American Society for Clinical Pharmacology and Therapeutics (ASCPT)

Affiliations: ASCPT Pharmacometrics & Pharmacokinetic Community and Biologics Community

US Food & Drug Administration Perspective on Immunogenicity

December 9, 2022

FDA Speakers:
Yow-Ming Wang, PhD, Office of Translational Science
Eric Brodsky, MD, Office of New Drugs
Center for Drug Evaluation and Drug Research
U.S. Food & Drug Administration

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- The views and opinions expressed in this presentation represent those of the presenters, and do not necessarily represent an official FDA position.
- 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.
- The labeling examples in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended templates.

American Society for Clinical Pharmacology and Therapeutics (ASCPT)

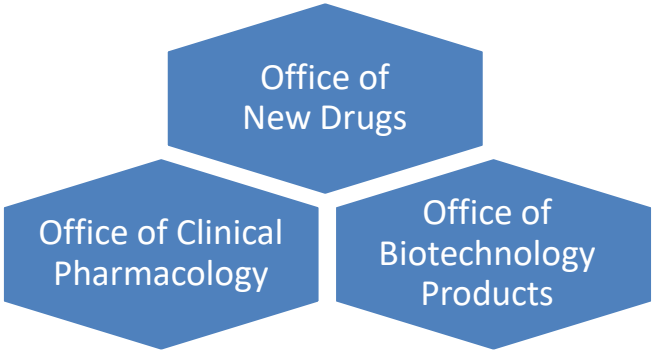
FDA's Review of Immunogenicity Data – With A Focus on ADA Impact on Pharmacokinetics

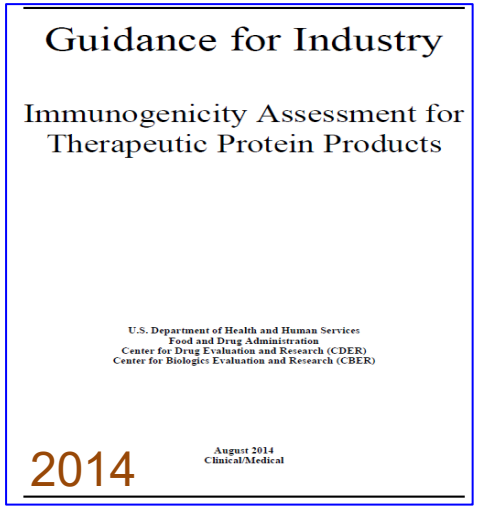
December 9, 2022

Yow-Ming Wang, PhD, *Associate Director for Biosimilars & Therapeutic Biologics*
Office of Clinical Pharmacology, Office of Translational Science
Center for Drug Evaluation and Drug Research
U.S. Food & Drug Administration

ADA = anti-drug antibodies

FDA's Multi-disciplinary Review of Immunogenicity Impact Starts During Early IND Interactions



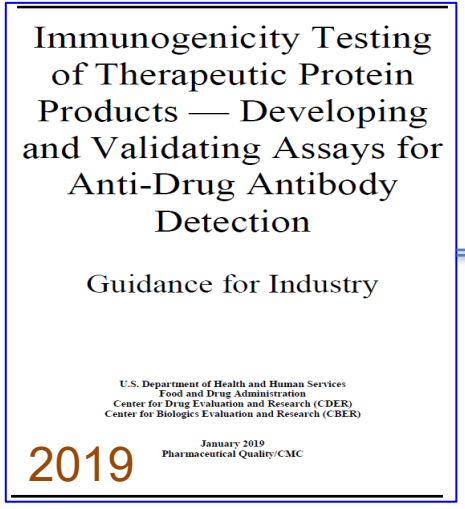

Guidance for Industry

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

2014

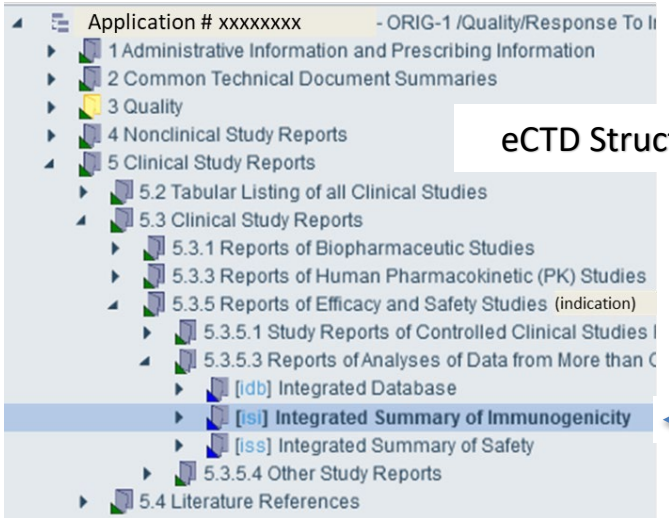

Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection

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

2019

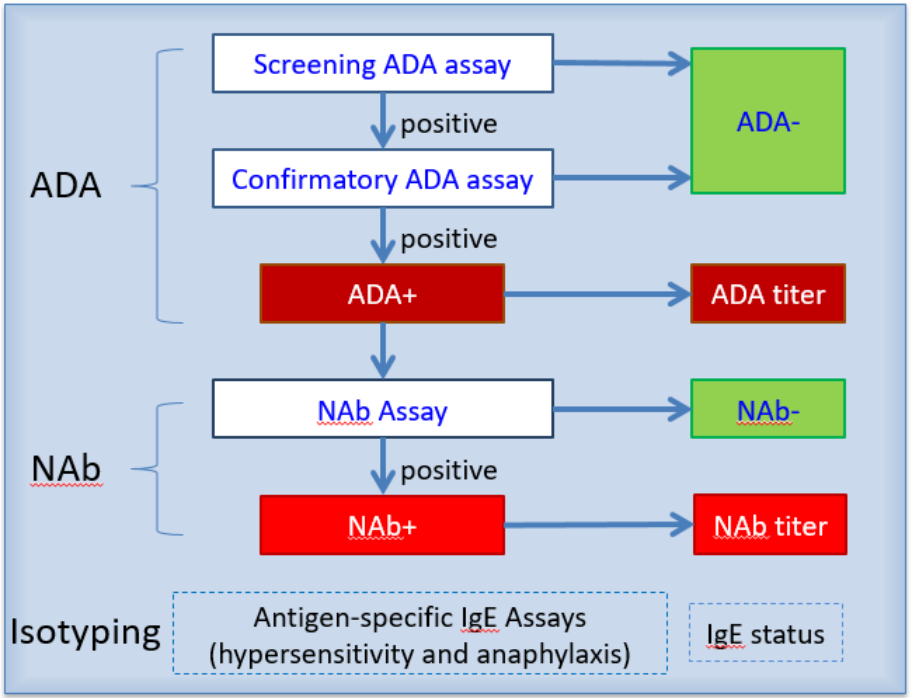


eCTD Structure

ISI: Integrated Summary of Immunogenicity

a. Immunogenicity Risk Assessment
b. Tiered Strategy and Stage-Appropriate Bioanalytical Assays
c. Clinical Study Design and Sampling Strategy
a. Clinical Immunogenicity Data Analysis
b. Conclusions and REMS, if applicable

Multi-tiered Approach for Immunogenicity Assessment



ADA, anti-drug antibodies; NAb, neutralizing antibodies; ECLIA, electrochemiluminescence

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
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January 2019
Pharmaceutical Quality/CMC

2019

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]

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 and higher dropout rate

Clinical impact?

