Promotional Labeling and Advertising Considerations for Prescription Biological Reference Products, Biosimilar Products, and Interchangeable Biosimilar Products

Questions and Answers

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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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) Alpita Popat, 301-796-1200, or (CBER) Office of Communication, Outreach and Development, 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)

April 2024
Advertising
Revision 1

Promotional Labeling and Advertising Considerations for Prescription Biological Reference Products, Biosimilar Products, and Interchangeable Biosimilar Products

Questions and Answers

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

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)

April 2024
Advertising
Revision 1

TABLE OF CONTENTS

Promotional Labeling and Advertising Considerations for Prescription Biological Reference Products, Biosimilar Products, and Interchangeable Biosimilar Products Questions and Answers

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

This revised draft guidance addresses questions firms[2] may have when developing FDA-regulated promotional labeling and advertisements (promotional communications)[3,4] for prescription reference products[5] licensed under section 351(a) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(a)) and prescription biosimilar products, including interchangeable biosimilar products, licensed under section 351(k) of the PHS Act (42 U.S.C. 262(k)). This guidance does not make any recommendations for nonprescription products. Unless otherwise

[1] This guidance has been prepared by the Office of Prescription Drug Promotion in the Office of Medical Policy in consultation with the Office of Therapeutic Biologics and Biosimilars in the Center for Drug Evaluation and Research and in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] In this guidance, the term *firms* refers to manufacturers, packers, and distributors, including representatives of these entities, of biological products licensed under section 351(a) or (k) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(a) or (k)).

[3] Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), FDA's authority includes provisions addressing labeling for all drugs and advertisements for prescription drugs. See, e.g., sections 502(a), (f), and (n) of the FD&C Act (21 U.S.C. 352(a), (f), and (n)); see also section 201(m) of the FD&C Act (21 U.S.C. 321(m) (defining *labeling*)). If a biological product meets the definition of *drug* under section 201(g) of the FD&C Act (21 U.S.C. 321(g)), it is subject to these provisions to the same extent as any other drug. See section 351(j) of the PHS Act (42 U.S.C. 262(j)).

[4] Promotional labeling is generally any labeling other than FDA-required labeling. Promotional labeling can include printed, audio, or visual matter descriptive of a drug that is disseminated by or on behalf of a drug's manufacturer, packer, or distributor (21 CFR 202.1(l)(2)). The FD&C Act does not define what constitutes an *advertisement* for a prescription drug, but FDA regulations provide several examples (21 CFR 202.1(l)(1)).

[5] *Reference product* means the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in a 351(k) application (section 351(i)(4) of the PHS Act (42 U.S.C. 262(i)(4))).

specified, the term *biosimilar product* as used in this guidance refers to a product that is licensed under section 351(k) of the PHS Act as biosimilar to or biosimilar to and interchangeable with a reference product.[6] This guidance discusses considerations for presenting data and information about reference products or biosimilar products in these promotional communications to help ensure that they are accurate, truthful, and non-misleading.

This revised draft guidance replaces the draft guidance for industry *Promotional Labeling and Advertising Considerations for Prescription Biological Reference and Biosimilar Products: Questions and Answers* (February 2020).[7] Changes from the 2020 draft guidance include additional recommendations and an example for interchangeable biosimilar products. In addition, editorial changes were made to improve clarity.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

Section 351(k) of the PHS Act provides an abbreviated licensure pathway for biological products shown to be biosimilar to or biosimilar to and interchangeable with an FDA-licensed reference product.

Section 351(i) of the PHS Act defines *biosimilarity* to mean "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."

To meet the standard for *interchangeability*, an applicant must provide sufficient information to demonstrate biosimilarity and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such

[6] See sections 351(i)(2), (i)(3), (k)(2), and (k)(4) of the PHS Act (42 U.S.C. 262(i)(2), (i)(3), (k)(2), and (k)(4)); see also section II of this guidance for information on biosimilarity and interchangeability.

