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CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

The role of clinical pharmacology in assessing clinical relevance of immunogenicity – a regulatory perspective

13th Open Scientific EIP symposium on Immunogenicity of Biopharmaceuticals (April 25-27, 2022)
EIP: European Immunogenicity Platform

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Disclaimer

- The presentation today should not be considered, in whole or in part as being statements of policy or recommendation by the United States Food and Drug Administration.

- Throughout the talk, representative examples of commercial products may be given to illustrate a methodology or approach to problem solving. No commercial endorsement is implied or intended.

Overview

- Introduction – the case for looking at immunogenicity impact on PK
- Recent advancements with enabling factors
- Approaches used to evaluate immunogenicity impact on PK
- Updates on two initiatives in Office of Clinical Pharmacology at FDA
- Summary

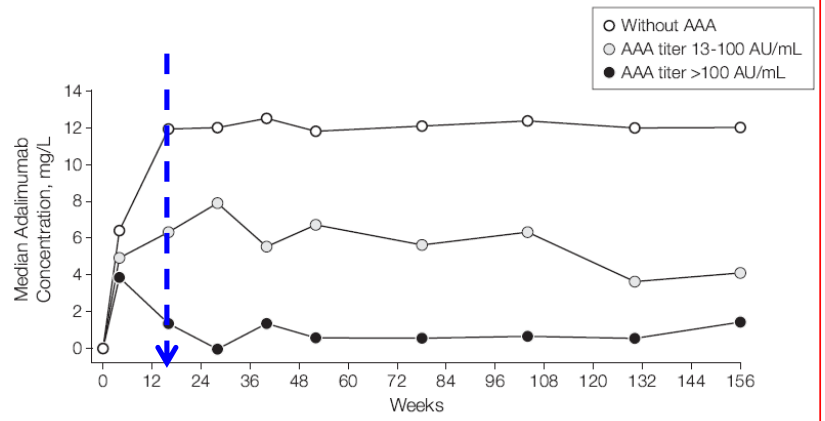
Why evaluate immunogenicity impact on PK?

PK is likely a more sensitive endpoint compared to efficacy endpoint

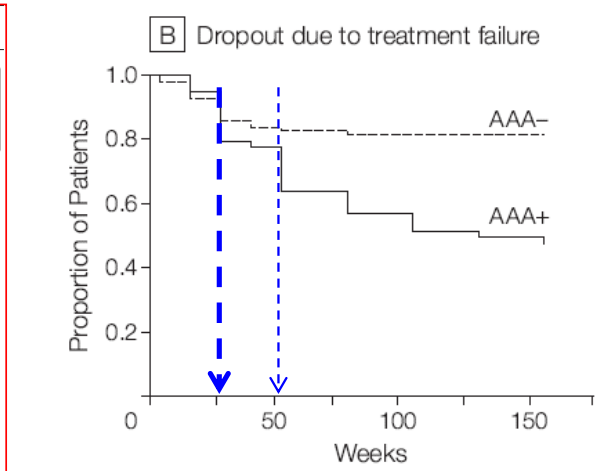
- Many literature reports regarding reduced drug concentrations, loss of efficacy due to ADA
- Example: antibody-positive patients - lower adalimumab concentration & higher dropout rate

Figure 4. Overall Patient Dropout and Dropout Due to Treatment Failure

Figure 2. Median Adalimumab Concentrations Over Time



Week	0	4	16	28	40	52	78	104	130	156
No. of patients										
Without AAA	196	187	177	164	145	139	131	118	107	93
AAA 13-100 AU/ml	45	43	42	37	34	34	28	24	19	17
AAA >100 AU/ml	31	31	28	27	22	19	16	14	11	8



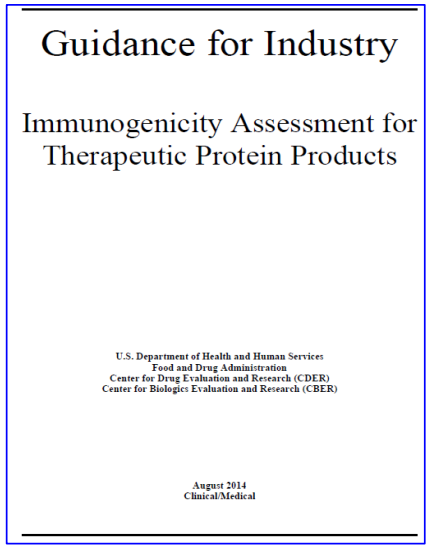
No. at risk

AAA–	196	151	135	118
AAA+	76	59	43	29

Bartelds *et al.* 2011 JAMA

FDA's multi-disciplinary review of immunogenicity impact starts from early IND interactions

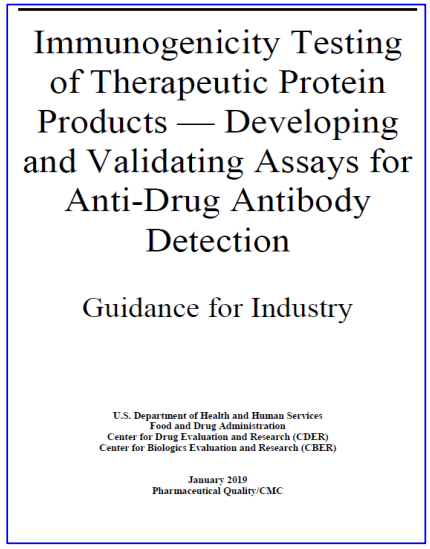
- Risk assessment
  - Patient-related factors
  - Product-related factors
- Multi-tiered testing strategy
  - Anti-drug antibodies (ADA)
  - Neutralizing ADA (NAb)
- Assay considerations
  - Sensitivity, specificity…
  - Drug-tolerance
- Study design considerations
  - Sampling design


Guidance for Industry

Immunogenicity Assessment for Therapeutic Protein Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

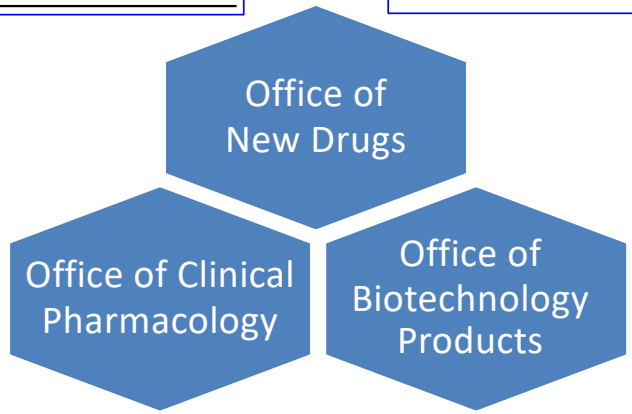
August 2014
Clinical/Medical


Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2019
Pharmaceutical Quality/CMC



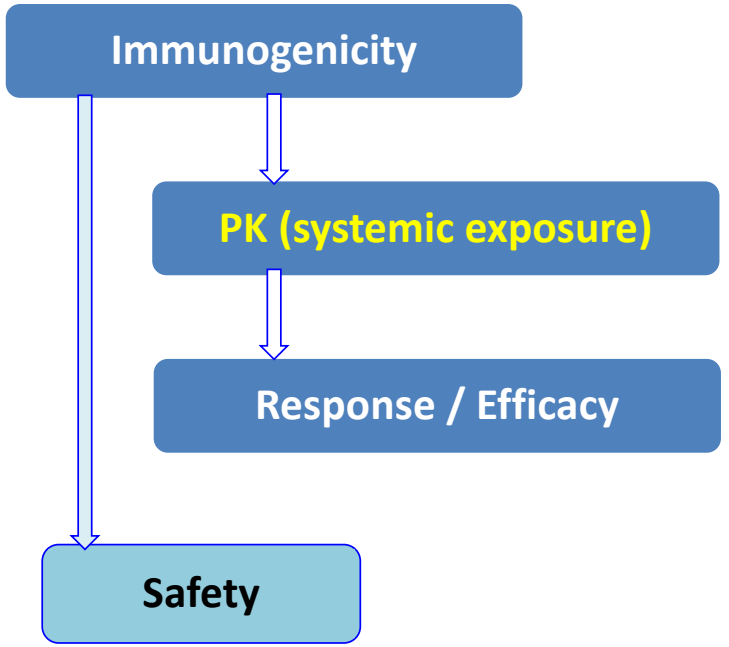
Immunogenicity information shared in product labeling

