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AUG 3 1 2016

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RE: Docket No. FDA-2016-P-0689

Dear Drs. Wen and Alexander-Scott:

This letter responds to your citizen petition, docket number FDA-2016-P-0689, filed on February 24, 2016 (Petition), in which you request that the Food and Drug Administration (FDA or Agency):

1. Amend current black box warnings on all opioid analgesic and benzodiazepine class medications to state:

   a. Labeling for all Opioid[1] Class Medications [to] read:

   WARNING: CONCURRENT USE WITH BENZODIAZEPINES REDUCES THE MARGIN OF SAFETY FOR RESPIRATORY DEPRESSION AND CONTRIBUTES TO THE RISK OF FATAL OVERDOSE, PARTICULARLY IN THE SETTING OF MISUSE.

   b. Labeling for all Benzodiazepine Class Medications [to] read:

   WARNING: CONCURRENT USE WITH OPIOIDS REDUCES THE MARGIN OF SAFETY FOR RESPIRATORY DEPRESSION AND CONTRIBUTES TO THE RISK OF FATAL OVERDOSE, PARTICULARLY IN THE SETTING OF MISUSE.

[1] Because the Petition's formal request at the outset is that FDA "[a]mend current black box warnings on all opioid *analgesic* and benzodiazepine class medications… [and to] [r]equire [M]edication [G]uides for both classes of medications" (emphasis added), FDA interprets the scope of the Petition to cover only opioid analgesic drugs and benzodiazepines.

2. Require [M]edication [G]uides for both classes of medications that specifically warn patients of the potential dangers of combined use of opioids and benzodiazepines.

(Petition at 1, 16-17)

We have carefully considered the Petition, and, for the reasons that follow, your Petition is granted in part and denied in part.[2,3] Specifically, the Petition is granted in that FDA has decided to require a boxed warning and new or revised medication guide for opioid analgesic and prescription opioid cough drugs and benzodiazepine drugs, alerting patients and prescribers to serious risks associated with concomitant use of opioids and benzodiazepines. The Petition is denied to the extent that the language in the boxed warning and medication guides differs from the language requested in the Petition, and to the extent that there are certain products that will not receive medication guides because of the distinct indications and uses of those drugs.

Today, on the basis of the information discussed below, FDA has notified application holders for opioid analgesics, prescription opioid cough products, and benzodiazepine drugs that, under section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C 355(o)(4)), safety labeling changes (SLCs) are needed for these drugs.[4] The purpose of these labeling changes, which are described below, is to make more prominent the risks associated with concomitant use of opioids and benzodiazepines, and opioids and other central nervous system (CNS) depressants, including alcohol.[5] Furthermore, the Agency is generally requiring new Medication Guides, or amending existing Medication Guides, to explain these risks to patients.

I. BACKGROUND

A. Opioids and Benzodiazepines: Overview and Interactions

Opioids are a class of drugs that includes oxycodone, morphine, and codeine, among others. Opioids primarily operate via the *mu*-opioid receptors in the central nervous system, resulting in analgesia, among other effects. Indications for these drugs include

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[2] Albeit largely based on evidence other than that advanced by Petitioners.

[3] FDA has received two citizen petitions, docket nos. FDA-2015-P-3959 and FDA-2016-P-1090, which pertain to related subject matters. The Agency is still carefully reviewing these petitions, so the present petition response and associated safety labeling change (SLC) actions should not be construed as a grant, denial, or other disposition of FDA-2015-P-3959, FDA-2016-P-1090, or other petitions that have not yet been answered by the Agency.

[4] Under section 505(o)(4) of the FD&C Act, FDA has notified holders of approved new drug applications (NDAs) and holders of approved abbreviated new drug applications (ANDAs) that reference NDAs that are not currently marketed.

[5] Due to the benefit/risk assessment for opioid medication-assisted treatment (MAT) to treat opioid addiction and dependence, the Agency is continuing to examine available evidence regarding concomitant use of benzodiazepines and opioid MAT drugs; therefore, at this time, FDA is requiring labeling changes for opioid analgesics, opioid cough products, and benzodiazepines.

analgesia[6] and cough suppression.[7,8] The patient populations taking opioids vary depending on the drug's indication, formulation/dosage form (e.g., parenteral, transdermal patch, oral), and release mechanism (e.g., extended-release, immediate-release), among other factors.[9] Particularly at high doses or in patients with certain underlying medical conditions, opioids can result in sedation and respiratory depression (i.e., slowed/shallow breathing).[10] This occurs because opioids can interfere with the body's response to low oxygen levels and to high carbon dioxide levels.[11]