[7] When final, this guidance will represent the FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

alternation or switch.[8] Interchangeable biosimilar products may be substituted for the reference product without the intervention of the prescribing health care provider (HCP).[9]

Once FDA licenses a biosimilar product, including an interchangeable biosimilar product, HCPs and patients can be confident of the safety and effectiveness of the biosimilar product, just as they would be for the reference product.

FDA is providing this guidance to address questions firms may have when developing FDA-regulated promotional communications for prescription reference products or prescription biosimilar products.

III. QUESTIONS AND ANSWERS

Q1. What are the general requirements for the content of FDA-regulated promotional communications for reference products and biosimilar products?

Prescription drugs, including those that are reference products or biosimilar products licensed under the PHS Act, are subject to the FD&C Act and FDA's implementing regulations, including misbranding provisions that address promotional communications for prescription drugs.

Among other things, prescription drug promotional communications must be truthful and non-misleading about the drug's safety and effectiveness, and promotional communications must convey information about a drug's effectiveness and its risks in a balanced manner and reveal material facts about the drug.[10] Whether a promotional communication is truthful and non-misleading involves a fact-specific determination that takes into account factors such as how the information is presented, the type and quality of the data relied on to support the presentation, and contextual and disclosure considerations. FDA regulations also require that applicants promptly revise promotional labeling and advertising for their biological products upon certain changes to the FDA-approved labeling, including changes to risk information in the FDA-approved labeling.[11]

Q2. How should firms identify reference products and biosimilar products in promotional communications?

Firms should carefully evaluate the context and content of the information presented in promotional communications to ensure that in each instance where the promotional

[8] See section 351(k)(4) of the PHS Act (42 U.S.C. 262(k)(4)).

[9] See section 351(i)(3) of the PHS Act (42 U.S.C. 262(i)(3)). Decisions regarding pharmacy-level substitution are subject to State pharmacy law.

[10] See, e.g., sections 201(n) and 502(a) and (n) of the FD&C Act (21 U.S.C. 321(n) and 352(a) and (n)); 21 CFR 1.21(a); and 21 CFR 202.1(e)(5).

[11] 21 CFR 601.12(a)(4).

communications address a reference product, address a biosimilar product, or collectively address some combination of biosimilar product(s) and/or reference product(s), the product or products are correctly and specifically identified.[12]

A biological product generally has a proprietary name, a proper name, and a core name. As used in this guidance, a biological product's proprietary name means the trademarked or brand name.[13] A biological product's proper name is the nonproprietary name designated by FDA in the license for a biological product licensed under the PHS Act.[14] For a biological product, we use the term core name to mean the component shared among an originator biological product, any related biological product, a biosimilar product, or an interchangeable biosimilar product as part of the proper names of those products.[15]

Correctly and specifically identifying the relevant biological product or products in promotional communications can help prevent presentations that are inaccurate because they attribute data or information to the wrong product. It can also help the audience identify which product or products are the subject of a particular presentation in a promotional communication. For instance, if a biosimilar product's FDA-approved labeling uses the core name of the reference product followed by the word "products" to convey that a risk applies to both the biosimilar product and the reference product,[16] it would also be appropriate for similar presentations about this risk in promotional communications for the biosimilar product to use this nomenclature. Also, if promotional communications describe, for example, a study supporting a demonstration of biosimilarity or interchangeability in which a non-U.S.-approved biological product was used

[12] Firms should also consider the requirements related to the placement, size, prominence, and frequency of the proprietary name and established name in prescription drug labeling and advertisements (see 21 CFR 201.10(g) and 21 CFR 202.1(b) through (d)). For prescription biological products, these requirements pertain to the placement, size, prominence, and frequency of the proprietary name and proper name of the product. See also the guidance for industry *Product Name Placement, Size, and Prominence in Promotional Labeling and Advertisements* (December 2017).

[13] The principles described in this guidance also apply to an approved brand name biological product that is marketed under its approved BLA without its brand name on the label.

[14] See section 351(a)(1)(B)(i) of the PHS Act (42 U.S.C. 262(a)(1)(B)(i)) and 21 CFR 600.3(k).