(why assess impact on PK? – systemic exposure drives efficacy)

6 ADVERSE REACTIONS
Immunogenicity

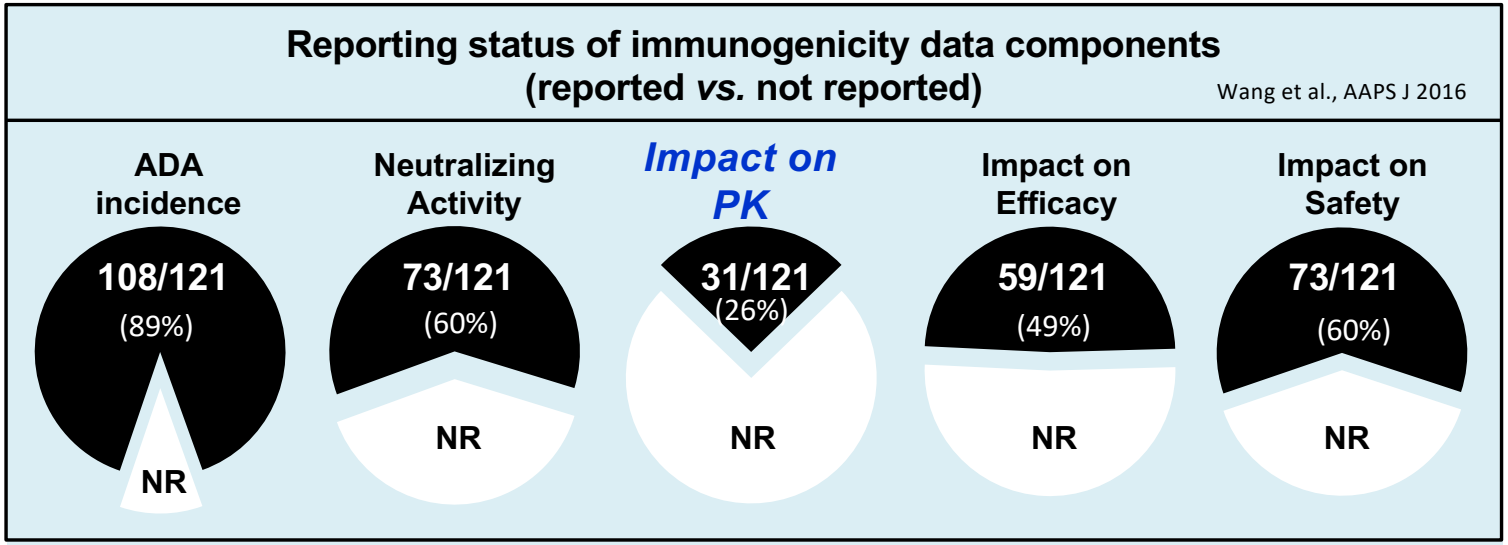
- Disclaimers
- Brief description of the clinical trials, study population, and dose/treatment
- Immunogenicity data
  1. Incidence of anti-drug antibodies (ADA)
  2. Neutralizing activity of ADA and incidence of neutralizing antibody (NAb)
  3. Impact on PK
  4. Impact on PD and efficacy
  5. Impact on safety
- Other information

Clinical impact?



Survey of immunogenicity data in labeling (02/2015)

- Immunogenicity incidence reported for ADA @ 90% & NAb @ 60% of 121 products
- Clinical impacts of ADA reported less frequently than incidences of ADA & NAb
- The impact of ADA on product PK was the least reported outcome
  - Given PK is likely a more sensitive metric for impact assessment, it's an under-utilized endpoint



NR: not reported; ADA: binding, anti-drug antibodies; PK: pharmacokinetics

Wang YM et al. The AAPS Journal, 2016, 18(2): 395-403

Clinical impact of ADA on PK vs. efficacy in labeling (02/2015)

- Limited data, n=31 products, with labeling info for impact on PK
- ADA can be clearing, sustaining, or having no effects at all
- Clearing ADA → reduced PK exposure → may led to reduced or loss of efficacy
- Congruence of effects on PK and efficacy confirms the value of assessing impact on PK

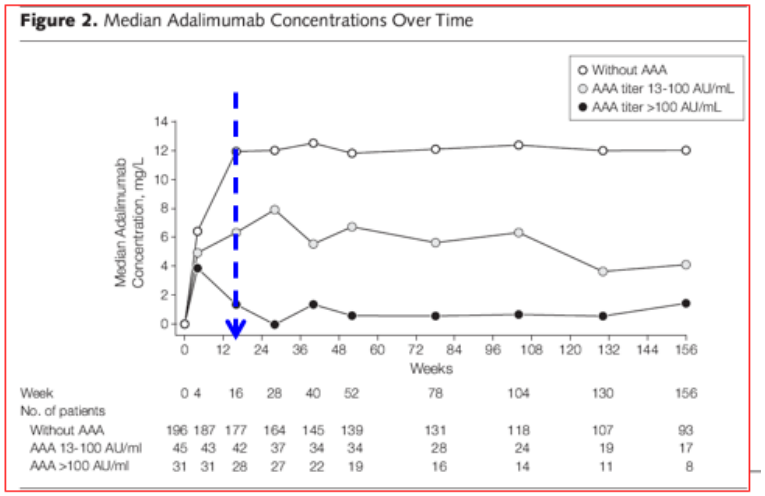
- **Clearing ADA: ↓ systemic exposure & efficacy (8/16)**
- **No change (↔) in systemic exposure & efficacy (6/16)**

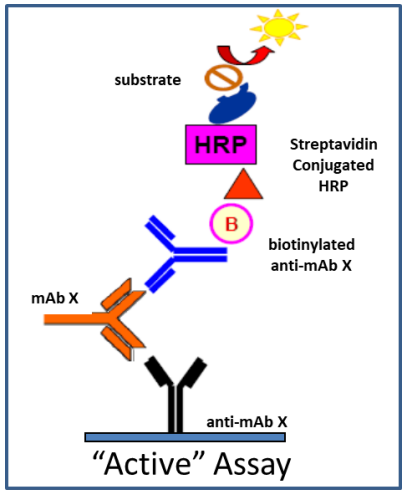
ADA type	Exposure (PK)	# of drugs	% Total # of drugs	Efficacy	# drugs reported	# drugs not reported
Clearing	↓	13	42%	↓	8	5
No effect	↔	10	32.2 %	↔	6	4
Sustaining	↑	6	19.4%	↓	1	4
				↔	1	
Inconclusive	Unknown	2	6.4%			2
Total # of drugs		31	100%		16*	15

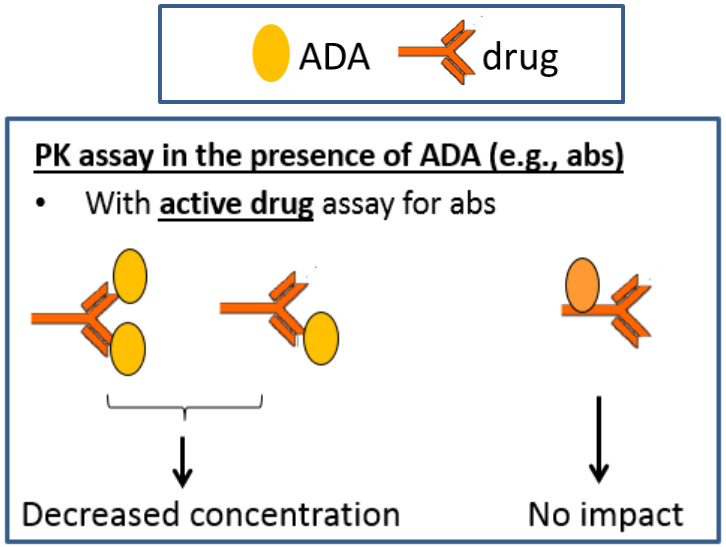
Wang YM et al. The AAPS Journal, 2016, 18(2): 395-403

