Medical Product Communications That Are Consistent With the FDA-Required Labeling — 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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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 http://www.regulations.gov. Submit written comments to the Division of Dockets Management (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) Catherine Gray at 301-796-1200; (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010; (CDRH) Angela Krueger at 301-796-6380; (CVM) Thomas Moskal at 240-402-6251; or (OC) Kristin Davis at 301-796-0418.

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)
Center for Devices and Radiological Health (CDRH)
Center for Veterinary Medicine (CVM)
Office of the Commissioner (OC)

January 2017
Procedural

Medical Product Communications That Are Consistent With the FDA-Required Labeling — 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
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
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
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or
Office of Communication and Education
CDRH-Division of Industry and Consumer Education
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 66, Room 4621
Silver Spring, MD 20993-0002
Phone: 800-638-2041 or 301-796-7100; Fax: 301-847-8149
Email: DICE@fda.hhs.gov
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm
and/or
Policy and Regulations Staff, HFV-6
Center for Veterinary Medicine
Food and Drug Administration
7519 Standish Place, Rockville, MD 20855
http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm
and/or
Office of Policy
Office of the Commissioner
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 32, rm 4232
Silver Spring, MD 20993-0002
Tel: 301-796-4830

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)
Center for Devices and Radiological Health (CDRH)
Center for Veterinary Medicine (CVM)
Office of the Commissioner (OC)

January 2017
Procedural

TABLE OF CONTENTS

Medical Product Communications That Are Consistent With the FDA-Required Labeling — 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 guidance provides information for firms[2] about how FDA evaluates firms' medical product[3] communications, including promotional materials, that present information that is not contained in the FDA-required labeling for the product but that may be consistent with the FDA-required labeling for the product. As used in this guidance and further explained below, information that is *consistent with the FDA-required labeling* is limited to information about the approved or cleared[4] uses of a product. The term *FDA-required labeling* as used in this guidance includes the labeling reviewed and approved by FDA as part of the medical product marketing application review process.[5] For products not subject to premarket approval, but instead subject to premarket notification requirements or exempt from premarket review, the term *FDA-required labeling* also includes the labeling relied on to provide adequate directions for use and other information required to appear on the label or in labeling.

[1] This guidance has been prepared by the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, the Center for Veterinary Medicine, and the Office of the Commissioner at the Food and Drug Administration.

[2] The term *firms* refers to medical product manufacturers, packers, and distributors and their representatives.

[3] The term *medical product(s*) refers to drugs and medical devices for humans, including those that are licensed as biological products, and animal drugs. See Q.1/A.1 in section III of this guidance.

[4] For ease of reference, when *approval* and *clearance* (and similar terms) are used in discussing devices, the terms refer to FDA permitting the marketing of a device via the premarket approval, 510(k), *de novo* classification, or Humanitarian Device Exemption (HDE) pathway and to devices that are exempt from premarket notification.

[5] Such labeling may include, for example, the FDA-approved prescribing information for a human drug (including a drug that is licensed as a biological product), including FDA-approved patient labeling, if any, that, under 21 CFR 201.100(d), must accompany any labeling distributed by or on behalf of the manufacturer, packer, or distributor of the drug; the FDA-approved prescribing information for an animal drug; or the labeling approved during the premarket approval process for a device.

FDA has received a number of questions concerning this topic. As a result, FDA is providing guidance in a question and answer format, addressing frequently asked questions.

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 guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

FDA determines whether a medical product is safe and effective for use under the conditions prescribed, recommended, or suggested in the proposed labeling submitted to FDA with the product's marketing application or submission (and for devices, also during the classification process).[6] In making this determination, FDA evaluates whether the conditions of use in the proposed labeling are supported by the required levels and types of evidence of safety and effectiveness and whether the benefits of using the product under those specific conditions of use outweigh the risks of the product. After FDA approves or clears a medical product, the FDA-required labeling sets forth the conditions of use under which the product has been shown to meet the relevant standard for marketing, and it provides directions and information on how to use the product safely and effectively under those conditions.

