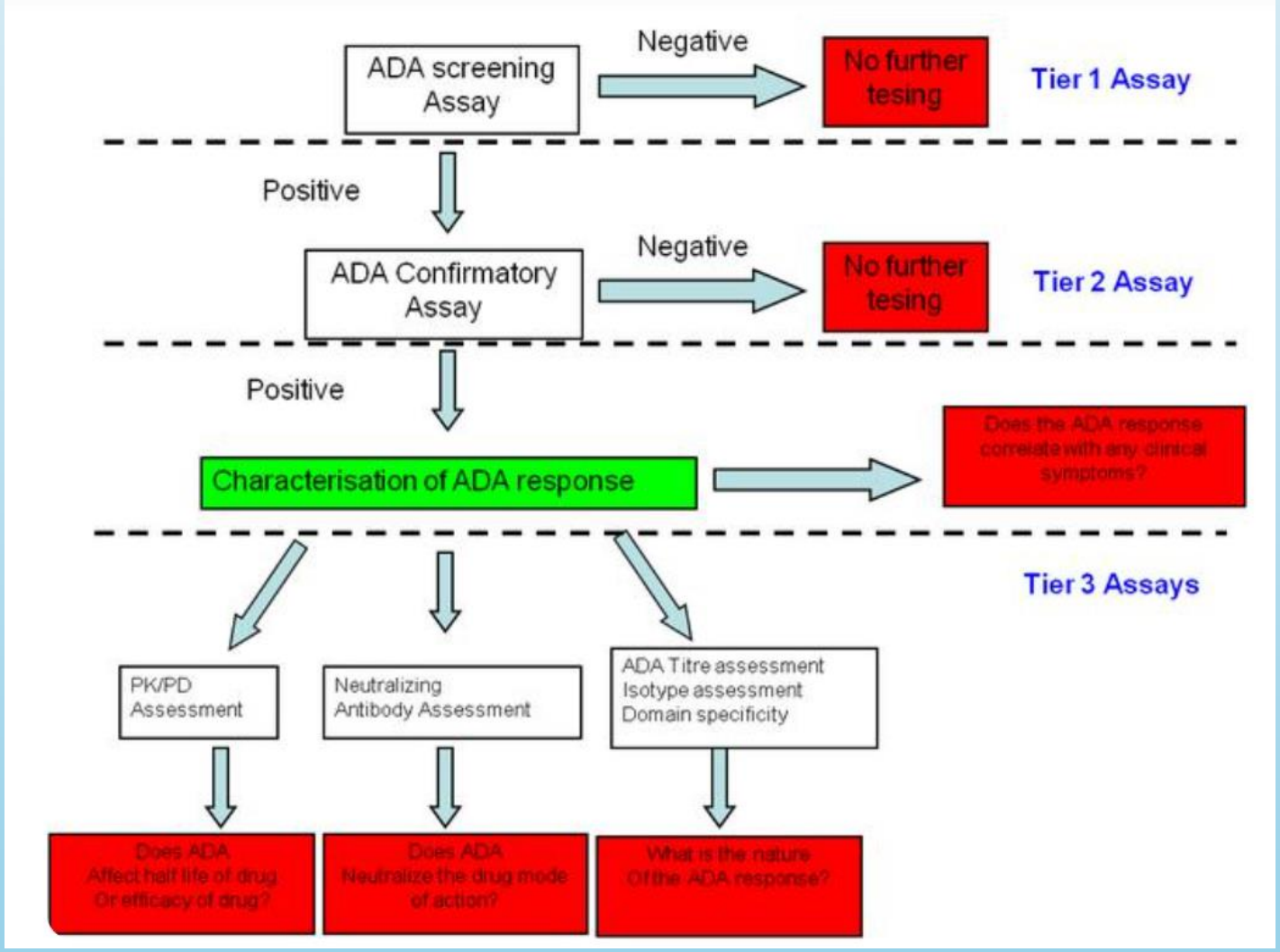
- ADAs: Anti-drug antibody

- Nabs: Neutralizing antibody

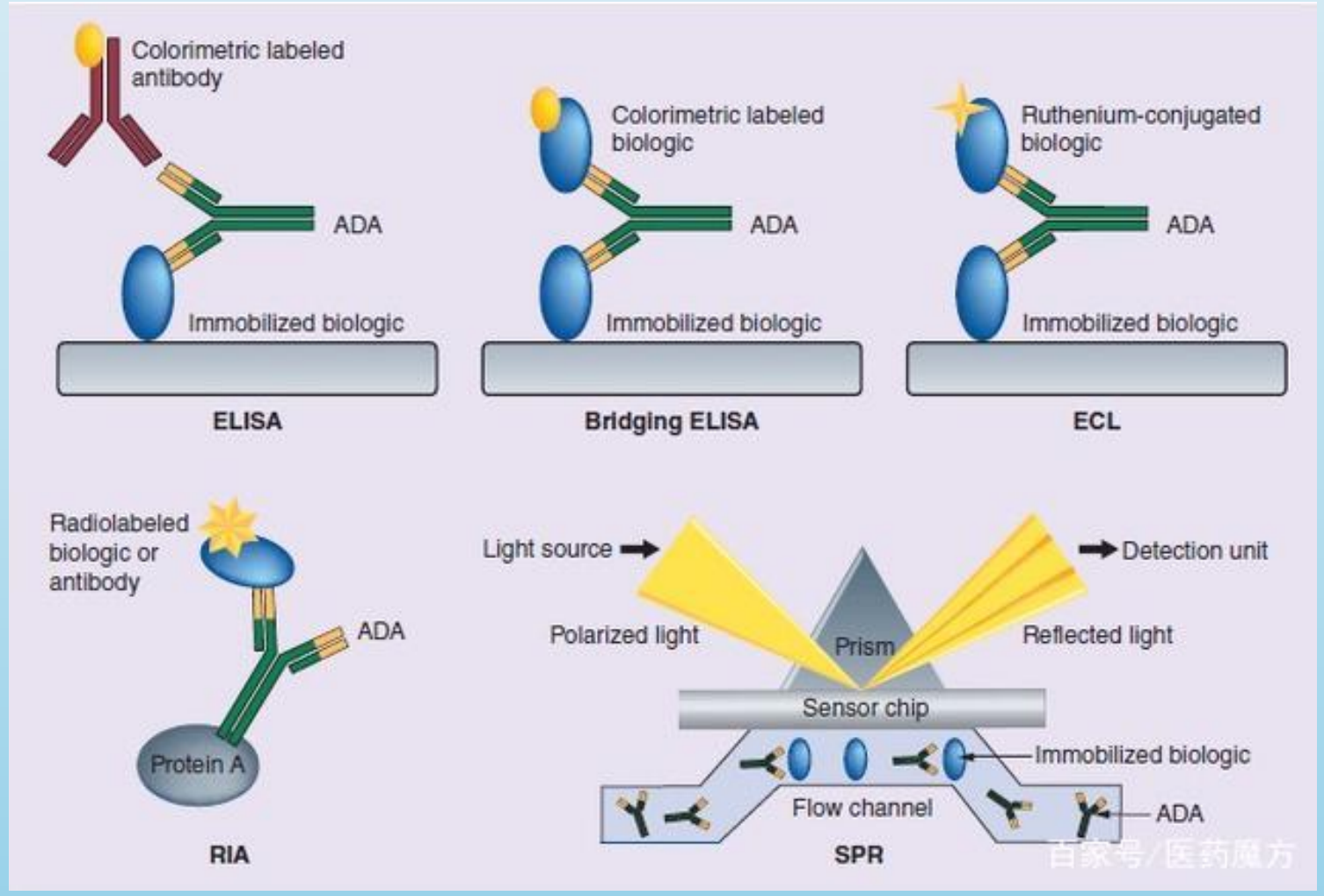
WHAT IS IMMUNOGENICITY TESTING

Immunogenicity assays provide a way to measure the potential immune responses of biologics and biosimilars. Often a single biologic will require a panel of assays to produce a thorough picture of potential immunogenicity. The FDA stipulates that assays should be designed in such a way that they provide **sufficient sensitivity**, are free from confounding interference, can detect physiological consequences, and account for potential risks based on the profile of the therapeutic and the target patient population.

