Immunogenicity Information in Labeling

April 5, 2022

Welcome

- Recording posted within 5 days: www.fda.gov/cdersbialearn
- Download the slides at right
- Attendance Certificate **available by request only for 2 weeks until (4/19/2022)**
- Certificate of attendance (BY REQUEST ONLY – Brenda.stodart@fda.hhs.gov) supports CEs from SOCRA, RAPS, SQA and ACRP.
  - Details: www.fda.gov/cdersbia
- Additional tutorials available through: www.fda.gov/cderlearn

CE for Physicians, Nurses, and Pharmacists

- 1.5 continuing education credits
- Fourteen days to claim credit (4/19/2022)
- Faculty disclosures
- Claim Code will be emailed

Get the Latest Regulatory Updates & Notifications for SBIA Webinars & Conferences

LinkedIn

Twitter

YouTube

SCAN ME

Hold phone camera to the image

Today's Presenters

Eric Brodsky, M.D.

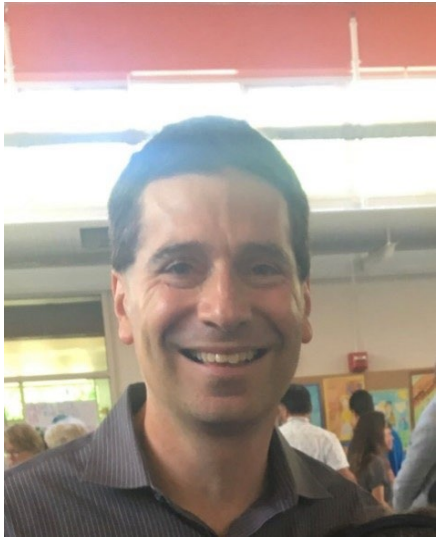
Associate Director

Labeling Policy Team

Office of New Drug Policy (ONDP)

Office of New Drugs (OND)

CDER | FDA



Today's Presenters

Daphne Guinn, Ph.D.

Regulatory Health Project Manager

Office of Clinical Pharmacology (OCP)

Office of Translational Science (OTS) CDER | FDA

CDER/SBIA Webinar
April 5, 2022

U.S. FOOD & DRUG ADMINISTRATION

Immunogenicity Information in Labeling

Daphne Guinn, *Regulatory Health Project Manager*, Office of Clinical Pharmacology, Office of Translational Science, CDER, FDA
Eric Brodsky, M.D., *Associate Director,* Labeling Policy Team, Office of New Drug Policy, Office of New Drugs, CDER, FDA

CDER = Center for Drug Evaluation and Research: SBIA = Small Business and Industry Assistance

Disclaimer

- The views and opinions expressed in this presentation represent those of the presenters, 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

Overview of Webinar

- What is immunogenicity and why should we care about immunogenicity?
- How does FDA evaluate immunogenicity?
- Immunogenicity information in labeling

Part 1: Learning Objectives

- Define immunogenicity
- Review the role of immunogenicity in FDA regulation
- Highlight why immunogenicity is important to consider for drug development
- Provide resources about FDA's approach to immunogenicity (e.g., FDA guidances)

What Is Immunogenicity and Why Is It Important To Consider For Drug Development?

Defining Immunogenicity[1]

- Immunogenicity is the ability of a substance to trigger an immune response in the body
- We can classify therapeutic immunogenicity into two broad categories:

Immunogenicity

Desired Immunogenicity

Undesired Immunogenicity

- Some biotherapeutic products
  - Proteins (e.g., monoclonal antibodies)
  - Nucleotides
- Some small molecules (e.g., peptides less than 40 amino acids)

[1] For the purposes of this presentation

Slide adapted from Rajanikanth Madabushi, Ph.D. 'Model Informed Drug Development Approaches for Immunogenicity Assessments' workshop (6/9/2021)

Undesired Immunogenicity

"... immunogenicity is defined as the propensity of the therapeutic protein product or other applicable drug product to generate an immune response to itself, a related structure, or product complex; and/or to induce *immunologically related adverse clinical events*"[1]

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

What is the Range of *Immunologically Related Adverse Clinical Events*?

Pharmacokinetics, Pharmacodynamics, Efficacy:

- No clinically significant effects
- Altered pharmacokinetics (e.g., bioavailability)
- Altered pharmacodynamics
- Change in efficacy

Slide adapted from Kristina Howard, DVM, Ph.D. from internal FDA seminar dated June 17, 2019

What is the Range of *Immunologically Related Adverse Clinical Events*?

