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

Guidance for Industry

DRAFT GUIDANCE

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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.

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)

February 2022
Labeling

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Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling — Content and Format Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist applicants with incorporating immunogenicity information into the labeling of human prescription biological products, specifically therapeutic protein products,[2] and of select drug products[3] that have immunogenicity assessments.[4]

[1] This guidance has been prepared by the Labeling Policy Team in the Office of New Drugs, the Office of Clinical Pharmacology, and the Office of Biotechnology Products in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, unless otherwise specified, all references to *biological products* pertain to human therapeutic protein products licensed under section 351(a) of the Public Health Service (PHS) Act (42 U.S.C. 262). 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. However, if the labeling for a reference product for a 351(k) application is revised so that the content and format of the immunogenicity information is consistent with the recommendations in this guidance, with respect to incorporating such immunogenicity information into the 351(k) product labeling, the 351(k) applicant should follow the general labeling recommendations in section III of the guidance for industry *Labeling for Biosimilar Products* (July 2018) (i.e., the biosimilar product labeling should incorporate relevant immunogenicity data and information from the reference product labeling, with appropriate modifications) and should no longer follow the recommendations in section IV.C.3 of that guidance. Therefore, in such a situation, the labeling of the 351(k) product, like the labeling for the reference product, would include subsection **12.6 Immunogenicity**, incorporating relevant immunogenicity data and information from the reference product labeling under that subsection and not in the ADVERSE REACTIONS section.

[3] This guidance applies to select drug products (e.g., peptides, oligonucleotides, low molecular weight heparins) regulated under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355). Given the relatively small number of drug products for which an immunogenicity assessment is conducted, this guidance and the examples provided herein focus primarily on biological products; however, the principles and recommendations described in this guidance should be applied to all affected products. For purposes of this guidance the term *product* includes biological products as described in footnote 2 and applicable drug products.

[4] For low molecular weight heparin products, see the guidance for industry *Immunogenicity-Related Considerations for Low Molecular Weight Heparin* (February 2016). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

This guidance provides recommendations to help ensure that clinically relevant immunogenicity information is included in and distributed appropriately across sections and subsections of product labeling,[5] in accordance with regulatory requirements for the content and format of human prescription drug and biological product labeling.[6] The goal of appropriate inclusion and distribution of clinically relevant immunogenicity information in the labeling is to enable health care practitioners to easily access, understand, and use this information to inform prescribing decisions and patient management, and to help enable safe and effective use of applicable products.

This guidance does not apply to products intended to induce a specific immune response to prevent or treat a disease or condition (such as vaccines and allergenic products).

When finalized, this guidance will supersede the immunogenicity labeling-specific recommendations in the guidance for industry *Labeling for Biosimilar Products* (July 2018)[7] and the guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2016).[8]

This guidance does not address scientific aspects of immunogenicity assessments, including the following:

[5] The term *labeling*, as used in this guidance, refers only to the Prescribing Information (PI). Other types of labeling, as defined in 21 U.S.C. 321(m), 21 CFR 201.100(d), and 21 CFR 1.3(a), are excluded for the purposes of this guidance.

[6] 21 CFR 201.56(d) and 201.57; see the final rule "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (also known as *PLR*), published January 24, 2006 (21 CFR 201.56 and 201.57; 71 FR 3922).

[7] Specifically, this guidance, when finalized, will supersede the recommendations in section IV.C.3., ADVERSE REACTIONS, Immunogenicity, of the guidance for industry *Labeling for Biosimilar Products*, including the statement "Immunogenicity information for therapeutic protein products is usually placed in a subsection in the ADVERSE REACTIONS section entitled *Immunogenicity*" and statements recommended for inclusion as the first paragraph in the ADVERSE REACTIONS subsection that precedes the immunogenicity data. The Agency intends to issue additional guidance on the recommended content and format of immunogenicity data in the labeling of biological products licensed under section 351(k) of the PHS Act.

[8] Specifically, this guidance, when finalized, will supersede the immunogenicity-related recommendations under the following sections of the guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*: (1) section IV.B., Subsection 12.2 *Pharmacodynamics* ("Information supporting the clinical impact of anti-product antibody formation on PD [pharmacodynamics] without a clinically significant change in PK [pharmacokinetics]. If both PK and PD are affected by anti-product antibody formation, information supporting the clinical impact of anti-product antibody formation will be included in subsection 12.3 *Pharmacokinetics*"); (2) section IV.C., Subsection 12.3 *Pharmacokinetics* ("Headings or subheadings can be added as appropriate (e.g., Anti-Product Antibody Formation Affecting PK)"); and (3) section III.A., Content and Organization, that additional labeling subsections under the CLINICAL PHARMACOLOGY section should be given sequential identifying numbers beginning with 12.6.