[15] See the guidance for industry *Nonproprietary Naming of Biological Products* (January 2017) for more information. See also the draft guidance for industry *Nonproprietary Naming of Biological Products: Update* (March 2019). FDA intends to revise the final guidance for industry *Nonproprietary Naming of Biological Products* and to amend sections in that document regarding the subjects addressed in the draft guidance for industry *Nonproprietary Naming of Biological Products: Update*.

[16] See the revised draft guidance for industry *Labeling for Biosimilar and Interchangeable Biosimilar Products* (September 2023). When final, this guidance will represent FDA's current thinking on this topic. This guidance generally recommends that in sections of FDA-approved labeling where the risk applies to both the biosimilar product and the reference product, it would be appropriate to use the core name of the reference product followed by the word "products" to convey, for instance, that a risk or other information necessary for the safe use of the product applies to both the biosimilar product and the reference product. The guidance also generally recommends, among other things, that the biosimilar product's proprietary name (or if a proprietary name is not available, the biosimilar product's proper name) should be used when providing directive statements and recommendations for preventing, monitoring, managing, or mitigating risks.

as a comparator (or otherwise mentions such a product), FDA recommends that the product be accurately identified as a non-U.S.-approved biological product.

Q3. When developing promotional communications for biosimilar products, what should firms consider if presenting information from the studies conducted to support licensure of the reference product when the information is included in the FDA-approved labeling of both the reference product and the biosimilar product?

When developing promotional communications for a biosimilar product that include information from the studies conducted to support licensure of the reference product that are reflected in both the reference product's FDA-approved labeling and the biosimilar product's FDA-approved labeling, firms should refer to the biosimilar product's FDA-approved labeling. FDA has recommended that a biosimilar product's FDA-approved labeling incorporate relevant data and information from the reference product's FDA-approved labeling, including clinical data that supported FDA's finding of safety and effectiveness of the reference product.[17]

For instance, if a biosimilar product is licensed for fewer than all conditions of use for which the reference product is licensed, the biosimilar product's FDA-approved labeling generally contains the data and information from the reference product's FDA-approved labeling that is relevant to the licensed conditions of use of the biosimilar product.[18] In general, a biosimilar product's FDA-approved labeling contains data and information from the CLINICAL STUDIES section of the reference product's FDA-approved labeling for the conditions of use for which the biosimilar product is licensed and also generally includes data and information from the reference product's FDA-approved labeling regarding clinical pharmacology studies, immunogenicity, and toxicity, among other information.

[17] See the revised draft guidance for industry *Labeling for Biosimilar and Interchangeable Biosimilar Products*. When final, this guidance will represent FDA's current thinking on this topic. Among other things, this guidance recommends that when clinical studies or specific data derived from studies with the reference product are described in biosimilar or interchangeable biosimilar product labeling, the reference product's proper name should be used.

[18] In certain circumstances, it may be necessary to include information in the biosimilar or interchangeable biosimilar product labeling relating to an indication(s) or other condition(s) of use for which the product is not licensed to help ensure safe use (e.g., when safety information in the reference product labeling is related to use of the biosimilar or interchangeable biosimilar product and is not specific to a particular licensed indication(s) or other condition(s) of use, or when information specific to only the biosimilar or interchangeable biosimilar product's indication(s) or other condition(s) of use cannot be easily extracted). See the revised draft guidance for industry *Labeling for Biosimilar and Interchangeable Biosimilar Products*. When final, this guidance will represent FDA's current thinking on this topic. See also the draft guidance for industry *Biosimilars and Interchangeable Biosimilars: Licensure for Fewer Than All Conditions of Use for Which the Reference Product Has Been Licensed* (February 2020). When final, this guidance will represent FDA's current thinking on this topic.

Q4. When developing promotional communications for a biosimilar product, what should firms consider if presenting data or information related to the safety or effectiveness of the biosimilar product that is not included in the FDA-approved labeling for that product?