The FDA-required labeling is the primary tool that FDA uses to communicate the essential information needed for the safe and effective use of the product, and firms have an obligation to update their FDA-required labeling as needed to ensure it is not false or misleading. The FDA-required labeling is subject to content requirements and limitations to help ensure it effectively communicates information. It is not intended to be an exhaustive summary of all that is known about a product for its approved or cleared uses.

Medical product firms have told FDA that they are interested in communicating, including in their promotional materials, data and information about the approved/cleared uses of their products that are not contained in their products' FDA-required labeling. We also recognize that firms have questions about how FDA determines when communications that contain data and information that are not in the FDA-required labeling are consistent with the FDA-required labeling, and how such communications are viewed by FDA.

The purpose of this guidance is to provide clarity for firms regarding FDA's thinking when examining the consistency of a firm's communications about a medical product with that

[6] See, e.g., sections 505(d)(1), (2), (4) and (5); 512(d)(1)(A), (B), (D) and (E); 513(a)(2)(B); and 515(d)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The determination of whether a human or animal drug is not a new drug because it is generally recognized as safe and effective likewise turns on conditions prescribed, recommended, or suggested in its labeling. See sections 201(p) and (v) of the FD&C Act.

product's own FDA-required labeling.[7] As is explained in the questions and answers in section III, firms' communications of information that is not contained in their product's FDA-required labeling but that are determined to be consistent with the FDA-required labeling are not alone considered evidence of a new intended use.

Because a communication that is consistent with a product's FDA-required labeling could nonetheless misbrand the product and subject a firm to enforcement action if the representations or suggestions made in the communication are false or misleading in any particular, this guidance also provides general (but not comprehensive) recommendations for conveying information that is consistent with the FDA-required labeling in a truthful and non-misleading way, as well as examples to illustrate these concepts. These general recommendations are specific to communications that are consistent with the FDA-required labeling; communication of information that is not consistent with the FDA-required labeling is outside the scope of these recommendations.

III. QUESTIONS AND ANSWERS

Q.1. What FDA-regulated products fall within the scope of this guidance?

A.1. This guidance applies to drugs and devices for humans, including those that are licensed as biological products, and animal drugs (collectively, *medical products*).

Q.2. How does FDA determine whether a firm's communication about a medical product is consistent with the FDA-required labeling for that product?

A.2. FDA determines whether the representations or suggestions in a communication about a product are consistent with the product's FDA-required labeling by considering the three factors below. If a communication fails to satisfy any one of these factors, it is not considered consistent with the FDA-required labeling. FDA recognizes that there is overlap in these factors and expects that communications that are not consistent with the FDA-required labeling may fail to satisfy multiple factors.

Factor 1: How the information in the communication compares to the information about those conditions of use in the FDA-required labeling identified in the bullets below[8] — If the answer to any of the following questions is yes, that indicates the communication is not consistent with the FDA-required labeling:

[7] This guidance does not address considerations relating to the approval of generic drugs and biosimilar products involving the submission of information to show that the condition(s) of use in the labeling proposed for the proposed generic or biosimilar product have been previously approved for the reference product. See sections 505(j)(2)(A)(i) and 512(n)(1) of the FD&C Act; section 351(k)(2)(A)(i)(III) of the Public Health Service Act (PHS Act).

[8] This guidance is not intended to provide a definitive FDA interpretation of *conditions of use* for all circumstances.

- **Indication** – Do the representations/suggestions about the product in the communication relate to a different indication than the one(s) reflected in the product's FDA-required labeling?

- **Patient Population** – Is the patient population represented or suggested in the communication outside the approved/cleared patient population reflected in the FDA-required labeling?

- **Limitations and Directions for Handling/Use** – Do the representations/suggestions in the communication conflict with the use limitations or directions for handling, preparing, and/or using the product reflected in the FDA-required labeling?