Benzodiazepines are a class of drugs that includes lorazepam, diazepam, and clonazepam, among others. Benzodiazepines are gamma aminobutyric acid (GABA) agonists, and they exert anxiolytic, sedative, muscle-relaxant, anticonvulsant and amnestic effects.[12] These drugs are indicated for a variety of conditions, including anxiety,[13] panic disorder,[14] insomnia,[15] epilepsy,[16] muscle spasticity,[17] and alcohol withdrawal.[18] As with opioids, the patient populations taking benzodiazepines will vary, depending on the drugs' indications, formulations/dosage forms, and release mechanisms, among other factors. At usually prescribed doses, benzodiazepines "have essentially no effect on

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[6] See, e.g., NDA 202080, Oxaydo oral tablets (oxycodone hydrochloride), labeling available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202080s002lbl.pdf.

[7] See, e.g., NDA 022442, Rezira oral solution (hydrocodone bitartrate; pseudoephedrine hydrochloride), labeling available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022442s000lbl.pdf.

[8] Buprenorphine and methadone are opioids that are indicated for analgesia and are also indicated for medication-assisted treatment (MAT) of opioid dependence/addiction. See, e.g., NDA 022410, Suboxone buccal film (buprenorphine hydrochloride; naloxone hydrochloride), labeling available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022410s020s022lbl.pdf.

[9] As previously described, we are interpreting the petition to request action on opioid analgesics only. See fn. 1.

[10] See Yaksh TL, Wallace MS. Chapter 18. Opioids, Analgesia, and Pain Management. In: Brunton LL, Chabner BA, Knollmann BC. eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e.* New York, NY: McGraw-Hill; 2011.

[11] See id.

[12] See, e.g., Saari TI, et al. Enhancement of GABAergic Activity: Neuropharmacological effects of Benzodiazepines and Therapeutic Use in Anesthesiology. Pharmacol Rev 2011;63:243-267.

[13] See, e.g., NDA 013263, Valium oral tablets (diazepam), labeling available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/013263s092lbl.pdf.

[14] See, e.g., NDA 020813, Klonopin Rapidly Disintegrating (clonazepam), labeling available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017533s053,020813s009lbl.pdf.

[15] See, e.g., NDA 018163, Restoril oral capsules (temazepam), labeling available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/018163s054lbl.pdf.

[16] See, e.g., NDA 020813, Klonopin Rapidly Disintegrating (clonazepam), labeling available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017533s053,020813s009lbl.pdf.

[17] See, e.g., NDA 013263, Valium oral tablets (diazepam), labeling available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/013263s092lbl.pdf.

[18] See, e.g., NDA 013263, Valium oral tablets (diazepam), labeling available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/013263s092lbl.pdf.

[respiration] in healthy subjects."[19] At higher doses, however, "they decrease the muscular tone in [the] upper airways, which increases the risk of airway obstruction[,]" and they reduce the body's response to increasing carbon dioxide levels.[20] Normally, rising carbon dioxide levels (which may occur when not enough air is moving in and out of the lungs), result in a stimulus to increase breathing; benzodiazepines can decrease the response to this stimulus.

Thus, in certain circumstances, either opioids or benzodiazepines independently can depress respiration. When combined, these drugs can cause greater respiratory depression than either drug would by itself,[21] as can other CNS depressant drugs when combined with opioids.[22] For this reason, the labeling of many opioid analgesics and benzodiazepine drugs currently contains warnings about the risks of concomitant use of opioid analgesics and benzodiazepines. To date, however, these warnings have not been presented in a boxed warning.

B. Relevant Authority

1. Safety Labeling Changes

Section 505(o)(4) of the FD&C Act[23] authorizes FDA to require certain holders of approved applications for prescription drug products to make SLCs— including requiring or modifying a boxed warning or Medication Guide — if the Agency becomes aware of "new safety information" that FDA believes should be included in the labeling of the drug. *New safety information* (NSI) is defined in part as:

> Information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3) of the FD&C Act), or peer-

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[19] Saari TI, et al. Enhancement of GABAergic Activity: Neuropharmacological effects of benzodiazepines and therapeutic use in anesthesiology. Pharmacol Rev 2011;63:243-267.

[20] Id.

[21] See, e.g., Jann M, Kennedy WK, Lopez G. Benzodiazepines: a major component in unintentional prescription drug overdoses with opioid analgesics. J Pharm Pract. 2014;27(1):5-16; Pattinson KT. Opioids and the control of respiration. Br J Anaesth (2008) Jun;100(6):747-58; Gueye PN, Borron SW, Risède P, et al. Buprenorphine and midazolam act in combination to depress respiration in rats. Toxicol Sci (2002);65:107-14; White JM, Irvine RJ. Mechanisms of fatal opioid overdose. Addiction (1999) 94(7), 961-972.