Clearing ADA associated with decreased drug concentration
(understanding of PK assay facilitate interpreting ADA impact)

- Example: <u>mAb with clearing ADA</u> (& neutralizing)
- Observed ADA+ with lower drug concentrations
- **Hypothesis:** (1) ADA bind to Fab region and (2) PK assay requires Fab arm (one or more) free

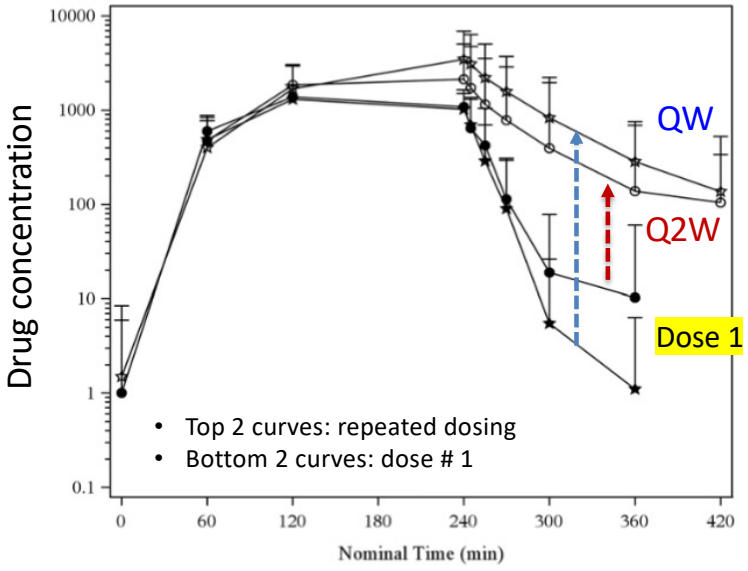


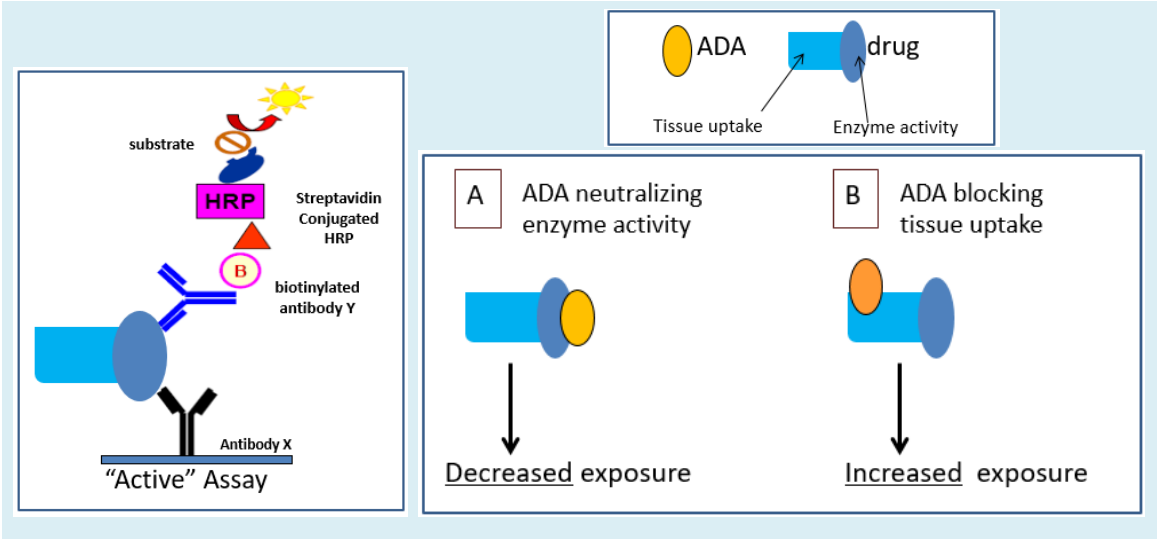




Sustaining ADA associated with increased drug concentration (understanding of PK assay facilitate interpreting ADA impact)

- Example: an enzyme replacement therapy with sustaining ADA
- Observed higher drug concentrations after repeated dosing
- **Hypotheses:** ADA that interfere with cellular uptake (elimination) of drug from circulation





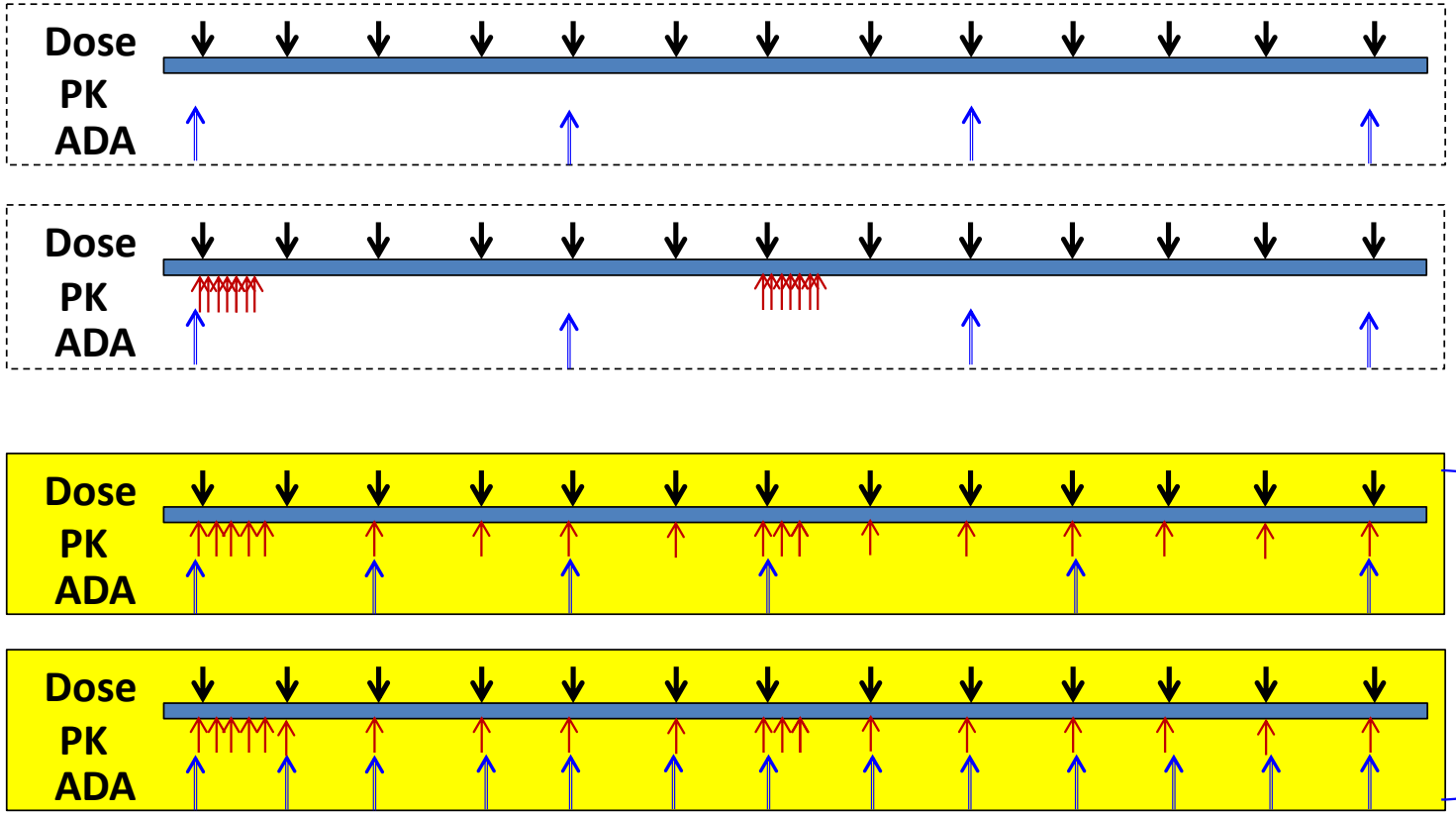
initiatives

Evaluating impact of ADA on PK – some enabling factors

- Resources: industry white papers, FDA guidance documents
- Best practices for immunogenicity assessment in clinical studies
  - Study design considerations
  - Data reporting
- Enhancement in ADA assay sensitivity, including improved drug tolerance
- Expansion of reporting from ADA+ vs. ADA- to including ADA titer data
- (Recent) Comprehensive communication via the integrated summary of immunogenicity (ISI) in regulatory submissions
- (Recent) Transition to standardized format for immunogenicity data submission, e.g., CDISC format for IS / ADIS data (.xpt)