- **Dosing/Administration** – Do the representations/suggestions about the product conflict with the recommended dosage or use regimen, route of administration, or strength(s) (if applicable) set forth in the FDA-required labeling?

Factor 2: Whether the representations/suggestions in the communication increase the potential for harm to health relative to the information reflected in the FDA-required labeling —

When reviewing a medical product's marketing application or submission (and in the device classification process), FDA weighs the benefits and risks of a medical product for the conditions of use prescribed, recommended, or suggested in the product's labeling and determines whether the benefits of using the product under those conditions of use outweigh the potential or probable risks of the product. Under certain circumstances, FDA may also consider additional risks and potential harms in determining whether a product meets the relevant standard for marketing. For example, FDA may assess the risks of abuse or misuse of certain products, the potential for harm to the health of humans from certain animal drug uses, or the potential for harm to health from secondary exposure to certain medical products. If a communication alters the benefit-risk profile of a product in a way that may result in increased harm to health, this indicates that the communication is not consistent with the FDA-required labeling.[9]

Factor 3: Whether the directions for use in the FDA-required labeling enable the product to be safely and effectively used under the conditions represented/suggested

[9] For example, if a firm's communication claims that its drug has superior effectiveness compared to another drug for treating a particular disease or condition, but its drug is reserved for third-line use due to severe risks associated with its use while the comparator drug is approved for first-line use as a result of its more favorable overall benefit-risk profile, such a communication has the potential to increase harm to the health of patients by suggesting use in a broader patient population (e.g., all patients with the disease/condition instead of just patients for whom first- and second-line therapies are not suitable) than the drug's benefit-risk profile justifies. This communication could also fail on other factors, but this example is provided to illustrate how factor 2 is applied.

in the communication — If the answer is no, that indicates the communication is not consistent with the FDA-required labeling.

Q.3. Does FDA view firm communications that are consistent with the FDA-required labeling, alone, as providing evidence of a new intended use?

A.3. No. If a firm's communication is consistent with the FDA-required labeling, that communication alone is not viewed by FDA as providing evidence of a new intended use. In addition, FDA does not view a communication that is consistent with the FDA-required labeling as failing to comply with the Federal Food, Drug, and Cosmetic Act's (FD&C Act) requirement that a medical product's labeling bear adequate directions for use (see section 502(f) of the FD&C Act) based solely on the fact that it presents data and information that are not reflected in the product's FDA-required labeling.

Firms also must ensure their communications satisfy other applicable requirements (see Q.6/A.6 and Q.7/A.7).

Q.4. What are examples of the kinds of information that could be consistent with the FDA-required labeling for a product?

A.4. Below are examples of some general types of information that could be consistent with the FDA-required labeling. Note that these examples are provided for illustrative purposes only and are not intended to be comprehensive or restrictive. Furthermore, not all representations or suggestions about a product that relate to the general categories described in this answer will be consistent with the FDA-required labeling for the specific product. That determination is fact-specific and is made by evaluating the particular representations or suggestions being made in a communication using the factors outlined in Q.2/A.2.

In addition, device firms should consider these examples in conjunction with the Agency's existing regulations, guidances, and policies, for example, regarding when a special control may trigger certain labeling requirements for a specific device type or when a modification to the indications for use of a device would trigger the need for a new premarket submission. If the information that a firm wants to communicate represents such a modification to the indications for use of the device, it would not be considered consistent with the FDA-required labeling.

Also, as is further discussed in Q.6/A.6, if the representations or suggestions in a firm's communication are false or misleading, the communication would misbrand the product and could subject the firm to enforcement action regardless of whether the communication is consistent with the FDA-required labeling.