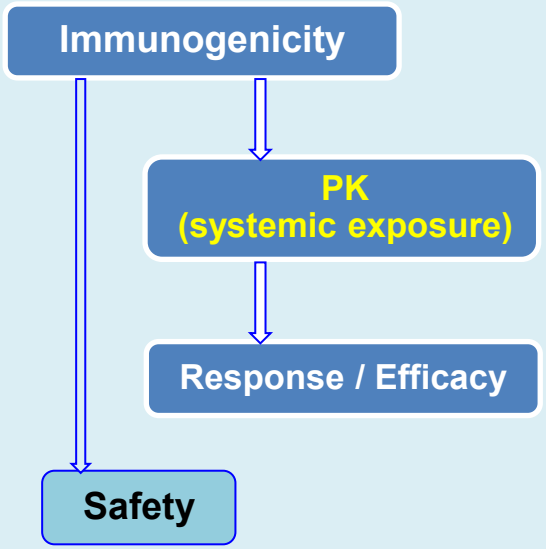
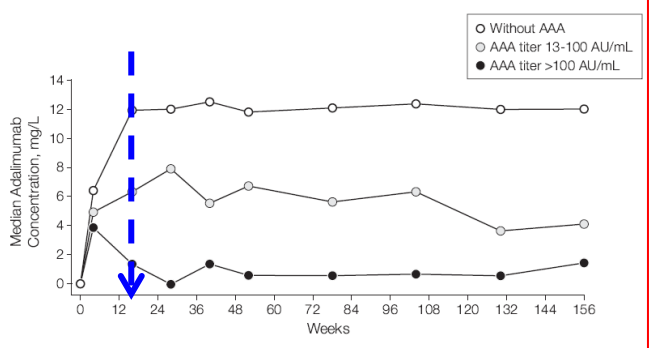
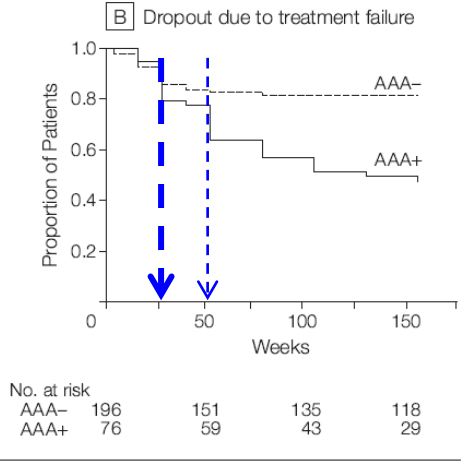


Figure 2. Median Adalimumab Concentrations Over Time



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

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

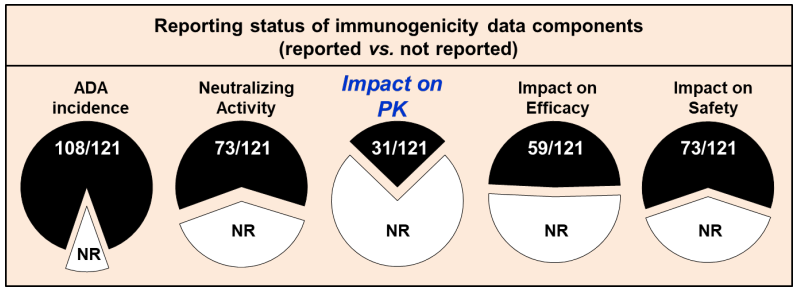


Bartelds *et al.* 2011 JAMA

Labeling Suggests High Congruence of Clinical Impact of ADA on PK vs. Efficacy (BLA approved by 2/2015)

Of 121 product labeling, **16** contain information for ADA impact on PK & efficacy

1. Clearing ADA associated with ↓ PK exposure and reduced efficacy (n=8 products)
2. ADA has no effects (↔) on either PK or efficacy (n=6 products)



Effects on PK & efficacy are congruent in 14 of 16 products (~90%)

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

ADA type	Exposure (PK)	# of drugs	% of drugs	Efficacy	# Drugs reported	# Drugs not reported
Clearing	↓	13	42%	↓	8	5
No effect	↔	10	32%	↔	6	4
Sustaining	↑	6	19%	↓ / ↔	1 / 1	4
# of drugs with PK impact		31*	74%	# w/ efficacy	16	15

*2 products had inconclusive ADA status

Enabling Factors for Evaluating ADA Impact on PK

- Resources: industry white papers, FDA guidance documents
- ADA assay considerations
  - Improved drug tolerance
  - Reporting of ADA titer data in addition to ADA+ vs. ADA-
- Best practices for immunogenicity assessment in clinical studies
  - Availability of integrated summary of immunogenicity (ISI)
  - Study design considerations
  - Data reporting
- (Recent activity) Transition to standardized format for immunogenicity data submission, e.g., CDISC format for IS / ADIS data (.xpt)

ADA Data Quality Improved with Increasing Drug Tolerance

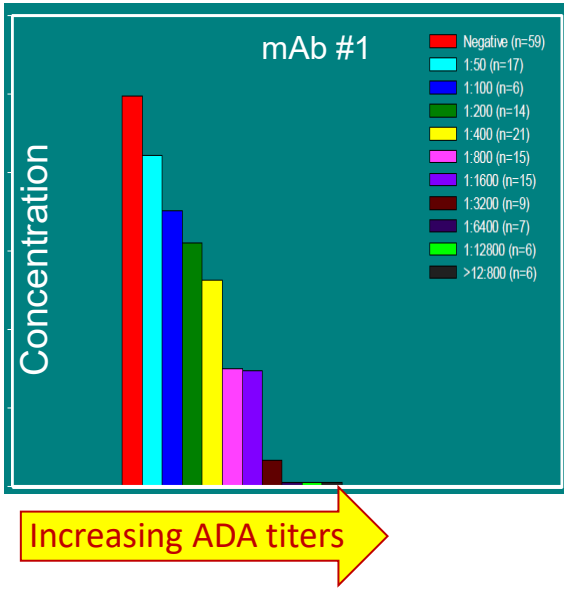
- Desirable state: Css-trough < drug tolerance (i.e., no drug interference in ADA assay)
- Improved drug tolerance → increased ability to detect ADA, e.g., higher ADA incidence
- ADA- are more reliably negative when ADA assays have a good drug tolerance
- Higher assay sensitivity → allows for deeper analysis to evaluate effects of ADA by the ADA titer (i.e., magnitude, intensity)

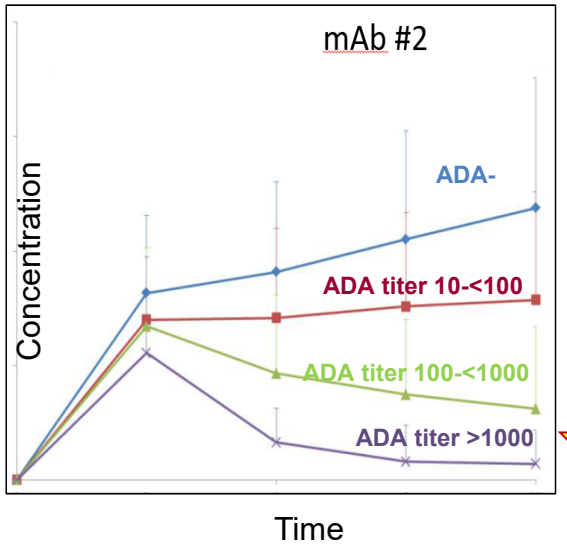
Product	Drug Tolerance (mcg/mL)		ADA+ Incidence		% ADA Inconclusive
	Old Assay	New Assay	Old Assay	New Assay	Old Assay
A1A	2[a]	49	6.5%[a]	61%	78%[a]
A2II	0.2	200	7.7%	52%	63%
A3G	0.049	50	2.8%	21%	69%
A4U	0.007	100	5%	6%[b]	~80%

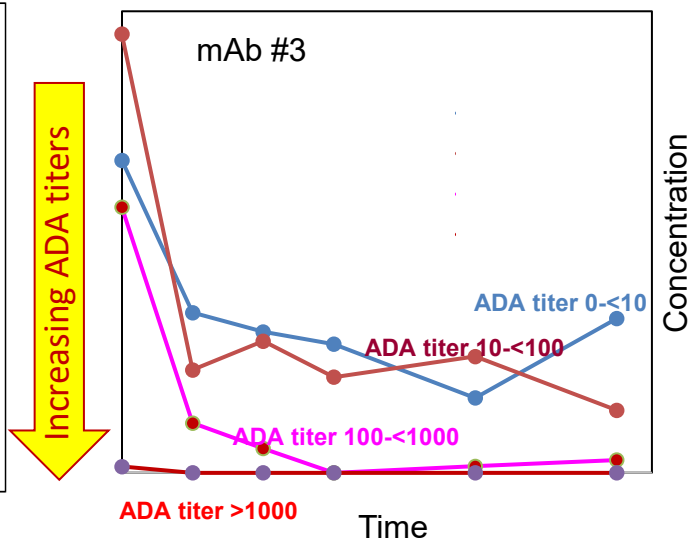
[a] A fraction of samples not analyzed for ADA. [b]ADA sample reanalysis involved a subset of study samples.