[22] See, e.g., Caputo F, Bernardi M. Medications acting on the GABA system in the treatment of alcoholic patients. Curr Pharm Des. 2010;16(19):2118-2125; Olsen R W, Sapp D W, Bureau M H, Turner D M, Kokka N. Allosteric actions of central nervous system depressants including anesthetics on subtypes of the inhibitory γ-aminobutyric $acid_A$ receptor—chloride channel complex. Ann. N. Y. Acad. Sci. 1991;625:145–154.

[23] See also the guidance for industry: *Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act* (July 2013) (available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm250783.pdf). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

> reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k) of the FD&C Act; or other scientific data deemed appropriate by the [Agency] about, among other things, a serious risk or an unexpected serious risk associated with use of the drug that the [Agency] has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since [a] risk evaluation and mitigation strategy (REMS) [for the drug] was approved, or since the last assessment of the approved REMS.[24]

Once the Agency notifies application holders that it has become aware of new safety information that it believes should be included in drug labeling, those application holders must respond within 30 days, either by submitting a supplement proposing changes to the approved labeling to reflect the NSI, or by notifying the Agency that they do not believe a labeling change is warranted and submitting a statement detailing the reasons why such a change is not warranted.[25] The Agency and the application holders may enter into discussions to reach agreement on whether the labeling for the drug should be modified to reflect the NSI. At the end of the discussions, FDA may issue an order requiring the SLCs to be made.[26]

2. *Regulations and Guidances: Boxed Warnings and Medication Guides*

Under FDA regulations, "[c]ertain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box."[27] FDA has explained that "[a] boxed warning is ordinarily used to highlight for prescribers one of the following situations:

- 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 that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)

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[24] See section 505-1(b)(3) of the FD&C Act (21 U.S.C. 355-1(b)(3)).

[25] Section 505(o)(4)(B) of the FD&C Act.

[26] Section 505(o)(4)(D)-(E) of the FD&C Act.

[27] 21 CFR 201.57(c)(1). Section 201.57 also contains the general format and requirements for the "Boxed Warning" section, in both the highlights and full prescribing information sections of labeling (21 CFR 201.57(a)(4) and (c)(1)). In addition, 21 CFR 201.56 sets forth the general requirements on content and format of labeling for human prescription drug products, including that the labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug (see 21 CFR 201.56(a)(1)).

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 (e.g., under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under [section] 505-1(f)(3) of the [FD&C Act] "Risk Evaluation and Mitigation Strategies" Elements to assure safe use)."[28]

Although boxed warnings are often based on observed serious adverse reactions, "there are instances when a boxed warning based on an anticipated adverse reaction would be appropriate."[29] One such example provided by the Labeling Guidance is that of a class-wide pregnancy contraindication in a boxed warning on all drugs in the class, even when there is human or animal data available for only *some* of the drugs in the class.[30]

A Medication Guide is a patient-focused document intended to inform patients about certain serious risks or adverse effects associated with a drug that FDA determines poses a serious and significant public health concern requiring distribution of FDA-approved patient information. A Medication Guide is a part of FDA-approved drug labeling, and as such, are subject to the requirements for labeling content and format set forth in §§ 201.56 and 201.57 (21 CFR 201.56 and 201.57).[31]

The regulations specific to Medication Guides provide that the guides "[apply] primarily to human prescription drug products used on an outpatient basis without direct supervision by a health professional."[32] According to 21 CFR § 208.1(c), a Medication Guide "will be required if the FDA determines that one or more of the following circumstances exists:

> (1) The drug product is one for which patient labeling could help prevent serious adverse effects.
>
> (2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.
>
> (3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness."

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[28] Guidance for industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (Labeling Guidance) at p. 11 (available at http://www.fda.gov/downloads/Drugs/Guidances/ucm075096.pdf).

[29] See id.

[30] See id. at p. 12.

[31] See Guidance: *Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies*, p. 4 (available at http://www.fda.gov/downloads/Drugs/.../Guidances/UCM244570.pdf) ("Medication Guides are part of labeling (21 CFR 201.57(c)) and are subject to the SLC provisions of section 505(o)(4) of the FD&C Act, added by FDAAA.").

[32] 21 CFR § 208.1(a).