- Development and validation of assays for anti-drug antibody detection[9]

- Immunogenicity risk assessment[10]

- Design and conduct of immunogenicity studies

- Scientific and clinical analysis of immunogenicity data (e.g., criteria for determining whether observed anti-drug antibodies affect the pharmacokinetics, pharmacodynamics, effectiveness, or safety of a product)

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidance means that something is suggested or recommended, but not required.

[9] For information on this topic, see the guidance for industry *Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection* (January 2019) and other applicable FDA guidances.

[10] See the guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014). During development of a biological product, sponsors should perform an immunogenicity risk assessment and discuss with FDA appropriate plans for immunogenicity study(ies), as needed, for their proposed products. This risk assessment is influenced by various factors, including, but not limited to, product quality attributes, the intended population, therapeutic context, and duration of product use.

II. BACKGROUND

Evaluation of immunogenicity risk and its potential clinical effect generally plays an important role in the assessment of a biological product's safety and effectiveness[11] for each proposed indication. For the purposes of this guidance, immunogenicity is defined as the propensity of a therapeutic protein product or other applicable drug product[3] to generate an immune response to itself, a related structure, or product complex; and/or to induce immunologically related adverse clinical events. Because most of the adverse events resulting from elicitation of an immune response to a therapeutic protein product appear to be mediated by humoral mechanisms, circulating antibody to the therapeutic protein product has been the chief criterion for defining an immune response to these products.[12] The focus of this guidance is on incorporating information on anti-drug antibodies into product labeling; however, the general labeling principles outlined in this guidance apply to other immune-mediated mechanisms (e.g., cell-mediated immune responses to therapeutic protein products) when such data are available and clinically relevant.

Anti-drug antibodies may or may not be associated with safety concerns or loss of effectiveness. Historically, immunogenicity information typically has been included in the ADVERSE REACTIONS section of labeling. However, such location may, for products whose anti-drug antibodies do not affect safety, unintentionally imply a relationship between anti-drug antibodies and adverse reactions. FDA believes that having a dedicated subsection (i.e., **12.6 Immunogenicity**) under the CLINICAL PHARMACOLOGY section allows a consistent location for summarizing data on anti-drug antibody incidence and its pharmacokinetic and pharmacodynamic effects, while reserving other sections (e.g., ADVERSE REACTIONS, CLINICAL STUDIES, WARNINGS AND PRECAUTIONS, as applicable) for description of only clinically significant effects. Presenting immunogenicity information in a consistent manner will enable health care practitioners to more easily identify and differentiate products associated with clinically significant anti-drug antibodies from products whose anti-drug antibodies are not associated with clinically significant effects on pharmacokinetics, pharmacodynamics, safety, or effectiveness. This guidance also provides recommendations for consistently stating when such information is unknown, if appropriate.

This guidance provides general recommended approaches to the inclusion and distribution of immunogenicity information in biological product labeling.[13] For product- and indication-specific questions, applicants are encouraged to contact the applicable FDA review division.

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[11] FDA will approve a 351(a) BLA if, among other things, the BLA demonstrates that the biological product that is the subject of the application is safe, pure, and potent. The standard for licensure of a biological product as potent under section 351(a) of the PHS Act has long been interpreted to include effectiveness (see 21 CFR 600.3(s) and the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)). In this guidance, we use the terms *safety and effectiveness* and *safety, purity, and potency* synonymously.

[12] See the guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products*.

[13] Additional published labeling guidances are available to assist applicants with developing labeling that complies with content and format requirements for human prescription drug and biological products. See the Prescription Drug Labeling Resources web page at https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources.