enabling factors

Study design consideration: Coinciding ADA sampling with PK is important for assessing immunogenicity impact on PK



Immunogenicity data reporting varies across BLAs

Consistency: take sample level data → determine subject level ADA+/ADA-

- **Two categories:**
  - ADA: ADA+, ADA-
  - NAb: NAb+, NAb- (among ADA+)
  - At sample level & subject level
- **Three categories:**
  - ADA: ADA+, ADA-, ADA inconclusive
  - NAb: NAb+, NAb-, NAb inconclusive
  - At sample level & subject level

White Paper AAPSJ article - URL

Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides—Harmonized Terminology and Tactical Recommendations

G. Shankar,[1,14] S. Arkin,[2] L. Cocea,[3] V. Devanarayan,[4] S. Kirshner,[5] A. Kromminga,[6] V. Quarmby,[7] S. Richards,[8] C. K. Schneider,[9,10] M. Subramanyam,[11] S. Swanson,[12] D. Verthelyi,[5] and S. Yim[13]

enabling factors

- **> 3 categories**
  - ADA-
  - ADA inconclusive
  - Treatment-emergent (induced) ADA: TE-ADA
    - Baseline ADA-, postdose ADA+
  - Treatment-boosted (enhanced) ADA:TB-ADA
    - Baseline ADA+, postdose ADA+ (much higher)
  - Non-treatment-emergent ADA
    - Baseline ADA+, postdose ADA+ (not much higher)
  - NAb reported for samples & subjects with TE-ADA and TB-ADA

Recent experience indicates an increasing adoption of White Paper recommendations

Drug interference in ADA assay - a prevalent issue in BLAs approved 2005-2011

- A simplified view for illustrative purposes: single fixed value for drug tolerance
- ADA assay drug tolerance < trough concentration at steady state in 13 of 22 products

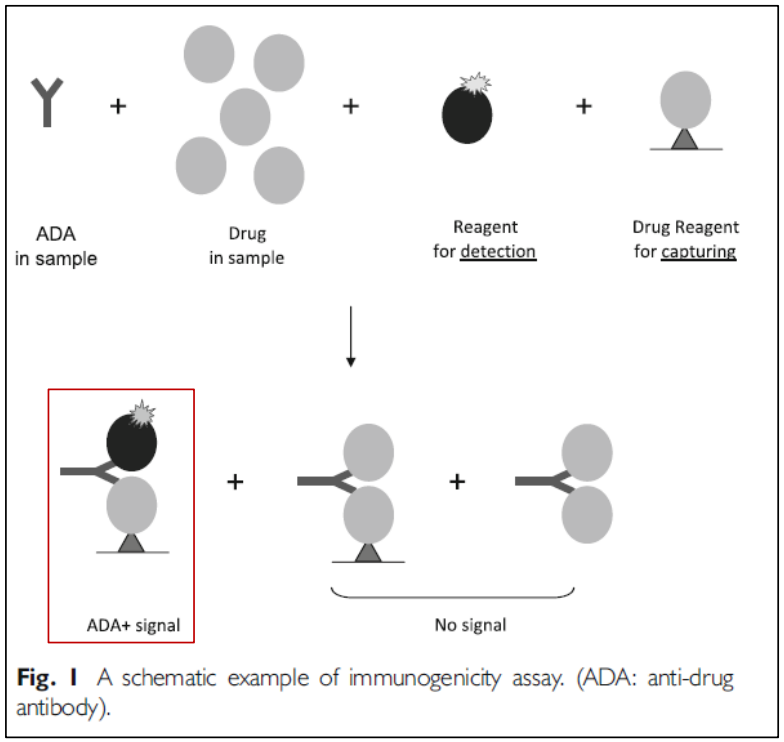
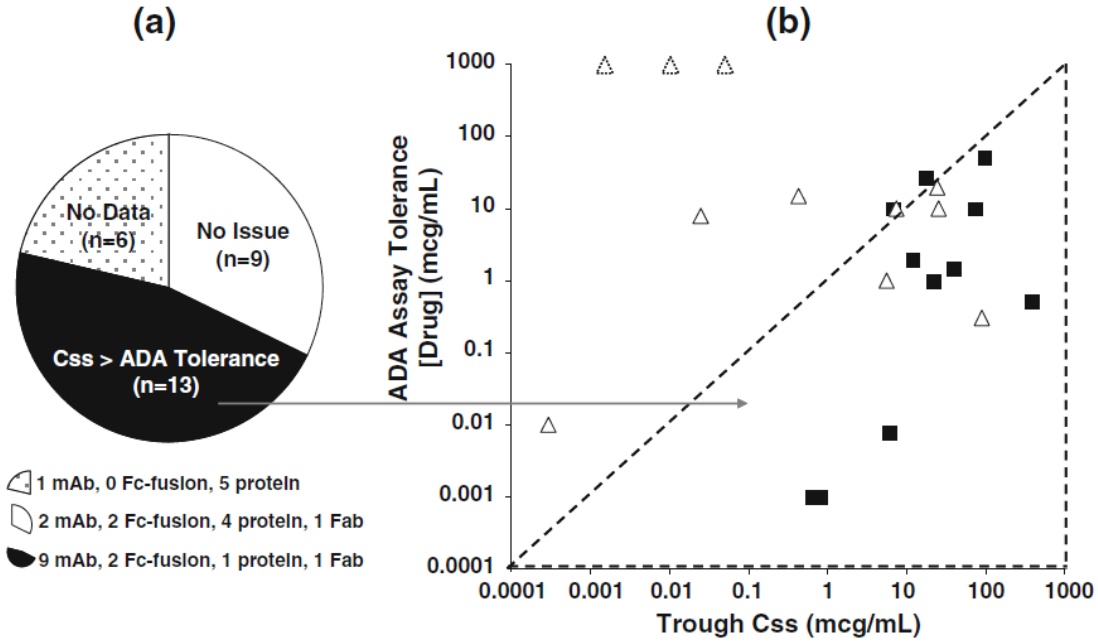


Fig. 1 A schematic example of immunogenicity assay. (ADA: anti-drug antibody).



Wang et al. 2012 Pharm Res

enabling factors

ADA data quality improves with higher drug tolerance

- Improved drug tolerance → increased ability to detect ADA, e.g., higher ADA incidence
- ADA- are more reliably negative when ADA assays have a good drug tolerance
- Higher assay sensitivity → allows for deeper analysis to evaluate effects of ADA by the ADA titer (i.e., magnitude, intensity)

Product	Drug Tolerance (mcg/mL)		ADA+ Incidence		% ADA Inconclusive
	Old Assay	New Assay	Old Assay	New Assay	Old Assay
A1A	2[a]	49	6.5%[a]	61%	78%[a]
A2II	0.2	200	7.7%	52%	63%
A3G	0.049	50	2.8%	21%	69%
A4U	0.007	100	5%	6%[b]	~80%

[a] A fraction of samples not analyzed for ADA. [b]ADA sample reanalysis involved a subset of study samples.