Safety: potential immune responses

- Cross-react with native protein or receptor
- Potentiate biologic product
- Immune complex formation
- Hypersensitivity reactions
- Cytokine release syndrome

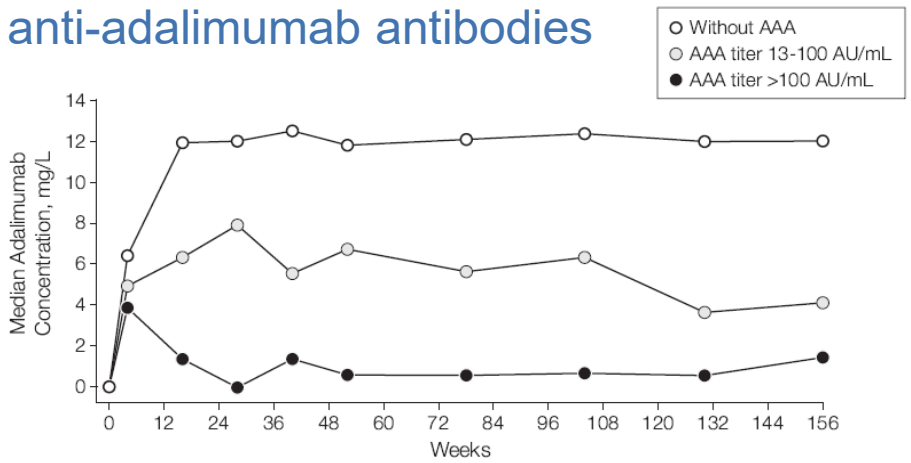
Slide adapted from Kristina Howard, DVM, Ph.D. from internal FDA seminar dated June 17, 2019

Reduced Adalimumab Concentrations and Loss of Efficacy Due to Immunogenicity (adalimumab 40 mg subcutaneously every other week in rheumatoid arthritis patients)

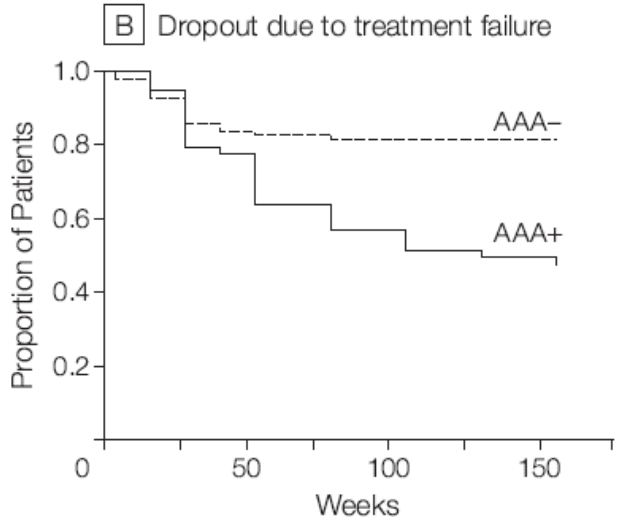
Figure 4. Overall Patient Dropout and Dropout Due to Treatment Failure

Figure 2. Median Adalimumab Concentrations Over Time

AAA = anti-adalimumab antibodies



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

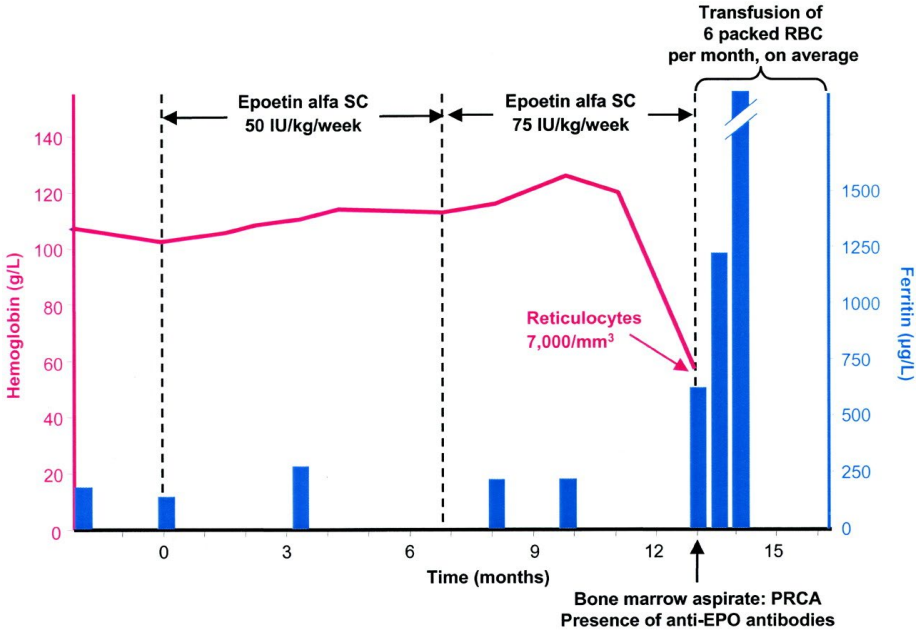


No. at risk				
AAA–	196	151	135	118
AAA+	76	59	43	29

Slide adapted from Yow-Ming Wang, PhD from Immunogenicity & Bioassay Summit (October 20-21, 2021)

