UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

IN RE: ZOFRAN (ONDANSETRON) PRODUCTS LIABILITY LITIGATION	**MDL No. 1:15-md-2657-FDS**
	This document relates to: All Actions

PLAINTIFFS' NOTICE OF FDA DENIAL OF GSK'S CITIZEN PETITION

Plaintiffs submit the following to apprise the Court of recent, significant regulatory action. Today, Plaintiffs received notice that the FDA denied GSK's Citizen Petition (FDA-2019-P-5151), attached here as Exhibit A. In its denial, the FDA concluded:

> Your request that FDA review and opine on certain pieces of information to answer a hypothetical question separate and apart from FDA's ongoing product review would divert scientific staff time away from pending drug applications, drug product safety review, and other work critical to our public health mission and therefore would detract from fulfilling the Agency's statutory obligations. In addition, because a request to consider a hypothetical question is not a request to "take or refrain from taking" an administrative action, it is not the appropriate subject of a citizen petition (see 21 CFR § 10.25(a)).

Plaintiffs further reserve the right to submit additional comment or briefing as they, or the Court, may deem necessary.

Respectfully submitted,

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Dated: January 15, 2021

CERTIFICATE OF SERVICE

I hereby certify that the foregoing Plaintiffs' Notice of FDA Denial of GSK's Citizen Petition, which was filed with the Court through the CM/ECF system, will be sent electronically to all registered participants as identified on the Notice of Electronic Filing.

/s/ *Kimberly D. Barone Baden*
Kimberly D. Barone Baden

Sabine Luik, M.D.
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January 15, 2021

Re: Docket No. FDA-2019-P-5151

Dear Dr. Luik:

This letter responds to your citizen petition submitted on behalf of GlaxoSmithKline LLC (GSK) and received on November 1, 2019 (Petition).[1] Your Petition requests that the Food and Drug Administration (FDA or Agency) review four categories of information concerning the use of Zofran (ondansetron) in pregnancy and "either refrain from taking action to alter Zofran's pregnancy-related labeling or take action to alter the labeling in light of these four categories of information, as the Agency deems appropriate" (Petition at 1).[2]

According to your Petition, these categories of information are:

(1) [T]hree animal reproductive toxicity studies performed to seek approval of Zofran in Japan;

(2) [I]nformation regarding the potential of ondansetron to inhibit hERG ion channels, which was described in publicly available literature and which the plaintiffs claim demonstrates a teratogenic mechanism of action;

(3) [T]he fact that GSK allegedly used multiple System Organ Class (SOC) codes from the MedDRA dictionary to code similar adverse events, such that "tabulations or analysis based on SOCs would dilute the total number of cardiac birth defects"; and

[1] On April 27, 2020, FDA issued an interim response pursuant to 21 CFR 10.30(e)(2), explaining that the Agency had been unable to reach a decision on your Petition due to the need to address other Agency priorities.

[2] Your Petition references pending multidistrict litigation, *In re Zofran (Ondansetron) Products Liability Litigation*, MDL no. 1:15-md-3657-FDS (D. Mass.), in which plaintiffs claim "that Zofran use in pregnancy causes a variety of birth defects" (Petition at 1). According to the Petition, "plaintiffs have claimed that GSK failed to fully inform FDA of four categories of information relating to Zofran, which they contend would have caused FDA to change Zofran's pregnancy labeling" (Petition at 1).

(4) [I]nformation concerning GSK's assessment of, and GSK's alleged involvement in, a 2004 epidemiological study by Einarson et al., as well as certain adverse events associated with that and other postmarketing studies.[3]

You further request that, if FDA deems it appropriate to change the labeling, FDA "inform GSK and the public which categories of information (if any) necessitated a labeling change, whether the Agency believes it did not already have the information, and/or why the information is material to the Agency's labeling decision" (Petition at 1). You specify that your Petition does not address current developments associated with "Zofran's safety profile and labeling as a result of newly available epidemiological studies and an assessment of Zofran's labeling by the [European Medicines Agency's] Pharmacovigilance Risk Assessment Committee" (Petition at 1).

FDA has considered your Petition, comments submitted to the public docket established for this Petition, and summaries submitted to the public docket of listening meetings on this Petition as well as materials submitted during those listening meetings. For the reasons described below, your request that the Agency review limited categories of information and "either refrain from taking action to alter Zofran's pregnancy-related labeling or take action to alter the labeling in light of these four categories of information, as the Agency deems appropriate" is denied without comment on the relevance, if any, of this information to ondansetron product labeling. As explained in further detail below, FDA evaluates whether safety-related labeling changes are warranted based on the review of *all* relevant information available to the Agency. Your request that FDA review and opine on certain pieces of information to answer a hypothetical question separate and apart from FDA's ongoing product review would divert scientific staff time away from pending drug applications, drug product safety review, and other work critical to our public health mission and therefore would detract from fulfilling the Agency's statutory obligations. In addition, because a request to consider a hypothetical question is not a request to "take or refrain from taking" an administrative action, it is not the appropriate subject of a citizen petition (see 21 CFR § 10.25(a)).