Improved Assays Allow Evaluating ADA Effect by Titers

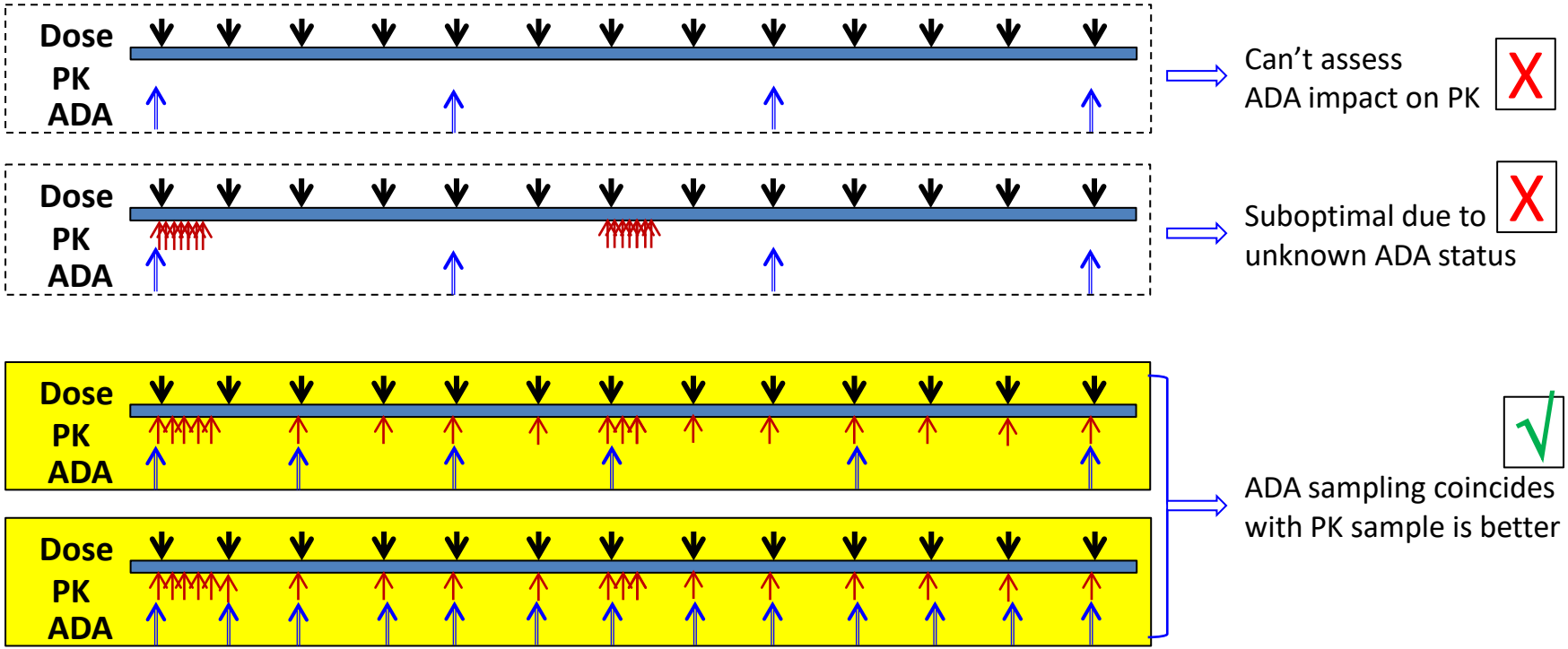
- Higher ADA titers associated with a lower drug concentration (PK) in all panels
- ADA with low titers may not affect drug concentration (PK), e.g., mAb #3







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-

- **2 categories:**
  - ADA: ADA+, ADA-
  - NAb: NAb+, NAb- (among ADA+)
- **3 categories:**
  - ADA: ADA+, ADA-, ADA inconclusive
  - NAb: NAb+, NAb-, NAb inconclusive

Categories are applicable at sample & subject level

- **> 3 categories**
  - ADA-
  - ADA inconclusive
  - ADA+
    - Treatment-emergent (induced) ADA: TE-ADA
      Baseline ADA-, postdose ADA+
    - Treatment-boosted (enhanced) ADA:TB-ADA
      Baseline ADA+, postdose ADA+ (much higher)
  - NAb+/NAb-: samples with TE-ADA and TB-ADA

White Paper AAPSJ article - URL

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

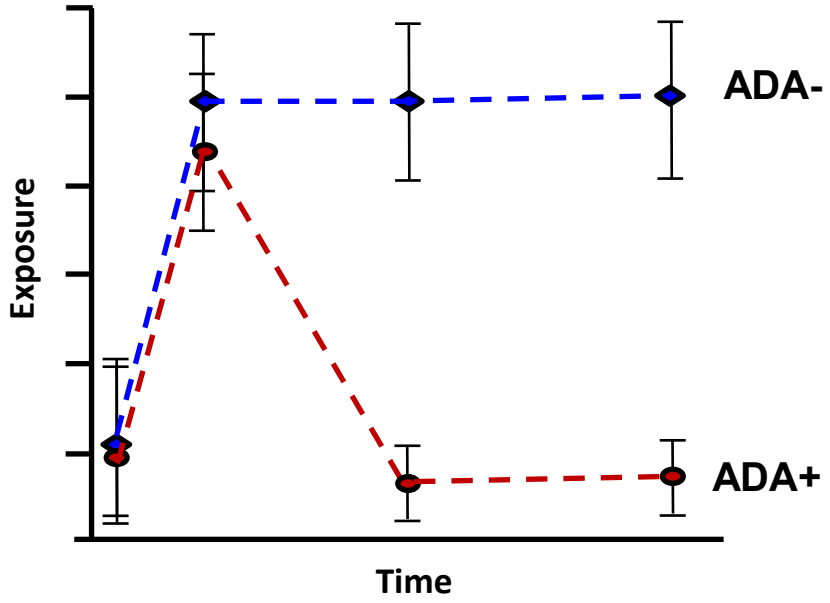
G. Shankar,[1,14] S. Arkin,[2] L. Cocea,[3] V. Devanarayan,[4] S. Kirshner,[5] A. Kromminga,[6] V. Quarmby,[7] S. Richards,[8] C. K. Schneider,[9,10] M. Subramanyam,[11] S. Swanson,[12] D. Verthelyi,[5] and S. Yim[13]

Recent experience indicates an increasing adoption of White Paper recommendations

Approaches to Compare Drug Concentrations (ADA+ vs. ADA-)

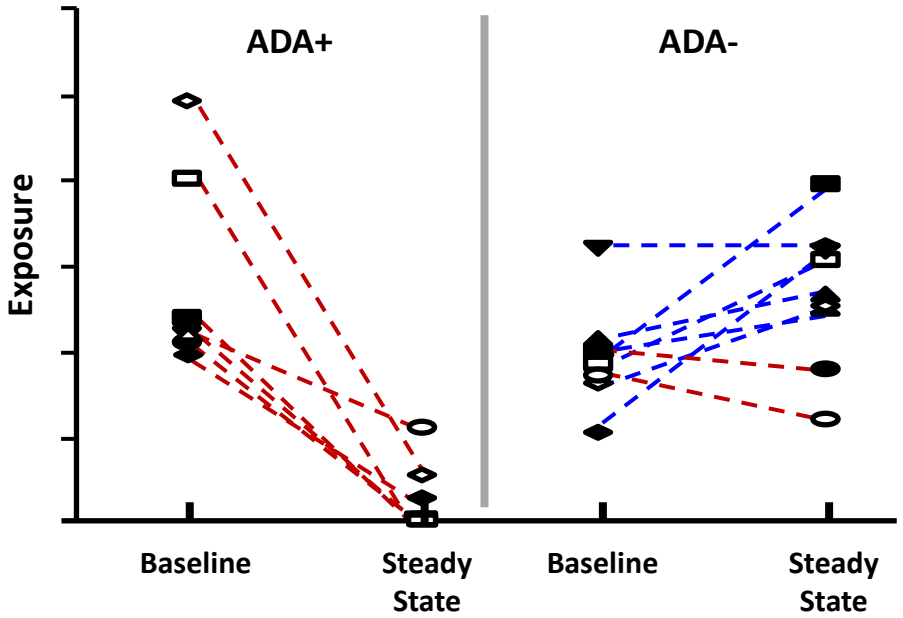
Between-subject comparison

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



Within-subject comparison

(ADA- @baseline)