II. FDA ACTION: OPIOID ANALGESIC, PRESCRIPTION OPIOID COUGH PRODUCTS, AND BENZODIAZEPINE BOXED WARNINGS AND MEDICATION GUIDES

FDA is deeply concerned about the potential risks to public health that occur when opioids are combined with benzodiazepines or other CNS depressants, including alcohol. As described in more detail below, the number of patients filling prescriptions for opioids and benzodiazepines on the same day has risen substantially, as have deaths associated with the concomitant use of these drugs. FDA is also aware of data regarding the risks of concomitant use of opioids with other CNS depressants, including alcohol. And so today, the Agency is taking action – beyond the requests in the Petition, as described in further detail below – to require boxed warnings and new or revised Medication Guides for opioid analgesics, prescription opioid cough products, and benzodiazepines about the risks of concomitant use of opioids and benzodiazepines, and the risks of concomitant use of opioids and other CNS depressants, including alcohol.

A. New Safety Information

FDA has become aware of information that the Agency believes should be included in labeling for opioid analgesics, prescription opioid cough products, and benzodiazepines regarding the serious risks of profound sedation, respiratory depression, coma, and death[33] associated with concomitant use of opioids and benzodiazepines, and concomitant use of opioids and other CNS depressants, including alcohol. Taken together, this information, which is derived from peer-reviewed publications, constitutes *new safety information* within the meaning of section 505-1(b)(3) of the FD&C Act, on the basis of which the Agency is requiring SLCs to opioid analgesics, prescription opioid cough products, and benzodiazepines.[34]

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[33] Profound sedation, respiratory depression, coma, and death constitute serious risks (or risks of a *serious adverse drug experience*) pursuant to section 505-1(b)(4) and (b)(5) of the FD&C Act (21 U.S.C. 355-1(b)(4) and (b)(5); § 201.57; see also the Labeling Guidance (available at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm075096.pdf).

[34] In support of opioid analgesic and prescription opioid cough product SLCs, see Dasgupta N, Funk M, Proescholdbell S, Hirsch A, Ribisl K, Marshall S. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. Pain Med 2015. Doi: 10.1111/pme/12907; Hwang C, Kang E, Kornegay C, Staffa J, Jones C, McAninch J. Trends in the concomitant prescribing of opioids and benzodiazepines, 2002-2014. Am J Prev Med 2016. In press. doi:10.1016/j.amepre.2016.02.014, Epub 2016 Apr 11; Jones C, McAninch J. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. Am J Prev Med 2015;49(4):493–501; Park T, Saitz R, Ganoczy D, Ilgen M, Bohnert A. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. BMJ 2015;350:h2698; see also Jones C, Mack K, Paulozzi L. Pharmaceutical overdose deaths, United States, 2010. JAMA 2013;309(7):657-9; Jones C, Paulozzi L, Mack K. Alcohol Involvement in Opioid Pain Reliever and Benzodiazepine Drug Abuse-Related Emergency Department Visits and Drug-Related Deaths – United States, 2010. MMWR 2014;63(40):881-5. In support of benzodiazepine SLCs, see See Dasgupta N, Funk M, Proescholdbell S, Hirsch A, Ribisl K, Marshall S. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. Pain Med 2015. Doi: 10.1111/pme/12907; Hwang C, Kang E, Kornegay C, Staffa J, Jones C, McAninch J. Trends in the concomitant prescribing of opioids and benzodiazepines, 2002-2014. Am J Prev Med 2016. In press.

FDA epidemiologists co-authored and recently published two analyses of ecological data pertaining to concomitant use of opioid analgesics and benzodiazepines. An analysis by Hwang et al. (2016) demonstrated that the frequency with which opioid analgesics and benzodiazepines are dispensed to the same patient has risen: the proportion of opioid analgesics recipients concomitantly dispensed a benzodiazepine prescription increased from 7 percent in 2002 to 10 percent in 2014, representing a relative increase of 41 percent.[35] An analysis of these prescriptions showed that roughly half of the patients dispensed concomitant prescriptions for opioids and benzodiazepines filled their prescriptions for both drugs on the same day, and the prescriber of both prescriptions was the same (although the prescriptions may not have been written on the same day).[36]

In addition, an analysis by Jones et al. (2015) demonstrated that there is significant morbidity and mortality associated with the concomitant use of opioid analgesics and benzodiazepines.[37] This analysis built on similar, earlier analyses of death certificate data published by Jones et al. (2013).[38] The Jones et al. (2015) analysis of Drug Abuse Warning Network (DAWN) and National Vital Statistics data concluded that, from 2004 to 2011, the number of emergency department (ED) visits in the United States involving the nonmedical[39] use of both opioid analgesics and benzodiazepines rose every year, with an average relative annual percentage increase of 19.1 percent.[40] Similarly, the number of deaths associated with opioid analgesic and benzodiazepine co-

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doi:10.1016/j.amepre.2016.02.014, Epub 2016 Apr 11; Jones C, McAninch J. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. Am J Prev Med 2015;49(4):493–501; Park T, Saitz R, Ganoczy D, Ilgen M, Bohnert A. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. BMJ 2015;350:h2698.