Bartelds *et al.* 2011 JAMA

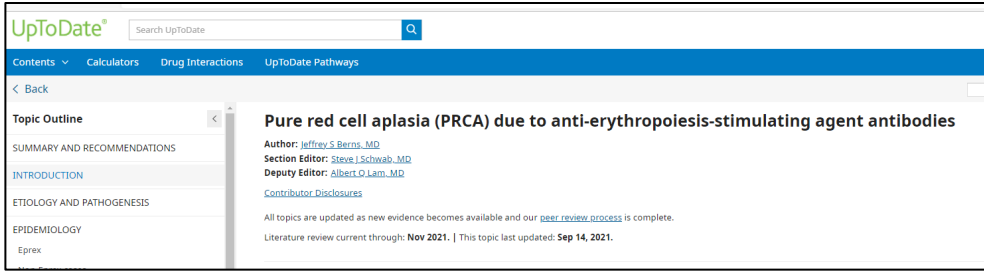
Pure Red Cell Aplasia Due to Immunogenicity to Epoetin alfa and Endogenous Erythropoietin



Rare event characterized by a rapid loss of endogenous reticulocytes due to **anti-epoetin alfa antibodies** most often seen in erythropoiesis-stimulating agent-treated patients with chronic kidney disease

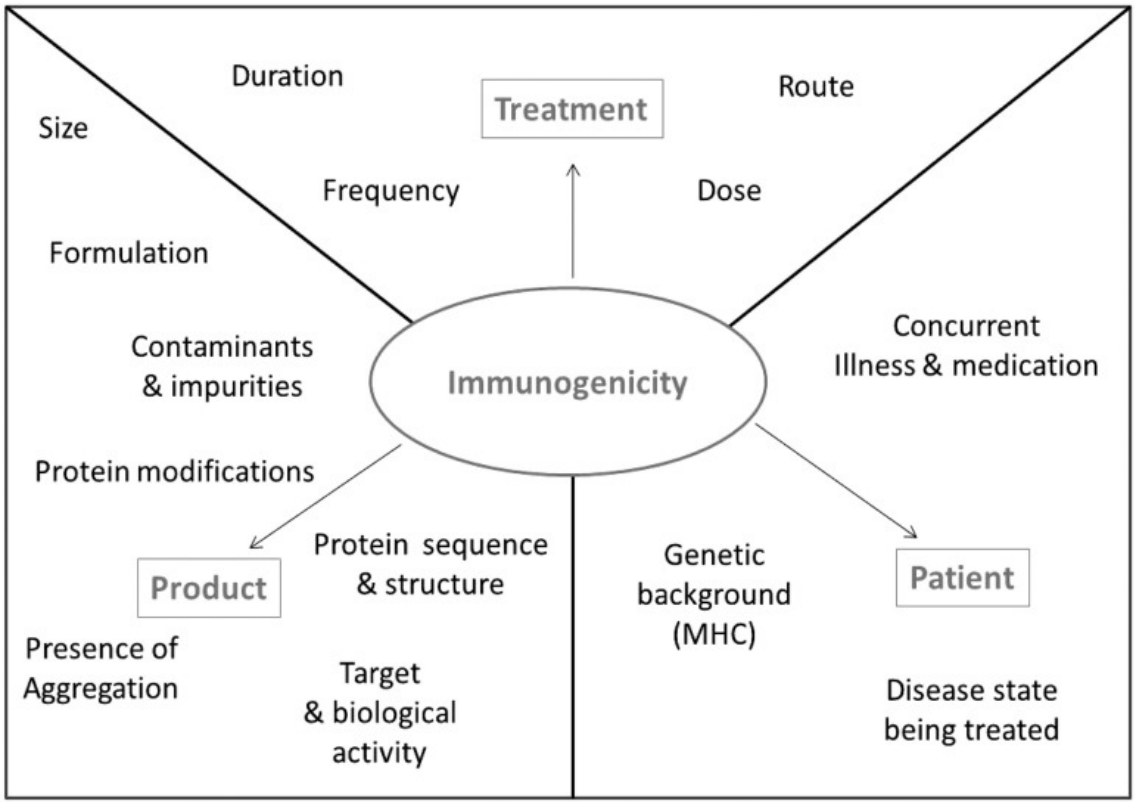
Rossert J, et al. J Am Soc Nephrol. 2004 Feb;15(2):398-406.

'UpToDate' page on **clinical management of pure red blood aplasia** due to immunogenicity (Accessed February 19, 2022)



How Does FDA Evaluate Immunogenicity?