Use multiple approaches to evaluate impact on PK

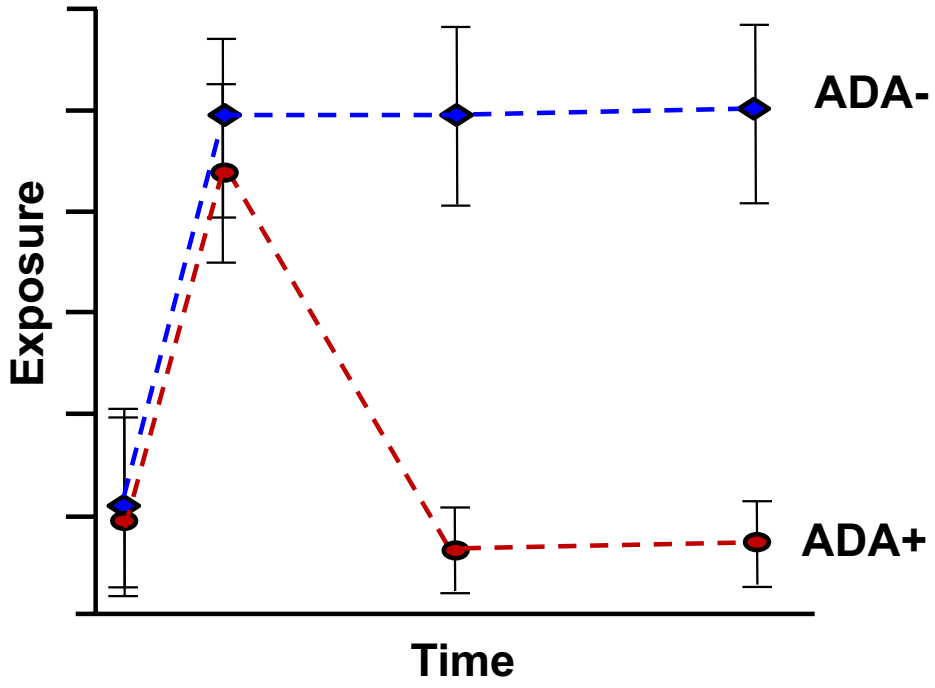
- **Between-subject** comparison of drug concentration: ADA+ vs. ADA-
  - Grouped by ***subject*** ADA status (assumes ADA+ at all timepoints for ADA+ subjects)
    - Other ways of grouping: persistent/transient ADA+ vs. ADA-, …
  - Grouped by ***sample*** ADA status at each timepoint
- **Within-subject** comparison of drug concentration: before vs. after ADA formation
  - Visualizing the impact on a subject-by-subject basis, not averaged across subjects, Removing the noise at population level
  - Useful in general, and when products have very high or very low ADA+ incidence
- Evaluating the effect by ADA titer

The goal: maximizing the understanding of ADA impact on PK

Comparison of drug concentrations based on ADA Status

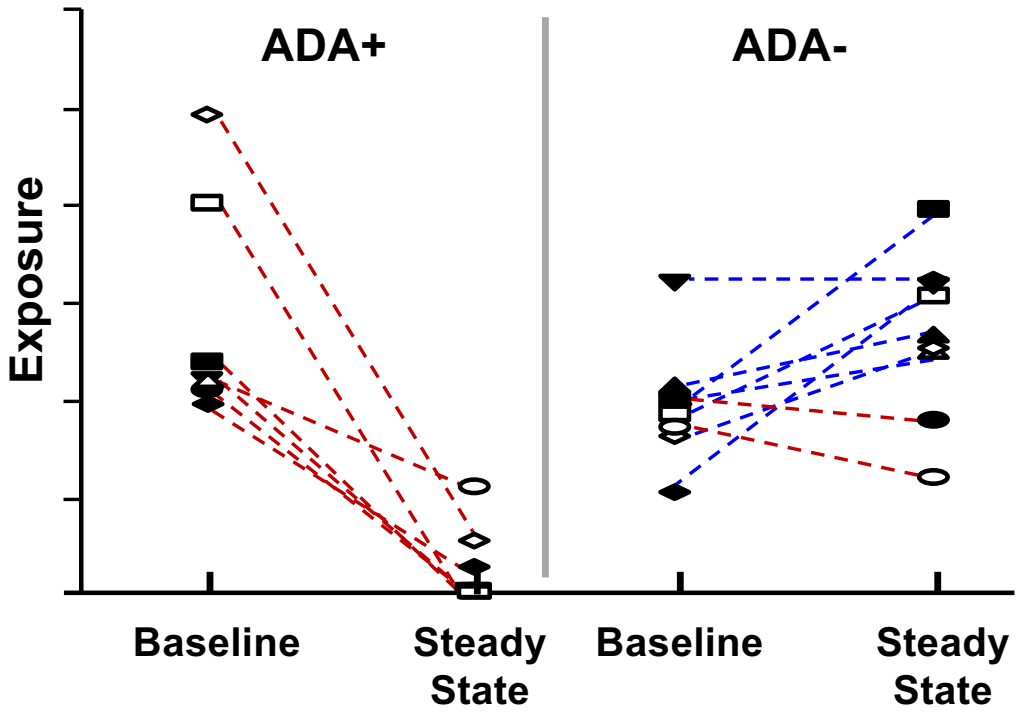
between-subject comparison

(by **subject** ADA status or by **sample** ADA status)



within-subject comparison

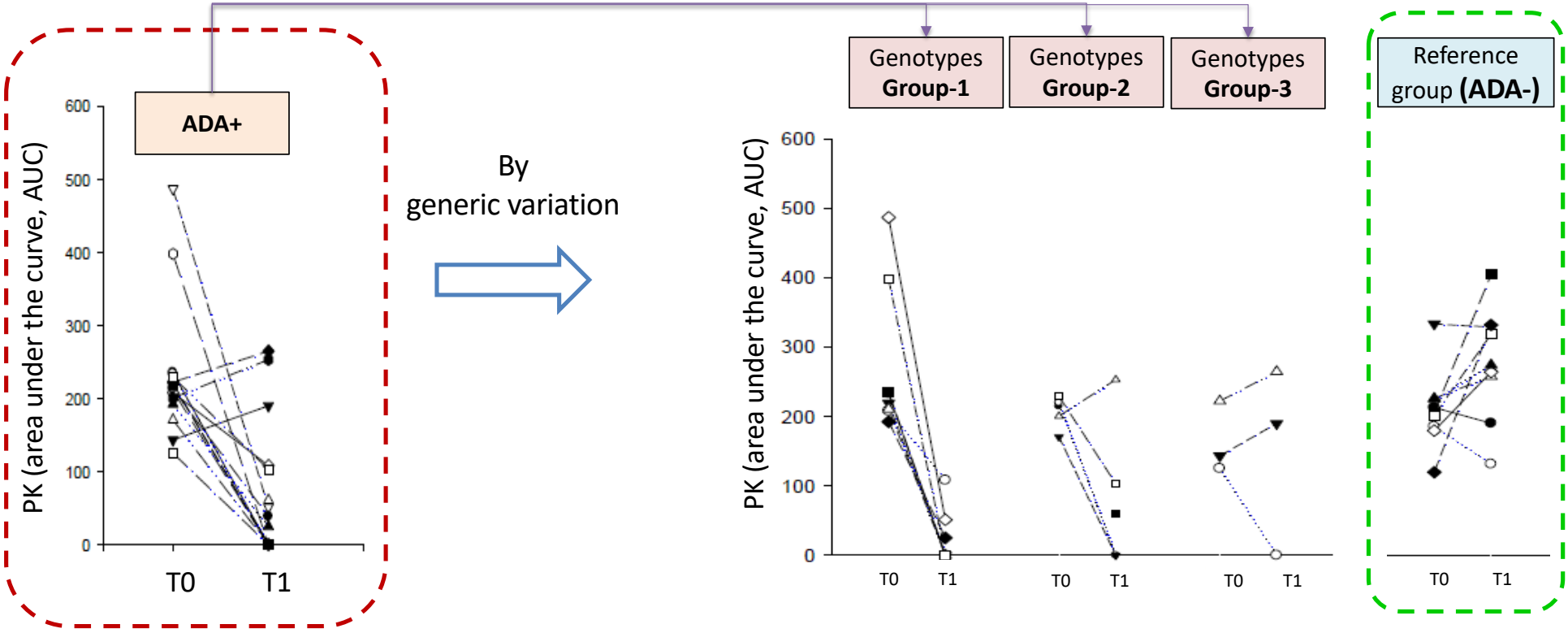
(ADA- @baseline)