MULTI-TIERED APPROACH TO ANTI-DRUG ANTIBODY TESTING



COMMON ASSAYS FOR ADA DETECTION



ASSAYS FOR NAb Activity

- cell-based bioassays
- non-cell-based competitive ligand binding assays

ADA screening and confirmatory assays[†]			
ELISA	ADAs captured by immobilized biologic and detected using a colorimetric labeled antibody	– Convenient (ease of use) – High-throughput – Inexpensive	– High chance of false-positive results – Loss of low-affinity ADAs during washes – High background – Not suitable for detection of ADAs against mAbs
Bridging ELISA	ADAs captured by immobilized biologic and detected with colorimetric labeled biologic	– More specific and selective than ELISA – Can be used where the biologic is a mAb – High-throughput	– Loss of low-affinity ADAs during washes
ECL	ELISA or Bridging ELISA technique with a ruthenium-conjugated antibody or biologic for detection, respectively	– Increased sensitivity vs. colorimetric conjugates – Bridging format can be used where the biologic is a mAb – High-throughput	– Reagents can be expensive – Loss of low-affinity ADAs during washes
RIA	ADAs captured on protein A beads and detected with a radiolabeled antibody or biologic	– More sensitive than ELISA – Moderate throughput – Inexpensive	– Radioactivity may deter investigators – Reagents require specific equipment and safety measures – Loss of low-affinity ADAs during washes
SPR	Sensor with immobilized biologic detects changes in mass following ADA binding	– Can detect low-affinity and rapidly dissociating ADAs – Can be used to determine ADA isotype	– May be less sensitive than other assays – Not for high-throughput – Expensive equipment and reagents
NAb detection			
Cell-based assay	Measures neutralization of cell responses using relevant cell lines	– Provides a functional biological readout – May be the preferred NAb assay of regulatory authorities	– High variability – Matrix interference – Low sensitivity – Low free drug tolerance – Longer assay time than ligand binding assays
Ligand binding assay	Measures neutralization of drug to target (e.g,. cellular receptor) binding	– Easier to implement and more sensitive and drug-tolerant than cell-based assays – Different detection systems (e.g., ELISA and ECL) can be used	– Does not provide the functional readout of cell-based assays

IS-Immunogenicity Specimen Assessments

A findings domain for assessments that determine whether a therapy induced an immune response.

	Identifier					
ISTESTCD	Immunogenicity Test/Exam Short Name	Char	(ISTESTCD)	Topic	Short name of the measurement, test, or examination described in ISTEST. It can be used as a column name when converting a dataset from a vertical to a horizontal format. The value in ISTESTCD cannot be longer than 8 characters, nor can it start with a number (e.g., "1TEST" is not valid). ISTESTCD cannot contain characters other than letters, numbers, or underscores.	Req
ISTEST	Immunogenicity Test or Examination Name	Char	(ISTEST)	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in ISTEST cannot be longer than 40 characters. Example: "Immunoglobulin E".	Req

IS

ISTESTCD	Immunogenicity Specimen Assessments Test Code	Terminology relevant to the immunogenicity specimen test codes of the CDISC Study Data Tabulation Model.
ADA_BAB	Binding Antidrug Antibody	A measurement of the binding antidrug antibody in a biological specimen. A binding antidrug antibody is an antibody that binds to a test article, and/or portion(s) of the test article.
ADA_NAB	Neutralizing Binding Antidrug Antibody	A measurement of the neutralizing binding antidrug antibody in a biological specimen. A neutralizing binding antidrug antibody is a type of ADA that binds to the functional portion of a test article leading to diminished or negated pharmacological activity.
ADA_NX	Neutraliz Cross-React Bind Antidrug AB; Neutralizing Cross-Reactive Binding Antidrug Antibody	A measurement of the neutralizing cross-reactive binding antidrug antibody in a biological specimen. A neutralizing cross-reactive binding antidrug antibody is a type of ADA that binds to an endogenous molecule that is structurally similar to an analogue test article and diminishes or negates its function.
ADA_X	Cross-Reactive Binding Antidrug Antibody	A measurement of the cross-reactive binding antidrug antibody in a biological specimen. A cross-reactive binding antidrug antibody is a type of ADA that binds to the endogenous molecule that is structurally similar to an analogue test article.
EVIGGASC	EBOV Specific IgG AB Secreting Cells	A measurement of the Ebola virus specific IgG antibody secreting cells in a biological specimen.
EVIGMASC	EBOV Specific IgM AB Secreting Cells	A measurement of the Ebola virus specific IgM antibody secreting cells in a biological specimen.
H1IGGASC	H1 Specific IgG ASCs; H1 Specific IgG Antibody Secreting Cells	A measurement of the H1 specific IgG antibody secreting cells in a biological specimen.
H3IGGASC	H3 Specific IgG ASCs; H3 Specific IgG Antibody Secreting Cells	A measurement of the H3 specific IgG antibody secreting cells in a biological specimen.
HIV1SR	HIV-1 Seroreactivity	A measurement of the HIV-1 seroreactivity in a biological specimen.
HIV2SR	HIV-2 Seroreactivity	A measurement of the HIV-2 seroreactivity in a biological specimen.
IGMABSC	IgM Antibody Secreting Cells	A measurement of the total IgM antibody secreting cells in a biological specimen.
TIGGASC	Total IgG ASCs; Total IgG Antibody Secreting Cells	A measurement of the total IgG antibody secreting cells in a biological specimen.
TLYMPIDX	T-Lymphocyte Proliferation Index	A relative measurement (ratio or percentage) of T-lymphocyte proliferation due to stimulation by an antigen of interest to a non-stimulated T-lymphocyte proliferation control.