Factors Impacting Immunogenicity

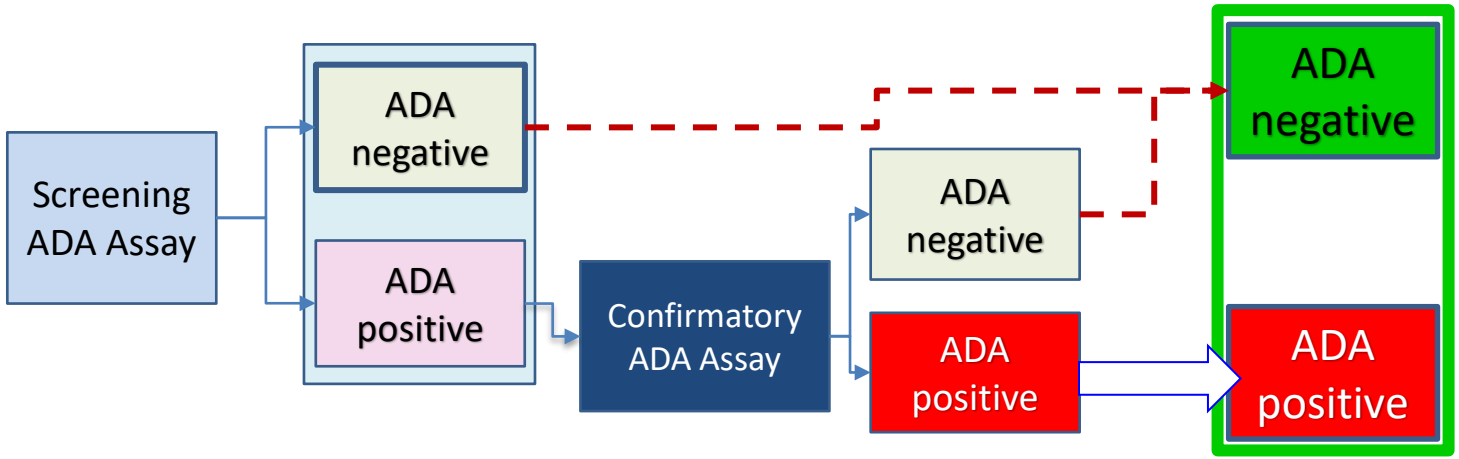


Ratanji KD et al. Immunogenicity of therapeutic proteins: influence of aggregation. J Immunotoxicol. 2013

Slide adapted from Kristina Howard, DVM, Ph.D. from internal FDA seminar dated June 17, 2019

How Does FDA Evaluate Immunogenicity?

Immunogenicity is most commonly measured in clinical trials by formation of **anti-drug antibodies (ADA)** (% of patients with ADA)



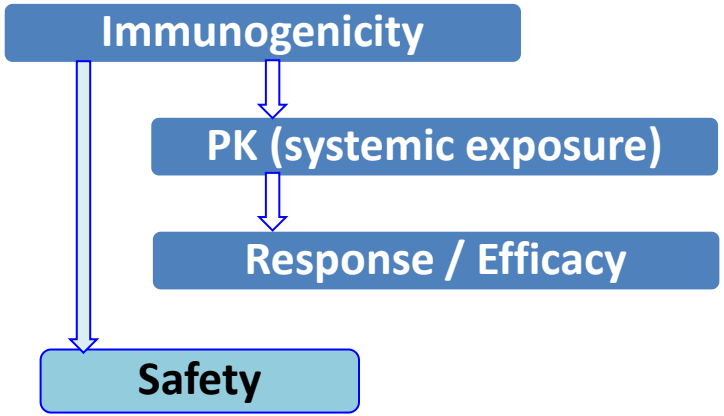
[1] Guidance for industry: *Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection* (January 2019)

Slide adapted from Yow-Ming Wang, PhD from Immunogenicity & Bioassay Summit (October 20-21, 2021)

How Does FDA Evaluate The Impact Of Immunogenicity?

Does the *presence or amount (titer) of ADAs* have a clinically meaningful impact on the drug or patient response (*safety and/or efficacy*)?

Differences in drug concentration, treatment response, or safety signals are evaluated between patients with and without ADAs (inter) and over time (intra)[1]



[1]*Guidance for industry: Immunogenicity Assessment for Therapeutic Protein Products (August 2014)*

Slide adapted from Yow-Ming Wang, PhD from Immunogenicity & Bioassay Summit (October 20-21, 2021)

Undesirable Immunogenicity: Therapeutic Protein Guidances

Guidance (2014): *Immunogenicity Assessment for Therapeutic Protein Products*

- Discusses product and patient risk factors that may contribute to immune response rates, as well as risk mitigation strategies

Guidance (2019): *Immunogenicity Testing of Therapeutic Proteins Developing and Validating Assays for Anti-drug Antibody Detection*

- Discusses the development and validation of immunogenicity assays

Slide adapted from Rajanikanth Madabushi, Ph.D. from 'Model Informed Drug Development Approaches for Immunogenicity Assessments' workshop (June 9, 2021)

Undesirable Immunogenicity: Biosimilar and Interchangeable Biosimilar Product Guidances

Guidance (2015): *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*

- Discusses assessment of biosimilarity which can include a comparison of clinical immunogenicity

Guidance (2017): *Considerations in Demonstrating Interchangeability to a Reference Product*

- Discusses assessment of interchangeability which can include a switching study to evaluate if switching results in differences in immunogenicity

Slide adapted from Rajanikanth Madabushi, Ph.D. from 'Model Informed Drug Development Approaches for Immunogenicity Assessments' workshop (June 9, 2021)

Undesirable Immunogenicity: Generic Drugs

Guidance (2016): *Immunogenicity-Related Considerations for Low Molecular Weight Heparin*

- Discusses an alternative ANDA approach that can be used to assess the effect of certain changes on the product's immunogenicity risk

Guidance (2021): *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin*

- Discusses identification, reduction, and mitigation of risks related to peptide-related impurities, which can include immunogenicity risk

Slide adapted from Rajanikanth Madabushi, Ph.D. from 'Model Informed Drug Development Approaches for Immunogenicity Assessments' workshop (June 9, 2021)

Today's Presenters

Eric Brodsky, M.D.