III. GENERAL PRINCIPLES

A. Labeling Content Requirements and Immunogenicity Information

For all prescription drug and biological products, labeling must contain a summary of the essential scientific information needed for the safe and effective use of the product,[14] and the labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular.[15]

Because a biological product's immunogenic potential may be relevant to the assessment of its safety[16] and/or effectiveness, a summary of this information is considered clinically relevant information to health care practitioners and, therefore, should be included in the product's labeling. Immunogenicity-related content should be communicated in the labeling in a manner that is understandable[17] to health care practitioners without specialized immunology or clinical pharmacology expertise. The inclusion of specific immunogenicity-related content, and its location within the labeling, are discussed in sections IV through IX of this guidance.

B. Format and Organization of Immunogenicity Information in Labeling

The Prescribing Information must be organized by standard headings (e.g., sections, subsections) as defined in regulations.[18] Although the location of immunogenicity information in labeling is not specifically identified in the regulations, additional subsections may be created within the standard sections to enhance labeling organization, presentation, or ease of use.[19]

FDA recommends the use of a dedicated subsection, **12.6 Immunogenicity**, under the CLINICAL PHARMACOLOGY section when summarizing results from immunogenicity studies (see section IV of this guidance). Similar to other subsections recommended by guidance (e.g., *Microbiology* (12.4), *Pharmacogenomics* (12.5)),[20] the subsection number 12.6 should be

[14] 21 CFR 201.56(a)(1).

[15] 21 CFR 201.56(a)(2).

[16] The word *safety* means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time (21 CFR 600.3(p)).

[17] A biological product's immunogenicity-related content can be presented as text, tables, and/or figures where appropriate to ensure clarity and understanding for the health care practitioner. For example, a table with appropriate footnotes of essential information such as the assay methodology may be more useful than text to communicate immunogenicity-related content for a biological product with multiple approved indications.

[18] 21 CFR 201.56(d)(1).

[19] 21 CFR 201.56(d)(2).

[20] See the guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*.

reserved for the *Immunogenicity* subsection. Additional subsections, when needed, should be given sequential identifying numbers beginning with 12.7.[21]

In addition to summarizing the results from immunogenicity studies in **12.6 Immunogenicity**, immunogenicity-related information may be appropriate for other sections of labeling (see sections V, VI, VII, and VIII of this guidance). When immunogenicity information is relevant to, and included in, more than one section of the labeling, cross-references should be used to refer the reader to the additional details or discussion contained in other relevant sections.[22]

Information recommended for inclusion in **12.6 Immunogenicity** and under other sections (e.g., WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, CLINICAL STUDIES) is described below and depends upon (1) adequacy of the methodology for detection of anti-drug antibodies, (2) sufficiency of data to draw clinical conclusions, and (3) whether the anti-drug antibodies may have clinically significant effect(s).

IV. IMMUNOGENICITY (12.6) SUBSECTION UNDER THE CLINICAL PHARMACOLOGY SECTION

For a biological product with immunogenicity data, the labeling should include an *Immunogenicity* (12.6) subsection under the CLINICAL PHARMACOLOGY section.[23]

A. When the Methodology for Immunogenicity Evaluation Is Inadequate

If the methodology for the submitted immunogenicity evaluation is inadequate, such that it precludes an assessment of the incidence of anti-drug antibodies, FDA recommends that the following or similar statement appear in the *Immunogenicity* subsection:

[21] See footnote 8. When this guidance is finalized, the recommendation that additional labeling subsections under the CLINICAL PHARMACOLOGY section be numbered sequentially beginning from 12.7 will supersede previous guidance recommendation that additional subsections be numbered from 12.6.

[22] For additional discussion of general format requirements and recommendations for organizing the PI, including use of cross-references, see the guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements* (February 2013).

[23] Less commonly, FDA may determine that immunogenicity studies are unnecessary for a particular type of biological product, and therefore a PI for such a product would not include the *Immunogenicity* subsection.

12.6 Immunogenicity

There is insufficient information to characterize the anti-drug antibody response to *[proper name]*[24] and the effects of anti-drug antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of *[core name]*[25, 26] products.

B. When the Methodology for Immunogenicity Evaluation Is Adequate

If the methodology for the submitted immunogenicity evaluation is adequate, such that it allows for an assessment of anti-drug antibody incidence, the *Immunogenicity* subsection should have the following:

- Include the following paragraph at the beginning of the subsection, preceding the presentation of immunogenicity data.

  12.6 Immunogenicity

  The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of *[proper name]* or of other *[core name]* products.[27]

- Report the incidence of anti-drug antibodies, including neutralizing antibodies, following the paragraph above. Applicants should consider the following:

  – Data should be summarized whether findings are positive (presence of observed anti-drug antibodies, regardless of titer) or negative (absence of observed anti-drug antibodies).