[35] Hwang C, Kang E, Kornegay C, Staffa J, Jones C, McAninch J. Trends in the concomitant prescribing of opioids and benzodiazepines, 2002-2014. Am J Prev Med 2016. In press. doi:10.1016/j.amepre.2016.02.014, Epub 2016 Apr 11.

[36] Id.

[37] Jones C, McAninch J. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. Am J Prev Med 2015;49(4):493–501.

[38] Jones C, Mack K, Paulozzi L. Pharmaceutical overdose deaths, United States, 2010. JAMA 2013;309(7):657-659. In Jones (2013), the authors observed that opioid analgesics were involved in over 77 percent of deaths where benzodiazepines were determined to be a cause of death, and that benzodiazepines were involved in over 30 percent of deaths where opioid analgesics were determined to be a cause of death.

[39] The authors define this as taking a higher than recommended dose, taking a drug prescribed for another person, drugs imbibed in drug-facilitated assaults, or documented misuse/abuse of a prescription drug as documented in the medical record. Jones C, McAninch J. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. Am J Prev Med 2015;49(4):493–501, p. 494.

[40] Jones C, McAninch J. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. Am J Prev Med 2015;49(4):493–501.

ingestion (whether medical or nonmedical) also rose every year during that time period, with an average relative annual percentage increase of 15.0 percent.[41]

Dasgupta et al. (2015) and Park et al. (2015) provide more direct evidence of increased mortality associated with concomitant use of benzodiazepines and opioid analgesics, in analyses that linked individual patients' prescription and adverse event data to demonstrate that patients receiving prescriptions for both drug classes had an increased risk of overdose death[42] compared to patients dispensed only opioid analgesics.[43] Dasgupta et al. examined the association between opioid analgesic dose and mortality risk among 629 North Carolina residents who died of an opioid analgesic-related overdose in 2010.[44] Linking state-based prescription drug monitoring program and death certificate data, the authors found that, in 61.4 percent of the reported opioid analgesic-related deaths, medical examiners determined that benzodiazepines also contributed.[45] They further observed that rates of opioid analgesic-related overdose death in North Carolina in 2010 were roughly 10 times higher among those dispensed opioid analgesics and benzodiazepines concomitantly compared to those prescribed only opioid analgesics.[46] Park et al.'s examination of Veterans Health Administration data found that the risk of fatal overdose increased among those receiving both opioid analgesics and benzodiazepines compared to those dispensed only opioid analgesics.[47] Compared to those patients taking opioid analgesics with no history of a benzodiazepine prescription, patients taking opioid analgesics with a history of a benzodiazepine prescription had a higher risk of fatal overdose (Hazard Ratio (HR)=2.33 [95 percent Confidence Interval (CI):2.05-2.64]), as did those with a current benzodiazepine prescription (HR=3.86 (95 percent CI:3.49-4.26)).[48]

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[41] Id.

[42] This term refers to fatal overdose, from prescribed or greater-than-prescribed doses.

[43] Dasgupta N, Funk M, Proescholdbell S, Hirsch A, Ribisl K, Marshall S. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. Pain Med 2015. Doi: 10.1111/pme/12907; Park T, Saitz R, Ganoczy D, Ilgen M, Bohnert A. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. BMJ 2015;350:h2698.

[44] Dasgupta N, Funk M, Proescholdbell S, Hirsch A, Ribisl K, Marshall S. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. Pain Med 2015. Doi: 10.1111/pme/12907.

[45] Id.

[46] Id.

[47] Park T, Saitz R, Ganoczy D, Ilgen M, Bohnert A. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. BMJ 2015;350:h2698 (Model 1).

[48] Park T, Saitz R, Ganoczy D, Ilgen M, Bohnert A. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. BMJ 2015;350:h2698.

Taken together, these four observational studies provide persuasive evidence of an increased risk of serious adverse events[49] associated with concomitant use of opioid analgesics and benzodiazepines compared to using opioid analgesics alone. The results of these studies support labeling language that warns of the risk of profound sedation, respiratory depression, coma and death associated with concomitant use of these drug classes.