Examples of some types of information that could be consistent with the FDA-required labeling include the following:

- Information based on a comparison of the safety or efficacy of a medical product for its approved/cleared indication to another medical product approved/cleared for the same indication (e.g., a firm's communication provides information from a head-to-head study indicating that its drug that is approved to treat high blood pressure in adults has superior efficacy to another drug that is also approved to treat high blood pressure in adults)

- Information that provides additional context about the adverse reactions associated with the approved/cleared uses of the product reflected in the product's FDA-required labeling (e.g., the FDA-required labeling for a product identifies nausea as a potential adverse reaction and further indicates the product can be taken with or without food. A firm's communication about the product provides information about how taking a product with food might reduce nausea)[10]

- Information about the onset of action of the product for its approved/cleared indication and dosing/use regimen (e.g., the FDA-required labeling for a product approved/cleared to treat major depressive disorder does not contain information about onset of action prior to the point in time designated as the study's endpoint, and a firm's communication provides information indicating that the product shows an effect relative to the control at 2 weeks)

- Information about the long-term safety and/or efficacy of products that are approved/cleared for chronic use (e.g., a firm provides postmarketing information for its product, which was approved/cleared for chronic use based on 24-week study data, regarding persistent safety and/or efficacy over 18 months)

- Information about the effects or use of a product in specific patient subgroups that are included in its approved/cleared patient population (e.g., a firm's communication provides information on the number of female patients that were studied in its pivotal clinical trials and the treatment effects in that patient group, or, in the case of a diagnostic product, the diagnostic performance in that patient group)

[10] In June 2014, FDA issued a draft guidance entitled *Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products — Recommended Practices* (Risk Information Draft Guidance), available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm400104.pdf. That draft guidance relates to "information that becomes available after a drug is marketed that rebuts or mitigates information about a risk already identified in the approved labeling or otherwise refines risk information in the approved labeling in a way that does not indicate greater seriousness of the risk" (Risk Information Draft Guidance, page 3 (footnote omitted)). To the extent there is overlap between the Risk Information Draft Guidance and this draft guidance, FDA recommends that firms consider the recommendations in both draft guidances. When final, these guidances will represent FDA's current thinking on these topics. Please check the FDA guidance Web page at http://www.fda.gov/RegulatoryInformation/Guidances/default.htm for the most current version of a guidance.

- Information concerning the effects of a product that comes directly from the patient (i.e., patient-reported outcomes) when the product is used for its FDA-approved/cleared indication in its approved/cleared patient population (e.g., a firm's communication provides information concerning patient compliance/adherence, or a firm's communication provides information about patients' perceptions of the product's effect on their basic activities of daily living)

- Information concerning product convenience (e.g., a firm's communication for its drug product, which is indicated for the treatment and prevention of ectoparasites in dogs, provides information about the convenient dosing schedule of the product for pet owners based on its long duration of effect)

- Information that provides additional context about the mechanism of action described in the FDA-required labeling (e.g., the FDA-required labeling for a drug product indicates it exerts its effects by binding to a certain receptor, and a firm's communication provides additional information about the product's selectivity for that receptor)

Q.5. What are examples of the kinds of information that are <u>not</u> considered consistent with the FDA-required labeling for a product?

A.5. Examples of some general types of information that are not considered consistent with the FDA-required labeling include the following. As with the examples provided in Q.4/A.4, note that these examples are provided for illustrative purposes only and are not intended to be comprehensive.

- Information about the use of a product to treat or diagnose a different disease or condition than the product is approved/cleared to treat or diagnose (e.g., a product is approved/cleared to treat cardiovascular disease, and a firm's communication provides information about using the product to treat diabetes)

- Information about the use of a product to treat or diagnose patients who are not included in the product's approved/cleared patient population (e.g., a device is cleared for use in individuals with cystic fibrosis (CF) for diagnosing a specific CF gene mutation and a firm's communication provides information about using the device in individuals who do not have CF to determine if they are carriers of the CF gene; an animal drug is approved only for use in feedlot cattle, and a firm's communication provides information about using the product in veal or dairy cattle)

- Information about the use of a product to treat a different stage, severity, or manifestation of a disease than the product is approved/cleared to treat (e.g., a product is approved/cleared only to treat severe asthma, and a firm's communication provides information about using the product to treat patients with mild asthma)