[24] For applicable drug products, depending on drug product-specific considerations, either the phrase "*[active moiety name]*" or "*[active ingredient name]*" should be used in place of "*[proper name]*" when conveying immunogenicity information.

[25] *Core name* means the component shared among an originator biological product and any related biological product, biosimilar product, or interchangeable product as part of the proper names of those products. Two examples of a core name are pegfilgrastim and infliximab. See the guidance for industry *Nonproprietary Naming of Biological Products* (January 2017).

[26] For applicable drug products, depending on drug product-specific considerations, either the phrase "*[active moiety]* products" or "*[active ingredient name]*" should be used in place of "*[core name]* products."

[27] For a fixed-combination product, portions of the recommended language should be modified accordingly, as appropriate. For example, for a fictitious fixed-combination product DRUG-X that is a combination of ingredient-A and ingredient-B, this introductory paragraph may be modified to state "The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude clinically meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of *[core name of ingredient-A and core name of ingredient-B]* products, or of *[core name of ingredient-A]* products or *[core name of ingredient-B]* products."

178 – Anti-drug antibody incidence(s) should be reported, regardless of whether a
179 correlation has been identified between the anti-drug antibodies and any changes in
180 pharmacokinetics, pharmacodynamics, safety, or effectiveness of the product.
181
182 – The duration of exposure to the drug and time period over which sampling for anti-
183 drug antibodies was conducted should be described with the anti-drug antibody
184 incidence data.
185
186 • Summarize the known effect(s) of anti-drug antibodies on the pharmacokinetics and
187 pharmacodynamics of the product (including the time period of observation) under the
188 headings Anti-Drug Antibody Effects on Pharmacokinetics and Anti-Drug Antibody
189 Effects on Pharmacodynamics, respectively.
190
191 *1. Clinically Significant Anti-Drug Antibodies*
192
193 If a product is associated with anti-drug antibodies that affect pharmacokinetics *and* the product
194 has a pharmacokinetic (PK)-efficacy and/or PK-safety relationship, the *Immunogenicity*
195 subsection should include the following (after the brief summary of anti-drug antibody-PK effect
196 as described under section IV.B of this guidance):
197
198 • Briefly identify the potential clinical effect(s) based on the known PK-efficacy and/or
199 PK-safety relationship; and
200
201 • Cross-reference the WARNINGS AND PRECAUTIONS section and/or other section(s),
202 as applicable, for more detailed discussion of the clinical effect(s) and pertinent clinical
203 recommendations (see Example 1 below).
204
205 Similarly, if a product is associated with anti-drug antibodies that affect pharmacodynamics
206 independent of changes in pharmacokinetics *and* the product has a pharmacodynamic (PD)-
207 efficacy and/or PD-safety relationship, the *Immunogenicity* subsection should include the
208 following (after the brief summary of anti-drug antibody-PD effect as described under section
209 IV.B of this guidance):
210
211 • Briefly identify the potential clinical effect(s) based on the known PD-efficacy and/or
212 PD-safety relationship; and
213
214 • Cross-reference the WARNINGS AND PRECAUTIONS section and/or other section(s),
215 as applicable, for more detailed discussion of the clinical effect(s) and pertinent clinical
216 recommendations.
217
218 The following two examples illustrate a fictitious biological product, DRUG-X (drugimab-
219 wxyz), having clinically significant anti-drug antibodies. In Example 1, anti-drug antibodies
220 were associated with PK changes leading to clinically significant effects. In Example 2, anti-
221 drug antibodies had clinically significant effects but were not known to be correlated with PK
222 changes.
223

Example 1:

> **12.6 Immunogenicity**
> …
> During the 6-month treatment period in Studies A, B, and C, 312/1200 (26%) of DRUG-X-treated patients developed anti-drugimab-wxyz antibodies.
>
> Anti-Drug Antibody Effects on Pharmacokinetics
> The presence of anti-drugimab-wxyz antibodies increased drugimab-wxyz clearance. After 6 months of dosing every 3 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. Anti-drugimab-wxyz antibody formation was associated with reduced efficacy *[see Warnings and Precautions (5.x) and Clinical Studies (14)]*.