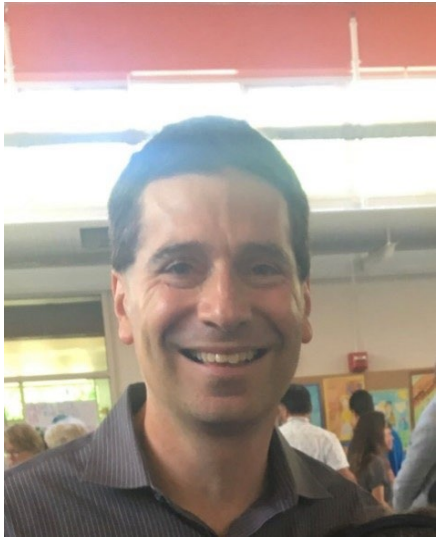
Associate Director,

Labeling Policy Team

Office of New Drug Policy (ONDP)

Office of New Drugs (OND)

CDER | FDA



Immunogenicity Information in Labeling

Part 2: Learning Objectives

- 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
- Describe when and how to incorporate immunogenicity information in other sections of labeling
- Provide recommendations on when to update immunogenicity information in labeling

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[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 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
- 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

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)

Immunogenicity Subsection (Subsection 12.6)

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

Immunogenicity Subsection (Subsection 12.6) Methodology is Inadequate

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

U.S. FOOD & DRUG ADMINISTRATION

Immunogenicity Subsection (Subsection 12.6) Methodology is Adequate

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

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

Clinically Significant ADA Example #1

(when methodology is adequate)
(*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

(when methodology is adequate) (*Immunogenicity* Subsection) (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
(when methodology is adequate)

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 (when methodology is adequate) (*Immunogenicity* Subsection) (1 of 2)

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 (when methodology is adequate) (*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 (when methodology is adequate) (*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 (when methodology is adequate) (*Immunogenicity* Subsection)

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 (when methodology is adequate) (*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.

ADVERSE REACTIONS Section (Section 6)

(1) Clinical Effects of ADA on AR Are Unknown[1] or (2) No Clinically Significant Effect of ADA on AR

Should not include any ADA information in the ADVERSE REACTIONS section

[1] See the exception for this category on a subsequent slide for “Narrow Therapeutic Index” drugs

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)].*

Clinical Effects of ADA on AR Is Unknown for a "Narrow Therapeutic Index" Drug:[1] ADVERSE REACTIONS Section

6 ADVERSE REACTIONS

…

6.1 Clinical Trials Experience

…

Immunogenicity: Unknown Clinical Effects of Anti-Drug Antibodies

There are insufficient data to evaluate the effect of ADA antibodies on AR *[see Clinical Pharmacology (12.6)].*

[1] "Narrow Therapeutic Index" drugs are defined for the purposes of this presentation as those for which minimal concentration changes may lead to serious toxicities or a loss of effectiveness

CLINICAL STUDIES Section (Section 14)

(1) Clinical Effects of ADA on Effectiveness Are Unknown[1] or (2) No Clinically Significant Effect of ADA on Effectiveness

Should not include any ADA subgroup effectiveness information in the CLINICAL STUDIES section

[1] See the exception for this category on a subsequent slide for “Narrow Therapeutic Index” drugs

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

Clinical Effects of ADA on Effectiveness Are Unknown for a "Narrow Therapeutic Index" Drug:[1] CLINICAL STUDIES Section

14 CLINICAL STUDIES

[[Include description and results of studies]]…

There are insufficient data to evaluate the effect of ADA on *[[include efficacy endpoint]].*

[1] "Narrow Therapeutic Index" drugs are defined for the purposes of this presentation as those for which minimal concentration changes may lead to serious toxicities or a loss of effectiveness

U.S. FOOD & DRUG ADMINISTRATION

WARNINGS AND PRECAUTIONS Section (Section 5)

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)].*

Clinically Significant Changes in Effectiveness Associated with ADA: W&P Section

W&P section should include clinically significant changes in effectiveness associated with ADA