However, FDA is also concerned that, in place of co-prescribing benzodiazepines with opioid analgesics, prescribers may substitute other CNS depressants that can also increase the risk for respiratory depression and death when used concomitantly with opioids. Studies by Jones et al. (2013) and Jones et al. (2014) indicate that concomitant use of opioid analgesics and central nervous system (CNS) depressants,[50] including alcohol,[51] is associated with serious adverse events. In Jones et al. (2013), the authors observed that opioid analgesics contributed to over 77 percent of deaths where benzodiazepines were determined to be a cause of death, and that benzodiazepines were involved in over 30 percent of deaths where opioid analgesics were determined to be a cause of death.[52] The authors also analyzed the contribution of a number of other, non-benzodiazepine CNS depressants – including barbiturates, antipsychotic and neuroleptic drugs, antiepileptic and antiparkinsonian drugs, anesthetics, autonomic nervous system drugs, and muscle relaxants – in these deaths, finding that these CNS depressants were contributory to death in many cases where opioid analgesics were also implicated.[53] Furthermore, in Jones et al. (2014), the authors analyzed DAWN data and found that nearly one fifth of opioid analgesic abuse-related ED visits involved alcohol as well.[54] The findings presented in these publications are consistent with risks that can be expected to be associated with the use of these drugs based on what is known about the pharmacology of these drugs; that is, "[t]he combination of opiates with other [CNS]

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[49] The adverse event observed in the studies by Jones et al. (2015), Park et al. (2015), and Dasgupta et al. (2015) was death, which, when due to drug overdose, is typically preceded by profound sedation, respiratory depression, and coma.

[50] See Jones C, Mack K, Paulozzi L. Pharmaceutical overdose deaths, United States, 2010. JAMA 2013;309(7):657-659.

[51] See Jones C, Paulozzi L, Mack K. Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse-related emergency department visits and drug-related deaths – United States, 2010. MMWR 2014;63(40):881-885.

[52] Jones C, Mack K, Paulozzi L. Pharmaceutical overdose deaths, United States, 2010. JAMA 2013;309(7):657-659.

[53] Id.

[54] Jones C, Paulozzi L, Mack K. Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse-related emergency department visits and drug-related deaths – United States, 2010. MMWR 2014;63(40):881-885.

depressant medications, such as general anesthetics, tranquilizers, alcohol, or sedative-hypnotics, produces additive depression of respiratory activity."[55]

Although the focus of the studies cited above is on benzodiazepines and opioid analgesics, the concomitant use risks evinced by these studies also support SLCs for prescription opioid-containing cough/cold products because the active ingredients act in the body through the same mechanisms, and the benefit/risk considerations for these products warrant the labeling changes discussed in section II.B. below. Thus, FDA has determined that information about the serious risks of profound sedation, respiratory depression, coma, and death associated with concomitant use of benzodiazepines or CNS depressants other than benzodiazepines, including alcohol, with opioid analgesics or prescription opioid cough products should be included in the labeling of both opioid analgesics and prescription opioid cough products.

B. Safety Labeling Changes

We consider the studies discussed above to be *new safety information* as defined in section 505-1(b)(3) of the FD&C Act. Thus, FDA is notifying application holders regarding the need to make SLCs reflecting this NSI, including the need to add or amend Medication Guides for these products to provide patients with this information.

Additionally, the Agency agrees with the Petitioners that the regulatory standard for a boxed warning has been met. That is, a boxed warning is appropriate to highlight the serious adverse reactions (including death) associated with concomitant use of opioids and benzodiazepines, which "can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding concomitant therapy, addition of another drug or managing patients in a specific manner, [or] avoiding use in a specific clinical situation)."[56]

Similarly, the Agency believes that the serious adverse reactions (including death) associated with the concomitant use of opioids and other CNS depressants, including alcohol, meets the same standard. Thus, the Agency is requiring sponsors to add new boxed warnings to their products.

However, because of differences in drug pharmacology, conditions of use, different risk-benefit assessments, and available data, the precise language of the new warnings for opioid analgesics, prescription opioid cough products, and benzodiazepines will vary slightly.

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[55] Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e, Chapter 18. Opioids, Analgesia, and Pain Management, Opioid Receptors (available at http://accesspharmacy.mhmedical.com/content.aspx?bookid=374&sectionid=41266224).

[56] Labeling Guidance, p. 11 (available at http://www.fda.gov/downloads/Drugs/Guidances/ucm075096.pdf).

1. Boxed Warning and Other Changes to Labeling

FDA is requiring a boxed warning for all three drug classes (opioid analgesics, prescription opioid cough products, and benzodiazepines) to inform prescribers that concomitant use of opioids and benzodiazepines "may result in profound sedation, respiratory depression, coma, and death." The language advises prescribers of opioid analgesics and benzodiazepines, whose patients may, in certain circumstances, require the therapeutic benefits of both drugs, to "[r]eserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate[, l]imit dosages and duration to the minimum required[, and f]ollow patients for signs and symptoms of respiratory depression and sedation."