We are instead responding to your Petition by providing background information on safety-related labeling for prescription drugs that may be helpful in clarifying FDA's expectations for application holders' submission of postmarketing safety-related information and corresponding updates to product labeling and FDA's approach to the review of such information in the context of relevant statutory and regulatory requirements. This description of the labeling review process is intended to convey the depth of FDA's engagement in the scientific evaluation of relevant data and information in determining the safety-related information that should be included in FDA-approved labeling, and the iterative, bilateral nature of the communications process between FDA and the applicant or application holder regarding the content and wording of product labeling. We also acknowledge that the current application holder for Zofran submitted a labeling supplement to FDA after the submission of this Petition. The supplement, the existence of which has been publicly disclosed by the application holder, remains under review.

[3] Petition at 2.

I. BACKGROUND

A. Prescription Drug Labeling

1. Overview

Under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA regulations, the Agency makes decisions on the approval of marketing applications, including supplemental applications, for drug products based on a comprehensive scientific evaluation of the drug product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling (see section 505(d) of the FD&C Act (21 U.S.C. 355(d))).[4] A new drug application (NDA) is "required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source" (§ 314.50 (21 CFR 314.50)). An NDA also must contain the proposed text of the labeling, including "annotations to the information in the summary and technical sections of the NDA that support the inclusion of each statement in the labeling" (§ 314.50(c)(2)(i)).

As part of its review of an NDA for a prescription drug, FDA reviews the proposed text of the labeling submitted by the applicant (see § 314.50(e)(2)(ii) and (l)(1)(i)). FDA communicates with the applicant about "scientific, medical, and procedural issues that arise" in the course of its review (21 CFR 314.102(a)). The "[d]evelopment of final labeling" generally is "an iterative process between the applicant and FDA" involving a series of communications regarding the proposed text of the draft labeling for the proposed product.[5] FDA may send an information request to the applicant requesting responses to questions or additional data or information based on the Agency's review of the draft labeling. FDA may recommend substantive revisions to data and information described in draft labeling based on the Agency's evaluation and analysis of data submitted in the application (including an amendment or supplement to the application) or otherwise available to the Agency. This may include, for example, recommended revisions to the presentation of clinical study data to reflect FDA's statistical reanalysis of submitted data. This also may include, for example, recommendations to add or remove safety-related information; to modify safety-related information to clarify the nature, severity, and frequency of the risk; or, as applicable, steps to prevent, mitigate, or manage the risk. FDA also may recommend nonsubstantive, clarifying revisions to draft labeling—for example, to communicate a risk more clearly and effectively to health care practitioners. FDA-approved drug product labeling summarizes the essential information needed for the safe and effective use of the drug and reflects FDA's finding on the safety and effectiveness of the drug under the labeled conditions of use (see § 201.56(a) (21 CFR 201.56(a))).

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[4] Although this response focuses on drug products subject to approval under section 505(c) of the FD&C Act, similar principles apply to biological products subject to licensure under section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)).

[5] See Center for Drug Evaluation and Research, *CDER 21st Century Review Process: Desk Reference Guide*, available at https://www.fda.gov/media/78941/download.

2. Certain Content and Format Requirements for Prescription Drug Labeling

FDA regulations govern the content and format of prescription drug labeling (see, e.g., §§ 201.56 and 201.57 (21 CFR 201.57); see also 21 CFR 201.100(c)). The regulations are intended to organize labeling information to more effectively communicate to health care professionals the "information necessary for the safe and effective use of prescription drugs."[6] FDA regulations require that the labeling of most prescription drug products include Highlights of Prescribing Information, which are intended to summarize the information that is most important for prescribing the drug safely and effectively and to facilitate access to the more detailed information within product labeling (see § 201.57(a)). FDA regulations further require that the labeling for most prescription drugs include, among other information, the following sections: Boxed Warning (if any); Contraindications; Warnings and Precautions; Adverse Reactions; and Use in Specific Populations, which includes a subsection on Pregnancy (see § 201.57(c)(1), (5), (6), (7), and (9)(i)).

a. Boxed warning

A boxed warning may be required for certain contraindications or serious warnings, particularly those that may lead to death or serious injury, as this information is especially important for a health care practitioner to consider in assessing the risks and benefits of a drug (see § 201.57(c)(1)). The boxed warning must briefly explain the risk and then refer to the Contraindications or Warnings and Precautions section, where the risk is explained in more detail (see § 201.57(c)(1)). A boxed warning is ordinarily used when:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug; or

- There is a serious adverse reaction[7] that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another

[6] Preamble to final rule, "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (71 FR 3922 at 3928, January 24, 2006) (Physician Labeling Rule). For the content and format requirements for the labeling of older prescription drug products that are not subject to the labeling requirements in § 201.57, see § 201.80 (21 CFR 201.80). The specific labeling requirements for older drug products differ in certain respects, and generally are not referenced in this response.