U.S. FOOD & DRUG ADMINISTRATION

Updating Immunogenicity Information in Labeling

Updating Immunogenicity Information in Labeling

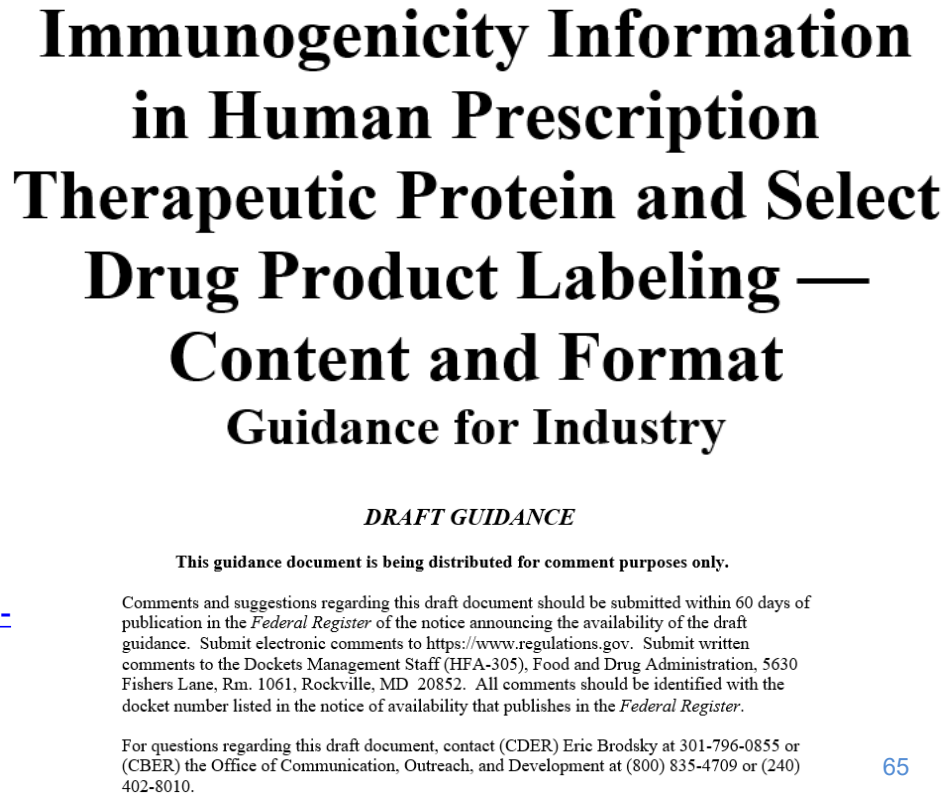
- When new immunogenicity data/information could affect prescribing decisions or the clinical management, applicants should submit to FDA proposed revised labeling containing the updated immunogenicity information
- When this guidance is final, FDA recommends that applicants propose labeling updates 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

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

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.

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

Challenge Question #1

Which of the following statements is **inconsistent** with FDA's recommendations for the *Immunogenicity* subsection (subsection 12.6)?

1. Summarize results from immunogenicity studies
2. Briefly identify potential ADA effects on pharmacokinetics
3. Provide the duration of exposure to the drug and time period for sampling ADA
4. Remove this subsection if there are insufficient data to determine clinical effects of ADA
5. Provide neutralizing antibodies

ADA = anti-drug antibodies

Challenge Question #2

What ADA information should appear in the ADVERSE REACTIONS section?

1. ADA incidence regardless of whether ADA are associated with AR
2. ADA incidence only when ADA are associated with AR
3. ADA incidence only when there is no clinically significant effect of ADA on safety
4. Adverse reactions associated with ADA (e.g., hypersensitivity reactions)
5. Both 2 and 4

ADA = anti-drug antibodies

Challenge Question #3

What immunogenicity information should appear in the CLINICAL STUDIES section?

1. ADA incidence only when ADA associated with clinically significant change in effectiveness
2. Adverse reactions associated with ADA (e.g., hypersensitivity reactions)
3. Routinely include subgroup effectiveness analysis by ADA formation
4. Include subgroup effectiveness analysis by ADA formation when ADA associated with clinically significant change in effectiveness
5. Both 1 and 4

Challenge Question #4

What immunogenicity information should appear in the WARNINGS AND PRECAUTIONS section, if known?

1. Succinct description of clinically significant adverse reactions or risks from ADA
2. Clinically significant changes in effectiveness associated with ADA
3. Numerical estimate of the rate of the clinically significant adverse reactions or risks
4. Clinically actionable recommendations (e.g., premedication to reduce risk of hypersensitivity reactions)
5. All the above

Challenge Question #5

Immunogenicity information in the labeling must, should, or may be updated when:

1. New immunogenicity data/information becomes available that could affect prescribing decisions (e.g., hypersensitivity reactions associated with ADA)
2. Applicant submits next supplement (e.g., to move ADA incidence from the ADVERSE REACTIONS section to new *Immunogenicity* subsection – subsection 12.6)
3. Only when new information becomes available that causes immunogenicity information in labeling to be inaccurate
4. Both 1 and 2

Q&A Session

Open Q&A begins shortly – type your questions in the Q&A pod now.