Firms have expressed interest in developing promotional communications that include data or information related to the safety or effectiveness of their biosimilar product that are not included in the biosimilar product's FDA-approved labeling (for example, studies that supported the demonstration of biosimilarity between the biosimilar product and the reference product are generally not included in the FDA-approved labeling for the biosimilar product).[19] Any such promotional communications for biosimilar products should be consistent with the principles outlined in the guidance for industry *Medical Product Communications That Are Consistent With the FDA-Required Labeling: Questions and Answers* (June 2018), and firms must also ensure that the communication satisfies applicable statutory and regulatory requirements.[20]

Q5. When comparing a reference product and its biosimilar product in promotional communications, what should firms consider?

FDA's licensure of a biosimilar product means that the Agency has determined that the biosimilar product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences in terms of the safety, purity, and potency of the product. Although assessment of each promotional communication involves a fact-specific determination, representations or suggestions that create an impression that there are clinically meaningful differences between the reference product and a product that has been approved as biosimilar to that reference product, such as promotional communications representing or suggesting that the reference product is safer or more effective than the biosimilar product or that the biosimilar product is safer or more effective than the reference product, are likely to be false or misleading.[21] Similarly, representations or suggestions that create an impression that a biosimilar product is not highly similar to its reference product are likely to be false or misleading.

Accordingly, FDA recommends that firms carefully evaluate promotional communications that compare a reference product and a biosimilar product and avoid presentations that represent or suggest that a licensed biosimilar product is not highly similar to the reference product or that a

[19] See the revised draft guidance for industry *Labeling for Biosimilar and Interchangeable Biosimilar Products*. When final, this guidance will represent FDA's current thinking on this topic.

[20] See footnote 10. We note that, as expressed in the guidance for industry *Medical Product Communications That Are Consistent With the FDA-Required Labeling: Questions and Answers*, the determination of whether or not a communication is consistent with the FDA-required labeling is separate from the determination of which specific labeling or advertising provisions of the FDA authorities apply to that communication.

[21] False or misleading presentations about the safety or effectiveness of a prescription drug in its labeling or advertisements misbrand the product and thus cause its distribution in interstate commerce, among other actions, to be prohibited. See sections 201(n), 301(a), and 502(a) and (n) of the FD&C Act (21 U.S.C. 321(n), 331(a), and 352(a) and (n)); 21 CFR 1.21(a); and 21 CFR 202.1(e)(5).

clinically meaningful difference in terms of safety, purity, or potency exists between the reference product and biosimilar product.

For example,[22] consider a scenario where promotional communications for a biosimilar product present data and information from a study supporting a demonstration of biosimilarity. The study compared response rates in patients treated with the reference product alone, response rates in patients treated with the biosimilar product alone, and response rates in patients transitioned from the reference product to the biosimilar product. While there were slight variations in the response rates for the three patient groups, there were no clinically meaningful differences in response rates among the patient groups. The presentation includes a header that the biosimilar product is just as effective as the reference product.

This presentation would not create a misleading impression that there is a clinically meaningful difference between the reference product and the biosimilar product as long as appropriate context is provided in the presentation (e.g., relevant study design information, material limitations of the data).[23,24] By contrast, the same data and information presented with a header that claims greater efficacy for the biosimilar product would be misleading.

Similarly, representations or suggestions that a biosimilar product is superior to its reference product based on a difference that is not clinically meaningful between the rates of occurrence of a particular adverse reaction from a study that supported a demonstration of biosimilarity between the reference product and biosimilar product would be misleading.

In some cases, presenting otherwise accurate information about a reference product or about a biosimilar product could contribute to a misleading presentation when provided in a comparative context. For example, presentations in promotional communications for a reference product that include a comparison of the number of indications for which the reference product is licensed to the number of indications for which the biosimilar product is licensed in a manner that creates the overall impression that the biosimilar product is less safe or less effective than the reference product simply because the biosimilar product is licensed for fewer indications than the reference product would be misleading.

Representations or suggestions in promotional communications for the reference product that the biosimilar product is less safe or less effective than the reference product in any of the indications licensed for the biosimilar product because the licensure pathway for the biosimilar product differs from that for the reference product also would be misleading.