[7] FDA applies the definition of *serious* in § 314.80(a) (21 CFR 314.80(a)). A serious adverse drug experience is defined as "[a]ny adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition" (§ 314.80(a)).

drug or managing patients in a specific manner, avoiding use in a specific clinical situation); or

- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted.[8]

b. Contraindications

The Contraindications section must describe any situations in which the drug should not be used because the risk of use "clearly outweighs any possible therapeutic benefit" (§ 201.57(c)(5)). This section should include observed and anticipated risks, but not theoretical risks.[9] This could include, for example, a situation where animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans (e.g., animal data demonstrate that the drug has teratogenic effects) and those risks do not outweigh any potential benefit of the drug to any patient.[10]

c. Warnings and Precautions

The Warnings and Precautions section must describe "clinically significant adverse reactions," other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur where "reasonable evidence of a causal association" between the drug and such hazards exists (§ 201.57(c)(6)(i)). FDA regulations require that the labeling "must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established" (§ 201.57(c)(6)(i)). FDA adopted that standard in part to "prevent overwarning" of potential risks, which, if included in the Warnings and Precautions section, could dilute other "more important warnings" or "deter appropriate use" of the drug.[11] FDA thus reserves this section for only a "discrete set" of hazards serious enough to affect prescribing decisions.[12] FDA regulations provide that a "specific warning relating to a use not provided for under the 'Indications and Usage' section may be required by FDA in accordance with sections 201(n) and 502(a) of the [FD&C Act] if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard" (§ 201.57(c)(6)(i)).

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[8] See FDA guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* (October 2011), available at https://www.fda.gov/media/71866/download (Warnings Guidance).

[9] See § 201.57(c)(5); see also Warnings Guidance at 8.

[10] See Warnings Guidance at 8.

[11] Preamble to final rule, "Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices" (73 FR 49603 at 49605–49606, August 22, 2008).

[12] See Warnings Guidance at 3.

d. Adverse Reactions

The Adverse Reactions section describes "the overall adverse reaction profile of the drug" (§ 201.57(c)(7)). FDA's regulations define an *adverse reaction*, for purposes of prescription drug labeling, as an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence (§ 201.57(c)(7)). The threshold for including an adverse reaction in this section is lower than that for the Warnings and Precautions section: An adverse reaction must be listed if "some basis" exists "to believe there is a causal relationship between the drug and the occurrence of the adverse event" (§ 201.57(c)(7)).

e. Pregnancy

The Pregnancy subsection is located under the Use in Specific Populations section (see § 201.57(c)(9)(i)). On December 4, 2014, FDA issued a final rule amending the regulations on the requirements for pregnancy and lactation information in prescription drug and biological product labeling (Pregnancy and Lactation Labeling Rule (PLLR)).[13] The PLLR revisions to the regulations were intended "to create a consistent format for providing information about the effects of a drug on pregnancy and lactation that would be useful for decision making by health care providers and their patients."[14] The labeling content and format requirements in § 201.57(c)(9)(i), as revised by the PLLR, took effect on June 30, 2015, with a phased implementation schedule for drugs (including biological products) that are the subject of NDAs, biologics license applications, and efficacy supplements that had been approved on or after June 30, 2001.[15] The PLLR also requires for all human prescription drug and biological products, including those for which an application was approved before June 30, 2001, that the Pregnancy subsection of labeling be revised to remove the pregnancy letter categories A, B, C, D, and X.[16]

Information in the Pregnancy subsection of labeling may present, in greater detail, a topic that is briefly summarized in another section of labeling (e.g., Warnings and Precautions).[17] FDA has explained that when a topic is discussed in more than one section of labeling, the section containing the most important information relevant to prescribing should typically include a succinct description and should cross-reference sections that contain additional detail.[18]

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[13] Final rule, "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling" (79 FR 72064, December 4, 2014) (PLLR).

[14] Id.

[15] See §§ 201.56(b) and 201.57(c)(9)(i). Because of this phased implementation schedule, there may be a period of time in which the pregnancy risk categories continue to appear on some ondansetron drug product labeling, while other ondansetron products have labeling that has been revised, consistent with the PLLR content and format requirements.