- Information about the use of a product as monotherapy when it is only approved/cleared for use in conjunction with one or more other products or therapeutic modalities (e.g., the FDA-required labeling for a product indicates it is for use as an adjunct to surgery and radiation, and a firm's communication provides information about using the product to treat patients who are not undergoing surgery and radiation)

- Information about using a product through a different route of administration or in a different tissue type than the product is approved/cleared for (e.g., a product is approved only for intramuscular injection, and a firm's communication indicates the product can be injected intravenously)

- Information about the use of a different strength, dosage, or use regimen than the approved/cleared strength, dosage, or use regimen (e.g., the FDA-required labeling for a drug indicates it should be taken twice a day 12 hours apart, and a firm's communication represents that the product can instead be taken once a day, with both doses being taken together in the morning)

- Information about the use of a product in a different dosage form than what is set forth in the FDA-required labeling (e.g., the product's approved dosage form is a capsule, and a firm's communication provides information about use of the product as an oral solution)

Q.6. What evidentiary support should a firm have for its communications that are consistent with the FDA-required labeling?

A.6. Communications that lack appropriate evidentiary support are likely to be false or misleading and can cause patient harm. Under the FD&C Act and implementing regulations, labeling and FDA-regulated advertising materials are required to be truthful and non-misleading, which includes revealing facts that are material about the product being promoted, including information about the risks of the product.[11] To be truthful and non-misleading, representations or suggestions made by firms about their products need to be grounded in fact and science and presented with appropriate context. Any data, studies, or analyses relied on should be scientifically appropriate and statistically sound to support the representations or suggestions made in the communication. In addition, the evidence should be accurately characterized in the communication, including limitations of the strength of the evidence and the conclusions that can be drawn from it (see Q.8/A.8). However, firms should note that if a communication relies on a study that is inadequate to support the representations or suggestions it presents, disclosure of the material limitations of that study does not correct the misleading message conveyed by the communication.

[11] See, e.g., sections 201(n), 502(a), 502(n), 502(q), and 502(r) of the FD&C Act; 21 CFR 202.1(e)(5).

The safety and effectiveness of the drug or device under the conditions of use in the FDA-required labeling have already been established by appropriate evidence during the premarket review process (and/or through the device classification process). Therefore, FDA would not consider representations or suggestions in a communication that is consistent with the FDA-required labeling to be false or misleading based only on the lack of evidence sufficient to satisfy the applicable approval/clearance standard. Nevertheless, the communication could be false or misleading for other reasons. Accordingly, the representations or suggestions should be supported and presented as described in this guidance.

For example, certain analyses of pivotal trial data may provide information that elaborates on the data reflected in the product's FDA-required labeling and could improve understanding of a product (e.g., information from separate analyses of the individual components of a composite endpoint that was successfully used as the primary endpoint and that are derived from appropriate statistical tests[12] and pre-specified in the statistical analysis plan). However, if the pivotal trial was, for example, not adequately powered to determine treatment effect on the individual components of the composite endpoint and/or type 1 error (false positive rate) was not controlled for these analyses, these analyses would generally not support conclusions about a treatment effect of the product on the individual components of the composite endpoint. In such a case, representing or suggesting that the data support such efficacy conclusions, either directly (e.g., by claiming the product has demonstrated efficacy on the individual components) or indirectly (e.g., by presenting p-values, which would imply a statistically rigorous conclusion where one does not exist), would be false or misleading.

Q.7. What other considerations apply to communications that are consistent with the FDA-required labeling?

A.7. In addition to the standards for scientific substantiation addressed in Q.6/A.6, firms should ensure their FDA-regulated promotional materials otherwise satisfy the applicable requirements of the FD&C Act and FDA's implementing regulations.