Because of the context of use, patients taking prescription opioid cough products face a different benefit/risk assessment in concomitant use of prescription opioid cough products and CNS depressants such as benzodiazepines.[57] Consequently, the boxed warning for these products will include stronger language recommending that prescribers "[a]void use of opioid cough medications in patients taking benzodiazepines[.]"

In addition, for reasons described in section II.A, above, the Agency also has determined that the standard for a boxed warning has been met to highlight the dangers of combining opioids and benzodiazepines or other CNS depressants, including alcohol, for opioid analgesics and prescription opioid cough products. Thus, FDA is requiring boxed warning language for opioid analgesics as follows:

> WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
>
> Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Warnings and Precautions (5.X), Drug Interactions (7.X)].
>
> - Reserve concomitant prescribing of TRADENAME and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
> - Limit dosages and duration to the minimum required.
> - Follow patients for signs and symptoms of respiratory depression and sedation.

FDA is requiring boxed warning language for prescription opioid cough products as follows:

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[57] Opioid cough products are indicated for the treatment of cough, which is generally a self-limited, non-serious event. Given the serious risks of profound sedation, respiratory depression, coma, and death, associated with the concomitant use of opioids and CNS depressants, including benzodiazepines and alcohol, the use of opioid cough medications should be avoided in patients taking CNS depressants, including benzodiazepines and alcohol.

> WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
>
> Concomitant use of opioids with benzodiazepines, or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.X), Drug Interactions (7.X)]*. Avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants or alcohol.

FDA is requiring boxed warning language for benzodiazepines as follows:

> WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS
>
> Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.X), Drug Interactions (7.X)]*.
>
> - Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
> - Limit dosages and duration to the minimum required.
> - Follow patients for signs and symptoms of respiratory depression and sedation.

FDA is also requiring updates to the Warnings and Precautions, Drug Interactions, and Patient Counseling sections of labeling for opioid analgesics, prescription opioid cough products, and benzodiazepines to reflect the risks of concomitant use of opioids and benzodiazepines and of opioids and other CNS depressants, including alcohol.

2. Medication Guides

The Agency has determined that the standard for requiring a Medication Guide for opioid analgesics, prescription opioid cough products, and benzodiazepines has been met.[58] Thus, the Agency is requiring that sponsors of opioid analgesics, benzodiazepines, and prescription opioid cough products create new or revised Medication Guides to communicate the serious risks associated with concomitant use of opioids and benzodiazepines, and opioids and other CNS depressants, including alcohol.[59]

3. Goals of Safety Labeling Changes

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[58] 21 CFR 208.1.

[59] There are some drugs for which FDA is not requiring Medication Guides at this time, however: parenteral opioid analgesics and benzodiazepine drugs, because of their administration by a trained professional in healthcare setting, and a benzodiazepine drug called Diastat (diazepam rectal gel), which has special conditions of administration. See http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020648s012lbl.pdf.

FDA intends these changes to prompt prescribers to more carefully and thoroughly evaluate, on a patient-by-patient basis, whether the benefits of concomitant use of opioids and benzodiazepines, or opioids and other CNS depressants, outweigh the serious risks, and to take into consideration the extent to which alcohol use by the patient may affect the risk-benefit analysis. If opioid analgesics and benzodiazepines, or opioid analgesics and other CNS depressants,[60] are co-prescribed, the required labeling changes emphasize that prescribers should "[l]imit dosages and duration to the minimum required[, and f]ollow patients for signs and symptoms of respiratory depression and sedation." For prescription opioid cough products, the required labeling changes emphasize that these products should be avoided in patients taking CNS depressants, including benzodiazepines. The Agency believes that the changes will improve communication of serious risks associated with the concomitant use of these products to both prescribers and patients, and, in so doing, help reduce the incidence of serious adverse events.

In accordance with section 505(o)(4) of the FD&C Act, the application holders for opioid analgesic, benzodiazepine, and prescription opioid cough products are required to submit, within 30 days, a supplement proposing changes to the approved labeling to reflect the NSI, or else notify the Agency that they do not believe labeling changes are warranted and submit a statement detailing the reasons why changes are not warranted.[61] If an application holder does not submit such a supplement, or if FDA disagrees with alternative language that the application holder proposes, the FD&C Act provides timelines under section 505(o)(4) for discussions to reach agreement on whether the labeling for the drug should be modified to reflect the NSI.[62] At the conclusion of these discussions, section 505(o)(4)(E) authorizes FDA to issue an order directing application holders to make labeling changes as appropriate.