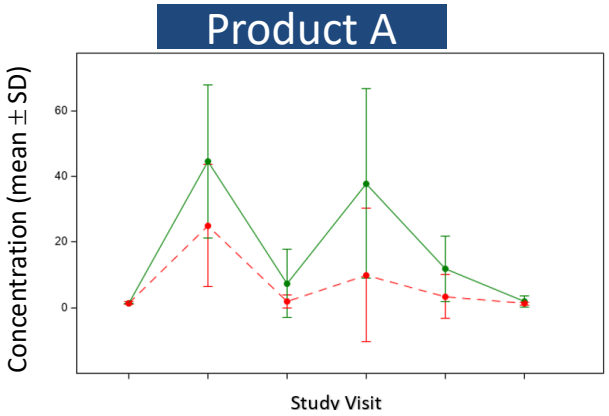
Assessing Immunogenicity Effect on PK with "IS Tool"

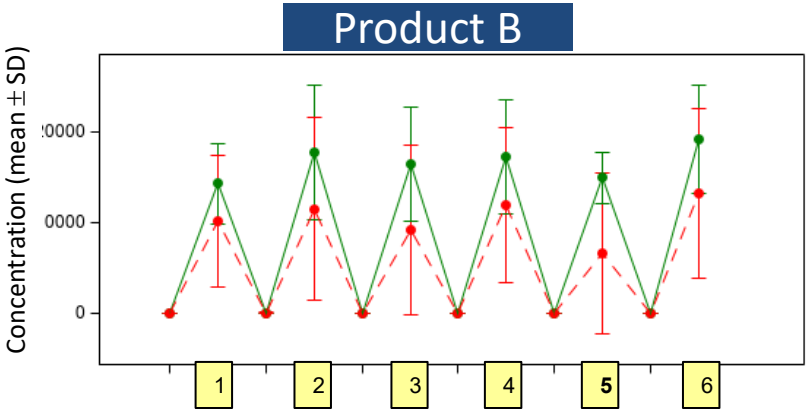
Temporal PK profiles

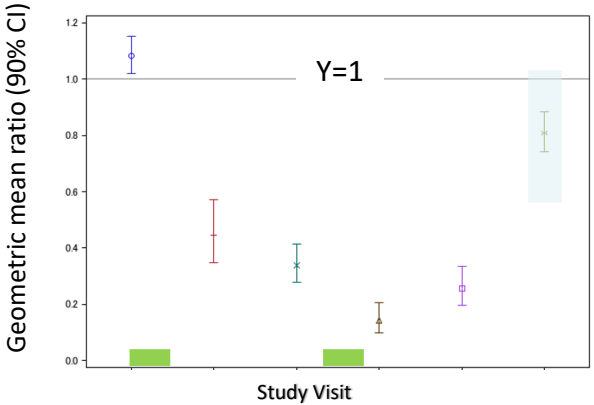
ADA- vs. ADA+

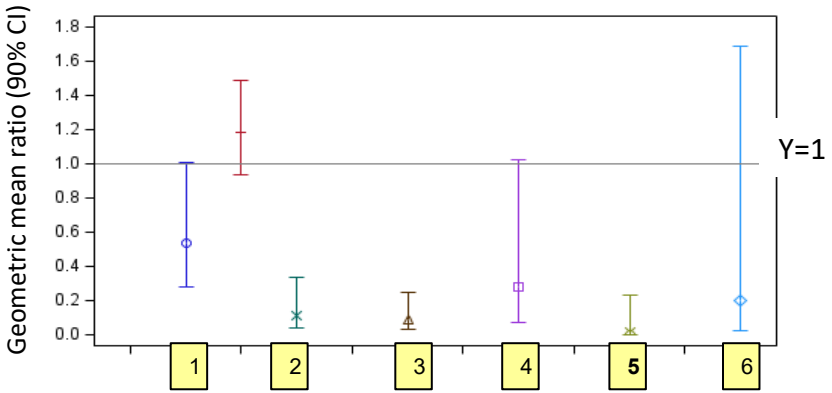
Statistical analysis

ADA+/ADA- ratio



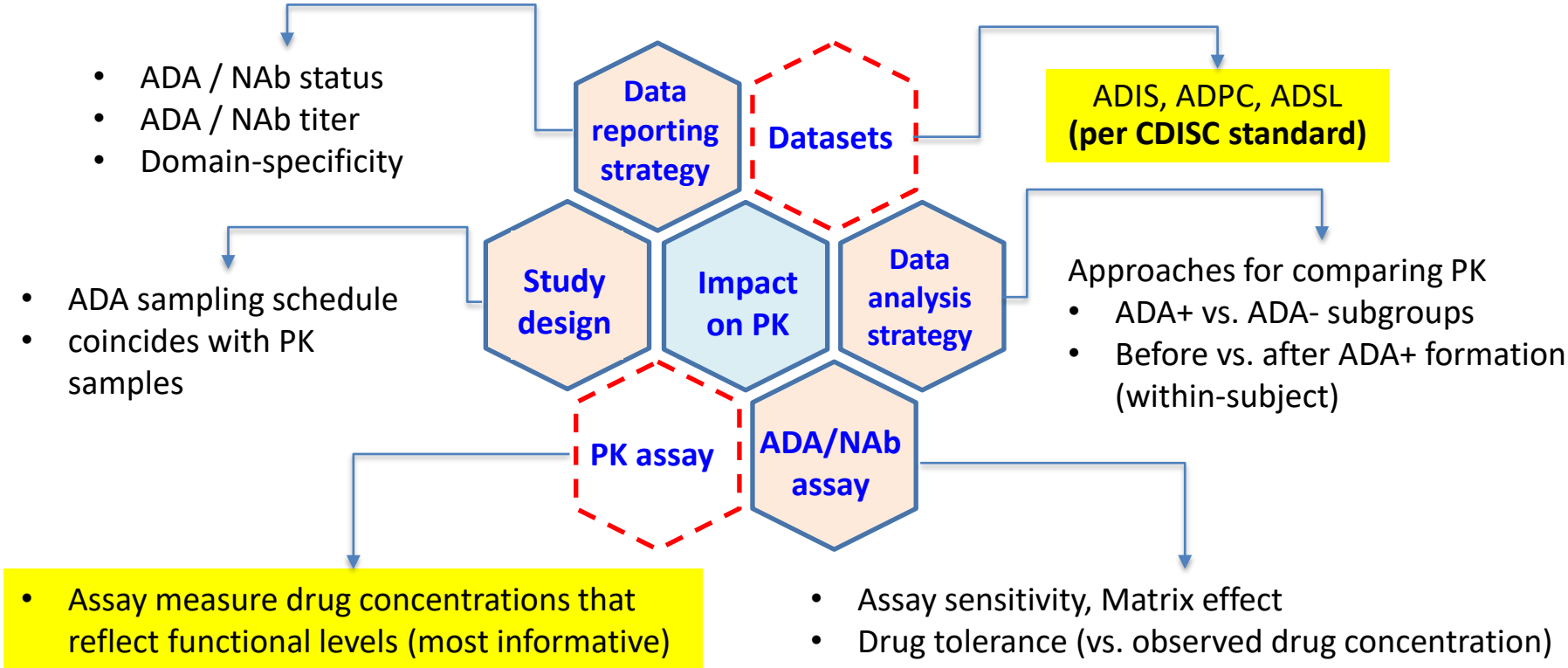






IS Tool: an OCP developed system

Summary - Multi-factorial Considerations for Evaluating Clinical Impact of Immunogenicity, PK is a Sensitive Endpoint



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- Dr. Christine Hon

OCP Management :

- Dr. Shiew Mei Huang
- Dr. Issam Zineh

Immunogenicity Information in Labeling

December 9, 2022
Eric Brodsky, MD, *Associate Director*
Labeling Policy Team, Office of New Drug Policy, Office of New Drugs
Center for Drug Evaluation and Drug Research
U.S. Food & Drug Administration

Immunogenicity Labeling Draft Guidance[1]

Assist applicants with incorporating immunogenicity information into labeling of therapeutic proteins and select drug products that have immunogenicity assessments[2]

[1] Draft guidance for industry, *Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling — Content and Format* (February 2022) (referred to as the Immunogenicity Labeling Draft Guidance herein). When final, this guidance will represent the FDA's current thinking on this topic.