Nothing in this draft guidance is intended to change a firm's existing obligations under the FD&C Act, the Public Health Service Act (PHS Act), or FDA's implementing regulations to update its FDA-required labeling to ensure that the

[12] See, e.g., FDA's guidance *E9 Statistical Principles for Clinical Trials* (September 1998), available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf; FDA's guidance *Design Considerations for Pivotal Clinical Investigations for Medical Devices* (November 2013), available at http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm373750.htm; and FDA's guidance *Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests* (March 2007), available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071148.htm.

labeling is not false or misleading or for other reasons.[13] In addition, as outlined in Q.4/A.4, this draft guidance is not intended to change the Agency's existing regulations, guidances, and policies regarding when a modification to the indications for use of a device would trigger the need for a new premarket submission.

Q.8. What does FDA recommend that firms consider when developing communications that are consistent with the FDA-required labeling to help ensure that the presentation of this information does not render the communication false or misleading?

A.8. The way a firm presents information that is consistent with the FDA-required labeling (including the express and implied claims made and the overall impression created by the communication as a whole) affects how the information is understood. The following are some high-level recommendations for firms to consider when developing their presentations of information that is consistent with the FDA-required labeling to help ensure the presentations do not mislead the applicable audience(s):

- Any study results or other data and information that are relied upon to support a firm's communication should be accurately represented in the communications. Moreover, material aspects of study design and methodology for any studies relied on should be clearly and prominently disclosed in firms' communications to allow audiences to accurately interpret the information (e.g., type of study, study objectives, product dosage/use regimens, controls used, patient population studied), and material limitations related to the study design, methodology, and results should also be disclosed in a clear and prominent manner.

- The communication should accurately characterize and contextualize the relevant information about the product, including by disclosing unfavorable or inconsistent findings. For example, if a firm presents efficacy results from a postmarketing study of its product that evaluated the effect of the product on two different endpoints, such as overall survival and progression-free survival, and the product failed to demonstrate an effect on one of these two endpoints, the firm should disclose this in the communication, rather than selectively presenting only the positive efficacy results.

- For communications that present data or information that is not in the FDA-required labeling, but where the FDA-required labeling contains other data or information related to what is being represented/suggested in the communication, the communication should also include the data or information from the FDA-

[13] See, e.g., 21 CFR 201.56(a)(2) ("[approved] labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading"); 21 CFR 314.70 and 601.12 (concerning supplements and other changes to an approved application, including labeling); 21 CFR 514.8(c) (concerning supplements and other changes to an approved application for a new animal drug, including labeling); 21 CFR 814.39 (concerning supplements to an approved premarket approval application (PMA), including labeling); and 21 CFR 814.108 (concerning supplements to an approved HDE application, including labeling).

required labeling to provide the audience with appropriate context. For example, if a communication provides postmarketing information about the types and rates of occurrence of adverse events that have been observed in practice, the communication should also include information from the FDA-required labeling about the types and rates of occurrence of adverse reactions observed in clinical trials to provide context.

The considerations described above are not intended to be a comprehensive summary of everything a firm should factor into its analysis of whether its presentations are truthful and non-misleading. FDA recommends that, before disseminating a communication regarding a medical product, firms should have qualified medical, legal, and regulatory personnel carefully review the communication to ensure it is not false or misleading.

Q.9. What are some examples of communications that are consistent with the FDA-required labeling and with the recommendations in this guidance?

A.9. Below are two examples of communications FDA would consider to be consistent with the FDA-required labeling and the recommendations in Q.6/A.6 and Q.8/A.8.

Example 1: Product B is an Immune Globulin Intravenous (Human), 10% liquid indicated for the treatment of primary humoral immunodeficiency (PI) and chronic immune thrombocytopenic purpura (IPT). Product B's firm develops promotional materials which communicate that clearance of Product B is comparable in males and females taking it to treat PI and IPT. These materials cite to the pharmacokinetic information obtained from the pivotal study of the product.