III. AGENCY RESPONSE TO THE PETITIONERS' EVIDENCE AND ARGUMENTS

Broadly speaking, the Petitioners base their requests for boxed warnings and Medication Guides on the following data and assertions:

- Biological effects ("synergistic effects"), arguing that concomitant use of benzodiazepines and opioid analgesics is more likely to cause fatal respiratory depression than either drug alone (see Petition at 3-5);
- Epidemiological data, which the Petitioners assert show that concomitant use-related overdose is common and increasing (see Petition at 6-9), and prescribing trends, which the Petitioners assert show that co-prescription is common and increasing (see Petition at 9-13);

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[60] Alcohol is not a prescription drug. However, prescribers should inform patients about the serious risks associated with concomitant use of alcohol.

[61] See section 505(o)(4)(B) of the FD&C Act.

[62] See section 505(o)(4)(D) of the FD&C Act.

- Suggestions that a boxed warning is needed because existing educational measures have not been sufficient to warn providers of the risks of co-prescribing (see Petition at 10-13); and
- Assertions that existing labeling is inconsistent and insufficient (see Petition at 14).

FDA agrees with certain of the Petitioners' sources regarding biological effects.[63] Without needing to comment further on the Petitioners' assertions or sources on this subject,[64] however, and based on the data and information cited in section II of this response, the Agency agrees that concomitant use of opioid analgesics and benzodiazepines carries a greater risk of death than the use of either drug alone. Furthermore, FDA acknowledges that current drug labeling for opioid analgesics and benzodiazepines varies with regard to wording and extent of warnings about concomitant use. FDA has determined that the current labeling of opioid analgesics, prescription opioid cough products, and benzodiazepines should be revised to amplify the warnings regarding the risks of concomitant use of opioids and benzodiazepines, or opioids and other CNS depressants, including alcohol. Without commenting on the characterization or sufficiency of the guidelines, educational measures, and other prescribing protocols referenced in the Petition, the Agency agrees with the Petitioners that more can and should be done to inform prescribers and patients about these risks, and to encourage more judicious prescribing and use of these drugs. For these reasons, the Agency has decided to require the labeling changes and Medication Guides described above.

FDA has carefully reviewed the data and sources cited by the Petitioners, and has concluded that the studies (other than Park et al. (2015) and Jones et al. (2013)) have significant limitations in terms of study design or analysis when used to determine risks of concomitant prescribing and use of opioid analgesics and benzodiazepines. As such, those studies do not provide sufficient evidence on which to base Petitioners' requested actions.

IV. CONCLUSION

FDA recognizes the devastating impact that the epidemic of opioid abuse and its related risks and consequences have had on the public health. Over the past few years, the Agency has prioritized efforts to reduce the risks of opioids, and on February 5, 2016, the Agency announced a comprehensive action plan to take concrete steps toward reducing the impact of opioid abuse on American families and communities.[65] Today, FDA has

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[63] See, e.g., Gueye PN, Borron SW, Risède P, et al. Buprenorphine and midazolam act in combination to depress respiration in rats. Toxicol Sci (2002);65:107-14; White JM, Irvine RJ. Mechanisms of fatal opioid overdose. Addiction (1999) 94(7), 961-972.

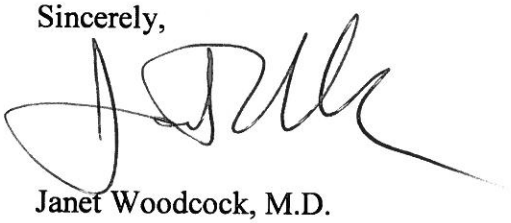
[64] Nothing in this Petition response should be interpreted as FDA's agreement or disagreement with the Petitioners' analysis of the studies in support of the assertion that the combination of opioids and benzodiazepines carries a greater risk of being fatal than the use of either drug alone.

[65] See Fact Sheet – FDA Opioids Action Plan (available at http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm).

taken another important step to make opioid analgesics, opioid cough products, and benzodiazepine drugs safer for patients who need them by amplifying and clarifying the serious risks of concomitant use of opioids and benzodiazepines, and opioids and other CNS depressants, including alcohol.

The Petition is granted in that FDA has decided to require a boxed warning and new or revised medication guide for opioid analgesic and prescription opioid cough drugs and benzodiazepine drugs, alerting patients and prescribers to serious risks associated with concomitant use of opioids and benzodiazepines. The Petition is denied to the extent that the language in the boxed warning and medication guides differs from the language requested in the Petition, and to the extent that there are certain products that will not receive medication guides because of the distinct indications and uses of those drugs.

Sincerely,



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