approaches

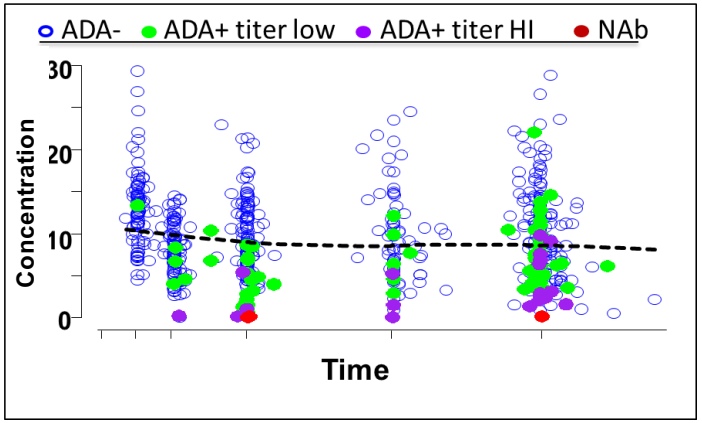
When feasible, explore ADA impact by genotype of subjects

- ADA impact on PK can vary by genetic variation

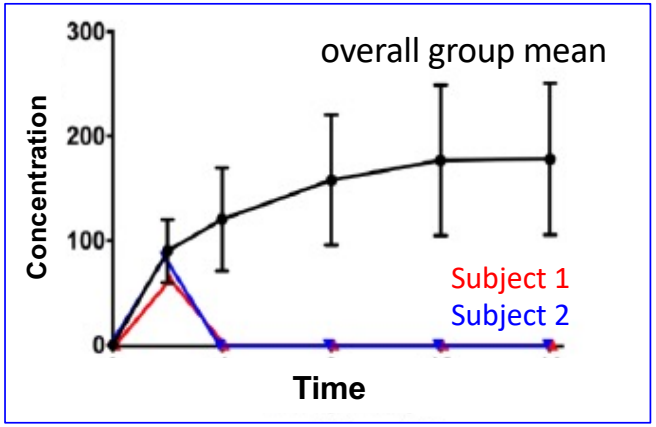


Examples of other types of analysis for clinical impact on PK

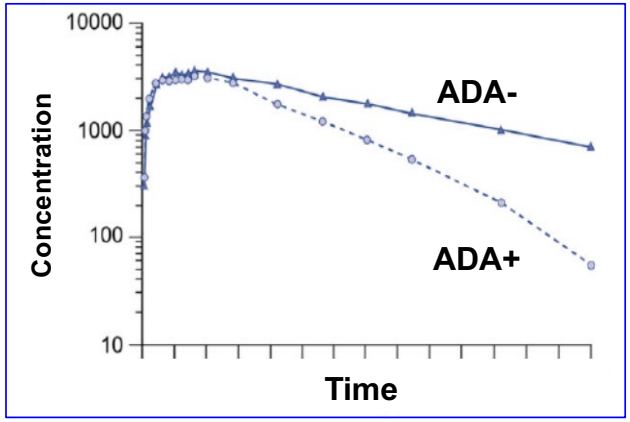
Multiple dose study
(ADA-, ADA titer H/L, NAb)



Multiple dose study
(NAb+ subjects vs. group mean)

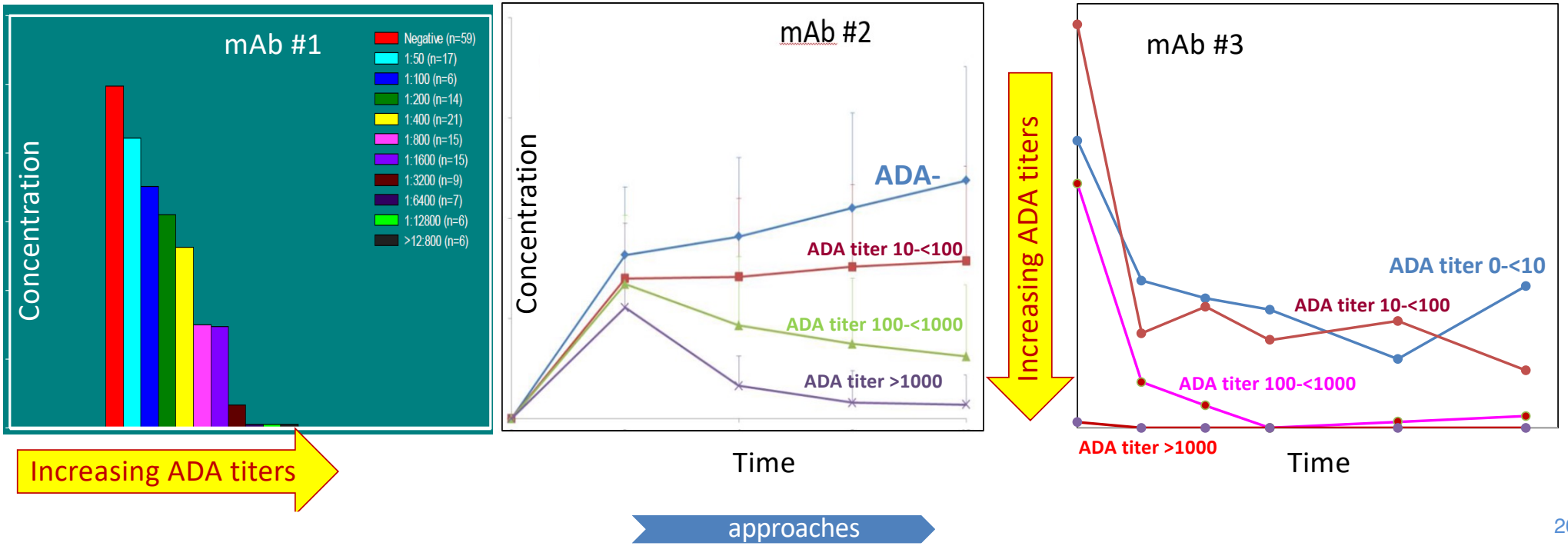


Single dose study
(temporal concentration profiles)



Improved sensitivity allows evaluating ADA effect by titers

- Higher ADA titers associated with a lower drug concentration (PK), all panels
- ADA with low titers may not affect drug concentration (PK), e.g., mAb #3