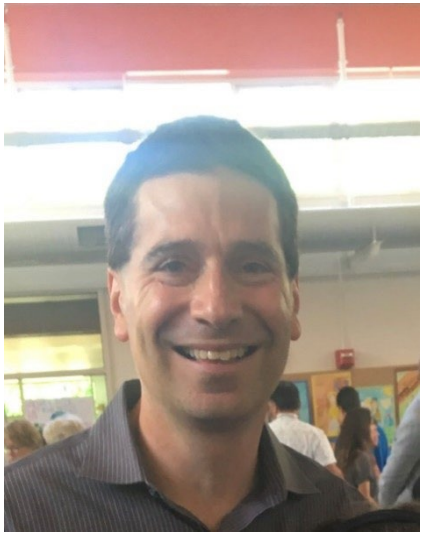
Learn about other resources from CDER Small Business & Industry Assistance:

Visit Our Website!

Additional questions or comments?

Email: CDERSBIA@fda.hhs.gov

Daphne Guinn, Ph.D.
Regulatory Health Project Manager
Office of Clinical Pharmacology (OCP)
Office of Translational Science (OTS)
CDER | FDA



Eric Brodsky, M.D.
Associate Director
Labeling Policy Team
Office of New Drug Policy (ONDP)
Office of New Drugs (OND)
CDER | FDA

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

SBIA Closing

- Recording posted within 5 days: www.fda.gov/cdersbialearn
- Certificate of Attendance (ONLY BY REQUEST – Brenda.Stodart@fda.hhs.gov) supports CEs:
- Details: www.fda.gov/cdersbia
- Additional tutorials available through: www.fda.gov/cderlearn

Certificate of Attendance Request

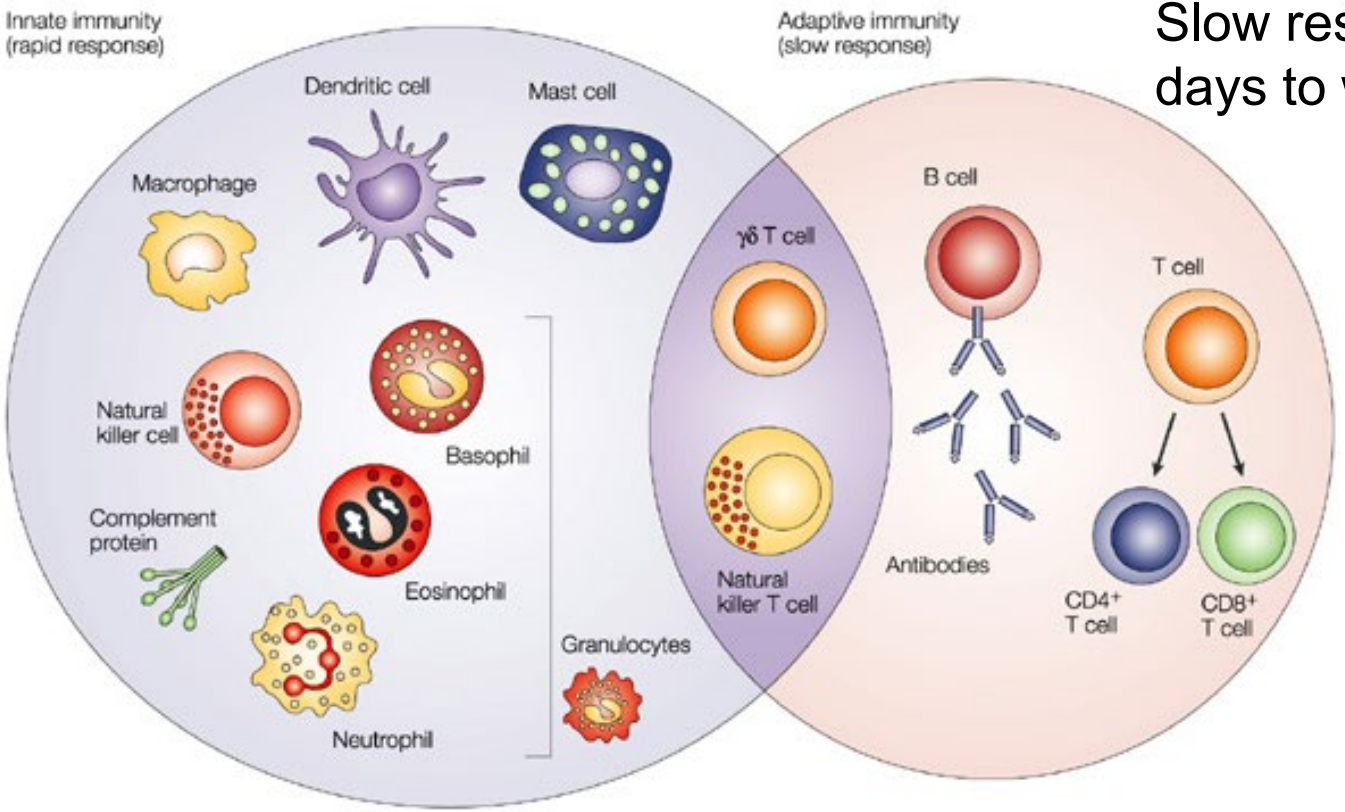
available for 2 weeks only (4/19/2022)