[2] Select drug products with immunogenicity assessments include peptides, oligonucleotides, and low molecular weight heparins

Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling — Content and Format

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Eric Brodsky at 301-796-0855 or (CBER) the Office of Communication, Outreach, and Development at (800) 835-4709 or (240) 402-8010.

See https://www.fda.gov/regulatory-information/search-fda-guidance-documents/immunogenicity-information-human-prescription-therapeutic-protein-and-select-drug-product-labeling

Immunogenicity Labeling Draft Guidance

Presenting immunogenicity information in a consistent manner will enable health care practitioners to more easily identify and differentiate between:

- Products associated with clinically significant immunogenicity
- Products whose ADA are **not** associated with clinically significant effects on PK, PD, safety, or effectiveness

ADA = antidrug antibodies; PK = pharmacokinetics; PD = pharmacodynamics

Historical Placement of Immunogenicity Information in Labeling[1]

Review of 71 therapeutic proteins and drug products approved by CDER during a recent five-year period (2014-2018) with immunogenicity information in labeling

- 98% of labeling included immunogenicity information in the ADVERSE REACTIONS section
- 30% of labeling did not include any statements regarding the immunogenicity impact on safety or effectiveness[2]

[1] Guinn, D., Madabushi, R., Wang, Y., Brodsky, E., Zineh, I., and Maxfield, K. *Communicating Immunogenicity-Associated Risk in Current U.S. FDA Prescription Drug Labeling: A Systematic Evaluation.* Ther Innov Regul Sci (2020). https://doi.org/10.1007/s43441-020-00161-z

[2] Categories of impact on safety or effectiveness include observed or potential impact, unknown impact, or no observed impact

FDA Recommends a Dedicated *Immunogenicity* Subsection

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
9 DRUG ABUSE AND DEPENDENCE
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
12.6 Immunogenicity
13 NONCLINICAL TOXICOLOGY
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Reserve other sections for description of only clinically significant effects of immunogenicity

Allows for a consistent location for summarizing immunogenicity data and its PK and PD effects

For Structured Product Labeling Developers

When selecting appropriate SPL codes for human prescription drug labeling, we recommend drug developers select the most specific, appropriate Logical Observation Identifiers Names and Codes (LOINC) – *Immunogenicity* subsection LOINC

Table 1: HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS PLR FORMAT PRESCRIBING INFORMATION		
Full Prescribing Information		
LOINC Code	**LOINC Name**	**Section/Subsection Name as Per 21 CFR 201.56(d) and 201.57(c) or by Guidance**
34090-1	CLINICAL PHARMACOLOGY SECTION	12 CLINICAL PHARMACOLOGY section
43679-0	MECHANISM OF ACTION SECTION	12.1 Mechanism of Action subsection
43681-6	PHARMACODYNAMICS SECTION	12.2 Pharmacodynamics subsection
43682-4	PHARMACOKINETICS SECTION	12.3 Pharmacokinetics subsection
49489-8	MICROBIOLOGY SECTION	12.4 Microbiology subsection
66106-6	PHARMACOGENOMICS SECTION	12.5 Pharmacogenomics subsection
88830-5	IMMUNOGENICITY	12.6 Immunogenicity subsection

Considerations for Subgroup Safety Analyses by Immunogenicity[1]

Percentage of drug-treated patients who developed hypersensitivity reactions[2] with:

- ADA compared to those who did not develop ADA
- High titer ADA compared to those who did not develop ADA
- High titer ADA compared to those who developed low-titer ADA

[1] For these analyses describe the duration of drug exposure and time period over which ADA sampling was conducted and identify the trials.

[2] In addition to hypersensitivity-ADA analyses, it may be reasonable to also perform injection site reaction-ADA analyses for drugs administered subcutaneously or infusion reaction-ADA analyses for drugs administered intravenously.

Considerations for Subgroup Efficacy Analyses by Immunogenicity[1]

Percentage of drug-treated patients who achieved a key efficacy endpoint (e.g., primary efficacy endpoint) with:

- ADA compared to those who did not develop ADA
- High titer ADA compared to those who did not develop ADA
- High titer ADA compared to those who developed low-titer ADA

[1] For this analysis describe the duration of drug exposure and time period over which ADA sampling was conducted and identify the trials.

Updating Immunogenicity Information in Labeling

- When new immunogenicity data/information could affect prescribing decisions or the clinical management, applicants should submit to FDA proposed revised labeling containing the updated immunogenicity information
- When this guidance is final, FDA recommends that applicants propose labeling updates to be consistent with the format and organizational recommendations in this guidance (e.g., during the next planned prior approval supplement)

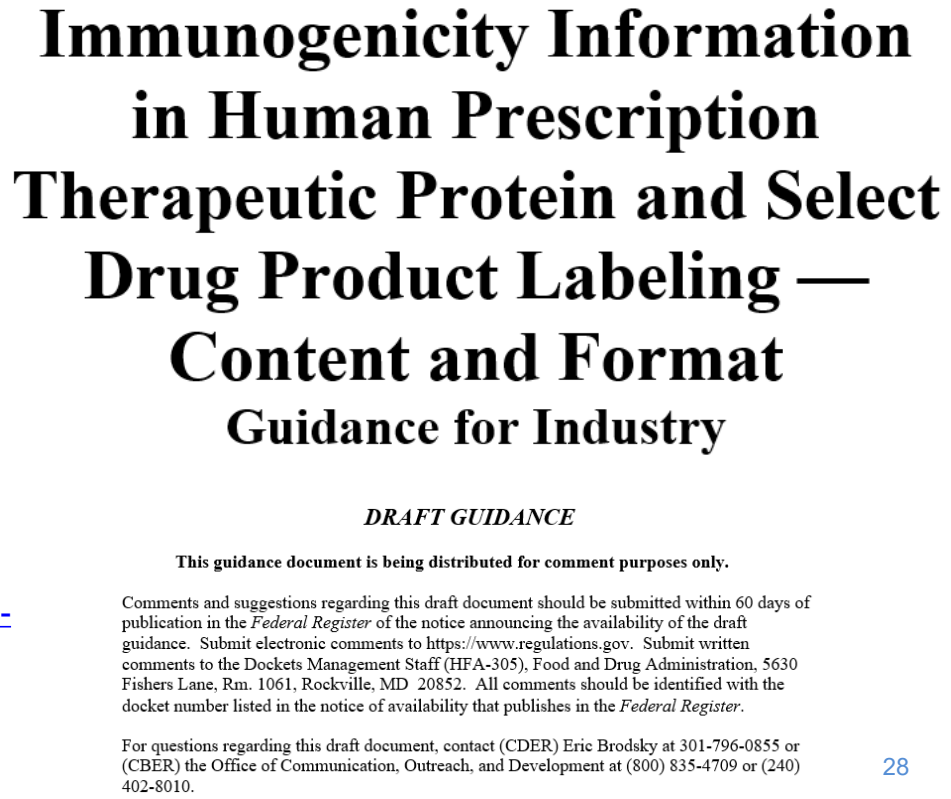
Updating Immunogenicity Information in Labeling

Applicants can voluntarily update their labeling to be consistent with the recommendations in this draft guidance

So far, 20 labeling updated to be consistent with recommendations in the guidance

Immunogenicity Information in Labeling: Comments to Docket

If you have any comments about the Immunogenicity Labeling Draft Guidance, please submit comments to the docket[1]



Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling — Content and Format

Guidance for Industry

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1 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/immunogenicity-information-human-prescription-therapeutic-protein-and-select-drug-product-labeling

Prescribing Information Resources

- 11 Description
- 12 Clinical Pharmacology
  - 12.1 Mechanism of Action, 12.2 Pharmacodynamics, and 12.3 Pharmacokinetics
  - 12.4 Microbiology
  - 12.5 Pharmacogenomics
  - 12.6 Immunogenicity

Guidance

- Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling (draft guidance)

Presentation

- Immunogenicity Information in Labeling (presentation and video)

- 13 Nonclinical Toxicology

Immunogenicity labeling resources

[1] https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/prescribing-information-resources

Frequently Asked Questions about Labeling for Prescription Medicines

For Healthcare Professionals and Patients

- What Is Prescribing Information?
- What are the Highlights of Prescribing Information?
- What are the key features of Highlights of Prescribing Information?
- What is the Table of Contents?
- What is the Full Prescribing Information?
- How Is Prescribing Information Approved?
- When Is Prescribing Information Updated?
- What Labeling is on the Packaging of Prescription Medicines?