[16] §§ 201.57(c)(9) and 201.80; see also 79 FR 72064 at 72095 (December 4, 2014).

[17] PLLR, 79 FR 72064 at 72085 (December 4, 2014).

[18] See FDA guidance for industry *Labeling for Human Prescription Drug and Biological Products—Implementing*

Under current labeling requirements, information in the Pregnancy subsection of labeling is presented under the following subheadings: Pregnancy Exposure Registry; Risk Summary; Clinical Considerations; and Data.[19] Although Zofran's labeling does not currently include the Pregnancy Exposure Registry or the Clinical Considerations subheadings, we briefly describe each pregnancy subheading listed in the rule below.

Pregnancy Exposure Registry. If there is a scientifically acceptable pregnancy exposure registry for the drug, the labeling must state that fact and provide contact information needed for enrolling in or obtaining information about the registry.

Risk Summary. The Risk Summary subheading is required under the Pregnancy subsection because certain statements must be included even when no product-specific data are available, given that all pregnancies have a background risk of birth defect, loss, or other adverse outcomes.[20] The Risk Summary must contain risk statement(s) that describe for the drug the risk of adverse developmental outcomes based on all relevant human data, animal data, and/or the drug's pharmacology.[21] When multiple data sources are available, the risk statements are required to be presented in the following order: human, animal, and pharmacologic.[22]

When human data are available that establish the presence or absence of any adverse developmental outcome(s) associated with maternal use of the drug, a risk statement based on human data must summarize the specific developmental outcome(s) and include its incidence and the effects of dose, duration of exposure, and gestational timing of exposure.[23] If human data indicate that there is an increased risk for a specific adverse developmental outcome in infants born to women exposed to the drug during pregnancy, the risk summary must contain a quantitative comparison of that risk to the risk for the same outcome in infants born to women who were not exposed to the drug, but who have the disease or condition for which the drug is indicated to be used.[24] When risk information is not available for women with the disease or condition(s) for which the drug is indicated, the risk summary must contain a comparison of the specific outcome in women exposed to the drug during pregnancy against the rate at which the outcome occurs in the general population.[25]

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the PLR Content and Format Requirements (February 2013), available at https://www.fda.gov/media/71836/download.

[19] § 201.57(c)(9)(i).

[20] § 201.57(c)(9)(i)(B).

[21] Id.

[22] Id.

[23] § 201.57(c)(9)(i)(B)(*1*).

[24] Id.

[25] Id.

When animal data are available, the risk statement based on such data must describe the potential risk for adverse developmental outcomes in humans and summarize the available data.[26] This statement must include: the number and type(s) of species affected; timing of exposure; animal doses expressed in terms of human dose or exposure equivalents; and outcomes for pregnant animals and offspring.[27]

With respect to pharmacology, when the drug has a well-understood pharmacologic mechanism of action that may result in adverse developmental outcomes, the Risk Summary must explain the mechanism of action and the potential associated risks.[28]

Clinical Considerations. The labeling under the Clinical Considerations subheading provides relevant information, to the extent it is available, under the headings Disease-Associated Maternal and/or Embryo/Fetal Risk, Dose Adjustment During Pregnancy and the Postpartum Period, Maternal Adverse Reactions, Fetal/Neonatal Adverse Reactions, and Labor or Delivery.[29]

Data. Under the subheading Data, labeling must describe the data that provide the scientific basis for the information presented in the Risk Summary and Clinical Considerations sections.[30] With respect to human data, both positive and negative study findings must be included.[31] This portion of labeling must describe the data regarding adverse developmental outcomes, adverse reactions, and other adverse effects.[32] Regarding animal data, this portion of labeling describes the nonclinical developmental toxicity studies that form the scientific basis for risk statement(s) in the Risk Summary that are based on animal data.[33] The labeling must describe the following: types of studies; animal species; animal doses or exposures described in terms of human dose or exposure equivalents and the basis for those calculations; duration and timing of exposure; study findings; presence or absence of maternal toxicity; and limitations of the data.[34]

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[26] § 201.57(c)(9)(i)(B)(*2*).

[27] Id.

[28] § 201.57(c)(9)(i)(B)(*3*).

[29] § 201.57(c)(9)(i)(C).

[30] § 201.57(c)(9)(i)(D)(*1*).

[31] § 201.57(c)(9)(i)(D)(*3*).

[32] Id.

[33] § 201.57(c)(9)(i)(D)(*4*).

[34] Id.