Is this consistent with the FDA-required labeling? Yes. This claim about the product is within the scope of the uses approved by FDA, as the FDA-required labeling reflects that the product is indicated for use in both males and females to treat PI and IPT, and does not contain any limitations or directions or other special considerations related to the gender of patients using the product. The representation about similar clearance of the product in males and females is not expected to increase the potential for harm to patients, and the directions in the FDA-required labeling enable the product to be safely and effectively used to treat PI and IPT regardless of gender. This would be an example of a communication that FDA would consider to be consistent with the FDA-required labeling.

Is this truthful and non-misleading? Yes, assuming the clearance information from the pivotal study is accurately reported in the firm's promotional materials and the material aspects of the underlying study design and methodology are disclosed, including any material limitations of the information. As indicated in Q.7/A.7, the firm should also ensure the rest of the information in the promotional materials is truthful and non-misleading and satisfies any other applicable requirements.

Example 2: An implantable device is approved for use as an adjunctive therapy for reducing symptoms of a chronic disease that are not adequately controlled by

medication. The device is clinician/patient-controlled based on the disease state and symptoms. The directions for use do not prescribe a specific use schedule. In the clinical study that supported the device's premarket approval application (PMA), approximately half of the patients using the device reported severe headaches, but many patients tolerate this risk because of the benefits of amelioration of symptoms associated with their chronic illness.

The firm enrolled patients with the implanted device in a postmarketing registry, which was designed to better identify and quantify rare adverse events and evaluate the longer-term effectiveness of the therapy. In addition to clinical visits for follow-up, patients used a diary to record device use, symptoms, and adverse events. Data from the registry suggest that patients who use the device more frequently and for shorter periods of time (such use is consistent with the approved labeling) have a reduced incidence of severe headaches associated with use of the device compared to that reported in the PMA-approved labeling.

The device firm develops promotional materials to communicate this information; these materials also outline specific information regarding the registry, including the number of patients enrolled in the registry, patient population, outcome measures, and a summary of the device use, as well as symptoms and adverse events reported in the patient diaries. The proposed communications clearly disclose that the trends related to the diary information are descriptive, not statistically powered, and not pre-specified, meaning the relationship between the use patterns described and the reduced incidence of severe headaches is only hypothesized and that no conclusions can be drawn from the data. They also disclose the data from the premarket clinical study along with the registry data to provide context.

Is this consistent with the FDA-required labeling? Yes. These representations about the use of the product are within the scope of the uses approved by FDA, as the product is being used for its approved indication in its approved patient population and in a manner that comports with the directions for use in the FDA-required labeling. These representations are not expected to increase the potential for harm to patients relative to the information reflected in the FDA-required labeling. The directions for use in the FDA-required labeling enable the product to be safely and effectively used under the conditions represented in the communication. While the communication provides supplementary information about use of the device in a specific manner, the information provided is consistent with the directions for use in the labeling, which do not prescribe a specific use schedule, and the information does not otherwise alter or compromise the directions for use in the FDA-required labeling. A firm's communication of this information would be considered consistent with the FDA-required labeling.

Is this truthful and non-misleading? If the data and information are being accurately reported in the firm's promotional materials and the material aspects of the underlying study design and methodology are disclosed in the materials, including material limitations of the information, FDA would consider this to be truthful and

non-misleading. Provided the rest of the information in the promotional materials is truthful and non-misleading, this is an example of a communication that FDA would also consider to be consistent with the recommendations in Q.6/A.6 and Q.8/A.8.

Q.10. What are examples of communications FDA would consider to be inconsistent with the FDA-required labeling or inconsistent with the recommendations in this guidance?

A.10. Below are two examples. The first example illustrates a communication that FDA would consider to be inconsistent with the FDA-required labeling, and the second example illustrates a communication that FDA would consider to be inconsistent with the recommendations in Q.6/A.6 and Q.8/A.8.

Example 1: A drug is indicated for the treatment of bovine respiratory disease (BRD) associated with certain susceptible bacteria in beef and non-lactating dairy cattle. The firm develops promotional materials to communicate information about the use of the drug to prevent BRD if used 5 days before shipment of cattle.