[1] https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/frequently-asked-questions-about-labeling-prescription-medicines

Summary: Immunogenicity Labeling Guidance

1. Recommends distinguishing between products associated with clinically significant immunogenicity with products with immunogenicity without identified clinically significant effects

2. Recommends a new dedicated subsection (*Immunogenicity* subsection – subsection 12.6) in the CLINICAL PHARMACOLOGY section


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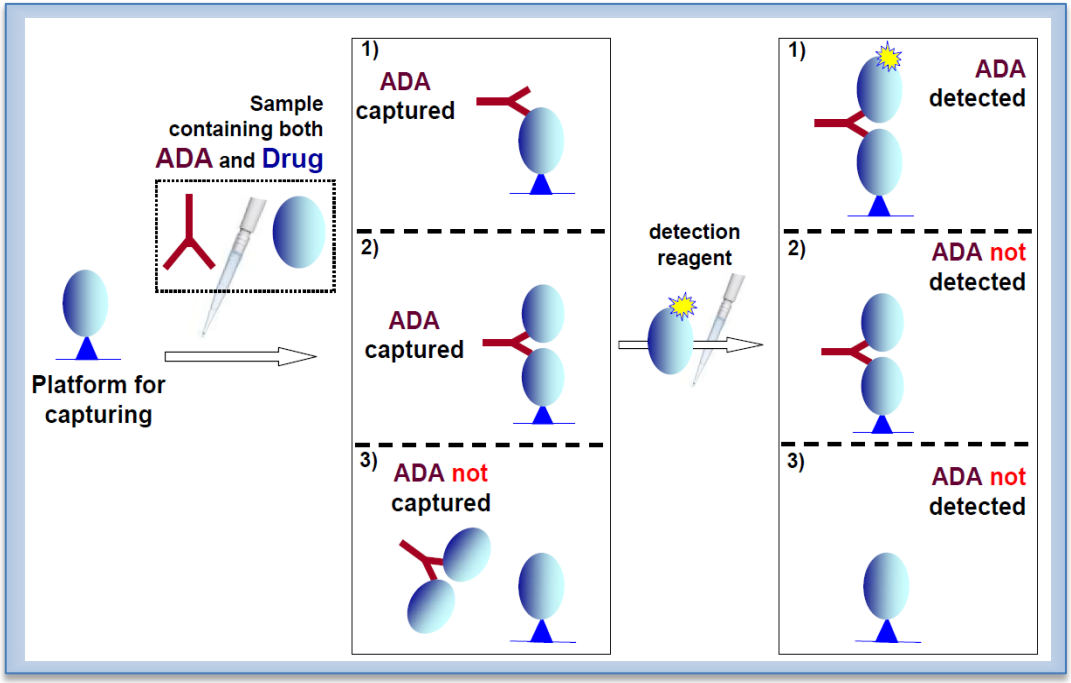
ADMINISTRATION

FDA's Backup Slides

ADA Impact on PK – Backup Slides

Drug Interference and Drug Tolerance



- Detection of ADA is highly dependent on assay sensitivity*
- Drug concentration in ADA sample can reduce the ADA assay sensitivity (i.e., drug interference)
- Drug tolerance is dependent on the ADA level: ↑ ADA level tolerates a higher drug conc. (i.e., higher drug tolerance)
- Drug tolerance maybe improved using approaches such as acid dissociation that disrupt ADA-drug complexes

Desirable feature of ADA assays

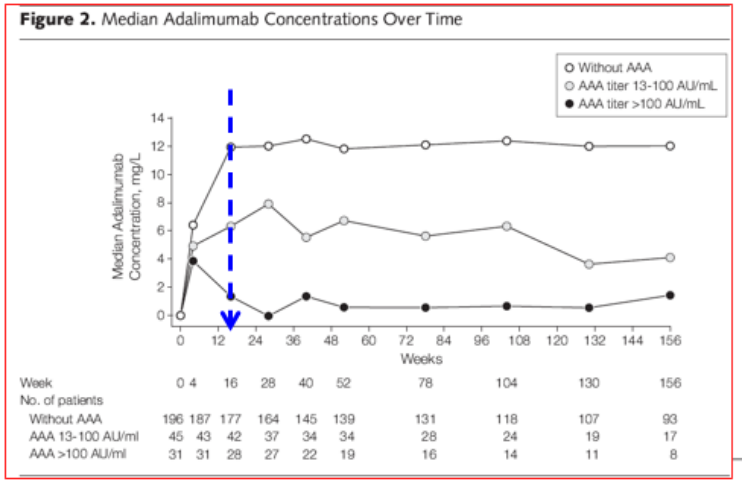
[drug tolerance level] > [trough drug concentration]

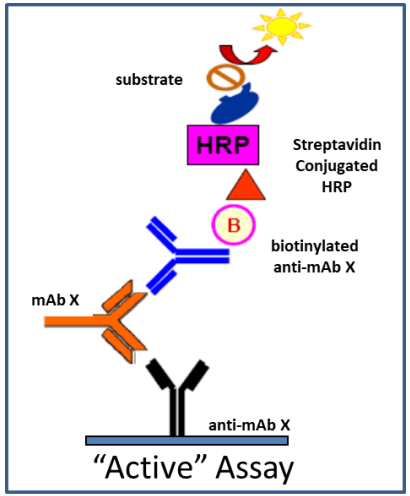
*FDA guidance recommends at least 100 ng/mL

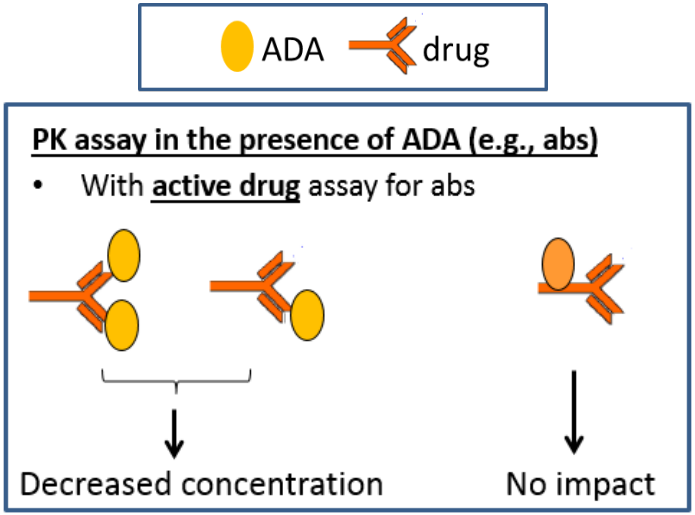
Clearing ADA Associated with Decreased Drug Concentration

(understanding of PK assay facilitate interpreting ADA impact)

- Example: mAb with clearing ADA (& 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