IS–Immunogenicity Specimen Assessments

is.xpt

Row	STUDYID	DOMAIN	USUBJID	ISSEQ	ISTESTCD	ISTEST	ISCAT	ISORRES	ISORRESU	ISSTRESC	ISSTRESN	ISSTRESU	ISSPEC	ISMETHOD	ISLOBXFL	ISLLOQ
1	ABC-123	IS	123457	1	HCAB	Hepatitis C Virus Antibody	SEROLOGY	3115.016	gpELISA unit/mL	3115.016	3115.016	gpELISA unit/mL	SERUM	ENZYME IMMUNOASSAY	Y	100
2	ABC-123	IS	123457	2	HCAB	Hepatitis C Virus Antibody	SEROLOGY	1772.78	gpELISA unit/mL	1772.78	1772.78	gpELISA unit/mL	SERUM	ENZYME IMMUNOASSAY		100
3	ABC-123	IS	123460	1	HCAB	Hepatitis C Virus Antibody	SEROLOGY	217.218	gpELISA unit/mL	217.218	217.218	gpELISA unit/mL	SERUM	ENZYME IMMUNOASSAY	Y	100
4	ABC-123	IS	123460	2	HCAB	Hepatitis C Virus Antibody	SEROLOGY	203.88	gpELISA unit/mL	203.88	203.88	gpELISA unit/mL	SERUM	ENZYME IMMUNOASSAY		100

IS-Immunogenicity Specimen Assessments

Row	STUDYID	DOMAIN	USUBJID	ISSEQ	ISTESTCD	ISTEST	ISCAT	ISORRES	ISORRESU	ISSTRESC	ISSTRESN	ISSTRESU	ISSPEC	ISMETHOD	ISLOBXFL	ISLLOQ
1	GHJ-456	IS	6017	1	PNPSAB14	Pneumococcal Polysacch AB Serotype 14	SEROLOGY	9.715	ug/mL	9.715	9.715	ug/mL	SERUM	ENZYME IMMUNOASSAY	Y	2.5
2	GHJ-456	IS	6017	2	VZVAB	Varicella-Zoster Virus Antibody	SEROLOGY	141.616	gpELISA unit/mL	141.616	141.616	gpELISA unit/mL	SERUM	ENZYME IMMUNOASSAY	Y	2.5
3	GHJ-456	IS	6017	3	PNPSAB14	Pneumococcal Polysacch AB Serotype 14	SEROLOGY	13.244	ug/mL	13.244	13.244	ug/mL	SERUM	ENZYME IMMUNOASSAY		2.5
4	GHJ-456	IS	6017	4	VZVAB	Varicella-Zoster Virus Antibody	SEROLOGY	870.871	gpELISA unit/mL	870.871	870.871	gpELISA unit/mL	SERUM	ENZYME IMMUNOASSAY		2.5

Clinical Immunogenicity Data Analysis

- Summary of immunogenicity analyses for all clinical studies with an immunogenicity component
- Results of linear or non-linear correlation analyses between ADA status and titers with PK, PD, efficacy and safety (Adverse event) data
- Drug levels measured in the samples tested for ADA
- Detailed discussion on the impact of pre=existing vs treatment-boosted vs treatment-induced
- Especially impact of pre-existing antibodies have on PK, PD, efficacy and safety

Thank You!

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