Immunogenicity Information in Labeling- Highlights from the new FDA draft guidance (or how you too can get a kick out of section 12.6)

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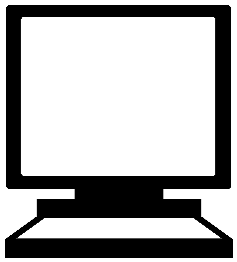
Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


FDA
Patients expect safe and effective medicine with every dose they take.


FDA
Pharmaceutical quality is
assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence
in their *next* dose of medicine.

Disclaimer

- The views and opinions expressed herein represent those of the presenter and do not necessarily represent an official FDA position.

- The labeling examples in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended templates

- Focus on CDER portfolio biologics regulated under section 351 (a) of US Public Health Service Act

Immunogenicity at FDA

- Who reviews it?
  - Depends on the biologic product class
    - CDER - monoclonal antibodies, growth factors, fusion proteins, cytokines, enzymes, hormones, therapeutic toxins
    - CBER- allergenics, blood and blood components including convalescent immune sera, cellular and gene therapies, vaccines

Immunogenicity labeling for CDER Products

- Who reviews it?
  - Multi-disciplinary collaboration between OBP immunogenicity assessors (suitability of ADA assays), OCP Clin/Pharm reviewers and OND clinical reviewers (clinical impact of ADA on PK/PD/efficacy/safety).

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

Guidance for Industry

February 2022
Labeling

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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

Overview of Presentation

- Discuss creation of the new dedicated labeling subsection 12.6 for immunogenicity information (*Immunogenicity* subsection)
  - Provide an overview on how to develop the *Immunogenicity* subsection
- Provide recommendations on when to update immunogenicity information in labeling

Immunogenicity Labeling Draft Guidance[1]

Assist applicants with incorporating immunogenicity information into labeling of 351(a) 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**

This guidance does not apply to biological products that are devices regulated under a biologics license application (BLA), vaccines, or allergenic products, or biological products that are licensed under section 351(k) of the PHS Act.

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 = pharmacokinetic; PD = pharmacodynamic

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 6)
- 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

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Immunogenicity Subsection (Subsection 12.6) under CLINICAL PHARMACOLOGY

Essentially all therapeutic proteins and selected drug products will have an *Immunogenicity* subsection (subsection 12.6)

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)

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Guidance Immunogenicity Label Examples for Section 12.6

The labeling examples in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended templates.

When Methodology for Immunogenicity Evaluation is Inadequate

(*Immunogenicity* Subsection)

12 CLINICAL PHARMACOLOGY

…

12.6 Immunogenicity

There is **insufficient information** to characterize the ADA response to *[proper name]* and the effects of ADA on PK, PD, safety, or effectiveness of *[core name]* products.

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

Label Examples when Methodology is Adequate

Clinically significant impact

- Example #1: ADA rates negatively associated with PK and efficacy
- Example #2: ADA rates associated with higher AE, but effect on PK or effectiveness are not fully characterized

Insufficient Data

- Example #3: low ADA rates preclude characterization of effect of PK, PD, safety and effectiveness
- Example #4: ADA impact on PK is detected but it is unknown if PK effects are clinically significant

Clinically insignificant inpact

- Example #5: ADA rates not associated with an impact on PK, PD or AE
- Example #6: ADA effects PK but these effects are not clinically significant.

When Methodology for Immunogenicity Evaluation is Adequate (*Immunogenicity* Subsection)

#1 Immunogenicity Clarification Statement

12.6 Immunogenicity

The observed incidence of ADA is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of *[proper name]* or of other *[core name]* products.

When Methodology for Immunogenicity Evaluation is Adequate (*Immunogenicity* Subsection)

#2 ADA data and #3 ADA effects on PK or PD and/or #4 potential clinical effects of ADA

Include the following in the *Immunogenicity* subsection:

- ADA incidence (including neutralizing antibodies)
- Known effects of ADA on:
  - PK under the Anti-Drug Antibody Effects on Pharmacokinetics heading
  - PD under the Anti-Drug Antibody Effects on Pharmacodynamics heading
  - Brief statement of potential clinical effects

Clinically Significant ADA Example #1

(*Immunogenicity* Subsection) (1 of 2)

12.6 Immunogenicity

[#1 Include immunogenicity clarification statement]

#2 ADA Data

During the six-month treatment period in Studies A, B, and C, 312/1200 (26%) of DRUG-X-treated patients developed anti-drugimab-wxyz antibodies.

Clinically Significant ADA Example #1

ADA rates are negatively associated with PK and efficacy **(2 of 2)**

#3 Effects of ADA on PK

Anti-Drug Antibody Effects on Pharmacokinetics

The presence of anti-drugimab-wxyz antibodies increased drugimab-wxyz clearance. After six months of dosing every three weeks, drugimab-wxyz serum trough concentrations in patients who developed anti-drugimab-wxyz antibodies ranged from < 0.1 (undetectable) to 2 mcg/mL compared to a range of 3 to 6 mcg/mL in patients who had not developed anti-drugimab-wxyz antibodies.