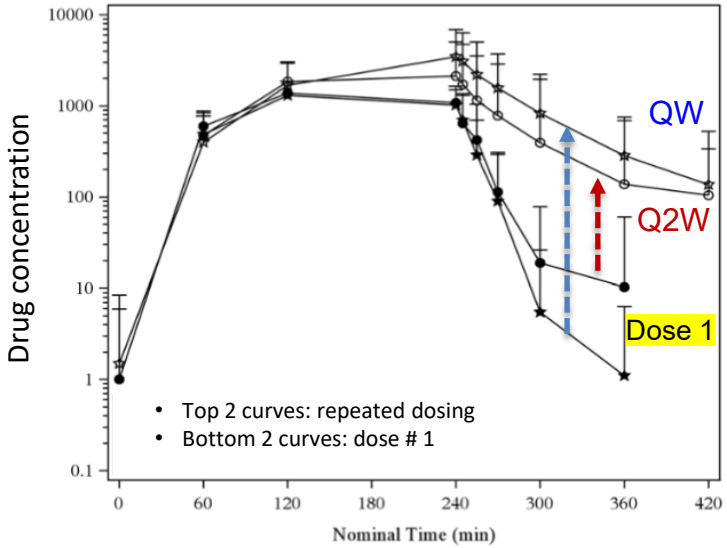


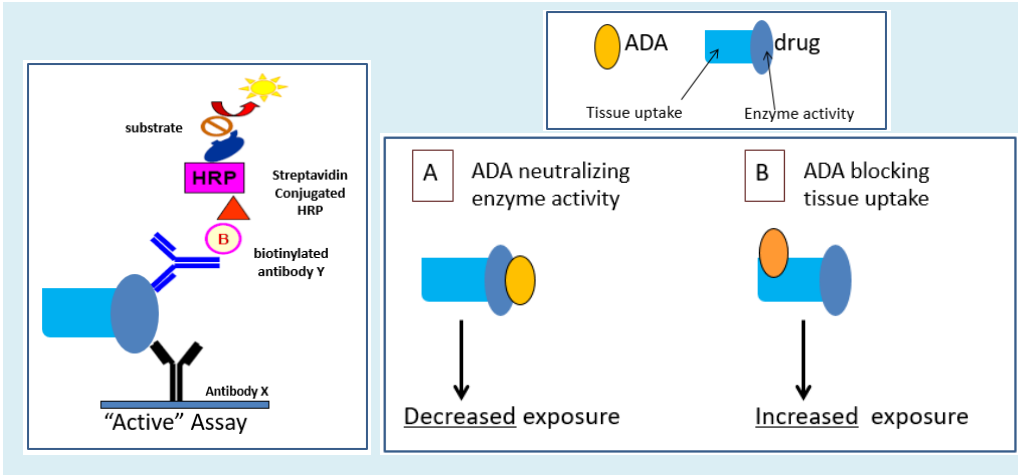




Sustaining ADA Associated with Increased Drug Concentration (understanding of PK assay facilitate interpreting ADA impact)

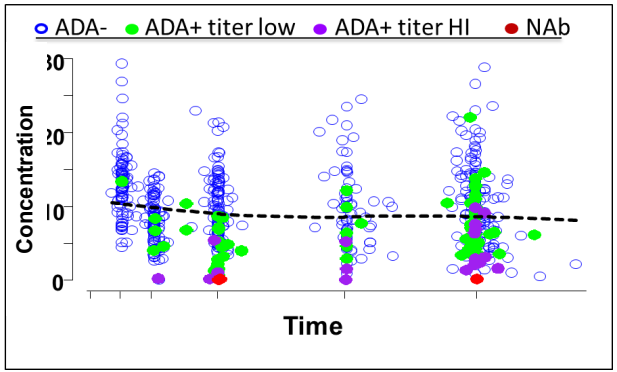
- Example: an enzyme replacement therapy with sustaining ADA
- Observed higher drug concentrations after repeated dosing
- **Hypotheses:** ADA that interfere with cellular uptake (elimination) of drug from circulation



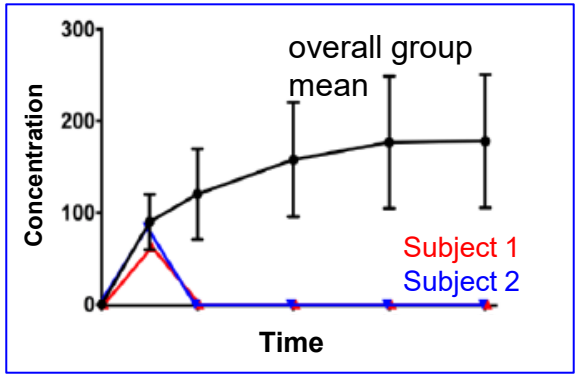


Examples of Other Types of Analysis for Clinical Impact on PK

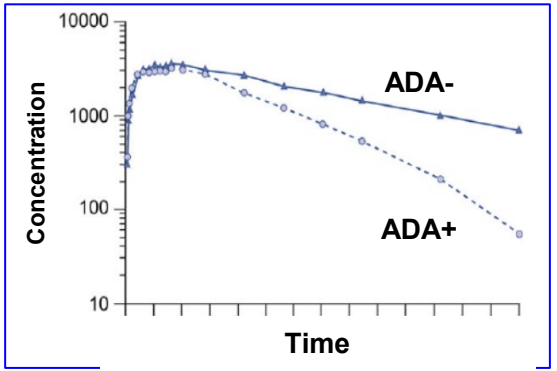
Multiple dose study
(ADA-, ADA titer H/L, NAb)



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

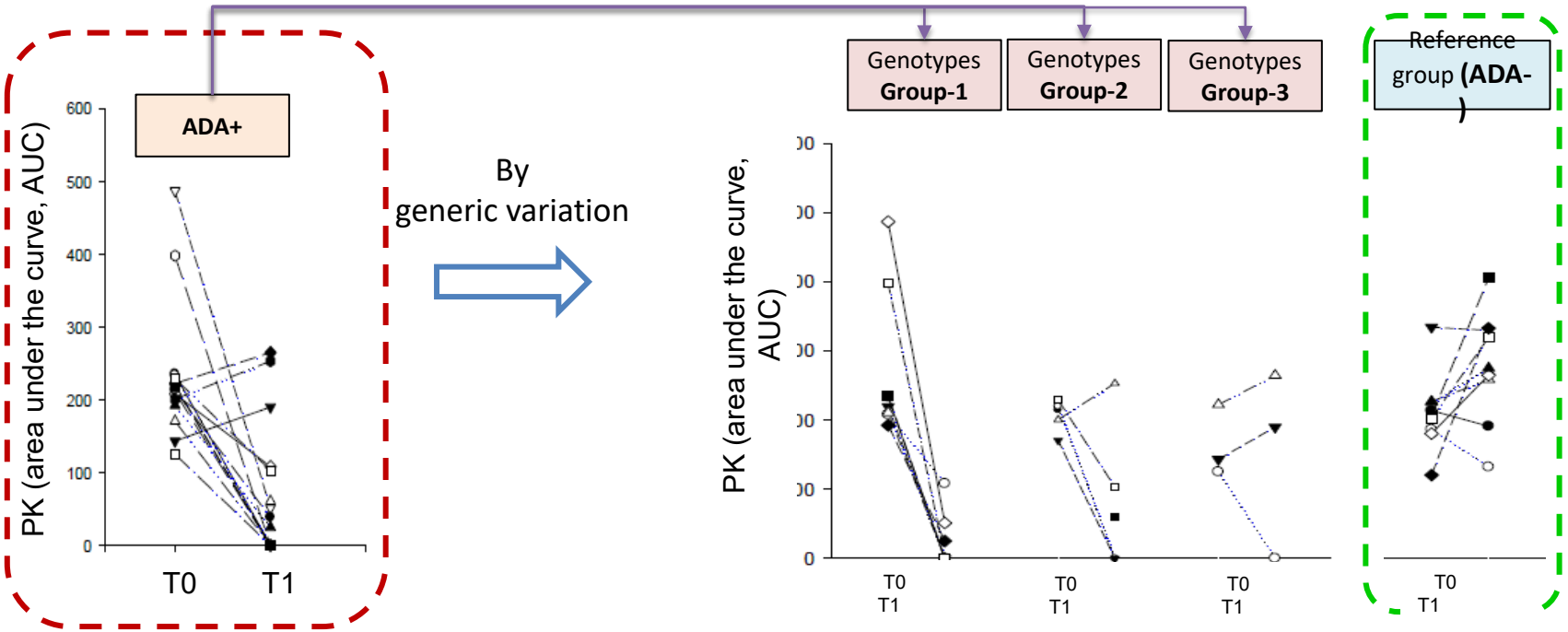


Single dose study
(temporal concentration profiles)