B. Postmarketing Safety Surveillance: Expectations for Application Holders and FDA Review

All drugs have risks, and health care practitioners and patients must balance the risks and benefits of a drug when making decisions about medical therapy. As a drug is used post-approval more widely and under diverse conditions, new information regarding the risks and benefits of a drug may become available. This may include new risks or new information about known risks. Accordingly, all application holders are required to develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA (see, e.g., § 314.80(b)). Application holders must promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers, and comply with applicable reporting and recordkeeping requirements (see, e.g., § 314.80(b), (c), and (j)).[35] FDA guidance for industry explains that "[a]fter a [safety] signal is identified, it should be further assessed [by the application holder] to determine whether it represents a potential safety risk and whether other action should be taken."[36]

FDA employs a multidisciplinary staff of health care professionals, epidemiologists, and other scientists to review adverse drug experience data by a variety of methods, including the application of computer algorithms as well as scrutiny of certain individual reports. FDA applies principles of risk-based safety surveillance after the approval of a drug and monitors the benefit-risk profile throughout the product life cycle and takes regulatory action (e.g., requesting or requiring revisions to product labeling, communicating new safety information to the public, requiring or modifying risk evaluation and mitigation strategies, withdrawing approval of the product) as appropriate. On the subject of this Petition, we note that FDA's approach to postmarketing surveillance of the use of drugs during pregnancy has a specific focus on detecting product-induced fetal effects. To optimize the detection and characterization of any adverse effects related to prenatal product exposure, FDA staff work collaboratively across the Agency and use all available postmarketing surveillance data sources (which may include, for example, adverse event reports, a prospective pregnancy registry study, epidemiologic studies). Reviewers consider the strengths and limitations of each data source throughout the review to inform the assessment of adverse drug effects to the pregnant woman and the fetus.

Application holders are required to submit periodic adverse drug experience reports to FDA at regular intervals for review (§ 314.80(c)(2)). Periodic adverse drug experience reports may supplement the spontaneous reports available to FDA reviewers for identifying potential safety

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[35] FDA also receives adverse drug experience reports directly from health care practitioners, researchers, consumers, and others (e.g., family members and lawyers). FDA learns about developments related to approved drugs through a variety of other sources. See, e.g., Appendix A to FDA guidance for industry *Safety Labeling Changes—Implementation of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act* (July 2013), available at https://www.fda.gov/media/116594/download (Safety Labeling Guidance).

[36] See FDA guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (March 2005), available at https://www.fda.gov/media/71546/download, at 9.

signals and learning about potential changes in the benefit-risk profile for marketed products.[37] Application holders also must comply with requirements for other postmarketing reports under § 314.81 (21 CFR 314.81) and section 505(k) of the FD&C Act. These requirements include submission of an annual report that includes a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product and a description of actions the applicant has taken or intends to take as a result of this new information (e.g., if appropriate, proposed revisions to product labeling (see § 314.81(b)(2)(i)).[38]

C. Safety-Related Labeling Changes

Application holders have an ongoing obligation to ensure that their drug product labeling is accurate and up-to-date.[39] When new information becomes available that causes information in labeling to be inaccurate, false, or misleading, the application holder must take steps to change the content of its labeling (see §§ 201.56(a)(2) and 314.70 (21 CFR 314.70)). For example, the labeling "must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established" (§ 201.57(c)(6)(i)). A drug is misbranded in violation of the FD&C Act when its labeling is false or misleading or does not provide adequate warnings (see sections 301(a) and (b) and 502(a), (f), and (j) of the FD&C Act (21 U.S.C. 331(a) and (b) and 352(a), (f), and (j)).

After FDA has approved an NDA, two mechanisms exist for substantively revising the product labeling, both of which require that the application holder file a supplemental application for FDA approval. For most substantive changes to product labeling, an application holder is

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[37] There are inherent limitations to a voluntary reporting system for adverse events associated with the use of a drug, including, but not limited to, underreporting, duplicate reporting, and reporting biases. Furthermore, for any given report, the reported adverse events may not be causally related to the products reported to have been taken. The event may have been related, for example, to the underlying disease being treated, to other medical conditions, or to another product taken at the same time. The number of cases reported to FDA's Adverse Event Reporting System cannot be used to calculate the incidence rates, to estimate drug risk for a particular product, or to compare risks between products.

[38] An annual report also is required to contain, among other things:

- "Copies of unpublished reports and summaries of published reports of new toxicological findings in animal studies and in vitro studies (e.g., mutagenicity) conducted by, or otherwise obtained by, the applicant concerning the ingredients in the drug product" (§ 314.81(b)(2)(v))
- "Published clinical trials of the drug (or abstracts of them) . . . and reports of clinical experience pertinent to safety (for example, epidemiologic studies or analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the applicant" (§ 314.81(b)(2)(vi)(*a*))
- "Summaries of completed unpublished clinical trials, or prepublication manuscripts if available, conducted by, or otherwise obtained by, the applicant" (§ 314.81(b)(2)(vi)(*b*))