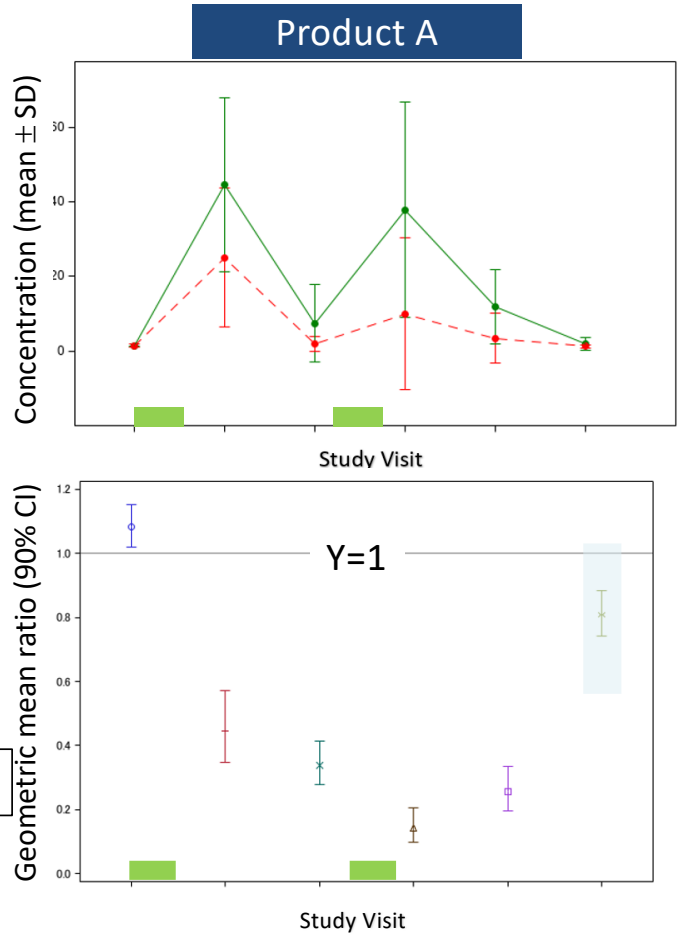
Initiative #1 –
Evaluating ADA impact on PK with “frontload IS review tool”

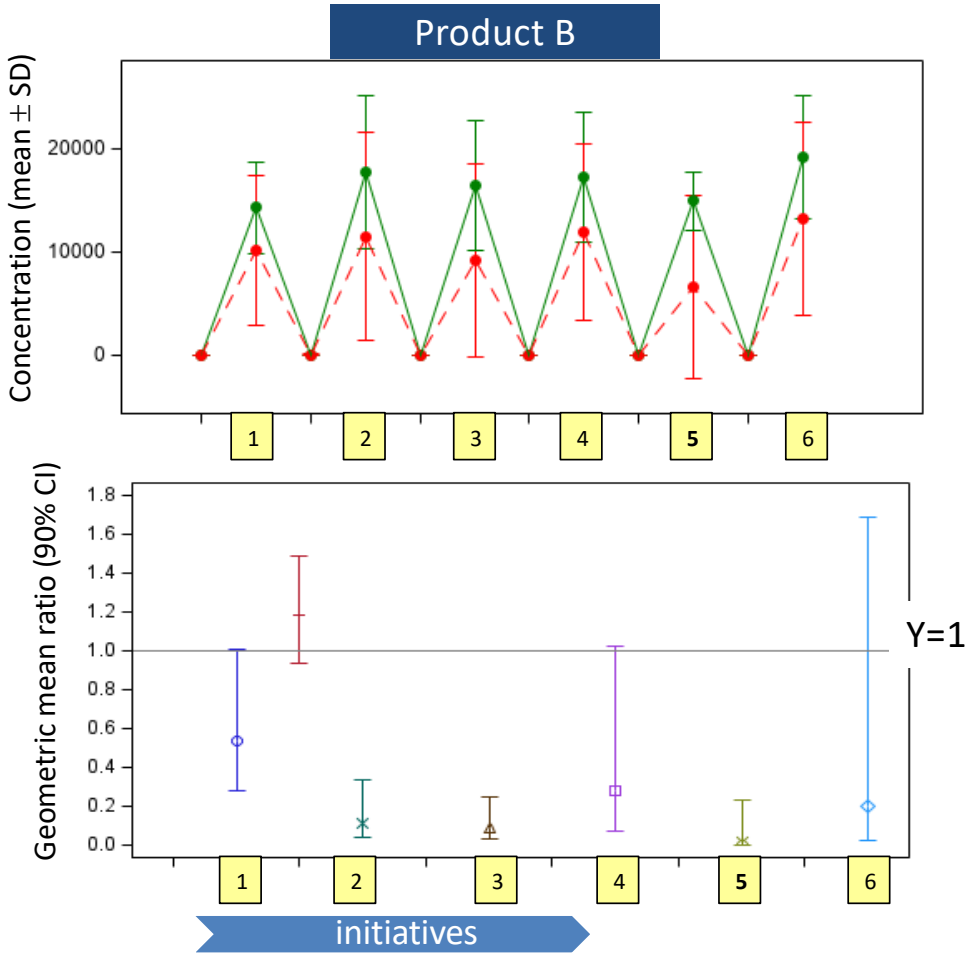
Temporal PK profiles

ADA- vs. ADA+

Statistical analysis

ADA+/ADA- ratio



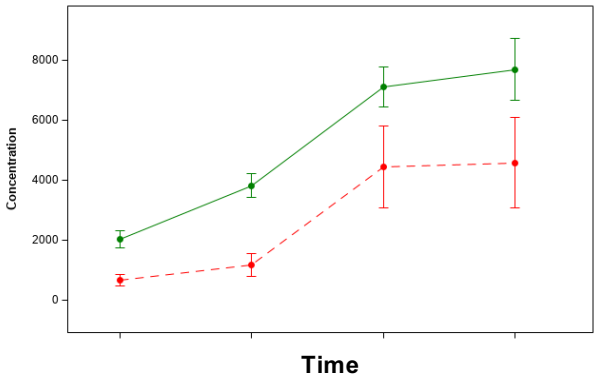


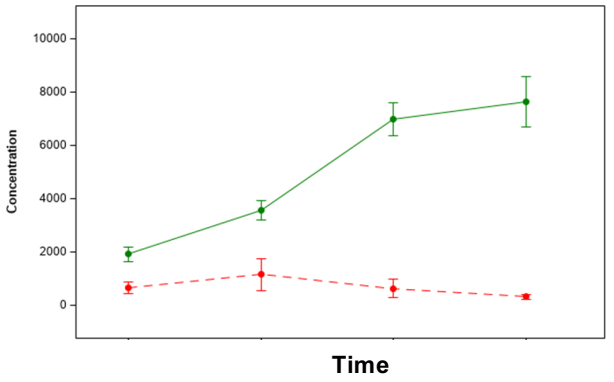
Other analyses with “frontload IS review tool”

Subject level (mean ± std error) | Product C | **Sample** Level (mean ± std error)