When Feasible, Explore ADA Impact by Subject Genotype

ADA impact on PK can vary by genetic variation



Use Multiple Approaches to Evaluate Impact on PK

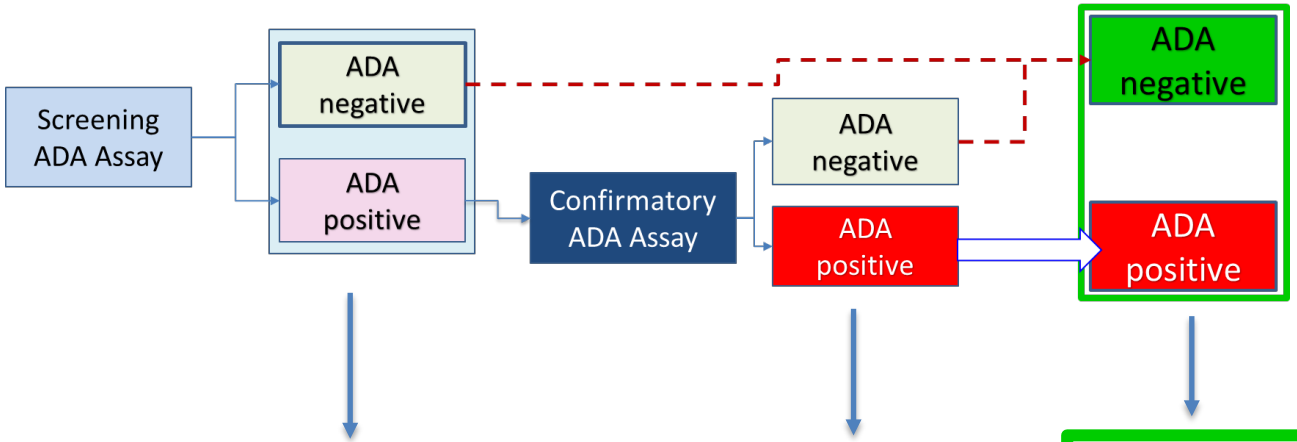
- **Between-subject** comparison of drug concentration: ADA+ vs. ADA-
  - Grouped by ***subject*** ADA status (assumes ADA+ at all timepoints for ADA+ subjects)
    - Other ways of grouping: persistent/transient ADA+ vs. ADA-, …
  - Grouped by ***sample*** ADA status at each timepoint
- **Within-subject** 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

"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

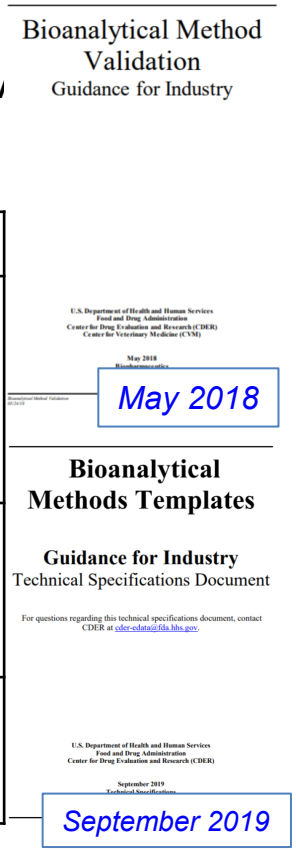


Sample #	Screening assay	Confirmatory assay	Integrated ADA status
1	Positive	Positive	Positive
2	Positive	Positive	Positive
3	Positive	Negative	Negative
4	Positive	Negative	Negative
5	Negative	**NOT TESTED**	**Negative**
6	Negative	**NOT TESTED**	**Negative**

FDA Initiative – Enhanced Communication about PK Methods

- The question – Do measured concentration data reflect active drug lev
- 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



Immunogenicity Information in Labeling - Backup Slides

Principles of Placing Immunogenicity Information in Labeling

Location of immunogenicity information in labeling depends on:

1. Adequacy of the methodology for ADA detection
2. Sufficiency of data to draw clinical conclusions, and
3. Whether the ADA may have clinically significant effect(s)

ADA-Associated Clinically Significant AR or Risks From ADA: W&P Section (1 of 2)

Succinct description of clinically significant AR or risks from ADA

5 WARNINGS AND PRECAUTIONS

…

5.x Severe Hypersensitivity Reactions Including Anaphylaxis

Severe hypersensitivity reactions (bronchospasm, angioedema, and anaphylaxis) have occurred in DRUG-X-treated patients.

ADA-Associated Clinically Significant AR or Risks From ADA: W&P Section (2 of 2)

Estimate of rate of clinically significant AR or risks from ADA

… In Studies A, B, and C, 2 out of 1,200 DRUG-X-treated patients with psoriasis developed anaphylaxis during the 6-month treatment period; one of those patients developed anti-drugimab-wxyz antibodies *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.6)].*

Clinically actionable recommendations

If DRUG-X-treated patients develop a severe hypersensitivity reaction, discontinue DRUG-X *[see Contraindications (4)].*

ADA Associated AR (Clinically Significant ADA) in ADVERSE REACTIONS Section

6 ADVERSE REACTIONS

...

6.1 Clinical Trials Experience

Summarize AR associated with ADA

...

Immunogenicity: Anti-Drug Antibody-Associated Adverse Reactions

In Studies A, B, and C in patients with psoriasis, hypersensitivity reactions (urticaria, pruritus, and flushing) occurred in 9% of DRUG-X-treated patients with anti-drugimab-wxyz antibodies and in 2% of DRUG-X-treated patients who did not develop anti-drugimab-wxyz antibodies during the six-month treatment period *[see Clinical Pharmacology (12.6)].* In these studies, one DRUG-X-treated patient with anti-drugimab-wxyz antibodies developed anaphylaxis *[see Warnings and Precautions (5.x)].*

ADA Associated With Clinically Significant Change in Effectiveness in CLINICAL STUDIES Section (1 of 2)

14 CLINICAL STUDIES

#1 Description and results

…

In Studies A, B, and C in patients with psoriasis, the primary endpoint was the proportion of patients who achieved a reduction in the PASI score of at least 75% from baseline to month 6 (PASI 75). At month 6, 89% (890/1000) of DRUG-X-treated and 10% (100/1000) of control-treated patients in the pooled studies achieved PASI 75, respectively.

PASI = Psoriasis Area and Severity Index

ADA Associated With Clinically Significant Change in Effectiveness in CLINICAL STUDIES Section

#2 Subgroup analysis by ADA response

… Among DRUG-X-treated patients who developed anti-drugimab-wxyz antibodies during the six-month treatment period, 50% (15/30) achieved PASI 75, compared to 90% (875/970) of DRUG-X-treated patients who did not develop anti-drugimab-wxyz antibodies ... *[see Warnings and Precautions (5.x) and Clinical Pharmacology (12.6)].*

PASI = Psoriasis Area and Severity Index

FDA's Labeling Resources for Human Prescription Drugs

For Industry

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FDA's labeling resources for human prescription drugs are primarily directed to industry staff who develop human prescription drug* labeling. Human prescription drug labeling (1) contains a summary of the essential scientific information needed for the safe and effective use of the drug; and (2) includes the Prescribing Information, FDA-approved patient labeling (Medication Guides, Patient Package Inserts, and/or Instructions for Use), and/or carton and container labeling.

If you are a healthcare professional, patient, or caregiver, visit Frequently Asked Questions about Labeling for Prescription Medicines.

- **Searchable Labeling Databases**
- **How May "Current" Labeling Be Different Than "FDA-Approved" Labeling**
- **Searchable Product Databases**
- **Imported-Drug Specific Labeling Resources**
- **Resources for Promotional Labeling and Other FDA-Regulated Products**

[1] https://www.fda.gov/drugs/laws-acts-and-rules/fdas-labeling-resources-human-prescription-drugs

Prescribing Information Resources

[1] https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/prescribing-information-resources

Notable Recently Published Labeling Guidances Over Past Three Years

- (Draft) Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling. February 2022.
- (Draft) Geriatric Information in Human Prescription Drug and Biological Product Labeling. September 2020.
- (Revised Draft) Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products - Content and Format. July 2020.
- (Draft) Instructions for Use - Patient Labeling for Human Prescription Drug and Biological Products and Drug-Device and Biologic-Device Combination Products - Content and Format. July 2019
- (Draft) Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products - Content and Format. July 2019.
- Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling. March 2019.