[39] See *Wyeth v. Levine*, 555 U.S. 555, 570–71 (2009) ("It is a central premise of the [FD&C Act] and the FDA's regulations that the manufacturer bears responsibility for the content of its label[ing] at all times"); see also section 505(o)(4)(I) of the FD&C Act and § 201.56(a)(2).

required to submit a prior approval supplement and receive approval for the proposed labeling changes before distributing revised product labeling (§ 314.70(b) and (2)(v)). However, in the interest of public health, FDA's regulations permit certain labeling changes based on "newly acquired information" about an approved drug to be distributed upon receipt by FDA of a changes being effected (CBE-0) supplement that includes the change (§ 314.70(c)(6) and (iii)). "Newly acquired information" is defined to mean "data, analyses, or other information not previously submitted to the Agency." See § 314.3(b) (21 CFR 314.3(b)). Newly acquired information may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses); however, such information will qualify as newly acquired information under FDA regulations only if the studies, events, or analyses "reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA" (§ 314.3(b)). Accordingly, nominally new information concerning risks of a materially similar type, severity, and frequency as those revealed in information previously evaluated by FDA is cumulative and not considered to be newly acquired information that could justify a CBE-0 supplement.

A CBE-0 supplement may be submitted, for instance, to add or strengthen a contraindication, warning, precaution, or adverse reaction to reflect newly acquired information if "the evidence of a causal association satisfies the [relevant] standard for inclusion in the labeling" (§ 314.70(c)(6)(iii)(A)). If FDA does not subsequently approve the supplement, however, the Agency may order the application holder to cease distributing the drug with the labeling changes (§ 314.70(c)(7)). Historically, FDA has also accepted a prior approval supplement instead of a CBE-0 supplement, particularly where significant questions exist on whether to revise or how to modify existing drug labeling.

A prior approval supplement or CBE-0 supplement that proposes a safety-related change to product labeling must include all relevant data and information to demonstrate that the applicable statutory and regulatory standards have been met (see, generally, sections 502 and 505(d) of the FD&C Act and §§ 201.57 and 314.70(b) and (c)). The applicant is expected to fully inform the FDA of all material data and information related to the proposed safety-related labeling change and provide a justification for the proposed labeling change that describes the applicant's evaluation of such data and information (including strengths and limitations of the data from the various sources available to the applicant).

During the review process, FDA communicates with the applicant about scientific, medical, and procedural issues that may arise and engages in an iterative process involving a series of communications.[40] As noted in section I.A.1 of this response, FDA may recommend substantive revisions to data and information described in draft labeling based on the Agency's evaluation and analysis of data submitted or otherwise available to the Agency. If FDA and the sponsor can reach agreement on the proposed labeling change (which may be modified by FDA or the applicant from the original submission), then FDA will approve the supplement. FDA will reject a supplement, however, if the proposed labeling change is false or misleading, or if it does "not comply with the requirements for labels and labeling in [21 CFR] part 201" (§§ 314.125(b)(6) and (8) (21 CFR 314.125(b)(6) and (8))). In such circumstances, FDA will send the applicant a

[40] All procedures and actions that apply to an application submitted to FDA generally apply to supplements (21 CFR 314.71(b) and (c)).

"complete response letter" (§ 314.110(a) (21 CFR 314.110(a))). A complete response letter reflects FDA's complete review of the data submitted and describes all of the specific deficiencies that the Agency has identified (§ 314.110(a)(1) and (2)).

FDA may determine that a sponsor's proposed labeling change is not warranted. For example, if the Agency's judgment is that there is no "reasonable evidence of a causal association" between a drug and a clinically significant adverse reaction, FDA would decline to approve the addition of a warning about that risk (see 21 CFR 201.57(c)(6)(i)). If FDA determines that a proposed safety-related labeling change submitted is not warranted at the time under the relevant statutory and regulatory framework, the applicant may not resubmit a substantially similar proposed labeling change in a CBE-0 supplement unless newly acquired information "reveal[s] risks of a different type or greater severity or frequency than previously included in submissions to FDA."[41]

FDA may also initiate safety-related labeling changes on its own. FDA may issue a supplement request letter in which the Agency requests that an application holder make certain labeling changes, typically in response to a safety review conducted by FDA to assess a potential association between a drug or drug class and certain adverse events. The Agency may recommend specific changes to the labeling for the application holder's consideration or request that the applicant further evaluate the safety concern and propose text to address the risk.