Trough concentrations

ADA- vs. ADA+

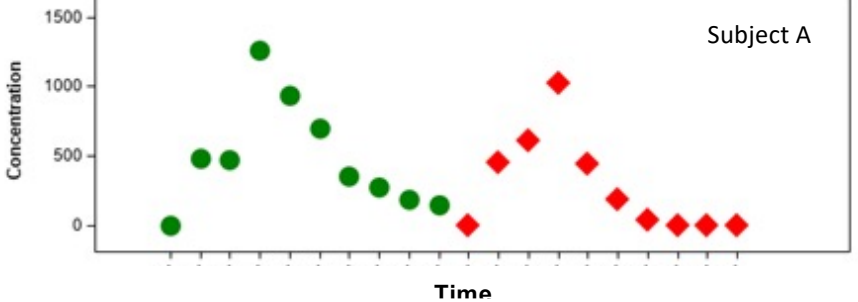


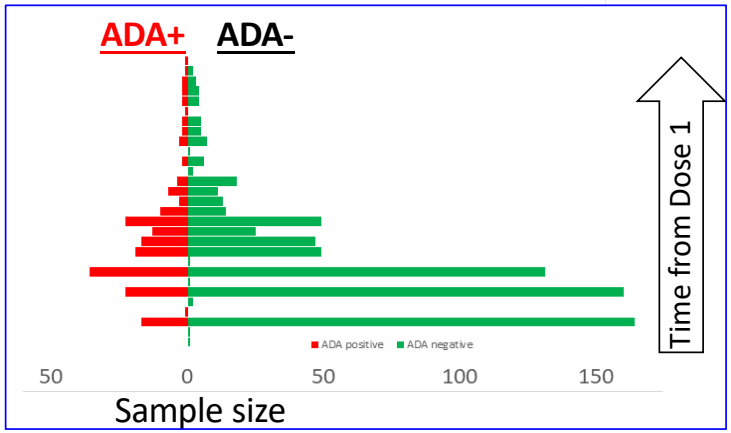


Product D

ADA- vs. ADA+

PK profile with ADA status per time point



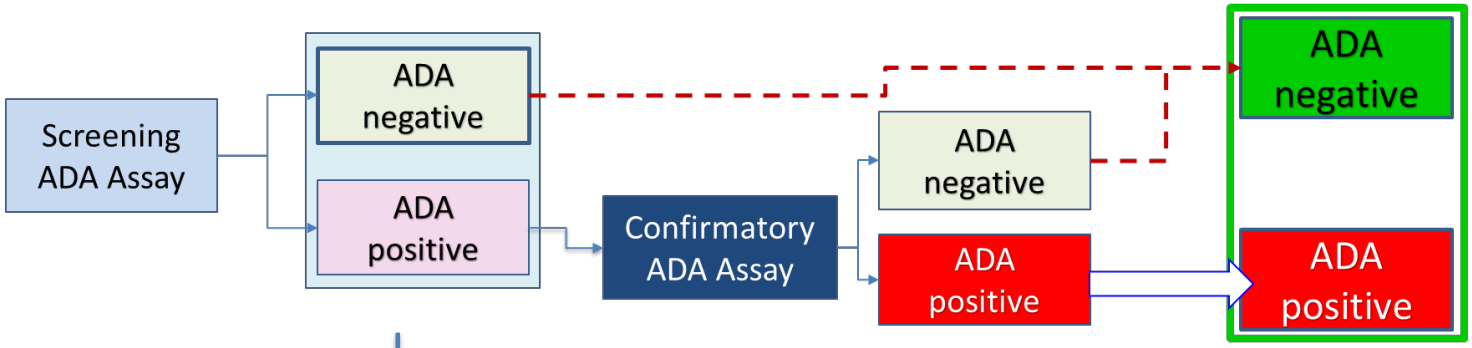


initiatives

"Frontload IS review tool" for evaluating the impact of immunogenicity on PK

- Benefits
  - Enhancement of review efficiency
  - Standardization of methods for evaluating ADA impact on PK
- Required datasets (ADaM or SDTM)
  - ADaM: immunogenicity dataset (**ADIS**), subject information (ADSL), and PK (ADPC)
- Current challenges
  - Limited number of immunogenicity dataset conforms with CDISC standards
  - Data reporting is inconsistent with best practice in some cases
- Resources:
  - The IS domain is described in SDTM Implementation Guide 3.2 & on the FDA Data Standards Catalog
  - FDA Guidance "Providing Regulatory Submissions In Electronic Format — Standardized Study Data"

Example of information request to update ADIS dataset: an integrated ADA result category for all samples

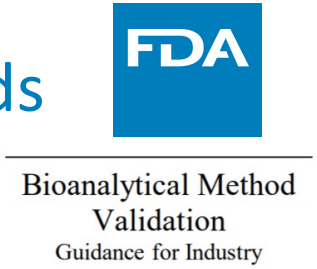


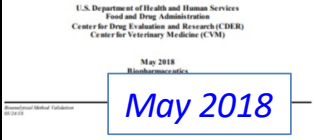
Sample #	Screening assay	Confirmatory assay	Integrated ADA status
1	Positive	Positive	Positive
2	Positive	Positive	Positive
3	Positive	Negative	Negative
4	Positive	Negative	Negative
5	Negative	**NOT TESTED**	**Negative**
6	Negative	**NOT TESTED**	**Negative**

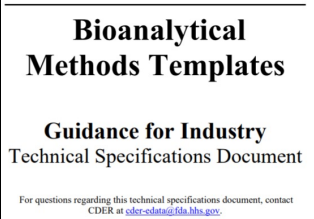
Initiative #2 – Enhanced communication about PK methods

- The question – Do measured concentration data reflect active drug levels?
- The goal – To facilitate interpretation of clinical relevance of ADA

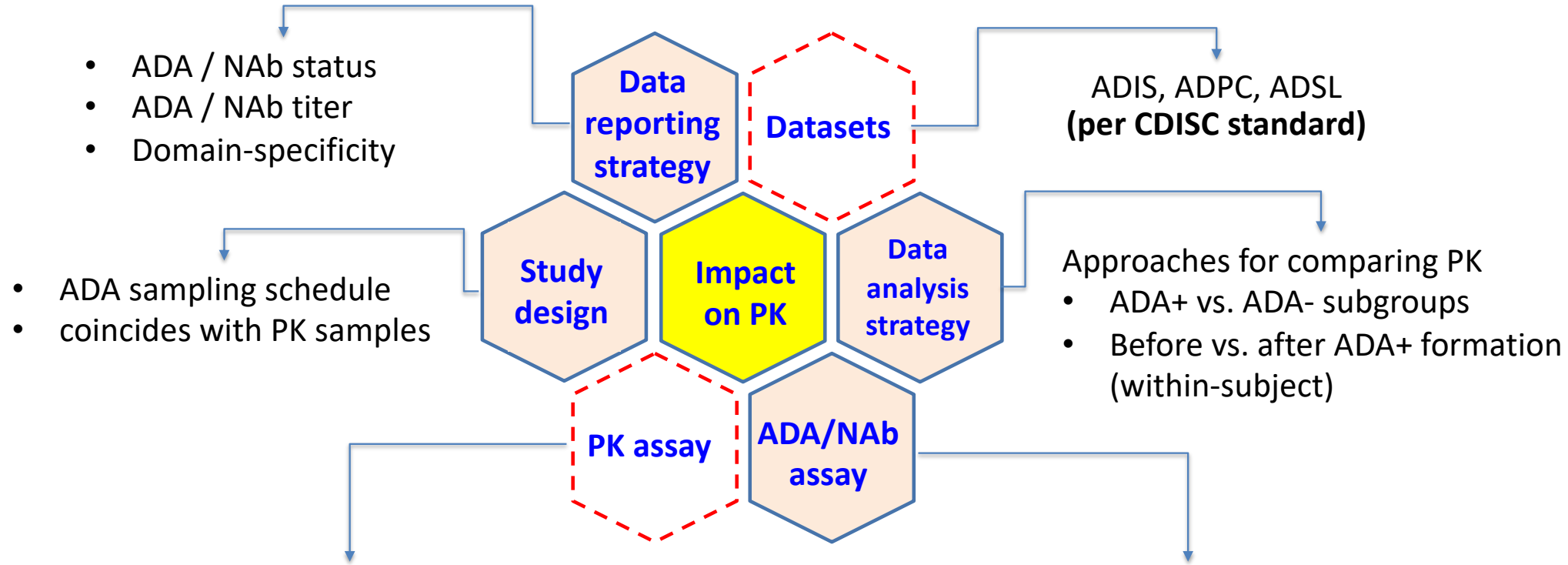
The context	Ligand binding assays
Proposed enhancements	• Describing where the capture and detection antibodies/reagents bind when interacting with the drug molecule • Describing results of target interference testing, when appropriate • Describing results of ADA interference testing, when appropriate
The documents	• Method validation reports • Summary of Biopharmaceutics and Associated Analytical Methods • Method templates
Why is it important?	• Active drug concentrations are more likely to correlate with efficacy • Better understanding of clinical relevance of ADA, e.g., impact on PK







Summary - Multi-factorial considerations for evaluating clinical impact of immunogenicity, **PK is a sensitive endpoint**



- ADA / NAb status
- ADA / NAb titer
- Domain-specificity

ADIS, ADPC, ADSL
(per CDISC standard)

- ADA sampling schedule
- coincides with PK samples

Approaches for comparing PK
- ADA+ vs. ADA- subgroups
- Before vs. after ADA+ formation (within-subject)

- Assay measure drug concentrations that reflect functional levels (most informative)

- Assay sensitivity, Matrix effect
- Drug tolerance (vs. observed drug concentration)

Acknowledgement

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- Dr. Xiulian Du
- Dr. Shiew Mei Huang
- Dr. Issam Zineh