Additional Slides

Innate versus Adaptive Immunity

Fast response = minutes to hours

Slow response = days to weeks



Innate Immunity

Adaptive Immunity

Nature Reviews | Cancer

Additional References

- Khanna R, et al. “Review article: a clinician’s guide for therapeutic drug monitoring of infliximab in inflammatory bowel disease”. Aliment Pharmacol Ther 2013; 38: 447-459.
- Singh SK. “Impact of Product-Related Factors on Immunogenicity of Biotherapeutics”. Jour Pharm Sci, Feb 2011; Vol 100 (2): 354-387.
- Van Walle I, et al. “Immunogenicity screening in protein drug development.” Expert Opin Biol Ther (2007) 7(3): 405-418.
- Ternant D & Paintaud G. “Pharmacokinetics and concentration-effect relationships of therapeutic monoclonal antibodies and fusion proteins.” Expert Opin Biol Ther (2005) 5(Suppl.1):S37-47.
- Wang Y-MC, Jawa V and Ma M. “Immunogenicity and PK/PD evaluation in biotherapeutic drug development: scientific considerations for bioanalytical methods and data analysis.” Bioanalysis (2014) 6(1),79-87.
- Bugelski PJ & Treacy G. “Predictive power of preclinical studies in animals for the immunogenicity of recombinant therapeutic proteins in humans.” Current Opin Mol Ther 2004 6(1):10-16.
- Bendtzen K. “Immunogenicity of anti-TNF-α biotherapies: II. Clinical relevance of methods used for anti-drug antibody detection.” Front Immunol. 08 April 2015.

Resources

- Draft guidance for industry, *Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling — Content and Format* (February 2022).
- Prescription Drug Labeling Resources
- Immunogenicity development guidances:
  - Immunogenicity Assessment for Therapeutic Protein Products (August 2014)
  - Immunogenicity Testing of Therapeutic Proteins Developing and Validating Assays for Anti-drug Antibody Detection (January 2019)
  - Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015)
  - Considerations in Demonstrating Interchangeability to a Reference Product (May 2019)
  - Immunogenicity-Related Considerations for Low Molecular Weight Heparin (February 2016)
  - ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin (May 2021)

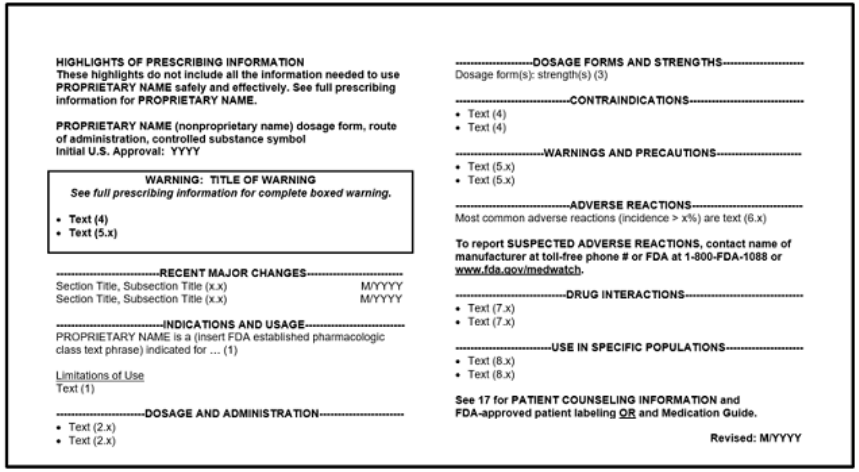
U.S. FOOD & DRUG ADMINISTRATION

Prescription Drug Labeling Resources

Prescription Drug Labeling Resources

FDA's *Prescription Drug Labeling Resources* website provides over 150 labeling resources for the Prescribing Information, FDA-approved patient labeling, and/or carton and container labeling for human prescription drugs, including biological products (including over 50 guidances with labeling content) - see Overview of Website.

Highlights of Prescribing Information: Format Sample



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/YYYY
Section Title, Subsection Title (x.x) M/YYYY

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use
Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/YYYY

See https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

Prescription Drug Labeling Resources Webpage (1 of 2)[1]

- Prescribing Information (PI) Requirements and Rules
- PI Guidances
- Presentations
  - Sections of the PI
  - Broad Labeling Content
- Safety-Related Labeling Resources
- PLLR Resources
- Sample Templates and Format Tools for PI
- Established Pharmacologic Class Resources

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

Prescription Drug Labeling Resources Webpage (2 of 2)[1]

- Product-Specific Labeling Resources
  - Generic Drugs
  - Biological Products
- Product Quality-Related Labeling Resources
- Resources for Other Labeling Types
  - Patient Labeling
  - Carton and Container Labeling
- SPL Resources
- Labeling-Related Databases

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


FDA
U.S. FOOD & DRUG
ADMINISTRATION