FDA also is authorized to require certain drug (and biological product) application holders to make certain labeling changes based on new safety information (or new effectiveness information) (section 505(o)(4) of the FD&C Act). Under section 505(o)(4) of the FD&C Act, as amended by the SUPPORT for Patients and Communities Act (Public Law 115-271), FDA "shall promptly notify" the application holder as the "responsible person" for a drug "[i]f the [FDA] becomes aware of new information, including any new safety information or information related to reduced effectiveness, that the [FDA] determines should be included in the labeling of the drug" (section 505(o)(4)(A) of the FD&C Act; see also section 505(o)(2)(A) of the FD&C Act (defining *responsible person*)). Within 30 days, the application holder then must either submit a supplemental application to change the labeling or notify FDA that it believes that no change is warranted and justify this position (section 505(o)(4)(B) of the FD&C Act). FDA is required to "promptly review and act upon such supplement," and, if FDA disagrees with the application holder's labeling proposal or disagrees with the application holder's reasons why no changes are warranted, FDA "shall initiate discussions" to reach agreement within 30 days (unless an extension is warranted) (section 505(o)(4)(C) and (D) of the FD&C Act). FDA may within 15 days of the conclusion of the discussion period issue an order directing the application holder "to make such a labeling change as the [FDA] deems appropriate to address the new safety or new effectiveness information" (section 505(o)(4)(E) of the FD&C Act).

[41] See §§ 314.3(b) (definition of *newly acquired information*) and 314.70(c)(6)(iii). See also *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1672 (2019) (". . . showing that [F]ederal law prohibited the drug manufacturer from adding a warning that would satisfy [S]tate law requires the drug manufacturer to show that it fully informed the FDA of the justifications for the warning required by [S]tate law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning").

The standard for new safety information that may trigger an FDA-initiated safety labeling change required under section 505(o)(4) of the FD&C Act is not the same as newly acquired information under the CBE-0 pathway. Although FDA has construed section 505(o) of the FD&C Act to provide the Agency with broad authority, not all labeling changes related to safety will be required and reviewed under section 505(o)(4) of the FD&C Act. For example, the Agency will not typically exercise this authority for changes made only to the Adverse Reactions section.[42]

D. Zofran (Ondansetron)

NDA 020007 for Zofran (ondansetron hydrochloride) injection was approved in 1991.[43] Zofran is a type three 5-hydroxytryptamine receptor antagonist indicated for use in the prevention of nausea and vomiting associated with chemotherapy and radiotherapy and the prevention of postoperative nausea and vomiting associated with anesthesia. FDA subsequently approved other ondansetron drug products,[44] and currently marketed Zofran products include the following: oral tablet, approved in 1992 under NDA 020103; oral solution, approved in 1997 under NDA 020605; and orally disintegrating tablet, approved in 1999 under NDA 020781.[45] These NDAs were originally held by GSK, but they are now held by Novartis Pharmaceuticals Corporation. FDA also has approved generic ondansetron drug products that are therapeutically equivalent to the Zofran oral tablet, oral solution, orally disintegrating tablets, and injection presentations.

Although no ondansetron drug product has been approved for the treatment of nausea and vomiting in pregnancy, FDA has been aware of the unapproved use of ondansetron for those purposes. In December 2010, FDA requested information from GSK on Zofran use in pregnancy.[46] In 2013, an individual, James Reichmann, submitted a citizen petition that voiced concerns about the use of ondansetron during pregnancy (Reichmann Petition).[47] The Reichmann Petition requested that FDA change the pregnancy category that was then in effect and notify obstetricians and gynecologists that there were risks posed to the fetus, neonate, and mother by the unapproved use of ondansetron for the treatment of nausea and vomiting in

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[42] See Safety Labeling Guidance.

[43] Zofran injection has been discontinued from marketing (see 82 FR 43388, September 15, 2017, describing FDA's determination that the product was not discontinued or withdrawn for reasons of safety or effectiveness).

[44] For the injection, oral tablet, and oral solution dosage forms of Zofran, ondansetron hydrochloride is the active ingredient. For the oral disintegrating tablet and oral film, ondansetron base is the active ingredient. For purposes of this response, we generally refer to ondansetron.

[45] Ondansetron is approved in an oral film dosage form under the brand name Zuplenz. NDA 022524 for Zuplenz was approved on July 2, 2010, and is held by Midatech Pharma U.S. Because Zuplenz is not the subject of your Petition, we do not discuss this product in depth.

[46] Zofran citizen petition—GSK presentation to FDA (March 5, 2020), slide 2 (Docket No. FDA-2019-P-5151-0072).

[47] See Docket No. FDA-2013-P-0048.

pregnancy.[48] In responding to the Reichmann Petition, the Agency reviewed studies cited in the Petition, supplements, and third-party submissions to the docket and performed an independent search of the published medical and scientific literature. The Agency concluded that the data available at that time were not sufficient to warrant labeling changes or issuing a safety notification to health care practitioners, and the Agency denied the requests in the Reichmann Petition in 2015.