Example 2:

> **12.6 Immunogenicity**
> …
> During the 6-month treatment period in Studies A, B, and C, 312/1200 (26%) of DRUG-X-treated patients developed anti-drugimab-wxyz antibodies. Anti-drugimab-wxyz antibody formation was associated with a higher incidence of hypersensitivity adverse reactions than observed in DRUG-X-treated patients without anti-drugimab-wxyz antibodies *[see Adverse Reactions (6.1)]*. The effect of anti-drug antibodies on pharmacokinetics and effectiveness have not been fully characterized.

2. Insufficient Data to Determine the Clinical Effect(s) of Anti-Drug Antibodies

When available data are too limited to assess the clinical effect(s) of anti-drug antibodies,[28] the uncertainty of effect on pharmacokinetics, pharmacodynamics, safety, and/or effectiveness should be described in the *Immunogenicity* subsection, for example:

> **12.6 Immunogenicity**
> …
> In the 6-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). Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of drugimab products is unknown.

When anti-drug antibodies are identified to have effects on pharmacokinetics and/or pharmacodynamics, but it is unknown whether the PK/PD changes are clinically significant (e.g., no identified PK-/PD-efficacy or PK-/PD-safety relationship), the anti-drug antibody effects on

[28] For example, assay methodology may be adequate to assess the incidence of anti-drug antibodies; however, a low incidence of anti-drug antibodies could preclude an assessment of whether the anti-drug antibodies affect safety and/or effectiveness of the product. Other reasons for insufficient data may include assay and sample size limitations.

pharmacokinetics/pharmacodynamics, as applicable, should be summarized under their respective headings (see section IV.B of this guidance) in the *Immunogenicity* subsection, followed by a statement that it is unknown whether the observed anti-drug antibody-associated PK/PD changes affect the safety or effectiveness of the product. For example:

> **12.6 Immunogenicity**
> …
> During the 1-year treatment period in Study A, 15/300 (5%) of DRUG-X-treated patients developed anti-drugimab-wxyz antibodies.
>
> Anti-Drug Antibody Effects on Pharmacokinetics
> Among DRUG-X-treated patients who developed anti-drug antibodies, 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 the observed anti-drug antibody-associated pharmacokinetic changes reduce effectiveness.

3. Clinically Insignificant Anti-Drug Antibodies

If data are sufficient to support a determination that observed anti-drug antibodies are not clinically significant (anti-drug antibodies having no clinical effect or having clinically insignificant effect on pharmacokinetics, pharmacodynamics, safety, and effectiveness of the product), the *Immunogenicity* subsection should include a statement about the lack of clinically significant effect. For example:

> **12.6 Immunogenicity**
> …
> During the 6-month treatment period in Studies A, B, and C, 312/1200 (26%) of DRUG-X-treated patients developed anti-drugimab-wxyz antibodies. There was no identified clinically significant effect of anti-drug antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of DRUG-X over the treatment duration of 6 months.

When anti-drug antibodies are identified to have effects on pharmacokinetics and/or pharmacodynamics, and the available data are sufficient to conclude that the anti-drug antibody-associated PK/PD changes do not affect safety or effectiveness, the anti-drug antibody effects on pharmacokinetics/pharmacodynamics, as applicable, should be summarized under their respective headings (see section IV.B of this guidance) in the *Immunogenicity* subsection, followed by a statement that these PK/PD changes were not clinically significant.
For example:

> **12.6 Immunogenicity**
> …
> During the 1-year treatment period in Study A, 15/300 (5%) of DRUG-X-treated patients developed anti-drugimab-wxyz antibodies.
>
> Anti-Drug Antibody Effects on Pharmacokinetics

Among DRUG-X-treated patients who developed anti-drug antibodies, 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 anti-drug antibody-associated pharmacokinetic changes were not identified to be clinically significant.

V. ADVERSE REACTIONS SECTION

A. Anti-Drug Antibodies Associated With Adverse Reactions

The ADVERSE REACTIONS section of labeling should summarize the adverse reactions associated with anti-drug antibodies (e.g., hypersensitivity, urticaria, rash, anaphylaxis), along with the treatment period during which anti-drug antibodies and adverse reactions occurred.