#4 Brief statement of potential clinical effects

Anti-drugimab-wxyz antibody formation was associated with reduced efficacy *[see Warnings and Precautions (5.x) and Clinical Studies (14)].*

Clinically Significant ADA Example #2

ADA rates associated with higher AE,
but effect on PK or effectiveness not fully characterized

12.6 Immunogenicity

[#1 Include immunogenicity clarification statement]

#2 ADA Data

During the six-month treatment period in Studies A, B, and C, 312/1200 (26%) of DRUG-X-treated patients developed anti-drugimab-wxyz antibodies.

#4 Brief statement of potential clinical effects

Anti-drugimab-wxyz antibody formation was associated with a higher incidence of hypersensitivity AR than observed in DRUG-X-treated patients without anti-drugimab-wxyz antibodies *[see Adverse Reactions (6.1)].* The effect of ADA on PK and effectiveness have not been fully characterized.

ADA = antidrug antibodies; AR = adverse reactions

Insufficient Data To Determine Clinical Effects of ADA: Example #3

Low ADA percentage; thus, it is unknown if ADA is clinically significant

12.6 Immunogenicity

[#1 Include immunogenicity clarification statement]

#2 ADA Data

In the six-month treatment period in Studies A, B, and C, the incidence of anti-drugimab-wxyz antibody formation was 1% (12 of 1,200 total DRUG-X-treated patients).

#4 Brief statement of potential clinical effects

Because of the low occurrence of ADA, the effect of these antibodies on the PK, PD, safety, and/or effectiveness of drugimab products is unknown.

Insufficient Data To Determine Clinical Effects of ADA: Example #4 (*Immunogenicity* Subsection) (1 of 2)

ADA has PK effects but unknown if PK effects are clinically significant

12.6 Immunogenicity

[#1 Include immunogenicity clarification statement]

#2 ADA Data

During the one-year treatment period in Study A, 15/300 (5%) of DRUG-X-treated patients developed anti-drugimab-wxyz antibodies.

Insufficient Data To Determine Clinical Effects of ADA: Example #4 (*Immunogenicity* Subsection) (2 of 2)

ADA has PK effects but unknown if PK effects are clinically significant

#3 ADA effects on PK and #4 brief statement of potential clinical effects

Anti-Drug Antibody Effects on Pharmacokinetics

Among DRUG-X-treated patients who developed ADA, 5 of 7 patients with drugimab-wxyz exposure data available had reduced drugimab-wxyz concentrations (approximately 20% lower compared to patients who did not develop anti-drugimab-wxyz antibodies). There is insufficient data to assess whether observed ADA-associated PK changes reduce effectiveness.

Clinically Insignificant ADA Example #5

(*Immunogenicity* Subsection)

ADA rates have no identified impact on PK, PD or AE

12.6 Immunogenicity

[#1 Include immunogenicity clarification statement]

#2 ADA Data

During the six-month treatment period in Studies A, B, and C, 312/1200 (26%) of DRUG-X-treated patients developed anti-drugimab-wxyz antibodies.

#4 Brief statement of potential clinical effects

There was no identified clinically significant effect of ADA on PK, PD, safety, or effectiveness of DRUG-X over the treatment duration of six months.

Clinically Insignificant ADA Example #6

(*Immunogenicity* Subsection)

ADA effects PK but these effects are not clinically significant

12.6 Immunogenicity

[#1 Include immunogenicity clarification statement] #2 ADA Data

During the one-year treatment period in Study A, 15/300 (5%) of DRUG-X-treated patients developed anti-drugimab-wxyz antibodies.

#3 ADA effects on PK and #4 brief statement of potential clinical effects

Anti-Drug-Antibody Effects on Pharmacokinetics

Among DRUG-X-treated patients who developed ADA, 5 of 7 patients with drugimab-wxyz exposure data available had reduced drugimab-wxyz concentrations (approximately 10% lower compared to patients who did not develop anti-drugimab-wxyz antibodies). These ADA-associated PK changes were not identified to be clinically significant.

Additional sections mentioned in the guidance- only if ADA have detectable effects

6 ADVERSE REACTIONS SECTION

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6.1 Clinical Trials Experience

List Anti-Drug Antibody-Associated Adverse Reactions

14 CLINICAL STUDY SECTION...

If ADA are associated With Clinically Significant Change in Effectiveness, provide a summary of results

5 WARNINGS AND PRECAUTIONS SECTION...

5.x Severe Hypersensitivity Reactions Including Anaphylaxis

List rate of clinically significant AR or risks of AR associated with ADA

List clinically actionable recommendations

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Updating Immunogenicity Information in Labeling

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

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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