The approved labeling for Zofran products describes data from published epidemiological studies that have evaluated whether there is an association between ondansetron use and major birth defects and explains that these studies have reported inconsistent findings and have important methodological limitations. The labeling also describes data from reproductive studies in rats and rabbits, and the Risk Summary explains that these studies did not show evidence of harm to the fetus when ondansetron was administered during organogenesis at a multiple of the maximum recommended human dose.[49] The labeling explains, as required by regulation, that "[i]n the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively" (see § 201.57(c)(9)(i)(B)).

The Agency continues to conduct risk-based postmarketing surveillance consistent with the standards and practices described in section I.B and I.C of this response. FDA also has continued to review safety-related data regarding ondansetron, including the newly available epidemiological studies.

II. DISCUSSION

In your Petition, you request that the Agency review four categories of information at issue in multidistrict litigation in which you are a defendant. You request that any action or inaction that the Agency take in response to the Petition be "in light of these four categories of information" (Petition at 1). Your Petition makes clear that it "does not address . . . developments" relating to "newly available epidemiological studies" and other recent data (Petition at 1). Based on this specific subset of information, you request that FDA "either refrain from taking action to alter Zofran's pregnancy-related labeling or take action to alter the labeling" (Petition at 1).

FDA's regulations provide that a person may "petition the Commissioner to issue, amend or revoke a regulation or order, or to take or refrain from taking any other form of administrative action" (21 CFR 10.25(a)). An administrative action "includes every act, including the refusal or failure to act, involved in the administration of any law by the Commissioner" (21 CFR 10.3(a)). Although your Petition purports to request administrative action in the form of altering (or refusing to alter) Zofran's pregnancy-related labeling, we have concluded that the limitations you have placed on your request render the question essentially hypothetical and therefore

[48] See Docket No. FDA-2013-P-0048.

[49] See Zofran (ondansetron hydrochloride) tablets, orally disintegrating tablets, and oral solution labeling, approved October 2017, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020103s035_020605s019_020781s019lbl.pdf.

inappropriate for the citizen petition process.

As discussed above, FDA administers the law in this area by evaluating whether proposed labeling changes would render the labeling false or misleading or otherwise in violation of FDA's labeling requirements (§ 314.125(b)(6) and (8)). This evaluation requires the review of *all* relevant information before the Agency (see, e.g., § 201.57(b)(9)(i)(B) (requiring the pregnancy Risk Summary to be "based on data from all relevant sources")).[50] Your Petition, however, seeks to limit the information under review and requests that FDA analyze and comment on those certain categories of information. At the same time, you acknowledge that there are more recent, relevant epidemiological studies, but you indicate that you are requesting that FDA *not* consider that information in responding to your Petition.

Those limitations are not consistent with the standards governing labeling review. Were FDA to respond to the request, any substantive conclusions reached would not necessarily determine the information that should be communicated in the Zofran labeling today. For example, even if FDA were to determine that none of the four categories of information, in isolation, warranted a change to the Zofran labeling, that determination could change when considering the evidence in combination with other, more recent information (see, e.g., 79 FR 72064 at 72079 (December 4, 2014) (describing the range of evidence that may be relevant to the Pregnancy subsection of labeling)). The Petition thus requests a decision that is independent from the administration of FDA's labeling laws. Because your request seeks a response to a hypothetical question, rather than an "act . . . involved in the administration of [FDA's] law[s]," it is not appropriate under 21 CFR 10.30.

Furthermore, FDA has serious policy and administrative concerns about engaging in the review requested by the Petition. To answer the substantive questions raised by the Petition, FDA would need to engage the scientific staff who review pending drug applications and current developments regarding drug product safety. Conducting the review would require these drug reviewers to evaluate these categories of information to answer the theoretical query of what the Agency might have done in the past with reference to certain information. Given that FDA has limited resources to conduct its scientific evaluations in each of many substantive medical areas presented by drug applications, responding to this Petition would detract from and burden the current review of pending drug applications and drug product safety. Diverting staff time away from pending drug applications and drug product safety review to answer theoretical questions related to third-party litigation would detract from fulfilling the Agency's statutory obligations and public health mission.

For these reasons, we decline to conduct the evaluation you request related to the four categories of information at issue in the litigation.

[50] See also Physician Labeling Rule, 71 FR 3922 at 3968 (January 24, 2006) (FDA-approved prescription drug labeling "reflects thorough FDA review of the pertinent scientific evidence").

III. CONCLUSION

Based on the reasons described in this response, we deny your request.

As with all FDA-approved products, we will continue to monitor and review available safety information related to ondansetron products throughout the product life cycles and will take further action if we determine it is appropriate to do so.

Sincerely,

Patrizia A. Cavazzoni -S

Digitally signed by Patrizia A. Cavazzoni -S
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