Depending on whether the adverse reactions were observed in clinical trials or in spontaneous reports or observational studies, the anti-drug antibody-associated adverse reaction data should be presented under either the *Clinical Trials Experience* (6.1) subsection or the *Postmarketing Experience* (6.2) subsection, respectively. The data should be presented under the heading Immunogenicity: Anti-Drug Antibody-Associated Adverse Reactions and should include a cross-reference to the *Immunogenicity* subsection for the detailed information on anti-drug antibody incidence and on anti-drug antibody-associated changes in pharmacokinetics and/or pharamcodynamics, if any (see section IV.B of this guidance). For example:

6.1 Clinical Trials Experience

…

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 6-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)].*

Since anti-drug antibody-associated hypersensitivity reactions, including anaphylaxis, may occur independent of or without demonstrated anti-drug antibody formation, a separate heading, if appropriate, can be used to summarize total overall hypersensitivity reactions, of which patients with anti-drug antibodies is a subset (e.g., separate headings such as Hypersensitivity Reactions Including Anaphylaxis and Immunogenicity: Anti-Drug Antibody-Associated Adverse Reactions under the *Clinical Trials Experience* subsection).

B. When the Clinical Effect(s) of Anti-Drug Antibodies on Safety Is Unknown

Generally, if the clinical effect(s) of anti-drug antibodies on safety (e.g., adverse reactions) is unknown (e.g., data are too limited to assess whether anti-drug antibodies are associated with adverse reactions), this uncertainty should be conveyed in the *Immunogenicity* subsection under

the CLINICAL PHARMACOLOGY section (see section IV.B.2 of this guidance) and not in the ADVERSE REACTIONS section of the labeling.

However, when the uncertain effect of anti-drug antibodies on adverse reactions is critical for health care practitioners to recognize (e.g., products for which minimal concentration changes may lead to serious toxicities or a loss of effectiveness, but for which anti-drug antibody-related PK effects are unknown), then a statement about this uncertainty should be included in the ADVERSE REACTIONS section under the *Clinical Trials Experience* subsection under the heading Immunogenicity: Unknown Clinical Effects of Anti-Drug Antibodies. A cross-reference to the anti-drug antibody incidence information in the *Immunogenicity* subsection should be included, as in the following example:

> **6.1 Clinical Trials Experience**
> …
> Immunogenicity: Unknown Clinical Effects of Anti-Drug Antibodies
> There are insufficient data to evaluate the effect of anti-drug antibodies on adverse reactions *[see Clinical Pharmacology (12.6)]*.

C. Anti-Drug Antibodies With No Clinically Significant Effect on Safety

If data are sufficient to support a determination that there is no clinically significant effect of anti-drug antibodies on safety, then the heading Immunogenicity: Anti-Drug Antibody-Associated Adverse Reactions is not applicable and, therefore, should not be included in the labeling.[29] For such a product, the immunogenicity information would be included only under the *Immunogenicity* subsection (see section IV.B.3 of this guidance), accompanied by the statement that there is no clinically significant effect of anti-drug antibodies on safety (and pharmacokinetics, pharmacodynamics, and effectiveness, as applicable).

VI. CLINICAL STUDIES SECTION

A. Anti-Drug Antibodies Associated With Clinically Significant Change in Effectiveness

When the development of anti-drug antibodies is associated with clinically significant changes in the effectiveness of a product, this information should be summarized in the CLINICAL STUDIES section, along with the time period of observation of the effect. The overall efficacy results from the clinical trial data should be presented along with the results for the drug treatment by anti-drug antibody status.

A cross-reference to the *Immunogenicity* subsection should be included using the format described previously (see section VI.A of this guidance).

[29] See 21 CFR 201.56(d)(4).

Depending on the clinical significance of the alteration in effectiveness, this information should additionally be considered for description under the WARNINGS AND PRECAUTIONS section, if appropriate. For example:

> **14 CLINICAL STUDIES**
> …
> In Studies A, B, and C in patients with psoriasis, the primary endpoint was the proportion of patients who achieved a reduction in the Psoriasis Area and Severity Index (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. Among DRUG-X-treated patients who developed anti-drugimab-wxyz antibodies (anti-drug antibody positive subgroup) during the 6-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 (anti-drug antibody negative subgroup) ... *[see Warnings and Precautions (5.x) and Clinical Pharmacology (12.6)].*

B. When the Clinical Effect(s) of Anti-Drug Antibodies on Effectiveness Is Unknown

Generally, if the clinical effect(s) of anti-drug antibodies on a product's effectiveness is unknown (e.g., methodology is adequate, but the data are too limited to assess any association of the anti-drug antibodies with changes in effectiveness), this uncertainty should be conveyed in the *Immunogenicity* subsection (see section IV.B.2 of this guidance) instead of the CLINICAL STUDIES section.