---

[22] See the response to Q7 for additional explanation of the use of examples in this guidance.

[23] For additional discussion of contextual considerations, refer to the guidance for industry *Medical Product Communications That Are Consistent With the FDA-Required Labeling: Questions and Answers*.

[24] See the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015) (explaining that "[c]linically meaningful differences could include a difference in the expected range of safety, purity, or potency of the proposed product and the reference product. By contrast, slight differences in rates of occurrence of certain adverse reactions between the two products ordinarily would not be considered clinically meaningful differences").

Q6. What else should firms consider when developing promotional communications for reference products or biosimilar products?

Promotional communications about a product's licensure as biosimilar to a reference product should be accurate.

When multiple products are licensed as biosimilar to and interchangeable with or biosimilar to but not interchangeable with the same reference product, promotional communications should avoid representing or suggesting that any of these products (i.e., the reference product, any interchangeable biosimilar product(s), or any non-interchangeable biosimilar product(s)) are less safe or effective than each other for their approved uses based on their licensure pathways. In addition, promotional communications for a reference product should avoid representing or suggesting that a biosimilar product is less safe or effective than the reference product because the biosimilar product has not been licensed as interchangeable with the reference product.

Further, FDA's licensure of a biosimilar product means that the Agency has determined that the biosimilar product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the biosimilar product and the reference product in terms of safety, purity, and potency. It is both normal and expected for biological products to have minor differences between batches. This means that biologics generally cannot be copied exactly, and that is why biosimilar products may not be identical to their corresponding reference product. Therefore, promotional communications for a biosimilar product that represent or suggest that a finding of biosimilarity means that FDA determined that the reference product and biosimilar product are identical to one another generally would not be accurate. Additionally, FDA recommends that promotional communications for reference products avoid representations or suggestions that the licensed biosimilar product is less safe or less effective than the reference product because it is not or may not be identical to the reference product.

Q7. What are some examples of applying the considerations in this guidance to promotional communications?

The following examples are intended to illustrate some of the general considerations outlined in this guidance. The examples in this guidance contain hypothetical scenarios for illustrative purposes only and focus on the topics addressed by this guidance; they do not describe every aspect of the promotional communication that would be necessary to satisfy all applicable requirements. As noted in Q1, whether a promotional communication is truthful and non-misleading involves a fact-specific determination that takes into account such factors as how the information is presented, the type and quality of the data relied on to support the presentation(s) in the promotional communication, and contextual and disclosure considerations.

Examples 1, 2, and 3 that follow use a fictional reference product JUNEXANT (replicamab-hjxf) and a fictional product named NEXSYMEO (replicamab-cznm) that is licensed as biosimilar to, but not licensed as interchangeable with, JUNEXANT. Example 4 uses a fictional reference product CLAREXANT (calipicamab-fjwo), a fictional product HILEZEO (calipicamab-tlsk) that is licensed as biosimilar to and interchangeable with CLAREXANT, and a fictional product

OMPIRAM (calipicamab-jrve) that is licensed as biosimilar to, but not licensed as interchangeable with, CLAREXANT.

Examples 1 and 2 illustrate scenarios where FDA would not expect to object to the presentations described.