Is this consistent with the FDA-required labeling? No. These representations about the use of the product are not within the scope of the uses approved by FDA. Treatment of BRD and prevention of BRD are distinct indications, and this drug is not approved for prevention of BRD. The benefit/risk profile of the product for the unapproved disease prevention indication could be materially different than for the approved treatment indication, and the FDA-required labeling for treatment of BRD does not provide directions for using the product for disease prevention. The administration of the drug to cattle 5 days before shipment to prevent BRD could increase the potential for harm to health (including harm to the health of cattle and of humans) from resistant bacteria originating from treated cattle. FDA considers appropriate risk factors, including considerations of animal and public health, in determining whether an animal drug product is safe and effective under particular conditions of use.

Example 2: Drug A is approved for the long-term, maintenance treatment of asthma patients 12 years of age and older. The safety and efficacy of Drug A for this indication was evaluated versus placebo treatment in a randomized, double-blind study. The study also included an active comparator (Drug B), approved for the same indication and with a comparable risk profile, which was similarly evaluated versus placebo. The study was not designed to test the non-inferiority or superiority of Drug A directly against Drug B (i.e., the Drug B arm was included for assay sensitivity). Drug A and Drug B demonstrated statistically significant improvements versus placebo in the co-primary efficacy endpoints, but Drug A's results showed a numerically greater improvement versus placebo than those for Drug B. Based on this study, Drug A's firm develops promotional materials to communicate that Drug A is clinically superior to Drug B for the long-term, maintenance treatment of asthma patients 12 years of age and older.

Is this consistent with the FDA-required labeling? Yes. The information the firm proposes to present is within the scope of the uses approved by FDA for Drug A. The communication relates to the indicated use of Drug A in the approved patient population at the same dosing strength and frequency recommended in the FDA-required labeling. The information is not expected to increase the potential for harm to the health of patients relative to the information reflected in the FDA-required labeling — both Drug A and Drug B are approved for the same indication and patient population and have similar risk profiles. Furthermore, the directions in the FDA-required labeling enable Drug A to be safely and effectively used under the conditions presented in the communication. This communication could be considered consistent with the FDA-required labeling.

Is this truthful and non-misleading? No. The communication is misleading because it makes a claim of superior effectiveness for Drug A versus Drug B based on a study that was not designed to evaluate superiority or non-inferiority of Drug A to Drug B. Thus, the communication would not be consistent with the recommendations in Q.6/A.6 and Q.8/A.8.

If the firm wishes to present data and information from this study, it should do so in a truthful and non-misleading way. For example, the firm could describe the study design and objectives, including the material limitations of both, and include prominent contextual information that the study was not designed to provide comparative efficacy data and should not be interpreted as providing evidence of superiority or non-inferiority of Drug A to Drug B. The communication should not contain representations or suggestions that are not supported by appropriate evidence, such as any representation or suggestion of Drug A's superior effectiveness over Drug B.

Q.11. What are the Agency's policies for communication of information that is <u>not</u> consistent with the FDA-required labeling (i.e., information about unapproved uses of approved/cleared medical products)?

A.11. FDA has issued a draft guidance describing its thinking on how firms can respond to unsolicited requests for unapproved use information related to their FDA-approved prescription drugs and FDA-approved or cleared devices.[14] In addition, FDA has

[14] FDA's draft guidance *Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices Practices* (December 2011), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatorylnformation!Guidances/UCM285145.pdf. When final, this guidance will represent FDA's current thinking on this topic.

provided separate guidances describing recommended practices for the dissemination by firms of scientific and medical publications discussing unapproved uses of approved drugs or approved or cleared devices.[15,16]

[15] FDA's guidance *Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publication on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* (January 2009), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm.

[16] FDA's revised draft guidance *Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices* (February 2014), available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm387652.pdf. When final, this guidance will represent FDA's current thinking on this topic.