However, when the uncertain effect of anti-drug antibodies on effectiveness is critical for health care practitioners to recognize (e.g., products for which minimal concentration changes may lead to a loss of effectiveness), then a statement about this uncertainty should be included in the CLINICAL STUDIES section. Such information should be presented alongside any other statements about efficacy results in subgroups that are included in the section (e.g., description of efficacy in subgroups such as age, sex, and race). A cross-reference to the *Immunogenicity* subsection should be included.

C. Anti-Drug Antibodies With No Clinically Significant Effect on Effectiveness

If data are sufficient to support a determination that there is no clinically significant effect of anti-drug antibodies on the effectiveness of a product, immunogenicity information should be included only under the *Immunogenicity* subsection (assuming that the product's anti-drug antibodies also do not affect safety), accompanied by the statement that there is no clinically significant effect of anti-drug antibodies on effectiveness (and pharmacokinetics, pharmacodynamics, and safety, as applicable) (see section IV.B.3 of this guidance).

VII. WARNINGS AND PRECAUTIONS SECTION

The WARNINGS AND PRECAUTIONS section should contain a succinct description of (1) clinically significant adverse reactions or other risks from anti-drug antibodies (e.g., a possible causal association between anti-drug antibodies and immune-mediated adverse reactions such as hypersensitivity reactions, including anaphylaxis) and (2) clinically significant changes in effectiveness associated with anti-drug antibodies.

The adverse reaction or other risk information should include, if known: a numerical estimate of the rate of each clinically significant adverse reaction or other risk; risk factors for the adverse reaction or other risk; and, if appropriate, any clinically actionable recommendations (e.g., use of premedication or concomitant medications to reduce the risk of hypersensitivity reactions; discontinuation of the product).

Cross-reference(s) should be made to the ADVERSE REACTIONS section and/or the CLINICAL STUDIES section, as applicable, for example:

> **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. 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)].* In both patients, anaphylaxis occurred after the second DRUG-X dose. If DRUG-X-treated patients develop a severe hypersensitivity reaction, discontinue DRUG-X *[see Contraindications (4)]*.

VIII. OTHER SECTIONS OF LABELING

Less commonly, immunogenicity-related information may be relevant to, and appropriate to include in, other sections of the labeling (e.g., BOXED WARNING, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS). Applicants should refer to the general concepts described in available section-specific and other guidances to determine whether immunogenicity-related information is appropriate to include in these sections.[30]

[30] Additional labeling guidances are available to assist applicants with developing labeling that complies with content and format requirements for human prescription drug and biological products. See the Prescription Drug Labeling Resources web page at https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources.

IX. PROCEDURAL INFORMATION — UPDATING IMMUNOGENICITY INFORMATION IN THE LABELING

Labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.[31] Therefore, when new immunogenicity data or information becomes available that could affect prescribing decisions or the clinical management of patients receiving the product, applicants should submit to FDA the proposed revised labeling containing the updated immunogenicity information for review as a supplement to the 351(a) biologics license application (BLA) (or to the new drug application (NDA), for applicable drug products).

To enable health care practitioners to easily access, understand, and use immunogenicity information in the labeling (e.g., placing immunogenicity information in a consistent manner within and across appropriate sections and subsections of labeling), FDA recommends, when this guidance is final, that regardless of whether new immunogenicity data or information becomes available application holders propose updates to their biological product labeling to be consistent with the format and organizational recommendations in this guidance (e.g., during the next planned prior approval supplement[32] to their 351(a) BLAs (or NDAs, for applicable drug products)).

If labeling for an approved biological product already includes a subsection 12.6 covering a clinical pharmacology topic other than immunogenicity, the existing subsection 12.6 (and subsections thereafter, if applicable) should be renumbered (see section III.B.1 of this guidance).

[31] 21 CFR 201.56(a)(2).

[32] FDA encourages an application holder who is not planning to submit an efficacy or labeling prior approval supplement (PAS) in the near future to voluntarily update the labeling by submitting a labeling PAS with proposed changes consistent with the format and organizational recommendations in this guidance.