> ***Example 1***: A firm is developing promotional communications for its biosimilar product, NEXSYMEO. In the promotional communications, the firm includes the route of administration, dosage form, and strength described in NEXSYMEO's FDA-approved labeling and a claim that NEXSYMEO has the same route of administration, dosage form, and strength as JUNEXANT in the conditions of use for which both products are licensed. This claim is supported by NEXSYMEO's licensure as biosimilar to JUNEXANT given that NEXSYMEO's licensure is based, in part, on information showing that the route of administration, dosage form, and strength of NEXSYMEO are the same as those of JUNEXANT.[25]
>
> Additionally, the promotional communications include a claim that HCPs can consider prescribing NEXSYMEO to treat patients who are new to replicamab product therapy for an approved indication and for patients currently being treated with JUNEXANT for the same indication. This claim is supported by data and information that were submitted as part of NEXSYMEO's application for licensure as biosimilar to JUNEXANT.
>
> ***Example 2***: As part of NEXSYMEO's application for licensure as biosimilar to JUNEXANT, FDA evaluated a comparative clinical study that included patients treated with a non-U.S.-approved comparator product to support a demonstration of no clinically meaningful differences between NEXSYMEO and JUNEXANT.
>
> NEXSYMEO's firm wants to present data and information from this study in promotional communications for NEXSYMEO. Data from this study are not included in the FDA-approved labeling for NEXSYMEO.
>
> The firm develops a presentation that is consistent with the FDA-approved labeling, as described in the guidance for industry *Medical Product Communications That Are Consistent With the FDA-Required Labeling: Questions and Answers*, and that follows the guidance's recommendations regarding appropriate scientific and statistical support for the outcome information presented. In addition, the firm clearly and prominently provides contextual information about the study design and methodology, the role the study played in the biosimilarity evaluation, relevant data from NEXSYMEO's FDA-approved labeling, and any material limitations of the data. The firm also accurately describes the comparator used in the study as a non-U.S.-approved product.

Examples 3 and 4 illustrate promotional communications that FDA would consider misleading.

> ***Example 3***: Promotional communications for JUNEXANT state that in a clinical study, patients on JUNEXANT experienced a numerically higher overall response rate than

[25] See section 351(k)(2) of the PHS Act (42 U.S.C. 262(k)(2)).

patients on NEXSYMEO. The basis for the statement is a comparative clinical study that supported a demonstration of no clinically meaningful differences in terms of safety, purity, and potency between JUNEXANT and NEXSYMEO.

Although this statement accurately conveys the reference product's higher numeric overall response rates observed in the study, the promotional communications do not disclose that this difference in response rates was not statistically significant, and they do not describe the study design or include other appropriate context. By focusing on the numerical difference in response rates, which was not statistically significant, the presentation misleadingly implies that JUNEXANT is superior to NEXSYMEO. It also misleadingly implies that there is a clinically meaningful difference between the products when the data presented in the promotional communications do not support this conclusion.

Example 4: Promotional communications for HILEZEO state that, unlike patients using OMPIRAM, patients using HILEZEO can be assured of HILEZEO's safety and effectiveness because HILEZEO is licensed as interchangeable with CLAREXANT while OMPIRAM is not. This presentation misleadingly suggests that because HILEZEO is licensed as interchangeable with CLAREXANT and OMPIRAM is not, HILEZEO is superior in safety and effectiveness to OMPIRAM.

Q8. How can firms request FDA review of draft promotional communications for reference products and biosimilar products before dissemination of those communications?

Firms voluntarily seeking FDA feedback on promotional communications for reference products or biosimilar products before dissemination of those communications should follow the current process for submitting draft promotional communications for comment.[26]

Q9. Are promotional communications for reference products and biosimilar products subject to postmarketing reporting requirements?

Yes, postmarketing reporting requirements for submitting promotional communications to FDA apply to promotional communications for reference products and biosimilar products.[27,28] Specifically, specimens of mailing pieces and any other labeling or advertising devised for promotion of the reference product or biosimilar product must be submitted to FDA at the time

[26] See 21 CFR 202.1(j)(4). See also the guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs* (April 2022).

[27] See 21 CFR 601.12(f)(4).

[28] For additional guidance on electronic submission of these promotional communications, see footnote 26. See also the draft guidance for industry *Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics* (January 2014). When final, this guidance will represent FDA's current thinking on this topic.

of initial dissemination of the labeling or at the time of initial publication of the advertisement, as applicable, and must be accompanied by a completed Form FDA 2253, Transmittal of Advertisements and Promotional Labeling for Drugs and Biologics for Human Use.[29]

[29] See 21 CFR 601.12(f)(4) (requiring that advertisements and promotional labeling for biologics be submitted "in accordance with the requirements set forth" in 21 CFR 314.81(b)(3)(i)). See also the guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.